Gaps in management and treatment of epilepsy in people with confirmed or probable neurocysticercosis

By

RICHARD MAMBO

A dissertation submitted to the University of Zambia in fulfillment of the award of the degree of Master of Science in Public Health

UNIVERSITY OF ZAMBIA

SCHOOL OF VETERINARY MEDICINE

DEPARTMENT OF CLINICAL STUDIES

LUSAKA

DECLARATION

I, **Richard Mambo** do hereby declare that this dissertation represents my own work and has not been previously submitted for the award of a degree or any other qualification at this or another University.

Signature: ----------

Date: ----------

ACKNOWLEDGEMENTS

This research would not have been possible without the support of the Solium Diagnostics Project (SOLID Project). I am highly indebted to my principal supervisor Dr. K. E. Mwape who unreservedly gave me enormous support and guidance throughout the research and for allowing me to use the research reagents and equipment. I also wish to thank my co-supervisor Dr. A. Phiri for the valuable support and tireless efforts in developing the research document. I am greatly indebted to Prof I.G.K Phiri, Prof J. Muma and Prof S. Gabriel for their scientific guidance. I wish to further thank Mr. Mwelwa Chembensofu the chief Scientist at the School of Veterinary Medicine, Paraclinical Studies Department, University of Zambia, Dr. Mubanga Chishimba a PhD student under SOLID project, and Dr. Gideon Zulu for the professional assistance rendered during the field work and laboratory analysis. To Chiara Trevisan, thank you so much for the comments and for helping me with questionnaires and data analysis.

Appreciation goes to The University of Zambia for according me a chance to pursue this program, The School of Veterinary Medicine for allowing me to conduct the study in the School, the Ministry of Health for authorizing me to collect data from health centres, Mtandaza Local communities for their cooperation, Messers Mirriam Phiri, Lizzie Kaira, Luke Mwenya, Esther Nkhoma, Sebastian Njobvu and the Mtandaza RHC staff for their support during field work.

To my family, thank you for the unending support and love during my study. I also extend my special thanks to my colleagues that were an inspiration to me. Above all, I thank God for his Love and Grace upon me. He kept me in good health throughout my study period.

Finally, my gratitude goes to all those who contributed in one way or the other, especially those that reviewed and gave comments towards the finalization of my project.

DEDICATIONS

This study is dedicated to my wife Clara and my children Joyce, Yvonne, Richard and Joshua for their patience during the days of my absence to attend to school programs. To my father and mother, brothers and sisters, your encouragements and continuous prayers have necessitated the successful completion of this study. To you all I say thank you very much and may God richly bless you.

CERTIFICATE OF APPROVAL

This dissertation submitted by RICHARD MAMBO is approved as fulfillment of the requirements for the award of the degree of Masters of Science in Public Health by Research at the University of Zambia.

Supervisor Name: ----------Signature---------- Date----------

External examiner ----------Signature---------- Date ----------

Internal examiner 1---------- Signature---------- Date----------

Internal examiner 2----------Signature---------- Date----------

ABSTRACT

Epilepsy is a disorder caused by many factors, including infection of the central nervous system with the larval stage of *Taenia solium,* leading to neurocysticercosis (NCC). People with epilepsy (PWE) in low-income countries often do not receive appropriate treatment, which besides the continuing epileptic seizures, may also lead to cognitive impairment, reduced quality of life, stigma, injuries, and possibly death. The objective of this study was to describe gaps in epilepsy management in a *T. solium* endemic rural area of Zambia.

A cross-sectional study was conducted in Sinda district of the Eastern Province of Zambia between August and October 2018. PWE identified from clinic records including PWE from a previous study were re-contacted. PWE not recorded in the clinic records, but with a reported history of epileptic seizures by community members were also included. Serum and stool samples of PWE were collected and tested for cysticercosis and *taeniosis* respectively. Two questionnaires were administered, one to PWE and one to local healthcare providers to describe management for epilepsy, the reasons for non-treatment as well as, non-adherence to treatment, and the associated risk factors.

A total of 146 PWE and 43 healthcare providers were interviewed. Sixteen of the PWE were diagnosed with definite NCC in a previous study. Samples were tested for 129 PWE out of the 130 who had never been diagnosed with NCC, and thereof 36 were diagnosed with probable NCC following the Del Brutto diagnostic criteria. Forty-four percent of PWE were on anti-epileptic drugs, however, only 26 (17.8%) were on regular anti-epileptic treatment, resulting in a treatment gap of more than 82%. Over 50% of healthcare providers did not know the relationship between epilepsy and NCC. The risk factors associated with lack of correct treatment were stock-outs of anti-epileptic drugs, long distance to health facilities, lack of diagnostic equipment and poor patient follow up, and PWE opting for traditional medicine.

The results of this study demonstrated that gaps in the management of epilepsy in PWE and NCC are substantial in Sinda district. The causes are multifactorial, involving shortcomings on the level of the health facilities, communities, and individuals. Significant improvements in the supply and dispensing of anti-epileptic drugs, accompanied by closer monitoring and follow-ups of PWE may be key in substantially reducing the management gap and subsequently address the challenges and suffering of PWE.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLE

LIST OF SYMBOLS AND ABBREVIATIONS

μg	Microgram
μl	Microlitre
M	Molarity
N	Normality
Ml	Millilitre
Mm	Millimetre
N	Sample size or number examined
Nm	Nanometres
%	Percentage
+ve	Positive
P	Probability
Ab	Antibody
Ag	Antigen
Ag-ELISA	Antigen Enzyme-Linked Immunosorbent Assay
ABZ	Albendazole
AEDs	Ant-Epileptic Drugs
AIDS	Acquired immune deficiency syndrome
CBZ	Carbamazepine
CNS	Central nervous system
CT	Computed Tomography
DCF	Data capture form
EEG	electroencephalogram
EITB	Enzyme-Linked Immuno-electrotransfer blot
ELISA	Enzyme-Linked Immunosorbent Assay
FGDs	Focus Group Discussions
HIV	Human immune virus
ILAE	International League Against Epilepsy
IgG	Immunoglobulin G
NCC	Neurocysticercosis

NHC	Neighborhood Health Committee
MoAb	Monoclonal antibody
MoH	Ministry of Health
MRI	Magnetic Resonance Imaging
OD	Optical density
OPD	Orthophenylenediamine
PB	Phenobarbitone
PBS	Phosphate buffered saline
PCR	Polymerase Chain Reaction
PZQ	Praziquantel
PWE	People with Epilepsy
PLWE	People Leaving with Epilepsy
RHC	Rural Health Centre
SAPE	Suspect adverse product experience
SOP	Standard operating procedure
STATA	Statistics/Data Analysis Software
SPSS	Statistical Package for Social Sciences
TAA	Test article administration
TBD	To be documented
T20	Tween 20
TCA	Trichloro acetic acid
WHO	World Health Organisation
ZNF	Zambia National Formulary
DALY	Disability Adjusted Life Years
DAB	Diaminobenzidine dehydrochlorid

CHAPTER ONE

1.0 INTRODUCTION

Epilepsy is a brain disease characterized by two unprovoked (or reflex) seizures occurring at least 24 hours apart, or one unprovoked (or reflex) seizure with a probability of further seizures similar to the general recurrence risk after two unprovoked seizures occurring over the next 10 years (Fisher *et al*., 2014). This definition also includes diagnosis of epilepsy syndrome. "An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Iasemidis, 2003; Fisher *et al*., 2005; 2014). Epilepsy is one of the most common serious neurological disorder affecting about 50 million people worldwide (Jacoby *et al*., 2005; Meyer *et al*., 2012). The disease is in the family of diverse disorders having in common excessive predisposition to seizures and is caused by many factors (Annegers *et al*., 1996). According to Annegers *et al*. (1996) causes of epilepsy include traumatic brain injury, cerebrovascular diseases, brain tumors, neurodegenerative diseases, perinatal insults, developmental disabilities, and infection of the central nervous system (CNS) which may result into neurocysticercosis (NCC). Infection of the CNS is caused by a number of parasites such as *Taenia solium, Echinococcus* species, *Schistosoma* species and *Toxoplasma gondii* (Carpio *et al*., 2016). *T. solium* is an important human parasite and a common cause of epilepsy in Africa (Figure 2.1), Latin America and Asia (Roma'n *et al.*, 2000). The infection occurs mainly in low-income countries and is associated with poverty, poor sanitation and free-range pig management (Mwape *et al*., 2013; Carpio & Romo 2014). *T. solium* is among the most prevalent parasites in the Eastern Province of Zambia (Sikasunge *et al*., 2008; Mwape *et al*., 2012; 2013)

Neurocysticercosis is a leading cause of preventable epilepsy in the developing world (O'neal *et al.*, 2012; Mwape *et al*., 2015; Rajshekhar, 2017). The proportion of NCC varies from country to country (Ndimubanzi *et al*., 2010; Meyer *et al*., 2015). Ndimubanzi *et al*. (2010) reported a pooled estimate of NCC in people with epilepsy (PWE) to be 29% worldwide. In a community based survey in India the prevalence of NCC was one per 1000 population (Rajshekhar, 2017), and in Latin American countries the median lifetime prevalence of NCC was calculated to be 17.8 per 1000 people (Tellez-zonteno and Hernandez- Ronquillo, 2017). However, Zambia's

prevalence of epilepsy due to NCC ranks among the highest in the world. Mwape *et al*. (2015) found that more than 50% of acquired epilepsy in Eastern Province of Zambia results from the infection of the CNS with the larvae stage of *T. solium*. The high prevalence of NCC among PWE of 51% was also reported in Tete Province of Mozambique in a study by Assane *et al*. (2017). *T. solium* causes the disease known as NCC when the larval stage is lodged in the CNS (Pittella, 1997; O'neal *et al.*, 2012).

The diagnosis and management of epilepsy due to NCC can be very difficult as this may require neuroimaging to make a definitive diagnosis. Immunodiagnostic tests have been developed to help with the diagnosis of cysticercosis. However, most immunodiagnostic tests vary in sensitivity and specificity making them not very reliable (Del Brutto *et al*., 2017). The World Health Organization (WHO) considers epilepsy as one of the most cost effective chronic conditions to treat (WHO *press*, 2006). However the epilepsy treatment gap, referring to PWE not receiving appropriate treatment, has been estimated to be above 90% in many resource-limited countries (Kale, 2010; Meyer *et al*. 2012). Cost-effective treatments such as phenobarbitone (PB), phenytoin and carbamazepine (CBZ) are available. A correct diagnosis can be made based on clinical manifestations. However, the majority of PWE in many low-income countries are not correctly diagnosed and thus do not receive appropriate treatment (Meyer *et al.*, 2009). Despite treatment generally being freely available, unmanaged epilepsy is still prevalent. This untreated or poorly managed epilepsy comes with devastating social consequences such as stigma and death (Birbeck, 2000).

Generally, epilepsy of any kind is associated with a number of challenges such as stigma, injuries, and fire burns which contribute significantly to the psychological and social burden on patients (Baskind and Birbeck, 2005, Meyer e*t al.*, 2009). For example, stigma leads to loss of employment or low acquisition levels of education on individuals with the condition (Baskind and Birbeck, 2005; Atadzhanov *et al.*, 2010). Furthermore, health conditions of epileptic people are continuously deteriorating, sometimes leading to premature mortality (Ding *et al.*, 2006; Moyano *et al.*, 2014)

1.2 Statement of the problem and Justification

It is estimated that about 80% of people suffering from epilepsy around the globe are found in the developing countries (Diop *et al.*, 2003). In the sub-Saharan Africa there is a prevalence rate

of 15 cases per 1000 population (Preux and Druet – Cabanac, 2005), and Tanzania has a prevalence rate of 13.2 cases per 1000 population (Winkler *et al*., 2009). The Zambian epilepsy statistics are comparable to the above. Birbeck *et al*. (2004), found the epilepsy prevalence in Zambia to be at 12.5 cases per 1000 population.

Studies have established a link between epilepsy and NCC in many poor countries (Ndimubanzi *et al*., 2010; Millogo *et al*., 2012; Mwape *et al*., 2015; Assane *et al*., 2017). NCC is a leading cause of preventable epilepsy in the developing world (O'neal *et al*., 2012). A study done in Katete district of Zambia found that 56% of epilepsy was a result of the infection of the CNS with the larva stage of *T. solium* (Mwape *et al*., 2015).

The management of epilepsy is reported to be a challenge in many developing countries (Del Brutto *et al*., 2001; Meyer *et al*., 2012). Diagnostic equipment such as Computed Tomography (CT) scans, Electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI) are scarce, which makes epilepsy diagnosis difficult. Shortage of medical doctors and erratic availability of anti-epileptic drugs (AEDs) adds to the epilepsy treatment gap (Chomba *et al*., 2010). The epilepsy treatment gap has been estimated to be above 90% in resource limited countries (Kale 2002, Meyer *et al*., 2009). PWE that start treatment are reported to stop treatment leading to serious health consequences such as cognitive impairment (Nau *et al*., 2017). Long distance to the health facilities, unavailability of AEDs and lack of knowledge on the consequences of non-adherence to AEDs are some of the reasons for treatment stoppages (Das *et al*., 2007; Chomba *et al*., 2010). Untreated or poorly managed epilepsy is a critical public health issue; as such patients face potentially devastating social consequences and poor health outcomes (Meyer *et al*., 2009; Deye *et al*., 2016). Many PWE remain untreated although effective treatments exist.

Epilepsy of any cause is associated with cognitive impairment and reduced quality of life, among many other challenges (Nau *et al*., 2017). There is need to identify and evaluate the treatment gaps in terms of access to diagnosis and treatment, and adherence to AEDs and factors associated with non-adherence. Although literature shows that mortality among people with epilepsy is high (Ding *et al*., 2006; Moyano *et al*., 2014), the chances of remission are also high (Cockerell *et al*., 1995; Fisher *et al*., 2014) and therefore the probability of such people being young, and fully contributing members of society is higher than in those with heart disease, where the afflicted population is mostly the elderly and less contributing (Scott *et al*., 2001).

To the best of my knowledge no study has been done in Zambia to determine and quantify the management gaps in PWE in an NCC endemic rural area.

1.3 Study objectives

1.3.1 General Objective

Therefore, this study aimed to assess the extent of epilepsy management gap and associated factors, in a rural area where NCC is a major cause of epilepsy.

1.3.2 Specific objectives

The specific objectives were:

i. To identify probable NCC patients among PWE using serological tests
ii. To determine the current management options in the country for PWE, with or without NCC
iii. To determine the levels of adherence to treatment in PWE
iv. To identify factors associated with none adherence to treatment among PWE

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Causes and distribution of epilepsy

Epilepsy represents approximately 0.5% of the total global burden of different diseases (Chin, 2012). It is one of the most neglected serious neurologic disorder and ranks among the most prevalent non-communicable diseases in developing countries (Scott, 2001). Liu *et al*. (2016) indicated that cerebrovascular diseases, traumatic brain injury, neoplasm, CNS infection, and drug withdrawal are the major causes of acute symptomatic seizures.

Epilepsy is estimated to affect at least 50 million people in the world out of which 10 million live in Africa where comprehensive or effective treatment is rare (Coleman *et al*., 2002; Diop *et al*., 2003). The prevalence range of epilepsy in Sub-Saharan Africa is between 4-13/1000 in comparison to 0.5–1.0/1000 in industrialized countries (Scott, 2001; Winkler *et al*., 2009). According to Coleman *et al*. (2002), the condition is associated with psychosocial problems, reduced life expectancy, stigma and an increased risk of accidental deaths. Furthermore, epileptic patients do not receive appropriate and adequate treatment, especially, in rural parts of developing countries (Kale, 2002). This usually results in devastating health outcomes for PWE.

2.2 Epilepsy and neurocysticercosis

Neurocysticercosis is the most common parasitic disease of the nervous system (Bournos and Cavazos, 2014). Not all parasites that affect humans might involve the CNS; however, the most common parasitic infection of the CNS is cysticercosis caused by *T. solium* (Carpio *et al*., 2016). Other parasites such as Toxoplasma gondii, Echinococcus spp and Schistosoma spp are less frequent infections. *T. solium* is a zoonotic parasite and causes two disease conditions in humans, taeniosis and cysticercosis (Flisser, 1994). Under normal circumstances man is the sole definitive host of the adult form of the tapeworm. However, man may act as an intermediate host and become infected with cysticerci of *T. solium* by ingesting eggs emanating from either himself as a tapeworm carrier (auto-infection) or from others in his close environment through contaminated food and water or from dirty hands (Sciutto *et al*., 2000). The cysticerci settle in

the muscles, subcutaneously or have a tendency to lodge in the CNS, a condition called NCC (Flisser, 1994; Garcia *et al*., 2005).

Other sources by which human acquire cysticercosis includes contaminated soil, water and vegetation (Sciutto *et al*., 2000). Chaurasia (2015) estimated the total number of people suffering from NCC, including symptomatic and asymptomatic cases to be between 2.56-8.30 million. The contribution of NCC to epilepsy is approximately 30% to 50% of cases in under resourced regions (Ndimubanzi *et al.*, 2010; Carpio and Romo, 2014). An individual with NCC is almost three times at risk of developing epilepsy than an uninfected individual (Gripper and Welburn, 2017).

Neurocysticercosis has been proposed as 'a leading cause of late–onset epilepsy in developing countries' (De Giorgio *et al*., 2004; Garcia *et al.*, 2005; Carpio and Romo 2014). The presence of seizures in many cases of NCC has been interpreted as being synonymous with epilepsy, especially in individuals where seizures are recurrent. The clear distinctions of the seizures in epilepsy and NCC have not been well elaborated. Epilepsy is said to be unprovoked frequent recurrent seizures of at least 24 hours apart (Carpio and Romo, 2014). However, Gripper and Welburn, (2017) argues that in NCC, seizures are provoked by the immune response triggered by the presence of the cysts in the CNS. The fact that individuals with NCC may remain asymptomatic for prolonged periods, a phenomenon thought to arise from a complex immune evasion response initiated by viable cysts allows them to remain undetected in the body for a long period of time (Garcia *et al.*, 2010; Gripper and Welburn, 2017). The overcoming of such mechanisms by the immune response, usually when the cysts die, is what brings out the symptoms, such as seizures, due to the acute inflammatory reaction (Garcia *et al.*, 2010). The provoked acute symptomatic seizures are potentially influenced by whether an individual cyst is in the viable, degenerative or calcified state (Carpio *et al*., 2016; Gripper and Welburn, 2017).

