The Prevalence of Neurological Disorders in the 70 years and Older Population of the Hai District in Northern Tanzania

Volume 1 of 2

Dr Felicity Dewhurst MBBS MRCP (UK)

MD Thesis

Institute of Health and Society

University of Newcastle Upon Tyne

November 2013

Abstract

The Prevalence of Neurological Disorders in the 70 years and older Population of the Hai District in Northern Tanzania

Aim

To determine the prevalence of neurological disorders in the 70 and over population of the Hai district in northern Tanzania through the production and utilisation of a screening questionnaire, and to describe the subtypes, the level of diagnosis, treatment and associated disability.

Introduction

There are limited data on neurological disorder and disability prevalence from developing countries despite a highlighted need from the World Health Organisation (WHO). This is partly due to the lack of a feasible and valid screening tool.

Methods

A screening questionnaire was created and validated for use in the elderly population of a developing country. A cross-sectional two phased epidemiological survey was then performed in the Hai district demographic surveillance site (DSS) (n=161,119). 2232 participants (1/4 of the DSS 70+ population) were screened. Positive responders underwent neurological assessment and were questioned regarding health seeking behaviour. Disability assessment was performed using the Barthel Index.

Results

The screening questionnaire was validated in one randomly selected village (n=277). Further substantiation was performed in a larger population (n=1955). The sensitivity and specificity were 87.8-97.0% and 90.4-94.9% respectively. In 2232 participants, there were 384 neurological diagnoses amongst 349 people. The age adjusted prevalence of

neurological diagnoses (95% confidence intervals (CI)) was 168.94/1000 (153.39 to 184.48). 58.6% had sought help for their symptoms, 14.6% had been correctly diagnosed and 10.6% were on appropriate treatment. The age adjusted prevalence of severe and moderate disability was 3.7% and 6.2% respectively. Those with neurological disorders had significantly greater odds of disablement.

Conclusions

This is the first screening instrument to measure the prevalence of neurological disorders specifically in an elderly population in Sub-Saharan Africa (SSA). It is feasible and valid with a high sensitivity and specificity. This is the first community-based neurological disorder prevalence study specifically in the elderly in SSA. It reveals high neurological morbidity and associated disability and low diagnosis and treatment levels.

Acknowledgments

I would like to thank all of the patients and their carers who agreed to take part in the study.

Additional thanks must go to all of the people who worked on the project; none of it would have been possible without all their hard work, time and effort;

- My supervisors Professor Richard Walker and Professor Raj Kalaria. Professor Walker co-ordinated the census and reviewed all diagnoses made.
- My colleague Dr Matthew Dewhurst who studied the same population and whom I worked with to collect demographic data and performing ECGs and blood pressure measurements.
- My assessors Dr Christopher Price and Professor Judith Rankin who have reviewed my satisfactory progress and the production of this thesis.
- Neurologists Dr William Howlett and Dr Naomi Warren who reviewed the neurological diagnoses made to ensure accuracy
- All the incredibly hard working staff in Tanzania, namely Dr Ahmed Jusabani, Golda Orega, Dr John Kissima, John Massawe Richard Amaro, Ali Mhina, Addess Moshi, Dr Paul Chaote and all the enumerators who provided interpretation and allowed us access to the demographic surveillance site.

Contents

Chapter 1. Introduction

Chapter 2. Methodology

Chapter 3. Results

Chapter 4. Discussion

Chapter 5. Conclusions

Appendices

First Author Publications

0.1 Dewhurst F, Dewhurst MJ, Gray WK et al. The prevalence of neurological disorders in older people in Tanzania Acta Neurol Scand 2013:127:198-207

0.2 Dewhurst F, Dewhurst MJ, Orega G et al. Neurological disorders screening in the elderly in low-income countries. J Neurol 2012: 259 (10): 2189-97

0.3 Dewhurst F, Dewhurst MJ, Gray WK et al. Rates of diagnosis and treatment of neurological disorders within a prevalent population of community-dwelling elderly people in sun-Saharan Africa Journal of Epidemiology and Global Health 2012: 2: 207-214

0.4 Dewhurst F, Dewhurst MJ, Gray WK et al. The prevalence of disability in older people in Hai, Tanzania. Age Ageing. 2012: 41(4):517-23

Chapter 1. Introduction

1.1 ICD 10 Version 2007 Diseases of the Nervous System

1.2 Epidemiology of Neurological Disorders of Lower Public Health Significance

1.3 Detailed diagnostic criteria of Neurological disorders

Chapter 2. Methodology

2.1 Neurological Disorders Information Sheet – English

2.2 Neurological Disorders Information Sheet – Swahili

2.3 Hai District Demographic Surveillance Site Neurological Disorders Prevalence Study Information Sheet – English

2.4 Hai District Demographic Surveillance Site Neurological Disorders

List of Tables

Chapter 1. Introduction

Chapter 2. Methodology

Chapter 3. Results

Chapter 4. Discussion

Chapter 5. Conclusion

List of Figures

Chapter 1. Introduction

Chapter 2. Methodology

Chapter 3. Results

Glossary of terms

AChR	Acetylcholine receptors
AD	Alzheimer's Disease
ADL	Activities of Daily Living
AEDs	Antiepileptic drugs
AF	Atrial Fibrillation
AIDS	Acquired Immune Deficiency Syndrome
AIMS	Abnormal Involuntary Movements Scale
AMMP	Adult Morbidity and Mortality Project
AMO	Assistant Medical Officer
ANS	Autonomic Nervous System
ASIA	American Spinal Injury Association
ASL	Above Sea Level
BP	Blood Pressure
BGS	British Geriatric Society
BI	Barthel Index
BMI	Body Mass Index
BMJ	British Medical Journal
BOD	Burden of Disease
CBD	Corticobasal Degeneration
CHW	Community Health Worker
CI	Cerebral Infarction
CN	Cranial Nerve
CNS	Central Nervous System
CO	Clinical Officer
COMT	Catechol-O-methyl transferase
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTS	Carpal Tunnel Syndrome

CXR	Chest X-ray
DALYS	Disability Associated Life Years
DAT Scan	Dopamine Transporter Scan
DFID	Department for International Development
DH	Drug History
DHS	Demographic Health Surveys
DLB	Dementia with Lewy Bodies
DM	Diabetes Mellitus
DMO	District Medical Officer
DSS	Demographic Surveillance Site
DVT	Deep Vein Thrombosis
ECG	Electrocardiography
Echo	Echocardiography
EEG	Electro-encephalography
EMG	Electro-myelography
EPS	Extrapyramidal syndrome
ET	Essential Tremor
FDG	Fluoro-deoxy-glucose
FDS	Framingham Disability Study
FGD	Focus Group Discussion
FH	Family History
GBD	Global Burden of Disease
GBDS	Global Burden of Disease Study
GBP	Great British Pound
GP	General Practitioner
GTCS	Generalised Tonic Clonic Seizures
HD	Huntington's Disease
HIV	Human Immunodeficiency Virus
IADL	Instrumental Activities of Daily Living

ICH	Intracerebral Haemorrhage
ICD	International Classification of Disease
ICF	The International Classification of Functioning, Disability and Health
IHD	Ischaemic Heart Disease
IHS	International Headache Society
ILAE	International League Against Epilepsy
IPD	Idiopathic Parkinson's Disease
KCMC	Kilimanjaro Christian Medical Centre
LACI	Lacunar Circulation Infarct
LACS	Lacunar Circulation Stroke
LOC	Loss of Consciousness
LP	Lumbar Puncture
MAOB	Monoamine Oxidase Inhibitor Type B
MDS	Movement Disorder Society
MND	Motor Neuron Disease
MRA	Magnetic Resonance Angiography
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MG	Myaesthenia Gravis
MGFA	Myaesthenia Gravis Foundation of America
MS	Multiple Sclerosis
MSA	Multiple System Atrophy
MSA-C	Multiple System Atrophy with predominant cerebellar ataxia
MSA-P	Multiple System Atrophy with predominant parkinsonism
NCS	Nerve Conduction Studies
ND	Neurological Disorders
NPH	Normal Pressure Hydrocephalus
NS	Nervous System
NIH	National Institutes of Health

NIMR	National Institute of Medical Research
NINDS	National Institute of Neurological Disorders and Stroke
NINDS-SPSP	National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy
NMI	Non Medical Investigators
NMJ	Neuromuscular Junction
OCSP	Oxford Community Stroke Project
OPCS	The Office of Population Censuses and Surveys
ORDR	Office of Rare Diseases Research
OT	Orthostatic Tremor
PACI	Partial Anterior Circulation Infarct
PACS	Partial Anterior Circulation Stroke
PDD	Parkinson's disease with dementia
PET Scan	Positron Emission Tomography Scan
PD	Parkinson's Disease
PMH	Past Medical History
PN	Peripheral Neuropathy
PNS	Peripheral Nervous System
POCI	Posterior Circulation Infarct
POCS	Posterior Circulation Stroke
POT	Primary Orthostatic Tremor
PPV	Positive Predictive Value
PSP	Progressive Supranuclear Palsy
PVD	Peripheral Vascular Disease
RCP	Royal College of Physicians
RD	Research Doctor
RHD	Rheumatic Heart Disease
rat-PA	Recombinant Tissue Plasminogen Activator
SAFE	Safe Assessment for the Elderly

SAH	Sub Arachnoid Haemorrhage
SCD	Sickle Cell Disease
SH	Social History
SN	Study Nurse
SPSS	Statistical Package for the Social Sciences
SSA	Sub-Saharan Africa
ST	Specialist Trainee
SUDEP	Sudden Unexplained Death in Epilepsy
TACI	Total Anterior Circulation Infarct
TACS	Total Anterior Circulation Stroke
TD	Tardive Dyskinesia
TFTs	Thyroid Function Tests
TIA	Transient Ischaemic Attack
TRIG	Tremor Investigation Group
TSIP	Tanzanian Stroke Incidence Project
TzSh	Tanzanian Shilling
UK	United Kingdom
UKPDS	United Kingdom Parkinson's Disease Society
US	United States
VP	Vascular Parkinsonism
WFN	World Federation of Neurology
WHO	World Health Organisation
WHO-DAS	World Health Organization Disability Assessment Schedules
WHO ICD 10	World Health Organisation International Classification of Disease – 10th Edition
YLDs	Years of healthy life lost as a result of disability
YLL	Years of Life Lost because of Premature Mortality

Statement of candidate's contribution to the work

I spent 9 months, from November 2009 to July 2010 living and working in Tanzania. Preceding this I made a preliminary visit for 1 week for pilot work and to meet the research team. I performed all training of local staff required for the project and to ensure capacity building in the district. I devised the Neurology screening questionnaire, performed the literature review and created the information sheets and proforma. I performed all interviews and examined all patients. I was responsible for the follow up of patients and for the distribution of paperwork to ensure patient's diagnosis and future treatment was known about and could continue locally. Professor Richard Walker organised the initial census. The project was performed in association with my colleague Dr Matthew Dewhurst who studied the same population and therefore was also involved with collecting the demographic data and in performing blood pressure (BP) and electrocardiogram (ECG) recordings.

Aims

The primary aim of this study was to determine the prevalence of Neurological Disorders and Consequent Disability in the 70 and over population of the Hai District Demographic Surveillance Site (DSS) in Northern Tanzania. This is the first community-based prevalence study specifically for Neurological Disorders in this age group in sub-Saharan Africa (SSA).

The subsidiary aims of this study were:

- To produce a validated and improved screening tool for the detection of Neurological Disease specific to the 70 years and older population.
- To describe the subtypes and nature of Neurological disorders in the Hai district of northern Tanzania, with respect to age, gender, disability, health seeking behaviour and prior treatment.
- To describe the disability level within the 70 and over population in the Hai district of Northern Tanzania and the proportion that is directly attributable to Neurological Disease.

At the completion of the study, I have identified the extent of all-cause neurological morbidity in the 70 years and older age group of a SSA population.

Chapter 1. Introduction

1.1 Introduction

1.1.1 *The Importance of Ageing*

Populations worldwide, but particularly in developing countries, are ageing rapidly. By 2050 an estimated 2 billion people will be aged 60 and over and 80% will reside in resource poor settings [1]. This epidemiological transition will generate an increase in non-communicable disease including neurological disorders. Collectively this provides a public health dilemma which low income countries are ill equipped to deal with [2]. In addition there is potential for these diseases to result in increased disability and dependence at a time when the Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) epidemic threatens traditional family networks.

The importance of studying the elderly is highlighted by data that estimates the population of over 50s in Africa will increase from 83 million in 1990 to 186 million in 2015 [2]. According to the WHO the 60 years and older age group is the fastest growing age group worldwide, with 650 million people aged 60 years and older in 2007, predicted to increase to 2 billion by 2050. It is important to study the cause of morbidity and mortality in this age group as 80% of deaths will be in this age group by 2050 [1].

1.1.2 *Neurological Disorders*

Neurological Disorders are known to cause significant morbidity and mortality in high-income countries. Little is known about the true prevalence of neurological disorders in SSA. There are no up-to-date community based epidemiological studies on this topic. There have only been three population-based assessments of the prevalence of adult neurological disease in Africa; Nigeria in 1982-85 [3], Tunisia in 1985 [4], and Ethiopia in 1986-88 [5], all predated the HIV epidemic, all used limited screening instruments [6] and none focused on the growing elderly population.

Anecdotal and projected prevalence figures indicate that Neurological Disorders also have significant public health consequences in SSA but are contradictory regarding the level of burden. The Global Burden of Disease Study estimated that neurological disorders account for 4.5% of morbidity in low income countries [7]. However, recent African hospital studies suggest that neurological disorders account for 20-30% of admissions [8, 9]. There is a general presumption that prevalence increases with age but there are no published community-based studies on the prevalence of Neurological Disorders specifically in the African elderly.

The World Health Organisation (WHO) highlight the public health importance of Non Communicable Diseases (NCD) stating they accounted for 59% of deaths globally in 2002 and predict this group of diseases will account for 69% of deaths in 2030. Of these neurological disorders cerebrovascular disease is an important contributor as it accounts for 8.6-11.0% of deaths[10].

1.1.2.1 *Justification of the measurement of neurological disorder prevalence as the primary aim.*

There is an urgent need to document the true prevalence of neurological disorders in the African community, to expose an expected high level of under diagnosis and treatment and to create an infrastructure to continue measurement and identification of patients for which cost effective treatment is available.. Accurate data on level of burden are paramount for health care planning especially in resource poor settings, a assessment of the contribution that neurological morbidity makes to the ageing population's NCD epidemic is essential.

Many Neurological disorders can be treated readily and inexpensively. Aspirin and Phenobarbital are two examples of inexpensive treatments available for the neurological conditions of stroke and epilepsy. It has recently been reported that African nations have between none and four neurologists per country [11] and very few neurosurgeons [12]. As a result the care of African patients with neurological

disorders is poor. Without accurate data to support the case for funding this poverty of care will remain. In particular funds are needed for the neurological education of primary care givers and the recruitment of specialists.

There are neurological disorders for which "active treatment" is not available; this may be because it is: unavailable only in sub-Saharan Africa, unavailable in low-income countries or unavailable worldwide. Identification of patients with such disorders is still beneficial. A diagnosis and explanation can have a positive impact on a patient's life, it can reduce stigma caused by ignorance and improve acceptance into society. In addition supportive, palliative care and rehabilitation techniques may still be used to improve quality of life [13].

It is important to document disease prevalence worldwide in order to identify variations. Neurological disorders are no exception to this general rule. Patterns of disease prevalence can vary widely across countries and regions worldwide. Variations in prevalence between developed and developing countries may expose aetiological differences (if data is ensured to be comparable)that in turn could generate hypotheses on disease causation to the benefit of the entire world. An example of such a situation is the increased incidence and prevalence of Coronary Heart Disease (CHD) and its risk factors in the South Asian Immigrant population of the UK compared with the white UK population or their counterparts in their native countries. Hypotheses created as a result of these observations examine the way that social and biological factors interact to cause variation in disease rates. This is an area of research that holds much promise for scientific advance. When differences in prevalence are found between regions and populations they should be viewed as an opportunity [14].

Another possible way to identify neurological morbidity would be to measure disability and then quantify what proportion is due to neurological disorders. "Measuring the disability level within the 70 and over population in the Hai district of Northern Tanzania and the proportion that is directly attributable to Neurological Disease " was one of our subsidiary aims and therefore I recognise the merit of recording disability in

the community. However, the use of disability to subsequently record neurological morbidity has a number of important limitations;

1. Difficulty in making comparisons

As described in our recent paper, entitled "The prevalence of disability in older people in Hai, Tanzania" [15] disability prevalence rates around the world vary significantly because of different definitions, study designs and the lack of a universal assessment instrument. Thus inter-study comparisons can be difficult. For example, review of the Tanzanian Disability Survey from 2008 [16] reveals that subjective questioning was used to produce a report of 'some' difficulty with seeing, hearing, walking, self-care or communicating and this defined disability. They report disability levels of 41.3% for the 70–74 age group, rising to 55.6%for those aged 80 years and older. In our experience, the majority of these people will still be fully independent and therefore it is difficult to contextualise these results and fully assess their significance. The importance of easy comparison for hypothesis generation on causation and effect needs to be highlighted.

2. Different definitions of disability

The WHO defines disability as an umbrella term covering impairments, activity limitations and participation restrictions, many disability scales only focus on one area of disability, for example, physical disability (as measured by the BI) [17-19].

3. Disability rates may underestimate morbidity caused by neurological disease in low income countries

Studies from both high- and low-income countries indicate that disability rates are higher in the developed world; however, the different measures used complicate interpretation [20-23].These differences may reflect increased risk factors for disability such as greater age, obesity, physical inactivity and higher prevalence of NCD in high-income countries and may also reflect increased mortality from disabling disease in low-income countries. Detection of e disorders before they become disabling and cause death is necessary to truly represent the burden they place on society.

4. By the time disability is established less may be possible to improve quality of life
Clearly models of rehabilitation from high-income countries may have limitations in SSA where there is limited resources and transportation, a community-based rehabilitation strategy maybe more appropriate but still the resources to provide such a programme may not be present. Prevention and early detection to prevent progression is therefore fundamental. To only measure disability would miss important cases that would be likely to progress.

1.1.3 *Epidemiological Studies*

There is an urgent need to document the true prevalence of neurological disorders in the African community and then to create an infrastructure to continue measurement and identification of patients who would benefit from the available cost effective treatment.. A feasible and valid screening tool for the detection of neurological disorders could be utilised for this dual purpose, it would enable evidence-based health care planning (a concept of paramount importance in resource poor settings) and it has the potential to rectify the large level of under diagnosis and treatment in the community.

Two phased community prevalence studies have long been established as the gold standard to document disease prevalence in low income countries [24, 25].
Hospital based studies of all neurological diseases suggest that neurological morbidity is the cause of 18-30% of medical admissions in SSA [11, 26-29], these contradict the Global Burden of Disease Study that suggests neurological disease accounts for only 3.9% of the total disease burden [7, 30]. These discrepancies in morbidity rates require investigation. However it is difficult to obtain accurate prevalence data in resource poor countries for many reasons which generally are a reflection of the lack of epidemiological infrastructure;

1. People do not present to hospital for geographical and financial reasons and therefore community based studies are likely to provide a better representation of true prevalence.

2. Demographic data on hospital diagnoses and deaths are limited and often non-existent.

3. Medical records are often hand held in exercise books or contained within rural clinics. They are often incomplete and are not computerised.

These epidemiological shortcomings have long been recognised, first described in 1982 by Schoenberg et al who developed the two phased approach to developing accurate prevalence data in a resource poor setting[25].

An initial screening phase utilising a screening tool that is feasible (acceptable, brief and easily administered by Non Medical Investigators (NMI), recruited from the local community and valid (sensitive- to detect all neurological cases and specific-to reduce second phase costs) precedes a second phase of physicians confirming disease in positive responders. NMI are ideal screeners as they are cheap to employ, readily available, know the geography of the community, and are more likely to be accepted by the population so as to increase participation rate.

1.1.3.1 *Screening questionnaires for neurological disorders*

Established instruments for identification of Neurological Disorders are unsatisfactory for the purpose of this thesis. The rationale for this is justified below [6, 31-36].

In 1981 the Neurosciences Program of the WHO developed a screening protocol consisting of 15 questions and 7 examination points. It was designed to pick up cerebrovascular disease, epilepsy, extrapyramidal disorders, peripheral neuropathy, intracranial neoplasms, and migraine headache. It was the standard tool for neuroepidemiological studies for many years[25, 26]. A literature review was performed to collect data on the deficiencies identified in the 1981 WHO protocol by

investigators, these were multiple and are presented below, the screening tool itself is initially presented to facilitate discussion:

Figure 1.1: The 1981 Original World Health Organisation Screening Tool

Q1. Have you ever lost consciousness?

Q2 Have you ever had episodes where you lost contact with your surroundings?

Q3 Have you ever had episodes of shaking of your arms or legs which you could not control?

Q4 Is your speech normal?

Q5 Have you had episodes of pain in the face?

Q6 Has your face or part of your face ever been paralyzed for more than 24 hours?

Q7 Have you ever had weakness in your arms or legs for more than 24 hours?

Q8 Have you been unable to walk properly?

Q9 Have you ever had loss of sensation or abnormal sensation affecting your arms and legs, lasting more than 24 hours?

Q10 Have you ever suffered from headache?

Q11 Do you suffer from severe headaches, chiefly on one side of the head, which come on from time to time?

Q12 In association with these headaches, do you suffer from visual disturbances: e.g. black spots or zigzag lines in front of your eyes?

Q13 In association with these headaches, do you suffer from nausea or vomiting?

Q14 In association with these headaches, do you suffer from weakness or numbness in the limbs that lasts less than a few days?

Q15 Do these headaches occur only when you have a febrile illness?

E1 Hold both arms above head for 30 s.

E2 Pick up matchstick from ground.

E3 Close your eyes. Feel cloth sample. Is it smooth or rough?

E4 Put your hands out in front of you. Close your eyes. Touch your nose with the right index. Repeat it using your left.

E5 Walk heel to toe along the white line (2 meter cloth).

E6 Stand with both feet together.

E7 Close your eyes and stand still for 15 s (only if able to perform E6).

1. Limitations of neurological disease ascertainment;

The WHO protocol was designed to assess the prevalence of 6 predefined diseases or groups of diseases. This is not a complete list of neurological disorders and therefore "all-cause" neurological disorder prevalence cannot be recorded (WHO ICD 10). This was highlighted by Gourie-Devi et al [37] who made their "symptom check list" or questions more comprehensive.

The WHO protocol does not focus on diseases of public health significance as data indicating disease burden was not available at time of production and will subsequently have changed, therefore, some neurological diseases of public health significance are not designed to be screened for and sensitivity for others is low (WHO). This is highlighted by Kapoor et al [32] who, when screening for neurological disorders in rural India, utilised the WHO screening protocol but added questions on head trauma as they felt this was of public health significance in their population.

2. The examination section of seven points complicates interpretation of the results and therefore the screening protocols use by NMI;

The examination points are an excellent and efficient test for multiple neurological signs however interpretation of results by NMI is problematic, this is supported by Morgante et al [38] who found the need to modify the WHO screening protocol, more specifically they had to qualify the possible different responses to the examination section making it more complex to read but easier to interpret.

3. The examination section reduces acceptability for participants;

Gourie Devi et al [37] found that it was not feasible to perform the examination section of the WHO screening protocol as they described that "people in semi-urban and rural (Indian) villages were reluctant to perform the clinical tests under instruction by field assistants and were insistent that a doctor carry out the tests". They therefore omitted the examination section from their tool.

4. The examination section fails to add anything to sensitivity and specificity;

Bower et al [39] recently reported that an examination section reduces specificity and feasibility but does not increase sensitivity. Sensitivity and specificity are arguably the most important statistics on which to judge the quality of a screening tool.

5. Low specificity increasing the cost and anxiety of false positives;

Original data on the unmodified WHO screening protocol from the 1980s and 1990s quote specificities of 80-85% [3, 4, 40]. More recent evaluation from Bower et al [26] revealed a specificity of 29.2%, the authors highlighted that Q1, Q2, and Q7 required modification with subsections to increase specificity. This low specificity is highlighted by Kapoor et al, when screening for neurological disorders in rural India they used the WHO screening tool but had to delete questions on headache as they felt they would reduce specificity [32]. They also highlighted that that two questions (Q8, Q9) had a very low specificity and these required modification before data collection began. Despite these modifications they still found specificity to be only 80%.Cruz et al highlighted Q2 and Q9 as poorly specific questions and rephrased them, subsequently they found specificity to be 78% [31]. Morgante et al also modified questions and provided clarifications for responses and found the specificity to be 85% [38].

6. Sensitivity to identify neurological morbidity;

Reports of sensitivity are high but variable. The original data from the unmodified WHO screening protocol from the 1980s and 1990s quote sensitivities of 91-95% [3-5]. More recent sensitivities of the unmodified protocol have been quoted as 98.4% [26]. Modified versions of the protocol have been reported to have sensitivities between 93-100% [31, 32].

7. Not widely applicable;

Kapoor et al criticise the WHO protocol in saying that it cannot be applied to different populations without completely retesting it in all respects (comprehension, sensitivity and specificity) [32].

Finally, Meneghini et al [41, 42] for numerous reasons describe the need to significantly modify the WHO protocol to develop their screening instrument for the Sicilian Neuroepidemiological Study (SNES) "questions and physical tests pertaining to some disorders were dropped. Other questions and brief tests were added or made suitable for the local situation". This modified protocol has been used in multiple regions since.

Other screening instruments have been piloted and used since [26, 41, 43-48]. A literature review was performed to collect data on published neurological screening tools or protocols. The full details of the search are included in the methods section of this thesis. Papers were included in the review if they detailed information on a neurological screening tool that screened for more than two neurological disorders. Some studies used numerous screening tools that only detected one or two neurological disorders to detect more than two neurological disorders, the features of the individual screenings tools were presented but not their combined sensitivity and specificity so these were not included [47]. Screening questionnaires from both developed and developing countries were included. As a result 12 different screening tools were reviewed from 21 articles, of these 3 articles described the 1981 WHO screening protocol as described above. Eight screening tools have been produced through modification of the WHO screening protocol and 3 screening tools have been produced without direct reference/modification of the WHO screening protocol. Only one screening tool was produced for and validated in an elderly population. However this tool only screened for parkinsonism and essential tremor and was therefore excluded from analysis [47].

Bower et al [26, 39] have recently published 2 papers on their screening instrument to measure the prevalence of neurological disability in resource poor settings. The screening instrument is a modified version of the 1981 WHO protocol. The authors researched the literature to identify deficiencies in the original tool. The modifications were mainly to: highlight diseases of public health significance, identify those people with neurological impairment secondary to non neurological or unclear diagnoses, ensure the tool was suitable to be used by non-medically trained staff, ensure the tool was acceptable to the population, sensitive enough to detect neurological morbidity in Africa and specific enough to minimise the cost and anxiety of false positives. The final screening instrument comprised a history and examination section. There were 24 history questions, 10 of which had between 1 and 6 subsections one of which needed to be positive for the question response to be positive overall. There are 16 examination points, these require a NMI to interpret: a pronator drift, complex tests of sensation, tests of coordination, bradykinesia, visual fields, cranial nerves, speech, hearing and gait. Their screening tool was very relevant to my research questions, it was also conducted in northern Tanzania, however they validated their screening questionnaire in a general adult population and did not focus on the elderly population.

The first paper published in 2009 uses a neurologist's diagnosis as the gold standard in determining the presence or absence of a neurological condition [26]. The exact details as to how this diagnosis was made are not expanded upon, it is not known if investigation or just clinical assessment was used. The study was performed in a hospital population in a tertiary referral hospital in northern Tanzania. This is a biased sub-population in a developing country as it comprises those who have the financial ability to be seen in an expensive hospital and are likely to be well educated. Many patients had a neurological condition which had been explained to them, as a result they were more likely to answer positively when questioned. This does not reflect the general population of a developing country, the proposed audience for the screening tool used in this thesis. The final screening instrument was only tested on 37 cases and 41 controls; the spectrum of subjects was therefore limited. There is no mention as to whether the interviewers were blinded to the presence of a neurological diagnoses, the supervising neurologist was not blinded in fact they appeared to provide a gold

standard diagnosis before screening occurred. Observer bias was therefore not avoided. There were discrepancies with results produced by different observers, in over 20% of cases there was disagreement between the neurologist screening and the NMI.

Sensitivity was found to be excellent at 100%. Specificity was however only 61% indicating that high cost and anxiety may still result from false positives. The authors did however improve on the specificity of the WHO screening protocol with which they made a direct comparison It scored 29.2% in their population. The authors report that their tool was extremely feasible and no participants were distressed by the completion of the tool but, of course this is a biased population who expected to be questioned and examined in hospital. A sample of the community may not be as amenable to such an intervention.

In summary the positive aspects of the screening instrument and the study were that it identifies most neurological diseases of public health significance and has a high sensitivity. The negative aspects were its poor specificity, small size, the hospital population studied, its lengthy and complicated questions with a complex examination section that reduces inter observer reliability.

It was acknowledged by the authors that this screening instrument must be piloted in its proposed area of use; a community setting and this is covered by their second paper, published in 2012 and set in the same community as my study population, with a second community population in Ethiopia [39]. Subjects were not randomly selected, for convenience households were seen in clusters. The abstract indicates 669 subjects were involved in the study across 2 sites, however only 25 known cases (in one site) were used to test sensitivity and these were of limited diagnoses (Parkinson's disease, stroke and epilepsy). All of these 25 cases knew of their disease and had been educated regarding it and were likely to answer positively. The gold standard for sensitivity was diagnoses from previous prevalence studies, the details of how these diagnoses were made were not obvious in the paper. Only 42 subjects (in the same site) were used to test specificity, the gold standard against which this was checked

was a neurologist's review, although the extent of this was not detailed. The authors state they reported the results of the same tool that they piloted in the hospital population but now state that the tool has only 22 questions (and 16 examination points as previously documented) there is no explanation provided for this discrepancy. The importance of using non medically trained staff as screeners was highlighted throughout both papers but despite this the authors used village health workers to screen. The health workers were blinded to diagnoses and so was the neurologist with regard to reviewing participants to test specificity. However, when reviewing cases to test sensitivity the presence of one of three neurological disorders was already known about. Inter observer variability was not tested.

The authors report a sensitivity of 100% for detecting a limited number of neurological diseases and a specificity of 82.4%. The authors go on to analyse the history section of the questionnaire in isolation, they reported a sensitivity of 100% and a specificity of 91.2%. They concluded that the examination section adds nothing, complicates the screen and is potentially prohibitive to NMIs.

Two papers by Meneghini et al [41, 49]reported the validation and utilisation of the 1987 Sicilian Neuro Epidemiologic Study (SNES) screening instrument. The initial paper provided an overview of how a two phased neurological prevalence survey in the Sicilian community was conducted [49]. It described the neurological screening instrument used: The screening instrument was a revised and adapted version of the WHO protocol. The authors describe how "their experience and other methodological considerations prompted significant modifications of the original screening instrument. Questions and physical tests pertaining to some disorders were dropped. Other questions and brief tests were added or made suitable to the local situation. For example a brief test of elbow tone was inserted for screening for parkinsonism."

The questionnaire was only translated into Italian and was not translated into the Sicilian dialect. This has the potential to cause problems for the elderly population who

may not have understood. Questions focussed on impairment of consciousness, uncontrolled limb movements, speech changes, facial paralysis, mouth drooping, limb weakness or paralysis, limb sensory abnormalities, rigidity, bradykinesia and tremor. Physical examination assessed arm strength, hand sensations, coordination, gait, standing with eyes open, standing with eyes closed, and elbow tone. Questions on self reported diagnoses of Parkinson's disease, epilepsy, stroke and peripheral neuropathy were also asked. A positive response was reported as one positive question, one positive examination section OR one, self reported diagnosis.

The authors report it took five to ten minutes to administer the screening instrument and it was easy to use.

The second paper describes the validation of screening instrument in more detail. The instrument only screens for 4 neurological disorders, parkinsonism, peripheral neuropathies, stroke and epilepsy, which although of great public health significance are far from a complete list and therefore cannot enable the documentation of the prevalence of all cause neurological disease [41]. The screening instrument was compared with a true and appropriate gold standard, clinical evaluation (history and examination not investigation) based on specified criteria.

Unfortunately the validation study did not include a large spectrum of subjects. The authors highlight the importance of a community survey and yet validate in a hospital population which is potentially biased; the patients are aware of their diagnosis (and although the direct question part of the questionnaire was removed for analysis) they are likely to be more aware of their symptoms and their relevance than an undiagnosed community population. No attempt was made to further validate in the community e.g. sample negatives. The authors do point out that their limitations are that the neurological diseases studied had resulted in inpatient admission and therefore the diseases are more likely to be advanced. They also acknowledge that the use of visitors to a neurology ward as controls has limitations as they may also have

increased awareness of diseases given a relative or friend may have one of the conditions. The authors state "biases may be encountered regarding hospital ambience, disease severity and non-representativeness of syndrome subtypes"

Only 108 subjects were studied and this included 21 controls. Conclusions drawn from such a small study may be considered tentative.. 'Screeners' were neurologists, therefore this study uses (and this instrument is only validated for) expert screeners. This makes it very difficult and expensive to recreate, potentially prohibitively so in developing countries. To the authors benefit the screeners were blinded to the patients' diagnoses which avoided observer bias. Inter-observer bias was not examined.

The features of the test demonstrated a favourable sensitivity, 100% for parkinsonism (n=21), 96% for peripheral neuropathies (n=22), 96% for stroke (n=22) and 96% for epilepsy (n=22). The specificity was 86% (n=21 hospital visitors free of any of the study diseases) this was relatively low and indicated that in a large community prevalence study a high number of false positives may make phase two difficult. Confidence intervals were not presented limiting conclusions.

In summary the SNES screening instrument was limited by only screening for four neurological diseases, a low specificity, expensive specialist screeners and poor validation in a hospital population.

Nicoletti et al [33] also utilised the SNES protocol to document the prevalence of neurological disorders in rural Bolivia. They report that they translated the questionnaire into Spanish and pre-tested it. They briefly state how they piloted the newly translated SNES screening tool in October 1994 in two small communities of 291 inhabitants which do not appear to be randomly selected. Pilot investigations and screening were carried out by varied health professionals including neurologists. The

authors report that revision of the questionnaire occurred and minor changes were made, however they do not report what those changes were or the revised sensitivities and specificities.

Vita and Morgante et al [38, 46] presented the findings of the validation of a screening tool (consisting of 9 questions and 7 examination points) in Sicily in 1989 for which field work was performed in 1984 [38, 46]. Their screening tool aimed to screen for some of the major neurological disorders, namely cerebrovascular diseases, epilepsy, extrapyramidal syndromes, peripheral neuropathies, migraine and intracranial neoplasms. The reasons for selecting these conditions were justified, as these disorders were of medical and social importance, but it is important to point out that this is far from a complete list of neurological diseases. The screening tool was produced through modification of the original WHO protocol. The screening tool was compared with the standard gold standard of full neurological history and examination by a person with neurological training with reference to diagnostic criteria. No laboratory tests were used. Diseases were coded using WHO classification 1975 edition. The validation study included a broad spectrum of subjects, a whole community (a small town) of 1638 were screened (eliminating sampling error). Only 37 subjects refused to take part, giving a final sample of 1601. All neurological disorders screened for were present in this population. Work up bias was avoided by avoiding sampling and by visiting patients, who were unable or refused to come to the clinic, in their own home. The screeners were medically trained and one of each team was a neurology specialist, which would limit the reproducibility of this procedure in resource poor settings with few neurologists. Inter observer reliability of the screening tool was not reported and observer bias was not avoided. The features of the test were an excellent sensitivity of 100%, however the specificity was only 85% and the positive predictive value was only 44%. The authors admit "this value is low and has to be enhanced by modifying the questionnaire before a much larger population is examined". The high number of false positives produced would make the second phase of a study performed with this tool expensive and unwieldy. Confidence intervals for the features of the test were not presented. The study also appeared to

identify a large number of neurological diseases not included in the questionnaire and it is not clear how this occurred [38, 46].

In summary these papers present the features of a screening tool validated for use in Italy. It identifies a limited number of neurological diseases and its validation using neurologists as screeners and its low positive predictive value indicate that its use in a developing country would be limited.

Gutierrez-del-Olmo et al [31] present the findings of the validation of a screening tool to detect neurological disorders in Madrid, Spain. The screening tool was described as "an extensive questionnaire and a brief screening neurological examination" designed to identify ,migraine, epilepsy, peripheral neuropathies, completed stroke, transient ischaemic attack (TIA) and Parkinson's disease (a far from complete list of neurological disorders). It was not however described in more detail or presented in an appendix so it is not known how it was produced and whether it was a modification of an already validated tool, however other literature indicates it was a modification of the WHO protocol. The gold standard for comparison was stated to be "examination by a neurologist". The validation study included a large number of subjects, 961. The choice of area was in close proximity to the specialist neurology hospital (for convenience for the neurologists and the subjects in the study), this however may introduce some bias as those geographically close to such a hospital may be more likely to have already received a neurological diagnosis than those living in rural areas or urban areas with less facilities. However the authors report that the age, occupation and economic distribution of the population closely matches the general Spanish population. Random sampling was used to identify 375 households for the study, however 32 were eliminated because no-one was home and 94 households refused to take part. This represents 27% of the population, a large percentage with the potential to introduce bias as the reasons for their refusals were not explored. This is a community study which is therefore more representative of the general Spanish population than a hospital population, however only households were included in sampling and institutions such as nursing homes which may contain large numbers of people with

neurological disorders were not included. Interviewers were medical students, therefore they had some medical training and would be more expensive to employ than NMI but would be cheaper and more available than trained doctors or neurologists. Inter observer bias was not examined.

The sensitivities of the screening tool were between 93-98%. The specificity was poor at 78% which is represented by the fact that of 961 people screened, 509 (52%) screened positive making the second phase very large and expensive. In addition to that, of the 509, 108 (21%) declined further examination. The screening results and medical records were used to classify refusers into probable presence or absence of neurological disease. It is not clear how these extrapolations were used in the results of the features of the screening questionnaire or the prevalence figures. It is acknowledged by the authors that seeing patients in their own home in the second phase would have increased the participation rate but this was not attempted due to time limitations. Positive predictive values and confidence intervals were not presented. The authors identify problem questions for false positives as being; "have you had episodes of loss of awareness or contact with your surroundings?" and "have you had tingling or pins and needles in your arms or legs that you could not explain?" The latter question was improved by defining that the symptoms had to last more than 24 hours. The authors also identified some problem examination sections. One sections asked participants to "get up and sit down from a chair 3 times without using your hands" with another asking participants to "walk 2 metres on your toes and two metres on your heels". They state elderly individuals with arthritis but with no neurological disorders had particular difficulty in performing these tasks.

This study highlights the increased number of false positives that can result from screening an elderly population and the problems this represents to previously published screening questionnaires.

Anderson et al [45] report the validation of a screening tool for the detection of 5 neurological disorders; epilepsy, parkinsonism, stroke, febrile seizures and TIAs in an urban community in Buenos Aires, Argentina. The instrument was based on that used in the Copiah County Study in 1982 [50]. A precise questionnaire was used to ask one member of the household about all other members of that household (no examination section was included). This method is cheaper, quicker and easier than direct questioning of individuals but has increased likelihood of error, particularly false negatives (for reasons of ignorance and stigma). The gold standard for comparison was full neurological history and examination. Interviewers were trained personnel with academic backgrounds as teachers or social workers, a protocol that would be relatively easy to recreate in other developing countries.

The validation procedure was complex and had 3 main sections;

1. Evolution of the screening questionnaire through drafts given to relatives and acquaintances of the authors and interviewers. This was to avoid embarrassing or confusing sections and to alter wording accordingly.

2. Sensitivity and Specificity were tested in a hospital environment. 10-15 individuals with the conditions and 10-15 controls were assessed by the authors and interviewers. They were not blinded to patient's conditions and the results of this phase are not presented in the paper.

3. A pilot site in a rural community (not representative of the final urban study site and not randomly selected) was used. The sample included 912 individuals from 281 households. All conditions were represented. The sensitivities presented were epilepsy 19/20 (95%), febrile seizures, 9/10 (90%), stroke 19/20 (95%), TIAs 8/10 (80%), Parkinsonism 24/24 (100%). The specificity estimate was 16/20 (80%); however it is not clear where this estimate comes from as all negatives were not examined. Confidence intervals and predictive values were not presented. Observer bias was reduced by the fact that interviewers did not have prior knowledge of participants'

neurological conditions. Questions about drooling were deemed embarrassing and so removed, questions with regard to speed of eating were removed for poor sensitivity and questions with reference to accurate timescales were removed as participants found them difficult to understand. It is not clear whether these modifications occurred before or after pilot testing. Inter observer reliability was not tested for.

In summary, Anderson et al present the validation of a screening tool which has a low specificity and only tests for 5 neurological conditions. Validation of the tool was a complex process that appears to have some discrepancies. The utilisation of NMI and the lack of an examination section would make it easy to use in a developing country [45].

Two papers from the late 1980s report the screening protocol from Gourie-Devi et al [37, 51] used in the neuroepidemiological study in Gowribidanur, India. They used a symptom check-list for 16 primary symptoms and 5 secondary symptoms. They state that they screened for more neurological disorders than the WHO protocol but they do not state what these were or how they were decided upon. The screening questionnaire was produced through modification of the WHO protocol questions. They did not utilise an examination section as they stated it would not be acceptable to the local community to be examined by trained screeners who were not doctors and were non-professional workers with schooling of 12 years, living in the study area. This improved the reproducibility of the study in other developing countries and the acceptability of the study within the local community. The symptom checklist was asked to the head of the household, this may improve case ascertainment (as each member of the household does not need to be seen) but it may also increase the number of false negatives (due to ignorance of the head of the household to another's symptoms or fear of stigma). The screening questionnaire was compared with the gold standard of history and examination by a neurologist. The validation study occurred in a large population representative of the main study population. A sample of 10% of the main study population was selected but it is not clear whether this selection was random. Unfortunately there were only 21 true cases of neurological disorders in the

sample and it was not detailed which disorders these were; it is therefore difficult to assess whether the pilot study results are representative of the screening questionnaires performance in the main study. The sensitivity and specificity were high at 95% and 98% respectively. However the positive predicative value was only 36%. This screening tool appears to be highly feasible in a developing country however its validation is unsatisfactory.

Gourie-Devi et al [44, 52]reports on the use of their screening questionnaire again in 1996 and 2004, where they pilot it in a large urban population. The questionnaire has been modified from its original form and now consists of only 12 questions. The pilot population was randomly selected and was therefore representative of a standard Bangalore population where the main prevalence study was to take place. To their credit they continue to use NMIs which are cheap and easy to employ. They report high sensitivity and specificity of 95% and 98% respectively but a positive predicative value of 68% indicating that a high number of false positives may be identified The details of their validation are again unclear. The large pilot study identifies a wide range of neurological disorders and so tests the questionnaires ability to successfully identify these.

Kapoor et al [32]report the performance of a modified version of the WHO protocol in rural India. They modified the screening tool by deleting questions on headache and adding questions on head trauma. The main validation of their screening tool occurred in a biased population of a health clinic where participants had known neurological disorders and their relatives acted as controls. As these groups will have more knowledge of the symptoms and signs of neurological disorders that the general rural population this may not be representative of the tools performance in the wider community. The size of this initial pilot was not specified. The tool was compared with the gold standard of full history and examination and it was partially validated in a wider population. A village (n=729) was selected, although not randomly, to be a pilot site for further evaluation of the screening tool and the preliminary report of

prevalence data. All the positive responders were examined by a neurologist; however the negative responders were not.

Reported sensitivities and specificities of the screening tool for the initial pilot were found to be 100% and 80% respectively. The positive predictive value was reported for the second village based pilot study as 62.1%.The question that produced the highest number of false positives were found to be "have you ever been unable to walk properly?" The low specificity and positive predictive value found in this study indicate that the second phase of a larger study may be unfeasible due to a high number of false positives.

Das et al [43] report the validation of a screening tool for the detection of the "major neurological disorders" such as epilepsy, stroke and Parkinsonism in the city of Kolkata. Their tool was based on national Institute of Mental Health and Neuro Sciences (NIMHANS) protocol but this is not referenced or expanded upon. The screening instrument was piloted against a gold standard of history and examination by a neurologist. Standard diagnostic criteria were used to define diseases. The screening tool was validated in a large pilot study of 3041 subjects although it is not clear how these subjects were identified and if randomisation was used.

Authors report that the sensitivity and specificity of the screening tool was 84% and 99.9% respectively. The low sensitivity indicates that a number of cases would be missed in future studies that use this tool. Positive and negative predictive values were 98.5% and 99.5% respectively. The authors report good inter-observer reliability but they do not present the data to support this. “Field workers” performed the screening, they were a minimum graduate in social science with experience of carrying out epidemiological surveys. Field workers required an intensive 3 months training which may be expensive and difficult to reproduce.

Das et al [53] go on to report the prevalence of neurological disorders specifically in a geriatric population. They use the same screening methodology as presented in the afore-mentioned study. No modification is made to the screening tool to accommodate this different population.

The Copiah County Study from the 1980s utilised a screening questionnaire to detect the disorders of cerebral palsy, epilepsy, stroke, Parkinson's disease, essential tremor and severe dementia[50]. The authors report the importance of designing the screening questionnaire with the population to be screened in mind; this is with particular reference to wording of the questions. Questions were directed to the head of the household about all other members in the house, this has the advantage of improved ascertainment whilst potentially increasing false negatives due to ignorance of the responder about others symptoms or for fear of stigma. The gold standard was neurological history and examination, no laboratory tests were used. The pilot study was conducted throughout the region of Hinds County this area was deemed to be representative of the population proposed for the larger prevalence study. The questionnaire was tested on known cases or known controls, which may introduce bias. No attempts for blinding were described. The size of the pilot study and the results were not described in more detail.

Quet et al [54] evaluated the performance of a modification of the WHO standard protocol in a rural community of central Mexico. This modification consisted of 12 standardised questions and 4 simple tasks for a quick evaluation of motor or sensory deficit, tremor and ataxia. Four more questions were added to improve sensitivity regarding epilepsy, psychomotor delay, diplopia and memory failure. Not only was the questionnaire evaluated against a gold standard of clinical examination (with reference to standard diagnostic criteria) performed by or under the observation of a neurologist, the performance of a questionnaire for individuals (IQ) was compared with a questionnaire for the household leader about everyone in the household (HQ). The HQ was the same as the IQ except for the examination section was removed. To

compare the questionnaires, the IQ and HQ were simultaneously and independently applied to each household during the screening phase.

As the study was performed in a large rural community an appropriate spectrum of subjects were included. Interviewers were semi-specialised medical, nursing or veterinary students, more expensive to employ than NMI. They were trained for 3 days before the study in order to minimize inter and intra observer variations, however these were not tested for. A whole region was screened so there was no possibility of sampling errors, however 15.5% of families refused to participate or could not be contacted in the study, and this has the potential to introduce bias. The authors found that the IQ detected significantly more patients (127/143, 88.8%) than the HQ (73/143, 51.0%). This difference was mainly due to the inability of the HQ to detect headaches: the IQ detected 74 of the 81 patients with headache (91.4%), while the HQ detected only 28 (34.6%). This therefore reduces the possibility that the lack of an examination section is the main contributing factor to the poor performance of the HQ. However, the usefulness of questionnaires remained significantly different when all ND excluding headaches were considered. In this case, the IQ detected 60 of the 70 neurological disorders (85.7%) while the HQ detected 47 of the 70 neurological disorders (67.1%). HQ does however detect the most severe neurological disorders and the authors therefore conclude that given its improved ease of use over the IQ, it could be used with this purpose in mind.

The major problem with this study was that negative responders to the screening questionnaires were not evaluated; therefore one can only calculate positive predictive value and not sensitivity, specificity, or negative predictive value.

1.1.3.1.1 *Screening questionnaires for neurological disorders in the elderly*

None of the screening tools already in existence for screening for multiple neurological disorders focussed on the elderly, a population likely to reduce a tool's specificity. The elderly are a unique population who require their own screening tool for neurological disorders for the following reasons;

1. Screening tools should be focussed on diseases of public health significance [39].This is different for the elderly population who have an increased prevalence of stroke, Parkinson's disease, essential tremor and epilepsy [53].

2. Elderly people have more co morbidities and this can often lead to decreased specificity through an increased number of false positives [55].

3, The elderly population is less likely to accept to be participants in a study with an examination section and more specifically for a medical examination to be performed by non-medical personnel [35, 56]. Therefore it is important that a screening tool designed specifically for the elderly omits an examination section so as to optimise participations rates.

1.1.3.1.2 *Examination sections of screening questionnaires for neurological disorders*

Flaws of the inclusion of an examination section in screening tools have been detailed above specifically with reference to the WHO protocol. After reviewing problems highlighted in the literature I reviewed how applicable these issues were to our local population, the following conclusions were made:

1. The elderly in our population did not want to be examined (however superficially, by a non medical personnel) - this was discovered during preliminary fieldwork where the population to be researched were informed of how brief the examination would be but they remained concerned.

2. The examination sections utilised in published tools vary in length from 7 to 16 examination points. The Non-Medical Investigators did not want to perform an examination nor interpret the results. The latter in particular was anticipated to be problematic. This is evidenced by the work from Bower et al [39]who state that

examination sections reduce specificity without making any improvement to sensitivity and Morgante et al [38] who highlight the need for clarification of examination responses complicates training. NMI did report that when questioning patients on symptoms they would feel happy to provide simple demonstrations of what they meant by certain symptoms to help participants understand.