In 2015, the WHO Foodborne Disease Burden Epidemiology Reference Group identified *T. solium* as a leading cause of deaths from food-borne diseases, resulting in a considerable total of 2.8 million disability-adjusted life-years (DALYs). Although *T. solium* is commonly endemic in many pork-eating countries, it is not always associated with low economic development. Owing to migration and movement of people across the world, NCC is commonly reported in the developed world as well (Murrell 2005).

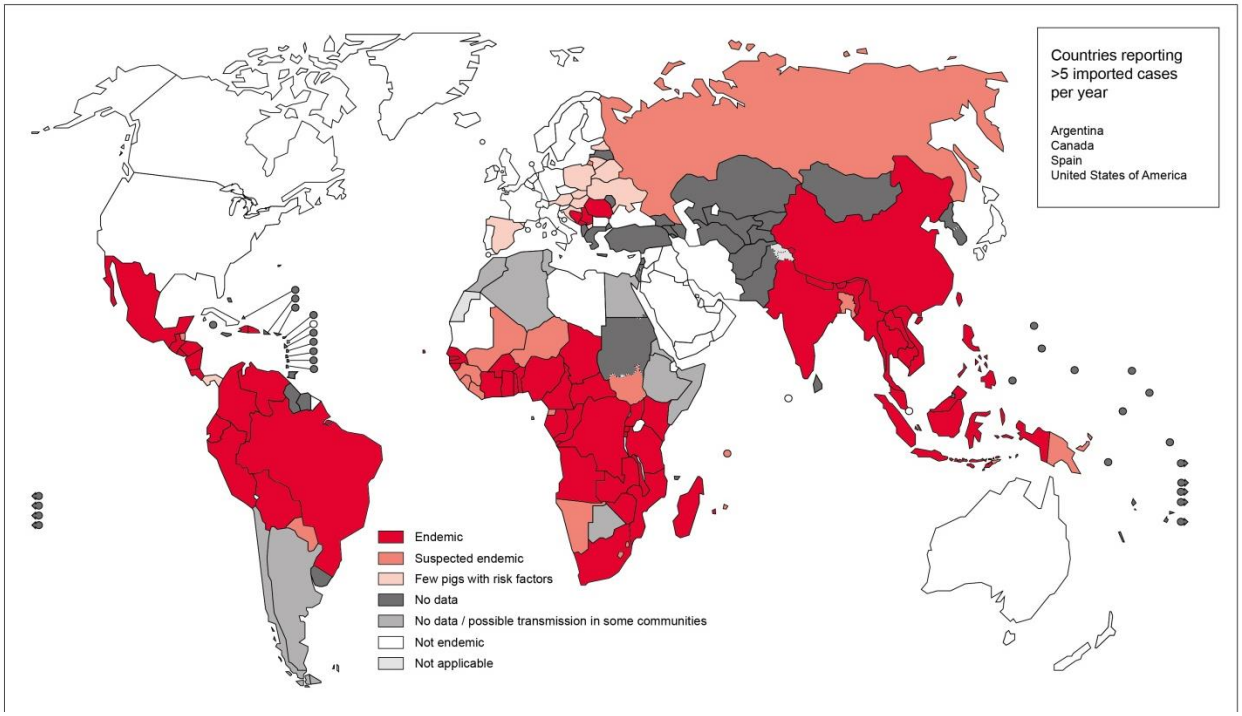


Figure 2.1: Endemicity of *Taenia solium* (https://www.who.int/taeniasis/Endemicity_*Taenia*_*Solium*_2015.jpg)

2.3 Clinical presentation of NCC and epilepsy

The most common clinical manifestations of NCC are epilepsy, seizures, chronic headaches, cerebrovascular disorder, focal neurologic deficits, intracranial hypertension, cognitive decline and depression (Del Brutto *et al*., 2017). However, its clinical manifestations vary widely. This variability is mainly related to the differences in number and location of lesions in an individual's CNS and the variation in the severity of the disease (Del Brutto, 2012*)*. Strictly speaking, these manifestations are nonspecific, and can have a wider array of neurologic and psychiatric conditions hence making it difficult to conclusively diagnose NCC without CT scanning (Del Brutto *et al.*, 2001). However, more than three quarters of symptomatic NCC patients (70% to 90%) present with seizures and epilepsy, and approximately one third present with headache (Carabin *et al*., 2011; Carpio and Romo, 2014). Depression is among the least of symptoms. Seizure and epilepsy are more frequent in patients with calcified lesions. Those with active lesions are more likely to present with increased intracranial hypertension, hydrocephalus or meningitis (Del Brutto, 2012).

The clinical course of NCC is unpredictable, which makes it almost difficult to categorize all cases into a proposed classification of the ILAE commission (Carpio and Romo, 2014). Most common manifestations of NCC such as seizures, headache, and brain insults may be caused by a number of neurologic conditions (Del Brutto *et al*., 2001). Neurocysticercosis-associated seizures may be categorized as either acute symptomatic seizures or as unprovoked symptomatic seizures (Carpio and Romo, 2014). Acute symptomatic seizures may result from transitional or degenerating cysts, and are a consequence of acute inflammatory response. In contrast, if seizures occur in the presence of viable cysticerci or calcified phase, they are unprovoked and, if recurrent, should be considered epilepsy (Carpio *et al.*, 2013). This is where the diagnosis of NCC on the basis of seizure becomes a challenge, because there are patients with multiple cysts or calcifications but do not present with a seizure (Carpio *et al.*, 2013). Seizures are most common in patients with cysts located in the parenchyma (Garcia *et al.*, 2005; O'neal *et al.*, 2012).

2.4 Diagnosis of neurocysticercosis and epilepsy

The most recommended NCC diagnosis is neuroimaging (Garcia, 2010; Del Brutto *et al*., 2001; 2017). However, neuroimaging studies may show abnormalities but are not pathognomonic (Nicoletti *et al*., 2005; Carpio *et al.*, 2016). Some serologic tests such as the Enzyme-linked Immunoelectrotransfer Blot (EITB) assay and Enzyme-Linked Immunosorbent Assay (ELISA) have been developed to support the diagnosis (Dorny *et al*., 2003; Garcia, 2010). Gabriel *et al*. (2012) proposed the inclusion of antigen ELISA serology results as a major criterion in the diagnosis of NCC in resource poor settings. But these diagnostic tests lack specificity and have decreased sensitivity in patients with a single lesion or those with only calcifications (Nicoletti *et al*., 2005; Del Brutto, 2012). This may lead to over-diagnosis or misdiagnosis in studies attempting to determine NCC prevalence in a specified population. Mostly false results, either positive or negative, occur with the most commonly used serological tests.

Del Brutto *et al*. (2001) proposed the criteria that included four categories of diagnosis – absolute, major, minor and epidemiologic – stratified on the basis of their singular diagnostic strength. Absolute allows unequivocal diagnosis of NCC, major strongly suggests the diagnosis but cannot be used alone to confirm NCC, minor criteria are frequent but nonspecific manifestations of NCC, while epidemiologic criteria is based on circumstantial evidence

favoring the diagnosis of cysticercosis. The interpretation of the four categories resulted in two degrees of diagnostic certainty – definitive and probable (Del Brutto *et al*., 2001). Definitive diagnosis is made when there is an absolute criterion or two major criteria plus one minor criterion and at least an epidemiologic criterion, as shown in table 2.1. While probable diagnosis is made when there is a presence of one major criterion plus two minor criteria or presence of one major plus one minor and one epidemiological criterion or, and presence of three minor plus one epidemiological criterion.

Del Brutto *et al*. (2017) in the latest revision of the proposed diagnostic criteria simplifies probable diagnostic category as including individuals presenting with only one type of major or minor neuroimaging criteria plus strong evidence of exposure (at least two clinical/exposure criteria) (Table 2.1). In addition, a probable NCC diagnosis can be entertained in individuals who have not undergone neuroimaging studies yet, provided they have seizures plus at least two other exposure criteria. However, if there is the presence of both a normal CT and MRI scan the diagnosis of NCC, even if other clinical/exposure criteria pointing to systemic cysticercosis are present, should be negated. In the absence of neuroimaging, history of seizures plus at least two other exposure criteria could suggest NCC; of course, lack of neuroimaging examinations prevents clinical interventions beyond symptomatic measures (Del Brutto *et al*, 2017).

Table 2.1: Revised diagnostic criteria for neurocysticercosis, (Del Brutto *et al*., 2017)

	Diagnostic criteria
1	**Absolute criteria**:
• Histological demonstration of the parasite from biopsy of a brain or spinal cord lesion • Visualization of subretinal cysticercus. • Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies.	
2	**Neuroimaging criteria**:
	(a) Major neuroimaging criteria:

• Cystic lesions without a discernible scolex • Enhancing lesions • Multilobulated cystic lesions in the subarachnoid space • Typical parenchymal brain calcifications	
	(b) Confirmative neuroimaging criteria:
• Resolution of cystic lesions after cysticidal drug therapy. • Spontaneous resolution of single small enhancing lesions. • Migration of ventricular cysts documented on sequential neuroimaging studies	
	(c) Minor neuroimaging criteria:
• Obstructive hydrocephalus (symmetric or asymmetric) or abnormal enhancement of basal meninges	
3	**Clinical/exposure criteria:** **Major clinical/exposure:**
• Detection of specific anticysticercal antibodies or cysticercal antigens by well-standardized odiagnostic tests • Cysticercosis outside the central nervous system • Evidence of a household contact with *T. solium* infection	
	Minor clinical/exposure:
• Clinical manifestations suggestive of neurocysticercosis • Individuals coming from or living in an area where cysticercosis is endemic.	

On the other hand, the diagnosis of epilepsy is difficult because there is no obvious sign a person has epilepsy, unless they are having a seizure (http://www.epilepsysociety.org.uk). A diagnosis can be made if one had two or more seizures of at least 24 hours apart (Fisher *et al*., 2005; 2014). There are some tests that can be used to diagnose epilepsy such as the EEG and brain scans. The EEG is the most common test used to diagnose epilepsy (Smith, 2005). Apart from diagnosis the EEG helps to determine seizure type and epilepsy syndrome in PWE, and thereby choice of AED and prediction of prognosis (Smith, 2005; Helmstaedter, 2013). However, the EEG has low sensitivity (ranging between 25 – 56%) for diagnosis of epilepsy because the cause of seizures or

loss of consciousness could be due to other conditions, such as fainting, migraines and panic attacks, which has similar symptoms (Smith, 2005). Further, these tests on their own cannot confirm or rule out epilepsy. The clinician has to be reasonably certain about seizure type based on the account provided by the patient or witness. In a situation where seizure history is unclear or un-witnessed, EEG can be used to distinguish seizure types (Smith, 2005; Fisher *et al*., 2014).

2.5 Management of NCC and epilepsy

The management of NCC includes the use of anti-parasitic drugs, surgery and symptomatic medication (Aneja and Dua, 2006). The anti-parasitic drugs used commonly are albendazole and praziquantel. Anti-parasitic medications destroy from 60% to 85% of the viable intracranial cysticerci (Garcia *et al*., 2002). These medications for NCC prevent complications, reduce morbidity and eliminate infestations. Albendazole therapy is the most preferred choice of the cysticidal drugs over praziquantel because it's cheap, effective in decreasing the number of cysts and long-term seizure frequency, and it is well tolerated (Baird *et al.*, 2013). However, Del Brutto et al. (2012) argue that the use of cysticidal drugs can have detrimental effects on patients with cysticercotic encephalitis because these drugs can exacerbate intracranial hypertension. This increases seizure frequencies, headaches and cause cerebral infarction in patients. It is recommended that steroids administration, such as dexamethasone or predinisolone, should precede or accompany cysticidal treatment on NCC patients (Winkler, 2013; Chaurasia, 2015). The steroids reduce complications resulting from body's immune response to dying cysts.

Strictly speaking, even as much as the cysticidal drugs may kill all the parasites in patients, it is not possible to talk of the 'cure' because as the cysts die they become calcified which in turn could aggravate long seizures (Carpio, 2013). This calls for much to be done by experts in as far as cure for NCC is concerned.

There is also surgery as one of the management methods for NCC. Open surgery involves the excision of large cysts or cysts in the ventricles (Garcia *et al.*, 2002; Burneo and Cavazos, 2014). Surgery was one of the primary therapies for NCC, however, in the recent years it has not been in frequent practice because of reports of high mortality, and it has now been reserved for those patients who become medically intractable (Garcia *et al*., 2002; Burneo and Cavazos, 2014).

In general, NCC seizures should be managed in a similar manner to other causes of secondary seizures, and AEDs are frequently used as the principal therapy for seizures (Burneo and Cavazos, 2014). The most and commonly used medications for epilepsy treatment in Zambia are; CBZ, PB, phenytoin and rarely, valproic (MoH *Standard treatment guidelines, 2017).* CBZ is used as the first line drug of choice in the management of epileptic seizures in Zambia, but because of the high price it is not always available in health facilities, instead PB which is reasonably cheap is frequently used (Birbeck *et al.*, 2000; Chomba *et al*., 2010).

2.6 Gaps in the management of epilepsy

Epilepsy/NCC if not managed well according to guidelines may cause devastating social consequences and complications on an individual (Ding *et al*., 2006; Nau *et al*., 2017). It is therefore important to look at the gaps that exist in the treatment and management of epilepsy and NCC. Kale (2002) estimated the epilepsy treatment gap in the low-income countries to be around 98%. This surely shows how the disease receives less attention in the resource limited countries. There are a number of possible causes of the wider treatment gap in the management of general epilepsy. The treatment gap is associated with a varied combination of factors other than good quality health care provision. Chin (2012) lists the leading causes of treatment gap for epilepsy as inadequate supplies and costs of anti-epileptic medications, lack of primary health workers trained to diagnose and treat epilepsy, limited access to health facilities particularly in rural areas, social stigma, misinformation, traditional beliefs and limited opportunities for specialty training in neurology. Inadequate skilled man power is one of the largest contributors to the treatment gap (Mbuba *et al*., 2012). Furthermore, the doctor to patient ratio is very high in developing countries. However, Chin (2012) argued that even when skilled man-power is available, and yet there are no diagnostic equipment and no consistent access to anti-epileptic drugs, the treatment gap cannot be narrowed.

In Gambia the gaps were found to be as a result of both health service provision by clinics and patient's beliefs on epilepsy (Coleman *et al*., 2002). Cultural attitudes, a lack of prioritization, poor health system infrastructure, lack of diagnostic tools, are just few of the contributing factors (Scott *et al*, 2001; Coleman *et al*, 2002; Meyer *et al*., 2012). Mostly clinics are not found with adequate supplies of the Ant-Epileptic Drugs (AEDs) which make some patients resort to buying them from private pharmacies (Coleman *et al*., 2002). Some patients look at epilepsy as a

spiritual condition hence resorting to traditional treatment (Coleman *et al*., 2002; Sebera *et al*., 2015).

Anti-epileptic drugs should be readily available in government health facilities because they are not that expensive compared to other medications like for HIV/AIDs and diabetes; sadly, a lot of people with epilepsy still remain untreated. Birbeck *et al*., (2012) argues that effective medications are inexpensive and epilepsy care can be provided at $25.00 per person with the condition every year. However, the main challenge remains the health care system without diagnostic equipment and inadequate health workers trained to diagnose and treat epilepsy in developing countries (Chin, 2012).

The comprehensive management of epilepsy and NCC requires the functioning health care system with adequate medical doctors. In most sub-Saharan African countries there is shortage of medical doctors. The doctor-patient ratio for Zambia was at 0.7 per 10000 people in 2007 (Chomba *et al*., 2007). Such shortage compromises the standard of care for PWE who require that after the diagnosis and start of treatment they are reviewed by a medical doctor occasionally (Chin 2012; Burneo and Cavazos, 2014).

2.7 Impacts of epilepsy

The burden of epilepsy has many aspects. In 2000 epilepsy burden accounted for approximately 0.5% of the whole burden of diseases in the world (Leonard & Ustun, 2002). In terms of Disability Adjusted Life Years (DALYs), the global burden of epilepsy is estimated at 7.8 million DALYs with 6.5 million of these occurring in *T. solium* endemic regions of the world (Torgerson and Macpherson, 2011). Epilepsy is responsible for both morbidity and mortality, mostly high in low income countries where the DALYs seem high. In 2013 epilepsy was estimated to account for about 116000 deaths globally (Wagner *et al*., 2016). In Africa alone, epilepsy ranks 19th in contributing to the total disease burden (Murray *et al*., 2012), and in West Africa epilepsy ranks 14th representing, probably, the high burden than anywhere else in the world (Vos *et al*., 2012). In Kenya the DALYs were found to be 4.3 per 1000 individuals. The reported high percentage of PWE without appropriate treatment greatly increases the burden and reflects a high disability weight (Leonard & Ustun, 2002). Seizures happen unpredictably and increase the risks of injury, hospitalizations and mortality, and adversely affect the mental health

of a patient, mostly causing anxiety, depression and cognitive impairment (Spitz *et al*, 1994; Kerr, 2012; Nau *et al*., 2017).

Cognitive and behavioral problems in epilepsy are frequent and have multiple causes, the most important being brain lesions, seizures, epileptic dysfunction, and treatment (Helmstaedter 2013). Anti-epileptic drugs have positive and negative effect on cognition (Helmstaedter 2013). In chronic epilepsy the patient's focus shifts from seizure control to the side effects of treatment and comorbidities (Wirrell, 2006; Kerr 2012; Helmstaedter 2013). Epilepsy is also associated with stigma which contributes significantly to the psychological and social burden on patients, especially in the developing countries where the prevalence of epilepsy is high (Baskind and Birbeck, 2005). The way the families and community perceive their PWE usually translate into limited social and economic opportunities, thus leading to increased physical vulnerability (Baskind and Birbeck, 2005; Atadzhanov *et al*, 2010). Most patients delay accessing treatment for fear of being stigmatised hence the condition worsening to the extent of causing so much dilapidation (Baskind and Birbeck, 2005; Nau *et al*., 2017). The burden of epilepsy is not only felt by the PWE, but also by family members and the communities were these people reside who experience loss of production years.

2.8 Prevention and control of NCC

Neurocysticercosis is a preventable disease, and the prevention can be achieved by a combination of strategies, focusing on both human and animal host, which are cost effective (Ngowi *et al*., 2008; Gabriël *et al*., 2016). The strategies may include detection and treatment of the tapeworm carriers, community health education on parasite transmission and improvement of hygiene and sanitary conditions, improving meat handling practices both at household and community levels and enforcing meat inspection policies, and limiting the animal reservoir by treatment of pigs (Roman *et al.,* 2000; Pawlowski, 2006; Gabriël *et al*., 2016). The other alternative is immunisation of the pig population with an effective vaccine available (Guo *et al*, 2004; Rassy *et al*, 2010; Assana *et al*., 2010). It is very important to note that only the tapeworm carriers and infected pigs are important in the transmission of cysticercosis. Neurocysticercosis patients are a health concern; but for them to be a public-health risk they should also carry an intestinal tapeworm (Willingham and Mugarura, 2008).

Any selected interventions would require community cooperation, political will, commitment and engagement to achieve sustainable control (Willingham and Mugarura, 2008; Gabriël *et al*., 2016). Health education should be intensified besides other control strategies. There are high chances that if people understand the problem (i.e. cysticercosis cycle) and benefits from the interventions in place, they would also find it easy to cooperate (Garcia and Del Brutto, 2000; Sarti and Rajshekhar, 2003). Control and elimination of *T. solium* would require an integrated approach involving the medics, veterinarians, environmentalists, societal and political will (Gabriël *et al*., 2016). The medics would be involved in treating of human tapeworm carriers, veterinarians will focus on pig treatment and educating farmers on hygienic meat handling procedures. The environmentalists will ensure that the environment is health and sanitation is improved through health education. Political will and societal acceptance are fundamental in the control and elimination of *T. solium* (Assana *et al*., 2013). Politicians are responsible for formulation of policies, and if given adequate information on transmission of *T. solium* they can be of great help in the control of the parasite. A one health approach involving all the above stakeholders and using combination of strategies focusing on both human and animal hosts would be appropriate in ensuring control and possibly elimination of *T. solium* (Assana *et al*., 2013; Gabriël *et al*., 2016)

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study area and population

This study was conducted in Mtandaza area in Sinda district of Eastern Province of Zambia (Figure 3.1). Mtandaza Rural Health Centre (RHC) is on the south east of Sinda district, sharing an international boundary with the Republic of Mozambique. People in this area access the health care services from Mtandaza RHC. This RHC catchment has a head count population of 16127 and 12 Neighbourhood Health Committees (NHCs). The climate of this area is tropical with two main seasons, the rainy season and the dry season. The common ethnic grouping of Mtandaza area is the Chewa speaking people. They practice subsistence agriculture raising animals and growing crops. People's homes in this area are of adobe and have few sanitary facilities, which in many instances are hardly used. The area was chosen because of reports of high numbers of PWE (clinic records) and endemicity of human and porcine cysticercosis (Sikasunge *et al*., 2008; Mwape *et al*., 2012; 2013). Previous studies in the area demonstrated prevalence of NCC (Mwape *et al*., 2015; Nau *et al*., 2017).

Figure 3.1: Map showing Mtandaza RHC where the study was conducted

The participants in this study were the known epileptic patients in the communities and those that were listed in the clinic records, presenting with epilepsy, epileptic signs such as seizures and convulsions. Healthcare providers of Sinda district also participated in the study.

3.2 Study design

A cross-sectional design was used in this study. A questionnaire (appendix 1) was administered to PWE under Mtandaza RHC, and a different questionnaire to health workers (appendix 2) responsible for the management of epilepsy and other conditions in Sinda district. The investigation was aimed at exploring the epilepsy treatment gap at 3 levels; individual epileptic patient, community and health system.

3.3 Sample size calculations and selection of participants

In this study sample size was not calculated as the study populations were very small such that everyone who fulfilled the inclusion criteria was recruited.

3.3.1 Recruitment of people with epilepsy

The study subjects were all PWE in the catchment and in clinic records of Mtandaza RHC. People with epilepsy were purposively recruited in the study. The purposive sample was investigated for NCC using the probable diagnostic category proposed in the revised diagnostic criteria by Del Brutto *et al*., (2017). The simplified probable diagnostic category can be utilized in individuals who have seizures plus at least two other exposure criteria such as; leaving in cysticercosis endemic areas, antigen or antibody positive for cysticercosis (Gabriel *et al*., 2012; Del Brutto *et al*., 2017).

i. Inclusion criteria

The participants included in this study were those that were 10 years of age or above; people with convulsive epilepsy according to the clinic records and those diagnosed in an earlier study (Mwape *et al*., 2015); resident within the study area, willing to participate in the study and sign consent/assent form.

ii. Exclusion criteria

Individuals that were less than 10 years of age; not from the study area; pregnant women and those that were seriously ill were excluded from the study.

3.3.2 Recruitment of health care workers

Healthcare providers responsible for the management of epilepsy in Sinda district were separately recruited for the study. The targeted healthcare providers were nurses, clinicians and medical doctors. Fourteen health centres and 9 health posts in Sinda district were included. One healthcare worker from each health post and at least two healthcare providers from each health centre, depending on the number of professional healthcare providers available at the facility, were included for the questionnaire interview. The experience of a practitioner was not considered when choosing who the questionnaire should be administered to.

3.4 Sample collection and processing

3.4.1 Community sampling

Using a record of residences of people with epilepsy held by Mtandaza RHC and prior-arrangements with the patients in each village, a team comprising the researcher, assistant researcher and two trained nurses visited each household. At each visit, the team encouraged PWE whose names did not appear in the RHC records and had never started treatment to also participate in the study.

3.4.2 Blood sampling

For each patient, about 5mls of blood sample was collected by a trained nurse into plain blood collecting tubes. To obtain the maximum amount of serum, the blood tubes were allowed to stand at 4°C overnight and then centrifuged at 3000g for 15 minutes. The supernatant (serum) was extracted and aliquoted into 1.8 ml and were stored at -20°C until use.

3.4.3 Stool sampling

Participants were provided with a stool sample container placed in a black plastic bag. Each participant was requested to fill the bottle with at least half full of the sample. The submitted stool samples were then divided into two aliquots; one was placed in 10% formalin for copro-antigen ELISA, and the other in 70% ethanol for polymerase chain reaction (PCR). The two aliquots were stored at room temperature until use.

3.5.0 Laboratory analysis of samples

All collected samples were transported in cooler boxes to the Cysticercosis Regional Reference Laboratory in Lusaka where serum samples were stored at -20°C until analysis and stool samples at room temperature.

3.5.1 Enzyme-linked-immunosorbent assay (ELISA)

Serum samples were examined for the presence of circulating cysticercus antigens using a double monoclonal antigen-based sandwich Ag-ELISA as described by Dorny *et al.* (2000) with minor modifications. This technique involves trapping the antigen (Ag) between two monoclonal antibodies (MoAb).

The sera were pre-treated using freshly prepared 5% trichloroacetic acid (TCA) (Sigma, Chemical Co.) w/v dissolved in distilled water. The pre-treatment was done to remove non-specific immune complexes to increase the sensitivity and specificity of the assay. After 5% TCA solution was made by dissolving 1 gram of TCA in 20 ml of distilled water, equal volumes of serum and 5% TCA were mixed. For the negative control sera, 75 µl of serum was used while 150 µl of serum was used for the pre-treatment of positive control and the test sera. These mixtures of sera and TCA solution were incubated for 20 minutes at ambient room temperature. After incubation the mixtures were centrifuged at 12,000 rpm for 9 minutes, 150 µl of the supernatant was removed and aliquoted into microtitre tubes. The pH of the collected supernatant was raised by adding an equal volume of 75 µl sodium carbonate/bicarbonate buffer (0.610M) at pH 10.0 (neutralization buffer) to the supernatant of the negative control sera and 150 µl of neutralization buffer to the supernatant of the positive control and the test sera. Two hundred µl of this mixture at final sera dilution of 1:4 was used in the Ag-ELISA protocol.

The assay involved coating 96 well ELISA plates (Nunc®Maxisorp, Pennsylvania, U.S.A). Monoclonal antibody B158C11A10 was used as 1st MoAb and was followed by biotinylated MoAb B60H8A4 as the detector antibody (2nd MoAb). The plates were coated with 100 µl of MoAb B158C11A10 diluted at 5µg/ml in carbonate buffer (0.06M, pH 9.6) (except for the two wells used as substrate control (SC) where only 100 µl of coating buffer were added), and incubated at 37°C on a shaker for 30 minutes. After coating, the plates were washed once with PBS-T20 and dried by tapping them on the blotting paper. Blocking to avoid non-specific

reactive sites was done by adding 150 µl of PBS-T20/1% NBCS (Blocking buffer) and then the plates were incubated on a shaker for 15 minutes at 37°C. Thereafter, the plates were emptied and dried. Without washing the plates, 100 µl of pre-treated sera, including the weak and strong positive and negative controls, at a dilution of ¼ was added to each well (except for the SC and conjugate control (CC) wells where 100 µl of Blocking buffer was added) and incubated at 37°C on a shaker for 15 minutes. After washing the plates five times with PBS-T20, they were dried followed by the addition of 100 µl of biotinylated MoAb B60H8A4 diluted at 1.2µg/ml in blocking buffer to each well (except for the SC wells where 100 µl of blocking buffer were added) and the plates incubated at 37°C on a shaker for 15 minutes. The plates were then washed five times with PBS-T20 and then dried. One hundred µl of streptavidin-horseradish peroxidase diluted at 1/10,000 in blocking buffer was added to each well (except for SC where blocking buffer was added) to act as conjugate after which the plates were incubated on a shaker at 37°C for 15 minutes. Then the plates were washed five times with PBS-T20 and then dried. After that, two tablets of the chromogen/substrate, orthophenylenediamine (OPD) were added to 12 ml of distilled water, to which 5 µl of H_2O_2 was added. To each of the wells was then added 100 µl of this solution and incubated at room temperature in the dark without shaking for 15 minutes. To stop the reaction, 50 µl of 4N H_2SO_4 was added to each well. The plates were read using an automated spectrophotometer at 492 nm with a reference of 655 nm.

The optical density of each serum sample was compared with the mean of 8 reference negative sera samples at a probability level of $p = 0.001$ to determine the results in the test (Dorny *et al.*, 2004). All positive and serum samples were done in duplicate. The two wells containing the same sample were checked that they gave roughly the same optical density. The average optical density was calculated for every sample. The cut off was calculated based on the optical densities of the negative samples using a variation of the student T-test (Sokal and Rohlf, 1981). The cut off that was determined was used to calculate a ratio (Ratio = average optical densities/cut off). When the ratio was greater than one, the sample was considered positive with 99.9% certainty.

3.5.2 Enzyme-Linked Immunoelectrotransfer Blot (EITB)

The EITB of combining two recombinant antigens on one strip – the rT24H protein that is specific for the detection of *T. solium* cysticercosis antibodies and the rES33 protein, which is

specific for the detection of *T. solium* taeniosis antibodies was performed on all serum samples. To prepare PBS/0.3% Tween 20 – 1 packet of PBS was added to 1 liter of deionized water and stirred until the crystals dissolved. While stirring with a magnetic stir bar 3 ml of tween 20 was added. To estimate the total needed PBS-0.3%Tw-5% nonfat milk, the number of samples was multiplied by 1ml. The total needed PBS-0.3%Tw-5% non-fat milk was again multiplied by 0.05 to get the grams of non-fat dry milk powder to add to PBS Tween. After adding non-fat dry milk powder stirring was done for 10 to 15 minutes. To develop the samples, 500 µl of PBS /Tween/Milk was dispensed to each trough in the Accutran incubation tray. The appropriate 5 µl of serum was added to each trough and mixed well. The antigen strips were placed in the incubation tray then covered gently and rocked at 4°C overnight. The next morning GAHG-POD-AC conjugate (1:8000 in PBS/Tw) needed was calculated, and set aside appropriate volume of PBS/Tween no milk (1ml per sample). This was kept at room temperature.

The 1 liter of PBS/Tween (no milk) was warmed in a microwave for 2 minutes, and allowed to swirl to dissipate heat. The warmed PBS tween was used to wash the strips in the Accutran trays. The strips were washed 4 times with incubation of 5 minutes in between washes. 500 µl of GAHG-POD-AC, optimally diluted (1:8000) in PBS/tween was added to each trough and incubated for 1 hour at room temperature with continuous gentle agitation on a rocker. Then Diaminobenzidine dehydrochloride (DAB) substrate was prepared - 25miligrams of DAB for 50mls of PBS only with 10ul of 30% hydrogen peroxide. The strips were washed 5 times, 3 times with PBS tween and 2 times with PBS only respectively, with 5 minutes incubation in between each wash. The PBS was removed and DAB substrate 500 µl was added to each trough and allowed to develop for 10 minutes at room temperature. To stop the reaction, the strips were washed 10 times with deionized water. The strips were then air dried on a sheet of transparency film facing up. The visible observation of the rES33 or rT24 protein band was considered a positive result for taeniosis or cysticercosis, respectively.

3.5.3 Coproantigen Enzyme-Linked Immunosorbent Assay

Stool samples were tested for *T. solium* circulating antigens using the copro-antigen detection ELISA as describedby Allan *et al*., (1990), and slightly modified by Mwape *et al.* (2012).

Briefly, equal volumes of phosphate buffered saline (PBS) and faecal samples were prepared and mixed in 15 ml falcon tubes. The mixed samples were left for one hour to soak with intermittent shaking, and then centrifuged at 2000g for 30 minutes to collect the supernatant for use in the assay. The ELISA procedure involved the coating of the polystyrene plates (Nunc®Maxisorp, Pennsylvania, U.S.A) with the capturing hyper immune rabbit anti-*Taenia* IgG polyclonal antibody diluted at 2.5 µg/ml in carbonate-bicarbonate buffer (0.06 M, pH 9.6). Following coating, the plates were incubated at 37 °C for 1 hour. The plates were washed once with PBS in 0.05% Tween 20 (PBS-T20) and all wells blocked by adding blocking buffer (PBS-T20+2% New Born Calf Serum) and incubated at 37 °C for 1 hour. Without washing the plates, 100 µl of stool supernatant was added to each of the coated plate except for the substrate control (SC) and the conjugate control (CC) where blocking buffer was added to keep them moist. After the incubation at 37°C for 1 hour on a shaker, the plates were washed 5 times with PBS-T20 and dried by tapping them on the blotting paper. One hundred microliter of biotinylated hyper immune rabbit IgG polyclonal antibody diluted at 2.5µg/ml in blocking buffer was added to all wells, as an antibody detector, except for the SC wells where only the blocking buffer was added. The plate was incubated for 1hour at 37°C and followed by 5 times washing with PBS-T20. One hundred microlitre of Streptavidin-horseradish peroxidase diluted at 1/10000 in blocking buffer was added to all wells as a conjugate except for the SC, and incubated at 37°C for 1 hour on a shaker. After washing 5 times, 100 µl orthophenylenediamine (OPD) prepared by dissolving 1 tablet into 6ml of distilled water and adding 2.5 µl of hydrogen peroxide was added to all the wells. The plates were incubated in the dark at room temperature. After 15 minutes of incubation 50 µl sulphuric acid (4N) was added to all the wells to stop the reaction.

To read the results on the plate, an automated spectrophotometer at 492 nm with a reference of 655 nm was used. To determine the test results, the optical density (OD) of each stool sample was compared with the mean of a series of eight *Taenia* negative stool samples plus 3 standard deviations (cutoff).

3.6 Questionnaire surveys

3.6.1 People with epilepsy

After sample collection, a researcher-administered questionnaire (appendix 1) was given to each patient. It was used to get data on the education level, types of AEDs and where they get them from, the frequency of drug refills, side effects that might arise from AEDs, and distance to where they get AEDs. The questionnaire also assessed reasons for not taking AEDs regularly or as prescribed and also explore if health workers explained to PWE the dosage and frequency of treatment for the particular AED prescribed, challenges PWE face when they go for drug collection, and possible measures to address the challenges mentioned. Being found with drugs during the questionnaire interview was used as a proxy measure of adherence to AEDs treatment.

3.6.2 Health care workers

At each health facility, a researcher-administered questionnaire (appendix 2) was used to assess health workers in terms of their knowledge on NCC, its relationship with epilepsy, and their attitude towards epilepsy and epileptic patients. Data was also collected on professional qualifications, years of experience, epilepsy diagnosis, prevalence of epilepsy, and number of PWE seen per week, challenges faced when attending to PWE, knowledge on NCC management and precautions taken when managing NCC. Experience of practitioner was not considered when administering the questionnaire. Preferably, the in-charge and any other curative staff were interviewed. Paramedics were not included for the questionnaire interview.

3.6.3 Observation of health facilities

The healthcare service was assessed based on accessibility of the health facilities by the population, the degree to which healthcare providers adhered to the epilepsy management guidelines (https://www.moh.gov.zm/docs/final), the availability of nurses, clinicians, environmental health officers and CHWs. Checks of pharmacy/treatment rooms on availability of AEDs, and diagnostics were done after the questionnaire survey. In addition, the 2016/2017 training curriculum for clinical officers at Chainama College of Health Sciences of Zambia (standard) was reviewed to see what it covered concerning epilepsy and NCC.

3.7 Statistical analysis

Statistical analyses were done using the R software 1.2.[32] Non-adherence was analysed in PWE who reported to be on AEDs. Pearson's $\chi 2$ was used to measure associations between PWE, demographic and healthcare-related variables and one binary outcome: currently on AED drugs or not. Univariate associations with each significant outcome were investigated using a multivariable logistic regression model. Predictor variables with a p-value >0.1 were excluded at each step; those with a p-value of ≤ 0.05 were retained in the final models. Missing values were considered to be missing completely at random and we did not impute for missing data.

3.8 Ethical considerations

The ethical clearance for the study was sought from ERES Converge IRB (Ref: 22-mar-2018); further approval was obtained from the Ministry of Health of Zambia local District health authority of Sinda district where the study was conducted. Meetings were held with the community leaders (village heads) and their subjects where the purpose of the study was explained and their permission requested to conduct the study in their area. Informed consent was also sought from the individual subjects to participate in the study. Subjects were not forced to participate. Participation was requested of individuals aged 18 and older after written informed consent. For individuals below the age of 18, permission was sought from their parents or guardians by way of written informed consent. After informed consent from their parents assent was gotten. To ensure privacy, codes were used for participants and on the samples.