The use of NMIs is important, as there are few medically trained people available to act as interviewers and NMIs can be relatively inexpensive to employ. Furthermore NMIs often have extensive local knowledge of people and geography. This can make them more acceptable to participants and so increase participation rates.

Gourie-Devi et al [52] report that "it was found that people in semi urban and rural villages in India were reluctant to perform clinical tests under instruction by field assistants and were insistent that a doctor carry out the tests" for that reason they omitted an examination section from their screening tool.

1.1.3.1.3 *Cultural specificity of screening questionnaires*

If a screening tool is proposed for use either in all developing countries or worldwide, efforts should be made to make its content culturally non specific, however, its wording should remain culturally specific through translation and back-translation to ensure ease of use. Sarangmath et al [57] looked at potential cultural issues when they designed a screening questionnaire for PD, they reported that if a questionnaire was not culturally non-specific NMI's responses had lower specificity when compared to Medical Interviewer's (MI) responses. Particularly important is the exclusion of questions regarding reading or writing to ensure screening questionnaires can be used in all literacy levels. The aim or the screening tool I used was for it to detect neurological disorders in the elderly in low income countries and therefore it was important to make its content culturally non specific but its wording correctly culturally specific.

1.1.3.1.4 *The sensitivity of screening questionnaires*

A screening questionnaire must have a high sensitivity (to ensure all neurological disorders are identified).The sensitivity of published screening tools varies from 84.0% to 100.0% (Those piloted in SSA 91.0%-100.0%) [3, 6, 26, 40], (Those piloted elsewhere 84.0% to 100.0%) [31, 33, 37, 41, 43-48, 53, 58].

1.1.3.1.5 *The specificity of screening questionnaires*

A screening questionnaire should have a high specificity (to reduce the number of false positives picked up which if numerous have the potential to make the study unfeasible due to the high financial cost of the second phase). The specificity of published screening tools used in SSA ranges from 29.2% to 85% [3, 6, 26, 40] and the specificity of those piloted in non SSA countries varies from 80% to 99.9% [31, 33, 37, 41, 43-48, 53, 58]. These screening tools were used in the whole of the adult population, not just the elderly (a population group known to reduce the specificity of the screening tool further due to multiple co morbidities). Previous investigators have commented that when screening mass populations it is important to accept poor specificity to achieve a high sensitivity [59]; however this should not be the case especially when screening an elderly population with an increased likelihood of false positives due to their co morbidities this increases the need to have a high specificity. The cases missed are often not disabled by their symptoms and a low specificity would make screening unwieldy and financially impractical.

It has been demonstrated that the WHO screening tool can be more sensitive and specific when neurologists are used as screeners, however this is generally financially and logistically unfeasible in resource poor countries with few neurologists [60, 61].

1.1.3.1.6 *Screening questionnaires for neurological disorders in SSA*

The majority of published screening tools have not been validated for use in SSA [31, 33, 37, 41, 43-48, 53, 58], which is not a criticism given they were never developed for this population but it does limit their use in this population without further validation.

1.1.4 *Disability*

Current data estimate 10% of the world's population are disabled [18], however there are few data on true prevalence of disability in developing countries, particularly amongst the elderly [62] despite the association between disability, increasing age and poverty (both cause and effect) [63],[64],[65], supportive data from the African community is required. In 2006, the United Nations (UN) highlighted the importance of disability to governments and international development agencies [18].The availability of high quality, internationally comparable up to date data on disability is integral for the planning, implementation, monitoring, and evaluation of inclusive policies.

Many disabling conditions can be prevented or treated readily and inexpensively. There are cost-effective measures for rehabilitation and disability improvement. Identification of those with disability and diseases that result in disability is clearly an important component in the reduction of the morbidity burden [66].

Reported disability prevalence rates around the world vary significantly because of different definitions, study designs, and lack of a universal assessment tool. This leads to comparison difficulties. In view of its simplicity, high validity, reliability, sensitivity and utility, the Barthel Index (BI) has been proposed as the standard measure of disability and the gold standard to which new measures should be compared [67, 68].

There is clearly a need to address health issues in the African Elderly and to accurately document levels of Neurological morbidity and disability.

1.2 Neurological Disorders

Neurological disorders are diseases of the central nervous system (CNS) (the brain and spinal cord), the peripheral nervous system (PNS) (the cranial nerves, peripheral

nerves, nerve roots, nerve plexus, neuromuscular junction and muscles) and the autonomic nervous system (ANS).

Psychiatric disorders are diseases in which the primary abnormality is one of thought, feeling or behaviour, producing either distress or impairment of function. These disorders include dementia which, although included in the neurological section of the World Health Organization (WHO) – International Classification of Neurological Disease (ICD) 10th edition (WHO-ICD 10) will not be elaborated on in this thesis. Further rationale for this decision is detailed later.

Hundreds of millions of people worldwide are affected by neurological disorders: For example, 50 million people have epilepsy; 62 million are affected by cerebrovascular disease; 326 million people suffer from migraine [69].

1.2.1 *Classification - WHO ICD 10*

ICD-10 was endorsed by the Forty-third World Health Assembly in May 1990 and came into use from 1994. The World Health Assembly adopted the WHO Nomenclature Regulations in 1967 that stipulate use of ICD in its most current revision for mortality and morbidity statistics by all Member States.

The ICD is the international standard diagnostic classification for all general epidemiology, many health management purposes and clinical uses. These include;

- The analysis of the general health situation of population groups
- Monitoring of the incidence and prevalence of diseases
- Assessing health problems in relation to variables such as the characteristics and circumstances of the individuals affected.
- Assessing requirements for resource allocation.
- Ensuring adequate quality control and up-to-date guidelines.
- Enabling accurate records of health and death to facilitate the storage and retrieval of diagnostic information for clinical, epidemiological and quality

purposes. These records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States[70].

The latest updates for ICD-10 were performed in 2007. A summary of the "Diseases of the Nervous System" section is detailed in appendix 1.1 [71].

The National Institute of Neurological Disorders and Stroke (NINDS) present the same disorders in an A to Z format [72].

Additional sub-classifications and diagnostic criteria from different health organizations are available and were utilised in this project with respect to different sub-types of neurological diseases. These are described within the relevant sections.

1.2.2 *Epidemiological and Clinical Diagnostic Divisions*

It is important to recognise the WHO ICD 10 for epidemiological studies especially when devising a screening tool as this allows full inclusion and consideration of all neurological diagnoses. Therefore, all patients diagnosed with a neurological condition have been allocated a WHO ICD 10 diagnosis. However, for practical reasons description of all the patients and the prevalence rates is often best performed with a more clinically relevant method to divide up the cases. This is done using a combination of the clinical and anatomical picture that the individual conditions produce. I used a practical combination of clinical classification and the ICD10 criteria to describe the prevalence rates (figure 1.1).

Figure 1.2: Epidemiological and Clinical Divisions of Burdensome Neurological Disorders. (WHO ICD 10 categories are presented in brackets) [71]

Central Nervous System Disorders

1. Movement Disorders (G20-G26)
    a. Tremor – all causes including cerebellar disease and Parkinsonism (G11.2-G46.4)
    b. Parkinsonism (G20-G23.1)
    c. Cerebellar Disorders (G11.2-G46.4)
    d. Other Dyskinesias (G25.5-G25.8)
2. Episodic and Paroxysmal Disorders (G40-G47)
    a. Headache Disorders (G44.1-G50.0)
    b. Stroke (G46.0-G46.7)
    c. Epilepsy (G40.6)
3. Systemic Atrophies/Degenerative Diseases affecting the Central Nervous System (G10-G13/G30-G32)
    a. Motor Neuron Disease (G12.2)
4. Injury resulting in CNS dysfunction
    a. Spinal Cord Injury (G95.2-95.9/S14.1)
5. Spinal cord dysfunction - other
6. Infection resulting in CNS dysfunction

Peripheral Nervous System Disorders

1. Polyneuropathies (G60-G64)/(G62.9)
2. Nerve, nerve root and plexus disorders (G50-G59)
    a. Cranial Nerves (G51.0-G52.8/S04.1)
    b. Upper Limb mononeuropathies (G56.0-G56.2)/(S54.0-S54.7)
    c. Lower Limb mononeuropathies (S74.0-S84.1)
    d. Plexus pathology (S14.3-S34.4)
    e. Root pathology (G54.2-G54.9)
3. Inflammatory/infectious diseases of the peripheral nervous system (A00-B99)
    a. Polio (A80.3)
    b. Leprosy (A30.9)

It is important to justify why the ICD 10 was used and why the diagnoses detailed above were the inclusive list. Systematic use of the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria ensured that the study was fully inclusive [20]. Cases with visual problems, hearing problems, dementia, and mild cognitive impairment, but no other signs or symptoms, were not considered to have a neurological disorder for the purposes of this study. A large proportion (46.9 %) of people in the study population responded positively when asked if they had problems with their vision. Likewise, large numbers of elderly people report problems with their hearing, mainly due to the high prevalence of presbyacusis. Inclusion of these diagnoses would substantially reduce a screening instrument's specificity. Questions about subjective deterioration in memory are notoriously unreliable for accurate detection of cognitive decline [21]. If detection of memory problems is desirable, I would recommend using an additional, appropriately validated, cognitive screening instrument. Overall, I feel the criteria set out above would be unlikely to miss a significant number of cases since very few neurological disorders are present with these excluded symptoms in isolation. Although the ICD 10 may have some flaws when used in low- and middle income countries, and some diagnoses may be difficult, it is a recognized international standard and allows direct comparison between studies carried out in different settings. Thus, I feel it was the most appropriate diagnostic criteria to use.

The disorders of Stroke and Dementia are included in several sections of the ICD 10, justification of their inclusion and exclusion respectively is therefore provided in more detail below:

Stroke is part of the "Diseases of the Nervous System" section of the ICD10 (section G00-G99). Specifically, it is part of episodic and paroxysmal disorders G40-G47 and comprises; G45 Transient cerebral ischaemic attacks and related syndromes and G46 Vascular syndromes of brain in cerebrovascular diseases. It is also mentioned under diseases of the circulatory system but this does not justify exclusion from neurological disorders.

Dementia is included in the "Diseases of the Nervous System" section of the ICD10 (section G00-G99), however only in part. A more complete description of dementia is included in the "Mental and Behavioural disorders" section more specifically "Organic, including symptomatic, mental disorders" (F00-F09), I The use of subjective memory questions for the diagnosis of dementia is fraught with difficulty and requires a specialised screening tool and prevalence study [73]. For these reasons dementia is excluded from this study.

Acceptance of the aforementioned definition of a neurological disorder means that stroke is and dementia is not a neurological disorder.

1.3 Diagnosis of Neurological Disorders – History, Examination and Investigation

The Neurological history and the physical examination are fundamental for an appropriate management plan (investigation and treatment) to be instigated [74].

1.3.1 *Neurological History*

A neurological history is composed of;

- Neurological symptoms recognition, namely;
  Seizures [75]
  Dyskinesias/Abnormal Movements [76, 77]
  Weakness - graded using the Medical Research Council (MRC) muscle power scale [75, 78]
  Sensory abnormalities [75]
  Ataxia/Coordination problems [75, 76]
  Dysphasias/ Speech abnormalities [72, 74-76, 79]
- Characterizing the pattern of the neurological disease over time
- Establishing precipitating factors and preceding and subsequent events
- Collateral history if required

- Interpretation of a neurological history based on knowledge of the hierarchal organization of the nervous system and the principles of functional localisation and pathological processes.[79].

1.3.2 *The Neurological Examination*

The detailed neurological examination consists of assessment of speech and language and gait and examination of the motor system, sensory system, cranial nerves and coordination [76]. Pathology in different areas of the nervous system produces different clinical signs [72, 74-76, 79, 80].

1.3.3 *Neurological Investigation*

A thorough history and examination remains the primary way to establish a differential diagnosis. Only when these have been satisfactorily performed should these be used to focus neurological investigation. Some investigations carry risks and all come at an expense, additionally within developing countries such as SSA they are often not available and clinical skills remain the only way to arrive at a diagnosis and instigate potential treatment [75].

Neurological Investigations available within the research area included, basic blood tests, simple x-rays, computerised tomography (CT) and electroencephalograms (EEG). Neurological Investigations not available within the research area were magnetic resonance imaging (MRI), angiography, nerve conduction studies (NCS)[75, 81, 82].

1.4 Prevalence and Incidence [83]

1.4.1 *Prevalence*

The prevalence of a disorder is “the number of live cases suffering from that disorder, usually expressed per 100,000 of the population (or per 1000 of the population if the disease is more common), at a defined time.” The prevalence of a disorder is affected by length of survival of those with the disease. For diseases with long survival times this is not an issue, but for diseases where patients may die soon after diagnosis, a

prevalence figure may be misleadingly low. In this case the incidence of the disease is a better marker of how common it is.

1.4.1.1 *Point Prevalence*

Point prevalence is a measure of the proportion of people in a population who have a disease or condition at a particular time, such as a particular date. This measure is best used for chronic conditions and was the measure used in this prevalence study.

1.4.1.2 *Period Prevalence*

Period prevalence is a measure of the proportion of people in a population who have a disease or condition over a specific period of time, say a season, or a year, this measure is better used for acute conditions.

1.4.2 *Incidence*

Incidence is "The number of instances of illnesses commencing or of people falling ill, during a given period in a specified population. More generally, the number of new health-related events in a defined population within a specified period of time. It may be measured as a frequency count, a rate, or a proportion." [84] In developing countries many patients may not receive medication for their illness. It is therefore possible that survival will be affected, meaning that patients may die earlier and thus lower prevalence. This would indicate that incidence is a better measure in these populations. However incidence studies are reliant upon patients seeking medical help quickly after symptom onset, something that often does not happen in developing countries due to financial restrictions and low availability of local healthcare resources.

1.4.3 *The appropriate measurement of neurological disease morbidity burden*

In the majority of Neurological disorders the disease has a chronic trajectory and therefore prevalence is a more accurate reflection of disease burden. The exception to this rule is Stroke and Neurological deficit caused by accidental injury; in these cases the rural setting, the age of the patient and their financial situation often prevent them from seeking help further complicating a successful incidence study. It was felt that an incidence study in rural Tanzania of all Neurological Disorders and their consequent disability, in this age group, would be difficult to undertake and prevalence was a more

accurate representation of morbidity. Chan et al [85] state that although incidence is a better measure of disease occurrence, it is difficult to obtain in chronic diseases[83].

1.5 Detailed description of Neurological Disorders

This prevalence study aimed to identify a complete list of neurological disorders as defined by the WHO ICD 10 (see figure 1.1);

The diagnostic criteria and epidemiology of the most common and public health relevant conditions namely, tremor, parkinsonism, cerebellar disorders, headache, stroke and epilepsy, have been described in full. The prevalence study also aimed to identify, dyskinesias, motor neuron disease, spinal cord dysfunction including injury, infection resulting in CNS dysfunction, polyneuropathies, nerve, nerve root and plexus disorders and inflammatory/infectious diseases of the PNS e.g. polio and leprosy. A more superficial review of the diagnostic criteria and epidemiology of these conditions has been included in appendix 1.2 and 1.3.The conditions are described in the order of the clinical/epidemiological divisions described above.

1.5.1 *CNS Disorders*

1.5.1.1 *Movement Disorders*

1.5.1.1.1 *Tremor Disorders*

1.5.1.1.1.1 *Definition*

Tremor: the Rhythmical, involuntary oscillatory movement of a body part [86].

1.5.1.1.1.2 *Clinical/Syndromic Classification of Tremor*

Practical classifications of tremor that are based upon aetiological or pathophysiological factors are not available therefore the gold standard remains a clinical classification. This is particularly relevant in epidemiological studies in developing countries where history and examination are, in the majority, the only tools

available for diagnosis. The clinical classification of tremor may be based upon the following factors that will make up a syndromic classification;

Table 1.1: Variants in the clinical analysis of tremor that dictates the Syndromic classification

Variant	Issues that indicate Syndromic classification
Anatomic or topographic distribution	▪ Head: Chin, Face, Tongue, Palate ▪ Upper extremity: Shoulder, Elbow, Wrist, Fingers ▪ Trunk ▪ Lower extremity: Hip, Knee, Ankle joint, Toes
Activities that activate tremor	▪ Rest Tremor ▪ Action Tremor ▪ Postural Tremor ▪ Simple Kinetic Tremor ▪ Tremor during target-directed movements (intention tremor) ▪ Task specific Tremor ▪ Isometric Tremor
Relative tremor frequency measured in cycles per second	▪ Physiologic and enhanced physiologic tremors have a relatively high frequency, often ranging from approximately 7 to 12 cycles per second. ▪ In contrast, the rate of many pathologic tremors is about 2 to 7 Hz. ▪ Primary orthostatic tremor (OT) is a notable exception, with a 13 to 18 Hz ▪ Cortical tremor, recognized as a form of rhythmic myoclonus, is characterized by irregular, postural and kinetic tremor-like jerks with a range between 7 to 18 Hz.

	▪ Cerebellar and rubral or Holmes tremors tend to be of relatively low frequency, primarily occurring below 4.5 or 5 Hz. ▪ The pure rest tremor seen in some with PD is characteristically greater than 4 Hz ▪ In classic ET, the rate of tremor may vary between 4 to 12 Hz
Specific data from the medical history	▪ Onset ▪ Family history ▪ Alcohol sensitivity ▪ Medication ▪ Drug abuse
Specific examination to detect concomitant neurologic conditions	▪ Akinesia/bradykinesia ▪ Muscle tone/dystonia ▪ Postural abnormalities ▪ Cerebellar signs ▪ Pyramidal signs ▪ Neuropathic signs ▪ Systemic signs e.g. thyrotoxicosis ▪ Gait and stance e.g. orthostatic tremor [86]

The syndromic classification of Tremors is as follows

1. Essential Tremor (ET)
2. Physiological Tremor
3. Enhanced Physiological Tremor
4. Indeterminate tremor syndrome
5. Primary orthostatic tremor
6. Dystonic tremor syndromes
7. Task- and position-specific tremors
8. Parkinsonian tremor syndromes
9. Cerebellar tremor syndromes
10. Holmes tremor
11. Neuropathic tremor syndrome
12. Drug-induced and toxic tremor syndromes
13. Psychogenic tremor
14. Myorrhythmia.

[86]

These are all detailed below:

1.5.1.1.1.2.1 *Essential Tremor (ET)*

The definition/clinical classification of ET is an ongoing, evolutionary process. Several classification schemes have been proposed, including the Tremor Investigation Group (TRIG) Criteria in 1995; the National Institutes of Health (NIH) Collaborative Genetic Criteria in 1996; the Consensus Statement of the Movement Disorder Society (MDS) on Tremor in 1997 and the Diagnostic criteria from Fahn et al proposed for use by Elan Louis et al in 1998. For epidemiological research it is important to have an agreed definition for both the diagnostic criteria of essential tremor and other forms of tremor. I produced diagnostic criteria based on the collaborative work of the above groups and this was the diagnostic criteria used in the study (table 1.2) [86-90].

1.5.1.1.1.2.1.5 *Simplistic Diagnostic Criteria for Essential Tremor based on the recognised published criteria from TRIG, NIH, and MDS*

Table 1.2: Simplistic Diagnostic Criteria for Essential Tremor based on the recognised published criteria from TRIG, NIH, and MDS

ET (any of)	**Enhanced Physiological Tremor**
Head tremor	No head tremor
Postural and action tremor visible on examination and reported to interfere with tasks	Lone postural tremor and/or barely noticeable action tremor not reported to interfere with tasks

1.5.1.1.1.2.2 *Physiological tremor*

A normal phenomenon that occurs in all contracting muscle groups, ranges in frequency from 8 to 12 Hz. Although seldom visible to the naked eye, physiologic tremor may be detected when the fingers are firmly outstretched.

1.5.1.1.1.2.3 *Enhanced physiological tremor*

- Both of;
    - Easy visibility of the tremor, mainly postural and high frequency
    - No evidence of underlying neurological disease
- 8 to 12 Hz
- Enhanced under conditions of stress, anxiety, fatigue, exercise, cold, hunger, stimulant use, alcohol withdrawal, or metabolic disturbances, such as hypoglycemia or hyperthyroidism.
- Often difficult to distinguish from essential tremor and it is proposed by some authors that it is a forme fruste of ET. This issue remains unresolved and it is currently seen as a different clinical entity.

1.5.1.1.1.2.4 *Indeterminate tremor syndrome*

- Fulfill the criteria for classic ET and
- Has additional neurologic signs that are insufficient for diagnosis of another neurologic disorder.
- Previously categorized as "possible ET type Ib" by the TRIG criteria

1.5.1.1.1.2.5 *Primary orthostatic tremor*

- A postural tremor of lower limb, trunk, and, possibly, upper limb muscles during stance yet absent when sitting or reclining.

- Orthostatic tremor is suppressed upon walking but is present in severe cases during gait.
- Sparse clinical findings – visible and occasionally only palpable fine amplitude rippling of legs when standing
- High frequency, 13 to 18 Hz present when standing but absent during tonic activation when sitting.

1.5.1.1.1.2.6 *Dystonic tremor syndromes*

Although consensus has not been reached concerning the definition of dystonic tremor syndromes, authors of the MDS consensus criteria have proposed a number of definitions within this general category.

- **Dystonic tremor** – tremor of a body part affected by dystonia
- **Tremor associated with dystonia** – tremor occurs in a body part not affected by dystonia but the patient has dystonia elsewhere
- **Dystonia gene associated tremor** – tremor as an isolated finding in a patient with a dystonic pedigree

1.5.1.1.1.2.7 *Task- and position-specific tremors*

- These tremors occur upon performance of specific, highly specialized, motor activities.
    - Writing tremors
    - Occupational tremors
    - Isolated voice tremors

1.5.1.1.1.2.8 *Parkinsonian tremor syndromes*

- Any form of pathologic tremor

- Patient has PD according to the brain bank criteria

1.5.1.1.1.2.9 *Cerebellar tremor syndromes*

- Pure or dominant intention tremor, uni or bilateral
- Frequency mainly below 5Hz
- Postural tremor may be present but no rest tremor
- Other forms of tremor, such as postural tremor, are deemed of cerebellar origin only when coexistent with other cerebellar signs.

1.5.1.1.1.2.10 *Holmes tremor*

- A symptomatic rest, intention, and possibly postural tremor due to lesions affecting the cerebellothalamic and dopaminergic systems— the brainstem, cerebellum, and thalamus and, possibly, their pathways.

1.5.1.1.1.2.11 *Palatal tremor*

- These rhythmic movements of the soft palate may occur subsequent to lesions of the brainstem and cerebellum, they are associated olivary pseudohypertrophy.

1.5.1.1.1.2.12 *Neuropathic tremor syndrome*

- Certain peripheral neuropathies are commonly associated with tremor, primarily kinetic and postural tremor of the affected extremities.

1.5.1.1.1.2.13 *Drug-induced and toxic tremor syndromes*

- Pharmacologic agents used to treat other medical conditions may induce tremor

1.5.1.1.1.2.14 *Psychogenic tremor*

- Suggested by a history of somatisation, the presence of unrelated neurologic signs, and sudden tremor onset or remissions.
- Additional signs may include a decrease of amplitude or variation of frequency upon distraction, unusual combinations of postural/intention and rest tremors, and co-activation resembling voluntary co-contraction during passive movements of a trembling limb about a joint.

1.5.1.1.1.2.15 *Myorrhythmia*

- A slow tremor of 2 to 4 Hz as seen in patients with lesions of the brainstem (similar to Holmes tremor) [86].

1.5.1.1.1.3 The *Epidemiology of Tremor*

ET is the most common pathologic tremor. The world-wide prevalence of ET (when including only community based studies which use a defined and accurate diagnosis of ET) ranges from 4.1–39.2/1000 across whole populations, becoming increasingly common with age; prevalence increases to 13.0-50.5/1000 in persons above 60 years of age [91]. The prevalence of ET appears to be higher in whites than blacks even within the same geographic location[92].

1.5.1.1.1.3.1. *Tremor Literature Review*

In the review of the literature on the epidemiology of tremor, I looked for community based epidemiological studies from SSA on tremor in general, the only studies of this nature looked specifically at essential tremor. There are no epidemiological studies on the prevalence of other tremors. Literature on unspecified tremor, observed as part of general neurological disorder surveys have only been briefly included in this review as results of this nature are impossible to interpret, put into context and compare with other studies. Therefore this section of the thesis will focus on Essential tremor, as the most common and well described tremor disorder. Worldwide review articles were also included in this review and references listed in relevant publications examined. Hospital based data was not included.

1.5.1.1.1.3.2. *Why hospital based prevalence studies cannot be used specifically in ET epidemiology*

A large number of patients may have undiagnosed ET in the community. In prevalence studies from Finland [93] and Singapore [94], only 2% and 10%, respectively, had been previously diagnosed. Only 10 cases of ET were identified amongst 2.1 million patients seen in outpatient clinics in a teaching hospital in Nigeria over a 25 year period [95]. As with all the neurological disorders, hospital based studies will grossly underestimate the prevalence of ET in SSA, and perhaps, peculiar to ET, in the rest of the world as well.

1.5.1.1.1.3.3 *The Prevalence of Essential Tremor in SSA*

As described above estimates of the prevalence of ET vary widely. There are few existing data, from reliable community based studies, on the prevalence of ET in sub-Saharan Africa (SSA) [91]. Previous community based studies in SSA investigated all neurological diseases, not just ET and were performed in the 1980s. The studies preceded the ongoing increase in the elderly portion of the population in SSA which is likely to substantially increase the number of prevalent ET cases. Only two cases were

reported in Nigeria from a population of 20 000, which gave a crude prevalence rate of 10/100 000 [3], and three cases in Ethiopia in a population of nearly 61 000 gave a crude prevalence rate of 5/100 000 [5]. Age standardised prevalence rates were not reported.

There have subsequently been two reliable studies of ET conducted in SSA, one in Tanzania in the same study site as is the subject of this thesis in 2008 and one more recent study from Nigeria, published in 2012.

Dotchin et al [96] completed the first large scale community based 2 phased epidemiological survey specifically of ET in SSA. The denominator population was accurately recorded as part of a census in this longstanding DSS as 161 071. A screening questionnaire was utilised but no effort was made to validate this questionnaire. Positive responders were examined by a UK physician and diagnoses were made in accord with the standard diagnostic criteria from the MDS. Unfortunately validation by a movement disorder expert was not possible. 222 patients responded positively to the screening questions and other methods were utilised to ensure no cases were missed, these identified a further 43. In all 65 (38 men, 27 women) individuals were diagnosed with ET. The mean age was 72 years and mean duration of symptoms was 11.3 years. The crude prevalence rate was 41/100 000 and age standardised prevalence compared with the UK population (2001) was 82/100 000. 61.5% of cases were aged 70 years and over.

The prevalence rates of ET in Hai were found to be higher than previously reported from SSA, but lower than those in the developed world. The methodology used may underestimate prevalence as people with mild symptoms may not have responded positively to the screening questions. In an American study, 13 of 46 patients diagnosed with ET had not reported tremor on screening questions [92] and further studies by Louis et al[97] reported that patients with mild tremor may not screen positively, stressing the importance of examining all subjects if possible. However

equally it could be argued that those persons with mild tremor may have physiological tremor, or tremor induced by the anxiety of seeing a doctor and therefore examining patients may increase false positives and reduce the specificity of screening. Dotchin et al's study had further limiting factors; a lack of video recordings or other methods of diagnosis verification by an expert physician and the lack of validation of the screening questionnaire, which might have been performed by examining a proportion of those participants that screened negative if a full pilot study was not possible.

Subsequent to the work performed by Dotchin and colleagues, Okubadejo et al [98] performed a multi phased door-to-door survey investigating the prevalence of essential tremor (ET) in an urban Nigerian community. Selection bias was avoided with the random selection of 3000 residents of an urban centre in Lagos. The sample size was modest and was dictated by financial and logistic constraints, as well as commitment to robust methodology to ensure maximum case discovery . Screening was carried out using a questionnaire to detect symptoms of movement disorders. 234 participants responded positively with regarding to tremors and were rescreened using an ET-specific questionnaire, a face-to-face interview and neurological examination, by an expert neurologist. This increased diagnostic accuracy. Although the performance of the ET specific questionnaire was examined and found to have very high sensitivity and specificity, the performance of the general movement disorder questionnaire used initially was not evaluated. Diagnosis of ET was based on the Movement Disorders Society (MDS) consensus diagnostic criteria for ET[86], allowing easy comparison of results. Of the 3000 participants, forty responded positively to the ET screening questionnaire, of which 36 (19 females and 17 males) had a final diagnosis of ET, giving a crude prevalence of 12 per 1000 (95% CI = 8.1- 15.9). Prevalence was age adjusted according to the "WHO New World population" and found to be 23.78/1000. Gender specific crude prevalence was 10.3 /1000 in males and 14.3/1000 in females. Age specific prevalence increased with advancing age in both sexes.

This Nigerian study was conducted in an urban centre, therefore there is likely to be a smaller percentage of elderly participants than if it was conducted in a rural setting.

Age adjustment does however allow for the population structure to be accounted for enabling comparison of Okubadejo's findings with those of other researchers.

The crude and age-standardized prevalence data obtained by Okubadejo et al. fall within the range previously reported from other populations (4.0 – 39.2/1000), but are higher than the values from earlier studies based in a rural community in the same ethno-geographical zone, but published three decades ago by Osuntokun et al[3]. The earlier study reported a crude prevalence rate (0.1/1000) ten times lower than the present study. It is likely that the latter more robust studies present much more reliable figures, more applicable to today's SSA society. In addition direct comparison of these data presupposes that the population structures of these countries are similar, they may not be. Further the lack of age-adjustment in the earlier West African study[99] and that of Tekle-Haimanot [40] make the conclusions that can be derived regarding differences in prevalence tentative.

It is not obvious why there are such differences in prevalence rates in the two SSA communities that are the focus of the two more recent studies in Tanzania and Nigeria. It is however worth noting that although age adjustment was carried out in both populations there is significant variation in the standard population used and so direct comparison of the results may be difficult. More studies are required to see if there is a true variation in the prevalence of ET in SSA, it is perhaps still likely that differences in prevalence estimates can be attributed to differences in study design and methodology, study population structure and diagnostic criteria.

The more recent Nigerian study does present prevalence rates more in keeping with other world epidemiological data. A recent study in Sile, Turkey demonstrated a crude prevalence rate of 30/ 1000 in persons above 18 years of age [100]. A recent study from Italy reported age and sex adjusted prevalence rates of 12/1000 for women and 19/1000 for men[101].

1.5.1.1.1.3.4 *Risk factors for ET and the effect on prevalence*

Reasons other than methodological differences for varied worldwide prevalence could be differences in exposure to risk and aetiological factors. Different risk factors are explored below with relevance to the literature:

1.5.1.1.1.3.4.1. *The effect of ageing on the prevalence of ET*

Aging is the most consistent documented risk factor associated with increasing prevalence of ET [102] a finding also corroborated by Okubadejo et al's[98] and Dotchin et al's [96] studies detailed above. There have been various studies specifically reporting the crude prevalence of essential tremor in the elderly (some where the aged population is the only focus of the study, some where the prevalence in this age group is specifically highlighted). Das et al [53] performed a study of 5430 people aged 60 years and older in India and found the crude prevalence of ET to be 13.76/1000. Benito-Leon et al [103] reported a crude prevalence rate of 48/1000 amongst 5278 people aged 65 years and older in a Spanish community study. Gilik et al reported a crude prevalence of 7.8/1000 in those aged 65 years and older, in a community door to door survey of 900 individuals. Louis et al [104] assessed the prevalence of essential tremor in 1965 people aged 66-102 in Manhattan US; they found that the crude prevalence rate in this whole population was 55/1000. However the prevalence for those aged over 95 was 217/1000 or approximately 1 in 5. Interestingly they found that for each 1 year of advancing age the risk of ET increased by 14%.

1.5.1.1.1.3.4.2. *The effect of family history on the prevalence of ET*

Genetics have also been implicated in ET as demonstrated by clustering of the condition within families [105]. About a third of the participants with ET reported by Okubadejo et al[98] had a positive family history of tremor in a first degree relative and it is possible that undiagnosed ET and recall bias would have lowered the reporting of a positive family history. Dotchin et al's [96] ET patients also reported a family history in approximately one-third of patients (28%). In some cases the first degree relatives had died at a young age, making it possible that they may have developed tremor had they lived long enough. It is however difficult to obtain accurate data on

family history in ET, Prakash et al [106] report the inaccuracy of family history reporting, with patients tending to under report family members with tremor, especially in mild cases, resulting in a sensitivity of only 43%. However, the specificity of these reports were high (94%), so if a family member is recorded as having a tremor, they probably do have ET.

1.5.1.1.1.3.4.3. *The effect of gender on the prevalence of ET*

A gender predilection has previously been reported in some ET studies; several studies have suggested ET is more common in men than in women [92, 93, 101, 107], but an older community based study in Papua New Guinea suggested women were more commonly affected than men [108]. Other studies [96, 98], have not found any male to female differences. The basis of a gender predisposition is unproven and there are no strong biological indications that could explain such findings. However, if such a difference does exist it is likely that environmental factors such as occupational and recreational exposures may contribute.

1.5.1.1.1.3.4.4. *The effect of ethnic variation on the prevalence of ET*

Significant ethnic variation has been reported by Louis et al [109] in the US where Caucasians were found to be five times more likely that African Americans to have physician diagnosed ET. It was however unclear from this study whether this reflects differences in access to medical care and health seeking behaviour of the communities or whether ethnic variation does exists. Another study in New York showed higher rates in whites compared with African Americans, with Hispanics having an intermediate prevalence [92].

1.5.1.1.1.3.5 *The Phenotype of ET*

Dotchin et al [96]found that the location of tremor in their patients was similar to that reported from other studies. Upper limb tremor was most common (80% of cases), followed by head tremor (54%). Head tremor was significantly more common in women ($p = 0.002$), as has been reported in other studies[110, 111]. Louis et al [92]

reported that 73% of patients had arm tremor and 27% had arm and head tremor. Okubadejo et al [98]reported that 100% of their patients had upper limb tremor whilst none had tremor of any other body parts including their head. This probably demonstrates that they underestimated the prevalence of ET by failing to pick up those patients with head tremor as it was not included in their initial screening questions.

Dotchin et al [96] found that some patients with severe tremor had a resting component (18.5%). In previous studies, up to 1 in 5 patients with ET have been reported to have a resting component [112].

Dotchin et al [96]reported that tremor was asymmetrical in 37% of patients. A study from New York reported that mild to moderate asymmetry was common in patients with ET, with nearly 90% of patients having a small but detectable difference between the two sides [113]. Okubadejo et al [98]also found that the majority of their patients reported that their tremors started asymmetrically but by the time of examination none of them demonstrated significant asymmetry, they speculate that ET is often thought to arise asymmetrically as it is noticed more in the dominant hand.

Dotchin et al [96] found only a third of patients reported an improvement in their tremor in response to alcohol in comparison with 50% in a previous study [113]. However, when this low percentage was adjusted by removal of those that did not drink alcohol (25%), it was found that nearly half of those that did drink alcohol noted some improvement more in keeping with previous literature.

1.5.1.1.1.3.6. *The social implications of ET*

In SSA it has been found that patients suffer from stigma because of their tremor [96]. This may make them less likely to answer questions regarding the prevalence of tremor correctly. Tremor is often thought to be a sign of alcoholism or evil spirits.

Social stigma as a result of neurological problems is common in Tanzania and awareness of neurological conditions is low, as in most of SSA. ET is associated with significant functional disability particularly in persons with an upper limb tremor [114]. Work and productivity can be significantly impacted by ET. In the UK and the US, up to 25% of patients with ET have to change jobs or retire because of their symptoms [105, 115]. The social and emotional burden can be partially relieved with treatment. To make progress, a change of local beliefs behind ET and other neurological conditions is necessary, as is education of the population and community health workers.

1.5.1.1.1.4 *Investigation of Tremor*

Routine investigations include thyroid function tests (TFTs) and copper and caeruloplasmin (if aged <50years). The indication for other investigation depends on clinical signs found on examination and differential diagnosis, they may include the following: cerebral MRI, genetic studies, Dopamine Transporter (DAT) or Positron Emission Tomography (PET) scan, NCS, Investigation for causes of neuropathy, Porphyria screen, Toxicology studies [116].However none of these investigations are routinely available in SSA and clinical diagnosis remains the standard.

1.5.1.1.1.5 *Management of Tremor*

The management of tremor depends on its severity and underlying cause. Propranolol (up to 320 mg/day) and primidone (up to 250 mg three times daily) are the main treatments for essential tremor; they may also be used for patients with dystonic tremor. Clonazepam can also be useful for patients with essential tremor. The treatment of choice for severe head tremor is intramuscular botulinum toxin. Propranolol, primidone, anticholinergics, and botulinum toxin may all have a role in treating other tremors but their efficacy has not been subject to rigorous study. Anticholinergic medications, direct acting dopamine agonist drugs, and Levodopa preparations can all variably decrease Parkinson's disease tremor.

Neuropathic tremors, tremor associated with multiple sclerosis, and other cerebellar tremors are difficult to treat effectively; the medication mentioned above can be considered but is often ineffective. Primary orthostatic tremor can be treated with

clonazepam. Phenobarbitone or levodopa can be tried as second line alternatives if clonazepam is ineffective, contraindicated or side-effects prohibit its use. Holmes' tremor can be treated with levodopa, dopamine agonists or anticholinergic drugs.

Stereotactic surgery can be effective in many of the tremor syndromes including Parkinson's disease [116].

The only medications widely available for treatment in sub-Saharan Africa are non selective beta blockers e.g. propranolol, phenobarbitone and Levodopa and supply of these medications may be unpredictable.

1.5.1.1.1.3.6. *The diagnosis and treatment gap of ET*

Okubadejo et al [98] reported that only 1 (2.8%) person had a prior diagnosis of ET and this was the only individual on treatment. Dotchin et al [96] found that no one they identified was receiving medication for tremor and very few had sought any medical help. Several factors including differing severity and impact of ET on activities of daily living, non-recognition or poor awareness of ET as a neurological or medical disorder amenable to treatment, and limited access to care may contribute to the treatment gap, these all highlight that prevalence of ET derived from hospital-based studies will reflect an low assessment of prevalence. Low treatment levels are also seen in developed countries; as many as 75-99% of patients with ET detected through population-based studies are reported to be previously undiagnosed and untreated [92, 117]. No studies from SSA have assessed the responsiveness of symptoms to simple drug treatments.

1.5.1.1.1.3.7 *The epidemiology of ET in summary*

ET is a common disorder worldwide, with a similar clinical phenotype and is largely undiagnosed. Prevalence increases substantially with age, an important finding given the scope of this thesis. It may be that ET is less common in black communities but further data is required. Improved public awareness and physician education is required to ensure that ET is recognized, and treatment offered where appropriate.

1.5.1.1.2 *Parkinsonism and Parkinson's disease (PD)*

1.5.1.1.2.1 *Features*

PD is a progressive neurodegenerative condition resulting from the death of the dopamine-containing cells of the substantia nigra. People with PD present with "parkinsonism", this has 4 cardinal symptoms and signs; rest tremor, bradykinesia, rigidity, and postural instability.

Parkinsonism can also be caused by drugs and other neurological conditions. These include multiple cerebral infarctions and degenerative conditions such as the Parkinson Plus syndromes, progressive supra-nuclear palsy (PSP) and multiple system atrophy (MSA). These are less common than idiopathic PD.

Although PD is predominately a movement disorder, other impairments of body function are frequently associated including psychiatric problems such as depression and dementia. Autonomic disturbances and pain may also occur. As the conditions progresses, significant disability and impaired quality of life occurs [118].

1.5.1.1.2.2 *Diagnostic criteria*

There is no consistently reliable test that can distinguish PD from other conditions such as Essential Tremor, Progressive Supranuclear Palsy, Multisystem Atrophy, Corticobasal Degeneration, Dementia with Lewy Bodies and drug induced Parkinsonism. The diagnosis is primarily clinical, based on history and examination [118]. Diagnosis of PD can be made without the aid of costly resources if clinical criteria are adequately applied, very useful in resource poor areas like SSA [13].It is generally accepted and recommended by the National Institute of Clinical Excellence(NICE) [73] that the diagnosis of PD should be based on clinical findings using the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria (BBC). Most experienced specialists have adopted these criteria. Studies have compared the accuracy of UKPDS-BBC with post mortem diagnosis finding that its application improves accuracy from 70% to 82% [119, 120].

A more recent UK PDS Brain Bank study revealed the sensitivity of the final UKPDS clinical diagnosis was 91% and the specificity positive predictive value were 98% and

99% respectively. The accuracy of diagnosis using the Brain Bank criteria increases as the condition progresses [121, 122]. Shrag et al's study published in 2002 also used the UKPDS-BBC, they demonstrated the misclassification of Parkinson's disease in the community in London when this criteria is not always used. They found that when patients with a diagnosis of PD are reviewed by a specialist and strict clinical UKPDS criteria are applied they have other diagnoses in 15% of cases (Multi system atrophy 2.3%, Progressive supranuclear palsy 3.1%, vascular parkinsonism 4.6%, non parkinsonian tremor 3.1%). The authors also found that approximately 20% of patients with PD who have already come to medical attention have received alternative diagnoses (atypical parkinsonism 0.8%, vascular parkinsonism 0.8%, non parkinsonian tremor 7.3%, on antiparkinsonian drugs 1.6%) [123].

The UKPDS-BBC was used to diagnose PD in this study.

1.5.1.1.2.3 *Causes and Risk Factors*

The cause of PD is unknown. Pure genetic forms account for less than 10 to 15% of cases [124]. Risk factors have been suggested but evidence for them is not consistent, they include; exposure to toxins, head trauma, frequent infections, diets high in animal fat and midlife adiposity [125].The most consistent association is an inverse relationship between cigarette smoking and caffeine consumption suggesting a protective effect [126]

1.5.1.1.2.4 *Epidemiology*

1.5.1.1.2.4.1 *Prevalence*

In the literature the prevalence of PD was originally reported to be less in SSA than the rest of the world. Three original prevalence studies were conducted in SSA in the 1980s and 1990s. Two (in Nigeria and Ethiopia) [3, 5] were part of community surveys for all neurological disease. One study from Togo [127] looked at the prevalence of neurological disorders along with endemic goitre.

All three studies used the WHO screening instrument and protocol for neurologic diseases. The screening questionnaire and protocol is not specific for parkinsonism, it includes one question on tremor and two related to bradykinesia (out of 15) and 5 (out of 7) tasks could relate to parkinsonism. The studies predated the HIV epidemic.

Osuntokun et al [3] performed a pilot study and then a community prevalence study in a rural community (the Yoruba tribe) in Nigeria in 1986. A population of 20,000 was surveyed, 6% were over 60 years of age. The study used diagnostic criteria for PD (any three of four diagnostic signs; resting tremor, rigidity, bradykinesia and postural instability) this increased sensitivity and accuracy of the conclusions with regard to prevalence. The crude prevalence rate was 10/100,000. Indirect age adjustment to the black population in Copiah, Mississippi allowed direct prevalence rates to be compared in the two populations. The crude prevalence rate was 59/100,000 and the age adjusted prevalence rate was 67/100,000 for those over 39 in Nigeria, five times lower than the 341/100,000 reported from the US [3].

Tekle-Haimanot et al [5] conducted a community survey in rural Ethiopia in the late 1980s in a population of 60,820, the reported crude prevalence rate was 7/100,000. Age standardisation was not performed. The diagnostic criteria for PD or Parkinsonism were not specified.

The two studies collectively reported from Togo in 1989 and 1995 both yielded crude prevalence rates of 20/100,000, they used the WHO protocol. No diagnostic criteria for PD were specified; however, two levels of diagnostic certainty were allowed (i.e., definite and possible) based on clinician's judgment. Age standardisation was not performed [127].

All of these studies were community based, hospital based surveys have not been included in this review (unless a community component was specified) as such studies are likely to greatly underestimate the prevalence rates. In SSA most patients with this chronic disease reside in the community and are not hospital in-patients (unless admitted because of a complicating or unrelated illness).Many do not present to hospital at all for geographical and financial reasons. Further, in SSAs there are few

neurologists and little neurological education of primary care givers to allow accurate diagnoses to be made. Despite the inclusion of only community based studies methodological differences and inconsistent diagnostic criteria may contribute to inaccuracies and differences in the prevalence rates. It is also unclear in some studies whether all cases of parkinsonism or just idiopathic PD were included.

In 2006 authors from my research group conducted a prevalence study of PD in the whole population of the Hai district DSS [128]. The denominator population was gained from a prior census and was 161,071. The prevalence of essential tremor was also reported, however this study was designed to identify patients with PD and therefore a six question tool was specifically designed for this purpose by the authors. Standard diagnostic criteria were used (UKPDSBCC) and cases were verified by a doctor trained in movement disorders and a movement disorder expert (the latter through the use of scripted videos). Other means of case discovery were used to increase diagnostic yield and the accuracy of the prevalence rates presented. The sensitivity and specificity of the screening questionnaire were not studied or presented by Dotchin et al. Other limitations included possible under detection due to stigma and one family member answered on behalf of the rest of the household which has been reported to reduce sensitivity [35, 129]. The age standardised (according to the UK population) prevalence rate found was 40/100,000. This figure is more in keeping with the rate of 67/100,000 reported in African Americans in Manhattan [130] but is still lower than other studies presented in the developed world. Dotchin et al's paper also presented male and female age specific rates in five year age bands. For the population aged 65 and over the crude prevalence rate was 2.22/1000 and age adjusted prevalence rate (according to the WHO standard population) was 2.07/1000. The authors felt that standardised methodology and more comparable diagnostic criteria played a part in the detection of more cases of PD in this population.

Winkler et al[131] reported the prevalence of parkinsonism in a population of northern Tanzania in 2010. The fieldwork for this study was carried out between 2003 and 2005. They performed hospital and community studies. In the former all patients admitted to the Haydom Lutheran Hospital (HLH) in northern Tanzania over an 8 month period (n=8676) with neurological symptoms and signs were assessed by a neurologist for

symptoms and signs of PD using the UKPDSBBC. The exact timing of the 8 month period is not specified. No consistent assessment (i.e. formal questionnaire) for neurological symptoms and signs prior to referral for neurologist review was used. The UKPDSSBBC was used by the assessing neurologist however, the diagnosis was limited by lack of levodopa to allow a dopamine challenge to take place.

The community section of the study involved selecting a population of nearly 1600 subjects aged 50 years and over in the southwest corner of the Mbulu district using random and cluster sampling. Other efforts were made to eliminate bias in subject selection regarding distance from HLH. A pilot study was performed to assess the feasibility of a 12 point questionnaire specific to the identification of parkinsonism. Sensitivities and specificities were not presented or apparently tested in this population (Validation had previously occurred in Spain in a Caucasian population). In addition to these limitations authors state that many different language group were spoken to in the study region and Kiswahili was often not understood. The questionnaire was only translated and back-translated in Kiswahili. An additional caveat of "patients with symptoms and signs relating to acute alcohol should be excluded" is mentioned in the methodology; however this had not been validated in the original questionnaire. A western neurologist reviewed all positive responders for a diagnosis of PD using the UKPDSBCC criteria. No second opinion on diagnoses was sought in either the hospital or the community study.

From the hospital study 2 patients were found to have definite Parkinson's disease, 1 had possible PD, and 5 had parkinsonism (the possible cause of which was not elaborated). The denominator population was quoted to be 8676 admissions and the authors quote a crude prevalence rate of 1/1000 (the crude prevalence of Parkinson's disease is 0.35/1000). There were no details with regard to age groups and therefore adjustments cannot be made. Further, the study is hospital based which means it is not possible to report a prevalence rate relevant to the local community for the reasons given above. Other factors that would affect prevalence calculations include:

All the patients were men; they are presumed to have preferential health care access over women.

The subjects identified may have come from a very wide area and therefore the denominator population is ill defined.

None of the patients identified presented to hospital because of their parkinsonism.

For the community the questionnaire was vague, presumably to increase sensitivity, Even so, only 18 positive responders were found, in addition only one diagnosis of essential tremor and 2 diagnoses of motor neurone disease (MND) were made. None of the community based subjects were diagnosed with parkinsonism or PD, a prevalence of zero. The authors calculate 95% confidence intervals and conclude that prevalence could fall between 0 per 1000 (the best estimate based on their observation) and 2.5/1000.

Table 1.3: Community Prevalence Studies of Parkinsonism in SSA

Country	Crude Prevalence	Age Standardised
Nigeria[3]	Parkinson's disease: 0.10/1000 Parkinson's disease >39yrs: 0.59/1000	Parkinson's disease >39 yrs: 0.67/1000*
Ethiopia [5]	Parkinson's disease: 0.07/1000	
Togo[127]	Parkinson's disease: 0.20/1000	
Tanzania[131]	Parkinsonism in hospital: 1.00/1000 Parkinson's disease in hospital: 0.35/1000 Parkinsonism in community in the 50 years and over population established using statistical analysis:2.35/1000 Actual prevalence of Parkinsonism in the community: 0.00/1000	
Tanzania [96, 128]	Parkinson's disease: 0.20/1000 Parkinson's disease >64yrs: 2.22/1000	Parkinson's disease: 0.40/1000 Parkinson's disease >64yrs: 2.07/1000**

* Indirect age adjustment to the black population in Copiah, Mississippi

**Direct age adjustment to UK population for 2001

The prevalence of parkinsonism and Parkinson's disease has been reported in other world regions however due to the extensive nature of this data, I have focussed on presenting and appraising data from key sources, namely Bharucha et al's [48, 132] prevalence study in Parsi Indians and Zhang et al's [133] prevalence study from rural and urban China to represent other developing countries and Wickremaratchi et al's [134] prevalence study and meta-analysis from the UK and the EUROPARKINSONISM Collaborative study from Europe [135].

Bharucha et al [132]performed a well-designed specific study on PD, they estimated prevalence rates in Parsis, ethnically different from Indians, between 6-328/100,000 [48, 132, 136-138]. Barucha et al used a standardised questionnaire specifically for PD and did not rely on the WHO generalised screen for neurological disorders [25].In addition they used standardised case definitions. Bharucha et al's [132] results demonstrate that Parsis have an age-adjusted prevalence rate of PD similar to white Caucasians but this figure is two times higher than other Indian studies [51, 58, 132, 137, 139-141]. The study differs from other Indian studies in terms of an urban setting but more significantly it is an ethnically different population, originally from Persia (members of the Aryan or Indo-Germanic family). Prevalence of other neurological disorders including Multiple Sclerosis are also similar in the Parsis to Caucasians [132, 142, 143]. Studies from non-Parsi communities in India show prevalence rates of PD, between 14-41/100,000 [136, 144]. PD forms 5-60% of total movement disorders with variations in geographical areas. PD was more prevalent in rural (41/105) than urban (14/105) population and was more common among men [144]. Age-specific rates increase from 28/100,000 in 4th decade to 573/100,000 in ninth decade [58, 145].

A large cross-sectional prevalence study of Parkinson's disease in China was undertaken in 1997–98 [133]. The authors assessed 29,454 residents aged 55 years and over (identified via a census, it included those in institutionalised care) from 79 rural and 58 urban communities in Beijing, Xian, and Shanghai. These are the 3 regional centres which differ significantly in: economic and medical development, cultural beliefs, lifestyle and life expectancy. Participants were selected through stratified, multistage, cluster sampling. All these methodological considerations exclude bias. A one stage standardised diagnostic protocol was used with good inter-rater reliability. This method was undoubtedly time consuming and expensive but would result in accurate prevalence figures. To increase accuracy second opinions were sought and re-examination performed in the case of disagreement. Standard diagnostic criteria were used [146] and diagnoses were supported by treatment trials and investigations. The authors identified 277 people with the disease and estimated the prevalence of Parkinson's disease for those aged 65 years and over to be 1·7% (95% CI 1·5–1·9)men and women combined, 1·7% (95% CI 1·4–2·0) for men, 1·6% (1·4–1·9) for women. Prevalence for people aged 65 years or older that were standardised

to the 2000 US population was 2·1% (1·8–2·5) for men, 2·0% (1·7–2·3) for women, and 2·1% (1·9–2·3) for both sexes. With the same standardisation method, prevalence for both sexes in Rotterdam, the Netherlands (2·2%), and in seven European studies (1·7%) shows that the prevalence of Parkinson's disease in China is similar to that in developed countries[133]. Standardised estimates for both sexes from a previous Chinese study [147] based on a slightly different age group (60 years and over) were lower (0·1%–1·0%) than this study from Zhang et al even when utilising their data from their 55 years and over cohort which had a prevalence 1·3%. The authors attribute this to the correction of several limitations of the earlier study, they surveyed urban and rural populations in diverse regions and reviewed high numbers of participants to yield statistically precise estimates. Their entire sample (n=29 454) received standardised neurological examinations by trained neurologists, which although expensive does eliminate false negatives that may have been produced by the screening phase.

Wickremaratchi et al [134] performed a prevalence study of PD amongst residents in Cardiff. To locate cases they screened GP databases, prescriptions and neurology clinic notes. Standardised diagnostic criteria were used for final case verification which included a review of notes and direct clinical assessment and therefore had a very high accuracy. A high participation rate was obtained, with 45 out of 54 (88%) of the eligible primary care practices, this provided a population denominator of 292 637 (96% of the Cardiff population).The authors reported a crude prevalence rate of 130 per 100 000 (95% CI 117 to 144) and an age standardised rate of 142 per 100 000 (95% CI 128 156), standardised to the 1997 England and Wales population. Prevalence rates increased with age and the authors found rates for men were greater at all ages; the male to female prevalence ratio was 1.43 (95% CI 1.17 to 1.76; p=0.001). The prevalence of PD in those aged 70-79 and 80+ was 738/100,000 and 1297/100,000 respectively when age adjusted. The authors found that the prevalence of young onset PD was high at 5.4% and 31.2% for PD patients with disease onset below the age of 50 and 65 years respectively. However they concluded that the incidence of young onset PD may be low but disease survival is high and therefore this increases the overall prevalence in the community. The authors overall prevalence rates were very similar to previous UK

studies where the crude prevalence was 113-164/100,000 [148-154]. Differences were felt to be due to heterogeneous methodology.

The authors acknowledge their main limitation was that they clinically examined only one-third of cases and older cases were less likely to be seen. In addition they did not invite cases with a diagnosis of essential tremor, a previous London study found that such patients may be incorrectly diagnosed tremor dominant PD[123, 150]. The authors conclude that there are no major geographical variations in the prevalence of PD in the UK and that the age adjusted prevalence rate has remained relatively stable over the past 40 years.

The authors of the EUROPARKINSON collaborative study [135] assessed and compared the prevalence of parkinsonism and Parkinson's disease in five European populations (France, Italy, The Netherlands and 2 in Spain) using similar methodology and diagnostic criteria. The authors highlight the difficulty of comparing prevalence rates if heterogeneous study methods are used. They have attempted to standardise 3 main aspects of their methodology: screening/"case finding strategy", diagnostic criteria and participation rate. Given the huge scale of this project it is not surprising that there are some discrepancies particularly in France, with case finding and diagnostic criteria, and that participation rate is variable (68-84%). Despite this the authors performed a very reliable community survey (with an unprecedented level of methodological homogeneity) comprising of 14,636 participants aged 65 years or older (which included those institutionalised). The questionnaire was specific for the identification of Parkinsonism although the sensitivities, specificities and methods of validation are not presented in the paper. The authors stress the importance of a community survey with standardised 2 phased methodology rather than reliance on records from primary and secondary care and this is highlighted by the fact that 24% of the subjects with Parkinson's disease were newly detected through the surveys. Thus any study based on previously made diagnoses is likely to underestimate prevalence even in developed countries. Other methods were used to increase reliability across studies; for example the medical records of most parkinsonian subjects were reviewed, by an adjudication panel composed of neurologists from each of the participating centres.

The overall prevalence (per 1000 of the population), age adjusted to the 1991 European standard population, was 23 for parkinsonism and 16 for Parkinson's disease. After adjusting for age and sex, the prevalence figures did not differ significantly across studies, except for the French study in which prevalence was lower but statistically significant. In addition there was no variation in rural compared to urban communities. Prevalence was similar in men and women. Prevalence of both parkinsonism and Parkinson's disease increased steeply with age and authors feel this is the correct conclusion. They felt that studies that demonstrate a decline in the oldest age group have used poorer methods of case discovery and have failed to pick up cases in this age category. There were no significant differences between prevalence rates in men and women. A substantial proportion of patients with Parkinson's disease went undetected in the general population. Large variation in the differing causes of parkinsonism in the different study populations was not accounted for.

1.5.1.1.2.4.1.1 *Variations in the worldwide prevalence of parkinsonism*

Prevalence estimates vary widely across world populations. Recent reports, contrary to previous reports, suggest the prevalence in developed and developing countries may be similar. If the prevalence of PD is indeed lower in developing countries in comparison to developed countries despite age adjustment this may indicate potential differing risk factors, whether these be environmental or genetic they are potentially important. Comparing prevalence studies for PD throughout the world, PD is apparently more prevalent in Caucasians. The Mayeux study [130] from Manhattan was the only study to report an increased incidence (but a reduced prevalence) of PD in African Americans compared with whites, however this may be explained by the fact that the census figures for African Americans in this area were falsely low. In general there is a growing body of evidence that the prevalence (particularly diagnosed) is lower in blacks than whites. A contrary note is that community studies suggest that 42-75% of black individuals are undiagnosed. Further, cases of undiagnosed PD are twice as likely to be African American rather than white. Current strategies for screening and detection of PD are limited because they rely on recognition of

symptoms and signs by affected individuals and this may be affected by race, culture and socioeconomic status[130]. Studies have shown an association of lack of melanin with PD and this may explain racial discrepancies; however more investigation into genetics and the role of melanin and environmental causes of PD are required.

Table 1.4: The Worldwide Prevalence of Parkinsonism and Parkinson's Disease

Country	**Crude Prevalence rate/1000**	**Age Standardised prevalence rate/1000**
Nigeria[3]	0.1-0.59	0.67 (US population)
Ethiopia[5]	0.07	
Togo[127]	0.20	
Tanzania[128, 131]	0.20-2.35	0.40-2.07 (UK population)
Indians – Parsis[132]	0.46	1.92 (US population)
Indians - Non Parsis[32, 53, 137, 145]	0.01-0.21	0.46-1.00 (US population) 3.30 (aged 60 years and over)
China[133]	17.00 (aged 65 years and older)	21.00 (aged 65 years and older) (US population)
UK[134, 148, 155]	1.30	1.39-1.42 (1997 England and Wales population) 16 (aged 65 years and older)
France, Italy, Netherlands, Spain[135]		16.00-23.00 (European population) (aged 65 years and older)
USA [130, 156]		0.61-3.14 (US population)

In conclusion prevalence estimates for Parkinson's Disease (PD) were thought to vary widely across populations[125]. However recent credible reports, contrary to previous reports, suggest that the prevalence in developed and developing countries may be similar when standardised age prevalence rates are applied [124] . Those studies that reflect the prevalence in the whole population as compared with studies of the elderly demonstrate lower prevalence rates. Parkinson's is a disease of the ageing brain,. it

becomes more common with increased age and is one of the many neurological conditions that demonstrate the importance of looking specifically at an elderly population [118].

1.5.1.1.2.4.2 *Incidence*

Few incidence studies have been performed and none in developing countries. In the United state incidence rates have been reported as 13 per 100,000 person-years. Incidence is lower in women, African Americans and by extension Africans, but this latter statement is controversial [157].

1.5.1.1.2.4.3 *Mortality*

Most mortality estimates show a two-fold increased mortality with PD independent of age [158]. PD patients in SSA may be subject to a higher early mortality, contributed to by lack of diagnosis, treatment and support. Life expectancy for patients with PD in Europe was severely limited before the introduction of levodopa, a situation that still exists in SSA. Dotchin et al[128] report the mortality rate of their Parkinson's disease cohort in the Hai district to be 34% for untreated patients within the first year. They also report mortality rates to be higher in women than men, but acknowledge compounding factors; the women were older and had more advanced disease at baseline. Mayeux et al [130] demonstrated increased mortality in black incident cases of PD in comparison to whites or Hispanics.

1.5.1.1.2.4.4 *Burden of disease*

Mathers et al [30] estimate the worldwide Disability adjusted life years (DALYs) for PD are 2,325,000. As it is a disease of older ages those countries with a higher income and an older population are affected the most. However as the population ages in developing countries their DALYs as a direct relation to PD will also increase [159]. Costs of PD include; medication, cost of physicians, cost of hospitals, chronic care facilities and loss of labour of patients and caregivers.

1.5.1.1.2.5 *Interventions*

There are no effective preventative or curative measures for PD. All established interventions are directed at the relief/palliation of symptoms.

1.5.1.1.2.5.1 *Medications*

Levodopa (in a preparation with a dopa decarboxylase inhibitor to increase the central availability of levodopa) is the most widely used therapy for PD. It provides partial relief of PD symptoms. Despite its benefits, chronic side effects after long term use can cause significant morbidity. It is the only medication widely available and in use in developing countries, and is still the gold standard treatment in developed and developing countries alike.

Many other treatments are now available for PD, but levodopa remains the most efficacious. These include; dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine Oxidase Type B (MAOB) inhibitors and amantadine.

No medical treatment has a proven role in preventing progression, but all provide relief of symptoms. Effective management of PD in its early and intermediate stages can be achieved if available drugs are used sensibly [118].

1.5.1.1.2.5.2 *Surgical Management*

Surgical treatment of PD in the form of deep brain stimulation is used in the developed world. In selected patients with advanced disease, responsive to Levodopa, not demented and in generally good health it may provide dramatic improvement [118].

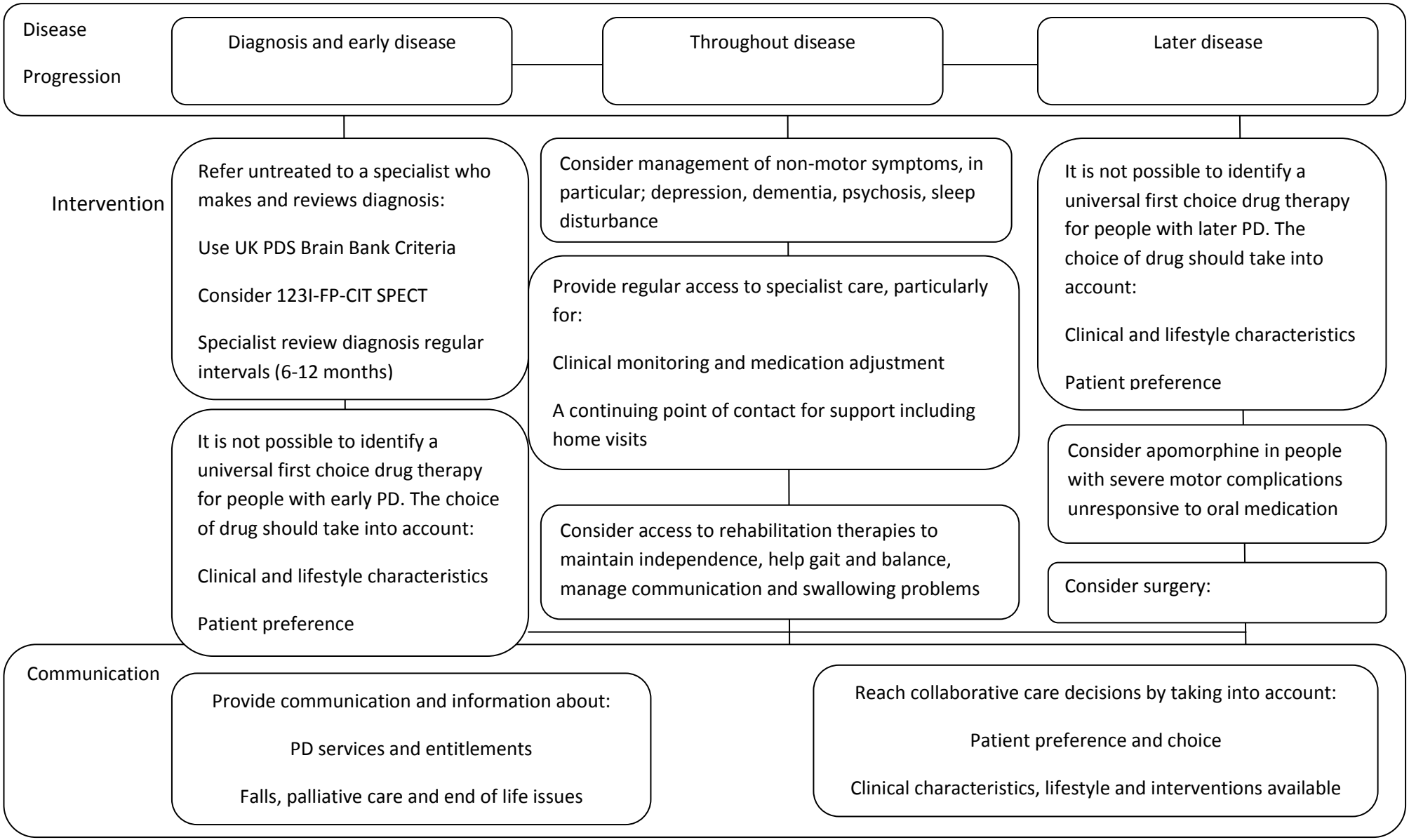
1.5.1.1.2.5.3 *Major challenges in the management of PD*

These are as follows;

- Increasingly complex pharmacological or even surgical requirements as the disease progresses;
- The need for a multidisciplinary team approach for comprehensive management, the consequent need for properly trained professionals (primary care physicians, neurologists, and PD-specialized neurologists, nurses, physiotherapists and speech therapists);

- Widespread access to current PD medications;
- Adequate allocation of resources to establish comprehensive management programmes [13].

Figure 1.3: National Institute for Health and Clinical Excellence (NICE) Guidelines: Interventions for people with Parkinson's Disease



1.5.1.1.2.5.3.1 *Major challenges in the management of PD in SSA*

Dotchin et al [160] detail the "challenge of PD management in Africa". Their recent paper explored how diagnosed and treated people (the great minority) have difficulty because of the intermittent availability of medication, in differing preparations, that is often unaffordable. Follow-up and education for patients, relatives and even healthcare professionals are often lacking. In a further paper [161] they documented their cohorts 3 year follow up; they do acknowledge that it is possible to identify and treat patients with PD in rural SSA but again the availability and affordability of medication needs to be addressed as does the education of healthcare providers.

Cilia et al [162] report the findings of an initiative in Ghana to gain insights into the pathophysiology of PD. They identified patients with PD, provided free treatment and follow up, they improved the abilities of local physicians to manage PD. They identified 45 patients with PD but no denominator population or details of how these cases were identified, was reported. They conclude that a large international Task Force for the diagnosis and treatment of PD in developing countries would be of benefit to the local and world population; this would directly improve the quality of life for those in developing countries but indirectly benefit those worldwide by providing insights into aetiology, pathophysiology and complications. The project has been expanded to Zambia and is planned to include other regions in SSA and South America.

1.5.1.1.2.6 *Other Causes of Parkinsonism*

As mentioned above the symptoms of Parkinsonism are not only caused by idiopathic PD. There are alternative causes;

- Parkinsonian-plus syndromes:
    - Progressive supra-nuclear palsy (PSP)
    - Multiple system Atrophy (MSA)
    - Corticobasal degeneration (CBD)
- Secondary parkinsonism:
    - Vascular

    - Drug-induced
    - Post-encephalitic
    - Hydrocephalus
- Degenerative disorders:
    - Dementia with Lewy Bodies
    - Alzheimer's disease
    - Parkinson-dementia-MND complex
- Genetic disorders:
    - Wilson's disease
    - Huntington's disease (akinetic rigid (Westphal) variant)
    - Dopa-responsive dystonia [76, 163, 164].

There are red flags to suggest a diagnosis other than Parkinson's disease;

- Early falls – Parkinson plus syndromes
- Early dementia – Dementia with Lewy Bodies, PSP, CBD
- Early pronounced autonomic features – impotence, postural hypotension – MSA
- Sudden onset of symptoms – vascular
- No rest tremor
- Symmetrical onset and signs
- Predominance of axial symptoms
- Poor therapy response
- Rapid progression [164]

1.5.1.1.2.6.1 *Progressive Supra-nuclear Palsy (PSP)*

1.5.1.1.2.6.1.1 *Clinical Features*

- Parkinsonism – particularly axial rigidity (neck and trunk movements are more affected than the limbs)
- Early falls

- Loss of vertical eye movements (unable to look up or down on command but able to follow a moving target in the early stages)
- Speech and swallowing difficulty
- Dementia
- Upper motor neuron signs in the limbs and bulbar musculature

The median age of onset is 60 to 65 years. The median disease duration at death is 5.9 to 9.7 years. The age adjusted prevalence is 6/10,000

1.5.1.1.2.6.1.2 *Pathological features*

Neurofibrillary tangles and neurophil threads in the basal ganglia and other parts of the brain stem and tau positive tufts.

1.5.1.1.2.6.1.3 *Response to Levodopa*

Good response is rare [76, 163-166]

1.5.1.1.2.6.1.4 *Diagnostic criteria*

Prior to the production of the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy (NINDS-SPSP) diagnostic criteria, seven different diagnostic criteria were proposed for PSP, they were derived from extensive clinical experience rather than systematically. The NINDS-SPSP rigorously produced diagnostic criteria after a systematic review of the literature and critique of existing diagnostic criteria. The performance of the NINDS-SPSP criteria has been evaluated retrospectively in a pathologically confirmed series and by their application to patients with other dementing and parkinsonian disorders. From this analysis, the NINDS-SPSP criteria appear to have superior specificity, sensitivity, and positive predictive value (50-83%, 93-100% and 83-100% respectively) when compared to other PSP diagnostic criteria. Their use is recommended by the movement disorders society and was therefore used in this study [167].

1.5.1.1.2.6.2 *Multiple system atrophy (MSA) (striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome)*

1.5.1.1.2.6.2.1 *Clinical Features*

- Parkinsonism
    - In the consensus statement – bradykinesia plus one of rigidity, postural instability or tremor is required
    - Tremor is present in 2/3 but <10% have the classic pill rolling resting tremor
- Dysautonomia (early)
    - Orthostatic hypotension
    - Impotence
    - Bladder dysfunction
- Cerebellar dysfunction – ataxia, Dysarthria, nystagmus
- Pyramidal signs – brisk reflexes, up-going (extensor) plantar reflexes
- Stimulus-sensitive Myoclonus
- Extreme forward flexion of the neck (antecollis)

Mean age of onset is 54 years.

1.5.1.1.2.6.2.2 *Response to Levodopa*

Good response seen in 20% and sustained in 13%. Dyskinesias or motor fluctuations may occur. Patients tend to require wheelchairs early due to loss of postural reflexes and ataxia [163, 164].

1.5.1.1.2.6.2.3 *Diagnostic Criteria*

I have used the criteria from the second consensus statement on the diagnosis of multiple system atrophy in this study because these most recent guidelines were created by consensus methodology using the collective experience of active

investigators. It is important to recognise that the criteria do not result from an evidence-based approach and await further validation but high predictive accuracy is anticipated. These criteria are simplified and easier to use than the first consensus statement. They are now widely accepted and used, they are expected to enhance future assessments of the disease [168].

1.5.1.1.2.6.3 *Corticobasal Degeneration*

1.5.1.1.2.6.3.1 *Clinical features*

- Cognitive impairment is a dominant feature occurring within one to three years of onset
- Apraxia
- Cortical sensory changes
- Alien limb behavior
- Parkinsonism manifests as an akinetic-rigid syndrome which is unresponsive to levodopa. Unilateral bradykinesia and rigidity occur with or without tremor.
- Limb dystonia
- Stimulus sensitive Myoclonus

Symptoms usually start after the age of 60. Symptoms spread contralaterally after one year.

Structural imaging shows cortical atrophy and functional imaging shows reduced cortical blood flow in the left fronto-parieto-temporal cortex and striatal hypoperfusion

There is no specific treatment, supportive care is required [76, 163, 164, 169].

1.5.1.1.2.6.4 Vascular Parkinsonism (VP)

Typical cases are lower body Parkinsonism with history of repeated strokes. They often do not respond well to treatment.

Accounts for 3-12% of cases of Parkinsonism [170]. Incidence and prevalence increases with age. Patients with VP are more likely to be older and men are at increased risk.

There are three different pathological patterns;

- Multiple lacunar infarctions with gait disorder, frequently associated with cognitive impairment and pseudobulbar palsy
- Sub-cortical arteriosclerotic encephalopathy (Binswanger's disease) with multiple white matter lesions, together with dementia and progressive gait disorder.
- Lacunar infarction of basal ganglia with clinical presentation indistinguishable from IPD.

1.5.1.1.2.6.4.1 *Clinical Features*

- Lower-body Parkinsonism with abrupt onset and stepwise progression, and without the classical resting tremor.
- Tend to have upright posture and wide base compared to stooped and narrow in IPD.
- Additional features may include pseudobulbar palsy, pyramidal signs with mixed increased tone of spasticity and rigidity, retropulsion, emotional lability, cognitive impairment and incontinence.
- Acute onset only seen in 25% of cases.
- Minimal response to levodopa [163, 164].

1.5.1.1.2.6.4.2 *Diagnostic Criteria:*

I used the Winikates and Jankovic vascular rating scale along with typical clinical features to support my diagnoses of vascular parkinsonism. This is because there is no other clinically relevant scale or specific diagnostic criteria and the gold standard for diagnosis is pathological evidence of a vascular disease in the absence of typical PD lesions (e.g. Lewy bodies). The Winikates and Jankovic criteria allow a purely clinical

diagnosis to be made, although imaging is obviously beneficial it was not possible in this study[171]

1.5.1.1.2.6.5 *Drug Induced Parkinsonism*

1.5.1.1.2.6.5.1 *Clinical Features*

May be clinically indistinguishable from idiopathic PD but a symmetrical presentation is typical.

1.5.1.1.2.6.5.2 *Culprit medication*

- Neuroleptics are most commonly implicated – Typical > Atypical
- Anti-nausea agents (e.g. prochlorperazine, metoclopramide, cinnarizine)
- Sodium valproate and tetrabenazine cause parkinsonism but at much lower rates. Antidepressants and calcium antagonists have been implicated largely through case reports

1.5.1.1.2.6.5.3 *Treatment*

Parkinsonism usually improves on withdrawal of the offending drug but this may take many months. If symptoms and signs persist for 6 months unmasked IPD is the likely diagnosis [163, 164, 172].

1.5.1.1.2.6.6 *Normal Pressure Hydrocephalus*

Parkinsonism may occur with normal pressure hydrocephalus

1.5.1.1.2.6.6.1 *Clinical Features*

Urinary incontinence, gait apraxia and dementia

It is clinically distinguished from PD by;

- Rigidity, tremor and bradykinesia occur less commonly
- No significant response to levodopa
- Structural neuro-imaging

1.5.1.1.2.6.6.2 *Treatment*

- Surgical shunting should be considered.

- However, the risks of surgery may outweigh potential benefit particularly when poor prognostic features including dementia, longstanding symptoms and cortical atrophy are present [163, 164, 173].

1.5.1.1.2.6.7 *Dementia with Lewy Bodies*

1.5.1.1.2.6.7.1 *Clinical Features*

Dementia with Lewy Bodies accounts for about 20% of all dementia. It may present as a predominant dementia with some extrapyramidal signs or initially as parkinsonism with early onset dementia. The term Parkinson's disease with dementia (PDD) has been used when parkinsonism predates the development of dementia by at least one year, and dementia with Lewy bodies (DLB) when dementia starts before that. Visual hallucinations, delusions and psychosis may occur in the absence of dopaminergic therapy. Cognitive decline is progressive but fluctuates.

1.5.1.1.2.6.7.2 *Diagnostic criteria*

Five previous clinical criteria produced through clinical experience have been used for the diagnosis of DLB. In 1996 the Consensus diagnostic criteria for DLB was produced, I used the criteria in this study as it is now the most widely used and has been validated against pathological confirmation. It has a reasonable diagnostic accuracy for this very challenging diagnosis. The sensitivity of a diagnosis of probable DLB varies from 0 to 83% (mean, 49%), specificity 79 to 100% (92%), positive predictive value (PPV) 48 to 100% (77%), and negative predictive value 43 to 100% (NPV) (80%). Prospective studies had a higher diagnostic accuracy than retrospective, and the sensitivity of 0% comes from one study with 4 clinical raters, the results of which substantially reduced the mean sensitivity [163].

1.5.1.1.2.6.7.3 *Management*

Atypical Neuroleptics, e.g. quetiapine, are often useful and cholinesterase inhibitors may also be effective [163, 164].

1.5.1.2 *Episodic and Paroxysmal Disorders*

1.5.1.2.1 *Headaches*

Headache disorders are common, they have a neurological basis, but headache rarely signals serious underlying pathology.

1.5.1.2.1.1 *Epidemiology*

Headache disorders are among the most common disorders of the nervous system. The huge public health importance of headache disorders arises from their causal association with personal and societal burdens of pain, disability, damaged quality of life and financial cost [13]. Worldwide the "headache burden" is thought to be underestimated with headache disorders being often under-diagnosed and under-treated. This is particularly true in developing countries including SSA.

Headache has been highlighted as one of the top ten most disabling conditions worldwide by the WHO and as a result has been the subject of recent global initiatives[10, 174]. The most recent of these initiatives began in 2004, "Lifting the Burden: The Global Campaign to Reduce the Burden of Headache Worldwide" [174, 175], is the collaboration between the WHO and the three major international headache organisations: the World Headache Alliance (WHA), the International Headache Society (IHS) and the European Headache Federation (EHF). The LTB campaign's main aims are to highlight the burden headache disorders represent despite their treatable nature and to improve quality of care worldwide, focussing on education. The LTB campaign's latest document, "Atlas of headache disorders" was published in 2011. An important part of this work was to obtain objective understanding of the scale of headache-related burden, to bring together all existing evidence of the burden of headache worldwide [174, 175].

The worldwide epidemiology of headache disorders is only partly documented. Many studies have been performed on migraine, but data on tension type headache (TTH),

(the most frequent headache disorder), are relatively sparse. In addition, most epidemiological studies have been performed in high income countries in Western Europe and North America. This section of this thesis will describe the burden headache presents to SSA using critical appraisal of the current literature in the field referenced to the rest of the world utilising the recent WHO publications. Population-based studies from SSA that investigate the prevalence of all types of headache have been included and two landmark papers from clinic populations in SSA will also be discussed. The recent publications specific to headache disorders in the elderly population will also be briefly described.

1.5.1.2.1.1.1 Headache Literature Review

In this review I have included population based epidemiological studies from SSA on migraine (ICD-10 diagnosis G43) and TTH (G44.2), the two types that affect the great majority of headache patients. In many studies no distinction is made between migraine with (G43.1) and without (G43.0) aura, this differentiation is difficult in epidemiological studies. As the two types of migraine are probably equivocal with regard to disability, the divisions are only briefly described.. To cover all headaches I have included epidemiological studies that investigated headache in general, or unspecified. Worldwide review articles have been included and references listed in relevant publications examined. The most recent epidemiologically robust publications that examine the prevalence of headaches specifically in the elderly population; however none of these were from SSA. Cluster headaches cause significant burden to individuals, but due to their low prevalence they do not represent as much societal cost and so literature specific to them was not included.

1.5.1.2.1.1.2 *Classification/diagnostic criteria*

The most widespread primary headache disorders include migraine, tension-type headache (TTH) and medication-over use headaches (MOH). The former two are particularly prevalent, globally widespread and are often chronic conditions [174].

The Headache Classification Committee of the IHS produced the gold-standard International Classification of Headache Disorders (ICHD-1) in 1988, they produced specific and unequivocal definitions of all headaches [176]. This classification was incorporated into the International Classification of Diseases in 1997 (ICD-10) [177]. The first edition of the classification has been shown to be reliable, valid and exhaustive. It has been modified to improve its performance in 2004 (ICHD-2) [178], but only minor changes were required to be made. This latest diagnostic criterion has been used to define headache in this thesis. On critical review of the literature the diagnostic criteria used has been noted whilst recognising that the IHS criteria is the international gold-standard.

I have summarized the criteria of relevance in the following table, this is included in the body of the thesis to explain the prevalence figures presented later.

Table 1.5: The International Headache Society Diagnostic Criteria for Headache and its Sub-Types

Main Division	Main Division – IHS ICHD –II Code	Main Division WHO ICD-10NA code	Subdivisions of importance	Sub- Division – IHS ICHD – II Code	Sub-Division WHO ICD-10NA code
Part I: The Primary Headaches					
Migraine	1	G43			
Tension-type headache	2	G44.2			
Cluster headache and other trigeminal autonomic cephalgias	3	G44.0			
Other primary headaches	4	G44.80			
Part II: The Secondary Headaches					
Headache attributed to head and/or neck trauma	5	G44.88	Chronic headache attributed to other head and or neck trauma	5.6.2	G44.88
Headache attributed to cranial or cervical vascular disorder	6	G44.81			

Headache attributed to non-vascular intracranial disorder	7	G44.82			
Headache attributed to a substance or its withdrawal	8	G44.4 or G44.83			
Headache attributed to infection	9	G44.821 and G44.881			
Headache attributed to disorder of homeostasis	10	G44.882	Headache attributed to arterial hypertension	10.3	G44.813
			Headache attributed to hypertensive crisis without hypertensive encephalopathy	10.3.2	G44.813
			Headache attributed to hypertensive encephalopathy	10.3.3	G44.813
Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures	11	G44.84	Headaches attributed to disorders of the neck	11.2	G44.841
			Headaches attributed to disorders of the eyes	11.3	G44.843

			Headaches attributed to disorders of the ears	11.4	G44.844
			Headaches attributed to disorders of the teeth, jaws or related structures	11.6	G44.846
Headache attributed to psychiatric disorder	12	R51			
Part III: Cranial Neuralgias Central and Primary Facial Pain and other headaches					
Cranial Neuralgias and central causes of facial pain	13	G44.847, G44.848 or G44.85	Trigeminal Neuralgia	13.1	G44.847
Other headache, cranial neuralgia, central or primary facial pain	14	R51	Headache unspecified	14.2	R51

[179]

The definition of when a headache becomes a "headache disorder" is variable within the literature, but is clearly defined by the WHO and is as follows;

- "A current or active headache disorder" is one that has been "symptomatic at least once within the last year".
- "A chronic headache disorder" comprises headaches on 15 or more days per month. This is generally called Chronic Daily Headache (CDH). It is mainly used to describe TTH, but in many headache studies, the term is used regardless of whether the headache is TTH or not [174, 178].

Most headache epidemiological studies provide 1-year prevalence estimates, i.e. headache occurring during the last year. In other studies, participants were asked about headache during their whole life (life-time prevalence).It is therefore very difficult to compare results from epidemiological studies of headache and there is a need to standardise data collection as with all epidemiological studies.

For the purpose of this study we enquired about recurrent headaches that were problematic to the patient, i.e. the headache affected their daily activities.

1.5.1.2.1.1.3 Level of burden of headache disorders

Headache disorders impose substantial personal and society burden. In the Global Burden of Disease Study (GBDS) [159], migraine alone was found to account for 1.3% of years lost due to disability (YLD) worldwide. Current calculations indicate that the disability attributable to tension-type headache is even larger. Therefore according to the WHO headache disorders are amongst the top 10 disabling conditions for the whole population, and amongst the top five for women [180].There are of course regional variations but headache disorders are a worldwide issue, affecting people of

all ages, races, socio-economic groups and geographical areas. No significant mortality is associated with the great majority of headaches, particularly primary disorders, the cost is significant morbidity, disability and financial loss[174].

1.5.1.2.1.1.4 The prevalence of headache disorders

Globally, the percentages of the adult population with a current headache disorder are: general headache 46%-75%, migraine 11% (with male to female ratio 1:3, apparently hormonally driven), TTH 42% (on average but >70% in some populations)[181] and CDH 3% (range 1.0-4%) [180, 182]. Much of the CDH may be attributable to MOH but the epidemiological data is lacking. MOH is more prevalent than other secondary headaches affecting 1% of some populations[183, 184]. In general women more than men are affected by headache disorders. In epidemiological studies from Africa the prevalence of general headache is lower at 22%, as is the prevalence of migraine. These figures are generalisations and averages that are not applicable to many world regions, particularly SSA as limited data from these areas were included due to the paucity of good quality studies. Gaps in the knowledge need to be filled to inform health policy. Furthermore, many of the epidemiological studies focussed on migraine, while the more common TTH and the more disabling CDH received little attention.

The table below demonstrates the mean 1 year prevalence (%) in adults aged 18-65 years of all headaches, migraine, TTH and MOH from population-based studies by WHO region. This is from the recent WHO 2011 "Atlas of headache disorders" and includes only the most epidemiologically robust data. As a result there were very few studies from Africa (n=2) and there was no inclusion on data reporting headaches in elderly populations. The results are slightly confused and difficult to interpret; for example prevalence for individual headaches may be higher than that for all headaches, because they are the results of different studies. The studies looking at specific headaches may have made greater effort to detect and include less frequent headaches. This illustrates the need for more robust epidemiological data.

Table 1.6: Mean 1 year Prevalence (%) of All Headaches, Migraine, Tension Type Headache and Medication Overuse Headache in Adults Aged 18-65 years from Population-Based Studies by World Health Organisation Region

	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific
All Headache	21.6 (n=2)	46.5 (n=1)	78.8 (n=2)	56.1 (n=8)	63.9 (n=1)	52.8 (n=4)
Migraine	4.0 (n=2)	10.6 (n=1)	6.8 (n=2)	14.9 (n=9)	10.9 (n=1)	10.4 (n=6)
TTH	Nr	32.6 (n=1)	Nr	80.0 (n=2)	34.8 (n=1)	19.7 (n=3)
MOH	Nr	Nr	Nr	1.0 (n=3)	1.2 (n=1)	Nr
CDH	1.7 (n=2)	4.0 (n=1)	Nr	3.3 (n=3)	1.7 (n=1)	2.1 (n=3)

n=number of studies in the WHO region contributing to the reported mean
Nr=not reported. Indicative of lack of relevant studies rather than absence of the disorder[174]

The recent review article by Stovner et al [180] comprehensively documented the prevalence of headache worldwide and found the following results. The global prevalence of current headache to be 47%, current migraine 10%, current TTH 38% and current CDH 3%. Consideration of studies restricted to adults gave similar results (46%, 11%, 42% and 3% respectively). They found life-time prevalence, as expected, to be somewhat higher: 66% for general headache, 14% for migraine and 46% for TTH. The authors did find that the prevalence for lifetime CDH was actually lower than current CDH at only 2.9% but this was based on only two studies. The authors explored the different prevalence of headache in general in the different continents and found it to be 50% in Asia, Australia, Europe and North America, but markedly lower (20%) in Africa. They found migraine to be most prevalent in Europe (15%) and least prevalent in Africa (5%). TTH appears to be much more common in Europe (80%) than in Asia or

the Americas (20–30%) (data from Africa was found to be lacking- however there has been recent data published from Tanzania after this review was completed). The authors found data on CDH to be relatively scarce and therefore probably less reliable, but they estimate a global prevalence of 3.4%. This condition appears to be most common in Central/South America (5%) and least common in Africa (1.7%). MOH is common among those with CDH with a prevalence of 1% in the adult population, although diagnosis can never be certain in epidemiological studies unless follow up is performed to ensure that the headache resolves after 2 months.

There are few properly conducted population studies based on IHS criteria for cluster headache but the recent review from Fischera et al. [185] reported a lifetime prevalence of 124/100,000 and a 1 year prevalence of 53/100,000. All the studies presented came from high income countries except for one from Malaysia [186] which found no cases and therefore a prevalence rate of 0/100,000 and Tekle-Haimanot's 1995 paper[187] from Ethiopia which found 5 cases and a 1 year prevalence of 32/100,000.

Stovner et al's [180] principal objective was to summarise all worldwide population-based studies on the most prevalent headache types. As a result their approach was uncritical and inclusive of many different studies with great variations in size, methodology and quality Indeed to have allowed for methodological differences would have been difficult, especially as the method in many studies is incompletely described. In a previous meta-analysis of headache epidemiological studies worldwide, the relative contribution to variations in the results from variations in methodology (compared with variations in age, gender distribution, race and continent) has been estimated at around 30% [188].

Although one can conclude that the burden of headache is large on all continents it is poorly described in large and populous regions, including SSA. Stovner et al [180] identified 107 population-based studies regarding headache (studies performed on the whole population or a representative sample) worldwide, of which only seven originated from the African continent, six of which were from SSA. As a result of the

limitations of Stovner's review and the subject matter of my thesis, I have reviewed the epidemiological studies of headache performed in SSA in more detail. There have been relevant publications since Stovner's review. A search of the literature for studies on all headaches from SSA, irrespective of the applied methodology, retrieved 13 studies. I was also able to retrieve 5 articles specific to the prevalence of headache in the elderly, although none of these were from SSA.

1.5.1.2.1.1.5 Critical appraisal of the SSA literature

1.5.1.2.1.1.5.1 The difficulty in interpreting hospital based headache studies: 2 working examples from SSA

Lisk et al [189] performed one of the first studies of headache in SSA, published in 1987. Limited conclusions can be drawn as they studied the patterns of headaches in 250 individuals that presented to a clinic, a biased population. The selection of the 250 people was not detailed so further bias could be present. The main conclusions were there were more females than males with a sex ratio of 2.2:1. (It was presumed that all headaches were severe as they had resulted in consultation in a specialist clinic.) The commonest cause, >40%, was migraine, both common and classical.. Next most common was tension headache, 20%, Sinusitis,15.6%, and hypertension 4.4%. The authors thought the latter surprising given the widespread medical problem that hypertension represents, but given it is in the majority a symptomless disease until malignant stages are reached, this does not seem unusual. The authors do conclude that the proportion of headaches attributed to migraine is very high and they attribute this to environmental and cultural factors, although do not expand on this further. Further interpretation of this biased review with poor methodology would be unwise especially as there is little detail given of the diagnostic criteria used. This study demonstrates the importance of standard diagnostic criteria and unbiased sampling of community populations to estimate prevalence..

Another study with results that are difficult to interpret was performed by Matuja[190] in Tanzania in 1991 as it merely studied types of headaches admitted to a neurology clinic over a 2 year period. Patients with recurrent headaches accounted for 319

(20.6%) of all new referrals, consisting of 47 (34%) with migraine (ratio of common to classical 4:1), 38 (27%) with psychogenic disorders, 18 (13%) with post traumatic headache, 16 (11%) with vascular-muscular contraction and 11 (8%) muscular contraction. Headaches were more common in the young and migraine was more common amongst females. Over two thirds of patients experienced severe headaches. The "neurology clinic" sample is extremely biased. Consultation with a specialist care service in Africa requires the financial and geographical means to attend. Headaches as a result may be more severe and more likely to be associated with other symptoms that an individual may interpret as worrying (migraine as opposed to TTH). The Ad-Hoc Committee Criteria (AHC) were used to define the headache diagnosis and so ease of comparison with other studies is further hampered and consequently impossible due to these numerous methodological issues.

1.5.1.2.1.1.5.2 **Community prevalence studies in SSA in selected populations**

Matuja et al [191]subsequently performed a community based study in southern Tanzania in 1995. This however represents another selected population and so generalisation of results is difficult. Although the rationale behind studying a productive population is obvious, the urban working population and students of higher education are not representative of the majority of Tanzania (demonstrated by the large proportion of men) and so extrapolation of results to the rest of the country is not possible. To the authors credit random selection was utilised. A self-administered questionnaire was used, methodology which would subsequently be difficult to reproduce in a country in which a significant proportion of the population are illiterate. The AHC criteria were used to define headache types. A total of 815 (52%), (620 (51%) men, 195 (60%) women) admitted to having suffered a headache requiring medication or medical consultation in the last year (more affordable in this population). 366 (23.7%) had recurrent headache, significantly more females than males 28.9% and 22.4%, respectively, highlighting the impact of the heavily male weighted biased sample. The most common headache type was combined vascular-muscular-type (35.8% of cases), followed by migraine (30.8% of cases). The study did demonstrate the societal impact of headache detailing that cases (175) had an average of 11.3 lost work days per year in comparison to the control group with an average of 5.7 lost work days per year for reasons other than headache.

Adoukonou et al [192] performed a study measuring the prevalence of migraine among the students of the Faculty of Health Sciences of Abomey-Calavi University, in Cotonou, Benin. A small cross-sectional study of 336 students was performed. Systematic random sampling limited selection bias. The questionnaire used to screen participants was designed originally for a French epidemiological survey and had been validated in France but not in Benin. Although this is a Francophile African nation cultural interpretations of questions may be very different. The questionnaire was completed by the subjects themselves leading to risk of question misinterpretation. The study was 2 phased and consequently a positive questionnaire was followed by history and examination by a neurologist to confirm the presence of migraine. Migraine was defined according IHS criteria. Lifetime prevalence was measured making comparison of the results gained difficult.

Among 336 students, 252 suffered from recurrent headache, and prevalence of headache was then 75.0% (95% CI: 69.9-79.5%). A total of 38 met migraine criteria. The lifetime prevalence of migraine was 11.3% (95% CI: 8.2-15.3%). The prevalence was significantly higher in females (18.3%) than males (6.8%). The mean age at onset of the disease was 15.0 years +/- 2.5. The mean attack frequency per month was 3.8 (+/-3.4) and the peak attack duration was between 4 and 6 hours. Psychological tiredness was the most frequent triggering factors (92.1%). The factors associated with migraine in multivariate analysis were female sex (OR = 2.6 [95% CI: 1.2-5.3]), single marital status (OR = 3.7 [95% CI: 1.2-11.9]) and presence of a family history of headache (OR = 2.9 [95% CI: 1.0-8.1]).

Migraine was frequent in students in Cotonou (Benin) compared with other studies in Africa. However this was a very limited study in a small and specialist sample of educated young individuals. The study did highlight the burden on a productive age group and the potential impact of psychological tiredness, but the results cannot be generalised or compared to the rest of the world’s data.

***1.5.1.2.1.1.5.3*Community prevalence studies in SSA in general populations**

Osuntokun et al [193]documented the prevalence of migraine headache as part of their pilot study to determine the feasibility of a survey to detect major neurologic diseases among rural populations in developing countries. They obtained data on the prevalence of migraine in a rural Nigerian population using the WHO screening questionnaire for neurological disorders. Subsequently a neurologist confirmed migraine using the AHC diagnostic criteria, in 62 out of 903 individuals, yielding a point prevalence rate of 69/1,000. The female to male ratio was 2:1. In 80%, a first-degree relative suffered from 'similar headaches'. The prevalence rate declined with increasing age once subjects were aged 40 or over.

Osuntokun [194]subsequently performed another community based study of headache of much larger proportions in a Nigerian town in 1992, utilising a questionnaire with a 92% sensitivity and 95% specificity with no second phase. 18,594 subjects were screened. The authors found that the lifetime prevalence of 1 (unspecified) headache was 51% (50% in males and 52% in females) and the lifetime prevalence of migraine was 5.3% (5.0% for males and 5,6% for females).

Levy et al [195]performed one of the first robustly designed prevalence studies of all cause headache alone in SSA, in an urban population of over 5000 from Zimbabwe, using a gold-standard 2 phased approach of questionnaire followed by interview. The AHC was used to define headaches and subtypes. The 1 year prevalence of headache was found to be 20.2% (17.6% in males and 27.0% in females). Headaches were defined as severe in one third of cases (more commonly younger age groups and women). The prevalence of migraine was found to be 4.2% with all of the cases being a common presentation. The prevalence of TTH was found to be only 0.7%.

Tekle-Haimanot et al [187] performed a similarly well designed prevalence study. The results can be generalised and compared to other rural populations. The IHS diagnostic criteria were used to develop a reliable and valid questionnaire for a door to door survey. Fifteen-thousand-five-hundred adults aged 20 years and older, who were randomly selected from a rural Ethiopian population of 250,000, were interviewed by. trained lay health workers. The 1-year prevalence of migraine headache was 3.0%

(4.2% for females and 1.7% for males) with the peak age specific rate in the fourth decade and a male to female sex ratio of 1:3. Migraine with aura was rare. Family occurrence of migraine in first-degree relatives was 30%. The 1-year prevalence of chronic tension-type headache was 1.7%, the 1 year prevalence of TTH was not reported.

Dent et al [196] performed a robustly designed door to door survey of the prevalence of headaches, (looking in more detail at migraine) in a general rural population of Tanzania in 1999. The authors used the gold standard IHS guidelines and questioned patients regarding headache in the last year making the findings of the study internationally comparable.

They performed a door-to-door 2 phased epidemiological survey on 3551 persons aged over 10 years within 1047 households. Whole villages were selected and seen, but the details of the rationale behind selection were not reported and so raises the question of whether bias was eliminated. The questionnaire was based on the IHS criteria, but details of the validation of the questionnaire were not included, in addition the 2 questions asked seemed to focus on lifetime prevalence despite the aim to detect 1 year prevalence. Diagnostic certainty could have been compromised by the use of medical students who screened and confirmed cases with a local physician in an advisory role only. They interviewed one representative family member not each member of the household, this introduces risks e.g. under reporting of this subjective illness. Diagnoses were made through a standard interview, not detailed in the report, and no follow up examinations of the subjects were performed to diagnose secondary causes of headaches. Questions regarding the severity of the headaches were very subjective and open to interpretation; headaches were said to have affected activities of daily living (ADL) if the subject had reduced their ADLs by half. The diagnosis of the most frequent type of headache experienced in the last year was recorded and duel diagnoses were not allowed for.

A total of 773 (23.1%; (95% CI 21.2-24.5)) responded positively to the screening question concerning the presence of headache during the previous year; 278 (18.8%; 95% CI 16.2-20.8) were males and 495 (26.4%; 95% CI 24.4-29.0) females. Amongst the

773 headache sufferers, a total of 167 respondents met the case definitions of migraine, resulting in a 1-year prevalence of 5.0% (95% CI 4.3-5.7); 2.5% (*n* = 37; 95% CI 1.5-3.6) in males vs. 6.9% in women (*n* = 130; 95% CI 5.4-8.5). The peak age specific prevalence rate was seen in males in the third decade of life (3.8%) and in females in the fourth decade (11.1%). 47 people (1.4% (95% CI 1.0-1.8) suffered from migraine headaches without aura and 120 people (3.6% (95% CI 3.0-4.2) fulfilled the criteria of migraine with aura. Of the 167 respondents reported to be suffering from migraine, a total of 128 individuals (76.6%) indicated they had experienced 'severe or very severe and incapacitating headaches'. The remaining 39 persons (23.4%), reported 'severe but not incapacitating headaches'.