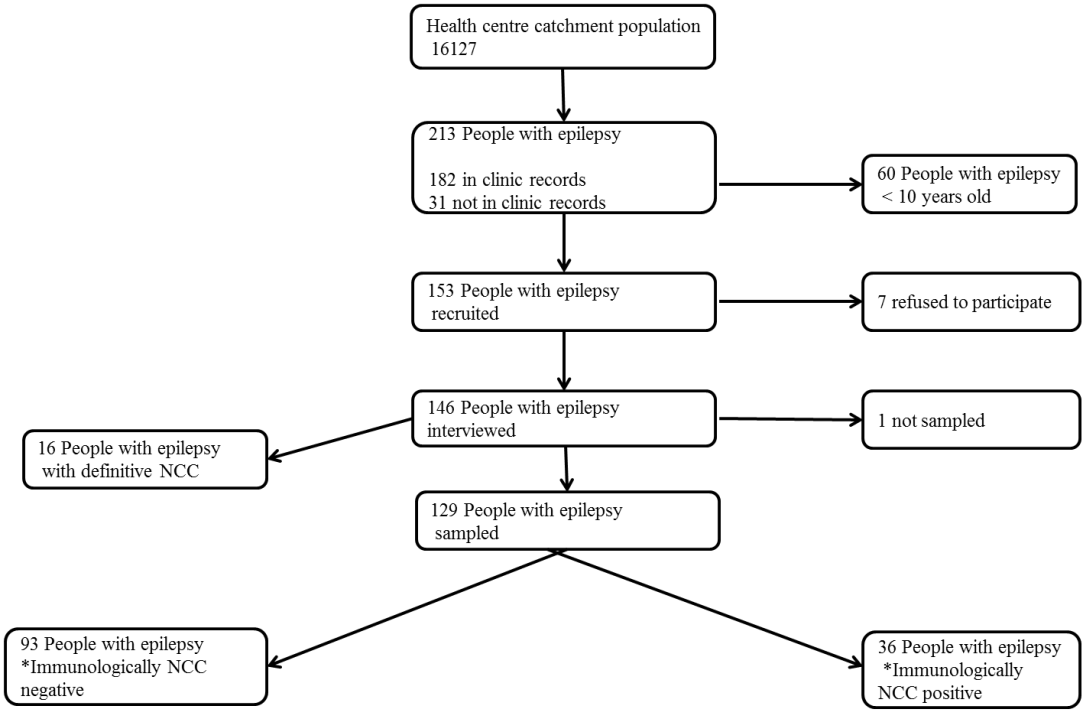
CHAPTER FOUR

4.0 RESULTS

4.1 Recruitment and population demographics

4.1.1 People with epilepsy

Figure 4.1 shows the recruitment flow for PWE enrolled into the study. A total of 213 PWE were identified in the study of which 182 via RHC records and 31 via the community (the latter had never attended a clinic for epilepsy treatment). Forty-four PWE from RHC records and 16 from the community were younger than ten years old and were excluded. One hundred forty-six participants were recruited for the study. Of these, 45 were included in the previous study, of which 16 PWE were diagnosed with definite NCC (Mwape *et al*.2015). Among the participants, 46% were female; and over 30% were younger than 20 years.



*Antigen/Antibody test results of; rT24, Ag ELISA, rES33 or copro-Ag

Figure 4.1: Schematic presentation of the participant recruitment

The population was 46% female; over 30% were younger than 20 years. This is representative of the demographic characteristics of the PWE in Mtandaza area. The minimum age was 10 and maximum age was 86 (Table 4.1).

Table 4.1: Age descriptive for PWE

AGE				
1st Qu.	**Median**	**Mean**	**3rd Qu.**	**NA's**
16.00	31.00	32.52	44.00	1

4.1.2 Health care workers

A total of 43 healthcare providers from 23 health facilities of Sinda district were interviewed. Of the 43, 58% were males; 14 were enrolled nurses, 11 registered nurses, 11 clinical officers, 4 nurse midwives, 2 medical doctors and1 mental health nurse.

4.2 Laboratory results

Samples were collected from 129 PWE who had never been diagnosed with NCC. Immunological tests were done on the samples for detection of cysticercal Ag or anticysticercal Abs and/or detection of *T. solium* tapeworm Ag or Abs (Table 4.2).

Table 4.2: Immunological positive test results

S/N	**Immunological tests**	**Number positive (N=129)**	**%**
	Ag ELISA only	16	12.4
	rT24H only	0	0
	Ag ELISA and rT24H	5	3.9
	Total cysticercosis	**21**	**16.3**
	Copro-Ag ELISA only	9	7.0
	rES33 only	4	3.1
	Copro-Ag and rES33	2	1.6
	Total taeniosis*	**15**	**11.6**

***** of which 3 are also cysticercosis Ag and/or Ab positive, but only counted as taeniosis

4.3 Diagnosis of NCC

Sixteen (16) were definitive NCC patients diagnosed in a previous study (Table 4.3). According to Del Brutto *et al*. (2017) all the 129 PWE could be categorized as probable NCC based on the minor exposure criteria such as clinical manifestations suggestive of NCC and coming from an endemic area. Further, out of the 129 PWE (Figure 4.2 above), 36 PWE were diagnosed to be probable NCC based on major clinical exposure criteria of detecting specific anticysticercal antibodies or cysticercal antigens by using immunological tests (Del Brutto *et al*., 2017).

Table 4.3: Distribution of NCC based on population demographics

	Number recruited	**(N) Probable NCC**	**(N) Definitive NCC (Mwape *et al*., 2015)**
Gender			
Male	80	25	9
Female	66	11	7
Age category			
10 – 19 years	46	12	0
20 – 49 years	76	18	9
50 years and over	24	6	7

4.4 Questionnaires results

4.4.1 Questionnaire for people with epilepsy

One hundred forty-six eligible PWE (95%) were interviewed. Of these, 45 (30.9%) were diagnosed with epilepsy by a neurologist in a previous study[8], 14 (9.6%) were diagnosed by a medical doctor at the hospital, 72 PWE (49.3%) were 'diagnosed' in their communities by the elderly people who knew about the signs and symptoms of epilepsy, and later diagnosed by

either a clinical officer or a nurse at their local health facility when they went to start treatment, and the remaining 15 (10.3%) had never been to the clinic for either diagnosis or treatment of epilepsy. For these 15 patients, the epilepsy diagnosis was solely based on 'diagnoses' by community members after noticing recurrent seizures. Fifty-one (34.9%) PWE had their first seizure at or before the age of 5 years. Seventy-nine (54.1%) PWE reported having had their first seizure after the age of 10 years, with the majority of them reporting the first seizure to have occurred between the age of 11 and 20 years (Table 4.4). Eighty six (58.9%) PWE had their last seizure within the month of the interviews; a proportion (26, 17.8%) reported to have had their last seizure more than a year before the interview.

Table 4.4: Reported age of patients at epilepsy onset.

Age	**(N=146)**	**(%)**
	n	
≤5 Years	51	34.9
6 - 10 Years	16	11.0
11 - 20 years	34	23.3
21 - 30 years	19	13.0
31 - 40 years	10	6.8
> 40 years	16	11.0

4.4.2 Health care workers' questionnaire

A total of 13 (30.2%) healthcare providers interviewed had been in service for less than a year, and 5 (11.6%) had been working for over 10 years. The majority had between 1 and 4 years of professional experience (Table 4.5).

Table 4.5: Healthcare provider's professional experience

Experience	(N=43) n	%
< 1 year	13	30.2
1 - 4 years	21	48.8
5 - 9 years	4	9.3
≥ 10 years	5	11.6

The healthcare providers expressed some understanding of what epilepsy was and had good knowledge of the guidelines, however, 24 (55.8%) of them did not know the relationship between epilepsy and NCC. The healthcare providers estimated the prevalence of active epilepsy in their health facilities to be on average between 6 and 11 cases per 1000 population.

3.4.3 Epilepsy treatment gaps

Of all the 146 PWE interviewed, the total number on AEDs was 64 (43.8 %), and only 26 (17.8%) were on regular epilepsy treatment for the previous 1 year (Figure 4.2). Eighty-two percent of PWE interviewed were either on irregular epilepsy treatment or on traditional medicine. In the study area, traditional medicine incorporates plant, animal, and mineral-based medicines, and spiritual therapies applied singularly or in combination to treat illnesses.

Sixty-seven (45.9%) PWE sought AEDs treatment only when in an epileptic attack and 15 (10.3%) were exclusively on traditional medicine and had never been on AEDs treatment. About 11 (7.5 %) were on both AEDs and traditional medicine. Twelve (8.2%) respondents reported taking more than one AED interchangeably. The most frequently used AEDs were PB (87,

59.6%) and CBZ (19, 13.0%). There was no special management of PWE with NCC in the study area apart from the use of AEDs, just the same with epilepsy due to other causes.

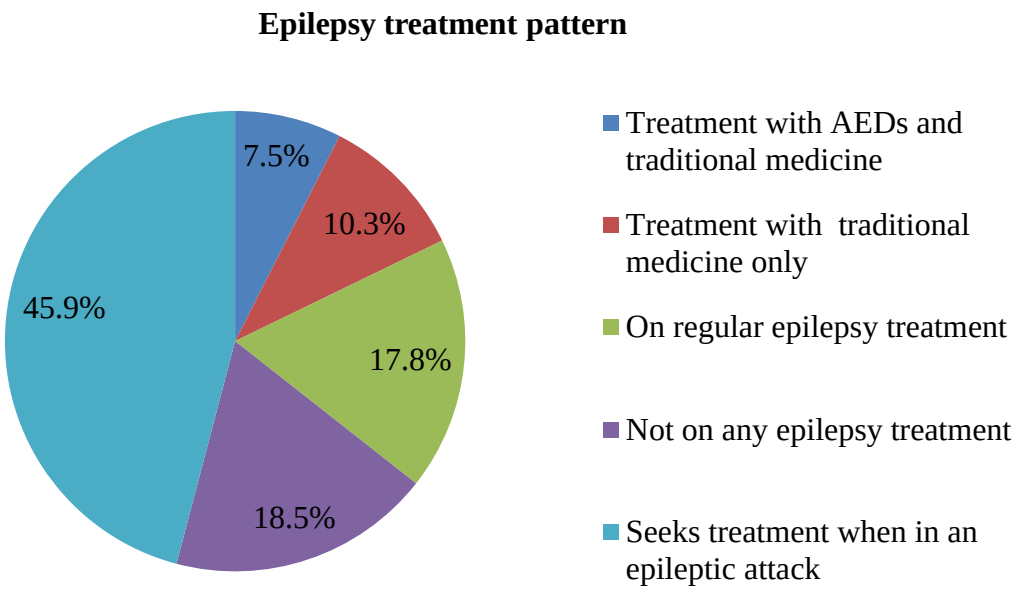


Figure 4.2: Treatment pattern of 146 people with epilepsy in Sinda district in 2018.

4.4.4 Factors contributing to management gaps

3.4.4 Factors contributing to treatment gaps

The factors that contributed to a high treatment gap were grouped into three categories; individual, community and healthcare service-related. Some of these factors were crosscutting as shown in Figure 3.

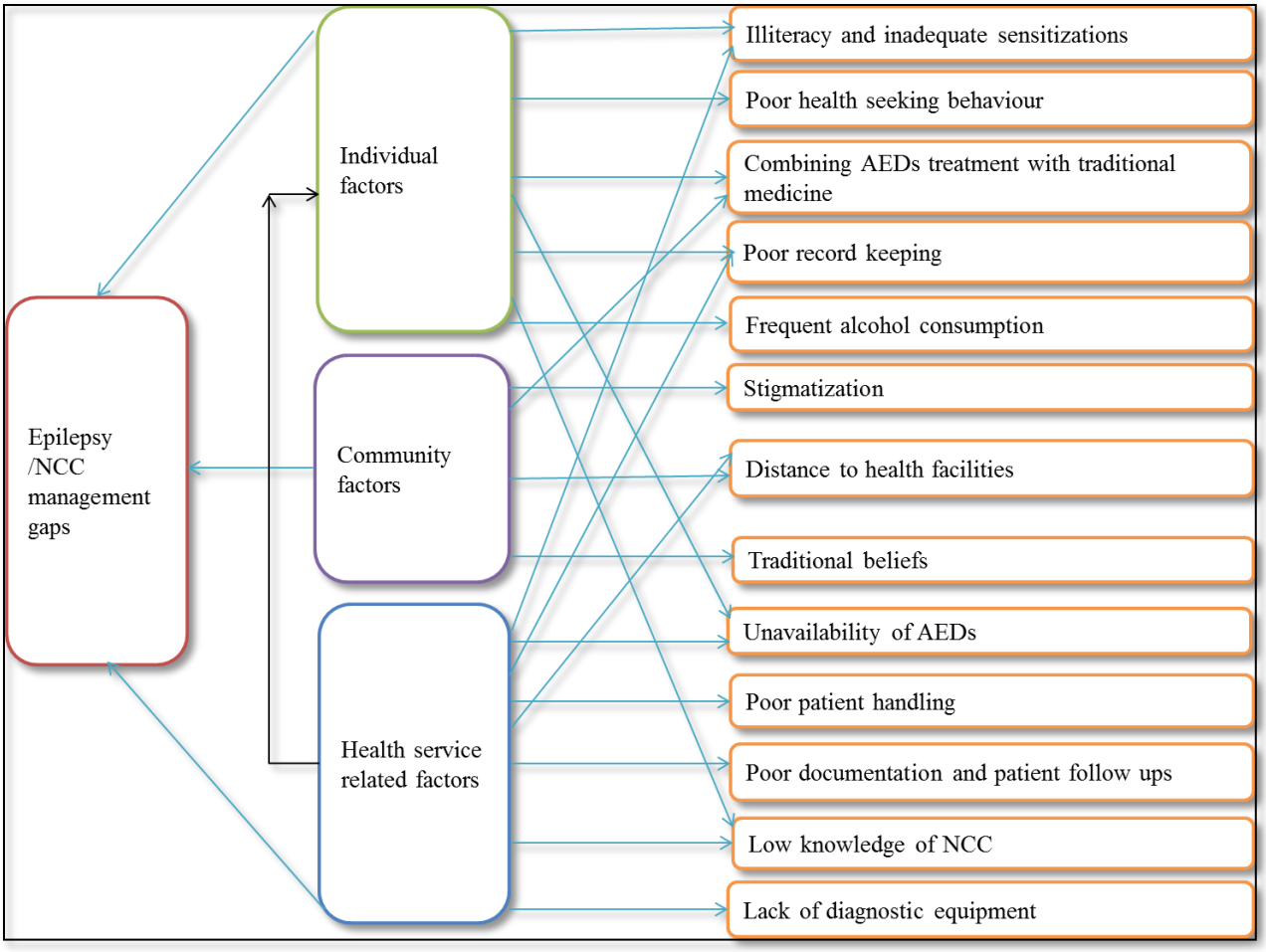


Figure 4.3: Schematic presentation of factors leading to high treatment gaps in the study area.

***Individual factors*:**

These factors included: illiteracy, poor health-seeking behaviour, poor keeping of treatment records (such as appointment and treatment cards), combining AEDs with traditional medicine and excessive alcohol consumption. Half (74, 50.7%) of PWE had never been to school (Figure 4.4), 64 (43.8%) attended at least some early grades of primary education, and 8 (5.5%) reached some high school grades, with only one of all PWE completing secondary education. PWE reported dropping out of school due to seizures, lack of finances, participating in cattle herding, and cultural practices such as traditional dances (*gule wamukulu*).

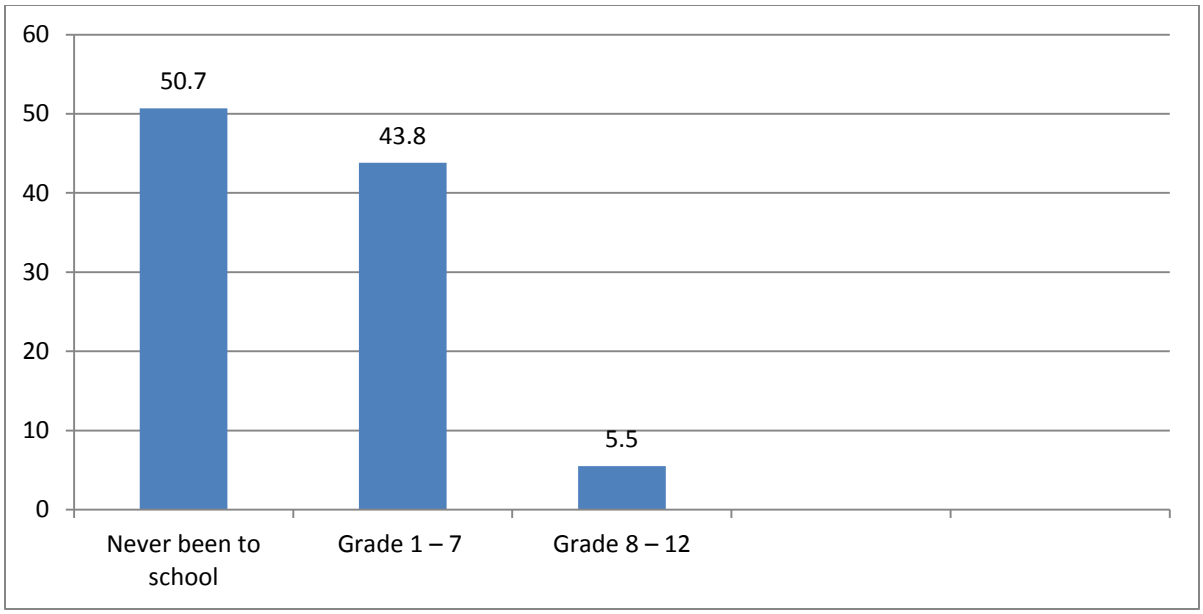


Figure 4.4: Education status for PWE

Non-availability of AEDs was associated with failure to be on current treatment (P-value =0.031; 95% CI, 1.25 – 109). About 41 (N=64, 64.1%) of PWE on medication reported having lived for more than one month without AEDs (Table 4.6 and 4.7). This was attributed to non-availability of drugs at the local clinic by 22 (34.4%) PWE, 21(32.8%) stopped experiencing seizures and had a belief that they were cured, while 4 (6.2%) had no one to help them with drug collection when they got sick, and that AEDs medication was considered not being effective and thus opted for traditional medicine 3(4.7%). Three (4.7%) reported that they had lost treatment records which were needed to access health services. Furthermore, four parents reported that they stopped collecting AEDs for their children because the same children refused to take medication. Five (7.8%) did not give any specific reason. Some PWE could not remember the last time they took the medication due to long periods without a supply of AEDs (Table 6), $p < 0.05$, (OR = 11.50, 95% CI, 2.71 - 48.78).

Table 4.6: Univariable associations with failure to be on AEDs at the moment of the study for PWE who reported to take treatment

	AEDs treatment				Odds ratio (95% CI)	p-value
	Yes (N = 64)		No (N = 65)			
	n	%	n	%		
Age category (years)						
10 to 19	18	28	21	32	0.86 (0.46 - 1.61)	0.631
20 to 29	7	11	16	25	0.51 (0.17 - 1.51)	0.226
30 to 39	16	25	12	19	1.56 (0.59 - 4.14)	0.376
40 to 49	11	17	5	7	2.57 (0.75 - 8.78)	0.133
50+	13	19	11	17	1.27 (0.45 - 3.57)	0.647
Gender						
Female	25	39	36	55	0.69 (0.42 - 1.16)	0.1613
Male	39	61	29	45	1.94 (0.96 - 3.90)	0.0646.
Literate						
Yes	32	50	33	51	0.97 (0.49 - 1.93)	0.93
No	32	50	32	49	1.00 (0.61 - 1.63)	1.00
Last seizure episode						
In the last 7 days	27	42	19	29	1.75 (0.68 - 4.47)	0.2428
Within this month	20	31	14	21	1.76 (0.65 - 4.78)	0.2692
In the last 6 months	13	20	16	24	0.81 (0.39 - 1.69)	0.5782
Over one year ago	4	6	16	25	0.31 (0.08 - 1.15)	0.0796.
Medication						
CBZ.	6	9	13	20	0.46 (0.17 - 1.21)	0.1172
CBZ, PB.	5	7	1	11	10.8 (1.0 - 114.2)	0.0474 *
PB.	49	76	38	59	2.79 (0.97 - 8.03)	0.0565.
PB., Tradi. Med.	0	0	1	2	NA	0.9875
CBZ., Trad. Med	3	5	3	5	2.1 (0.33 - 14.05)	0.4177
Trad. Med.	1	14	1	2	0.24 (0.02 - 2.36)	0.2211
Drugs last intake						
I cannot remember	1	2	37	57	0.027 (0.004 - 0.196)	0.0004 *
> one month ago	11	17	24	37	16.96 (2.05 - 139.96)	0.0086 *
Within this month	38	59	4	6	351 (37.5 - 3293)	2.82e-07 *
Within this week	14	21	0	0	NA	0.9899
Side effects						
Yes	21	32	19	29	1.18 (0.56 - 2.49)	0.660
No	43	67	46	67	0.93 (0.62 - 1.42)	0.751
Frequent alcohol consumption						
Yes	14	22	14	22	1.18 (0.56 - 2.49)	0.751
No	50	78	51	78	0.93 (0.62 - 1.42)	0.660
Distance to the clinic						
Within 5 km	32	50	28	43	1.49 (0.73 - 3.07)	0.274
More than 5 km	32	50	37	57	0.76 (0.46 - 1.27)	0.303
Over one month period without AEDs						
Yes	41	64	63	97	11.50 (2.71 - 48.78)	0.000171 *
No	23	36	2	3	0.057 (0.013 - 0.25)	0.000923 *
Drugs always present at clinic						
Yes	10	16	18	28	0.48 (0.20 - 1.15)	0.100
No	54	84	47	72	1.15 (0.78 - 1.69)	0.486

Feeling with caretaker						
Good	55	86	51	79	1.79 (0.41 - 7.91)	0.438
Bad	3	5	5	8	0.60 (0.14 - 2.51)	0.484
Neglected	3	5	3	5	1.67 (0.19 - 14.27)	0.641
I do not know	3	5	6	9	0.83 (0.11 - 6.11)	0.858

PB. Phenobarbitone**; CBZ.** Carbamazepine**; Trad. Med.** Traditional medicine; **AED**. Anti-epileptic drug; **NA**. Not applicable

Table 4.7: Multivariable model of factors associated with failure to be on medical treatment for epilepsy.

Association with failure to adhere to treatment	OR (95% CI)	p-value
Drugs last taken more than one month ago	11.7 (1.25 – 109)	0.03119 *
Drugs last taken within this month	329 (31.46 - 3455)	1.32e-06 *
Non-availability of AEDs at the clinic	0.047(0.007 - 0.317)	0.00169 *

Community factors

Community factors consisted of stigmatization, long distances to health facilities, traditional beliefs, seeking traditional medicines, and combining AEDs with traditional medicine. About 9 (6.2%) PWE reported stigma as the reasons for delaying to start epilepsy treatment, and four parents (2.7%) reported collecting AEDs for their teenage children who feared being stigmatized when they went to the clinic. Furthermore, seventy-nine PWE (54.1%) that had used AEDs stayed more than 5km from the health centre where they collected drugs. They walked to go for drug collection; with 47 (33.2%) having access to bicycles and one (0.8%) who was always taken to the health centre on an ox-cart. Fifteen (10.3%) respondents said epilepsy was a disease that came due to witchcraft or a spiritual sickness and came as punishment for indiscipline, and they believed that only traditional medicine could cure it.

Health service-related factors

Service-related factors included: unavailability of AEDs, poor documentation and patient follow-ups, inadequate or no diagnostic equipment, and catchment areas too large to service adequately. Non-availability of AEDs was a primary contributing factor to a high treatment gap. AEDs were reported not to always be available by 54 PWE (N=64, 84.4%). About 38 (88.4%) healthcare providers reported erratic availability of AEDs, stating that 3 to 4 times in a year a health facility would go for more than a month without AEDs in stock.

Healthcare provider's knowledge of NCC was also a factor of concern. Of the healthcare providers interviewed 24 (55.8%) did not know the relationship between epilepsy and NCC and 18 (41.8%) said they had never heard of NCC. Healthcare providers reported challenges with the diagnosis for both epilepsy and NCC due to a lack of equipment and logistics.

There was no facility in the district that could diagnose the cause of epilepsy. This was a challenge in terms of management of the condition. Further, 29 (67.4%) healthcare providers reported facing challenges with PWE, such as patients not coming with treatment records to show which AED they were taking and missing scheduled appointments. Additionally, PWE sent their relatives for drug collection which made it difficult for healthcare providers to do assessments on the effectiveness of treatment, while other PWE easily forgot instructions on taking AEDs.

Nine percent of healthcare providers reported that some PWE had developed a preference for a specific AED and did not accept to be given alternative AEDs. If their AED of choice was out of stock, they would rather stay without any drug until their drug of choice was available. The

reasons given to healthcare providers by PWE for such preferences were that some AEDs cause dizziness while others said a particular AED does not suppress seizures in them.

When PWE were asked how they perceived the care given at the clinic when they went for drug refills, 119 (81.5%) said they were given care just like any other patient who visited the health facility, 9 (6.2%) of PWE perceived being given poor care by healthcare providers, 7 (4.8%) felt neglected and 10 (6.8%) did not give an answer. Thirty-nine PWE (26.7%) reported that they faced other challenges when they went to the clinic for drug supplementation. The challenges included long waiting times as they had to queue up with other patients who came with other ailments. This at times resulted in having a seizure whilst waiting. Some reported being turned away unattended to when they had missed previous appointments. Other challenges were drug stock-outs which resulted in added costs when they could be referred to a far but alternative facility for drug collection; parents or guardians were not allowed to collect drugs for them, and also frequent trips to the clinic due to inadequate drugs supplied to them.

4.5 Observation of health facilities

Twenty-three health facilities in Sinda district were observed. Every health facility had at least one nurse. Nine health centres had a clinical officer and the hospital had 2 medical doctors. Nineteen of the health facilities had the Zambian Ministry of Health standard treatment guidelines available. The guidelines described management of epilepsy but nothing on NCC. The same was for the Chainama college training curriculum for clinical officers which did not describe NCC.

At the time of the study, both CBZ and PB were out of stock in 17 out of the 23 health centres. The AEDs stock out was reported to be a result of non-availability at the district pharmacy and was noticed to have lasted for more than a month in many instances. It was noted that AEDs

were not part of the Zambian Ministry of Health essential drugs kit package for health centres and that they had to be ordered separately.

CHAPTER FIVE

5.0 DISCUSSION

This study assessed factors affecting the management of PWE in Sinda district of the Eastern province of Zambia. The high treatment gap of more than 80% may be an underestimation as the study only included PWE of 10 years of age and older. The findings are comparable to those reported in Togo, Kenya, and Gambia and elsewhere in sub-Saharan Africa, where treatment gaps of more than 80% were recorded (Kale 2002; Guinhouya *et al*., 2010). This is the first study in Zambia to look at gaps in the management of PWE in an area highly endemic for *T. solium*, a major cause of epilepsy (Mwape *et al*., 2015). The study also looked at factors contributing to this treatment gap. The findings of this study justify the study by Nau et al (2017) who reported cognitive impairment and reduced quality of life among PWE in Eastern Province of Zambia.

Over 53% of PWE epilepsy interviewed had late on-set seizures which started after the age 10 years and such may not be associated with febrile seizures. Despite establishing the problems of *T. solium* and its effects (diagnosis, treatment and awareness of taeniosis, epilepsy and NCC), prevalence rates have remained high. Identification of the gaps will help manage the low uptake of services and effects of the diseases. It will also harness sector-wide interventions i.e. personal, community and health facilities. NCC contributes to the high prevalence of epilepsy (Ndimubanzi *et al*., 2010; Mwape *et al*., 2015; Assane *et al*., 2017). The prevalence of epilepsy in Sinda district of Eastern province was found to be 6 -14 per 1000 population; similar to what was reported in Tanzania and in other Sub-Saharan countries by Winkler *et al*. (2009), and Preux and Druet – Cabanac (2005),respectively.

All the PWE were tested for cysticercosis using serological tests. The serological examinations indicated that 28% of PWE had probable NCC, similar to that reported in sub-Saharan Africa (Ndimubanzi *et al*., 2010). However, these results may not represent the true prevalence of NCC in PWE as only serological tests were used for NCC diagnosis. Serological tests lack specificity

and have reduced sensitivity in individuals with a single cyst or if a cyst is located in the CNS or just have calcifications (Nicoletti *et al*., 2005; Del Brutto, 2012; Rajshekhar, 2017). A definitive diagnosis requires the use of MRI and/or CT scanner which are expensive. Gabriel *et al*. (2012) proposed antigen ELISA to be added as a major criterion for the diagnosis of NCC in resource limited countries. They argued that Ag-ELISA was cheaper and needed inexpensive equipment which made it more applicable in poorly equipped laboratories with limited financial resources compared to CT scan or MRI. Unfortunately the antigen ELISA only exist at regional laboratories, at the Regional reference laboratory of the University of Zambia, School of Veterinary Medicine. If this diagnostic method is scaled up to rural laboratories may help to reduce epilepsy due to NCC management gaps.

The management of epilepsy was the same irrespective of the cause. Health facilities did not disaggregate the causes of epilepsy because of diagnostic challenges. As such the magnitude of the treatment gap between epilepsy due to NCC and epilepsy arising from other causes could not be compared. Except that in PWE due to NCC there is likelihood that seizures would eventually reduce over time due to clearing of the causative agent, either by anthelminthic medication or natural involution (Garcia *et al*., 2003). About 56% of the definitive diagnosed NCC epileptic patients reported to have had their last seizure in over a one-year period. The explanation could be that the causative agent could have cleared due to host immune response, natural involution or through indirect treatment during school mass drug administration (MDA) with anthelminthic medication or at clinic as a coincident when treating other ailments. This finding is in line with a study by Mwape *et al*. (2013) which showed that cysticercosis infections could clear over time due to factors such as immune status, age, sex of the host and administration of cysticidal medication. The clearing of the causative agent may feel like a relief to many affected individuals, but the percentage of epilepsy due to NCC in this study (28%) which may benefit from such clearing is somewhat low, and the majority of PWE have to be on AEDs for a longer period if not for the entire life time (Liu *et al*., 2016).

The determinants of a large treatment gap in this study were grouped at three levels; individual factors, community factors and service related factors. The individual based treatment gap was partly the service related gap (e.g. stock outs of AEDs). The PWE could not adhere to epilepsy treatment due to shortages of drugs at health facilities. Under normal circumstances PWE were

expected to be found with AEDs during the questionnaire interview. Unfortunately, this was not the case, as the majority of PWE did not have the drugs due to drug stock outs at their health facilities.

Many people in the rural communities have little understanding of the importance of taking medications as prescribed. The PWE did not understand the importance of taking the AEDs as a preventive therapy. PWE took the AEDs with the expectation that epilepsy will be cured. Thus, many of them did not take epilepsy medication for prevention, but took it only after relapse of seizures. This was usually because of a belief that the disease had been cured, consequently leading to complications such as uncontrolled epileptic episodes. This belief makes them abandon taking medication once seizures are temporarily suppressed. The finding is similar to what was reported by Nau *et al*. (2017) that PWE that start treatment are reported to stop treatment leading to serious health consequences.

Furthermore, PWE did not either report AEDs side effects or if the prescribed dosage was achieving the purpose to their health service providers, but instead many of them just stopped taking the medication. Health service providers also did not make follow ups on PWE to monitor adherence and the effectiveness of the AEDs. Information, education and communication on the importance of taking the AEDs for prevention of seizures would substantially reduce the treatment gap. The information, education and communication should be spearheaded by the health care professions, community drug adherence supporters and community health workers. This would require targeting not only PWE but also the key informants in their communities. The key informants would help to monitor adherence and to educate PWE and others in the community on the importance of taking AEDs as lifelong undertaking for prevention of seizures.

Literacy levels and, to some extent, alcohol consumption play a role in the large treatment gap (Cook *et al*., 2001; Carpentier *et al*., 2012). More than 50% of PWE had never been enrolled to primary school, and among those that had a chance to enroll for school, many could not complete primary education. Thus, illiteracy may contribute to non-adherence to the prescribed treatment, either leading to overconsumption or under-consumption of AEDs (Scott *et al*., 2001; Carpentier *et al*., 2012). Under-consumption can lead to seizure relapses due to inadequate dosage, while overconsumption of AEDs exposes patients to higher risks of AED dose-dependent cognitive

adverse events (Kwan *et al*., 2010). Some PWE interviewed reported to take drugs not as prescribed, but took it at their own time when they felt like doing so. Many of the PWE interviewed were small scale farmers and performed vegetable gardening. Much of their time was spent at the fields and gardens which made them not to take their medication left at home at prescribed frequencies, hence affecting adherence. The PWE comprised of frequent alcohol consumers. However, only 6% came out openly to say they drunk almost every day. Alcohol drinking is associated with impaired adherence to medication, particularly with taking medications off schedule (Cook *et al*., 2001; Hamerle *et al*., 2018). Expanding opportunities for conventional education (primary, secondary, and possibly tertiary) in rural set ups and among PWE, and also intensifying on the ongoing sensitizations on effects of alcohol on medication would be key for enhancing adherence to treatment.

The community also contributed to the wide treatment gap. People in the area associated epilepsy to spiritual sicknesses which resulted from witchcraft, and did not see conventional treatment as a solution, hence resorting to traditional treatment. Buck *et al*. (1997) reported negative beliefs and attitudes about epilepsy as contributors to non-adherence to AEDs. People in rural communities have misconceptions and give several explanations about the disease. Epilepsy is believed to be an evil spell that comes as punishment for one engaging in evil activities, yet others associate it with demons or witchcraft. Such beliefs and explanations about epilepsy play a major role on the treatment gap as they influence health seeking behavior (Coleman *et al*., 2002; Diop *et al*., 2003). Even when conventional treatment is initiated in PWE, they still combine the medication with traditional treatment. Modification of communities' beliefs and attitudes would be an important step towards improvement of treatment seeking and adherence to AEDs (Mbuba *et al*., 2012). Stigma associated with epilepsy contributes significantly to the psychological and social burden on patients. Some parents reported that they collected drugs for their PWE who failed to collect for themselves due to fear of being stigmatized. Many patients delay accessing treatment for fear of being stigmatized hence the condition worsening to the extent of causing so much damage (Baskind and Birbeck, 2005). Creating awareness and advocacy about epilepsy in the communities would help to bring the disease 'out of the shadows', rule out misconceptions, reduce stigma and eventually narrow the treatment gap (Birbeck, 2000; Coleman *et al*., 2002; Sebera *et al*., 2015).

The service related factors included staff knowledge and training, diagnosis, health facility distribution (big catchment areas) and stocking of the AEDs. Above 95% of health care professionals interviewed, had some basic knowledge of epilepsy management. However, over 50% did not understand the relationship between epilepsy and NCC. Knowledge about NCC was observed to increase with health care professionals' qualification and years of experience. Many of the health care professionals that worked for 5 years or longer had some understanding of NCC, though insignificant, increasing with their experience of service. This was noted in medical doctors who participated in the questionnaire survey. There is thus need for in-service training of health care professionals that provide care in the rural health centres as part of continuous professional development especially on these neglected tropical diseases. The few specialists and medical doctors who are mostly concentrated in urban areas, besides their role of management and treatment of complex conditions should play a supervisory role and provide technical support and training on basic management of epilepsy and NCC to frontline health workers working in rural clinics (Meyer *et al.*, 2012). Health care professionals should be encouraged to embrace the dynamism of science and to keep updating themselves with current knowledge to ensure evidence based practice in their everyday clinical practice (Sackett *et al.*, 2000).