The authors only present crude prevalence rates which limits the comparability of the data, however the rates of migraine headache found were similar to those in other studies from SSA but substantially lower than reports from Europe and North America where prevalence ranges from 7.5% in Hungary [197] to 27% in Germany [198], and 12–15% in the USA [199] and Canada [200]. Rates in this SSA population were higher than in China, where prevalence rates ranging from 0.6 to 1.0% have been reported [201-203]. This study adds substantially to the scanty data available from SSA, however, due to the retrospective character of data collection and the lack of personal interview with each study participant, there are some limitations

Houinato et al [204] determined the prevalence of migraine in a rural community of Benin. A cross-sectional two phased study was completed on 1113 people (selected through random sampling to reduce bias) aged 15 and over. The questionnaire used had been validated in France and sensitivity was reported to be >80% but validation was not performed on the local population. Trained medical students carried out the survey followed by a full neurological examination by a neurologist for those that screened positive. Confirmed cases were defined by the IHS criteria [176]. Participation rate was good at 93.4% Substantially more females than males were included in the sample 63.4% and 36.6% respectively. apparently representative as in rural Benin there is male exodus to urban areas.. Of the 1113 persons, 37 had migraine. The lifetime prevalence of migraine was low at 3.3%, (males 2.2%, females 4.0%) despite a predominant female population. The study findings are difficult to compare with

worldwide data as lifetime prevalence rather than 1-year prevalence data was recorded.

Winkler et al [205, 206] performed a robustly designed community door to door study to assess the prevalence of general headache, TTH and migraine using the IHS diagnostic criteria. The study was within the rural catchment area of the Haydom Lutheran Hospital in northern Tanzania. The close proximity of the study area to the hospital could introduce bias given the relative ease of medical consultation. The authors point out however that it is a unique study area as it has a very mixed population that based on their languages could represent all the main cultural groups of East Africa. The study used a Kiswahili questionnaire based on the IHS diagnostic criteria, however many of the population surveyed only spoke local languages complicating the accurate use of the questionnaire. Characteristics (sensitivity and specificity) of the validated questionnaire were not presented by the authors. 3 questions about current, 1 year and lifetime headache were asked to the head of household with the concomitant risks discussed above.. Medical students made the diagnoses based on histories alone, however validation was provided by a neurologist. Only the primary headache diagnosis was recorded and other co-existing headaches were not included in the prevalence figures. An attempt was made to exclude secondary headache, positive responders were asked if the headache was associated with any other disease.

A total of 7412 participants were screened. 1404 of the study population stated that they had suffered from headaches in their lifetimes, corresponding to 18.9% (1404/7412; male 13.6%, 509/3731; female 24.3%, 895/3681). When patients who experienced headache exclusively related to a secondary medical condition were excluded, the remaining lifetime prevalence of overall primary headache was 13.5% (1004/7412; male 9.8%, 366/3731; female 17.3%, 638/3681). The 1-year prevalence rate of overall primary headache was 12.1% (895/7412; 95% CI 11.3, 12.8). After age adjustment to the WHO population, the 1-year prevalence rate was 17.5%. The 1-year crude prevalence of headache was significantly higher in females (15.8% (583/3681); 95% CI 14.7-17.1) compared with males (8.4% (312/3731); 95% CI 7.5-9.3], resulting in a male to female ratio of 1:1.9. The peak age-specific 1-year prevalence rate for all

individuals and for women was found in the fifth decade with prevalence rates of 26.5% (109/411; 95% CI 22.3, 31.1) and 35% (75/214; 95% CI 28.7, 41.8), respectively. In men those aged 61 years and over showed the highest prevalence with a rate of 19.8% (32/162; 95% CI 13.9, 26.7).

Five hundred and twenty-one headache sufferers met the case definitions of TTH, resulting in a 1-year TTH prevalence of 7% (521/7412, 95% CI 6.5-7.6; age-adjusted rate 10.4%); 5.3% (196/3731; 95% CI 4.6-6) in men compared with 8.8% (325/3681; 95% CI 7.9-9.8) in women with a gender ratio of 1:1.7. ETTH made up 5% (374/7412; 95% CI 4.5-5.5; age adjusted rate 7.1%), CTTH 0.4% (27/7412; 95% CI 0.2-0.5; age-adjusted rate 0.5%) and TTH, according to IHS 2.3, 1.6% (120/7412; 95% CI 1.3-1.9; age adjusted rate 2.8%). The peak 1-year prevalence rate TTH was 18.7% (59/316; 95% CI 14.5, 23.4) and occurred in people aged 60 years and over.

A total of 316 respondents met the criteria of overall migraine headache, including chronic daily migraine headache and migrainous disorders. The calculated 1-year prevalence was 4.3% (95% CI 3.8-4.7). The exclusion of children aged 0–5 led to a 1-year prevalence of 5.4% (316/5858, 95% CI 4.9-5.9). Eighty-one of the patients with migraine headache were men (2.2%, 95% CI 1.7-2.7) and 235 women (6.4%, 95% CI 5.6, 7.2), with a male : female ratio of 1:2.94 ($P<0.001$). After exclusion of seven people of unknown age, the 1-year prevalence rate of overall migraine headache was 4.2% (309/7405,95% CI 3.7-4.7) with an age-adjusted rate of 6.0%. As many western studies have dealt with adult populations starting between 12 and 20 years (23–30), the authors also calculated the crude prevalence rate for study participants aged 21 years and over, which was 8.5% (250/2927, 95% CI 7.5, 9.6). The age distribution of people with migraine demonstrated a peak in the fourth decade with a prevalence rate of 10.3%. The authors found that prevalence of migraine gradually increased to this point and then slowly declined with age. 132 patients did not fulfil all criteria for migraine headache; hence, these patients had to be classified as migrainous disorders with a crude prevalence rate of 1.8% (132/7412. 95% CI 1.5, 2.1). The remaining 184 patients met all criteria for migraine resulting in a 1-year prevalence of 2.5%.

This study represents the first report of the prevalence of TTH in a rural Tanzanian population, and shows that headache in general and, more specifically, TTH and migraine are less prevalent than in Western countries; however they are still common and troublesome. The main limitations of the study, proxy reporting and the concurrent epilepsy prevalence study (a condition with known stigma)may have led to under-reporting of symptoms. The inclusion of young children (often excluded from headache prevalence studies) and the crude exclusion of secondary headaches may have also falsely lowered the prevalence results.

Table 1.7: Epidemiological Studies of Headache in Sub-Saharan Africa

Country 1st author year ref	Population	Diagnostic criteria used	Method	N	Age years	Prevalence period	Headache prevalence %	Migraine total %	Classical (with aura) %	Common (without aura)%	TTH %	Chronic headache %
Benin Adoukonou 2009 [192]	Cross sectional – students	IHS	Self administered questionnaire	336	16-46	Life	75.0	11.3	4.8	6.6	-	-
Benin Houinato 2009 [204]	Community rural	IHS	Personal interview	1113	15-80	Life	-	3.3	1.1	2.2		
Ethiopia Tekle-Haimanot 1995 [187]	Community rural	IHS	Personal interview	15000	20+	1 year	4.7	3.0	0.3	2.7	1.7	1.7
Nigeria	Communi	AHC	Personal	906	All	Unknown		6.9	-	-		

Osuntokun 1982 [193]	ty rural		interview									
Nigeria Ogunyemi 1984 [207]	Students	AHC		1756	16-42	Life		16.7	3.9	12.9		
Nigeria Longe 1988 [99]	Community rural	Unknown	Personal interview	2925	All	Unknown		6.3	0.4	5.9		
Nigeria Osuntokun 1992 [194]	Community urban	AHC	Personal interview	18954	All	Unknown	51.0	5.3				
Sierra Leone Lisk 1987[189]	Clinic patients with headache	?	Personal Interview	250	?	Unknown	-	42.4	10	32.4	22	
Tanzania	Clinic	AHC	Personal	319	5-59	2 years	20.6	(34.0%			19	

Matuja 1991 [190]	patients with headache		Interview					of 20.6%)				
Tanzania Matuja 1995 [191]	Community urban, students, workers	AHC	Self administered questionnaire	1540	20-40	1 year	23.7	7.2			35.8	
Tanzania Dent 2004 [196]	Community rural	IHS	Personal interview	3351	11+	1 year	23.1	5.0	3.6	1.4		
Tanzania Winkler 2009-10 [205, 206]	Community rural	IHS	Personal Interview	7412	All	1 year	12.1 (age adjusted rate 17.5%)	4.3 (age adjusted rate 6.0%)	1.2	1.3	7.0 (age adjusted rate 10.4%)	
Zimbabwe Levy 1983 [195]	Community urban	AHC	Personal interview	5028	5-70	1 year	20.2	4.2	0	4.2	0.7	

AHC : Ad Hoc Committee Criteria[208], IHS: International Headache Society[179], All prevalence rates are crude unless otherwise stated

Detailed comparison of the prevalence of headache found in this study, SSA and the rest of the world is included in the discussion and so is not elaborated further here.

1.5.1.2.1.1.6 *The burden of the different headache types*

Stovner et al[180] attempted to translate prevalence into burden through data on duration and severity of symptoms. They found that although TTH is generally less burdensome than migraine to the individual sufferer, however the total societal burden of this headache type is larger than that of migraine because of its much higher prevalence. The higher prevalence of TTH vs. Migraine is observed worldwide but to a much lesser extent by the SSA studies, this could result from variations in methodology and reporting as opposed to a true variation in the burden of different headache types.

1.5.1.2.1.1.7 *The Social and economic burden of headache*

Globally, information on the societal impact of headache exists in very few countries: 18 % of countries worldwide (and only 6% of African countries) surveyed as part of the WHO LTB campaign responded regarding the societal burden that headache represents[174].

Headache disorders are a public-health concern given the large amount of associated disability and financial costs to society. Headache is particularly burdensome as it predominantly affects those in their "productive years". In the United Kingdom, 25 million working/school days are lost every year because of migraine alone; this loss increases substantially when tension headache is included [174].

The WHO state it would be highly informative to health policy if accurate information existed within countries on direct and indirect costs attributable to headache, given the huge disparity between the two. However, little such information exists worldwide especially from SSA.

1.5.1.2.1.2 *Risk Factors for headache*

Globally, there are four categories of risk factor:

- Social (20.8 %), including quality of life, domestic circumstances and life events
- Other medical conditions (15.8 %), including hypertension, depression and infectious diseases
- Drugs or medications (12.9 %), particularly medication overuse
- Lifestyle factors (7.9 %), including substance abuse and dietary habits[174].

1.5.1.2.1.3 *Diagnosis and Management*

History and examination is usually all that is required to diagnose headache disorders. Investigations are generally not required to support the diagnosis. Despite this a minority of people with headache disorders worldwide are professionally diagnosed. The diagnosis rates for migraine and TTH are about 40 % and for MOH only 10 %. Specialists use IHS diagnostic criteria [179] to support diagnosis in only 56 % of countries with lower usage reported in Africa. Failure in diagnosis is often due to help not being sought; a recent study in the US and the UK demonstrated only half of those identified with migraine had seen a doctor in the previous 12 months. The majority of people with headaches are reliant on self diagnosis and over-the-counter medications [174].

1.5.1.2.1.3.1 *Treatment*

The main classes of drugs to treat headache disorders include: analgesics, anti-emetics, anti-migraine medications, and prophylactic medications - WHO found these were available in the majority of countries surveyed, however there was limited response to the surveys from SSA and the national availability of medications does not mean availability to all, especially in resource poor settings where access to healthcare is unequal. Globally, guidelines or recommendations are used for the management of headaches in 55% of countries worldwide; however this percentage is much less in SSA.

1.5.1.2.1.3.2 *Barriers to effective management*

Barriers to care could be summarised as;

1. Clinical Barriers
    a. Lack of professional education (Worldwide, only four hours of undergraduate medical training are committed to headache disorders)
    b. Patient-related problems including co-morbidities
    c. Lack of health-care resources including non-availability of medications
2. Social Barriers - Poor awareness of headaches in the general public
3. Political/Economic Barriers - Many governments do not acknowledge the substantial burden of headache on society

Suggested changes:

1. Professional education
2.Improved awareness
3. Improved availability of healthcare, including improved organisation and delivery of healthcare services for headache
4. Political recognition that the problem exists
5. Support of National professional organisations [173]

1.5.1.2.2 *Stroke*

1.5.1.2.2.1 *Definition*

The WHO definition for stroke is “rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer, with no apparent cause other than vascular origin” [209].

Stroke is a syndrome caused by interruption in the flow of blood to part of the brain by either;

1. Occlusion of a blood vessel – ischaemic stroke
2. Rupture of a blood vessel – haemorrhagic stroke

The occlusion of the blood vessel can sometimes be temporary and present as a reversible neurological deficit, which is termed a transient ischaemic attack (TIA) [75, 76].

1.5.1.2.2.2 *Diagnostic Criteria and Clinical Classification*

1.5.1.2.2.2.1 *Ischaemic versus Haemorrhagic*

Stroke is a clinical diagnosis, brain imaging is required to accurately distinguish ischaemic from haemorrhagic stroke. When imaging is unavailable, clinical scores can be useful to identify patients with intracerebral haemorrhage e.g. The Siriraj Stroke Score [210]. However this score is only useful when patients are seen at the time of the stroke, its sensitivity and specificity were good in initial studies but have been reported as more disappointing since, particularly in SSA. Celani et al [211] argue scores such as the one above whilst useful to identify patients at low risk of haemorrhage, leaves many strokes where it is difficult to be certain of aetiology [211].

Ischaemic stroke can be secondary to embolism, thrombosis or rarely vertebral or carotid artery dissection [75].

Haemorrhagic stroke is usually secondary to rupture of the deep perforating arteries due to chronic hypertension. Rarely it is due to a subarachnoid haemorrhage but this is a distinct epidemiological entity [75].

1.5.1.2.2.2.2 *Vascular localization in the cerebrum*

The cerebral circulation branches into anterior and posterior divisions, supplied by the internal carotid and the vertebrobasilar arteries respectively, and connected by the circle of Willis.

The anterior cerebral branch from the internal carotid supplies the anterior and medial parts of the cerebral hemisphere and small branches also supply the hypothalamus, internal capsule and anterior part of the basal ganglia. A stroke in this territory may preferentially involve the contralateral leg.

The middle cerebral artery supplies the more lateral parts of the cerebral hemisphere so the patient is more likely to have their face and arm affected as well as sensory loss. Branches also supply the internal capsule and the basal ganglia.

Vertebrobasilar disease may give rise to brainstem signs by impairment of the posterior cerebral artery supply affecting the circulation to the occipital lobe, inferior part of the temporal lobe, thalamus or hypothalamus [75, 76, 79].

1.5.1.2.2.3 *Clinical Classification of Stroke*

The widely recognised clinical classification of stroke is the Oxfordshire Community Stroke Project (OCSP) (Bamford) Stroke Classification [212]. I used this to sub-classify stroke patients dependent on their symptoms and signs at the time of the stroke onset. Bamford classification is widely accepted and used in epidemiological studies; it is simple enough to use whilst it still recognises clinically useful subgroups. I understand that the subgroups relate to outcome in cerebral infarction and not haemorrhage so conclusions on outcome will not be accurate when no cerebral imaging is available.

1.5.1.2.2.3 *Epidemiology of stroke*

SSA is undergoing epidemiological development and a consequent health transition. Stroke and other vascular diseases increasingly contribute to the burden of disease and interventions to stop this rapid progression are urgently needed.

The annual incidence of stroke in high income countries is 2-3/1000. There are few community stroke incidence studies from SSA but similar high incidence has been reported from one study from SSA, more specifically from the DSS that is the subject of this thesis [213]. Hospital incidence is lower than in high-income regions, but selection bias has to be considered and incidence appears higher in young people than in the rest of the world.

The prevalence rates range from 0.5% to >1% in those aged over 65 years in developed countries. Generally the prevalence is reported to be lower in SSA with age adjusted rates half that figure. However the prevalence of disabling stroke is reported in some studies to be as prevalent and with demographic transition it is thought that the overall prevalence will soon equal that of developed countries.

Stroke is the third most common cause of death worldwide, and the leading neurological cause of death in SSA. Hospital based studies from SSA demonstrate that stroke is one of the leading causes of neurological admissions and death [28]. Stroke mortality may surpass stroke mortality in high income countries, and as expected increases with age. The recently updated Global burden of disease study estimated that over 80% of stroke deaths occur in low-income and middle-income countries [214-216].

This section will describe the burden stroke presents to SSA. A critical appraisal of the literature is referenced to the rest of the world Population-based studies from SSA investigating the prevalence of all types of stroke have been included together with the most recent and epidemiologically robust publications specific to stroke prevalence in the elderly population. The review focuses on prevalence, however to fully describe burden and variations in prevalence, incidence and mortality will also be considered.

1.5.1.2.2.3.1 *What is the best way to measure stroke burden worldwide?*

Disease burden in SSA is best estimated by community populations. Hospital data is subject to selection bias through geographical and financial constraints on the general population of low income countries. The burden of stroke, a disease by definition of sudden onset, is at first glance best reflected by incidence, prevalence after-all depends on incidence and case fatality [216]. However in sub-Saharan Africa, incidence studies prove very difficult to perform in the community because of the lack of medical

infrastructure many "stroke victims" do not consult help; they go undetected unless specific systems for reporting exist [213]. Thus stroke prevalence studies, particularly in demographic surveillance sites with a known denominator population, have arguably provided the most accurate and up-to-date measures of stroke burden in SSA. It is however important to recognise their limitations:

Firstly, stroke and its sub types prevalence estimations are complicated by the difficulty of retrospective diagnosis months or years after the event.

Secondly, prevalence figures tend to under estimate because of under-representation of fatal cases, and confusion with co-morbidities such as arthritis and dementia.

Thirdly, the majority of stroke prevalence studies in developed countries are performed with very different methodology e.g. screening through postal questionnaires [217, 218]. Poor or non-existent postal services, low literacy level and lack of initial stroke diagnosis preclude this and other non "in-the-field" methodology in SSA. As in most low-income countries as for other neurological conditions, two phased door-to-door surveys are the gold-standard [34].

Fourthly the majority of recent stroke studies done in high income countries are incidence studies (for the reasons mentioned above) therefore to accurately document differences between burden in low and high income countries, population-based incidence studies with long-term follow-up and assessment of case fatality are required in SSA.

1.5.1.2.2.3.2 *Stroke Prevalence*

The surveillance of stroke prevalence in SSA began in the 1980s, with landmark studies from Nigeria and Ethiopia.

Between 1982 and 1989, Osuntokun et al's [3, 25, 99] work aimed to establish the prevalence of neurological disorders in rural Nigeria. The gold-standard two phased approach was used to perform three studies. Surveys were carried out by trained nurses, primary health-care officers, medical students or teachers using the Original 1981 WHO Neurological disorders screening instrument. This asked the following questions to detect stroke (the question numbers apply to those that were assigned on the original screening tool);

Q3 Is your speech normal?
Q6 Has your face or part of your face ever been paralysed for more than 24 hours?
Q7 Have you ever had weakness in your arms or legs for more than 24 hours?
Q9 Have you ever had loss of sensation of abnormal sensation affecting your arms or legs, lasting more than 24 hours?

Other questions and examination points may have also detected stroke particularly stroke affecting the posterior circulation. The diagnosis of stroke was then confirmed (or refuted) in positive cases by a neurologist or a neuro-surgeon.

The initial study was in Aiyete, a community of about 2000 people, 903 individuals were screened to pilot the research protocol. This study demonstrated that the screening tool had a sensitivity of 95% and a specificity of 80% for detecting general neurological disorders. The validity of the screening tool in specifically detecting stroke was not reported. Stroke cases could therefore have been missed. Four participants were found to have had a stroke, resulting in a crude prevalence of 443/100,000 [25]. In Udo, 2925 people were screened and two had had a stroke resulting in a crude prevalence rate of

68.4/100,000.30 [99]. The largest study was performed in Igbo-Ora, stroke was diagnosed in 11 of 18 954 people screened, resulting in a crude prevalence of 58 per 100 000 [3].

There were two main limitations of these studies. Firstly their size, which at initial review appear more than adequate, but when one considers that typically 44% of the population in SSA was less than 15 years old [216] then the representation of the older age groups (those predominately affected by stroke) is limited. Secondly the diagnostic criteria used was not detailed, thus the accuracy of diagnoses is difficult to assess.

Between 1986 and 1988, a door-to-door survey was done on a random sample of 60 820 rural Ethiopians of all ages [5]. Lay health workers, who had been trained by neurologists, did a census and identified people with symptoms and signs of neurological disorders with the previously validated (in Nigeria) WHO questionnaire. Neurologists regularly verified diagnoses. Again a small number of stroke cases (9) were found, this time in the adult population ranging from 28-85 years, giving a crude prevalence 15 per 100 000. The low rate may reflect, low stroke incidence, high case fatality, recovery from stroke or failure to detect cases. Investigation as to the causation was not performed.

Walker et al [34] performed the largest study (n=148 135) to date of the prevalence of stroke in SSA in the Hai district DSS (the study population that is the focus of this thesis). The authors limited their study to the detection of disabling hemiplegic stroke, which although practical, limits the comparability of the data with the rest of the world. The authors utilised the gold-standard two phased approach. Highly trained enumerators (experienced in epidemiological surveys and graduates of higher education but inhabiting the villages in which they surveyed) performed a screen for hemiplegic stroke at the same time as the 1994 census. This provided accurate denominator data at the same time. The questions were as follows;

Is there anyone in the household with a history of stroke?
Is there anyone in the household with weakness down one side of the body?

Does anyone in the household require assistance with dressing, eating or toileting?" These questions had not been validated in a pilot study and so their sensitivity and specificity for identifying stroke cases was not known.

Cases were verified amongst positive responders by a UK Geriatrician, with extensive experience of stroke, who used the WHO definition of stroke as diagnostic criteria. Other methods of case ascertainment were used to improve the reliability of the prevalence figures.

108/148135 people were identified as having a disabling hemiplegic stroke, the crude prevalence of stroke in the whole population was therefore 73/100000. However the authors sensibly recalculated prevalence rates in those aged 15 years and over and a recalculated crude prevalence was found to be 127/100,000, (155 for men and 103 for women). Age standardisation was performed to the Segi world population giving a prevalence of disability from stroke of 154/100 000 in men and 114/100 000 in women. The crude prevalence rates for those aged 65 and over were 876/100,000 (975/100,000 for men and 786/100,000 for women). The median age of patients was 70 years old and the median age at first stroke was 65. 21% of patients were bedbound. The age specific prevalence of stroke survivors requiring help with at least one activity of daily living (ADL) was 69/100,000 for men and 90/100,000 for women.

Walker et al demonstrated that prevalence of disabling hemiplegic stroke was low in comparison to high income countries (age standardised rates for stroke with residual disability was approximately half that found by previous studies in high income countries), they felt this was mainly explained by the age structure of the population with <6% of participants being aged 65 and over. Mortality rates may have also been higher.

The Southern Africa Stroke Prevention Initiative (SASPI) team [219] reported the prevalence of stroke survivors in rural South Africa. A demographic surveillance site, Agincourt (population 68 525) was utilised. Workers trained in DSS activity carried out a

screen for stroke and completed the annual census which provided the demographic data. The questions asked of over 15s were used to detect hemiplegic stroke only;

Has (person) ever had weakness down one side of the body?
Has (person) ever had a stroke?
For those who screened positive to either question a clinician trained in stroke carried out a clinical assessment with the diagnostic criteria defined by the WHO.

A total of 42,378 individuals were aged over15 years. There were 982 positive responses to the questionnaire, however the authors were only able to examine 724 individuals (74%), for various reasons including refusals and inability to re-identify, this could introduce bias.. 103 stroke cases were identified resulting in a crude prevalence of 243/100 000. To their credit the authors did adjust for those they were unable to examine and the prevalence increased to 300/100 000 (95% CI, 250-357). The age-standardised (to the Segi World population) prevalence of stroke was 290 per 100 000 (95% CI 238–343). In men the prevalence was 281 per 100 000 (200–362), and in women 315 per 100 000 (243–387). Sixty-six percent of stroke survivors needed help with at least 1 activity of daily living (Segi age-standardized prevalence, 200/100 000). The crude prevalence of those aged 65 years and older was 1490/100,000.

The Tanzanian and SASPI studies both have the advantage of accurate denominators and careful assessment of people who screened positive for stroke. However, the accuracy of the screening questions in the census has not been assessed and a large number of false positives were picked up during screening. This hopefully provides reassurance of the sensitivity of the questions but does mean reproduction of the studies will be time consuming and difficult. In addition both studies assessed the prevalence of hemiplegic stroke only, this is pragmatic as most patients who have ongoing disability from their stroke are likely to be hemiplegic in nature. Other stroke types are more likely to recover or affect vital respiratory centres so result quickly in death.

Gradual health transition might explain differences in the prevalence of stroke in these most recent robust prevalence studies from SSA. Firstly the lifestyle risk factors of South Africans may be higher than Tanzanians, stroke risk factors have recently been shown to be common in all population groups in South Africa [220]. Secondly Tanzanians may have a higher case fatality than South Africans in rural areas.

The age-standardized prevalence of stroke in high-income countries reported in a recent review of studies since 1990 ranged from 461 to 833 per 100 000. The largest of these came from Auckland, New Zealand, where age adjusted prevalence of stroke was found to be 833/100,000 [221].

Both SSA studies assessed the prevalence of stroke survivors who need help with at least one ADL, in order to demonstrate stroke burden more completely. This allows direct comparison with the Auckland Stroke Study [221] as shown in the table below;

Table 1.8: The Age-Standardised (Segi World Population) Prevalence/100,000 of Stroke and Stroke Survivors Needing Help with Everyday Activities in Tanzania, South Africa, and Auckland, New Zealand [216].

	Tanzania [34]	South Africa [219]	New Zealand [221]
Stroke Survivors			
Men	154	281	991
Women	114	315	706
Total		290	833
Stroke Survivors needing help with at least one ADL			
Men	69	218	156
Women	90	188	188
Total		200	173

The prevalence of stroke in Tanzania is half that of South Africa which is in turn a third of that found in Auckland. The prevalence of stroke survivors who required help was higher in South Africa than in both Tanzania and New Zealand. This finding may reflect inadequate rehabilitation after stroke in rural South Africa in comparison to New Zealand, and increased death from disabling stroke in Tanzania, but may also reflect that many very disabling strokes were picked up in South Africa and mild strokes went unrecorded. Indeed methodological differences could explain the differences between the prevalence rates; the Auckland Stroke Study followed on from incidence studies and therefore probably recorded mild strokes which would not have been picked up by either of the SSA studies. However both sub-Saharan African countries may have a lower prevalence of stroke when compared with New Zealand, because of a higher mortality and case fatality, these factors therefore need to be examined when reflecting on stroke burden [216].

The trend of overall lower prevalence rates of stroke in SSA vs. high income countries was supported by Danesi et al's [222] robust 3 phased community based epidemiological study in Lagos, Nigeria in 2007. The authors used a modification of the WHO protocol in the first stage, a stroke-specific questionnaire in the second stage and neurological examination of all persons screening positive for stroke in the third stage. To validate the process and add strength to the prevalence figures the authors also examined an equal number of individuals that screened negatively. Overall, the crude prevalence rate of stroke in urban Nigeria was 114/100,000 (males: 151/100,000; females: 69/100,000). The authors calculated the age-adjusted prevalence rates according to the USA population and demonstrated the following prevalence rates per 100,000 amongst the different age groups: 35-44 years = 0.9, 45-54 years = 33, 55-64 years = 71, 65-74 years = 98, 75-84 years = 204 and >85 years = 74. As expected prevalence generally increases with advancing age.

In contrast a high prevalence of stroke was observed in Cossi et al's [223] recent robust two phased epidemiological study which assessed the prevalence of stroke amongst 15,155 individuals aged 15 years and older. They utilised the WHO questionnaire. 321 possible stroke cases were identified, however stroke was only confirmed in 70 cases. The crude prevalence of stroke was 460/100,000 (870/100,000 and 770/100,000 adjusted to the WHO and SEGI World Population). The mean age of the patients at onset was 56 years. Sixty percent of stroke survivors had a Rankin score of 2 or more, indicating that even mild cases of stroke were identified. Although numbers are small, this study demonstrates a higher prevalence than previously reported in SSA, highlighting the increasing burden that stroke represents.

1.5.1.2.2.3.3 *Stroke Incidence*

Comparing incidence rates of stroke worldwide is difficult due to differing definitions, methodology and data presentation. The importance of complete, community-based case ascertainment to include strokes managed outside the hospital is key [224].

The recent review article by Feigin et al [225] shows a divergent trend in stroke incidence rates over the last 40 years, with a 42% decrease in stroke incidence in high-income countries and a greater than 100% increase in stroke incidence in low to middle income countries. In 2008, the overall stroke incidence rates in low to middle income countries have, for the first time, exceeded the level of stroke incidence seen in high-income countries, by 20% [226-230]. These trends are more pronounced in the older age groups.

Walker et al [213] performed the first rigorous study of stroke incidence in SSA. It is the only study to date to include community-based identification of stroke in the region, it provides reliable data on the incidence of stroke in rural and urban Tanzania. The Tanzania Stroke Incidence Project (TSIP) recorded stroke incidence in two DSS (one rural (Hai) and one urban (Dar-es-Salam)) over a 3-year period from June, 2003. The rural DSS is also the subject of this thesis.

A robust system of stroke identification was put in place. Trained experienced enumerators (present in each village) reported cases of stroke to clinical officers. Stroke cases were then assessed by physicians experienced in the diagnosis of stroke utilising the WHO diagnostic criteria. Diagnosis was made by clinical examination and CT scan in the majority of patients. Several other methods of case ascertainment were used to maximise cases identified. Patients who died from stroke during the data collection period were identified via verbal autopsy and included in the incidence numbers. There were 636 strokes during the 3-year period (453 in Hai (in a population of 159,814) and 183 in Dar-es-Salaam (in a population of 56,517)). Overall crude yearly stroke incidence rates were 94·5 per 100 000 (95% CI 76·0–115·0) in Hai and 107·9 per 100 000 (88·1–129·8) in Dar-es-Salaam. When age-standardised to the WHO world population, yearly stroke incidence rates were 108·6 per 100 000 (95% CI 89·0–130·9) in Hai and 315·9 per 100 000 (281·6–352·3) in Dar-es-Salaam. Incidence rose sharply after 65 year of age, with only one age band exception in Dar es Salam. Incidence for age bands 65-74, 75-84, 85+ were 568.2, 1392.6, 1980.5/100,000 per year respectively in Hai and 2291.7, 3809.5 and 2439.0/100,000 per year in Dar es Salam.

There were a number of weaknesses to the study which limit conclusions. Firstly the urban population was small particularly in the older age bands. Secondly there were some refusals to take part and this might have introduced selection bias.

Overall this was a landmark study of incidence in SSA and prompts discussion about incidence variation through its easy comparison to the rest of the world's data. The reasons for the much higher incidence of stroke in Dar es Salam have been speculated by the authors. It is known from the literature that risk factors for stroke are higher in urban areas, particularly diabetes, hypertension and obesity [231, 232].

A stroke register was set up in the 1970s in Ibadan, Nigeria, covering a population of 803 000 [233]. The crude yearly incidence of first stroke was 25 per 100 000 for men and 13 per 100 000 for women. However, small numbers of staff and reliance on patients presenting to western style medicine mean that these incidence figures are likely to substantially underestimate the problem.

Incidence rates of individuals presenting to hospital with stroke in Harare, Zimbabwe were studied by Matenga [234]. The crude annual stroke incidence was 31/100 000 (95% CI 27–34). Standardised to the world population, the incidence was 68/100 000. The denominator of the whole population of Harare was used but only those who presented to hospital with their stroke could be identified so the nominator was likely to be an underestimate and the denominator approximate. .

Rosman [235] estimated the incidence of stroke from hospital admissions in South Africa and found a crude incidence of stroke of 101 per 100 000 in a population aged 20 years and over.

The incidence rates reported by Walker et al [213] are higher than those seen in the previous hospital-based studies described above. Such studies do not seem to be

representative of the whole population as they are a select sample who can afford to choose to consult western medicine. Any accurate stroke incidence study must take place in the community, the reasons for this are highlighted by previous studies of stroke mortality which shows that only 56% of people in the Hai DSS and 30% in the Dar-es-Salaam DSS who die from stroke do so in hospital, clearly a substantial number do not present to hospital at all [236].

In general studies from SSA do support an expected marked rise in incidence with age, a property of an ageing population. The age-standardised incidence rates in the Hai DSS are similar to those seen in many methodologically rigorous studies of European and North American populations [225]. However, age-standardised incidence rates in Dar-es-Salaam were higher than seen in most studies in developed countries.

The Northern Manhattan Stroke study [237] in the 1990s reported an incidence for those aged 20 years or older of 93 per 100 000 in white people and 223 per 100 000 for black people. Assuming there are no strokes in people under age 20 years, these rates correspond to about 66 per 100 000 for whites and 158 per 100 000 for blacks across all ages. In comparison to the population screened by Walker et al [213] incidence rates in Hai were lower for those aged 75 years and under than in Northern Manhattan. In general stroke incidence rates in rural Tanzania were comparable with blacks in Manhattan, but in urban Tanzania the incidence rate is substantially higher.

I have presented evidence that worldwide, the incidence of stroke has been decreasing, but this decrease is occurring in developed countries due to improved prevention measures. However it seems that incidence rates in developing countries have increased substantially, although more, reliable incidence studies are required from many world regions. The reasons for the higher incidence of stroke in urban areas of developing countries are not yet clear but seem to be key to the reasons behind increased incidence in these countries overall. It seems that risk factors (including hypertension) are probably to blame. Urbanisation in Africa, as in other parts of the developing world, is increasing

rapidly. Without urgent installation of stroke prevention measures, incidence rates in developing countries will continue to increase and it will not be long before the trend of overall incidence rates reverses and starts to increase again [213, 225, 238].

1.5.1.2.2.3.4 *Stroke Mortality and Case Fatality*

Stroke mortality data can come from a number of sources, including hospital data, death certifications, GBDS, verbal autopsy data from demographic surveillance sites and epidemiological studies. Hospital based studies have not been included in this review because as previously mentioned these are unlikely to be representative of the general African community. Universally, a large proportion of patients with stroke are not admitted to hospital [224]. Other studies excluded from this review were those that produced unreliable data due to flaws in methodology [239-242].

1.5.1.2.2.3.4.1 *Stroke Mortality*

SSA is undergoing a demographic transition; with this causes of death will not only alter from infectious to NCD but in addition the pattern of vascular disease and death will change from one dominated by haemorrhagic stroke to one dominated by cardiovascular disease, peripheral vascular disease and ischemic stroke.

Death certification in high income countries provides easily accessible stroke mortality data, although it may not be very reliable [243]. Death certification is certainly unreliable in SSA with many stroke deaths going unreported, as there is no formal death certification system this method substantially underestimates stroke burden [244]. Death certification data that does exist does not use appropriate diagnostic criteria making results hard to interpret [245]. Despite this the Global Burden of Disease study (GBDS) use vital registration data, sample death registration studies (predominantly from urban hospital populations), epidemiological studies, and the newly developed cause-of-death model (Cod-Mod) for estimating cause of death in regions with little or no cause-of-death data. GBDS 2002 found infectious diseases and perinatal disorders dominated the causes of death in Africa, while non-communicable diseases dominated in high-income countries.

There were estimated to be 359 000 stroke deaths (3% of all deaths) in Africa compared with almost 1.5 million (16% of all deaths) in Europe. Stroke caused an estimated 52% of vascular deaths (deaths caused by either stroke or ischaemic heart disease) in Africa compared with 38% of vascular deaths in Europe[214-216].

Studies have demonstrated that through verbal autopsies cause of death data from SSA can be produced [246]. This involves interview with a family member to ascertain symptoms leading up to and therefore the probable cause of death. Specific stroke death data has been published from two sites in SSA; The Agincourt Health and Population Unit, Bohlabelo, rural north-east of South Africa[219] and the three DSS in Tanzania [236] (Dar es Salaam [urban], Hai [prosperous rural], and Morogoro [impoverished rural])comprising the Adult Morbidity and Mortality (AMMP) (the focus of this thesis is the Hai district DSS). The former reported a sensitivity and specificity of verbal autopsies for stroke to be 87% and 97%, whilst the latter reported 100% for both parameters [236, 247]. However these validation calculations were based on very small numbers (only twelve strokes in the Tanzanian study) and the gold-standard was clinical diagnosis which did not include brain imaging.

The South African site found stroke caused 6% of all deaths in a population of 63 000 between 1992 and 1995. Stroke was the commonest cause of death in the age 55–74 years group, and the second commonest cause of death in the 75 years and over group. Important statistics when considering the age group focussed on in this thesis. The crude stroke mortality was 127 per 100 000 (95% CI 93–160) over age 35 years [247].

The large AMMP found that stroke caused 5.5% of adult deaths in a total population of 307 820. Age-adjusted stroke mortality for individuals over age 15 years in the prosperous rural and urban regions in Tanzania were up to 3-10 times higher than in the England and Wales (when rates age adjusted to the Segi world population), particularly in the 15-64 years age group, although this was not statistically significant[236].

One can conclude that age-specific stroke mortality in SSA is at least as high as in England and Wales [248], and perhaps higher in younger age groups, but larger and more reliable studies are required given doubt has been cast on the accuracy of verbal autopsy data in general [249]. However, verbal autopsies do provide the only detailed mortality data from SSA, and stroke is potentially one of the easier diagnosis to confirm.

A dated community epidemiological study on stroke mortality occurred between 1975 and 1980. It was a detailed 5 year follow-up of 4075 people aged 15–64 years in Accra, Ghana. Cause of death was determined from death certificates, inquiry from health care workers, and lay recorders. Stroke was found to cause 8% of all deaths [250]. Limitations of this study meant that this probably underestimated the number of stroke deaths; there was no validated method of diagnosing stroke included and an undetermined number of people died outside the area.

1.5.1.2.2.3.4.2 *Is stroke mortality changing in sub-Saharan Africa?*

Based on vital registration data, there was little difference between stroke mortality amongst developed and developing countries in 1950s. However since then mortality in developed countries has improved substantially. It appears that there has been an improvement in stroke mortality in South Africa at least but more information is needed from the rest of SSA to base conclusions on mortality transitions [216, 251-255].

Although mortality rates may be higher in SSA than in high income countries, the absolute numbers of deaths due to stroke remain low, explained by the population structure, 44% of the population are under 15 years of age, and only 3–6% over 65 years[246, 247]. However with demographic transition this will change [216, 243, 256-258].
It is worth noting that mortality rate is of course influenced by incidence rate and case fatality [243].

1.5.1.2.2.3.4.3 *Case Fatality Rates*

Between 2000 and 2008, early (21 days to 1 month) case fatality ranged from 17% to 30% in high-income countries and from 18 to 35% in low to middle income countries. Early stroke case fatality has decreased in both high-income and low to middle income countries over the past decade but is now 25% higher in the latter [225, 238].

As with any epidemiological data from SSA the most reliable is community based and prospective. However only one community based study of case fatality exists, therefore prospective hospital-based studies were also included in this review. Retrospective studies were deemed too unreliable because of missed data.

The Ibadan stroke register (the only community based study)reports case fatality at 3 weeks as 35% for all stroke and highest for cerebral haemorrhage and subarachnoid haemorrhage at 61% and 62% There were significant limitations to the conclusions made from this study as CT scanning was not always performed and follow up showed a huge drop out with only 24% of participants traceable at 3 months [259].

Early total stroke case fatality (up to 1 month) derived from prospective hospital studies, is approximately 33% [234, 235, 260].

Only one study from The Gambia has used long-term follow-up over 4 years to determine case fatality, time to death, and likely cause of death [261]. This study included all patients admitted to hospital with a diagnosis of stroke or who had a stroke as an inpatient over a period of 1 year. Both first-ever and recurrent strokes were included and patients with subarachnoid haemorrhage were excluded. None of the patients had a CT scan. Patients were followed up at home or hospital at 1 month and 6 months and again between 3 years and 4 years after their stroke. Case fatality in the 106 cases at 1 month and 6 months and 4 years was 27%, 44% and 75% respectively. Less than 4% of patients were lost to follow up. There are limitations of this study, it is hospital based and therefore mild or very severe strokes are likely to be excluded, in addition CT scanning was not

performed and this does limit the accuracy of the diagnosis made. However it does allow comparison to world data and at one month case fatality is not much higher than worldwide studies (27% vs. 23% respectively) [238].

One recent hospital-based study from Senegal [216, 262, 263] found a hospital case fatality of 29% at 1 month and 51% at 1 year in 170 patients who had had CT, was recently reported from Senegal. However the CT scans were done up to 1 month after the event and therefore interpretation of the results is difficult [264, 265].

Stroke seems to be an increasing problem in sub-Saharan Africa. A study from Accra that investigated stroke admissions from the early 1960s to the early 1990s found a large increase in both admissions and fatality in the early 1990s compared with the 1960s; in the 1990s, stroke was the leading cause of death, accounting for about 17% of deaths on medical wards, and fatality range from about 42% to 50% over this time period [266].

1.5.1.2.2.3.5 *Stroke Subtypes*

Mensah et al's review [267] observes that assessment of stroke subtype is very challenging in SSA mostly due to limited availability of neuro-imaging. In general, studies examining this problem are small and hospital based [235, 260, 268, 269]. In the limited number of studies that are available cerebral haemorrhage accounts for 26% to 33% [269] of strokes, higher than in developed countries [268]. Hypertension is the single most important reversible risk factor for stroke, particularly haemorrhagic stroke. This is demonstrated by Mating et al's[268] study of admissions with stroke to two teaching hospitals in Harare. Hypertension was present in 27 (93%) of the 29 patients with cerebral haemorrhage and in 49 (53%) of the 93 patients with ischaemic stroke [268]. Detection, treatment and control of hypertension in these patients was poor but is paramount to reduce stroke mortality in SSA [270].

As part of their TSIP Walker et al [213] performed one of the only studies examining the proportion of ischaemic vs. haemorrhagic strokes in the community in SSA. Diagnosis of stroke was confirmed by CT scan in 159 of 201 patients (102 of 132 from Hai and 57 of 69 from Dar-es-Salaam) identified by the TSIP system. 64 of 132 patients from Hai had a CT scan done within 15 days of stroke onset: 11 had evidence of a haemorrhagic stroke, 52 were normal or had evidence of stroke caused by cerebral infarct, and one had a subarachnoid haemorrhage. In Dar-es-Salaam, 17 of 69 patients had a CT scan done within 15 days: three had evidence of a haemorrhagic stroke and 14 were normal or had evidence of stroke caused by cerebral infarct. CT head scan done more than 15 days post-stroke is unreliable because of the potential to misdiagnose haemorrhagic stroke [241]. Within the subgroup of patients who had a CT scan within 15 days of stroke, Walker et al found a lower incidence of haemorrhagic stroke (17.2% in Hai and 17.6% in Dar-es-Salam) compared with ischaemic stroke than reported in previous studies of stroke in sub-Saharan Africa [260, 271-273]. The percentages of strokes caused by haemorrhage and infarct were similar to those seen in studies in the developed world [211, 274]. However these conclusions have some limitations: The number of patients who had a CT scan within 15 days of stroke was small and potentially not representative. Patients, who died soon after stroke included in the numbers those not having a CT scan), might have been more likely to have had a haemorrhage. Despite its limitations this community based study is the best representation of the true picture of disease burden.

1.5.1.2.2.3.6 *The Epidemiology of Stroke in Summary*

The prevalence of disabling stroke in sub-Saharan Africa is potentially at least as high as in high-income areas although the overall prevalence of stroke (114–460/100 000) is lower (just under half that found in high income regions).

Stroke incidence from hospital-based studies is lower than in community-based studies in high-income regions, but it is higher in people under 65, although it is not as high as in age matched African Americans.

Although the absolute number of stroke deaths remains low as a result of the population structure (44% of people are under 15 years of age), the age-adjusted stroke mortality among adults in sub-Saharan Africa appears rather similar to that occurring in high-income regions, and stroke mortality may have increased however accurate data is lacking.

Although comparable community-based case-fatality studies are lacking, the available case fatality data from hospital studies reveal a rate of approximately 30% at 1 month higher than 20% in the comparable older population of the rest of the world.

Community based incidence studies with follow-up are required to determine whether the low overall prevalence of stroke results from low incidence or high case fatality or a combination of the two. As risk factors for vascular disease increase, and the populations age, so the burden of vascular disease will certainly increase in SSA. Indeed, without intervention, stroke and heart-disease-related deaths in developing countries are expected to increase from 3 million in 1998 to 5 million in 2020 [216]. The burden of stroke is likely to become epidemic unless interventions are put in place.

1.5.1.2.2.3.7 *Disability After Stroke*

85 percent of patients survive immediately after stroke, with approximately 10 percent recovering almost completely, and 25 percent recovering with minor impairments. Thus, approximately 40 percent experience moderate to severe impairments that require special rehabilitative care. About 10 percent will require care in a nursing home or other long term facility. [275]

Mathers et al estimate the Disability Adjusted Life Years (DALYs) for cerebrovascular disease as 72,024,000 DALYS worldwide, with the burden being very similar for females (36,542,000) and males (35,482,000). The burden is highest in East Asia and the Pacific, followed by South Asia, Europe and Central Asia. The burden in SSA is higher than in the Middle East and North Africa [159]. Corresponding to the anticipated increase in the

number of stroke cases will be an increase in the number of people with disabilities surviving after stroke in low-income countries[276].

1.5.1.2.2.4 *Risk Factors for Stroke*

- Increasing age – particularly after 55
- Hypertension
- Previous cerebrovascular disease
- Ischaemic Heart Disease (IHD)
- Atrial Fibrillation (AF)
- Diabetes Mellitus (DM)
- Peripheral Vascular Disease (PVD)
- High Cholesterol
- High plasma fibrinogen
- Sickle cell disease (SCD)
- Rheumatic heart disease (RHD)
- Smoking
- Alcohol
- Obesity [75, 76, 277]

1.5.1.2.2.5 *Investigations for Stroke*

Blood tests are important post stroke to identify modifiable risk factors.

Electrocardiogram (ECG) is also necessary to detect atrial fibrillation and if present instigate treatment and anticoagulation if possible [75].

Non-contrast computerized tomography is a reliable diagnostic tool which allows accurate differentiation between ischaemic and haemorrhagic stroke and excludes other causes of brain damage [13]. However, it is not always available (or affordable for patients) in developing countries.

Further investigation such as carotid Doppler and echocardiogram (echo) can also be important in determining causation and secondary prevention [75].

1.5.1.2.2.6 *Interventions for Stroke*

Several intervention strategies are available for stroke, but only a few can be applied in developing countries.

1.5.1.2.2.6.1 *Population-Based Interventions*

Public health policies to address risk factors for stroke include tobacco, alcohol, dietary and lifestyle education and control. Public health programs to control rheumatic fever will reduce rheumatic heart disease and the subsequent risk of embolic strokes [276].

1.5.1.2.2.6.2 *Personal Interventions*

Treatment strategies for acute ischemic stroke include;

1. General management [276]

- Good nursing care
- Attention to complications:
    - Bronchoaspiration/pneumonia
    - Fluid and electrolyte imbalance
    - Control of blood sugar
    - Prevention of deep vein thrombosis (DVT)

2. Specialised Stroke Units[276]

Experience in developed countries suggests that specialized stroke units provide the best care for acute stroke patients [278], but in developing countries such units are impractical.

3. Platelet antiaggregants [276].

- Aspirin can prevent early stroke recurrence if given during the acute phase of stroke (within 48 hours) [279, 280]
- Low dose of aspirin is optimal to ensure positive benefit/risk ratio [281].
- When a CT is not available simple guidelines for the use of aspirin should be developed based on the Siriraj score to identify those very unlikely to have had a haemorrhage and who would therefore benefit from aspirin [210].

4. Thrombolytic therapy [276].

Tissue plasminogen activator and recombinant tissue plasminogen activator (rt-PA) gives clear benefits when given within 3 hours of the first symptoms in patients with cerebral infarction. (Number needed to treat to prevent one death or disability = 9) [282]. The

requirement for a CT scan within 3 hours and highly qualified staff precludes it use in most developing countries, including SSA.

Secondary prevention after a Stroke or TIA [276]

1. Risk Factor Management

Hypertension, diabetes, high lipid levels, smoking, and alcohol use modification is beneficial both for primary prevention and prevention of recurrence of stroke/TIA.

2. Platelet antiaggregants

- Aspirin therapy is effective in preventing recurrence of stroke, with low daily doses being at least as effective as higher daily doses [281].
- Antiplatelet combination therapy using agents with different mechanisms of action, such as the combination of extended release dipyridamole and aspirin, have been shown to reduce the risk of stroke over aspirin alone [283].
    - Combination therapy with aspirin and clopidogrel offers no advantage over aspirin alone and also increases the risk of haemorrhage [284].

3. Anticoagulant therapy

- Warfarin is clearly effective in preventing embolic strokes in patients with atrial fibrillation it should therefore always be considered and the risk/benefit ratio calculated [285, 286].
- Anticoagulant therapy should also be considered in rheumatic heart disease.
- However, many developing countries lack the facilities to monitor anticoagulation therapy and prohibit its use. This puts many at increased risk of stroke.

4. Surgical Treatment
    - In patients with symptomatic carotid disease with stenosis of more than or equal to 70 percent, carotid endarterectomy has been shown to be of benefit [287-289].
5. Rehabilitation

Rehabilitation aims to restore as much independence as possible to stroke patients. Rehabilitation in a multidisciplinary stroke unit reduces deaths, disability, and care requirements [278], but such facilities are very low in number in developing countries.

Home-based rehabilitation services can have some benefits but these are reported to be modest [290]. They may however be the only short term solution in many low-income countries, where at present the majority of patients will be treated either at home or in a small community hospital with no rehabilitation service. Some stroke victims will be unable to seek help at all [276].

There is a gap between developed and developing countries in terms of stroke prevention, diagnosis, treatment and rehabilitation caused by the lack of trained specialists and expertise, lack of equipment, inadequate diagnostic evaluation and insufficient funds in resource-poor countries. Stroke research and training are grossly underfunded [13].

1.5.1.2.3 *Epilepsy*

1.5.1.2.3.1 *Definition*

Epilepsy: Recurrent (i.e. two or more) unprovoked seizures [291]

Seizures: Discrete events caused by transient hyper synchronous, abnormal neuronal activity [75].