A large proportion of the PWE were not hospital diagnosed. Their diagnosis was based on elderly opinion in their communities who had some knowledge on most common epileptic signs such as seizures. They would make an 'initial diagnosis', put the patient on traditional medication, and only visit the clinic when there was a complication. Even when the patient visited the health facility clinicians would just treat the seizures without establishing their causes. Diagnosis of epilepsy in the study area was a challenge as the district had no epilepsy diagnostic equipment and tests such as serological tests, the EEG, MRI or CT scanner. In health facilities, diagnosis of epilepsy was made based only on signs and symptoms. It was always difficult for health care professionals to establish causes of epilepsy, and thus were unable to differentiate between parasitic and non-parasitic causes of epilepsy. A previous study in the area established that more than 50% of epilepsy was caused by the larva stage of *T. solium* which lodges in the brain, leading to NCC (Mwape *et al.*, 2015). Without diagnostic equipment these parasitic infections are missed and are just managed as any other epilepsy case with AEDs. If epilepsy is

caused by NCC, then even if a patient is on AEDs, the cause is not treated, only the symptoms may temporarily resolve.

Mismanaged NCC can lead to detrimental social consequences if, for instance, anthelminthic drugs (albendazole or praziquantel) are administered on routine treatment or during MDA without taking any precaution (Del Brutto, 2012; Winkler, 2013; Chaurasia, 2015). When albendazole or praziquantel is administered to NCC patients, acute perilesional inflammation follows due to dying cysts (Garcia *et al*., 2004; Del Brutto, 2012). This exacerbates intracranial hypertension resulting in increased seizure frequencies and headaches (Chaurasia, 2015; Gripper and Welburn, 2017). The seizures are associated with inflammatory responses generated in response to cyst degeneration (Gripper and Welburn, 2017). It is advised that high dosage of corticosteroids (dexamenthasone or predinisolone) should precede or accompany anthelminthic treatment to reduce the effects caused by the degenerating cysts (Garcia *et al*., 2004; Winkler, 2013; Chaurasia, 2015). Furthermore, the use of seizure control drugs should be continued during and after administering of anthelminthic drugs. The narrowing of the epilepsy treatment gap requires timely diagnosis and intervention of the condition by ensuring that the diagnostic equipment is made available and accessible to the majority, and also availability of skilled personnel to carry out the diagnosis.

The distribution of health centres among the population and erratic availability of AEDs in health facilities were among the main contributors to the treatment gap. The geographical proximity of health facilities to homes for PWE plays a critical role on service utilisation. Distance affects use and access to health services in many resource constrained areas (Mbuba *et al*., 2012). Distance which many of the PWE cover to health facility coupled with non-availability of AEDs makes it unlikely that adherence to treatment will be sustained. The erratic supply of AEDs was one of the main contributors to the large treatment gap.

A contributing factor to these shortages could be that the AEDs are not part of the Essential Drugs Health Centre Kit, but are ordered separately. The AEDs should be added to the Essential Drugs Health Centre Kit to avoid unnecessary shortages in health facilities. Further, adopting and operationalizing of the primary health care system would help reduce the treatment gap (Coleman, 2002). This would require integrating epilepsy into other existing chronic diseases such as asthma and HIV/AIDS programs, and involving primary health workers such as the

CHWs in distributing AEDs to listed patients. PWE would only be required to cover long distances to the clinic for diagnosis, initial prescription, for periodical assessments and when need to change the drug is indicated. This strategy proved to be effective in Tanzania when it was utilized over a long period (Jilek-Aall & Rwiza, 1992), and it can still be adopted and fine-tuned by many resource limited countries.

In Zambia, a study was conducted in two provinces (Lusaka and Southern province) to assess the availability of AEDs in 111 pharmacies (Chomba *et al.*, 2010). The findings were that AEDs availability was inconsistent in all the pharmacies, and 45.9% of government pharmacies had no AED in stock. This is likely to be the same situation or even worse for other provinces which are further away from Lusaka, the capital. This current study reports AEDs non-availability as a main contributor to the large treatment gap. About 88% of the health care professionals of Sinda district reported that AEDs were not always available in their health facilities, and 34% of PWE mentioned non-availability of AEDs at their clinic as the main reason for not adhering to treatment. PWE could go to the clinic for drug refills and find no drugs available were given an appointment to come after a week or so and still found nothing, and maybe just given analgesia such as paracetamol or referred to the nearest hospital for AEDs.

The most frequently used AED was PB followed by CBZ. The Zambian Ministry of Health Standard Treatment Guidelines (2017) describes the standard of care for epileptic patients. The first line drug of choice for epilepsy is CBZ, and PB comes in as a second line drug. However, CBZ was never available in many instances; instead PB the second line drug of choice was used frequently as initial treatment (Chomba *et al*., 2010; Birbeck *et al.*, 2000; 2012). This made the management of epilepsy difficult as over 60% of patients reported to start taking CBZon the first visit and on subsequent visits could not find the drug available and were switched to PB before adequate follow up to monitor tolerance and effectiveness of the drug.

The treatment guidelines clearly explain how dosages are supposed to be increased for each specific AED and when discontinuation of treatment is supposed to be done. The use of two or more AEDs is rarely justified (MoH 2017). Further, the Zambia National Formulary, for MoH (ZNF 2017) clarifies that switching from one AED to another should be done cautiously with specialist advice. Unfortunately, the guidelines are never followed consequently leading to detrimental effects on the health of PWE. The two MoH documents above mention epilepsy but

are silent on the management of NCC. The curriculum for Clinical Officers highlights epilepsy but it is silent on NCC as one of its causes (Clinical Officers curriculum 2014). These are the professionals that attend to the majority of patients in rural areas where the epilepsy burden is high. The curriculum contributes to NCC/epilepsy management gap and therefore, to narrow the gap, there is need for the training curriculum for clinical officers and nurses to include the management of both NCC and epilepsy.

CHAPTER SIX

6.0 Conclusion and recommendations

This study has demonstrated that the gaps in treatment and management of epilepsy of any cause exist and were found to be high. An individual epileptic patient, the community and service related factors, singly and collectively, contributed to the high treatment gap.

To reduce the treatment gap, there is urgent need to raise awareness on epilepsy preventive medication especially in rural communities, broadening the educational opportunities to rural communities, integrating community-based epilepsy care into other chronic diseases managed by CHWs. Furthermore, policy makers to prioritize epilepsy medication in the national budgets as is done on other medications for other chronic conditions such as asthma, diabetes and HIV/AIDS and, adding the AEDs to the Essential Drugs Health Centre Kit. There is also need to make epilepsy/NCC diagnostic equipment available and accessible by the poor majority especially in rural set ups and, promoting in-service trainings to health care professionals in basic skills of diagnosing and managing epilepsy.

Meaningful success on narrowing the epilepsy treatment gap depends on a policy environment, political will, and collaboration from all stakeholders (local and external).

6.1 Study limitations

The study had several limitations. Firstly, the majority of PWE in our study were defined as PWE by the community elderly based on seizure episodes only which could have led to false diagnosis of epilepsy. Without a careful review of the history of each patient done by trained personnel to verify that the patient met criteria for diagnosis of epilepsy and seizure types, there

is a possibility that people with psychogenetic non-epileptic seizures only could have been included. Secondly, there was no neuroimaging done for NCC diagnosis due to financial constraints, as such only probable diagnosis could be made. Thirdly, due to stigma, there was a possibility that some PWE were not captured for recruitment. This as well might have read to under-reporting of the treatment gap. Fourthly, this study looked at adherence as being found with drugs at only one point during interviews as opposed to checking clinic visit records, pharmacy records and monitoring of seizures through home visits by CHWs. Alternatively, monitoring AEDs in blood samples over time could have indicated missing doses, the timing of administration and other variations. Pregnant women, children and seriously ill PWE were not included in the study to avoid inconveniences that may come due to their vulnerable state. This could have underestimated the reported treatment gap in this study.

6.0 REFERENCES

1. Allan J.C., Avila G, Garcia NJ, Flisser A, Craig PS (1990) Immunodiagnosis of taeniasis by coproantigen detection. *Parasitology* (3): 473–477.

2. Almeida, C..R., Stoco, P.H., Wagner, G., Sincero, T.C., Rotava, G., Bayer-Santos, E., Rodrigues, J.B., Sperandio, M.M., Maia, A.A., Ojopi, E.P., Zaha, A., Ferreira, H.B., Tyler, K.M., Dávila, A.M., Grisard, E.C., and Dias-Neto, E. (2009). Transcriptome analysis of *Taenia solium* cysticerci using Open Reading Frame ESTs (ORESTES). *Parasit Vectors.* 31; 2(1):35. doi: 10.1186/1756-3305-2-35

3. Andersen R. (1995) Revisiting the behavioual model and access to medical care: does it matter? J *Health Soc Behav*; 36: 1–10.

4. Aneja S. and Dua T. (2006). Neurocysticercosis: management issues. *Indian Pediatr.* Mar;43(3):227-35.

5. Annegers, J.F., Rocca, W.A., & Houser, W.A., (1996). Causes of epilepsy: contribution of the Rochester epidemiology project In Moyo clinic proceedings. Elsevier Volume 71, Issue 6, Pages 570-575

6. Assana E., Kyngdon C. T., Gauci C.G., Geerts S., Dorny P., De Deken R, (2010). Elimination of *Taenia solium* transmission to pigs in a field trial of the TSOL18 vaccine in Cameroon. *Int J Parasitol*.; 40:515–9.

7. Assana, E., Lightowlers, M. W., Zoli, A. P., & Geerts, S. (2013). *Taenia solium* taeniosis/cysticercosis in Africa: risk factors, epidemiology and prospects for control using vaccination. *Vet Parasitol*, 195(1-2), 14-23. doi: 10.1016/j.vetpar.2012.12.022

8. Assane Y.A., Trevisan C., Schutte C. M., Noormahomed E.V., Johansen M.V., Magnussen P. (2017). Neurocysticercosis in a rural population with extensive pig production in Angónia district, Tete Province, Mozambique. *Acta Trop.* 2017 Jan; 165:155-160. doi: 10.1016/j.actatropica.2015.10.018.

9. Atadzhanov M., Haworth A., Chomba E. N., Mbewe E. K., & Birbeck G. L. (2010). Epilepsy-associated stigma in Zambia: What factors predict greater felt stigma in a highly stigmatized population? *Epilepsy & Behavior*

10. Baird, R.A., Wiebe, S., Zunt, J.R., Halperin, J.J., Gronseth, G. and Roos, K.L., (2013). Evidence-based guideline: Treatment of parenchymal neurocysticercosis Report of the

Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, 80(15), pp.1424-1429

11. Baskind, R., & Birbeck, G. L. (2005). Epilepsy-associated stigma in sub-Saharan Africa: the social landscape of a disease. *Epilepsy & Behavior*

12. Birbeck GL , 2000 . Seizures in rural Zambia. *Epilepsia* 41: 277 – 281 .

13. Buck D, Jacoby A, Baker GA, Chadwick DW (1997). Factors influencing compliance with anti-epileptic drug regimens. *Elsevier* .doi.org/10.1016/S1059-1311(97)80060-X

14. Burneo J. G. and Cavazos J. E. (2015). Neurocysticercosis and Epilepsy. *Current Review In Clinical Science*

15. Cameron A, Roubos I, Ewen M, Mantel- Teeuwisse AK, Leufkens HGM, and Laing RO. (2011) Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Organ*.;89:412-421.

16. Carabin H., Ndimubanzi P.C., Budke C.M., Nguyen H., Qian Y., Cowan L.D,, Stoner J.A., Rainwater E., Dickey M. (2011). Clinical Manifestations Associated with Neurocysticercosis: A Systematic Review. *PLoS Negl Trop Dis* 5(5): e1152. https://doi.org/10.1371/journal.pntd.0001152

17. Carpentier N., Jonas J., Frismand S., Vignal J., Rikir E., Baumann C., Lapicque F., Saint-Marcoux F., Vespignani H., Maillard L. (2012). Direct evidence of nonadherence to antiepileptic medication in refractory focal epilepsy. *Epilepsia* DOI: 10.1111/j.1528-1167.2012.03695.x

18. Carpio A., Romo M. L., Parkhouse R. M. E., Brooke S., Tarun D. (2016). Parasitic diseases of the central nervous system: lessons for clinicians and policy makers. Expert Rev Neurother. 2016 Apr 2; 16(4): 401–414. doi:10.1586/14737175.2016.1155454

19. Carpio, A. (2013). Neurocysticercosis and Epilepsy. INTECH Open Access Publisher. (book)Carpio, A. and Romo, M.L.,(2014). The relationship between neurocysticercosis and epilepsy: an endless debate. *Arquivos de neuro-psiquiatria*, 72(5), pp.383-390

20. Chaurasia, R.N. (2015). Treatment of Neurocysticercosis. *Int J Neurorehabilitation*, 2, pp.2376-0281.

21. Chin J.H. (2012) Epilepsy treatment in Sub-Saharan Africa: closing the gap. *Afr Health Sci;*12:186–92

22. Chomba E. N., Haworth A., Mbewe E., Atadzhanov M., Ndubani P., Kansembe H., Birbeck G. L. (2010). The Current Availability of Antiepileptic Drugs in Zambia: Implications for the ILAE/WHO "Out of the Shadows" Campaign. *The American Society of Tropical Medicine and Hygiene*

23. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. (1995). Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet,* 1995, 346: 140–144

24. Coleman R., Loppy L., Walraven G. (2002). The treatment gap and primary health care for people with epilepsy in rural Gambia. *Bulletin of the World Health Organisation 80(5):378-83*

25. Cook R.L., Susan M.S., Susan C.H., William C., Judith A.E., Joseph C., (2001). Problem drinking and medication adherence among persons with HIV infection. *J Gen Intern Med*.;16(2):83-8.

26. Croker C., Roshan R., Laurene M. (2010). Use of Statewide Hospital Discharge Data to Evaluate the Economic Burden of Neurocysticercosis in Los Angeles County (1991–2008)

27. Das K., Banerjee M., Mondal G.P., Devi L. G., Singh O.P., Mukherjee B.B., (2007). Evaluation of socio-economic factors causing discontinuation of epilepsy treatment resulting in seizure recurrence: a study in an urban epilepsy clinic in India. Seizure 16: 601 – 607

28. De Giorgio C.M, Medina M.T, Duron R., Zee C., Escueta S. P. (2004). Neurocysticercosis. *Epilepsy Curr*.;4:107–11

29. Del Brutto O.H., (2012) Neurocysticercosis, Continuum (Minneap Minn). (6 *Infectious Disease*):1392-416. doi: 10.1212/01.CON.0000423853.47770.90.

30. Del Brutto O.H., Nash T.E., White Jr. A.C., Rajshekhard V., Wilkinse P.P., Singh G., Vasquez C.M., Salgado P., Gilman R.H., Garcia H.H. (2017). Revised diagnostic criteria for neurocysticercosis. *J Neurol Sci*.

31. Del Brutto O.H., Rajshekhar V., White A.C. Jr, Tsang V.C., Nash T.E, Takayanagui O.M., Schantz P.M, Evans C.A, Flisser A., Correa D., Botero D., Allan J.C., Sarti E., Gonzalez AE, Gilman RH, García HH. (2001). Proposed diagnostic criteria for neurocysticercosis. *Neurology* 57: 177–183.

32. Del Brutto O.H, Santibáñez R., Idrovo L., Rodrìguez S., Díaz-Calderón E., Navas C., Gilman R.H., Cuesta F., Mosquera A., Gonzalez A.E., Tsang V.C., García H.H. (2005). Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. *Epilepsia* 46: 583–587.

33. Dent W., Helbok R., Matuja W. B., Scheunemann S., Schmutzhard E. (2005) Prevalence of active epilepsy in a rural area in South Tanzania: a door-to- door survey. *Epilepsia*; 46: 1963–9.

34. Diagnosing epilepsy | Epilepsy Society. http://www.epilepsysociety.org.uk › diagnosing-epilepsy.

35. Ding D, Wang W, Wu J, Ma G, Dai X, Yang B, Wang T, Yuan C, Hong Z, de Boer HM, Prilipko L, Sander JW. (2006). Premature mortality in people with epilepsy in rural China: a prospective study. *Lancet Neurol;* 5:823–7. Doi: 10.1016/S1474-4422(06)70528-2 PMID: 16987728

36. Diop A G., de Boer H M., Mandlhate C, Prilipko L, Meinardi H. (2003). The global campaign against epilepsy in Africa. *Acta Trop*. 2003 Jun;87(1):149-59.

37. Dorny P., Brandt J, Zoli A., and Geerts S. (2003). Immunodiagnostic tools for human and porcine cysticercosis, *Acta Trop*,87: 79-86.

38. Dorny P., Phiri I.K, Vercruysse J, Gabriel S., Willingham AL 3rd, Brandt J, Victor B, Speybroeck N, Berkvens D. (2004). A Bayesian approach for estimating values for prevalence and diagnostic test characteristics of porcine cysticercosis. *Int J Parasitol* 34: 569–576.

39. Dorny P., Vercammen F., Brandt J., Vansteenkiste W, Berkvens D, Geerts G (2000). Seroepidemiological study of Taenia saginata cysticercosis in Belgian cattle. Veterinary *Parasitology* 88(1–2): 43–49

40. Druet-Cabanac, M., (2002). Epilepsy in subsaharan Africa. Thèse, *Fac. Med. Limoges*, France.

41. England MJ, Liverman CT, Schultz AM, Strawbridge LM, (2012) Epilepsy Across the Spectrum: Promoting Health and Understanding; Washington DC: National Academy of Sciences. *Epilepsy Behav*. 2012 Oct;25(2):266-76. doi: 10.1016/j.yebeh.2012.06.016.

42. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S.(2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014 Apr;55(4):475-82. doi: 10.1111/epi.12550.

43. Fisher, R.S., Boas, W.v. E., Blume, W., Elger, C., Genton, P., Lee. P., & Engel, J., (2005). Epileptic seizure & epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*

44. Flisser A (1994). Taeniasis and cysticercosis due *Taenia solium*. *Prog Clin Parasitol*. 1994;4:77-116

45. Gabriël S, Blocher J, Dorny P, Abatih EN, Schmutzhard E, Ombay M, Mathias B, Winkler A S (2012). Added Value of Antigen ELISA in the Diagnosis of Neurocysticercosis in Resource Poor Settings. *PLoS Negl Trop* Dis.6:e1851.doi: 10.1371/journal.pntd.0001851PMID:23094118

46. Gabriël S., Dorny P., Mwape K., Trevisan C., Braaed U.C., Magnussen P., Thys S., Bulaya C., Phiri I.K., Sikasunge C.S., Makungu C., Afonso S., Nicolau Q., Johansen M.V. (2016). Control of *Taenia solium* taeniasis/cysticercosis: The best way forward for sub-Saharan Africa? http://dx.doi.org/10.1016/j.actatropica.2016.04.0100001-706X/

47. Garcia H. H., Del Brutto O. H., Nash T. E., Clinton W. A. Jr., Tsang V. C. W., Gilman R. H. (2005). New concepts in the diagnosis and management of neurocysticercosis (*Taenia solium*). *Am. J. Trop. Med. Hyg*., 72(1), 2005, pp. 3–9

48. Garcia H.H., Gonzalez A.E., Rodriguez S., (2010). Neurocysticercosis: unraveling the nature of the single cysticercal granuloma, *Neurology* 75, 654–658.

49. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH, Herrera G, Evans CA, Gonzalez AE; (2004). Cysticercosis Working Group in Peru. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 350: 249–258.

50. García, H. H., Gonzalez, A. E., Evans, C. A., Gilman, R. H., & Cysticercosis Working Group in Peru (2003). *Taenia solium* cysticercosis. *Lancet* (London, England), 362(9383), 547–556. doi:10.1016/S0140-6736(03)14117-7

51. García, H.H., Evans, C.A., Nash, T.E., Takayanagui, O.M., White, A.C., Botero, D., Rajshekhar, V., Tsang, V.C., Schantz, P.M., Allan, J.C. and Flisser, A., (2002). Current consensus guidelines for treatment of neurocysticercosis. *Clinical Microbiology Reviews*, 15(4), pp.747-756.

52. Gripper L. B. and Welburn S. C. (2017). The causal relationship between neurocysticercosis infection and the development of epilepsy - a systematic review. *Infectious Diseases of Poverty* (2017) 6:31DOI 10.1186/s40249-017-0245-y

53. Guinhouya KM, Aboki A, Kombate´ D, Kumako V, Ape´tse´ K, Belo M, (2010). The epilepsy treatment gap in six primary care centres in Togo (2007-2009). *Sante.* 2010 Apr-Jun;20(2):93-7. doi: 10.1684/san.2010.0193.

54. Guo, Y.J., Sun, S.H., Zhang, Y., Chen, Z.H., Wang, K.Y., Huang, L., Zhang, S., Zhang, H.Y., Wang, Q.M., Wu, D. and Zhu, W.J., (2004). Protection of pigs against *Taenia solium* cysticercosis using recombinant antigen or in combination with DNA vaccine. *Vaccine*, 22(29), pp.3841-3847.

55. Hamerle M., Leyli G., Alexander K., Florian W., Martin H. (2018). Alcohol Use and Alcohol-Related Seizures in Patients With Epilepsy. *Front. Neurol*., 05 June

56. Helmstaedter C. (2013). THE IMPACT OF EPILEPSY ON COGNITIVE FUNCTION. Journal of Neurology, *Neurosurgery & Psychiatry*; 84:e1

57. .Iasemides, D.L. (2003). Epileptic seizure prediction and control. *IEEE Trans Biomed Eng*. 2003 May;50(5):549-58

58. Ibinda F, Wagner RG, Bertram MY, (2014). Burden of epilepsy in rural Kenya measured in disability-adjusted life years. *Epilepsia*; 55:1626–33. 48

59. Jacoby A, Snape D, Baker G. (2005) Epilepsy and social identity: the stigma of a chronic neurological disorder. *Lancet Neurol* 4:171–178.

60. Jansen S., White R., Hogwood J., Jansen A., Gishoma D., Mukamana D., Richters A. (2015). The "treatment gap" in global mental health reconsidered: sociotherapy for collective trauma in Rwanda. *Eur J Psychotraumatol*. 2015; 6: 10.3402/ejpt.v6.28706.

61. Jilek-Aall L, Rwiza HT. (1992) Prognosis of epilepsy in a rural African community: a 30 year follow-up of 164 patients in an outpatient clinic in rural Tanzania. *Epilepsia;* 33:645-50

62. Kale R. (2002) Global campaign against epilepsy: the treatment gap. *Epilepsia* 43(Suppl. 6):31–33.

63. Kerr M.P. (2012). The impact of epilepsy on patients' lives. *Acta Neurologica* ScandinavicaTellez-Zenteno J.F., Hernandez-Ronquillo L. (2017) Epidemiology of neurocysticercosis and epilepsy, is everything described? Epilepsy and Behavior, 76, pp. 146-150.

64. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Mosh SL, Perucca E, Wiebe S, French J. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51:1069–1077. Erratum in: *Epilepsia* 51:1922

65. Leonardi M. and Ustun TB. (2002). The global burden of epilepsy. *Epilepsia*; 43 Suppl 6:21–5.

66. Liu S., Yu W., Lü Y., (2016) The causes of new-onset epilepsy and seizures in the elderly

67. Lowerey, P. (2014). "Top Ten" list of food-borne parasites released. Retrieved 1 June 2015, from *www.fao.org/news/story/en/item/237323/icode*

68. Mbuba CK, Ngugi AK, Fegan G, Ibinda F, Muchohi SN, Nyundo C. (2012). Risk factors associated with the epilepsy treatment gap in Kilifi, Kenya: a cross-sectional study. *Lancet Neurol*;11:688–96.

69. Mbuba CK, Ngugi AK, Newton CR, Carter JA. (2008) The epilepsy treatment gap in developing countries: A systematic review of the magnitude, causes, and intervention strategies. *Epilepsia*; 49:1491-1503

70. Meyer A L., Dua T, Boscardin J, Escarce JJ., Saxena S, Birbeck G L. (2012) Critical determinants of the epilepsy treatment gap: A cross-national analysis in resource-limited settings. *Epilepsia*, 53(12):2178–2185, 2012 doi: 10.1111/epi.12002

71. Meyer A, Dua T, Ma J, Saxena S, Birbeck G. (2009) Global disparities in the epilepsy treatment gap: a systematic review. *Bull World Health Organ* (2010) 88:260–266.

72. Meyer A.C., Sokhi D., Ngugi A., Solomon T., Févre E. (2015). Prevalence of epilepsy, human and porcine cysticercosis in western Kenya. University of Liverpool [Corporate Author] Yale University [Corporate Author] Aga Khan University East Africa [Corporate Author] *International Livestock Research Institute*

73. Millogo A; Nitiéma P; Carabin H; Boncoeur-Martel MP; Rajshekhar V; Tarnagda Z; Praet N; Dorny P; Cowan L; Ganaba R; Hounton S; Preux PM; Cissé R, (2012). Prevalence of neurocysticercosis among people with epilepsy in rural areas of Burkina Faso. *Epilepsia* [Epilepsia], ISSN: 1528-1167, 2012 Dec; Vol. 53 (12), pp. 2194-202; PMID: 23148555

74. Moshé SL, Perucca E, Ryvlin P, Tomson T. (2015). Epilepsy: new advances. *Lancet*; 385: 884–98

75. Moyano LM, Saito M, Montano SM, Gonzalvez G, Olaya S, Ayvar V, Gonza´ lez I, Larrauri L, Tsang V. C. W., Llanos F, Rodrı´guez S, Gonzalez A. E., Gilman R H., Garcia H. H. (2014). Neurocysticercosis as a Cause of Epilepsy and Seizures in Two Community-Based Studies in a Cysticercosis-Endemic Region in Peru. *PLoS Negl Trop Dis* 8(2): e2692. doi:10.1371/journal.pntd.0002692

76. Murray, C. J. L., Vos, T., Lozano, R., Naghavi M., Flaxman A.D., Michaud C. Memish ZA (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380 (9859), 2197-2223.

77. Murrell, K. D., Dorny, P., Flisser, A., Geerts, S., Kyvsgaard, N. C., McManus, D., Zawlowski, Z. (2005). WHO/FAO/OIE Guidelines for the surveillance, prevention & control of taeniosis/cysticercosis K. D. Murrell (Ed.) Retrieved from http://www.oie.int/doc/ged/d11245.pdf

78. Mwape, K. E., Phiri, I. K., Praet, N., Muma, J. B., Zulu, G., Van den Bossche, P., . . . Gabriel, S. (2012). *Taenia solium* Infections in a Rural Area of Eastern Zambia-A Community Based Study. *PLoS Negl Trop Dis*, 6(3), e1594. doi: 10.1371/journal.pntd.0001594

79. Mwape, K. E., Phiri, I. K., Praet, N., Speybroeck, N., Muma, J. B., Dorny, P., & Gabriel, S. (2013). The incidence of human cysticercosis in a rural community of Eastern Zambia. *PLoS Negl Trop Dis*, 7(3), e2142. doi: 10.1371/journal.pntd.0002142

80. Mwape, K.E., Blocher, J., Wiefek, J., Schmidt, K., Dorny, P., Praet, N., Chiluba, C., Schmidt, H., Phiri, I.K., Winkler, A.S., Gabriël, S., (2015). Prevalence of neurocysticercosis in people with epilepsy in the Eastern province of Zambia. *PLoS Negl Trop Dis*, 9(8), p.e0003972.

81. Nau A. L. , Mwape K. E. , Wiefek J. , Schmidt K. , Abatih E., Dorny P., Praet N., Chiluba C., Schmidt H., Phiri I. K., Winkler A. S., Gabriël S., Blocher J., (2017). Cognitive impairment and quality of life of people with epilepsy and neurocysticercosis in Zambia

82. Ndimubanzi, P. C., Carabin, H., Budke, C. M., Nguyen, H., Qian, Y. J., Rainwater, E., ... Stoner, J. A. (2010). A systematic review of the frequency of neurocyticercosis with a focus on people with epilepsy. In *PLoS Neglected Tropical Diseases* (11 ed., Vol. 4).

83. Ngowi, H. A., Carabin, H., Kassuku, A. A., Mlozi, M. R. S., Mlangwa, J. E. D., & Willingham III, A. L. (2008). A health-education intervention trial to reduce porcine cysticercosis in Mbulu District, Tanzania. *Prev Vet Med*, 85(2008), 52-67. doi: 10.1016/j.prevetmed.2007.12.014

84. Nicoletti A., Bartoloni A., Sofia V., Bartalesi F., Chavez J. R., Osinaga R., Paradisi F., Dumas J., Tsang V. C. W., Reggio A., Hall A. (2005). Epilepsy and neurocysticercosis in rural Bolivia: a population-based survey. *Epilepsia* 46:1127–1132.

85. Nwani PO, Nwosu MC, Enwereji KO, Asomugha AL, Arinzechi EO, Ogunniyi AO. Epilepsy treatment gap: prevalence and associated factors in Southeast Nigeria. Acta *Neurol Scand* 2013;128:83–90.

86. O'Neal SE; Townes JM; Wilkins PP; Noh JC; Lee D; Rodriguez S; Garcia HH; Stauffer WM,(2012). Seroprevalence of antibodies against *Taenia solium* cysticerci among refugees resettled in United States. Emerging Infectious Diseases [*Emerg Infect Dis*], ISSN: 1080-6059, Mar; Vol. 18 (3), pp. 431-8; PMID: 22377408

87. Pal DK, Carpio A, Sander JW (2000) Neurocysticercosis and epilepsy in developing countries. *J Neurol Neurosurg Psychiatry* 68: 137–143.

88. Pawlowski Z. S. (2006). Role of chemotherapy of Taeniasis in prevention of neurocysticercosis. https://doi.org/10.1016/j.parint.2005.11.017

89. Pittella J.E. (1997). Neurocysticercosis, *Brain Pathology*. 7 681–693.

90. Praet N, Rodriguez-Hidalgo R, Speybroeck N, Ahounou S, Benitez-Ortiz W, Berkvens D., Van Hul A., Barrionuevo-Samaniego M., Saegerman C., Dorny P. (2010) Infection with versus exposure to *Taenia solium*: what do serological test results tell us? *Am J Trop Med Hyg* 83: 413–415.

91. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL *https://www.R-project.org/*.

92. Rajshekhar V. (2017) Neurocysticercosis: Diagnostic problems & current therapeutic strategies. *Indian J Med*

93. Roman, G., Sotelo, J., Del Brutto, O., Flisser, A., Dumas, M., Wadia, N. & Spina-França, A. (2000). A proposal to declare neurocysticercosis an international reportable disease.

94. Sackett, D. L., Straus, S. E., Richardson, W. S., Rosenberg, W., & Haynes, R. B. (2000). Introduction. In: Evidence-based medicine: how to practice and teach EBM (2nd ed., pp. 1-12). Edinburgh: Churchill Livingstone. (UH Manoa Hamilton RC80 .E95 2000)

95. Sarti E. and Rajshekhar V. (2003). Measures for the prevention and control of *Taenia solium* taeniosis and cysticercosis *Acta Trop*, 87, pp. 137–143

96. Scott R. A., Lhatoo S. D. & Sander J. W.A.S. (2001). The treatment of epilepsy in developing countries: where do we go from here? Bulletin of the World Health Organization Print version ISSN 0042-9686

97. Sebera F., Munyandamutsa N., Teuwen D. E., Ndiaye I. P., Diop A. G., Tofighy A., Paul B., Peter D. (2015). Addressing the treatment gap and societal impact of epilepsy in Rwanda — Results of a survey conducted in 2005 and subsequent actions

98. Shorvon, S. D. (2010). Hand book of epilepsy treatment.Spitz, M.C., Towbin, J.A., Shantz, D., & Adler, L.E. (1994). Risk factors for burns as a consequence of seizures in persons with epilepsy.

99. Sikasunge CS, Phiri IK, Phiri AM, Siziya S, Dorny P, Willingham III A. L., (2008) "Prevalence of Taenia solium porcine cysticercosis in the Eastern, Southern and Western provinces of Zambia," *Veterinary Journal*, vol. 176, no. 2, pp. 240–244, 2008. View at Publisher · View at Google Scholar

100. Smith S. J. M. (2005). EEG in the diagnosis,classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry*. 76 (Suppl 2): ii2–ii7.doi: 10.1136/jnnp.2005.069245

101. The Zambian Ministry of Health *Standard treatment guidelines* (2017), https://www.moh.gov.zm/docs/final_standard-treatment-guidelines

102. Torgerson PR, Macpherson CN (2011). The socioeconomic burden of parasitic zoonoses: global trends. *Veterinary parasitology* 182: 79–95.

103. Vos T, Flaxman AD, Naghavi M, (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*;380:2163–96.

104. Wagner RG, Ibinda F, Tollman S, Lindholm L, Newton CR, Bertram MY (2016) The Burden of Epilepsy Using population-based data to define the burden and model a cost-effective intervention for the treatment of epilepsy in rural South Africa WHO, 2006. Disease Control Priorities Related to Mental, Neurological, Developmental and Substance Abuse Disorders. Geneva, Switzerland: *World Health Organization*

105. Willingham iii, A.L., & Mugarula, A. (2008). *Taenia solium* tapeworm and epilepsy in Uganda. *International Epilepsy News* 2008

106. Wilson M, Bryan RT, Fried JA, Ware DA, Schantz PM, Pilcher JB, Tsang VC. (1991) Clinical evaluation of the cysticercosis enzyme-linked immunoelectrotransfer blot in patients with neurocysticercosis. *J Infect Dis*. Nov; 164(5):1007-9

107. Winkler AS (2013) Epilepsy and neurocysticercosis in sub-Saharan Africa. *Open access peer-reviewed chapter.* DOI: 10.5772/53289

108. Winkler AS, Kerschbaumsteiner K, Stelzhammer B,Meindl M, Kaaya J, Schmutzhard E. (2009). Prevalence, incidence and clinical characteristics of epilepsy — acommunity-based door-to-door study in northern Tanzania. *Epilepsia*; 50:2310–3.

109. Winkler, A.S., Willingham, A.L., Sikasunge, C.S. and Schmutzhard, E., (2009). Epilepsy and neurocysticercosis in sub-Saharan Africa. *Wien Klin Wochenschr*. 121 Suppl 3:3-12. doi: 10.1007/s00508-009-1242-3

110. Zambia National Formulary (ZNF 2017)

7.0 APPENDICES

7.1 Appendix 1: Questionnaire for people with epilepsy

Hello my name is ……..……... I am from Mtandaza Rural Health Centre and am a student at the University of Zambia. I am doing a study to investigate the gaps in management and treatment of general epilepsy and epilepsy due to neurocysticercosis (NCC). My investigation involves following up individuals diagnosed with epilepsy and NCC and their adherence to prescribed treatment through a questionnaire interview. The questionnaire will take approximately 10 minutes. Your answers will be kept confidential.

1) Code of interviewee: …….

2) Age of interviewee: ……...

3) Gender of interviewee:

a. Male b. female

4) Village name: …….

5) How far did you go with your education?

a. Grade 1 to 4
b. Grade 5 to 7
c. Grade 8 to 9
d. Grade 9 to 12
e. Never been to school
f. Other, please specify

6) Do you experience seizures of any kind?

a. Yes b. No

7) When did you have your first seizure?

a. In the last 7 days
b. Within this month
c. In the last 6 months
d. 1 to 2 years ago
e. Over 2 years ago

8) At what age did your seizures start? If the mother is around can help to answer even for an adult patient.

9) Do you have any family member suffering from epileptic seizures?

a. Yes b. No

10) Where was the epilepsy diagnosis made?

a. At the local clinic b. At the hospital c. Any other, specify

11) Are you on epilepsy/seizure treatment?

a. Yes b. No

If no, why are you not on medication?

12) If yes, what medication do you take? (More than one answer possible)

a. PB c. Phenytoin

b. CBZ d. Any other, specify

13) When did you last take your seizure medication?

a. Today d. More than one month ago

b. Within this week e. I cannot remember

c. Within this month

14) When did you last go for drug collection?

a. Within this week c. More than 1 month ago

b. Within this month d. I can't remember

15) How often do you go for drug refills?

a. Everyday c. Monthly

b. Weekly d. Whenever my drugs finish

16) Do you currently have the drugs in the house?

a. Yes b. No

17) What dosage are you currently taking? Specify of which medication

18) How often do you take your medications?

a. As prescribed by a health care provider c. Any time I feel like taking medication e. I do not take it at all

b. When I have a seizure d. When I am reminded to

19) Do you experience side effects when taking anti-epileptic drugs?

a. Yes b. No

20) If yes on question 20, mention the side effects

21) Apart from epilepsy medication, are you taking any other medicines for other conditions?

a. Yes b. No

22) If yes on number 22, please specify the medication and dosage

23) Has anyone explained about the effect those drugs could have on your epilepsy medication?

a. Yes b. No

24) Have you been taking alcohol in the last 2 years?

a. Yes b. No

25) How often do you take alcohol?

a. Every day c. Twice a month e. Other

b. Twice a week d. Once a month

26) Where do you get the drugs for your seizures from?

a. At the local clinic c. At the hospital e. Any other specify

b. Buy from the pharmacy d. From my neighbour that has the same condition

27) How far is it from your home to where you collect drugs from?

a. Within 5km b. 5 to 10kms c. More than 10km

28) Do you pay for your epilepsy medication?

a. Yes b. No

If yes, how much do you pay?

29) Have you ever gone for more than one month without drugs?

a. Yes b. No

30) If yes, what was the reason?

a. Drugs not available at local clinic

b. Was very sick and could not go to the clinic

c. Had no transport

d. I was away from home area

e. I had no money to buy

f. Other

31) What transport do you usually use to go for drug collection?

a. Bicycle

b. Motorbike

c. Car

d. Feet

e. any other

32) When you go for drug collection/refill, do you always find drugs available at your clinic?

a. Yes

b. No

33) If no, what explanation are you given by health care providers?

a. No drugs in stock at the health centre

b. Not due for drug collection

c. No explanation

d. other

34) Do health care providers explain to you about the drugs you are given in terms of name of drug, dosage and frequency, and when to come back for refill?

a. Yes

b. No

35) How do you feel you are attended by health care providers when you go for drug collection?

a. Good

b. Bad

c. Neglected

d. I do not know

36) Do you face any challenges when you visit the Health Centre for drug collection?

a. Yes

b. No

If yes, mention the challenges

37) What measures do you think should be put in place to address the challenges you are facing?

The questionnaire is finished. Thank you for your time and answers. We will make sure your data will be kept confidential.

7.2 Appendix 2: Health care provider's questionnaire

Hello my name is ……..……... I am from Mtandaza Rural Health Centre and am a student at the University of Zambia. I am doing a study to investigate the gaps in management and treatment of general epilepsy and epilepsy due to neurocysticercosis (NCC). My investigation involves questionnaire interview on both health care providers and individuals diagnosed with epilepsy and NCC, and following up epileptic patients on treatment adherence. The questionnaire will last about 10 minutes. Your information will be kept anonymous.

Do you agree to take part in this survey?

a. Yes b. No

Name of Health Facility: ……

Gender of interviewee:

a. Male b. Female

2) What is your qualification?

a. □Zambia Enrolled/Certified Midwife e. □ Clinical Officer Psychiatry

b. □Zambia Registered Nurse f. □Medical doctor

c. □Zambia Enrolled Nurse g. □Other _____

d. □Clinical Officer General

3) For how long have you been in this profession? ……

4) Have you ever heard or read about "epilepsy"?

a. □ No b. □ Yes—If yes, please give the local names for this disease.

5) How much do you know about epilepsy?

a. □ Nothing c. □ A lot

b. □ A little bit

6) What is the prevalence of epilepsy in your catchment area?

7) How do you tell if a person has epilepsy?

8) Do you diagnose epilepsy?

a. Yes b. No

9) If yes on number 8, how do you do it?

10) How many patients with epilepsy do you see per week?

11) How do you manage epilepsy patients at your facility?

12) How would you describe the availability of anti-epileptic drugs at your facility?

a. Always available
c. Never available

b. Sometimes available
d. Not sure

13) Are there instances where epileptic patients are turned away without getting their drug supplies?

a. Yes
b. No

14) What are some of the reasons for turning away patients without their anti-epileptic drugs?

15) Do you explain to your patients about the drugs you give to them in terms of name of drug, dosage and frequency, and when to come back for refill?

a. Yes
b. No

16) Are there any challenges that you face with patients when they come for drug collection?

a. Yes
b. No

17) If yes, mention the challenges

18) Have you ever heard of neurocysticercosis (NCC)?

a. Yes
b. No

19) If yes on number 18, what is the relationship between NCC and epilepsy?

20) How do you manage NCC?

21) How do you manage NCC at your health institution?

22) Do you give cysticidal drugs to NCC patients?

a. Yes
b. No

23) If yes, what cysticidal drugs are mostly available at your health centre? (Tick all that apply)

a. Praziquantel
b. Albendazole

c. Mebendazole

e. Any other, specify

d. Niclosamide

24) Are there any precautions you take when giving these cysticidal drugs to NCC patients?

a. Yes

b. No

If yes, which ones

25) Are there reports of any side effects after taking the cysticidal drugs?

a. Yes

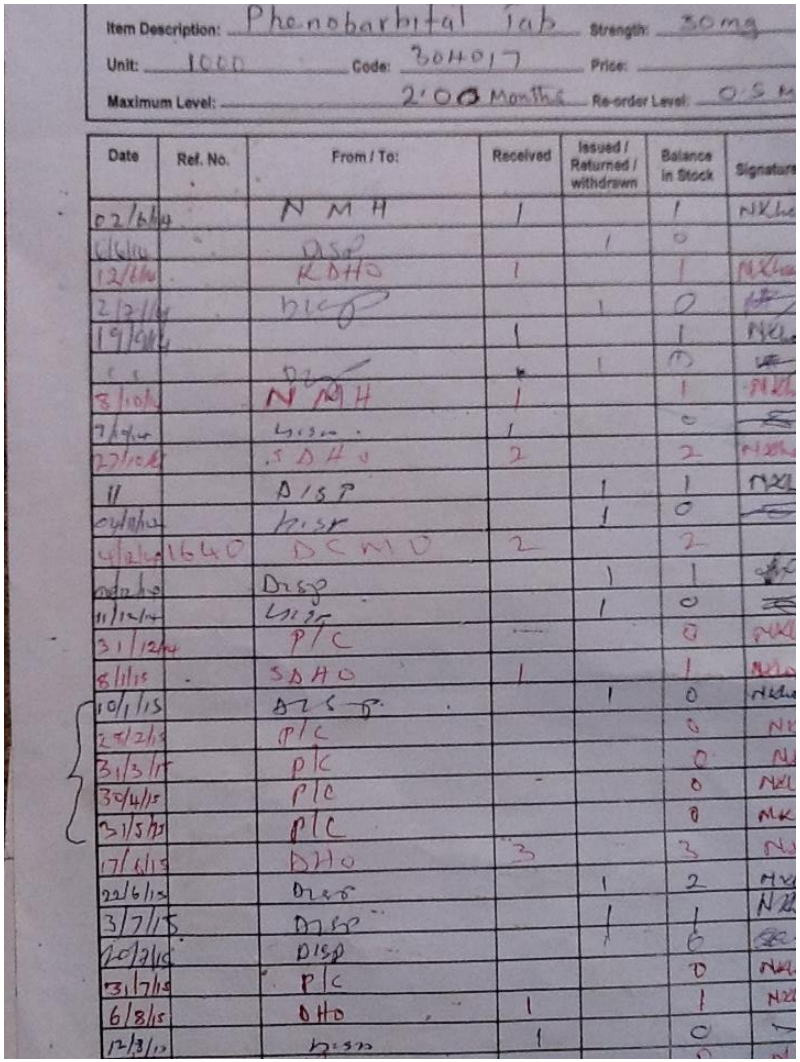
b. No

26) If yes, what are the side effects mostly reported?

27) If you had control over the situation, what measures do you think should be put in place to address the challenges you have mentioned above?

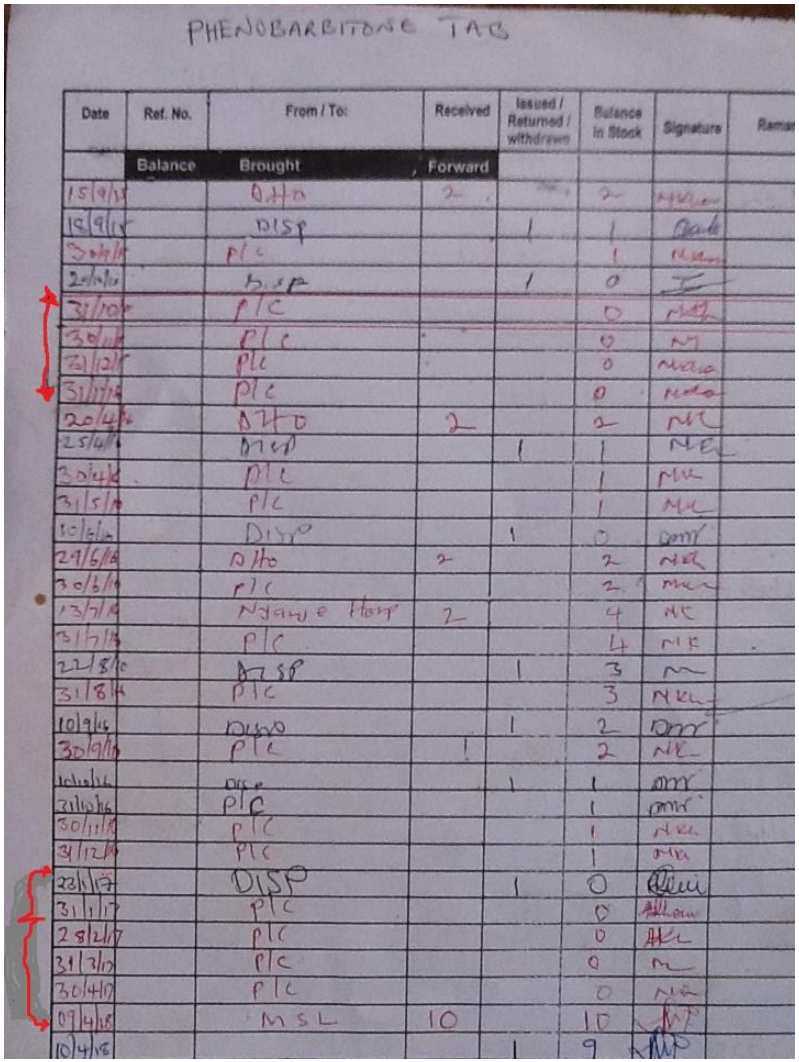
The questionnaire is finished. Thank you for your time and answers. We will make sure your data will be kept anonymous.

7.3 Appendix 3: AEDs Stock control cards for phenobarbitone



Item Description: Phenobarbital Tab Strength: 30mg
Unit: 1000 Code: 304017 Price:
Maximum Level: 2'000 Months Re-order Level: 0.5 M

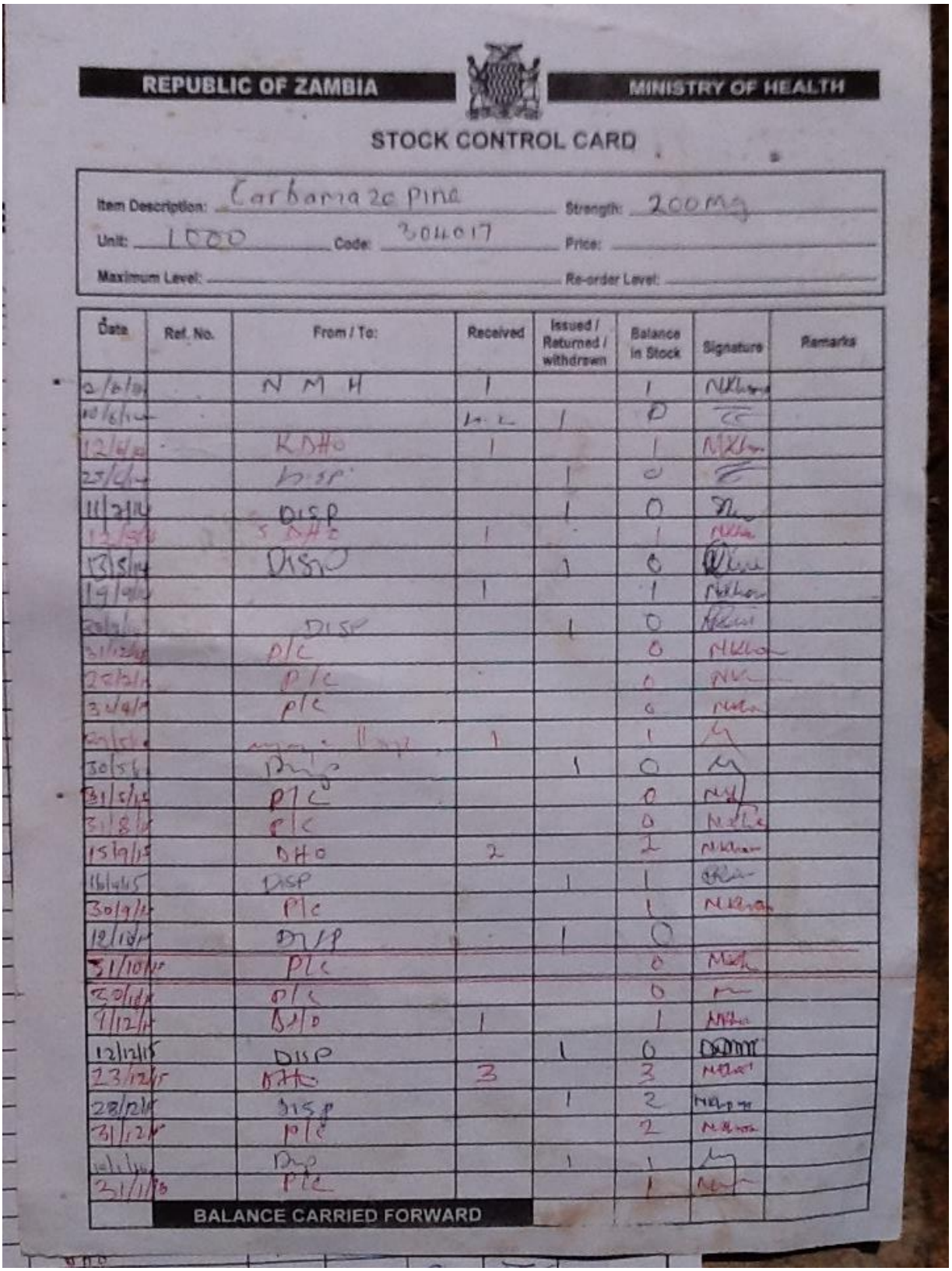
Date	Ref. No.	From / To:	Received	Issued / Returned / withdrawn	Balance in Stock	Signature
02/6/14		NMH	1		1	NKL
6/6/14		DISP		1	0	
12/6/14		KDHO	1		1	NKL
2/7/14		DISP		1	0	
19/9/14			1		1	NKL
		DISP		1	0	
8/10/14		NMH	1		1	NKL
7/11/14		DISP	1		0	
27/10/14		KDHO	2		2	NKL
11		DISP		1	1	NKL
29/10/14		DISP		1	0	
4/12/14	1640	DCMO	2		2	
9/12/14		DISP		1	1	
11/12/14		DISP		1	0	
31/12/14		PIC			0	NKL
8/1/15		SDHO	1		1	NKL
10/1/15		DISP		1	0	NKL
28/2/15		PIC			0	NKL
31/3/15		PIC			0	NKL
30/4/15		PIC			0	NKL
31/5/15		PIC			0	NKL
17/6/15		DHO	3		3	NKL
22/6/15		DISP		1	2	NKL
3/7/15		DISP		1	1	NKL
20/7/15		DISP			0	NKL
31/7/15		PIC			0	NKL
6/8/15		DHO	1		1	NKL
12/8/15		DISP	1		0	



PHENOBARBITONE TAB

Date	Ref. No.	From / To:	Received	Issued / Returned / withdrawn	Balance in Stock	Signature	Remarks
	Balance	Brought	Forward				
15/9/15		DHO	2		2	NKL	
15/9/15		DISP		1	1		
30/9/15		PIC			1	NKL	
2/10/15		DISP		1	0		
31/10/15		PIC			0	NKL	
30/11/15		PIC			0	NKL	
31/12/15		PIC			0	NKL	
31/1/16		PIC			0	NKL	
20/4/16		DHO	2		2	NKL	
25/4/16		DISP		1	1	NKL	
30/4/16		PIC			1	NKL	
31/5/16		PIC			1	NKL	
10/6/16		DISP		1	0		
29/6/16		DHO	2		2	NKL	
30/6/16		PIC			2	NKL	
13/7/16		Nyanwe Hosp	2		4	NKL	
31/7/16		PIC			4	NKL	
22/8/16		DISP		1	3	NKL	
31/8/16		PIC			3	NKL	
10/9/16		DISP		1	2		
30/9/16		PIC			2	NKL	
14/10/16		DISP		1	1		
31/10/16		PIC			1	NKL	
30/11/16		PIC			1	NKL	
31/12/16		PIC			1	NKL	
23/1/17		DISP		1	0		
31/1/17		PIC			0	NKL	
28/2/17		PIC			0	NKL	
31/3/17		PIC			0	NKL	
30/4/17		PIC			0	NKL	
09/4/18		MSL	10		10		
10/4/18				1	9		

7.4 Appendix 4: AEDs Stock control cards for carbamazepine



REPUBLIC OF ZAMBIA — MINISTRY OF HEALTH

STOCK CONTROL CARD

Item Description: Carbamazepine Strength: 200mg

Unit: 1000 Code: 304017 Price:

Maximum Level: Re-order Level:

Date	Ref. No.	From / To:	Received	Issued / Returned / withdrawn	Balance in Stock	Signature	Remarks
2/6/14		NMH	1		1		
10/6/14				1	0		
12/6/14		KDH	1		1		
25/6/14		DISP		1	0		
11/7/14		DISP		1	0		
12/8/14		KDH	1		1		
13/8/14		DISP		1	0		
19/8/14			1		1		
28/8/14		DISP		1	0		
31/12/14		PIC			0		
25/3/15		PIC			0		
3/4/15		PIC			0		
5/5/15		[illegible]	1		1		
30/5/15		DISP		1	0		
31/5/15		PIC			0		
31/8/15		PIC			0		
15/9/15		DHO	2		2		
16/10/15		DISP		1	1		
30/9/15		PIC			1		
12/10/15		DISP		1	0		
31/10/15		PIC			0		
30/11/15		PIC			0		
7/12/15		DHO	1		1		
12/12/15		DISP		1	0		
23/12/15		KDH	3		3		
28/12/15		DISP		1	2		
31/12/15		PIC			2		
16/1/16		DISP		1	1		
31/1/16		PIC			1		
		BALANCE CARRIED FORWARD					