Provoked seizures: Occur during, or closely related with, an acute cerebral or systemic insult such as cerebral infection, head injury, stroke, metabolic disturbance, or alcohol withdrawal. They may be isolated or recurrent [75].

Unprovoked seizures 3 types:

- Secondary or symptomatic epilepsy: A late consequence of an antecedent condition such as cerebral infection, stroke or head injury
- Idiopathic: No clear antecedent aetiology but takes the form of particular syndromes with specific clinical and EEG characteristics
- Cryptogenic: No obvious cause and does not fit a specific syndrome [75].

1.5.1.2.3.2 *Classification*

Seizures should be classified according to the International League Against Epilepsy (ILAE) classification which separates seizures into partial, generalised and unclassifiable. The

standard definition relies on clinical and EEG criteria [292]. Modification of this allows classification on purely clinical grounds where investigations are limited and it is this modification that is routinely used for epidemiological research in resource poor settings and was used in this thesis [291, 293].

Partial (focal) seizures

- Simple partial seizures – no alteration of consciousness
- Complex partial seizures-alteration, or loss, of consciousness
- Partial seizures evolving to secondary generalised seizures

Generalised seizures – involvement of both cerebral hemispheres from onset

- Absence seizures
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Generalised Tonic-clonic seizures (GTCS)
- Atonic seizures

Unclassified epileptic seizures [291, 292]

1.5.1.2.3.3 *Risk Factors and Causes*

- Family History
- Prenatal and perinatal: Obstetric complications, prematurity, low birth weight, neonatal asphyxia, neonatal seizures
- Traumatic brain injuries
- CNS infections: Neurocysticercosis, Malaria, Onchocerciasis and other parasites
- Brain tumours
- Neurodegenerative conditions
- Stroke

1.5.1.2.3.4 *Epidemiology*

The main focus of the critical review of the literature presented here will be the prevalence of epilepsy in SSA with brief discussion on the incidence of epilepsy as this is also utilised to reflect the burden of disease. However it is appreciated that any discussion regarding epilepsy in Sub-Saharan Africa would not be complete without mentioning risk factors, the treatment gap and mortality related to the disease and how they contribute to the burden of disease. These will therefore be briefly discussed.

There is a lack of reliable data on the incidence of and prognosis for epilepsy in sub-Saharan Africa but prevalence data demonstrate that epilepsy is two or three times more common than in industrialised countries. The high prevalence of epilepsy and low life expectancy indicate incidence is high. Relative contributions of causes of epilepsy are difficult to determine, only a few case-control studies have been done in sub-Saharan Africa. Data indicates that infections particularly cysticercosis, cause the majority of cases. Accurate causal studies are urgently needed to implement informed prevention programmes, increase detection and reduce societal burden. In addition there is a need for relatively low cost treatment and education initiatives to reduce the treatment gap and associated stigma respectively [294, 295].

1.5.1.2.3.4.1 *The burden of epilepsy*

Epilepsy affects approximately 50 million people worldwide, with 80% residing in resource poor settings, the majority of which are in SSA [296, 297]. Epilepsy was estimated to account for 0·5%-1% of the global burden of disease, accounting for 7,307,975 disability adjusted life-years in 2005[13, 297, 298]. However these figures are flawed given they did not take into account the limited data from low-income countries [295].

1.5.1.2.3.4.2 *Biased or non-representative studies*

There are many estimates of the burden of epilepsy using hospital based studies, including 2 recently published in northern Tanzania by the same group of authors. They conclude that epileptic seizures account for 3% of all hospital admissions and 27% of neurological

diagnoses made in hospital[299] and febrile seizures and epileptic seizures account for 20.6% and 13.9% of admissions with impairment of consciousness respectively [300]. It is however difficult to extract meaning from these figures as the majority of the population in low income countries do not present to hospital for reasons related to geography, finance and health beliefs. Hospital studies are not considered further in this review.

The non-representative nature of hospital data is highlighted by Quet et al. [54, 301] as part of the Limoges studies (detailed below). Many differences were found to be statistically significant between people with epilepsy (PWE) surveyed from the general population and PWE recruited from hospitals. They showed that hospital-based surveys leads to a selection of a PWE, which is not representative of the entire population. However, this can also be the case for some community based studies where surveys in remote areas, which may be affected by particular environmental or hereditary factors, can produce results that are difficult to extrapolate to an entire country.

1.5.1.2.3.4.3 *Difficulties collecting accurate epidemiological data from developing countries; the additional complexities that epilepsy presents*

As previously mentioned in this thesis, deriving accurate epidemiological data on the prevalence of any neurological disorder is difficult as it requires time consuming cross-sectional surveys and medical records are incomplete and unreliable. As a result of methodological constraints and inconsistencies, epidemiological studies on epilepsy are difficult to compare. Screening questionnaires used to identify patients with epilepsy, cannot be used across different populations with diverse social or cultural backgrounds. The lack of specialised personnel, particularly in neurology, and the almost complete absence of diagnostic equipment (there are 75 EEGs and 25 CT scanners in tropical Africa), means that the accuracy of diagnosis cannot be confidently assessed. The Stigma related to epilepsy adds an extra complexity to the derivation of incidence and prevalence data as this prevents victim identification even when directly questioned. In addition most studies that have been performed have focussed on convulsive epilepsies, as they are the easier to detect reliably through the increased morbidity suffered by the patient. Unfortunately

as a result there are limited accurate estimates of non-convulsive epilepsies (difficult to accurately detect through simple questioning and clinical examination alone) and reported prevalence rates should be considered underestimates of the true burden of disease. The use of different terminologies to classify seizures and epilepsy also hinders study comparison. High income countries do not have such data collection problems and regular censuses, well established medical records systems and lack of stigma through education means collection of incidence and prevalence data is relatively easy [294, 295].

Preux and Druet-Cabanac [294] state multiple source analyses can also be used to complement door-to-door surveys, even this gold-standard may underestimate epilepsy burden. For example Debrock et al. [302] used multiple sources including a door to-door survey, medical registries, and interviews of key informants to estimate the prevalence in two villages (3000 inhabitants) in Benin. 50 patients were identified by the door-to-door method, the prevalence was therefore 15·9 per 1000 (95% CI 11·8–20·4). Key informants found 16 more PWE and prevalence rose to 21·1 per 1000 (95% CI 16·5–26·9). The capture-recapture method was then utilised and the prevalence was finally found to be 35·1 per 1000 (95% CI 23·3–46·9), which shows that the door-to-door survey could have underestimated the true prevalence of epilepsy by up to 50%.

Attempts to standardise epidemiological data on epilepsy: The Limoges questionnaire

The best way to collect complete, prospective and standardised epidemiological data is the use of a standardised questionnaire and methodology. The Limoges questionnaire was just such a questionnaire, it was produced in 1994, it was created to detect epilepsy as part of a 2 phased survey, and has been employed since in various continents in tropical latitudes in order to produce a people with epilepsy (PWE) database. Its sensitivity and specificity have been reported as 95.1% and 65.6% respectively [301]. In Africa between 1994 and 2004, 13 epidemiologic surveys in 12 countries were performed using this prescribed methodology. 7 of these (recruiting 1,118 PWE) were carried out in the community rather than the hospital population, (two cross sectional and five case control studies), 6 of these have been published. The location of these published studies was as

follows; Benin [302], Burkina-Faso [303], Burundi [304], Cameroon[305], Mali [306], Central African Republic [307]. Further studies have been performed using this questionnaire since 2004, namely Crespin et al's [308] study in Benin. The prevalence data, when present, is detailed in the table below with specific reference that they were performed using the Limoges questionnaire.

The use of such a questionnaire needs to be continued as it has been validated for use in SSA and it facilitates easy comparability of burden levels. The authors do acknowledge that it is a very lengthy questionnaire, much of which concerns generalised data not specific to the epilepsy prevalence. They therefore recommend that study coordinators identify which specific items of data they wish to collect (other than those for the diagnosis of epilepsy, which should be left intact). The authors do also state that to improve this questionnaire and its use, information on anti-epileptic drug (AED) use should always be recorded and new questions could be integrated to study socio-cultural aspects of epilepsies such as representations, stigmatisation, and quality of life.

1.5.1.2.3.4.4 *Incidence*

In a recent review and meta-analysis, the incidence of epilepsy ranged from 49 to 215 per 100 000 people per year in five well undertaken studies in SSA which appears to be the extent of such studies in this region [294, 309].

The demographic characteristics of the populations studied were similar but the methods were different. Two studies repeated cross-sectional surveys with an interval of 2·5 years in Uganda [310] and 3·5 years in Ethiopia [311]. The three others were retrospective and used the onset of seizures to estimate the average annual incidence over 5–10 years [312-314]. The significant heterogeneity in the incidence of epilepsy in these studies can partially be accounted for by the different and sometimes biased (in the case of retrospective reporting) methodology. However this heterogeneity was also observed between the Ugandan and Ethiopian studies, it may be, therefore, in part at least, be a true reflection and could have resulted from variations in risk factors: for example, the

highest incidence of epilepsy was reported from Uganda (twice that found in Ethiopia) in an area with a high prevalence of onchocerciasis. However this specific risk factor as a cause remains a unproven theory and further research is required in this area [309].

Winkler et al's[315] more recent study demonstrated average yearly incidence rates to be 81/100,000. However, again these results need to be interpreted with care as they are based on retrospective medical history only.

Prospective studies including a register of epilepsy ascertained by a neurologist would give a more realistic estimate of the incidence of epilepsy in sub-Saharan Africa[294].

In general the annual incidences were high (49–215 per 100 000 inhabitants) compared with those found in industrialised countries in non-tropical areas (40–70 per 100 000 inhabitants) [316].

1.5.1.2.3.4.5 *Prevalence*

The prevalence of active epilepsy in people of all ages from Europe and North America is 5–8 per 1000 [317, 318]. Higher rates have been reported in studies from Asia, South and Central America and in particular from SSA. More data are available on the prevalence rather than incidence of epilepsy in low income countries, explained by the methods required to gain accurate epidemiological data in these regions, as described above. Prevalence estimates vary widely from country to country in SSA depending, in particular, on the methods used. Preux and Druet-Cabanac's 2005 review[294], only looked at door-to-door surveys, acknowledging any methodology, other than the gold-standard, could lead to misleading results. The authors observed that studies with data from only medical registries or passive ascertainment systems gave lower estimates and a falsely reassuring picture of the true burden of disease. The median prevalence of epilepsy in SSA has been reported as 14-15/1000 with an inter-quartile range of 10-21 [294, 295].That is not to say that the rates were consistent, rates were highly varied from 5 to 75 per 1000, higher rates were seen in children and young adults, rural areas, and studies with small

population sizes. Therefore, the prevalence of epilepsy in the whole population of sub-Saharan Africa cannot be generalised [294].

1.5.1.2.3.4.5.1 *Reasons for variations in the prevalence of epilepsy*

Wide variations in epilepsy could be due to;

1. Differing definitions of epilepsy/The nature of epilepsy studied (lifetime vs. active, generalised vs. all cause)

Most of the studies in SSA assessed only convulsive epilepsies. This exclusion of non-convulsive seizures (along with under-reporting levels secondary to stigma) is said to underestimate the prevalence of epilepsy by two to four times[295, 319, 320]. Focal epilepsy seems to be more common in low income countries although comparison of the proportion of seizure types is difficult because of the different sources of epidemiological data and types of investigations [294, 321]. This conclusion is even in spite of the fact that many focal seizures are not detected in the surveys given the exclusion of non-convulsive seizures and the fact that there are few facilities for, and expert interpreters of, electroencephalography and neuro-imaging in poor regions [322]. The increased prevalence of focal epilepsy is likely to be secondary to the increased prevalence of risk factors that cause secondary epilepsy, which in turn may be more amenable to cure [295].

2. The differences in the samples of populations studied; a general vs. selected population, urban vs. rural

Consistent findings from epidemiologic studies of epilepsy in developing countries including SSA indicate that the prevalence is higher in rural than urban areas of the same country [323-325]. The higher prevalence of epilepsy in rural areas might be caused by an increase in risk factors in these populations but may also reflect the fact that many people who develop epilepsy do not migrate to urban areas for work, or if they develop epilepsy whilst in urban areas, might lose their jobs and return to their rural homes [326].

3. The methodological quality of the study: not allowing for stigmatisation and the quality of clinical assessment.

The underreporting levels secondary to stigma and the exclusion of non-convulsive seizures may possibly underestimate the prevalence of epilepsy by two to four times[295, 319, 320].

4. Risk factors

In some sub-Saharan Africa areas, consanguinity is reported to be very high amongst epileptic patients, for example in some areas of Mali it is thought to be as high as 96% [306]. The stigmatization of PWE potentially forces them to intermarry thereby increasing the genetic transmission of epilepsy and prevalence rates in pockets of the community.

The prevalence of epilepsy has been observed to be variable in the same country and ethnic community under the same methodology. Two Nigerian studies, used the same protocol to investigate two population groups from the same community living 20 km apart. They observed very different results 5.3/1000 in Igbo-Ora [25] and 37/1000 in Aiyété[327]. The researchers felt this highlighted the impact of risk factors on prevalence particularly sanitary conditions, neonatal infections and birth trauma. In contrast the prevalence may be very similar, as observed in Togo [314, 328-330].

Ngugi et al. [331] quantify that over 50% of the variation in the global estimates of the lifetime prevalence of epilepsy can be attributed to the differences between studies in rural and urban areas, between children and adults, and in the size of the denominator in the study

The true prevalence of epilepsy in SSA is still hotly debated. A few large-scale studies showed prevalence nearer that found in industrialised countries. The question is; have these studies underestimated the prevalence because of non-ascertainment of cases or are the smaller scale studies misleading because of genetic influences of inbreeding and consanguinity, consequences of specific aetiological factors or over inclusion of provoked

seizures? There is also the possibility given the reasons outlined above, that this discrepancy lies in factors specific to different geographic zones in sub-Saharan Africa [294].

1.5.1.2.3.4.5.2 *Critical review of the recent prevalence literature*

The section below discusses the recent prevalence studies in SSA in more detail and attempts to draw meaningful conclusions from their data:

Edwards et al [319] present the results of their very large study in a poor rural area on the coast of Kenya, which adds substantially to the data on the burden of epilepsy in SSA. The population represents the entirety of a demographic surveillance system with regular enumeration being performed every 4 months, eliminating bias. They assessed those people aged 6 years and older of which only 3% of the population were aged 65 or older. Their methodology was reasonably robust and standardised. They undertook a three phased study. The initial phase consisted of asking the head of the household 2 questions. Unfortunately the authors only present the sensitivity of these questions in children, but they do report this to be 100%, although it is not known how this conclusion was drawn. As discussed previously, surveys of the head of the household has its limitations compared with asking the patient themselves especially with a stigmatising condition like epilepsy. They then go on to state that there was a second screening phase, they do not report the qualifications of the screeners, and the details of the screening instrument were not included in the paper, instead the reader is directed towards a webpage. To their credit the sensitivity and specificity of the second phase is reviewed by re-examining a proportion of those who screened negative, this was found to be 94.8% and 52.3% respectively. Therefore although the sensitivity is reassuring about the prevalence figures presented the specificity may preclude replication of this study given the number of false negatives likely to be identified. The diagnosis made was unfortunately only clinical, but this does represent the majority of encounters in SSA and it was verified by a number of neurologists to add to its reliability. The standardised diagnostic criteria from the ILAE,

was used. The authors reported the prevalence of active convulsive epilepsy (non-convulsive seizures were excluded from the prevalence figures.)

The overall prevalence of active convulsive epilepsy was 2·9 per 1000 (95% CI 2·6–3·2); after adjustment for non-response and sensitivity of the questionnaire, prevalence was reported to be 4·5 per 1000 (4·1–4·9). Substantial heterogeneity was noted in prevalence, with evidence of clustering, this was thought to be due to environmental and genetic factors. The prevalence of those aged 50 and over was 2.1 (95% CI 1.7-2.7). Crude prevalence alone was presented, no attempt was made to age adjust and the distribution of population by age was not presented in full.

The authors go on to describe the clinical and neurophysiologic features of patients with active compulsive epilepsy in a further paper in 2010 [332]. They found that: Approximately half of the 445 people with active compulsive epilepsy (ACE) were children aged 6 to 18 years. Seizures began in childhood in 78% of those diagnosed. Overall 71% of patients with ACE had evidence of focal abnormality. The authors conclude that: The predominance of focal features suggests that much of the epilepsy in this region has identifiable causes, many of which could be prevented [332].

Hunter et al [333] present the findings from their very large 2009 community based prevalence study performed in the same demographic surveillance site as is the subject of this thesis. Robust methodology supports their conclusions, although there were a number of limitations that the authors acknowledge and that will be explored below;

The authors utilised a previously validated questionnaire which to their credit they validated again in a Tanzanian Kiswahili speaking population. Unfortunately this was only performed on a small number of cases and controls from a hospital population. They obtained a very favourable sensitivity of 100% but the specificity of 54.5% explained the time consuming nature of the work and how this study might be difficult to replicate.

A large and unbiased adult population of 103,026 were assessed using the gold standard 2 phased methodology. Additional case finding methodology was also used to pick up cases which adds to the validity of the prevalence rates but calls into question the sensitivity of the questionnaire as a further 82 cases were found in this way.

Seizure types and epilepsies were classified according to current recommendations of the ILAE and use of CT, EEG, and verification of cases by neurologists added to the robust nature of each diagnosis.

The prevalence of active epilepsy in this population was estimated with age-standardisation to the WHO standard population to allow ease of comparison to other world regions. Two hundred and ninety-one cases of active epilepsy, all with convulsive seizures, were identified. The age-standardised prevalence was 2.91/1000 adults (95% CI 2.58–3.24); the crude prevalence adjusted for non-response was 3.84/1000 adults (95% CI 3.45–4.20).The crude prevalence of those aged 60 years and older was found to be 1.17/1000 (95% CI 0.66-1.68)

Unfortunately the authors were not able to assess nearly one third of those who responded positively to the screening questionnaire, an inability to trace these individuals may be related to stigma and may indicate why the prevalence rate presented is low.

Focal-onset seizures accounted for 71.5% of all cases identified. The high proportion of focal onset seizures indicates a large burden of acquired, and possibly preventable, epilepsy in this population.

The key limitations of the studies by Edwards et al [319] and Hunter et al [333] that hamper comparison with other findings are the exclusion of people with non-convulsive epilepsy (non intentionally in the case of Hunter et al). In high income countries partial epilepsies (with focal onset) are more common than generalised onset epileptic disorders

or that account for at least account for 50% of all epileptic disorders [320, 334]. If this pattern also applies in Africa an estimated total prevalence would be 6-10 per 1000 population.

Winkler et al [315] performed a study of 7,399 people. They reported the prevalence of epilepsy using robust methodology in 2003-2004. The authors avoided bias by utilising random sampling and allowing for representation of villages of varying distances from a health centre. A previously validated questionnaire was used, modified and validated further for their population. In hospital, clinic and community pilot studies they found it to have a high sensitivity and specificity of 92.5% and 97.5% respectively. The specificity was however substantially lower in the main study. The authors utilised standardised diagnostic criteria, however all diagnoses made were purely clinical but were performed by an experienced neurologist.

The prevalence rates were age standardised to the WHO standard population to allow ease of interpretation. The prevalence rate of epilepsy was 11.2/1,000 (95% CI 8.9–13.9/1,000) and the age-adjusted prevalence rate was 13.2/1,000. The prevalence rate of active epilepsy was 8.7/1,000 (95% CI 6.7–11/1,000), with an age-adjusted rate of 9.1/1,000. The crude prevalence rate of active epilepsy for those aged 55+ was 6.0/1000.

Prevalence rates of epilepsy were reported recently from 3 villages in Burkina Faso from a study conducted in 2007 of 888 individuals aged 7 years and over [335]. However due to the rather flawed methodology the results need to be interpreted with caution. The selection of villages was based on pig rearing practices and hearsay that the villages had a high prevalence of epilepsy and therefore the authors admit that the prevalence rates may not represent that from the rest of the country.

The authors used a previously validated questionnaire but it was not adapted for or validated in this community. They used the standard definition for epilepsy from the ILAE and utilised the two phased gold standard approach. A study physician, who was not a neurologist, confirmed or refuted the purely clinical diagnosis. 14/70 people who screened positive were not examined by the physician for various reasons, thus cases may have been missed.

The lifetime prevalence of epilepsy was 4.5% (95% CI 3.3%-6.0%). Thirty-four (87.2%) of the 39 PWE had active seizures, giving an overall prevalence of 3.9% (95% CI = 2.8%; 5.4%) for active epilepsy.

The main limitations were acknowledged by the authors as being;
1. Biased selection of villages
2. Stigmatisation of disease resulting in probable under-reporting
3. Limited detection of non-convulsive epilepsy due to the methods used.

The authors acknowledge that their estimates are higher than those reported in Burkina Faso study in 1993 (1.1%; 95% CI 0.9%-1.2%). The methodology of this study was more robust involving random selection of 18 villages in 2 provinces and therefore it may be that the former study's prevalence figures are more representative of the entire country. However it may also be that there is a true difference in prevalence of epilepsy between the investigated areas and the nearly 20-year time lapse between the studies.

Crepin et al [308] not only performed a well executed community prevalence study in amongst 11,668 individuals in a rural area of Benin they also explored the relationship between epilepsy and malnutrition in the form of a case control study. Unfortunately the denominator population was achieved from a census that preceded the study by 3 years. A questionnaire (the Limoges) validated for detecting epilepsy in tropical countries was used but it was not validated further in this specific population. The entirety of a population was screened with a 94% ascertainment so no bias was produced through

sampling errors. The initial screen was performed by trained local physicians and confirmation of cases in the second phase was performed by a neurologist. Final diagnosis was purely clinical but took into account a collateral history and internationally recognised criteria. All types of seizures were included adding to the comparability of their results. The prevalence of epilepsy was 12.7/1000; 95% CI: 10.8 – 14.8. Most subjects with epilepsy had generalized tonic– clonic epilepsy. All, but one, had had at least one seizure during the last 5 years (active epilepsy). A certain degree of neurological impairment (abnormal mild neurological signs, cognitive impairment) was found in 26% of the subjects. Almost 82% had had their first seizure before the age of 20. The median number of seizures per year was 12. Both the high number of seizures per year and the fact that the majority of the cases were convulsive indicates that the prevalence of epilepsy may have been underestimated.

Sims et al [336] performed a nationally representative population based survey of the prevalence of epilepsy in Rwanda of the whole population in 2005. They used random sampling across the country and screened 6757 people with an impressive 80.8% response rate. They did use a standard questionnaire but this was in the majority used to pick up musculoskeletal impairment and had only one question that related to epilepsy which had not been validated for this purpose. To their credit they did validate it partially by re-examining a further 10% of those who screened negative and reassuringly picked up no further cases. They used standardised diagnostic criteria, however a physiotherapist made the diagnosis on a clinical basis with no verification using investigation or expert review by a neurologist.

Fifty-one people responded ‘yes’ to the screening question, and 47 of them (92%) were confirmed to have epilepsy based on follow-up questions, giving a prevalence of epilepsy in the screened population of 0.7% (0.5–0.9%). With a population of 8.44 million, this extrapolates to around 59,000 people in Rwanda affected by epilepsy [95% CI 42,000–76,000]. Prevalence was adjusted to the European Standard Population. The overall age-

adjusted prevalence was 0.6. For those aged 50 years and older the crude prevalence was 4.7/1000.

Table 1.9: The Prevalence Data of Epilepsy from Sub-Saharan Africa Over the Last Thirty Years, Demonstrating its Heterogeneous Nature.

Country (with reference below)	Year	N	Prevalence per 1000 (crude prevalence is presented unless otherwise stated)	95% CI	% age <20years Or more details on age if specified	Population
Benin (Agbogbome) [337]	1995	530	24.5	10.9-38.1		Rural
Benin (Savalou) [338]	1996	1443	15.2	8.7-21.7		Rural
Benin (Zinvie)* [302]	2000	3134	33.5	22.3-44.3		Rural
Benin* [308]	2007	11668	12.7	10.8-14.8		Rural
Burkina Faso [312]	1993	16627	10.6	9.1-12.2	76.3	Rural
Burkina Faso [335]	2007	888	45.0 Active epilepsy 39.0	33.0-60.0 28.0-54.0		Rural
Cameroon [339]	1989	500	70.0	46.3-93.6		Rural
Cameroon (Bilomo)*	2000	1900	58.4	46.9-		Rural

[340]				69.1		
Ethiopia (Butajira) [341]	1990	60820	5.2	4.6-5.8	59.8	Rural
Ivory Coast [342]	1988	1176	7.6	2.5-12.7		Rural
Ivory Coast [343]	1990	920	59.0	43.0-75.0		Rural
Ivory Coast (M'Brou) [344]	1995	2960	18.2	13.2-23.2		Rural
Kenya [345]	1988	2960	18.2	13.2-23.2	50+ 2.1 (95% CI 1.7-2.7)	Rural
Kenya [319]	2003	151408	2.9	2.6-3.2	Populations aged 6+ years. 3% aged 65+ years. Prevalence those aged 50+ 2.1 (95% CI 1.7-2.7)	Rural
Liberia [346]	1983	4436	28.0	23.0-33.0		Rural
Madagascar [347]	2001	925	20.8	11.3-30.3		Urban
Mali* [306]	2000	5243	15.6	12.2-19.0		Rural
Nigeria [99]	1989	2925	6.2	3.3-9.1		Rural

Nigeria (Aiyete) [25]	1982	903	37.0	24.2-49.8		Rural
Nigeria (Igbo-Ora) [327]	1987	18954	5.3	4.2-6.4		Urban
Rwanda [336]	2005	6757	7.0 Adjusted to European population 6.0	5.0-9.0	Prevalence of those 50+ years 4.7	Urban and Rural
Senegal [348]	1986	7682	8.3	6.2-10.4		Rural
Senegal [349]	1996	2903	21.0	15.5-26.5		Rural
Tanzania [313]	1992	18183	10.2	8.7-11.7		Rural
Tanzania [294]	1999	4905	8.6	6.0-11.1		Rural
Tanzania [315]	2003-2004	7399	Crude 11.2 Age-adjusted 13.2 Crude active epilepsy 8.7 age-adjusted rate of 9.1 crude prevalence	8.9–13.9	Prevalence of those 55+ years 6.0	

			rate of active epilepsy for those aged 55+ was 6.0			
Tanzania [333]	2009	103026	Age adjusted 2.9 Crude 2.8 Crude adjusted for non response 3.8	(2.6-3.2) (2.5-4.0) (3.5-4.2)	Crude 60+ 1.2 (0.7-1.7)	Rural
Togo (Akebou) [328]	1996	4182	13.1	9.6-16.6		Rural
Togo (Kloto) [314]	1991	19241	12.3	10.7-13.9		Rural
Togo (Kozah) [329]	1989	5264	16.7	13.1-20.3		Rural
Togo (Tone) [330]	2000	9143	18.6	15.7-21.5		Rural
Uganda [350]	1996	4743	13.0	9.7-16.3		Rural
Zambia (Chikankata) [351]	2004	55000	12.5	11.5-13.5		Rural

*Those studies utilising the Limoges questionnaire

1.5.1.2.3.4.5.3 *The potential of prevalence to underestimate burden due to high mortality*

Although the prevalence of epilepsy is two to three times higher in low income countries in comparison to high income countries, it is not as high as the incidence would suggest. This discrepancy is probably because mortality from epilepsy is substantially higher in the former although cure from resolution of secondary epilepsy (which is also more common in low-income countries) is also a possibility [295]. In high income countries mortality in PWE (as measured by the standardised mortality ratio [SMR]) is two to three times that of the population without epilepsy after adjustment for age [352]. The ratio is markedly higher in low income countries; however, only limited data are available, and what is available is based on very small numbers. In Uganda, the SMR is as high as 7·2, although this calculation was based on only 18 deaths [353]. In Ethiopia, the crude mortality in patients with epilepsy was 31·6 per 1000, twice the mortality rate estimated in people without epilepsy which was 16·4/1000 [311]. This observation was based on 20 deaths in a population of 316 patients in 2 years.

There is very little information on long-term follow-up of PWE, however the 2 studies that have been performed found PWE had a significantly increased risk of death. Jilek-Aall and Rwiza [354] performed a 30-year follow-up of 164 patients in an outpatient clinic in rural Tanzania. They reported mortality in PWE as 2 times the general population and that treatment significantly reduced the number of deaths due to epilepsy-related events.

In Cameroon Kamgno et al [355] found that 128 PWE had a six-times greater risk of dying than controls, but most of the patients did not receive appropriate and regular treatment.

In conclusion the mortality associated with epilepsy in low-income countries is substantially higher than in high-income countries. In the majority this is felt to be a consequence of untreated epilepsy however this is another under-researched area [295]. Mortality will hopefully decrease as effective treatment for epilepsy becomes widespread.

It is not only the chronic management of epilepsy that is fundamental but also the management of epileptic emergencies such as status epilepticus as demonstrated by the recent article by Mpimbaza et al with commentary from Herman [356].

1.5.1.2.3.4.6 *Risk Factors*

The literature reports that the main contributor to the increased prevalence of epilepsy in low income countries in comparison to high, is the higher number of risk factors e.g. infections such as, neurocystercercosis, onchocerciasis, falciparum malaria, meningitis, encephalitis and opportunistic infections related to HIV, trauma, particularly head injury related to road traffic accidents, falls and violent attacks, prenatal and perinatal injury, malnutrition, brain tumours and genetic factors.

The majority of studies that assess risk factors for epilepsy are purely descriptive in nature and therefore the contribution that each of the risk factors represents is difficult to measure as the evidence is often purely circumstantial [294].

There have been a few case control studies in SSA providing more than inferred relationships between each of the risk factors specifically prior febrile seizures [357-359], family history [304, 359], head injury [357, 358], perinatal complications [304, 359], CNS infections[359], Onchocerciasis[360], Cysticercosis [304, 360]. However, a high proportion of the case control studies did not find a cause [305-307].

A more recent nested case–control study was performed by Edwards et al[319], the factors associated with increased risk for convulsive epilepsy in adults and children were family history of febrile or non-febrile seizures and head injury. In children aged 6–18 years, adverse perinatal events and their mother being a widow were potential risk factors.

All studies had small numbers with limited power to detect any differences between cases, control and methodological bias as other variables were not considered. The true

impact of each specific risk factor still needs to be assessed in more detail. Many of these risk factors can be prevented with inexpensive interventions yet few studies have focussed on the impact of risk factor reduction, there is need for research and follow up action in this area [295].

The need for more research is supported by Winkler et al's recent review article [361]. They claim that neurocysticercosis (NCC) accounts for 30-50% of acquired epilepsy in SSA; their recent case controlled imaging study demonstrated definitive and probable NCC in 14% of epileptic cases in comparison to only 2% in the control group. The study was potentially open to bias, a hospital population may have more severe epilepsy than a community epileptic population and the control group, also from the hospital and imaged for another reason, were potentially from a wealthier cohort than average and therefore would have less exposure to taenia solium. The authors conclude that NCC is the most important cause of secondary epilepsy in SSA and feel that identification of cases through appropriate diagnostic tools (specifically serology and neuro-imaging) followed by appropriate treatment is urgently required. Further prevention of this disease would significantly reduce the epilepsy burden.

However Pal et al [362] in their article "Neurocysticercosis and epilepsy in developing countries" conclude that for both neurocysticercosis and epilepsy, there is a dilemma about whether limited public resources would better be spent on general economic development, which would be expected to have a broad impact on the health and welfare of communities, or on specific programmes to help individual affected people with neurocysticercosis and epilepsy. The approaches require detailed economic evaluation and comparison.

Neurocysticercosis is however unusual with respect to the clinical management conundrum that it represents. The other causative infections appear to be more straightforward with the general message being prevention and cure of neuro-infections, should be the priority in the fight against epilepsy in SSA. In her recent article Singhi [363]

concludes that central nervous system infections and epilepsy are the main cause of seizures and acquired epilepsy worldwide and that prevention of CNS infections is the only definitive way forward to reduce the burden of epilepsy in developing countries.

1.5.1.2.3.4.6.1 *Malnutrition and Epilepsy*

Crepin et al[308] compared malnutrition rates in PWE with controls in Benin in 2005. Standard diagnostic criteria were used for epilepsy and for malnutrition and controls were age and sex matched although it was not possible to match for poverty and sanitary facilities. The investigators were not 'blinded'.

A total of 131 cases and 262 controls were included. This failed to reach the minimum estimated number of subjects required but achieved sufficient power due to a higher than expected malnutrition odds ratio. The authors found that malnutrition was significantly more frequent in cases than controls (crude pOR=2.9; 95% CI: 1.6-7.4) (crude prevalence 22.1% vs. 9.2%, p = 0.0006). Feeding difficulties were more frequent and health status was worse in cases. Because problems relating to malnutrition might be secondary to feeding difficulties due to cerebral palsy, cognitive impairment, head injuries, or a history of cerebral malaria, these co-morbidities should have been accounted for but were not.

The authors found an association between epilepsy and nutritional status but no inference can be made about the direction of this association because of the study design (cross-sectional study sampling on prevalent epilepsy status correlated with prevalent malnutrition). The best design for the study would have been a cohort study in order to test one direction of the hypothesis (malnutrition as the exposure factor or epilepsy as the exposure factor) but this kind of study is more difficult to carry out in a developing country. It is difficult to establish the direction of the link between epilepsy and malnutrition in developing countries because the few studies on this relationship that have been published have conflicting methodologies Further, conclusions disagree on the direction of this link.

In conclusion additional differently designed studies, such as a cohort study, need to be done to further clarify the direction of the association between malnutrition and epilepsy. However Crepin et al's [308] study does suggest that it is important to pay attention to the nutritional status of people with epilepsy in order to implement global programs to fight against this condition..

Earlier studies using the Limoges methodology have also shown an association between epilepsy and malnutrition but have found this to predominate in children rather than adults, it is not known if this is a result of improvement of nutrition or death in childhood [301].

1.5.1.2.3.4.6.2 *Age and epilepsy*

There is a marked difference in the age of onset of epilepsy in low income countries in comparison to high. The latter has a bimodal distribution with peaks of incidence in childhood and those aged over 65 [316]. In the former it is generally understood that incidence is increased in children and young adults. Age at seizure onset is reported in few studies, but is usually susceptible to recall bias. When available, seizure onset was before age 20 years in more than 60% of cases. This young incidence results from the initial 2 risk factors presented above, infection and trauma. However it is worthy of note, especially for this thesis with its focus on the older population, that studies in the older age groups are limited. As the population of developing countries continue to age and the prevalence of NCDs such as stroke increases as will the burden of epilepsy in these age groups, again demonstrating the impact that the "double burden" of disease will have on SSA [25, 295, 311, 327, 341].

1.5.1.2.3.4.7 *Treatment of epilepsy in SSA and reducing the treatment gap*

It is estimated that up to four-fifths of the potential market for anti-epileptic drugs (AEDs) is in low-income (LI) and lower middle income countries (LMICs).The proportion of PWE who require treatment but who are not receiving it is known as the treatment gap (TG) [364]. Substantial global disparities in the epilepsy treatment gap were identified by

recent systematic reviews that show that 60-90% people with epilepsy in low-income countries and fewer than 10% in high-income countries were untreated or insufficiently treated for their epilepsy [295, 365-368].

Studies using the Limoges protocol found the TG to be 55.7% (95% CI 52.7–58.7), this was identified by simple questioning which may be unreliable[301].

In northern Tanzania more than three quarters (75.9%) of the people with epilepsy identified through a community based study did not take antiepileptic drugs (AEDs), despite proximity to a hospital that stocked them [315]. Another study from northern Tanzania reported the TG to be 68.4% (95% CI 63.0–73.7) [333]. In the Gambia, the continuous treatment rate in PWE was less than 10% [369]. In the Kilifi district of Kenya the TG has recently been reported to be 62.4% (95% CI 58.1–66.6)[364, 370]. In Rwanda it was found that 41% had or were currently receiving treatment and 38% had been to a traditional healer [336]. In Benin only 42% of patients took antiepileptic treatment at the time of the study and this included traditional treatment (54% of cases were on phenobarbitone, 39% on traditional treatment, and 7% on both traditional and modern treatment) [308]. A study from Senegal, however, shows a narrower TG with 23% of patients not receiving adequate treatment [371].

Even if patients are supposedly on treatment in SSA, in the majority this may not be optimal. In an urban zone of Nigeria only 30% of patients were seizure-free after 2 years of treatment [372]. Factors contributing to this low remission rate were poor treatment compliance and a history of six or more seizures before treatment onset. This demonstrates that the identification of treatment gap requires more than questioning a patient if they are on treatment, as is done in the majority of studies..

Information on individual compliance with AEDs is usually gathered just by asking the patient and was done in this manner in all the studies described above except for the one in the Kilifi district of Kenya. Recognising that self-reported drug adherence is heavily

biased Mbuba et al [370]also measured the presence or absence or AEDs in the blood. They found that that sensitivity and specificity of self-reported adherence compared with AEDs detectable in the blood was 38.1% (95% CI 31.1–45.4] and 80.8% (76.0–85.0) respectively. They state that assessment of adherence to treatment calls for an objective measure, like AED levels in the serum, although they appreciate how difficult this is in the majority of clinical encounters in SSA. They found the TG as defined by the presence of therapeutic levels of AEDs in the serum was 70.3% (65·9–74·5) (92% of PWE agreed to have their blood taken). Mbuba et al's study has its own limitations;

1. Compliance is typically characterised by highly variable AED serum concentration, which increased after supervised drug intake, this would require more than one blood test and would be even more difficult to perform in SSA.

2. It is not known what the normal therapeutic range of AEDs are in an indigenous African population and the study presumes them to be the same as a white population which might not be correct, particularly as malnutrition and protein deficiencies might influence concentrations.

3. Drugs with a long half life might still be detectable in the serum long after medication has actually been taken.

Derivation of a true objective surrogate measure for the epilepsy TG could prove very difficult in resource-poor countries, but remains an important goal if the TG is to be identified and closed.

The TG has been found to be typically twice as high in rural areas in comparison to urban areas, this is presumed to be because medical infrastructure, resources, and personnel are largely focused in urban regions [323-326].

The general message for the treatment of epilepsy in SSA is that there is an urgent need to reduce the TG by modification of the factors that contribute to it; these are mainly two fold access to healthcare and adherence to treatment. Both of these were expanded in a recent systematic review, and were (in order);

1. Inadequate skilled manpower
2. Cost of treatment
3. Unavailability of medications
4. Cultural beliefs about the causations
5. Use of traditional medicine
6. Distance from the health centre
7. Stigma attached to taking anti-epileptic medication [364]

These factors all need to be addressed as part of government initiatives [300, 373].

The recent study performed by Mushi et al [374] concludes that poor knowledge and strong cultural and religious beliefs characterise the experience of PWE in SSA. Epilepsy-related stigma contributes to overall disease burden, and PWE face many degrees of exclusion. There is a need to educate communities and change attitudes.

These studies highlight that any epilepsy treatment programme needs to be about more than just the distribution of drugs; it is also fundamentally important to address lack of knowledge in patients, communities and healthcare workers.

1.5.1.2.3.4.7.1 *Treatments available in SSA*

It is the older AEDs that are available in the majority of low income countries, namely phenobarbital, phenytoin, carbemazepine, and sodium valproate, over 70% of patients will respond to one of these AEDs [375].

The cheaper of these drugs, phenobarbital and phenytoin are available in SSA and have been the focus of programmes to reduce the TG. They are not however without their problems, e.g. side-effects and interactions to other drugs used to treat co-morbidity such as HIV [376, 377].

Chisholm and Saxena's [378] recent article explores cost effective strategies to combat neuropsychiatric conditions in sub-Saharan Africa and South East Asia, they performed simultaneous evaluations of the cost effectiveness of 44 individual or combined interventions for five key neuropsychiatric conditions. They established that alcohol control measures and drug treatment for epilepsy and depression were the most effective and proposed that these should be the focus of neuro-psychiatric treatment campaigns.

1.5.1.2.3.4.8 *The epidemiology of epilepsy in summary*

Epilepsy in SSA is a disorder with high prevalence and incidence, severe prognosis in terms of morbidity and mortality, and a strong link to infection. The burden of epilepsy can be reduced in poor parts of the world by alleviating poverty and by reducing the preventable causes, namely perinatal insults, parasitic diseases, and head injuries. Education of medical professionals, particularly primary healthcare workers and local communities is fundamental to address the diagnosis and treatment gap and reduce stigma.

Reviewing the literature highlights the need for further studies, with good methodological design and standardised questionnaires. General population surveys with a sufficient number of participants should be prioritised, and population groups not previously focussed on, like the elderly should be highlighted. Longitudinal studies are also needed to better estimate incidence, morbidity, mortality and causation.

1.6 Epidemiology of "All Cause" Neurological disorders

It is fundamental to know about the prevalence of Neurological Disorders as ever-increasing demand for health services forces health planners to make choices about

resource allocation. Information on relative burden of various health conditions and risks to health is an important element in strategic health planning [13].

The WHO's Global Initiative on Neurology and Public Health highlights the paucity of information about the prevalence and burden of neurological disorders and a lack of policies, programmes and resources for their treatment and management [379].

There are few publications from SSA in international journals of neurology and international collaboration is often relied upon to forward research in this area. The WHO acknowledges the fact that there is a vast gap in the knowledge concerning the public health of neurological disorders. Their 2006 document entitled 'Neurological Disorders: Public Health Challenges' provides the public health perspective for neurological disorders in general and presents updated estimates and predictions of the global burden. Their figures are however estimates and predictions and worldwide prevalence data are lacking [13].

With awareness of the massive burden associated with neurological disorders came the recognition that neurological services and resources were disproportionately scarce, especially in low income and developing countries. Furthermore, a large body of evidence shows that policy-makers and health-care providers may be unprepared to cope with the predicted rise in the prevalence of neurological and other chronic disorders and the disability that results from the extension of life expectancy and ageing of populations globally [380]. The neurologist-population ratio in African countries varies from 1 per 162,885 persons to none in 11 countries, compared with 1 per 29,200 in the US [11].

In response to the challenge posed by neurological disorders, WHO launched a number of global public health projects; these include the Global Initiative on Neurology and Public Health whose purpose is to increase professional and public awareness of the frequency, severity and costs of neurological disorders and to emphasize the need to provide neurological care at all levels including primary health care. This global initiative has also

highlighted the paucity of information on the burden of neurological disorders but in addition has demonstrated the lack of policies, programmes and resources for their management [379, 381, 382]. Limited workforce, poor equipment and little research blight SSA's ability to cope with neurological disorders. Capacity needs to be built in research, diagnosis and treatment of neurological diseases which will undoubtedly require education of the primary healthcare workforce [383].

In response to these findings, WHO and the World Federation of Neurology (WFN) recently collaborated in an international Survey of Country Resources for Neurological Disorders involving 109 countries and covering over 90% of the world's population. The survey collected information from experts on several aspects of the provision of neurological care around the world, ranging from frequency of neurological disorders to the availability of neurological services across different countries and settings. The findings highlight the inadequacies and inequalities for patients with neurological disorders worldwide (especially in SSA) including access to healthcare [384, 385].

This prevalence study aimed to identify a complete list of neurological disorders as defined by the WHO ICD 10 (see figure 1.1);

The diagnostic criteria and epidemiology of the most common and public health relevant conditions namely, tremor, parkinsonism, cerebellar disorders, headache, stroke and epilepsy have been described in full as these have been highlighted as particularly burdensome by the WHO and the WFN in their most recent publications. [13, 384, 385].

This prevalence study also aimed to identify, dyskinesias, motor neuron disease, spinal cord dysfunction including injury, infection resulting in CNS dysfunction, polyneuropathies, nerve, nerve root and plexus disorders and inflammatory/infectious diseases of the PNS e.g. polio and leprosy. A more superficial review of the diagnostic criteria and epidemiology of these conditions has been included in appendices 1.2 and 1.3.

In this part of the literature review, I focussed on community based epidemiological studies that investigated the prevalence of "all-cause" neurologic disease in SSA. Due to lack of up-to-date data from SSA I have included robust community based epidemiological studies from other developing countries. Worldwide review articles were included. and references listed in relevant publications examined. The data from the GBDS was also utilised.

It is justified to review most of the literature from SSA and exclude other world regions because of the following factors;

Despite diverse socioeconomic and environmental factors, there are many common traits across SSA, namely:

- The wide-based age-specific pyramid with high fertility and mortality and short life expectancy. Over 680 million people live in sub-Saharan Africa, more than half are under age 15 years. Life expectancy was 45·8 years in 2002 and the mortality of children under age 5 years was 164·2 per 1000
- Mainly rural populations despite rapid urban migration
- Widespread poverty and unequal distribution of the health services. Only 46·4% of the rural population have access to drinkable water and 55% have access to sanitation facilities. These extreme conditions of poverty facilitate the transmission of parasitic and bacterial infections.
- The absence of sound infrastructures for collection of epidemiological data.

A review at this almost continental level is justified because the lack of studies limits analysis at a sub-regional or country level. Data from SSA differ from those gathered in the north of Africa probably due to lower rates of infectious disease and better medical infrastructures [294].

1.6.1 *The Global Burden of Disease Study and its ability to reflect the burden of neurologic disease in SSA*

The Global Burden of Disease Study (GBDS) has recently produced evidence that pinpoints neurological disorders as one of the greatest threats to public health, highlighting that unless immediate action is taken globally, the neurological burden is expected to become an even more serious and unmanageable problem in all countries[7, 13].

The Global Burden of Disease study (GBDS) is the on-going international collaborative project between the WHO, the World Bank and the Harvard School of Public Health which started in 1993 by carrying out a study to assess the global burden of disease for the year 1990. The methods and findings of the 1990 GBD study have been widely published [7, 386, 387]. The GBD approach is one of the most widely used frameworks to provide information on population's disease burden. The GBD framework is based on the use of a common metric and mathematic model (DisMod) to summarize the disease burden from diagnostic categories of the WHO ICD in order to prepare consistent estimates of incidence, prevalence, duration and mortality [388]. A time based metric was designed that measures both premature mortality (years of life lost because of premature mortality or YLL) and disability (years of healthy life lost as a result of disability or YLD, weighted by the severity of the disability). The sum of these two components, disability-adjusted life years (DALYs), provides a measure of the future amount of healthy life (years expected to be lived in full health) lost as a result of the incidence of specific diseases and injuries [7]. One DALY can be thought of as one lost year of healthy life. Neuropsychiatric disorders were concluded to be major causes of lost years of healthy life as measured by DALYs, and were significantly underestimated when measured by mortality alone [7].

As a follow-up to the 1990 GBDS, WHO undertook a new global assessment of the burden of disease for the year 2000 and subsequently in 2002. The GBDS 2000 drew on a wide range of data sources to develop internally consistent estimates of incidence, prevalence, severity, duration, and mortality for over 130 major diseases, for 14 epidemiological sub regions of the world [159].

There is limited epidemiological data that addresses the burden of "all-cause" neurological diseases in SSA. There is a scarcity of community based prevalence, incidence and mortality studies. This is evidenced by the GBDS where data on adult mortality was absent in 42 of the 53 countries [389]. However despite these limitations the GBDS makes the following estimations that outline the impact of neurological disease: Neurologic disorders affect 250 million people in the developing world, this number is expected to increase as the infectious burden of disease (HIV and malaria contribute significantly to neurologic disease burden) is coupled with the NCD epidemic and the ageing population [390],[391]. The leading causes of disability as indexed by DALYs in Africa include primary neuro-psychiatric disorders, and infectious and cardiovascular diseases with neurologic implications [389]. In 2005 6.29% of DALYS were attributed to neurological disorders worldwide, this is projected to increase to 6.39% in 2015 and subsequently to 6.77% in 2030. Half the burden of the DALYs is attributed to cerebrovascular disease, 12% to Alzheimer's disease and other dementias, 8% to epilepsy and 8% to migraine. When this is divided up and expressed as an overall percentage, dependent on the countries income, it is projected to be higher in high income countries, 10.9% in comparison to 4.5% in low income countries. However DALYS per 100,000 are highest for neurological disorders in lower middle and lower income countries at 1514 and 1448/100,000 in 2005 respectively. Neurological Disorders account for 12% of total deaths, of which 85% are due to cerebrovascular disease. This is also projected to increase from 2005 to 2030. YLDs are projected to be 14% in 2005 and still be 14% in 2030 [30].

The use of the GBDS in SSA is weakened by a number of factors; much of the data is extrapolated from South Africa to the rest of SSA, arguably a very different socioeconomic population, the rest of the data is based on very few poor quality studies and consequently inaccuracies result. Relevance and accuracy of data is very important in programme planning, understanding of disease process including the role of risk factors. Calculation of burden of risk factors based on inappropriate models will result in misdirected disease-prevention strategies. However in the absence of other information,

it is appropriate to use model based estimates as nothing else exists. However such estimates are not effective monitoring devices and therefore quality data collection on adult health in SSA is required [392, 393].

In conclusion, Neurological Disorders represent a much higher burden than digestive disease, respiratory disease and malignant neoplasms when measured using the GBDS. They are a serious threat to public health. Most burden is in low and low middle income countries and strategies to improve world health should concentrate on this issue [30].

1.6.2 *"All Cause" Neurological Disorder Prevalence data*

1.6.2.1 *Hospital based studies*

Winkler et al. [394] recently reviewed hospital-based prevalence studies of neurological disorders in rural African settings. They concluded that out of 8676 admissions 740 patients (8.5%) were given a neurologic diagnosis, the most frequent of which were seizures (26.6%) and infectious diseases (18.1%). The overall mortality of neurologic disease was 21%.

Other hospital-based studies from SSA estimate that neurological disorders make up 3.0–33.1% of all hospital admissions and 4.2–7.5% of out-patient reviews and conclude that the most common reasons for admissions are stroke and neurological conditions occurring secondary to infection[28, 395].

These studies and Winkler et al's review do emphasise that neurological disease contributes substantially to morbidity and mortality burden however, it is not possible to elaborate on them further as their joint methodology and consequently their conclusions are highly biased. Poor access to healthcare for the majority of the population of SSA means that hospital based studies are a poor reflection of overall morbidity burden.

1.6.2.2 *Community prevalence studies from SSA*

The only community-based studies from SSA on the prevalence of all cause neurological diseases are from over 20 years ago.

Osuntokun et al [3] performed the first large scale community based 2 phased epidemiological survey of all major neurological disorders in SSA reporting a crude prevalence rate of 11.1/1000 or 62.1/1000 if lifetime prevalence of headache is included. A whole Nigerian town with a stable population of 19,954 was surveyed, with almost 100% participation rates, eliminating selection bias. All ages were surveyed including children. The neuroepidemiological protocol developed by the neurosciences programme of the WHO was utilised, it had previously been piloted in this community and had a sensitivity of 95% and a specificity of 80%. The population surveyed had significant input from medical practitioners from local medical schools which although beneficial for project acceptability potentially introduced population bias and therefore it is difficult to extrapolate results to the rest of the country. However all other demographic parameters like age and sex distribution matched the rest of the country. Diagnostic criteria were used, however a mixture of lifetime prevalence (for headache) and point prevalence rates were included.

Tekle-Haimanot et al [5] subsequently performed a larger "all-cause" neurological disorder prevalence study in the community in rural central Ethiopia between 1986 and 1988. All ages were surveyed. The authors reported a crude prevalence rate of 14.9/1000. Again the neuroepidemiological protocol developed by the neurosciences programme of the WHO was utilised, it had been previously piloted in this community and found to have a good sensitivity and specificity (91% and 85% respectively). All major neurological disorders were identified. The study was large, surveying 60,820 inhabitants, who were randomly sampled, eliminating selection bias. Every effort was made to ensure good participation rates (95-100%), including recruitment of enumerators (which were then highly trained) from the local population and treatment of treatable neurological

disorders.. The head of the household answered on behalf of the household members, thus as discussed previously stigmatising or subjective conditions could be under-reported. Cases were confirmed by expert neurologists. The study area had very low levels of literacy in comparison to the general Ethiopian population (88.6% vs. 40%) perhaps an indication that the population surveyed was not representative of the Ethiopian population as a whole.

Both epidemiological studies were landmark studies of their time however the age of the data limits its use today. In the Nigerian study 58% of patients were aged below 20 years and only 2.82% of the population were aged 70 years and over. In the Ethiopian study, 59% of the inhabitants were aged below 20 years, with a median age of 14.5 years. Although this represented the age distribution of SSA at the time, demographics have changed since these studies were performed, the ageing of the population will impact significantly on the relative contribution of neurological disorders. This population structure with the lack of age adjustment means that prevalence rates reported are difficult to compare with worldwide prevalence rates, particularly those from our prevalence study which reports on a purely elderly population.

Table 1.10: The prevalence of Neurological disorders in Nigerian and Ethiopian Community Populations in the 1980s

Neurological Disorder	Nigeria Crude prevalence rate/1000 [3]	Ethiopia Crude prevalence rate/1000[5]
All	11.10 (Including lifetime prevalence of headache 62.1)	14.90
Headache	Lifetime prevalence 51.00	
Epilepsy	5.33	5.19
Speech disturbance Deaf Mutism Other speech	0.15	2.56 1.25 1.31
Poliomyelitis	0.15	2.41
Mental retardation	0.10	1.69
Peripheral Neuropathy Leprosy Traumatic Peripheral Neuropathy Injury Bell's Palsy Hereditary PN (including Charcot-Marie-Tooth) Others	2.68 0.10	1.54 1.03 0.24 0.13 0.10 0.30
Complications of spondylosis	1.12	
Hemi paresis Early childhood Cerebrovascular Post-traumatic Unknown aetiology	0.58	0.62 0.29 0.15 0.30 0.15

Cerebral palsy	0.10	0.20
Optic atrophy		0.16
Perceptive deafness		0.12
Tropical spastic paraparesis		0.10
Syncope	0.10	
Parkinson's disease	0.10 (aged 40+ 0.59)	0.07
Motor Neurone disease	0.15	0.05
Chorea/athetosis		0.05
Ataxia		0.05
Tremors Essential Tremor Cerebellar degeneration	0.20 0.10 0.10	0.05
Torticollis		0.02
Myopathy		0.02
Hemifacial spasm		0.02
Organic psychosis	0.10	
Muscular dystrophy	0.05	
Pyomyositis	0.05	
Spina bifida	0.05	
Alcohol dependence	0.05	
Cerebral malaria	0.05	

1.6.2.3 ***Community based prevalence studies from multiple low income country sites***

Mateen et al [396] documented reportable neurologic diseases in refugee camps in 19 countries including Burundi, Cameroon, Central African Republic, Democratic Republic of Congo, Chad, Ethiopia, Guinea, Kenya, Namibia, Rwanda, Tanzania, Uganda, Zambia from SSA. The data presented is difficult to interpret as it is presented in the format of the number of health visits required for neurological disease rather than in terms of prevalence. It does however indicate that non-communicable neurological diseases

including epilepsy and cerebrovascular disease contributed far more to morbidity burden than neurologic infectious disease in refugee camps and targeted programmes to address stroke and epilepsy in the camps should be a priority. The authors highlight the issues of under-reporting of all neurologic diseases in these settings.

1.6.2.4 *Community based prevalence studies from developing countries other than SSA*

In 1985 Attia Romdhane et al[397] carried out a neuroepidemiologic population based prevalence study in Tunisia using the WHO protocol as used in the Nigerian and Ethiopian studies described above. The study site of Kelibia was chosen as it was broadly representative of the general population of Tunisia. The major neurological survey in Tunisia was followed by a control survey to check the reliability of the initial survey's results. Random sampling, training of interviewers, diagnostic criteria and review by neurologists all added to the reliability of results. The age adjusted (according to the WHO population) prevalence of "all-cause neurological disorders was found to be 59.5/1000 inclusive of migraine and 25.5/1000 exclusive of headache disorders

Using two phased methodology, Gourie-Devi et al. [52] screened a randomly sampled 102,557 urban and rural dwellers from Bangalore, India, for neurological disorders and quote an age-adjusted prevalence of 33.6 per 1000 in the general population and 50.1 per 1000 in the >60 years population. Interestingly, they found prevalence rates to be almost twice as high in rural areas (40.7 per 1000) compared to urban dwellers (21.9 per 1000) and linked this to lower socioeconomic status. They utilised an acceptable and standardised screening instrument and claim their large study population is representative of the rest of India.

Das et al [43, 53] quote a crude prevalence of 60.9/1000 in the 60 and over age group in Kolkatar, India and 11.79/1000 in the general population with an age adjusted rate of 15.2/1000, but this was performed in the US 2000 population. A two-phased approach was used with random sampling, trained interviewers, case verification by neurologists and use of diagnostic criteria all of which increased the reliability of the results. However

the screening questionnaire used was only designed to pick up stroke, essential tremor, epilepsy, parkinsonism and dementia. The exclusion of other less common neurological disorders complicates the interpretation of results and their comparability to other study data.

Table 1.11: The Prevalence of Neurological Disorders from Developing Countries other than Sub-Saharan Africa

Neurological disorders	**Tunisia age adjusted prevalence rate/1000** [397]	**Bangalore, India age adjusted prevalence rate/1000** [52]	**Bangalore, India age adjusted prevalence rate/1000 Over 60 population [52]**	**Kolkata crude prevalence rate/1000** [43]	**Kolkata crude prevalence rate/1000 60+ population** [53]
Total	59.50	33.60	50.10	11.79	60.9
Headaches Migraine	34.00	9.67			
Epilepsy	3.64	8.26		5.58	2.57
Febrile Convulsions	0.52				
Dementia	0.47			0.88	7.89
Parkinsonism	0.68	0.76		0.46	3.30
Tremors Essential Tremor	3.57	4.08			13.76
Huntington's chorea	0.43				
Other abnormal movements	0.29				
Stroke	1.84	2.62		4.87	33.93
Transient Ischaemic attack	0.27				
CNS tumour	0.44				

Head trauma	0.36				
Multiple sclerosis	0.12				
Hereditary spinocerebellar disease	0.30				
Intracranial infection Including encephalitic and meningitic sequelae		0.30			
Other or unspecified CNS disorder	0.62				
Cerebral palsy	0.83				
Metabolic encephalopathy	0.15				
Mental retardation	1.06	1.16			
Chromosomal anomaly	0.24				
Congenital CNS malformation	0.47				
Late effects of poliomyelitis	0.37				
Anterior horn cell disorder	0.20	0.95			
Hereditary muscular	0.32				

dystrophy					
Peripheral nerve disorders		0.99			
Hereditary peripheral neuropathy	0.19				
Diabetic polyneuropathy	0.97				
Upper-or lower limb mononeuritis	0.34				
Trigeminal neuralgia	0.21				
Facial nerve disorders Bell's palsy	2.62	0.77			
Optic nerve disorder	0.31				
Ocular movement disorder	0.23				
Perceptive deafness	1.26				
Vestibular disorder	0.20				
Nerve root radiculopathy	1.78				
Other neurologic disorder	0.41				

Older studies from India include those performed by Razdam et al[137] in Kashmir and Saha et al[61] in West Bengal. Both studies utilised the WHO protocol in the general population. They yielded crude prevalence rates of 9.67/1000 and 29.07/1000 respectively.

Gourie-Devi [52] and Das[53] both present data specific to the elderly population, they demonstrate significantly higher rates of neurological morbidity. However no study performed to date has been designed specifically for and carried out only in the aged population. This is despite the fact that many neurological conditions are more prevalent in the elderly and an ageing population will further increase their prevalence. This is particularly true for stroke, Parkinson's disease, essential tremor and peripheral neuropathy. Some conditions, however, are not represented in this age group in low-and middle-income countries as the mortality rate in this environment precludes those with these conditions from living to old age. These include traumatic spinal injuries and hereditary disorders. This highlights the unique nature of the elderly population.

These recent population based studies from India demonstrate that in terms of methodological issues it is possible and necessary to conduct population based "all-cause" neuroepidemiological studies in situations of low income, scarce resources and address the need to focus resource on the elderly.

1.6.2.5 *Community prevalence studies from developed countries*

Broe et al. [155] quoted the prevalence of neurological disorders as 214.1 per 1000 in the 65 and over age group in the UK. In the general population of developed countries, prevalence rates vary from 68 to 142 per 1000 [398, 399].

Hospital studies in developed countries are a much better reflection of disease burden than in developing countries because of better access to healthcare. Perkin [400] reported

that in a survey undertaken by the association of British Neurologists, 16 conditions, namely, epilepsy, headaches other than migraine, migraine, cerebrovascular disease other than transient ischaemic attacks, multiple sclerosis, faints and blackouts, cervical disk disease, peripheral nerve palsies, transient ischaemic attacks, dizziness and giddiness, Parkinson's disease, lumbosacral spinal disease, cranial nerve palsy, peripheral neuropathy, facial pain, dementia, constituted 74% of the outpatient workload.

1.6.3 *Deaths from Neurological disorders*

Neurologic disorders cause 12% of deaths globally [401]. The burden of neurological disorders is substantially underestimated by mortality, morbidity is a much better reflection. In 2005, over 92 million years of healthy life were lost as a result of neurological disorders worldwide.

1.6.4 *The Epidemiology of "All Cause" Neurological Disorders in Summary*

The current literature attempts to demonstrate the high burden that neurological disorders represent to SSA, contributing significantly to the NCD epidemic. However it is either outdated, predictive or not conducted in general populations. Further accurate community based epidemiological studies are required to accurately document burden and facilitate the evidence-based healthcare planning that is needed for neurological disorders and other NCDs in resource-poor settings [383].

1.7 Treatment of Neurological Disorders

Most neurological problems are dealt with by general practitioners (GP) and hospital physicians, not by neurologists [402]. Developments in the management of neurological disorders are therefore relevant to doctors without specialist neurological training particularly in places with few neurologists like SSA [403].

In the past 5 years, new treatments have become available for neurological disorders previously considered untreatable (multiple sclerosis, Alzheimer's disease, motor neurone disease). Although the high cost of these treatments has sometimes led to issues with health budgeting and precludes their likely use in SSA in the near future[403].

The World Health Organization has launched a programme to scale up the treatment of people with neurological disorders, especially in poor countries, where more than 75% of people affected receive no treatment or care. The agency says that rich nations also have substantial gaps in treatment, with up to half the patients affected by these conditions left untreated [404].

1.8 The Cost of Neurological Disorders

A study conducted in Europe estimated that the annual economic cost of neurological diseases (dementia, epilepsy, migraine and other headaches, multiple sclerosis, Parkinson's disease and stroke) amounted to €139 billion (approximately US$ 180 billion) in 2004. This study only partially included direct non-medical costs (e.g. community care and informal care) and indirect costs. The results also demonstrated that the cost of dementia increases by 25% when informal care is included. In the same study, the annual cost of traumatic brain injuries was estimated at €3 billion; this figure is, however, a gross underestimate as it was based only on hospitalization attributable to trauma and omitted rehabilitation and lost workdays. Unfortunately, no equivalent estimates are available for developing countries [13].

1.9 Research Funding for Neurological Disorders

The research interest in rare neurological conditions is disproportionately larger than that in common conditions. There should be a change in the focus of medical research towards the most common conditions that are responsible for the greatest disability, death, economic cost, and loss of quality of life [405]. It is recognised that funding for research into a disease should be proportional to that disease's burden on society [406]; however,

conditions that account for 90% of the global burden of disease receive less than one tenth of the world's health budget [407].

1.10 Services available to support patients with neurological disorders in Africa

23 African Nations, with a population totaling 270 million people, had only 1-4 neurologists per country. Eleven nations with a population totaling 26 million have no neurologist [11]. There are less than 0.01 neuro-surgeons per 100,000 people in Africa, compared to 1.02/100,000 people in Europe [12].

1.11 Background information about Tanzania

Tanzania lies in sub-Saharan East Africa and has a population of 45 million (see figure 1.4). It covers an area of 945,087 square kilometres. Life expectancy is 55yrs for men and 56yrs for women. By 2025 the population is expected to rise to 67.4 million. 45% of the population are less than 15 years of age and 3% are over 65 years. The infant mortality rate is 58/1000 and 5.0% of men and 7.6% of women have HIV/AIDS [408]. Tanzania is one of the poorest countries in the world; approximately 90% of the population live off less than $2 US per day. Tanzania is defined by the WHO as within Mortality stratum Afr-E, having a high child and a very high adult mortality. Their broad group is High Mortality Developing. Tanzania's income category is low.

The Hai district lies in the north-east of the country on the slopes of Mount Kilimanjaro, the highest mountain in Africa. The Chagga are the predominant tribe, and most work as subsistence farmers, growing maize or bananas on "shambas" (small holdings). The majority of the population are Christian, but there are some Muslim and other denominations. Most of these people are born, brought up and live their entire life in the same village. Most villages have either a health centre or a village dispensary; there are 3 small local hospitals within the district. The main tertiary referral hospital is Kilimanjaro Christian Medical Centre (KCMC) in the town of Moshi in the adjacent district of

Kilimanjaro. It serves a population of 11 million people and has 450 inpatient beds. KCMC has a resident consultant Neurologist.

Within the Hai District there is a Demographic Surveillance Site with a population of 161,119 within 52 villages at the latest census on 1st June 2009. Further details of this unique epidemiological site are included in the methods section of this thesis.

Figure 1.4: Map of Tanzania

[409]

1.12 The Ageing Population; The Elderly in Africa

Populations worldwide, but particularly in developing countries, are ageing rapidly. In 2050, an estimated 2 billion people will be aged 60 and over and 80% will reside in resource poor settings [1]. The numbers of elderly people in sub-Saharan Africa are growing rapidly with increasing life expectancy while at the same time the proportions of children in the populations are declining. The number of people 80 years and above has increased tenfold in large parts of Africa since the 1950's, and the number of widows is growing fast. All this has several implications, including erosion of the social support from extended families and a dramatic change in the disease pattern. Multiple illness and permanent disability will become more common. African health care systems are ill-prepared for this transition, and social security for the elderly needs to be improved in the coming years. Local and regional research into morbidity and well-being is important for policy formulation. Improved health in childhood and middle age will probably be followed by improved health in old age, and this may offset the burden on the health care system of the growing number of elderly [410].

The extension of life expectancy and the ageing of populations globally are predicted to increase the prevalence of many non communicable, chronic, progressive conditions including neurological disorders. The increased capacity of modern medicine to prevent death has also increased the frequency and severity of impairment attributable to neurological disorders. This has raised the issue of restoring a life of acceptable quality for people who suffer from the sequelae of neurological disorders [13].

In the United Kingdom, the proportion of people over the age of 65 is expected to increase from 18% in the current population to 30% by 2030 [411]. By the year 2050 in the United States an estimated 15 million people will be over the age of 85 alone, compared with 3 million in 1990 [412]. The world population aged over 55 years increases by one million people per month. Eighty per cent of growth is in developing countries where, by the year 2020, the elderly population is likely to exceed one billion. Over the next 30 years the proportion of the world's elderly population living in developing countries is projected

to increase from 58% to 72% [413]. Since 1900 life expectancy has increased by 30 years in the US [414].

1.12.1 *The cost of the ageing population*

The ageing population produces substantial ethical and economic problems. Dworkin [415] states that $80 billion was spent treating patients with Alzheimer's disease in the United States alone in 1991. Hacker [412] reports that in the United States “spending on hip fractures, for example, is projected to increase from $1.6 billion in 1987 to as much as $6 billion in the year 2040 (in constant US dollars)” [412]. In view of these statistics, it is hardly surprising that there are increased calls for age to be used as the principal criterion for rationing [416].

More than half of the patients in hospital are 65 years or over. There are proposals to decrease innovations to increase life expectancy and increase innovations to increase quality of life. Additionally the importance of value conscious innovation is increasingly stressed. This is very applicable to developed countries but in developing countries the elderly population often do not have access to cheap long standing treatments which could in turn prolong and increase the quality of their lives [414].

1.12.2 *Arguments against ageism*.

Some form of rationing is necessary in medicine, and to use age as a criterion for rationing has been suggested. The adoption of ageist policies, however, may not result in the implied savings unless care is also withdrawn and ageist policies, which deny elderly people treatment because of their age, are both unfair and discriminatory.

It is the mark of a civilized society to look after its most vulnerable members, which includes the elderly. Treatment should still be rationalised based on patient benefit and this often is irrespective of age [416].

1.12.3 *Healthcare for the elderly in Africa*

Current public health policies in many Third World countries, supported by international agencies, focus on maternal health, contraception, and infant health. Ageing of society in Africa, Asia, and South America will result in more chronic, non-communicable diseases and these will become a prime health concern. .

There is an urgent need for research into the health care needs of elderly people worldwide. The ageing population will have a dramatic effect on the patterns of health care required and we need to make plans to deal with the medical problems associated with ageing in high and low income countries.

Some developing countries are proposing legislative measures to tackle the problems of ageing; these include Botswana, Mauritius, South Africa and Zimbabwe. These countries have developed policies and programs that will provide health, economic and social services to the elderly population. For example; Botswana's government has commissioned a study on the needs and care of the elderly in order to guide further policy on elderly care, Mauritius has produced an initiative to promote integration of the elderly into society and the Zimbabwe National Population project has listed the following strategies to be implemented;

- The introduction of legislation on care of the elderly;
- The provision of the elderly with pensions and some form of public assistance
- Making the health system more sensitive to the needs of the elderly
- The provision of adequate resources for the elderly looking after AIDS orphans

- Identifying ways in which the elderly can continue to make active contributions to the economic, social and cultural life of their families and communities. [417]

In Africa, family provides the majority of care for the sick and elderly population. Few formal systems for care exist. An increase in the dependent elderly and a change in social structure from extended to nuclear families will be detrimental to this current care provision and the need for institutionalisation of the elderly will present itself. Most African countries will be unable to deal with this due to a lack of social and economic infrastructure. This therefore requires government action [418].

1.12.4 *Screening of the Elderly population*

The MRC trial of the assessment and management of older people in the community reported a high frequency of unreported and unmet needs of elderly people. Recurrent review of elderly people is required [419].

1.12.5 *Aids and the Elderly*

Elderly Africans have HIV and AIDS too is the overall message from Awofeso et al [420]in their correspondence to the British Medical Journal (BMJ) in 2010. They call for the myth that HIV is only a problem for the under 50s and elderly Africans are not sexually active to be dispelled.

Many patients who were infected with HIV as youths now live into their 50s, 60s, and longer, and the average age at infection has increased [421]. The demographic health surveys (DHS) conducted between 2003 and 2007 contain limited data on self reported prevalence of HIV in men aged 50-59 in 13 African nations. On the basis of these data, the average HIV prevalence was 5%. However, self reporting grossly underestimates HIV

status, as exemplified by a 2001-2 study of 133 male Ethiopian cataract patients aged 50-59, which found an HIV prevalence of 9.1%, higher than the 1% prevalence reported in the DHS, as well as a 6.3% HIV prevalence in Ethiopians aged 15-49 years[422].

It is true that elderly Africans are more likely to live in rural areas outside the urban populations with increased (and rising) prevalence rates.[423] However, HIV education, diagnosis and treatment initiatives need to consider the needs of the elderly who as a group are still susceptible[424].

Not only do the elderly populations personally suffer from HIV and AIDs, they endure the impact the epidemic has on junior members of their family. The loss of children and grandchildren to the HIV epidemic results in reduced support and the lack of carers for dependent elderly. Additionally the elderly often become the sole carers of orphaned grandchildren [425].

1.13 Disability

Current data estimate 10% of the world's population are disabled [18] however, there are few data on true prevalence of disability in developing countries, particularly amongst the elderly [62] despite the association between disability, increasing age and poverty (both cause and effect). In 2006, the United Nations (UN) highlighted the importance of disability to governments and international development agencies [18]. The availability of high quality, internationally comparable up to date data on disability is integral for the planning, implementation, monitoring, and evaluation of inclusive policies. The Royal College of Physicians (RCP) has recognized the impact of disability and the importance of addressing it since the 1980s. They highlighted that the subject is administratively complex and that many different organizations are involved when this problem is addressed in developed countries. The Working Party on Rehabilitation Medicine of the RCP (1978) was of the opinion that rehabilitation is an integral part of total patient care, and is therefore the concern of all clinicians [63].

1.13.1 *The Impact of ageing on disability*

Populations worldwide, but particularly in developing countries, are ageing rapidly [1]. This epidemiological transition will include increases in non-communicable disease including neurological disorders [2]. These diseases have the potential to result in increased disability and dependence. Prevalence of disability does indeed increase with age worldwide[63],[64],[65], but supportive data from the African community is required.

1.13.2 *Defining disability*

One can define the different aspects and effects of disability;

Impairment - the specific deficit

Activity limitation (formerly 'disability') - limitation in functional capacity

Participation restriction (formerly 'handicap') - the impact on function and quality of life [426].

The social model of disability (the outcome of the interaction of a person and their environment) is replacing the medical model of disability [18], and is highlighted by the International Classification of Functioning, Disability and Health (ICF) developed by the World Health Organisation (WHO) [17].

1.13.3 *Treating disability*

Interventions should be aimed at both the individual level and the societal level [18]. Many disabling conditions can be prevented or treated readily and inexpensively. There are cost-effective measures for rehabilitation and disability improvement. Identification of those with disability and diseases that result in disability is clearly an important component in reducing the morbidity burden in SSA [66].

Rehabilitation is an integral part of “total patient care” [63]. WHO defines rehabilitation as an active process by which those affected by injury or disease, realize their optimal physical, mental and social potential [17]. Rehabilitation is best administered by specialised multidisciplinary services however, such services are limited or non-existent in many developing countries so knowledge transfer from experts to primary caregivers or family members is fundamental, clearly the western model of rehabilitation cannot be copied in SSA. To address this situation, a community-based rehabilitation strategy has been introduced by the WHO in many low income countries worldwide successfully influencing the quality of life of persons with disabilities.

1.13.4 *Different methods of measuring disability- why use the Barthel Index (BI)?*

Reported disability prevalence rates around the world vary significantly because of different definitions, study designs, and lack of a universal assessment tool, leading to difficulty making comparisons. The complex model of social disability is hard to measure. Clinical evidence shows that in most elderly people, independence and quality of life are strictly related with motor function. According to the WHO, health status in the elderly is best defined in terms of function, physical mobility is the milestone in preserving function [19]. To generate meaningful general prevalence one must determine which component most reflects a person’s level of disability and allows it to be easily comparable to another; arguably physical function in an elderly population of a rural community in a developing country [18].

The BI, developed in 1965 [427] is an ordinal scale comprising ten Activities of Daily Living (ADL) with varying weighting. The original BI was scored in steps of five points to give a maximum total score of 100. A widely adopted modification (converted by dividing by 5) revised the score to range from 0-20 [428]. The Barthel Index (BI) is widely used and recommended by the British Geriatric Society (BGS) and the Royal College of Physicians for

routine use in the assessment of older people [426] [429] [430]. It is culturally and disease non-specific and simple modification allows easy use in developing countries. This allows easy comparison between disability levels worldwide and reduces the need for validation in SSA. It has good inter-rater (a skilled observer is unnecessary) and inter-disorder reliability [431] [428].

In view of its simplicity, high validity, reliability, sensitivity and utility, the BI has been proposed as the standard measure of disability and the gold standard to which new measures should be compared [67] [68].

There is little consensus on the cutoffs of the BI for level of disability for epidemiological studies or medical trials. Uyttenboogaart et al [432] compare the BI to the Modified Rankin Score (MRS) demonstrating that MRS 1 (No significant disability) corresponds with BI 19+, MRS 2 is equivalent to BI 18, MRS 3 to BI 15. Celani et al [433] suggest a score of 19 or above as a pivotal score for not requiring help from another person. Kay et al [434] conclude that a score of 16 or less was the optimal cutoff for self reported dependency. There is consensus that MRS of 2 or less reflects independence (equivalent to BI 18 or more). Heslin et al reported cutoffs of <15 as severe disability, 15-18 as moderate disability, 19 or 20 as mild/no disability [435].

In summary, I selected the BI for use in this thesis because it is recommended by the RCP and the BGS for use in the elderly, it is quick and easy to do and it is possible for a wide range of surveyors to perform it consistently. The use of a simple and commonly used screening tool and the focussed population group allowed direct comparison to a European population studied by Heslin et al [435]in 2001. They measured BI on 4004 elderly aged 70+. I used their cut offs for mild, moderate and severe disability as described above as they are roughly equivalent to other cut offs described and approved in the literature and it facilitated comparison.

1.13.4.1 *The World Health Organisation Disability Assessment Schedules (WHO-DAS)*

The WHO has designed a set of Disability Assessment Schedules (known as the WHO-DAS) which have a long series of activity and participation based questions. While some of these questions are internationally comparable (e.g., standing for long periods), some are less so (e.g., conducting household responsibilities). Furthermore, even the 12-question WHO-DAS is too long to be of use for a census, which many countries must rely on due to limited resources for carrying out household surveys [436]. The 10/66 research group also observe problems with over and under "zero" reporting in their disability studies [62].

Whilst the most recently proposed screening tool I felt the WHO-DAS was not appropriate for our study given its length and lack of current recommendations from geriatric organisations.

1.13.5 *Published literature on disability levels*

Overall, as generally defined, disabled people represent a significant proportion of the world's population. Data from developed countries and some recent studies in developing countries (Brazil, Ecuador, India, Nicaragua, Vietnam, and Zambia) suggest that an estimated 10-12% of the population are disabled. This estimate is in line with the United Nations' often cited figure of 10%, an informed guess based on data from developed countries [18].

Reported disability prevalence rates around the world do however vary dramatically but in general are lower in developing countries. Rates reported in Kenya [437] and Bangladesh are <1% [438]. Allain et al's Zimbabwean study who found less than 4% of people aged 60 and over experienced difficulty with self maintenance of ADLs [20]. Fitaw et al looked at the prevalence of disability in Ethiopia, reporting the crude disability rate of 3.8% using

the WHO international classification functioning disability and health (ICF) when all age groups were studied [21]. Rates in developed countries are substantially higher, 20% in New Zealand [22] and using the Townsend disability scale, The Medical Research Council Cognitive Function and Ageing Study and Resource Implications Study found 11% of men and 19% of women aged 65 and over were disabled in the UK [23]. This variation may be caused by several factors: differing definitions of disability, different methodologies of data collection, and variation in the quality of study design and population group studied [438],[437],[22], however our directly comparable study indicates a real difference between disability rates in developed and developing countries in the elderly population at least. Comparable data from younger age groups is required to extrapolate this conclusion to the general population.

1.13.6 *Disability levels in the elderly*

The previously mentioned Cognitive Function and Ageing Study report that 38% of disabled people were aged 85 or over. They concluded that very elderly people make up a large proportion of those in need of long term care, demonstrating the economic and social burden that an ageing population represents [23]. Heslin et al in 2001 reported disability levels using the BI on 4004 elderly aged 70+ in multiple European centres. Of the total sample, 9% (10% of women and 7% of men) and 26% were severely and moderately disabled respectively [435], demonstrating significant functional impairment in this age group that is substantially higher than levels quoted in the general adult population.

1.13.7 *Disability levels in Non Communicable Disease (NCD)*

The 10/66 dementia research group concluded in their recent paper that NCD particularly (in decreasing order) dementia, stroke, limb impairment, arthritis, depression and eyesight problems are significantly associated with disability [62]. Further research needs to be done in developing countries.

1.14 Stigma: The Perception of Neurological Disorders in Africa

Stigma has been defined as "a deeply discrediting attribute that reduces a person to one who is in some way tainted and can therefore be denigrated." It is a problem that affects the health of individuals and society globally. It has an impact on individual's social, psychological, physical and spiritual wellbeing. It prevents individuals presenting with diseases that carry stigma, it is detrimental to healthcare and research studies designed to benefit the local and global population [439].

In Africa stigma may result from a history of neurological disorder and the consequent physical or mental abnormality. For most chronic neurological disorders, the stigma is associated with the disability rather than the disorder itself. Exceptions are epilepsy and dementia which are directly associated with stigma and discrimination. The amount of stigma associated with chronic neurological illness is determined by:

- The attribution of responsibility for the illness
- The degree to which it creates discomfort in social interactions (often how visually alarming the condition is)
- The amount of disability that the condition creates reducing the individuals perceived "social value."

Stigma has social, psychological and physical effects;
Social – people may be prevented from being part of the community, children may be taken out of school, marriages may be prevented and whole families may be ostracised.
Psychological – Isolation and depression can result.
Physical – the patient does not present to healthcare professionals due to the stigma attached to the condition and therefore it remains untreated and a disabling factor in the patient's life.

Tackling stigma is often about addressing the views of those who stigmatise or discriminate against others. Education on causation is one of the key factors as beliefs of witchcraft, contagious or hereditary nature of illnesses are often strongly held especially

within developing countries such as Africa. Mshana et al report the stigma associated with stroke and the common beliefs that stroke is often seen as a result of witchcraft. The association with supernatural phenomenon means that this disease is not only disabling physically but also stigmatising [440]. Studies have shown that programmes to reduce stigma related to epilepsy in African communities through education and treatment can successfully reduce the stigma attached to the condition[441].

Stigma is also a major issue within the ageing population, Butler in his book from 1975 reports a deep and profound prejudice against the elderly [442], which is supported by more up to date reports of ageism in communities particularly with regard to health care rationing [416]. This problem has been established and published in developed countries since the 1970s, however the perceived burden of the elderly has only just begun to impact on the developing world and has the potential to change attitudes from one of respect to one of discrimination and resentment.

1.15 Summary

- The Burden of Neurological Disease is high and increasing further as a result of the ageing population. Data are however based mostly on predictions, studies from developed countries and outdated studies. Accurate data from SSA are lacking but are required for evidence based healthcare planning in resource poor areas.
- Cost effective interventions (either treatment or prevention) for many neurological conditions are available. Resources are inadequate and unequally distributed in low income countries. Accurate prevalence figures will help resource prioritisation.
- Current screening tools for the detection of neurological disorders are unsatisfactory particularly for use in the elderly population of low income countries and for use by NMI.
- Neurological disease and an ageing population produce an increased burden of long term disability – the extent of disability has not been measured in the elderly population of SSA or in the majority of other developing countries.

- Stigma and discrimination is associated with neurological disease, particularly in developing countries and this needs to be addressed.

Chapter 2. Methodology

2.1 Literature Search Strategy

I performed an all encompassing literature review focused on my research aims. Given the broad nature of the research subject, it was important to break down reviews based on the main aim and the subsidiary aims and this is described in detail below. Actual MESH headings/text words have been listed as well as a flow chart of the number of hits and exclusions. The inclusion and exclusion criteria have also been detailed. Given the number of literature reviews performed, those displayed below are limited to the key searches of the main and primary subsidiary research aims.

Literature searches were performed using "all resources" from The University of Newcastle upon Tyne databases, including Books at Ovid, Journals at Ovid, Medline, Embase, EBM Reviews, NHSEED, CAB Abstracts, Embase, Health Management Information Consortium and PsycINFO. Literature was also found following references from sourced articles.

With regard to the primary aim of the study; "to determine the prevalence of Neurological Disorders and Consequent Disability in the 70 and over population of the Hai District Demographic Surveillance Site (DSS) in Northern Tanzania", the key conditions of Tremor, Parkinsonism, Stroke, Headache and Epilepsy were the focus, details of the searches are described below

Table 2.1: Literature Search for Neurological Disorders

Search Order	Search Term	Hits
1	Neurological Disorder	58873
2	Neurological Disease	26672
3	Neurological Disability	4740
4	Prevalence	1686144
5	Sub-Saharan Africa	45800
6	1 or 2 or 3	83126
7	4 and 5 and 6	173
7	Limit 6 to English Language, Human	169
8	Of 7 Excluded all those only identifying 1 neurological disorder and those relating only to children or using investigations	16
9	Neurological disorders (title)	345
10	Neurological disability (title)	213
11	Neurological disease (title)	2504
12	Prevalence (title)	238628
13	9 or 10 or 11	3062
14	12 and 13	21
15	Limit 14 to English Language, Human	19
16	Of 15 Excluded all those only identifying 1 neurological disorder and those relating only to children or using investigations	9
17	Additional from references	-

Table 2.2: Literature Search for Tremor

Search Order	Search Term	Hits
1	Tremor	90903
2	Prevalence	1686144
3	Sub-Saharan Africa	45800
4	1 and 2	8646
5	1, 2 and 3	56
6	Limit 6 to English Language, Human	55
7	Of 7 Excluded all those only identifying 1 neurological disorder and those relating only to children or using investigations	18
	Additional from references	-

Table 2.3: Literature Search for Parkinsonism and Parkinson's disease

Search Order	Search Term	Hits
1	Parkinsonism	61872
2	Parkinson's Disease	180734
3	Prevalence	1687302
4	Sub-Saharan Africa	45827
5	1 or 2	218758
6	3 and 5	17444
7	3, 4 and 5	77
8	Limit 7 to English Language, Human	76
9	Of 8 Excluded all those relating only to children or not related to prevalence	38
10	Additional from references	-

Table 2.4: Literature Search for Epilepsy

Search Order	Search Term	Hits
1	Epilepsy	358963
2	Prevalence	1686144
3	Sub-Saharan Africa	45800
4	1 and 2	22197
5	1, 2 and 3	325
6	Limit 6 to English Language, Human	308
7	Of 7 Excluded all those relating only to children or not related to prevalence	43
	Additional from references	-

Table2.5: Literature Search for Stroke

Search Order	Search Term	Hits
1	Stroke	724709
2	Prevalence	1687302
3	Sub-Saharan Africa	45827
4	1 and 2	88053
5	1, 2 and 3	612
6	Limit 6 to English Language, Human	597
7	Of 7 Excluded all those relating only to children or not related to prevalence	62
	Additional from references	-

Table 2.6: Literature Search for Headache

Search Order	Search Term	Hits
1	Headache	357798
2	Prevalence	1687302
3	Sub-Saharan Africa	45827
4	1 and 2	36998
5	1, 2 and 3	481
6	Limit 6 to English Language, Human	479
7	Of 7 Excluded all those relating only to children or not related to prevalence	5
8	Headache (title)	46309
9	Prevalence (title)	238798
10	8 and 9	977
11	Sub-Saharan Africa (title)	7542
12	10 and 11	0
13	3 and 10	0
14	Developing countries	1754928
15	10 and 14	15
16	Additional from references	-

With regard to the first subsidiary aim of the study; "To produce a validated and improved screening tool for the detection of Neurological Disease specific to the 70 years and older population", the search is detailed below.

Table 2.7: Literature Search for Screening Tools for Neurological Disorders

Search Order	Search Term	Hits
1	Neurological Disorder	58873
2	Screening tool	43256
3	Screening questionnaire	14646
4	Screening instrument	10611
5	2 or 3 or 4	65341
6	1 and 5	720
7	Limit 6 to English Language, Human	697
8	Of 7 Excluded all those only identifying 1 neurological disorder and those relating only to children or using investigations	13
9	Sub-Saharan Africa	45800
10	5 and 9	22
11	Limit 10 to English Language, Human	20
12	Of 11 Excluded all those only identifying 1 neurological disorder and those relating only to children or not related to prevalence	3 (all my articles)
13	Neurology (title)	24261
14	Neurological (title)	59236
15	13 or 14	82963
16	Screening (title)	289698
17	15 and 16	233
18	Limit 17 to English Language, Human	174
19	Of 18 Excluded all those relating only to children or not related to prevalence	7
20	Additional from references	-

Additional references were gained from journal, website specific search engines and from recommendations. Several references were obtained through the British Library after assistance from North Tyneside General Hospital Library.

It is important to highlight that searches were limited to studies from SSA unless research in the field was limited in which case the search was extended to include developing countries. Studies from developed countries were only included where literature was extremely limited or studies were recommended and deemed of very high importance. Review articles from developed countries were otherwise used for comparison.

2.2 Ethical Approval

Ethical approval was sought in the UK from Newcastle and North Tyneside Health authority Joint Ethics Committee, locally in Tanzania from Tumaini University, Moshi and nationally in Tanzania from the National Institute of Medical Research (NIMR) ethics committee (Dar-es-Salaam). Ethical approval was granted from Tumaini University and from NIMR but the UK committee deemed it unnecessary to be considered as all the research was being carried out it Tanzania. All participants were given an information sheet in Kiswahili. All participants signed written consent forms in Kiswahili (in the case of those who could not write, a thumb print was obtained). Any patient who could not speak Kiswahili had the information sheet and the consent form translated verbally into their tribal language and understanding was checked. All participants were free to withdraw from the study at any stage. Written consent was gained for photography and video recording as appropriate. All information sheets and consent forms were translated by the Neurology Nurse Specialist and then back translated by another specialist research nurse to ensure accurate translation. Please see appendices 2.1-2.7 for information sheets and consent forms.

2.3 Inclusion and Exclusion Criteria

2.3.1 *Inclusion Criteria*

In order to be included in the study, patients had to;

- Be alive and living within the Hai district project area and within one of the 12 randomly selected villages on January 1st 2010
- Be aged 70 or over on January 1st 2010
- Have given informed consent or assent provided by a family member in the case of cognitive impairment
- Have neurological symptoms or signs in keeping with a World Health Organisation International Classification of Disease (ICD 10) Neurological Diagnoses

2.3.2 *Exclusion Criteria*

Patients who were excluded from the study were as follows;

- Those who were not aged 70 or over on January 1st 2010
- Those who did not live in the Hai district project area and who were not within one of the 12 randomly selected villages
- Those who did not have symptoms or signs in keeping with a World Health Organisation ICD 10 Neurological Diagnosis

2.4 Prevalence Studies

Point prevalence of a disorder is defined as the number of live cases suffering from that disorder, expressed per 100,000 of the population (or per 1000 of the population if the disease is more common), at a specified time. There are a number of methods of accurately determining prevalence; the appropriate method depends on the study setting.

2.5 Deciding on the Basic Methodology

2.5.1 *Flawed Methods*

Case finding studies use primary care or hospital notes to pick up known disease cases. This approach fails to pick up undiagnosed cases in the community. This is particularly relevant in developing countries where presentation to health care is limited by financial and geographical constraints and many people remain undiagnosed. In Tanzania, there are no formal general practitioners (GP) or GP registers so use of such a system would not be possible.

Pharmacy searches can be utilised when diseases are treated with specific medications, which are primarily used for that disease. There are limitations to this approach which render it unsuitable., It would fail to identify undiagnosed cases and many neurological diseases cannot be treated within the western world let alone developing countries. Further, local pharmacies in Hai often do not stock medication for neurological disorders and their records are likely to be unreliable. Finally dispensary workers do not have adequate knowledge to diagnose neurological conditions and prescribe appropriate medications.

2.5.2 *The Gold standard approach*

A door-to-door study is the best way to find diagnosed and undiagnosed cases in the community. However, this is time and labour intensive; therefore, the two-phased approach to community prevalence studies has been long established as the gold standard to document true prevalence in low income countries [24, 25]. An initial screening phase with a tool that is feasible (acceptable, brief and easily administered by NMI) and valid (sensitive- to detect all neurological cases and specific-to reduce second phase costs) precedes physician confirmation of disease in positive responders. NMI are ideal screeners

as they are cheaper to employ, readily available, know the geography of the community, and are more likely to be accepted by the population so as to increase participation rate.

I followed a two step approach, with a screening tool designed specifically for use within the elderly and not based on the flawed WHO tool. I worked through the WHO ICD 10 criteria for Neurological Disease [71] to ensure that all relevant diseases were addressed by at least one question.

2.6 Geographical area

The Hai district is in northeast Tanzania on the slopes and surrounding plains of Mount Kilimanjaro. It lies between Moshi and Arusha, with an area of 13,000 km^2. It stretches over three ecological zones delineated by altitude; these are as follows;

- The lowland zone
    - 750 and 1000 m above sea level (asl),
    - Minimal rainfall (about 325 mm a year)
    - Warm to hot temperatures
    - Sparse population density (about 70 people per km^2).
- The midland zone
    - 1000 and 1600 m asl and
    - Higher rainfall (about 1560 mm a year)
    - Moderate temperatures
    - Higher population density (about 150–160 per km^2).
- The high zone is within Kilimanjaro National Park
    - Above 1600m
    - Uninhabited
    - Heavy rainfall
    - It provides water to the lower zones via springs and rivers.

- Cool temperatures

Piped water is available in most villages and is plentiful in the highland and midland zones but is often polluted with chemical and biological waste. The lower zones often have water shortages and droughts.

The district has 4 administrative divisions, 11 wards, and 61 villages. The Hai demographic surveillance site (DSS) covers three of the four divisions of the district, and has permanent boundaries. It has a population of 161,119 (January 2009) within 52 villages. 8869 were aged 70 and over (5.50%). Most villages in the DSS area are rural and the remainders are peri-urban. The main tribal groups are the Chagga and the MMasai. Major religious groups in the area are Christians (79% of people) and Muslims (20% of people). The tribal languages are commonly spoken in the villages, but the national language, Kiswahili is widely understood and spoken. Arable, livestock and cottage industries are the main economic activities, with the majority of inhabitants subsistence farmers. The district has 139 primary schools, 13 secondary schools (both public and private) and 5 post-primary technical schools.

The district has three hospitals, two large health centres, 39 dispensaries and 61 village health posts. The tertiary referral hospital is Kilimanjaro Christian Medical Centre (KCMC) and this is located in Moshi 8km from the nearest border of the Hai district. About 85% of children below the age of five are vaccinated against five major communicable diseases. Community-based data show that main causes of death in the district are: HIV/AIDS, cancer, perinatal, acute febrile illness including malaria, pneumonia, diarrhoeal diseases, injuries (both intentional and unintentional), nutrition and maternal. Wood is the main source of fuel. 36 of the 61 villages have electricity, but the use is limited because of cost and very few households have electricity.

There are 710 kilometers of road and an international airport (The Kilimanjaro International Airport) 10km from the nearest border. Most roads are unpaved and are often impassable for vehicles during the rainy season. [443].

2.7 The Adult Morbidity and Mortality Project (AMMP)

The Hai district was one of three DSS in Tanzania used in the AMMP [443]. The other two sites were an urban population in Dar-es-Salaam and a poor rural area in Morogoro; Hai was originally chosen as a relatively affluent rural area. The AMMP was originally funded by the UK Department for International Development (DFID) and was carried out in partnership between the Tanzanian Ministry of Health and the University of Newcastle upon Tyne. The same staff were employed for this research as were by the AMMP.

2.8 The Research Team

The Research Staff on the project were as follows;

The District Medical Officer (DMO): Approval was sought from the DMO to carry out research in his administrative district. This ensured a good relationship and increased the likelihood that he would act on the findings to improve healthcare in the district. Indeed the relationship gave us an excellent opportunity to feedback findings, recommend treatment guidelines and capacity requirements..

Two Assistant Medical Officers (AMOs) and 3 Clinical Officers (COs) acted as project supervisors. They had previously worked on the AMMP and so were highly trained in DSS activity. They were clinicians within the rural community (roughly equivalent to western general practitioners). On the project, they facilitated the day to day running of the

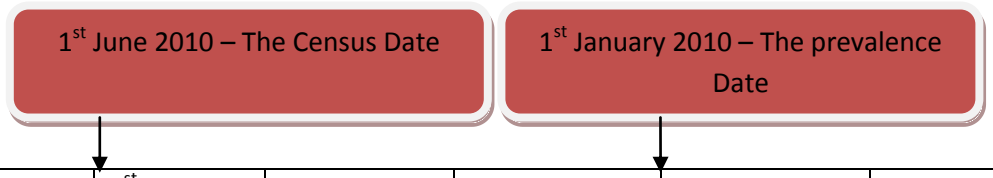
research and provided a translation service and local advice as required. A supervisor worked with the Research Doctor (RD) (myself) each day I was in the field.

The Project Study Nurse (SN): A Neurology Specialist Nurse from KCMC worked with the RD (myself) each day I was in the field. She provided a nursing and translation service.

The Enumerators/Non Medical Investigators (NMI): Each village had one or two (large villages only) local people trained in DSS activity and have been involved in prior prevalence studies. There are a total of 60 enumerators. They are healthcare professionals, teachers or village administrators. They had carried out the 2009 census within each of their villages and knew the composition of each household within their village. They were the target administrators of the demographic details, neurology screening and disability questionnaires.

2.9 Timing of the Study:

Figure 2.1: Timeline of the Study



	May 2009	1st June 2009	June 2009 – October 2009	November 2009 – January 2010	January 2010 – February 2010	February 2010 – July 2010	July 2010 – August 2010
Pilot of previously used screening tools in the Proposed Population	→						
2009 Household Census of the Hai District Surveillance Site		→					
Production of new screening tool specific to the Elderly/ A developing country/ Use by lay community workers			→				
The Pilot Study				→			
Two workshops on the use of the screening tool					→		
The Main Prevalence Study						→	
Follow up of Cases							→

2.9.1 *Justification of the Timescale*

There were multiple reasons for this timescale. Firstly it was realistic. A full Neurological history and examination took on average one hour to complete. During the pilot study it was estimated that a maximum of 8 patients could be seen per day as all patients would have to have the neurology screening questionnaire followed by a full neurological history and examination to confirm whether the patient was a true or false, positive or negative. For the main study it would be possible to see a maximum of eight patients per day as these patients would have been screened positive and so a full neurological history and examination would have to be performed to assign them true or false positive. All patients would have to be seen by the RD (myself) to ensure continuity. The numbers of working days were limited by religious celebrations, public holidays and severe weather in the rainy season which precluded transportation.

2.10 The Census

The initial census in the Hai DSS was in 1992, to provide baseline information. Between then and 2003 an annual door-to-door census has been carried out by the AMMP by the 60 enumerators. Each household and each individual has a unique identifying number. The census in August 2005, funded by the Tanzanian Stroke Incidence Project (TSIP) demonstrated a population of 161,000, of whom 7829 were 70 years and over (70 – 74 = 3208, 75 – 79 = 1790, 80 – 84 = 1528, 85 – 89 = 636, 90+ = 667). The last census in June 2009 demonstrated a population of 161,119, of whom 8669 were 70 years and over (70 – 74 = 3159, 75 – 79 = 2531, 80 – 84 = 1447, 85+ = 1732). This updated the demographic data and enabled us to "target" households where there was an individual 70 years and over.

According to the leading data analyst for the 2009 Census and the supervisors in Hai no-one refused to give information for the census.

2.11 The Pilot of Previously used screening tools in the proposed population

Preliminary work took place in May 2009 to pilot other previously published neurological screening tools in the target population (people aged 70 and over in the DSS) with the target administrators – the NMI with advice from the Supervisors. It was felt that pre-existing tools would not be specific enough to be used in the 70 and over population because their high level of co-morbidities would result in a high false positive rate, the reasons for this are discussed in the introduction. Additionally, the NMI felt that screening tools that included an examination section would be too complicated for their use. Direct questioning of the target population informed me that they would not accept examination (however superficial) by someone who was not a medical professional. The negative aspects of an examination section are discussed in detail in the introduction. Overall it was concluded that using a screening tool without an examination section would not only be fundamental for the success of our project it would ensure that such a tool was transferrable for use in other developing countries where funding may be limited and utilisation of screeners with limited training/NMI would be required. This extends the niche of the screening tool and its use in neuro-epidemiological studies in the future.

2.12 The Production of a New screening Tool

I produced a completely new screening tool. Question wording was built on experience of the type of questions that had worked in previous prevalence studies in this community [34, 96, 128, 213, 333]. Question content was informed by systematically working through the WHO ICD 10 criteria for neurological diagnosis to ensure that the screening tool was all inclusive i.e. all neurological disorders of public health significance in this age group were covered. Direct questions on burdensome, easily identified neurological disorders were asked at the end of the questionnaire. The production of the screening tool was therefore all my own work and was not produced through modification of another screening tool published or otherwise.

Table 2.8: Conditions the Neurological Screening Questionnaire was Designed to Identify

WHO ICD Code	Neurological Disorders
G00 – G09	Sequelae of inflammatory/infect diseases of CNS
G10 – G13	Systemic atrophies primarily affecting the CNS
G20 – G26	Extra-pyramidal disorders
G30 – G32	Other degenerative diseases of CNS
G35 – G37	Demyelinating diseases of the CNS
G40 – G47	Epilepsy and paroxysmal disorders
G50 – G59	Nerve, Nerve root and Plexus disorders
G60 – G64	Polyneuropathies and PNS disorders
G70 – G73	Diseases of myoneural junction and muscle
G80 – G83	Cerebral palsy and other paralytic syndromes
G90 – G99	Other disorders of the CNS
H 2.4	Ptosis of the eyelid
Chapter XIX - XX	Injury resulting in CNS dysfunction

[71]

Table 2.9: Conditions the Neurological Screening Questionnaire was not Designed to Identify

Condition	Reason for Omission
Conditions whose symptoms and signs had resolved completely.	It would not be possible to get an accurate enough history to secure a positive diagnosis due to problematic recall in this community and language barriers. Additionally very few participants would have medical records to confirm or refute the diagnosis. This does not include those conditions that have symptoms or signs that recur e.g. epilepsy and recurrent headaches.
Visual problems	As a separate part of the study all patients were asked if participants had problems with their vision. 46.9% answered positively to this question. Including a question regarding vision in a neurological screening questionnaire for use in the elderly would substantially reduce specificity and would pick up many people with ocular diagnoses.
Hearing problems	A majority of elderly people will report deterioration /problems with their hearing it was felt, therefore, that it would not be appropriate to include a question about hearing. This would pick up a large amount of people with presbyacusis and would reduce the specificity of the tool.
Disorders of the autonomic nervous system	These conditions are notoriously difficult to screen for and diagnose with limited resources. Treatment is not available in developing countries. Additionally conditions that produce problems with the autonomic nervous system e.g. Parkinson's Disease will have other neurological symptoms and signs and they will therefore be picked up with other questions.

2.12.1 *Question Modifications*

Each of the Questions was modified from its original form in order to increase the sensitivity and the specificity of the tool; these modifications are detailed in the table below, which demonstrates the original question, the final question and the reason for modification.

Table 2.10: Neurological Screening Questionnaire Individual Question Modification Performed Prior to the Pilot Study in Order to Increase Sensitivity and Specificity

Original Question	Final Question	Reasons for modification
Do you have attacks in which you fall with loss of consciousness and have violent shaking of the limbs?	Do you have **recurrent** attacks in which you fall **with** loss of consciousness **and** have **violent** shaking of the limbs?	Attacks have to be recurrent (more than 1) for a diagnosis of epilepsy to be made. Participants had to have all three aspects of a seizure to answer positively i.e. falls, loss of consciousness and violent shaking of the limbs. This had to be stressed in the question otherwise there were a high number of false positives ranging from simple falls or syncope to shivering or rigors.
Do you have brief attacks of shaking or trembling in one arm or leg or in the face?	Do you have **recurrent** attacks of **violent** shaking in **one** arm and/or **one** leg and/or in **one** side of the face that are **not** just brief tremors of the hands after working hard?	Attacks have to be recurrent (more than 1) for a diagnosis of epilepsy to be made. Importance of violent shaking on one side of the body stressed to ensure specificity not reduced by shivering or rigors. Initially many people answered positively to this question when they had been working hard – their dominant hand was particularly affected so this was included as a negating factor.

Do your arms or legs shake, apart from maybe when you have drunk alcohol?	Do your arms or legs shake **multiple** times **every** day not just when you have drunk alcohol or have been working hard?	Many people reported that they were occasionally tremulous- this was often after a period of illness, hard work or having consumed alcohol. Using these as negating factors and adding in the requirement for the tremor to be present multiple times every day increased the specificity of this question substantially. People often reported shaking of the legs due to pain – this was excluded in the introductory paragraph again increasing the specificity of the question.
Do you shuffle your feet and/or take tiny steps when you walk?	Do you shuffle your feet **and** take tiny steps when you walk **not** just because of pain?	Often elderly people reported tiny steps "because they were old" and occasionally shuffling was reported due to tiredness. Both of these when asked alone had a low specificity. When asked together (shuffle your feet **and** take tiny steps) they were very specific and sensitive for neurological gait disorders as long as pain was excluded as an underlying cause.
Does your head shake?	Does your head shake **all** or **most** of the time (outside so it is visible not inside because of dizziness and not just when you are or have been carrying something on your head)?	"All or most of the time" was added to the question to increase the specificity as many false positives reported head shaking when they had been carrying something on their head or when they were saying no to someone. The addition of outside so it is visible, not inside because of dizziness, was also very important to ensure specificity of the question, as many elderly people reported dizziness. Also the vocabulary in Swahili is not as extensive as English, so many words have multiple meanings and the Swahili for shaking can also be taken

		to mean dizziness.
Do you have recurring abnormal movements that you cannot control?	Do you have **recurrent** abnormal movements anywhere on your face or body **multiple** times **every** day that you cannot control and that are not just brief shivers or brief jerks of your whole body when you are resting?	Many elderly people reported jerks of their body when they were falling asleep at night or when they were resting, these were thought to be myoclonic jerks and non-pathological. Thus this was specified in the question to increase specificity. The addition of multiple times every day was important in order to exclude shivering.
Do you have weakness down one side of your body?	Do you have **constant** weakness down one side of your body **that is there now**?	Often elderly people reported weakness at the end of the day, or due to tiredness – the use of the word constant excluded these people. General body weakness was occasionally reported due to age – the phrase 'one side of the body' maintained the specificity of this question. Pain was a common cause of a positive answer and this had to be excluded in each case.
Do you have persistent weakness in any of your arms or legs?	Do you have **constant** weakness in any of your arms or legs or hands or feet **that is there now**?	Constant and persistent have very similar meanings in Swahili. Specifying the weakness was in the arms or legs or hands or feet was important to exclude those people who reported whole body weakness due to age or tiredness.
Is one side of your face weak?	Do you have **constant** weakness of one or both sides of your face **that is there now**?	Facial weakness was often reported due to tiredness, ensuring that it was constant and there at the time when the question was asked established that the problem was pathological and maintained the

		specificity of the question.
Do you have persistent weakness of your eyelids?	Do you have **persistent** weakness of one or both of your eyelids **that is there now or** that gets worse towards the end of the day that is **not** just because you are tired?	Weakness of the eyelids was often reported due to tiredness and so this had to be included in order to maintain specificity of the question. The worsening of the problem towards the end of the day ensured that the ocular Myaesthenia patients were picked up.
Do you have problems speaking?	Do you have **persistent** problems speaking **not** just because you have a sore throat or mouth **and** that affects you most of the time?	It was important to include the word persistent, this ensured that people who lost their trail of thought were not picked up as positive – this was a commonly described problem. Some people also reported problems when they were drunk, cold or ill and so the word persistent helped to exclude these potential false positives. It was very common for people to report problems speaking due to oral pathology such as tooth pain and so this was excluded by the question. .
Do you have altered sensation (tingling or numbness) in your arms or legs?	Do you have **constant** loss of sensation (numbness) in your arms or legs or hands or feet **that is there now** and **not** just due to cold or pain?	Cold and pain in the legs/arms were a common cause for a positive response to this question before they were excluded. It was important to ensure that the numbness was constant as people often reported numbness from sitting too long or lying on one side. Almost everyone reported tingling sensation that occurred daily in their arms or legs and consequently for a patient to answer positively to the question they had to report a loss of sensation.

Do you have difficulty with your coordination, such as stirring tea with a spoon or buttoning clothes?	Do you have **persistent** problems with your coordination such as stirring tea with a spoon or buttoning clothes that is **not** due to pain in your hands or arms or because of drinking alcohol?	Alcohol was a common cause of coordination problems and so this had to be specifically excluded. Coordination was a difficult concept for people to grasps and therefore it was important to include culturally non-specific examples of how this may come across – "stirring tea and buttoning clothes."
Do you have sustained contractions of your muscles that you have no control over?	Do you have sustained/persistent contraction of your muscles that you have no control over and that produce abnormal positions of part of your body, that are **not just** in your **legs** or **just** at **night** or **just** cramp? If they happen whilst doing a certain task do they occur **most** of the times you do that task?	Many elderly patients reported pain and stiffness in their hands and so this had to be excluded as a positive response. Occasional hand cramps/spasms were also thought to be non pathological and the wording of the question was modified to exclude them. Leg cramps and nocturnal cramps were also incredibly common but thought to be non pathological so it was also important to exclude them. It was important to include a sub- question to pick up task specific dystonias. This question was subsequently removed from the screening tool altogether and the reasons for this are elaborated on later in the thesis.
Do you have severe pain affecting one side of your face?	Do you have **recurrent** short attacks of severe shock like pain affecting **one** side of your face?	The inclusion of this question was to pick up trigeminal neuralgia. It had to be very specific in its wording to ensure that oral pain, ocular pain and ear pain were excluded as potential causes as these were common complaints. Occasional facial pain was a common symptom so the inclusion of the word recurrent was very important.

Do you have recurrent headaches?	Do you have **severe recurrent** headaches that **stop** you doing your normal daily activities?	Almost everyone reported recurrent headaches at some point – this was commonly associated with working in the sun and not drinking frequently. Specifying that they had to be severe and recurrent and affect ADLs meant that only disabling headaches were picked up.
Has anyone ever told you that you have a neurological disorder (a disorder affecting your brain, spinal cord or nerves)? What is it? Is it still there?	Has anyone ever told you that you have a neurological disorder (a disorder affecting your brain, spinal cord or nerves)? a) What is it b) Is it still there?	The sub questions were very important as often people did not know whether a disorder affected their brain, spinal cord or nerves and consequently they answered positively – often due to arthritis. Education of the enumerators was important in ensuring this question worked.
Have you ever been told that you have or had epilepsy or epileptic fits or seizures?	Have you been told that you have epilepsy or epileptic fits or seizures?	To ensure that the problem of epilepsy (controlled or not controlled) was ongoing the word ever was removed from the question, this ensured people who reported febrile convulsions as children or seizures in times of illness were excluded.

Has anyone ever told you that you have Parkinson's disease?	Have you been told that you have Parkinson's Disease?	This is a very specific question and it remained the same.
Have you ever had a stroke?	Have you ever had a stroke **that resulted in** long term problems/disability?	As mentioned above we only wanted to pick up patients with stroke with lasting deficit, this was because many patients reported a stroke that they had previously recovered from completely and it was very difficult to ascertain if this was actually the case, or if a stroke had been wrongly diagnosed when relying on history alone.
Have you ever had polio?	Have you ever had polio **that resulted in** long term problems/disability?	Many people reported polio outbreaks as a child, so it was important to specify that a positive answer should only be in someone with lasting problems/disability as a result of polio.
Have you ever had leprosy?	Have you ever had leprosy **that resulted in** long term problems/disability?	People reported that they were aware of people who used to live in their community with leprosy whom they came into contact with and so they may have had it at some point. Some people reported that they had previously had a strange rash which may have been leprosy. It was therefore very important to ensure that leprosy had resulted in long term problems/disability before a positive response was confirmed.

Three questions were removed altogether:

1. Do people tell you that you have episodes when you are distant or unreachable?

During the first days in the field it was found that the majority of people answered positively to this question. Elderly people in Tanzania often felt that they were distant when they were thinking about something or because they could not hear properly. This appears to be a cultural interpretation of the phrase. After discussion with our translators it was felt that there was no other way to enquire about the phenomenon of absence seizures, which this question was attempting to identify.. After repeat literature review it was felt that absence seizures were very rare in the elderly and that if present they were associated with generalised tonic clonic or partial seizures. Therefore this question was removed and it was not felt that this would affect the sensitivity of the tool but would greatly improve the specificity.

2. Do you have severe wasting of your muscles?

During the first days in the field it was found that everyone answered positively to this question. They all stated their muscles had reduced in size because they were old. Additionally there was a problem with translation of this question – wasting and loss of weight have the same translation in Swahili and consequently many people felt they had lost weight as they had got older and therefore answered positively. Its removal did not reduce the sensitivity, because if severe wasting was present due to a neurological disorder this was picked up by one of the questions with regard to weakness.

3. Do you have problems understanding

This question was put in to pick up patients with receptive dysphasia. This is notoriously difficult to diagnose alone and is unlikely to occur without another symptoms or signs associated with stroke. It was also non specific as it picked up people with hearing problems. Even when the question was changed to – do you have problems

understanding (not due to hearing problems), it continued to have poor specificity as it picked up participants with cognitive impairment.

2.12.2 *The Final Screening Questionnaire*

This comprised of 22 questions, 16 of which enquire about symptoms and were as follows;

1. Do you have **recurrent** attacks in which you fall **with** loss of consciousness **and** have **violent** shaking of the limbs?
2. Do you have **recurrent** attacks of **violent** shaking in **one** arm and/or **one** leg and/or in **one** side of the face that are **not** just brief tremors of the hands after working hard?
3. Do your arms or legs shake **multiple** times **every** day not just when you have drunk alcohol or have been working hard?
4. Do you shuffle your feet **and** take tiny steps when you walk **not** just because of pain?
5. Does your head shake **all** or **most** of the time (outside so it is visible not inside because of dizziness and not just when you are or have been carrying something on your head)?
6. Do you have **recurrent** abnormal movements anywhere on your face or body **multiple** times **every** day that you cannot control and that are not just brief shivers or brief jerks of your whole body when you are resting?
7. Do you have **constant** weakness down one side of your body **that is there now**?
8. Do you have **constant** weakness in any of your arms or legs or hands or feet **that is there now**?
9. Do you have **constant** weakness of one or both sides of your face **that is there now**?
10. Do you have **persistent** weakness of one or both of your eyelids **that is there now or** that gets worse towards the end of the day that is **not** just because you are tired?

11. Do you have **persistent** problems speaking **not** just because you have a sore throat or mouth **and** that affects you most of the time?

12. Do you have **constant** loss of sensation (numbness) in your arms or legs or hands or feet **that is there now** and **not** just due to cold or pain?

13. Do you have **persistent** problems with your coordination such as stirring tea with a spoon or buttoning clothes that is **not** due to pain in your hands or arms or because of drinking alcohol?

14. Do you have sustained/persistent contraction of your muscles that you have no control over and that produce abnormal positions of part of your body, that are **not just** in your **legs** or **just** at **night** or **just** cramp?

If they happen whilst doing a certain task do they occur **most** of the times you do that task?

15. Do you have **recurrent** short attacks of severe shock like pain affecting **one** side of your face?

16. Do you have **severe recurrent** headaches that **stop** you doing your normal daily activities?

A further 6 questions enquired directly about specific diseases. These were as follows;

17. Has anyone ever told you that you have a neurological disorder (a disorder affecting your brain, spinal cord or nerves)?
    a) What is it
    b) Is it still there?
18. Have you been told that you have epilepsy or epileptic fits or seizures?
19. Have you been told that you have Parkinson's disease?
20. Have you ever had a stroke **that resulted in** long term problems/disability?
21. Have you ever had polio **that resulted in** long term problems/disability?
22. Have you ever had leprosy **that resulted in** long term problems/disability?

Direct questions were not asked as part of the original WHO screening tool [6] and it has been criticised for this omission. Therefore we felt that the addition of these latter 6

questions was important, they act as “double check” for those patients with the conditions specified.

The questionnaire was translated into Swahili and back translated to ensure accurate interpretation. The questions were to be asked in Swahili with a local tribal interpretation if necessary.

The questionnaire above had been modified from the original one to increase specificity without reducing sensitivity as detailed below. The form that is described above is the questionnaire that was used and analysed in the pilot study and the results section of this thesis.

A preliminary paragraph on the screening instrument reminded each NMI of the purpose of the screening instrument, that participants should have symptoms or signs at the time of screening or a disorder in which the symptoms or signs occur recurrently, that substance abuse, arthritis, and pain should always be ruled out as a cause for the symptoms and that a carer can answer on behalf of the patient if the patient is not able to answer accurately themselves. This final point was left up to the discretion of the trained interviewer, who recorded who answered the questions. The exact wording of the paragraph was as follows;

For use to pick up the prevalence of neurological disorders resulting in disability in the elderly population aged 70 and over. Participants should have symptoms or signs at the time of screening or a disorder in which the symptoms or signs occur recurrently. A carer can answer on behalf of the participant if the participant is not able to answer accurately themselves. This is left up to the discretion of the trained interviewer, who records who

answers the questions. Arthritis and pain should always be ruled out as a cause for the symptoms.

Table 2.11: Description of what Each Question of the Neurology Screening Questionnaire was Designed to Pick Up

Question	**Condition it was designed to pick up.**	**Non Neurological Conditions that we did not want to pick up – conditions that the enumerator was instructed to ensure the problems were not caused by.**
Do you have **recurrent** attacks in which you fall **with** loss of consciousness **and** have **violent** shaking of the limbs?	Generalised Tonic Clonic Seizures (GTCS). Falls AND Loss of Consciousness AND Violent Shaking. If the patient loses consciousness they will not remember hitting the floor. The attacks should still be occurring or the patient should be on medication to control them.	Falls with no Loss of Consciousness (LOC). Falls with LOC but no shaking. Shaking with no LOC. Fainting. Patients unwell with infection/Malaria.
Do you have **recurrent** attacks of **violent** shaking in **one** arm and/or **one** leg and/or in **one** side of the face that are **not** just brief tremors of the hands after working hard?	Partial seizures Hemifacial spasm Violent shaking of **one** side of the body. Violent twitching of **one** side of the face.	Brief tremor of the hand after working hard or when tired. Very brief jerks of one side of the body. Brief occasional tremors. Shaking when standing because of

		pain or weakness.
Do your arms or legs shake **multiple** times **every** day not just when you have drunk alcohol or have been working hard?	Parkinson's Disease. Essential Tremor. Other Tremor disorders. Tremor occurring multiple times every day. Tremors occurring every time hands are at rest. Tremors occurring every time person does certain actions like drinking tea or eating with a spoon. Constant tremor whether resting or doing something.	Tremor that only occurs occasionally Tremor only occurring after working hard Tremor only occurring when unwell e.g. with an infection like malaria. Tremor occurring only when just got up in the morning. Tremor occurring only when drunk. Tremor only occurring in certain specific situations, e.g. those that makes the patient anxious.
Do you shuffle your feet **and** take tiny steps when you walk **not** just because of pain?	Parkinson's Disease Abnormal walking due to weakness of the legs, e.g. previous stroke. Tiny steps AND shuffling NOT caused by pain.	Abnormal walking caused by pain or arthritis. Abnormal walking caused by frailty due to old age.
Do you have **recurrent** abnormal movements anywhere on your face or body	Dyskinesias Occurring multiple times every day.	Shivering of the body caused by cold.

multiple times **every** day that you cannot control and that are not just brief shivers or brief jerks of your whole body when you are resting?		Occasional brief jerks of the whole body when resting. Abnormal movements occurring very infrequently.
Does your head shake **all** or **most** of the time (outside so it is visible not inside because of dizziness and not just when you are or have been carrying something on your head)?	Essential Tremor. Shaking of the head occurring all or most of the time. Shaking of the head that is visible.	Shaking of the head when saying no. Shaking of the head caused by carrying something on the head. Shaking of the head inside - dizziness Brief shivers of the whole body.
Do you have **constant** weakness down one side of your body **that is there now**?	Stroke. Injury to one side of the brain or spinal cord resulting in hemiplegia.	Pain. Injury to the bones or muscles on one side causing pain. Being less strong on left hand side JUST because right handed and vice versa. Previous weakness that has now completely resolved. Deformity on one side without weakness.

		General body weakness due to old age.
Do you have **constant** weakness in any of your arms or legs or hands or feet **that is there now**?	Monoplegia/paralysis. Paraplegia/paralysis. Hemiplegia/paralysis. Quadriplegia/paralysis.	Pain. General body weakness due to tiredness or age. Deformity of the fingers due to arthritis or farming. Deformity without weakness.
Do you have **constant** weakness of one or both sides of your face **that is there now**?	Upper or lower motor neuron facial palsy.	Asymmetry of one side of the face that has always been there – with no actual weakness. Weakness of the eyes/loss of vision.
Do you have **persistent** weakness of one or both of your eyelids **that is there now or** that gets worse towards the end of the day that is **not** just because you are tired?	Ptosis caused by cranial nerve pathology or Horner's syndrome. Ocular Myaesthenia gravis. Unilateral or bilateral.	Tiredness. Visual problems – weakness of the eyes. Wrinkles.
Do you have **persistent** problems speaking **not** just because you have a sore throat or	Dysphasia. Dysarthria.	Very occasional problems. Problems with speech due to sore

mouth **and** that affects you most of the time?	Dysphonia.	tongue, mouth or problems with teeth. Slurred speech when drunk. Problems when cold/teeth chattering. Very occasional difficulty finding the right word. Problems only when ill or that has now resolved.
Do you have **constant** loss of sensation (numbness) in your arms or legs or hands or feet **that is there now** and **not** just due to cold or pain?	Loss of sensation – multiple causes e.g. Peripheral neuropathy. Mononeuropathy. Polyneuropathy. Stroke. Brain or spinal cord injury. CONSTANT Loss of sensation THAT DOES NOT GO AWAY. LOSS of sensation NOT JUST pricking sensation.	Pain. Cold. Sitting in particular positions. Lying on part of body Loss of sensation of whole body.
Do you have **persistent** problems with your coordination such as stirring tea with a spoon or buttoning clothes that is **not** due	Cerebellar ataxia. Sensory ataxia.	Problems with precise actions due to pain. Problems when drunk

to pain in your hands or arms or because of drinking alcohol?		Lack of coordination when using non-dominant hand.
Do you have sustained/persistent contraction of your muscles that you have no control over and that produce abnormal positions of part of your body, that are **not just** in your **legs** or **just** at **night** or **just** cramp? If they happen whilst doing a certain task do they occur **most** of the times you do that task?	Dystonia. Constant or frequent. Contraction of the muscle with twisting movements and distorted postures of parts of the body that the person cannot control. If get spasms of the hand when doing actions such as pruning, washing, should happen every time do that action. Should cause distortion of position of the body.	Cramps. Infrequent cramps when been working hard. Leg cramps at night or just at rest. Cramps anywhere just at rest. Stiffness when just got up/cramps when been sitting for a long time. Just in legs. Pain in joints. Pain in muscles. Spasms of hands occurring very occasionally – often when been working for a long time.
Do you have **recurrent** short attacks of severe shock like pain affecting **one** side of your face?	Trigeminal neuralgia. Facial pain - Severe AND Recurrent AND Very brief (lasting less than one second) AND Stabbing or shock like Often triggered by touch, eating and talking.	Eye pain/symptoms. Sinus pain/symptoms.

Do you have **severe recurrent** headaches that **stop** you doing your normal daily activities?	Disabling headaches –multi-factorial. Migraine. Other headache syndromes. Severe **AND** recurrent headaches **THAT** Affect ADLs.	Headaches when the person can still carry on normal daily activities despite the headaches. Headaches just when ill for another reason e.g. Malaria.
Has anyone ever told you that you have a neurological disorder (a disorder affecting your brain, spinal cord or nerves)? What is it Is it still there?	All neurological disorders. The chance to describe the disorder ensures that the problem is still present and that the problem is a neurological disorder. Patients with a disorder affecting their brain, spinal cord or nerves that is causing ongoing problems, Constant or recurrent symptoms. Need to document what they say the diagnosis is. Need to document if it is still there.	Disorders that are not neurological. Disorders that have completely resolved.
Have you been told that you have epilepsy or epileptic fits or seizures?	Epilepsy with ongoing seizures or controlled on treatment.	People who had epilepsy when they were a child or a young adult but do not have seizures now AND are not on treatment.
Have you been told that you have	Parkinson's Disease.	

Parkinson's Disease?		
Have you ever had a stroke **that resulted in** long term problems/disability?	Stroke with residual deficit.	Symptoms that have completely resolved.
Have you ever had polio **that resulted in** long term problems/disability?	Polio with long term disability e.g. LMN weakness/Monoplegia/paraplegia.	Polio that has not resulted in disability. Polio that just gave the person flu like symptoms. Polio that caused weakness at the time but from which the patient has completely recovered.
Have you ever had leprosy **that resulted in** long term problems/disability?	Leprosy that has resulted in disability. Paraesthesia. Amputations.	Leprosy with no long term disability. Leprosy with rash only and no numbness.

2.12.3 *Modification of the screening tool at the end of data collection*

One question; Question 14 "Do you have sustained contraction of your muscles that you have no control over and that produce abnormal positions of part of your body, that are **not just** in your **legs** or **just** at **night** or **just** cramp? If they happen whilst doing a certain task do they occur **most** of the times you do that task?" was designed to pick up dystonia and other rare conditions such as paramyotonia which cause abnormal contraction of muscles. It was removed after the data collection part of the study was completed. It was felt that accurate and practical use of this question was problematic for the following reasons;

1. **As detailed in the introduction these conditions are very rare.** The estimates on prevalence of dystonia vary from 0.007 – 0.391/1000 depending on the type of dystonia and the population group studied [444-447]. The prevalence of paramyotonia is even less, approximately 1/100,000, it is classed as a rare disease by the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) [448].
2. **These conditions require the following for a definitive diagnosis;**
    - **a.** A very accurate history with an accurate family history – difficult in this setting when using interpreters and where many patients hide symptoms due to fear of stigma and therefore do not disclose them to family members. Admitting positive family history has implication for future marriages in the family and consequently is frequently not disclosed despite direct questioning
    - **b.** An examination that allows reproduction of the conditions that produce the symptoms. This was very difficult as the condition's symptoms often only occurred in certain circumstances or on exposure to cold. These were both difficult phenomenology to reproduce during village fieldwork in SSA.
    - **c.** Specialized investigations
        - i. Neurophysiology – NCS and EMG
        - ii. Blood tests – Voltage Gated Sodium Channels in Paramyotonia

These investigations are not widely available in Tanzania, SSA and most developing countries. Their use is not practical in simple low budget prevalence studies.

3. **Complex wording of this question was required in order to maintain its specificity.** Consequently this question was very difficult to teach to NMI and if this was not done carefully it was felt this question still had the potential to produce a large number of false positives and have a low specificity.

It was also felt that identification of these conditions was not beneficial to the individual patients. Patients picked up using this question appeared to have task specific dystonia and paramyotonia. Accurate confirmation of these diagnoses was not possible for the reasons detailed above. It seems more probable given the rarity of these conditions the symptoms were caused by simple (and more common) musculoskeletal problems. In addition these patients did not find the problems disabling and had practical solutions to resolve the symptoms.

In summary it was felt that the removal of this question would be beneficial to maintain the simplicity and specificity of the questionnaire whilst it would not compromise the sensitivity of what the questionnaire was designed to do; identify patients with disabling neurological conditions.

The final screening questionnaire in English and Swahili is attached in appendix 2.8 and 2.9

2.12.4 Training the NMI in the use of the screening questionnaire

Fifteen people (ten females) were recruited from the local population to act as NMI. All NMI were graduates of higher education and their occupations included teachers, village administrators, and those running small businesses.

2.11.4.1 The Workshop

Formal training of the NMI on the use of the screening questionnaire occurred over 2 days. Two workshops were held for the NMI involved in the pilot study in October 2009 and a further two workshops were held in January and February 2010 for the NMI involved in the main study (the pilot NMI were also invited to attend these workshop to share their expertise). Each was one day long and they were a week apart. Their purpose was to teach the NMI how to use the screening questionnaire and what diseases needed to be identified. The NMI and the supervisors, were invited to participate and all attended. Each question from the screening tool was presented as part of a power point presentation. The audience was shown text, pictures and videos where appropriate of the conditions relevant to each question. They were also shown a video demonstrating how the question should be asked and typical positive and negative responses to the question. Prior to the result of whether the question should be scored positively or negatively the enumerators were asked to score it themselves and to give reasons for their score. Small group and one to one teaching was then performed to ensure each NMI was competent to perform the screening questionnaire. Question and Answer sessions were held for any queries. Teaching material was given to be taken home with full explanations of positive and negative responses to each question. These could be referred to in the field. Please see appendices 2.11 to 2.13.

2.12.4.2 Further training in the field

Further training and observation was provided in the villages. The NMI screened under direct observation of the RD and the SN for the initial visits to a village. The number of days this took place depended on the enumerator's competence. The NMI was allowed to screen alone when deemed competent to do so by both the RD and the SN. NMI were deemed competent to screen independently when their responses were consistent with that of the RD. Once the NMIs were deemed competent their response to the screening questionnaire was taken as final and not modified. When independent screening was taking place in a village the RD and the SN were present to answer any queries that the enumerator may have. On the rare occasion that this was not the case they were always directly contactable by mobile phone. All enumerators had their own mobile phone.

In conclusion this comprehensive training programme reduced any filtering that might be done by the NMIs and provided assurance that positive cases would be detected.

2.12.4.3 Blinding of the RD to the results of the screening questionnaire

In both the pilot and the main study, the RD was blinded to the results of the questionnaire prior to the completion of a full history, examination and conclusion as to the presence or absence of a neurological disorder. In the pilot study the RD did not know if the patient was a positive responder and which question they had responded positively to. In the main study population, as all participants seen by the RD were positive responders, the RD was blinded only to which question the participant had answered positively.

2.13 The Pilot Study

The pilot study took place between November 2009 and January 2010. We initially carried out final question modifications as detailed above. Then all participants in the pilot village were assessed using the final questionnaire to evaluate its sensitivity and specificity. The village of Mudio was selected to be the Pilot Village. It was randomly selected using a random number generator. To our benefit it was a convenient village 20 minutes drive off the main road, it had its own health centre which made it easier to see the ambulant patients and 2 enumerators facilitated work in the village up to 5 days per week.

From the census it was reported that 345 patients aged 70 and over resided in Mudio, but it became evident that 5 were recorded twice. 32 people aged 70 and over who lived in Mudio but were not on the census were also seen. The main reason for them not being on the census was that they had turned 70 between the census date and our prevalence date of the 1st January 2010. In a minority of cases patients had travelled to another area during the census. Collecting accurate information on patient age can be difficult in SSA, as few people have a birth certificate [443]. Age was calculated from birth year and confirmed using memory prompts (e.g. age at independence) where necessary. This method has been previously validated [449]. We do recognise that there was a potential incentive for participants to say they were aged 70 or over in order to be included in the study but all possible attempts were made to try to eliminate this cause of bias. It is however impossible to say this problem was eradicated completely.

In total it was not possible to see 95 patients for the following reasons; 40 refused to be seen, 21 had died, 22 had moved and 12 were too young. Therefore altogether 277 patients were seen.

All these pilot participants were seen by the RD with the SN and a NMI. A demographic section with an age ascertainment section preceded the screening tool itself. Subsequent

to this a full Neurological History and Examination was performed by the RD. The level of Disability was also investigated with a Barthel Index. Patients were either seen at the village health centre, central large houses that could accommodate numerous patients after consent from the home owners or patient's own homes. None of the patients who answered the screening questionnaire refused to take part in the full history and examination. As a result of the screening questionnaire and the full neurological history and examination patients were allocated to one of four groups, true positives, false positives, true negatives and false negatives. From this sensitivity, specificity, positive predictive value and negative predictive value were calculated.

2.13.1 *The Pilot Study Proforma*

All sections of the Pilot Study Proforma (appendix 2.10) were asked by the RD and the SN to all people in the Pilot Study. The sections were as follows;

- Demographics
- The Barthel Index
- Measurement of blood pressure – 3 supine and 1 standing
- Height and Weight Measurement
- Neurological history
- Past medical history
- Drug history
- Social history
- Family history
- Neurological examination
- Summary
- Diagnosis
- Management plan

The Neurology screening questionnaire was asked by the NMI after 2 days of workshops and further training within the village until the NMI was deemed competent by the RD as detailed above.

2.14 The Random Selection of the Main Study Villages

We planned to see one-quarter of the entire population aged 70 years and over in the DSS. The number required was calculated from the numbers of people aged 70 and over on the census in June 2009. Using a random number generator and stratification for upland and lowland villages, 12 villages in total (1 in pilot and 11 additional), with a total census population of 2425 aged 70 and over were selected. Exclusions, refusals and additions are shown in Figure 3.2, giving a final cohort of 2232 people. Villages were stratified to ensure there were representative proportions from each of the upland and lowland areas that reflected the proportions in the whole DSS. In the DSS, of those aged 70 years and over, 76.2% live in upland areas and 23.8% in lowland areas. We studied eight upland villages (n=1683, 75.4%) and four lowland villages (n=549, 24.6%). Stratification for upland and lowland was felt necessary because of different trial origins and socioeconomic status, with those in upland areas being more prosperous due to them having better agricultural land.

2.15 The Prevalence Date

The prevalence date was January 1st 2010 selected to enable the majority of patients with neurological conditions identified from screening to be included in the prevalence figures. As many Neurological disorders are progressive and some elderly people are likely to have died in the nine months during which the study was ongoing the early prevalence date ensured that the majority of patients screened could be included in the study. To ensure the prevalence data was accurate patients were only included in the numbers if they had their neurological condition on or before January 1st 2010. This did not exclude any patients with neurological diagnoses, this is to be expected since most neurological diseases are chronic in nature. No patients seen during the pilot study died before the prevalence date.

2.16 The Main Prevalence Study

We performed the main prevalence study from February to July 2010. It was felt that the most accurate way of screening would be to bring all patients aged 70 and over (who were able) within a village to a central meeting place (often a village dispensary and more than one was utilised in large villages) to be screened whilst the RD and SN were there seeing positive responders. The RD and the SN saw those that screened positive, as previously stated, they were blinded to the results of the screening questionnaire prior to neurological assessment. Those that screened negative were also observed walking, providing consent and holding a conversation by the RD or SN to ensure that no obvious diagnoses were missed. Approximately two weeks were spent in each of the remaining villages. The duration varied dependent on the size of the village. The days were not usually consecutive as enumerators were often not available all days of the week as they had other employment. Therefore two or even three villages were often "active" at the same time to ensure flexibility and continued work. Using this method we were able to organise our time so that villages that were problematic to access in the rainy season were seen before or after this period. The rainy season, although unpredictable, usually starts at the beginning of March in Northern Tanzania, and lasts for two months or more. During this time many of the dirt roads higher up the mountainside become impassable, thus access to patients that live in very remote rural areas was problematic. Even with this prioritisation and organisation, due to the prolonged rains in 2010 which lasted from early March to mid July, access to many of the villages, particularly along smaller roads to patient's houses, was difficult, but with the use of a four wheel drive vehicle it was achieved. On some days, field work had to be abandoned due to extreme weather. However all of the patients, from the 11 villages in the main study, were seen despite inclement weather.

As Neurological disorders and other co morbidities common to "old-age" have the potential to cause severe disability it was anticipated that a proportion of the elderly

patients would have to be seen in their own home. This would obviously take longer and a few days at the end of the allocated two weeks in each village were set aside for this.

None of the patients that responded positively to the screening questionnaire refused to take part in the study. However there was one patient who was screened when the study doctor was in mobile phone contact only and subsequently could not be traced as she had travelled out of the district.

The breakdown of patients seen in the Main Study is shown in the results section (table 3.17). This table includes data on those who refused to be seen, those who had died, those who had moved away and new additions to the village's 70 and over population since the census was performed 6 months earlier. The reasons for the new additions were mostly due to participants turning 70 between the census date and the prevalence date as described in the section Pilot Study Population above.

2.16.1 *The Main Study proforma*

The Main Study Proforma (Appendix 2.14 and 2.15) was very similar to the Pilot study Proforma. The difference was that it was divided into 2 main sections;

1. Sections that were asked by the Enumerator to all people aged 70 and over (Appendix 2.14 The Participant Selection Proforma for the Main Study)
2. Sections that were asked by the RD and SN only to those people that screened positive (Appendix 2.15 The Main Study Proforma)

The other difference was the addition of a sub-section in the initial section which included questions that asked people to self report visual problems, diabetes, hypertension and

hypertension treatment. This was not required in the Pilot Study as all patients were asked a past medical history and drug history section which explored these problems.

Sections in the participant selection proforma that were asked by the Enumerator/NMI to all people aged 70 and over were;

- Demographics
- Neurology Screening Questionnaire
- The Barthel Index
- Height and Weight Measurement
- Simple questions on Visual problems, diabetes, hypertension and daily compliance with hypertension treatment
- Measurement of blood pressure

Sections in the Main Study proforma that were asked only to those people that screened positive were;

- Check box for true positives or false positives
- Details of responses to Neurology screening questionnaire
- Neurological History
- Past medical history
- Drug history
- Social history
- Family history
- Neurological examination
- Summary
- Diagnosis
- Management plan.

The Past Medical History (PMH), Drug History (DH), Family History (FH) and Social History (SH) sections allowed risk factors and health beliefs to be explored.

The proforma ensured that the questions were carried out in the same order with each patient. A scoring system was defined for each closed question: 1=no, 2=yes. For more

detailed questions, possible answers were thought out in advance and also assigned a numerical value e.g.

Traditional Healer Intervention? **Yes** **No**

Type of Treatment		**Length of Treatment:**	
1. Oral medication	|___|		
2. Bath	|___|	1. Less than one wee k	|___|
3. Inhalation	|___|	2. 1 – 2 weeks	[___]
4. Topical	|___|	3. 2 weeks – 1 month	[___]
5. Roots/leaves	|___|	4. More than one month	[___]
6. Scarification	|___|		
7. Other (state):_____	|___|		

This ensured that it was quick and easy to complete the proforma and to enter results from the proforma into Excel and SPSS databases.

For specific neurological conditions, the gradation of severity through the use of scoring systems was performed and additional classification systems were utilised.

- Essential Tremor – Movement Disorder Society (MDS), National Institutes of Health (NIH), Tremor Investigation Group (TRIG) [86-90, 450]
- Other Tremors – Movement Disorder Society (MDS) [86]
- Parkinson's Disease – UK PDS Brain Bank Criteria/Modified Hoehn and Yahr [118, 122]
- Vascular Parkinsonism – Winikates criteria [171]

- Progressive Supranuclear palsy – National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) [167]
- Stroke – The Oxford Community Stroke Project Classification (OCSP)/Bamford Classification [212]
- Tardive Dyskinesias – American Psychiatric Association Task Force [451]
- Headaches – International Headache Society (IHS) [179]
- Epilepsy – International League Against Epilepsy (ILAE) [291, 292]
- Motor Neuron Disease – National Institute of Neurological Disorders and Stroke (NINDS) [452]
- Spinal Injury – American Spinal Injury Association (ASIA) [453, 454]
- Myaesthena Gravis – Myaesthenia Gravis Foundation of America (MGFA) [455]

The Bamford Classification [212] is designed to classify the type of stroke at the time of presentation. Patients were therefore put into categories based on the symptoms and signs they described when they initially had the stroke rather than at the time they were seen by the RD and the SN. This relies on retrospective information from the patients and the patient's family and so has its limitations in terms of accuracy but it was felt this was the most appropriate way of using this classification system.

All data was entered into a specially designed Microsoft Excel database which used numerical values to save time and to allow direct conversion into the Statistical Package for the Social Sciences (SPSS) version 17 for analysis. Data entry was performed by the RD whilst on location in Tanzania on a lap top computer. This ensured that little time had passed between seeing the patient and entering their results. It also allowed any missing values or further questions to be followed up by the RD while still in Tanzania. Additionally each true positive had a word document completed about them, this detailed in depth their neurological history, examination, diagnosis, treatment plan and plans for follow up.

2.17 Examination

Examination was performed either in a health centre, dispensary or private house. Adequate privacy was ensured at each place. This comprised basic medical and detailed neurological examination, followed by height, weight, BP and ECG recording. The latter were completed because the study was performed in association with my colleague Dr Matthew Dewhurst who studied these records in the same population, the protocols for these are therefore described below but will not be elaborated on further.

2.18 Photographs and Video recording

Pictures and videos were taken if relevant to the case and the patient consented. There were standardised scripted video examinations: one for patients who screened positive for tremor, another for patients who were thought to have Parkinson's disease or Parkinsonism, another specified movement disorder or if the diagnosis was in doubt. All videos were reviewed by a movement disorder expert (RW) or a Neurologist (NW or WH) who was blinded to the diagnosis made by the RD.

2.19 Blood pressure recording

Blood pressure (BP) was recorded after the patient had been sitting quietly for 5 minutes. It was recorded 3 times with 1 minute between each recording. If possible, the patient was asked to stand for 3 minutes and a further blood pressure was recorded. The mean BP was recorded as the mean of the 2nd and the 3rd blood pressure recordings. This is as per the standard research protocol [456, 457].

2.20 ECG Recording

A standard 12 lead ECG was recorded after the patient had been lying down for 5 minutes.

2.21 Nutritional examination

The patients' height and weight was recorded to calculate a body mass index (BMI). Some patients were physically unable to stand; therefore, height and weight could not be measured. In these cases demi-span was recorded and approximate height was subsequently calculated. Demispan is the distance from the midline of the sternal notch to the tip of the middle finger along either horizontally outstretched arm. The following equations calculate height: for a man: height = (1.40 x Demispan in cm) + 57.8 and for a woman, height = (1.35 x Demispan in cm) + 60.1 [458].

2.22 Diagnosing Neurological Disorders

There are diagnostic tests available for some Neurological Disorders, however, even within the western world clinical diagnosis is often the gold standard. As resources within sub-Saharan Africa are limited by a lack of facilities and additionally by the patient's finances, neurological investigation in a population mainly made up of subsistence farmers is impossible and in any case, does not reflect normal circumstances. As discussed above multiple clinical criteria for each disease were used to make each diagnosis. CT scans are available in Northern Tanzania as are basic blood tests. However our patients could not afford these investigations. Magnetic resonance imaging, nerve conduction studies, electomyelography and blood tests diagnostic of specific neurological disease are not available in this region of Tanzania.

2.22.1 *Ensuring the correct neurological diagnoses were made*

All true positives, false positives and all pilot study patients were discussed with a consultant geriatrician, neurologist or movement disorder expert depending on the diagnosis made by the RD, for example all movement disorders were discussed with a movement disorder expert , all stroke patients were discussed with a consultant

geriatrician, and all remaining neurology cases were discussed with a Consultant Neurologist either within Tanzania (Dr William Howlett) or back in the UK (Dr Naomi Warren) . Full neurological history and examination were discussed in each case. Scripted videos were recorded and shown to the expert where appropriate e.g. movement disorders. The expert was blinded to the diagnosis made by the RD in each case, however this is limited by the fact that the movement disorder expert and the geriatrician knew that the cases that they were to assess had been identified as movement disorder and stroke respectively.

2.23 Patients with Neurological Diagnoses

Patients with a Neurological diagnosis were given a full explanation of their condition. Those that were amenable to treatment that was routinely available within Tanzania were given a month's supply of treatment along with a full explanation of side effects, any monitoring required and a prescription to obtain more when they ran out. Unfortunately due to our financial constraints we were not able to offer a longer supply except in the case of Parkinson's disease. Although patients often could not afford repeat prescriptions, there were 3 opportunities for them to get free or cheaper health care and these possibilities were pointed out to them as there was limited awareness of these schemes. They were as follows;

- Free health care is available to all patients aged 70 and over through application to their local village council. This then has to be approved by the district medical officer. This process is often lengthy and logistically difficult
- Families of government workers, or those people who have ever been government workers, are entitled to free health care
- 10,000 Tanzanian shillings (£5) can be paid per year to the local government dispensary or health centre and this entitles a person and their whole family to free health care for one year.

Table 2.12: Neurological diagnoses with available treatment in Tanzania.

Neurological Diagnosis	Additional investigations offered	Treatment Available	Cautions	Side effects	Follow up offered as part of the study?
Stroke	BP BM	Aspirin. BP treatment. Diabetes treatment if diabetic. Walking aid requirement assessment.	Aspirin given if no CTH done based on best evidence if no CT scan available.	Side effects of BP treatment, diabetes treatment and aspirin explained.	No
Essential tremor	BP ECG	Propranolol	Propranolol given unless contraindicated by BP, PR interval or other ECG abnormalities or h/o cardiac syncope.	Hypotension Syncope Wheezing Claudication	Yes
Parkinson's Disease	BP	Levodopa	Not to be stopped suddenly. Ongoing supply available.	Postural hypotension Nausea	Yes – long term with ongoing

				Dyskinesias Hallucinations	treatment
Epilepsy	BP ECG 24 hour or 7 day event recordings to exclude other causes of collapse if indicated by the history	Phenobarbitone or Phenytoin	Not to be stopped suddenly. Ongoing free supply available as part of Tanzanian Government Strategy.	As per medication prescribed.	Yes
Orthostatic Tremor		Phenobarbitone or Clonazepam	Not to be stopped suddenly.	As per medication prescribed.	Yes
Hemifacial spasm		Carbemazepine		Nausea and vomiting Dizziness Tiredness	
Trigeminal Neuralgia		Carbemazepine			
Polyneuropathies	BM/Diabetic screen	Diabetic treatment Vitamin/food		As per medication prescribed	No

		supplements			
Headache		Simple analgesia		As per medication prescribed	No

Infectious diseases like leprosy were deemed treatable if in the acute phase. Other conditions were deemed treatable if effective rehabilitation strategies would improve morbidity.

2.23.1 *Questioning those with neurological disorders about health seeking behaviour, previous diagnoses and treatment*

All participants identified with a neurological dosorder were asked if they had sought treatment for their condition, whether they had recieved a diagnosis and whether they were currently being treated. Treatment seeking included visiting traditional healers and un-registered private pharmacies and dispensaries as well as more formal healthcare facilities. If patients responded that they had recieved a diagnosis details of the diagnosis given were taken, a diagnosis was deemed correct if it corresponded with that of the RD and the consultant expert. If patients responded that they were receiving treatment the type and level of treatment was checked and recorded. Patient handheld records were reviewed where possible but this was in a limited number of cases as very few patients had them or if they did very little was recorded in them. Other formal records did not exist except in the tertiary referral hospital (KCMC) which very few of the participants had visited.

A correct diagnosis was defined as a diagnosis that corresponded to that made by the research doctor and the expert consultant this was expressed as a percentage of all of those people with a neurological disorder, not just those who had sought treatment, this was because this reflects the true diagnosis gap as most people did not seek help for their symptoms for geographical and financial reasons, therefore this is also a failing of the healthcare system in Tanzania.

Correct treatment was defined as the treatment that was recommended by the WHO and expert review articles for the condition diagnosed [459] this was expressed as a percentage of all of those people with a neurological disorder, not just those who had sought treatment, this was because this reflects the true treatment gap as most people did not seek help for their symptoms for geographical and financial reasons, therefore this is also a failing of the healthcare system in Tanzania[460].

2.24 Patients with multiple Neurological Diagnoses

For every patient who responded positively to the screening questionnaire, or was brought to our attention by an alternative method, a diagnosis was reached. In some cases patients had more than one diagnosis, and each diagnosis was taken into account in the analysis of results and the prevalence of multiple diagnoses was also recorded. Whether the patient was a true positive, false positive, false negative or true negative was established by reflecting on what answers were given to the questionnaire in order to bring them to the attention of the RD. For example, one patient had essential tremor, a previous stroke and osteoarthritis. However, in this case the reason he had answered positively to the screening questions was because of his tremor, abnormal gait and weakness following his stroke. Arthritis contributed to pain when walking, but he was more limited by the stroke. The most disabling neurological diagnosis was recorded as the primary diagnosis, in this case the stroke. The essential tremor was recorded as his secondary diagnosis. Other incidental non neurological diagnoses were also recorded. All True Positives were assigned a WHO ICD 10 code and were split into epidemiological and clinical diagnostic divisions (see appendix 3.1).

2.25 False Positives and True and False Negatives

As with the Neurological cases, many of the false positives and the true and false negatives had no access to medical care for their medical needs. As much information and explanation about their condition was imparted at the time of examination by the RD as possible. If the patient was deemed negative by the enumerator but had a medical problem they wanted to discuss with the RD this service was offered. As part of another project which was ongoing at the same time each patient had their Blood Pressure measured and an Electrocardiograph (ECG) performed. Treatment for any problems demonstrated by their investigations was given, as was a prescription which described ongoing medication requirements. This was always fully discussed with the patient (and

their family if necessary and, if appropriate, with consent from the patient). Many patients had severe arthritis and had limited access to analgesia due to financial constraints. A small supply of analgesic (paracetamol) was given in each of these cases following assessment for contraindications. In some cases further investigations would be needed to make the diagnosis and these were explained to the patient and their family if present, and appropriate referral letters were given.

2.26 Other case finding methods

Multiple other case finding methods were used to guarantee no cases were missed to ensure our prevalence data was as robust as possible.

2.26.1 *Positive family history*

In the Main study proforma a family history of neurological disorders/symptoms was taken (either similar to the symptoms of the patient or other neurological symptoms). This was particularly relevant to conditions such as essential tremor. Any patients who mentioned relatives living within the studied villages who were 70 or above and who had neurological symptoms were asked for the relative's details. It was anticipated that if the patients had not already been picked up by the screening questionnaire then these individuals would be visited by the RD. The supervisors assisting with the study would be able to contact the relative and gain permission for the visit and explain again about the project before the assessment. This system was not however required as all patients brought to our attention by this method had already been identified by the screening questionnaire.

2.26.2 *Tanzanian stroke incidence project*

The Hai DSS has been the site of the Tanzanian stroke incidence project (TSIP) which began in June 2003. An area of Dar es Salaam was also studied [213, 461]. The last follow up for this project was in July 2008. The stroke project research doctor was able to tell us about any patients aged 70 and over on our prevalence date who had confirmed strokes within our randomly selected villages and who were still alive with neurological deficit at last follow up. These names were checked against our positive list, again all these patients had already been identified by the screening questionnaire and they had all been seen by the RD.

2.26.3 *The Hai Parkinson's disease and Essential Tremor Project*

The Hai DSS had been the site of the Hai Parkinson's Disease Prevalence Project with a prevalence date of the 1st March 2006 [96, 128].The last follow up for this project was in January 2010. The Parkinson's disease project research doctor was able to tell us of any patients aged 70 and over on our prevalence date who had Parkinson's disease or Essential Tremor within our randomly selected villages and who were still alive at last follow up. These names were checked against our positive list, again all of these patients had already been identified by the screening questionnaire and they had all been seen by the RD.

2.26.4 *The Hai Epilepsy Prevalence project*

The Hai DSS has been the site of the Hai Epilepsy Prevalence project which began in January 2009.The last follow up for this project was in August 2010. The Epilepsy project research doctor was able to tell us of any patients aged 70 and over on our prevalence date who had confirmed Epilepsy within our randomly selected villages. These names were checked against our positive list, again all these patients had already been identified by the screening questionnaire and they had all been seen by the RD.

2.26.5 *Local village elder reporting*

In each village there are a number of elderly, respected individuals in positions of authority and there is a "Ballozi", each village is split into "cells" consisting of ten households and the elected Ballozi is in charge of those cells. Both of these groups of people inform the enumerators of any significant events, (including illnesses) in the village. This reporting system was utilised to identify potential false negatives.

2.26.6 *Methods not used*

At the start of the methods section, I have discussed various alternative methods for detecting cases of Neurological Disorders including medical records and pharmacy searches. These were not employed in this study because they were not felt to be able to add anything to the methods already described. For example, following up prescriptions of medication for Neurological Disorders, as we felt so few patients would know their diagnosis and be on treatment this would be futile and in any case pharmacy records were not accessible. We were unable able to chase up death certificates as less than 5% of deaths are certified, or use disease registers as no formal systems exist. We did not try to find patients through hospital records. The only hospital with formal accessible hospital records was KCMC. We did ask a sample of the 70 and over population in Mudio, the Pilot Village, if they had ever been to KCMC. The response was low thus the potential to find cases this way would also be low.. Most local hospitals, health centres and dispensaries employed the system that the patients carried their records with them in the form of an exercise book and no other records were kept. Consequently they were asked to bring this with them when they were seen and these were reviewed.

2.27 Follow up

All participants identified as having a neurological (or other) disorder were given information on the condition and possible treatments at the time of diagnosis, by the RD. The patients were given the NMI's contact details and instructed to contact the NMI who would contact the RD if they had any further questions. Information sheets on each condition were not used as the majority of patients were either illiterate or had limited skills in reading and writing. However all patients were provided with a written piece of paper detailing their condition and relevant treatment options if available. This could be used to inform healthcare professionals that may be involved in their future care. Patients were followed up if they were diagnosed with Parkinson's disease, epilepsy, orthostatic tremor and essential tremor if the patient wished to be treated.

Table 2.13: Details of Patient Follow up Performed as Part of the Prevalence Study

Disease	Details of follow up
Parkinson's Disease	Ongoing lifelong follow up and treatment provided Monthly follow up and treatment provided by local Assistant Medical Officer. Yearly follow up to be provided by a UK PD specialist. At initial follow up visit diagnosis was confirmed based on the UKPDS Brain Bank Criteria and response to treatment was assessed.
Essential Tremor	One follow up visit Assessed response to treatment Assessed for side effects to treatment Provided more treatment if required/appropriate Reiterated information about the condition
Epilepsy	One follow up visit Assessed response to treatment Provided more treatment if required – reiterated free treatment available from all government hospitals, health centres and dispensaries Reiterated information about the condition
Orthostatic tremor	Two follow up visits Assessed response to treatment If unresponsive a further medication supplied/ if responsive a resupply given Response assessed again at second visit

	Assessed for side effects at each visit Reiterated information about the condition

2.28 Statistics

Statistical advice was sought from Dr Keith Gray from Northumbria Health care Foundation Trust. Statistical analyses were performed using Statistical Package for the Social Sciences SPSS software, version 17.0.

2.28.1 *Calculation of age standardised prevalence rates*

Direct age standardisation to the World Health Organisation (WHO) standard population (table 2.14) was calculated to give age-standardised prevalence rates. Using WHO data for the percentage of the population in each age band, an expected number of cases could then be calculated for the standard population. Dividing the number of cases in each age band by the proportion of people in the Hai population in that age band and then multiplying by the proportion of people in that age band from the standard population gave the expected total number of cases were the population age structure to follow that of the standard population. The age-standardised prevalence rate per 1000 of the population was then calculated.

Table 2.14: WHO World Standard Population

n Distribution (%) based on world average population between 2000-2025

Age group	World Average 2000-2025
0-4	8.86
5-9	8.69
10-14	8.60
15-19	8.47
20-24	8.22
25-29	7.93
30-34	7.61
35-39	7.15
40-44	6.59
45-49	6.04
50-54	5.37
55-59	4.55
60-64	3.72
65-69	2.96
70-74	2.21
75-79	1.52
80-84	0.91
85-89	0.44
90-94	0.15
95-99	0.04
100+	0.005
TOTAL	100

[462]

2.28.2 Calculating the Standard Error and Confidence Intervals

Confidence intervals (CIs) for prevalence and odds ratios were calculated based on the assumptions of the binomial distribution.

Since this was a point prevalence study, the distribution of cases within the population would be most closely approximated by a binomial distribution rather than a Poisson distribution, this was because patients either had or did not have a neurological disorder on the point prevalence date

The standard error was therefore calculated using the formula;

Standard Error=√p(1-p)/n

p=proportion=number of cases/background population

95% Confidence intervals = p+/-1.96xSE (multiple p and SE by 100 for a percentage or by 1000 for CI per 1000)

Using the binomial distribution, some 95% CI report a negative rate, as this is impossible these values have been corrected to zero.

If I had been calculating incidence or period prevalence I would have used the Poisson distribution.

2.28.3 Calculating Sensitivity, Specificity, Positive Predictive Value and Negative predictive value

A number of measures of the performance of my screening questionnaire is given.
Sensitivity is the proportion of those with a neurological disorder who screened positive.
Sensitivity=true positives/(true positives + false negatives)
Specificity is the proportion of those without a neurological disorder who screened negative.
Specificity=true negatives/(true negatives + false positives)
Positive predictive value is the proportion of subjects with a positive test that are correctly diagnosed
Positive predictive value=number of true positives/(number of true positives + number of false positives)
Negative predictive value is the proportion of subjects with a negative test that are correctly diagnosed

Negative predictive value=number of true negatives/(number of true negatives + number of false negatives)

The accuracy of a test is the proportion of all cases correctly classified by the screening instrument.

Accuracy=(true positives + true negatives)/(true positives + false positives + true negatives + false negatives)

2.28.4 The use of other statistical tests

Chi squared and Odds Ratios were used to test the significance of differences found in disability data between different groups, i.e. those with neurological disorders and those without.

Odds Ratio definition=the ratio of the odds of an event occurring in one group compared to another

Cohen's Kappa was used to determine the level of agreement between two tests. In this study I used Cohen's kappa to indicate the level of agreement between our tool and clinical opinion. A value of 1 indicates complete agreement and a value of 0 indicates a level of agreement that would be no better than chance.

Dr Keith Gray constructed a logistic regression model to help identify independent predictors of moderate or severe disability. Stepwise methods were used to construct the model and the robustness of the model checked by examination of residuals, Cook's distances, loading of variables on individual eigenvalues and collinearity diagnostic tests. I understand the basis of these tests and their application for this purpose.

2.29 Critique of study design

2.29.1 *Limitations of study design*

A main concern was that the screening questionnaire would fail to pick up patients with neurological disorders because they incorrectly answered negatively to a question. We attempted to prevent this from happening by making the questionnaire as sensitive as possible, making the questions as simple as possible and by teaching the NMI about the conditions we wanted to identify therefore they could challenge the patient about answers they felt were incorrect. We also utilised multiple other case finding methods and briefly observed all participants who screened negative to eliminate this potential error as much as possible. Thus I did not rely solely upon the screening questionnaire, even though I was confident it would be highly sensitive as well as specific. However, it is worthy of note that if patients wished to hide their symptoms because of the stigma associated, they might not be discovered. It was not possible with the time or resources available for a medically trained individual to visit each person within the population of 2232, so some form of screening would have to take place first. The screening questions covered all the main neurological disorders apart from poor vision, deafness (not specifically neurological diagnoses) and disorders of the autonomic nervous system as these were either felt to be too common in the elderly or too difficult to detect, as detailed above.

To rely on history and examination and not utilise investigation, limits the accuracy of diagnosis particularly when the diagnosis is dependent on subjective symptom reporting such as sensation. However this does accurately reflect clinical work in SSA.

2.29.1 *Strengths of study design*

Every history and examination was undertaken by the same RD with the same SN. This ensured all participants in the study were treated in exactly the same way.

The community based two phased approach is the gold standard for recording prevalence of Neurological disorders in resource poor settings [6, 25]. This robust methodology ensured that we identified previously undiagnosed patients something a hospital based approach fails to do. All patients too frail to attend medical facilities were seen within their own home, particularly important to truly reflect prevalence in conditions such as neurological disorders which have the potential to be very disabling.

The team of enumerators/NMI and supervisors employed within this study had previously worked on a stroke incidence study [213], a PD prevalence study [96, 128] and an Epilepsy prevalence study in the same area. This ensured the team were competent and confident in their roles in the research team. It also meant that the population studied were familiar with regular censuses and medical studies and so were not only happy to be involved in the study also understood it would potentially be to their benefit. This ensured the maximum possible participation rate. The use of local personnel ensures capacity building in the local area which is very important when studying a population.

The WHO ICD criteria are a widely recognised and used set of criteria for making the diagnosis of Neurological Disorders; other more specific criteria that are internationally recognised were also used for specific neurological disorders. This not only adds to the accuracy of the diagnosis, but also adds to the comparability with other studies where the same criteria have been used.

The number of different case finding methods covered were from as wide a variety of sources as possible, to try and prevent missed cases. Whilst I recognise that it is possible that cases may have been missed, especially those in the early stages of disease, I believe I have covered as many of the options available as possible.

2.30 Wheelchair and walking aid provision

Whilst performing the Pilot and Main Study, I found many people who were disabled as a result of neurological disorders and other conditions (most commonly arthritis). For financial and logistical reasons appropriate walking aids and wheelchairs were not available to them. The RD was able to assess everyone involved in the study for their need for walking aids and wheelchairs. Through charitable donation the RD was able to assess these patients again with a walking aid and wheelchair expert from KCMC who was able to produce customised walking aids and wheelchairs for all those who needed them. A total of 21 wheelchairs, 25 walking frames and 6 pairs of crutches were supplied.

Chapter 3. Results

3.1 The Census and the Demographics of the Hai District DSS Census Population

The date of completion of the Hai District DSS census was the 1st of June 2009 with a remarkable 100% response. There were no households who refused to take part in the survey. The population of the Hai district DSS was 161,119. 58,093 (36.06%) were aged less than 15, 103025 (63.94%) were aged 15 and over and 8869 (5.50%) were aged 70 and over. 3159 (1.96%) were 70-74, 2531 (1.57%) were 75-79, 1447 (0.90%) were 80-84 and 1732 (1.07%) were aged 85 and over. 83,180 (51.63%) were female and 77939 (48.37%) were male. Of the 70 and over population 4844 (54.62%) were female and 4025 (45.38%) were male. This is shown in detail in the table below.

Table 3.1 Age and Sex divisions In the Hai District DSS from the 01/06/2009 census

Age group	Female	%	Male	%	Total (Males and Females)	%
0-14	28794	34.6	29299	37.6	58093	36.1
15-19	8114	9.8	8648	11.1	16762	10.4
20-24	5225	6.3	4719	6.1	9944	6.2
25-29	5487	6.6	4467	5.7	9954	6.2
30-34	5381	6.5	4961	6.4	10342	6.4
35-39	5216	6.3	4852	6.2	10068	6.3
40-44	4800	5.8	4234	5.4	9034	5.6
45-49	4156	5.0	3630	4.7	7786	4.8
50-54	3727	4.5	2986	3.8	6713	4.2
55-59	2911	3.5	2437	3.1	5348	3.3
60-64	2390	2.9	1949	2.5	4339	2.7
65-69	2135	2.6	1732	2.2	3867	2.4
70-74	1684	2.0	1475	1.9	3159	2.0
75-79	1351	1.6	1180	1.5	2531	1.6
80-84	824	1.0	623	0.8	1447	0.9
85+	985	1.2	747	1.0	1732	1.1
TOTAL	83180	100	77939	100	161119	100

A census can only identify those living in the area on a certain date. Those who were temporarily away for work or other reasons were not included if deemed to be no longer living in the area by other household members. Of those aged 70 years and over very few were likely to work away from home and so this was not deemed to be a big problem. Those who had travelled on the census date and who had since returned by the prevalence date were included in the study and denominator. They were requested to present themselves by the NMI who had extensive knowledge of the village. These inclusions and exclusions are shown in figure 3.1, "Identification of the pilot population" and figure 3.2, "Identification of the main study population".

3.1.1 *Division of the Census Population by village*

The populations of the villages of the Hai District DSS are shown in the following table. The number of patients aged 70 and over in each village is also described as is the geographical location of the village (upland or lowland). The villages highlighted in bold are those 12 that were randomly selected to take part in the study. They represent a quarter of the 70 and over population of the Hai District DSS. As previously discussed the population of these villages recorded on the census was slightly different from the population seen as part of the pilot and main study. This is for multiple reasons all of which were explained in the methods and are elaborated on further in the results.

Table 3.2: Division of the Hai District DSS population by village demonstrating representation from the 70 and over population

Village	Whole population of Each Village	Percentage of whole population of Hai District DSS represented in each village	Population aged 70 and over from the census	Percentage of population 70 and over represented in each village	Population aged 70 and over seen as part of the Pilot and Main Study	Percentage of population aged 70 and over represented in each of the Pilot and Main Study Villages	Geographical location	Altitude
BOMANG`OMBE	11558	7.2	216	2.4	136	1.53	LOWLAND	995
FOO	3969	2.5	394	4.4	N/A	N/A	UPLAND	1565
ISUKI	1853	1.2	126	1.4	N/A	N/A	UPLAND	1399
KAWAYA	2722	1.7	88	1.0	N/A	N/A	LOWLAND	851
KIA	1501	0.9	16	0.2	N/A	N/A	LOWLAND	919
KIKAVU CHINI	3743	2.3	116	1.3	N/A	N/A	LOWLAND	805
KILANYA	1848	1.1	151	1.7	N/A	N/A	UPLAND	1588
KIMASHUKU	2452	1.5	79	0.9	N/A	N/A	LOWLAND	909
KWA SADALA	3018	1.9	78	0.9	83	0.94	LOWLAND	1033

KWARE	3251	2.0	189	2.1	148	1.67	LOWLAND	1071
KWATITO	1083	0.7	28	0.3	N/A	N/A	LOWLAND	909
KYEERI	2959	1.8	195	2.2	N/A	N/A	UPLAND	1670
KYUU	1778	1.1	120	1.4	118	1.33	UPLAND	1396
LEMIRA KATI	1514	0.9	139	1.6	N/A	N/A	LOWLAND	1420
LENGOI	2013	1.2	62	0.7	N/A	N/A	LOWLAND	833
LOSAA	1345	0.8	77	0.9	N/A	N/A	UPLAND	1560
LUKANI	1272	0.8	116	1.3	115	1.30	UPLAND	1594
LYAMUNGO KATI	2254	1.4	190	2.1	N/A	N/A	UPLAND	1520
LYAMUNGO SINDE	1869	1.2	138	1.6	N/A	N/A	UPLAND	1315
MAMBA	1952	1.2	157	1.8	N/A	N/A	UPLAND	1340
MASHUA	2394	1.5	137	1.5	N/A	N/A	UPLAND	1353
MBATAKERO	669	0.4	18	0.2	N/A	N/A	LOWLAND	940
MBORENI	1371	0.9	86	1.0	N/A	N/A	UPLAND	1330
MBOSHO	1740	1.1	139	1.6	N/A	N/A	UPLAND	1295
MBWEERA	3297	2.0	194	2.2	194	2.19	UPLAND	1330
MIJONGWENI	3681	2.3	130	1.5	N/A	N/A	LOWLAND	820
MKALAMA	2605	1.6	91	1.0	N/A	N/A	LOWLAND	864
MTAA WA SHABAHA	1023	0.6	33	0.4	N/A	N/A	LOWLAND	915

MTAKUJA	1685	1.0	43	0.5	N/A	N/A	LOWLAND	920
MUDIO	5522	3.4	345	3.9	277	3.12	UPLAND	1257
MULAMA	1824	1.1	123	1.4	N/A	N/A	UPLAND	1274
MUNGUSHI	7884	4.9	184	2.1	N/A	N/A	LOWLAND	1050
MUROMA	1874	1.2	119	1.3	N/A	N/A	UPLAND	1296
NGIRA	2234	1.4	160	1.8	N/A	N/A	UPLAND	1275
NGOSERO	968	0.6	35	0.4	N/A	N/A	LOWLAND	822
NGUNI	2498	1.6	159	1.8	N/A	N/A	UPLAND	1580
NKUU NDOO	2038	1.3	222	2.5	N/A	N/A	UPLAND	1620
NKUU SINDE	2132	1.3	234	2.6	N/A	N/A	UPLAND	1314
NKWANSIRA	2080	1.3	133	1.5	N/A	N/A	UPLAND	1240
NRONGA	2299	1.4	287	3.2	N/A	N/A	UPLAND	1670
NSHARA	7805	4.8	411	4.6	386	4.35	UPLAND	1170
ROO	5308	3.3	305	3.4	265	2.99	UPLAND	1250
RUNDUGAI	7686	4.8	225	2.5	N/A	N/A	LOWLAND	861
SAAWE	2609	1.6	185	2.1	192	2.16	UPLAND	1476
SANYA STATION	3219	2.0	91	1.0	N/A	N/A	LOWLAND	933
SHARI	3611	2.2	318	3.6	N/A	N/A	UPLAND	1390
SHIRI NJORO	2841	1.8	111	1.3	N/A	N/A	LOWLAND	1018
SHIRIMGUNGANI	3090	1.9	118	1.3	182	2.05	LOWLAND	860
SONU	2926	1.8	257	2.9	N/A	N/A	UPLAND	1306

TELLA	2692	1.7	163	1.8	N/A	N/A	UPLAND	1241
TINDIGANI	1250	0.8	25	0.3	N/A	N/A	LOWLAND	915
UDURU	2289	1.4	167	1.9	N/A	N/A	UPLAND	1296
URORI	2825	1.8	142	1.6	136	1.53	UPLAND	1086
USARI	2231	1.4	134	1.5	N/A	N/A	UPLAND	1190
USWAA	3218	2.0	269	3.0	N/A	N/A	UPLAND	1190
WARI	3745	2.3	401	4.5	N/A	N/A	UPLAND	1440
Total	161119	100.0	8869	100.0	2232	25.2	N/A	

The table below records the percentage of the whole population that resides in upland and lowland villages. It also shows separately the percentage of the 70 and over population that resides in upland and lowland villages and the percentage of the 70 and over population from the studied villages that reside in upland and lowland villages – both from the census and from the actual study numbers. This is to demonstrate that more elderly live in upland villages. There is no documented reason for this although we can speculate that this is because those in the lowland villages die earlier and/or there is a younger population in lowland villages as many of them are near to the main transport links and there are more opportunities for employment away from the subsistence farms. The table also demonstrates that the studied population is representative of the 70 and over population in the whole of the Hai District DSS with regard to the percentage of people that come from upland and lowland areas.

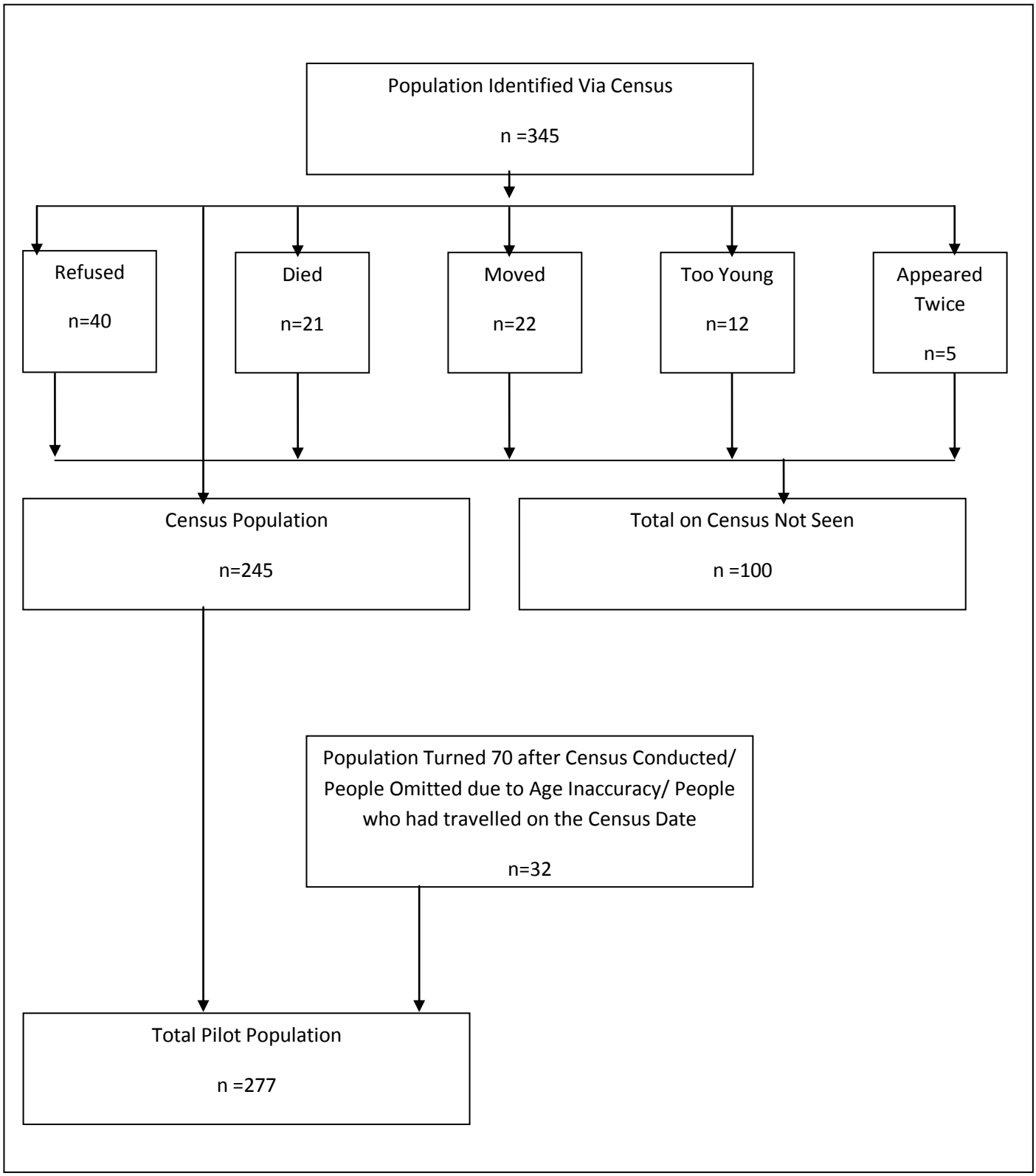
Table 3.3: Representations from geographical areas in the whole Hai District DSS population, the whole 70 and over population, and the 70 and over population in the studied villages

Geographical Location	Whole Hai District DSS Population – All Ages – Frequency	Whole Hai District DSS Population – All Ages - Percentage	Whole Hai District DSS Population – Aged 70 and over - Frequency	Whole Hai District DSS Population – Aged 70 and over – percentage	Study Villages Population Aged 70 and over from the census – frequency	Study Villages Population Aged 70 and over from the census – Percentage	Study Villages Population Aged 70 and over actually seen– frequency	Study Villages Population Aged 70 and over actually seen– Percentage
Lowland	69456	43.1%	2115	23.8%	601	24.8%	549	24.6%
Upland	91663	56.9%	6754	76.2%	1818	75.2%	1683	75.4%
Total	161119	100.0%	8869	100.0%	2419	100.0%	2232	100.0%

3.2 The Pilot Study

From the census, it was reported that 345 patients aged 70 years and older resided in Mudio, but it became evident that 5 were recorded twice. 32 people aged 70 and over who lived in Mudio but were not on the census were also seen. The main reason for them not being on the census was they had turned 70 between the census occurring and our prevalence date of the 1st January 2010. In a minority of cases patients had travelled to another area during the census. Collecting accurate information on patient age can be difficult in SSA, as few people have a birth certificate [443]. Age was calculated from birth year and confirmed using memory prompts (e.g. age at independence) where necessary. This method has been previously validated [449]. I do recognise that there was a potential incentive for participants to say they were aged 70 or over in order to be included in the study but all possible attempts were made to try to eliminate this cause of bias. It is however impossible to say this problem was eradicated completely. In total it was not possible to see 95 patients for the following reasons; 40 refused to be seen, 21 had died, 22 had moved and 12 were too young. Therefore altogether 277 patients were seen.

Figure 3.1 Identification of the pilot study population



3.2.1 *The Demographics of the Pilot Population*

3.2.1.1 *Age breakdown*

The proportions of patients aged 70 and over in the different age brackets are shown in the table below. This is expressed as a percentage of the 70 and over population and as a percentage of the whole pilot village population. This can be compared to the percentage of people in the age brackets in the whole Hai District Demographic Surveillance site. This demonstrates that from an age point of view the pilot village is representative of the whole DSS population.

Table 3.4 Demonstration that the age breakdown of the 70 and over population in the Pilot study was representative of the whole Hai District DSS population

Age Divisions	People in the Pilot Study	Percentage of the 70 and over population in the Pilot Village	Percentage of the whole population in the Pilot Village	People in the whole Hai District DSS	Percentage of the 70 and over population in the whole Hai District DSS	Percentage of the whole population in the whole Hai District DSS
70-74	109	39.4	2.0	3159	35.6	2.0
75-79	75	27.1	1.4	2531	28.5	1.6
80-84	38	13.7	0.7	1447	16.3	0.9
85+	55	19.9	1.0	1732	19.5	1.1
Total	277	100.0	5.0	8869	100.0	5.5

Table 3.5 Further Division of the older age bracket in the Pilot Village Population

Age Divisions	Frequency	Percentage
70-74	109	39.4
75-79	75	27.1
80-84	38	13.7
85-89	33	11.9
90-94	9	3.2
95-99	11	4.0
100+	2	0.7
Total	277	100.0

This is representative of the background Hai District DSS population.

3.2.1.2 *Sex breakdown*

The proportion of males and females in the pilot population was also representative of the background Hai District DSS population.

Table 3.6: Demonstration of the comparable breakdown of the 70 and over population by sex in the Pilot Village and the Hai District DSS population

Sex	People Aged 70 and over in the Pilot Village	Percentage of the 70 and over population of the Pilot Village	People Aged 70 and over in the Hai District DSS	Percentage of the 70 and over population in the Hai District DSS
F	152	54.9	4844	54.62
M	125	45.1	4025	45.38
Total	277	100.0	8869	100.0

3.2.1.3 *Tribe*

In the Pilot Study 275 (99.3%) people were from the Chagga Tribe and 2 (0.7%) were from other tribes. This is representative of the background Hai District DSS population in that the majority of the population were from the Chagga tribe. However, there was not appropriate representation from the other tribes. This is one of the disadvantages of choosing a pilot population from one village for geographical and logistical convenience.

3.2.1.4 *Religion*

In the Pilot Study 182 (65.7%) people were Christian and 95 (34.3%) were Muslim. This was representative of the whole Hai District DSS population.

3.2.1.5 *Marital Status*

Of the people in the Pilot population 131 (47.3%) were married, 131 (47.3%) were widowed, 7 (2.5%) were divorced, 5 (1.8%) were separated and 3 (1.1%) were single.

3.2.2 *Where the Pilot Population were seen*

As described in the methods section we attempted to see all the patients in a place of convenience for them. In the majority of cases it was possible and practical for them to come to the village health centre or dispensary. When the village was large people were also seen at another convenient central location e.g. a private house that we had been given permission to use. If the person was unable to travel to a central location they were seen in their own home. Due to our level of flexibility on the place patients were seen and our ability to see patients in their own home, there was no introduction of bias. The most disabled, and potentially patients with neurological disorders would, have to be seen in their own homes. Of the Pilot population 118 (42.6%) people were seen in a central large private house, 109 (39.4%) were seen at the local health centre and 50 (18.1%) were seen in their own homes.

3.2.3 *Proportion of the pilot population born in, and ever lived outside, the Hai District DSS*

The population of the Hai District DSS and the pilot and main study population are fairly static especially with reference to the 70 and over population. The majority of the people (97.8%) were born within the Hai District DSS and few (21.3%) had lived outside the Hai District DSS at any point in their lives.

3.3 The screening questionnaire

3.3.1 *Analysis of the performance of the screening questionnaire when used in the Pilot Study*

3.3.1.1 *Analysis of sensitivity and specificity of the screening questionnaire in the Pilot Study*

The screening tool had a high sensitivity and specificity. As already described in the methodology the screening questionnaire was modified before the pilot study. It was subsequently modified with the removal of one question (question 14) after the main study because it identified non disabling rare conditions the diagnosis of which is very difficult to confirm in these circumstances. Presented below is the sensitivity and specificity of the screening tool with and without the question. The final performance of the questionnaire is without question 14; sensitivity is 87.8% and specificity 94.9%.

Table 3.7: The overall sensitivity and specificity analysis of the screening questionnaire in the Pilot Population

	True Negative	**True Positive**	**False Negative**	**False Positive**	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**Accuracy**
Screening tool including original Q14	180	77	10	10	88.5	94.7	88.5	94.7	92.8
The Final Screening tool - Screening tool excluding original Q14	185	72	10	10	87.8	94.9	87.8	94.9	92.8

3.3.1.2 *The ability of the questions to identify key disorders*

There was only one question to pick up headache (Q15), this correctly identified all 22 cases of headache. It incorrectly identified 2 false positives, this question therefore had a sensitivity of 100% and a specificity of 99.2% if used on its own to identify patients with headaches that affect their ADLs.

Tremor was identified by Q3, Q5 and Q6, they identified 12 out of the 19 cases of tremor, 7 cases were not identified, these were only identified on examination by the RD, the participant themselves had never noticed them and was not concerned by them. The sensitivity of the questions for tremor was 63.4% and the specificity was 99.6%.

As there are many different types of strokes, stroke can be identified by many of the questions (Q4, Q7-Q10, Q11-Q13, Q19). All 12 cases of stroke were correctly identified by these questions giving a sensitivity of 100%. However the questions identified 7 false positives giving them an overall specificity of 97.4%.

Parkinsonism was identified by Q3, Q4 and Q6, all 5 cases of Parkinsonism were identified giving these questions a sensitivity of 100%, 1 false positive was also identified giving a specificity of 99.6%.

Two questions were designed to identify cases of epilepsy (Q1 and Q2). There was only one case of epilepsy in the pilot study and this was a case of partial epilepsy with secondary generalisation, this was found by both questions, therefore questions 1 and 2 had 100% sensitivity for picking up epilepsy. The direct question regarding epilepsy did not identify the patient as they had not been previously diagnosed.

3.3.1.3 *Conditions not represented in the Pilot Population*

It is worth noting that some conditions were not present in the pilot population and therefore the true sensitivity for identification of these conditions could not be established. Additionally, because of the diagnosis gap in most of the neurological conditions, patients with a clear diagnosis had often not been told that they had a certain condition and if they had the diagnosis was often forgotten. Therefore, in the latter direct questions on the presence of neurological disease the response was not recorded as a false negative if the patient responded negatively due to a lack of a diagnosis. After all, the questions ask if the patient had ever been told they have a certain condition. In all these circumstances the patients were identified by other questions. The latter questions therefore act merely as a double check to ensure that patients with a diagnosis are not missed.

3.3.1.4 *False Negative Patients*

All the False Negative patients from the pilot study (described below) would not have benefitted from screening positive. They did not want to be brought to the attention of medical personal as they did not find their conditions disabling and there was no immediate concern from an individual health perspective. However, there could be longer term benefit for such patients e.g. in the case of the tremors progression may occur and these people could be forewarned and informed of potential future treatments should their condition become disabling. In the case of sensory peripheral neuropathy causative factors like diabetes could be investigated and treatment offered to stop the condition progressing. Standard foot care could also be explained. The exact nature of the false negative patients is described in the table below.

There is a high level of under-diagnosis of neurological conditions in SSA. Patients with a clear diagnosis were often not aware of their diagnosis. Therefore, the direct questions had a low yield. The response was not recorded as a false negative if the patient responded negatively due to lack of diagnoses. All cases were picked up using other questions. These questions merely acted as a double check, in this population

but their inclusion is justified because these conditions are of high public health significance and if this screening tool is proposed for use in other developing countries the level of awareness of neurological conditions and diagnosis will vary. It is still beneficial to identify patients that have been previously diagnosed to record prevalence and also because some of these patients may not have received treatment for a number of reasons which could be rectified..

Table 3.8: False negatives and explanation for their lack of detection by the screening tool

Diagnosis	Number of Patients	Explanation for why the patient was not picked up	Could the sensitivity of the screening tool be improved to pick up this condition?
Multiple Mononeuropathies – traumatic	1	Patients did not describe weakness or loss of sensation of the arm. This was because the condition did not bother him. He was still able to work as a farmer and had ways of coping with his disability which ensured he could function fully. Therefore, when asked he denied any problems.	As this patient did not appreciate that he had weakness and sensory loss in his arm, there is no alternative way of picking up this problem through simple questioning. Any examination section would pick this patient up, but for reasons already discussed it would limit a screening tool's use by NMI.
Enhanced physiological Tremor	5	All patients denied any tremor when questioned as part of the questionnaire and when questioned as part of a full neurological history. The presence of tremor was only found on examination and a secondary history after the tremor had been discovered. In all cases the tremor did not bother the patient and had not been noted by the patient. Therefore, it was non-disabling.	As the patients denied any tremor when directly questioned and had not noticed any tremor the only way of picking up these problems would be to include an examination section. Again this would limit a screening tool's use NMI.
Essential Tremor	2	All patients denied any tremor when questioned as part of the questionnaire and when questioned as	As the patients denied any tremor when directly questioned and had not noticed any tremor the

		part of a full neurological history. The presence of tremor was only found on examination and a secondary history after the tremor had been discovered. In all cases the tremor did not bother the patient and had not been noted by the patient. Therefore, it was non-disabling.	only way of picking up these problems would be to include an examination section. Again this would limit a screening tool's use by NMI.
Median Nerve Damage - Traumatic	1	Patient was not aware that there was loss of sensation in a median nerve distribution in his hand as a result of a laceration. He stated that it did not alter his ability to work as a farmer so it was therefore not a problem for him. The condition was non-disabling to the patient so was not reported as a response to direct questioning as part of the screening tool or as part of a neurological history.	An examination section would be the only way of bringing this patient to the attention of investigators.
Peripheral Neuropathy	1	The patient denied any sensory disturbance when asked as part of the screening questionnaire or on direct questioning as part of a neurological history. The condition was only revealed on examination.	A detailed examination section would be required to pick up this condition. This would make a screening questionnaire lengthy and would require highly trained investigators.

3.3.1.5 *False Positive Patients*

The patients that screened false positive are described in the table below. All efforts to increase the specificity of the screening questionnaire (i.e. to stop false positive results occurring) had been made prior to the pilot study. Other options to increase the specificity of the tool are explored in the table – along with their flaws and the fact that they are impractical without complicating the screening tool further.

Table 3.9: False positives and explanation for their false detection by the screening tool

Brief description of the case	**Questions which were falsely positive**	**Could the specificity of the screening tool be improved to prevent this false positive?**
Patient who described weakness of his right hand side since he had an abscess in his neck. When asked as part of the screening questionnaire he stated that the weakness was constantly there and present at the time of screening. There was no evidence of weakness on examination. When asked again he stated the weakness was only there during times of ill health.	Questions 7 and 8	The questions both stress that the weakness should be constant and should be there at the time of questioning. Despite this the patient still answered positively. An examination section would be the only way of ensuring that weakness was definitely present.
The patient had recently recovered from a period of ill	Questions 3	The question regarding headaches specifies that they

health caused by a tooth abscess. This had resulted in severe headaches and rigors. These were both picked up as positive despite full resolution and only present for a short period of time.	and 15	should be recurrent, not brief periods of ill health. Despite this the patient still answered positively. There is no way of eliminating this problem. The question regarding tremor specifies that the tremor should occur multiple times every day. This was not the case with this patient and despite this she still answered positively. There is no way around the discrepancy between the response to the questionnaire and the history other than to stress the emphasis and wording of each question.
A patient who had mild occasional headaches responded positively when asked if he had severe recurrent headaches that stopped him from doing his activities of daily living. When asked again he answered negatively to the question. When asked why he had initially answered positively he replied that he wanted to ensure that he saw the doctor.	Question 15	Some patients may answer positively to questionnaires just to bring themselves to medical attention that they would normally have to pay for/would not be available to them. There is no way of getting around this problem except to stress the wording of each individual question and to clarify if a positive result is really positive.
A patient described eyelid weakness. On examination there was no ptosis present. On further questioning it was revealed that he meant weakness of his eye (poor eyesight) not weakness of his eyelids.	Question 10	When the enumerators were trained to use the screening tool it was stressed that we were looking for weakness of the eyelids and not the eyes. This seemed to be the only way of getting around false positives caused this way without unnecessarily complicating the question.

A patient described brief violent shaking episodes of his right arm. He stated that these episodes had been recurrent. When asked as part of a full neurological history he subsequently denied actual shaking and stated he felt as though the arm was shaking due to severe pain coming from his shoulder.	Question 2	Emphasis of the question is the only way to try to eliminate false positives of this nature.
A patient with a psychiatric history described seizures and a loss of sensation in his whole body. This positive response was not backed up when a collateral history was obtained and when a full examination was performed.	Questions 1 and 12	A collateral history should always be obtained when there is doubt as to the patient's competence of answering questions correctly. This was stressed to the enumerators during training.
A patient described leg weakness. On further questioning and on examination this was found to be pain and not actual weakness.	Question 8	Patients find it difficult to distinguish pain and weakness. The importance of the difference was stressed to the enumerators during training. This was felt to be the only way round this potentially common problem.
A patient described weakness of his left hand side as a result of an accident. On further questioning, and on examination, this turned out to be pain alone.	Questions 7 and 8	Patients find it difficult to distinguish pain and weakness, the importance of the difference was stressed to the enumerators during training. This was felt to be the only way round this potentially common problem.
A patient described loss of sensation from his knees down. On examination this was not present and he stated that	Question 12	There is no way of eliminating this kind of false positive other than to stress the wording of the question.

this was only when it was cold. This is stressed as a negative factor in the question and it is also stressed that the numbness should be constant.		
A patient described loss of sensation of the right index finger and middle finger. On examination this was found to be normal. The patient denied any loss of sensation when asked again.	Question 12	Inconsistency of response is inevitable. Re-questioning of patients in view of a positive response was a factor highlighted to the enumerators in training. A detailed examination would eliminate these false positives but would make screening lengthy and unpractical.

3.4 The Main Study

We elected to see one quarter of the Hai District DSS population in the main study due to resource limitations and time constraints. 2232 Patients were seen from the 12 randomly selected villages. Every opportunity was taken to ensure that the main study population was representative of the background population.

3.4.1 *Identification of the Main Study Population*

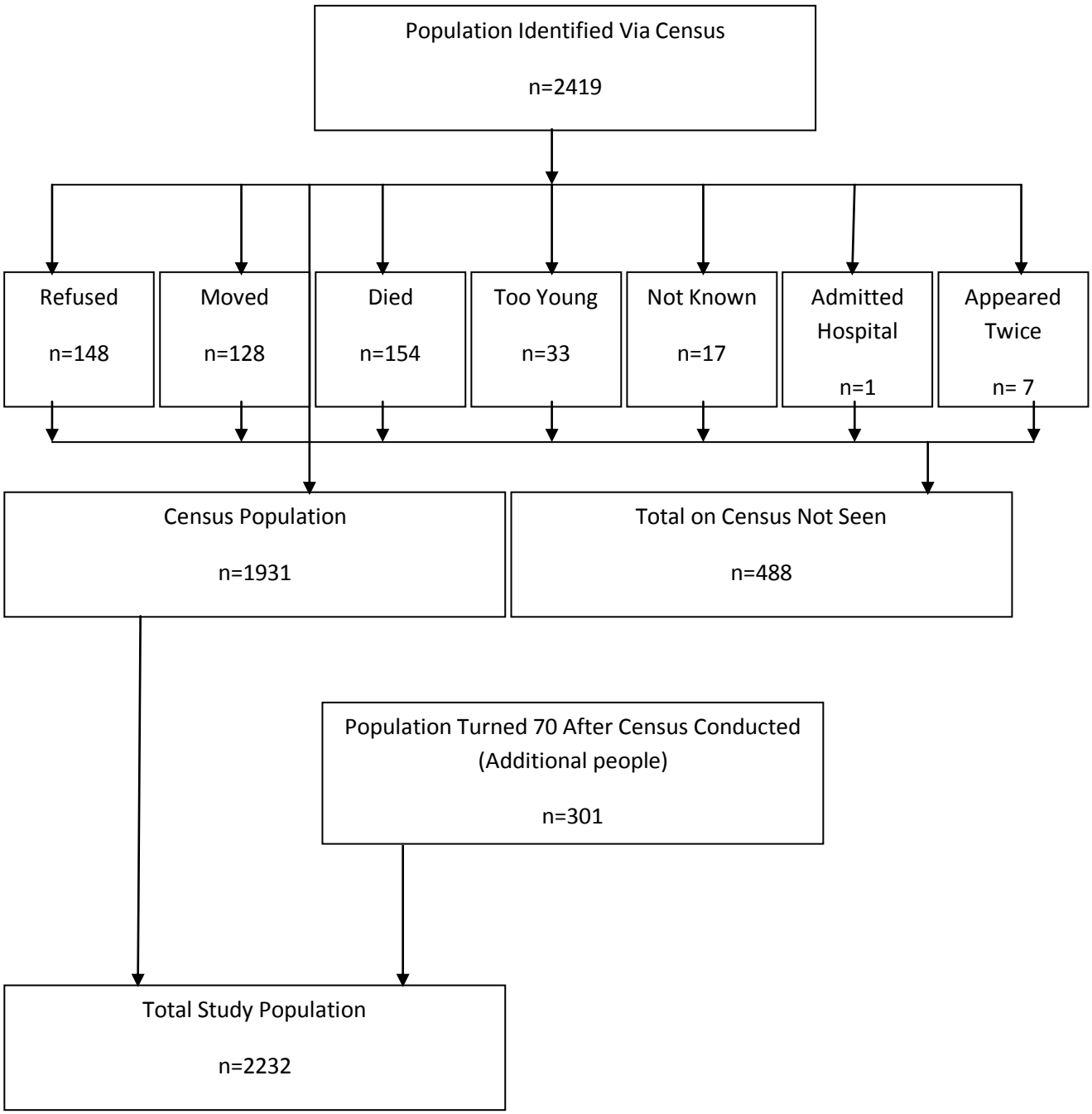
The village breakdown of the main study population is demonstrated in the table and diagram below. As described with regard to the pilot population additional people were seen as part of the study for three main reasons;

1. People that had turned 70 after the census was conducted on 01/06/2009 and before or on the prevalence date of the 01/01/2010
2. People that had been omitted on the census due to inaccuracy, recorded as falsely young – again every effort was made to ensure age was reported correctly through date sign posting.
3. People that had travelled on the census date but had returned by the prevalence date.

Table 3.10: Identification of the Main Study Population

Village	Patients Seen	Patients 70 or over on the census	Difference	Geography	Patients refused	Patients moved	Patients died	Patient too young	Not known	Admitted	Recorded on census twice	Total not possible to see	Extras
Boma	136	216	-80	Lowland	20	40	20	5	17	1	0	103	23
Kware	148	189	-41	Lowland	12	13	12	4	0	0	0	41	0
Kwasadala	83	78	5	Lowland	1	10	12	0	0	0	0	23	28
Kyuu	118	120	-2	Upland	8	4	10	0	0	0	0	22	20
Lukani	115	116	-1	Upland	9	4	12	2	0	0	0	27	26
Mbweera	194	194	0	Upland	1	1	7	0	0	0	0	9	9
Mudio	277	345	-68	Upland	40	22	21	12	0	0	5	100	32
Nshara	386	411	-25	Upland	47	3	32	3	0	0	0	85	60
Roo	265	305	-40	Upland	10	14	14	2	0	0	0	40	0
Saawe	192	185	7	Upland	0	11	6	0	0	0	0	17	25
Shirumgungani	182	118	64	Lowland	0	2	6	0	0	0	0	8	72
Urori	136	142	-6	Upland	0	4	2	5	0	0	2	13	6
Total	2232	2419	-187	N/A	148	128	154	33	17	1	7	494	301

Figure 3.2 Identification of the Main Study Population



3.4.1.1 *Upland and Lowland Villages*

The representation of the upland and lowland villages in the main study population is representative of the background Hai District DSS 70 and over population. In the main study, 75.4% of people were from upland villages and 24.6% were from lowland villages. In the background Hai District DSS 70 and over population 76.2% were in upland villages and 23.8% were in lowland villages.

3.4.2 *The Demographics of the Main Study Population*

3.4.2.1 *Age breakdown*

The mean age of Males was 77.9 (77.4 to 78.3) n = 976. The mean age of females was 77.7 (77.3 to 78.1) n = 1256. The mean age of the whole population was 77.7. The proportions of patients aged 70 and over in the different age brackets are shown in the table below. This is expressed as a percentage of the 70 and over population and as a percentage of the whole main study population. This can be compared to the percentage of people in the age brackets in the whole Hai District Demographic Surveillance site. This demonstrates that from an age point of view the main study population is representative of the whole DSS population.

Table 3.11: Demonstration that the age breakdown of the 70 and over population in the Main study was representative of the whole Hai District DSS population

Age Divisions	People in the Main Study	Percentage of the 70 and over population in the Main Study	Percentage of the whole population in the Main Study	People in the whole Hai District DSS	Percentage of the 70 and over population in the whole Hai District DSS	Percentage of the whole population in the whole Hai District DSS
70-74	877	39.3	1.7	3159	35.6	2.0
75-79	625	28.0	1.2	2531	28.5	1.6
80-84	344	15.4	0.7	1447	16.3	0.9
85+	386	17.3	0.8	1732	19.5	1.1
Total	2232	100.0	4.4	8869	100.0	5.5

Table 3.12: Demonstration of the further Divisions of the older age bracket in the Main Study Population

Age Divisions	Frequency	Percentage
70-74	877	39.3
75-79	625	28.0
80-84	344	15.4
85-89	221	9.9
90-94	89	4.0
95-99	40	1.8
100+	36	1.6
Total	2232	100.0

3.4.2.2 *Sex Breakdown*

The proportion of males and females in the main study population was also representative of the background Hai District DSS population.

Table 3.13: Demonstration of the comparable breakdown of the 70 and over population by sex in the Main Study and the Hai District DSS population

Sex	People Aged 70 and over in the Main Study	Percentage of the 70 and over population of the Main Study	People Aged 70 and over in the Hai District DSS	Percentage of the 70 and over population in the Hai District DSS
F	1256	56.3	4844	54.6
M	976	43.7	4025	45.4
Total	2232	100.0	8869	100.0

3.4.2.3 *Males and Females age structure*

Although the study has more females than males, there were no differences between males and females in terms of the age structure of the participants.

Table 3.14 Demonstration of the comparable age structure of males and females in the main study population

Sex	**Age**	**Frequency of participants in the main study population**	**Percentage of the participants in the main study population**
Male	70-74	384	39.3
	75-79	285	29.2
	80-84	135	13.8
	85+	172	17.6
	Total	976	100.0
Female	70-74	493	39.3
	75-79	340	27.1
	80-84	209	16.6
	85+	214	17.0
	Total	1256	100.0

3.4.2.4 *Tribe*

The tribal divisions of the main study population were more representative of the Hai District DSS than the pilot study population was. There was however still an underrepresentation of the MMasai tribe. However, overall the majority tribe was MChagga and this was appropriate.

Table 3.15: Tribal representations of the Main Study Population

Tribe	**Number of People in each Tribe aged 70 and over in the Main Study**	**Percentage in each tribe aged 70 and over in the Main Study**
MZARAMO	6	0.3
MNDENGEREKO	4	0.2
MCHAGGA	2033	91.1
MMASAI	7	0.3
MPARE	38	1.7
MNYAMWEZI	7	0.3
MSUKUMA	2	0.1
OTHER	135	6.0
Total	2232	100.0

3.4.2.5 *Religion*

The religious divisions were representative. This was particularly important when considering health seeking behaviour.

Table 3.16: Religious Representations of the Main Study Population

Religion	Number of People in each Religion aged 70 and over in the Main Study	Percentage in each Religion aged 70 and over in the Main Study
CHRISTIAN	1763	79.0
MUSLIM	466	20.9
PAGAN	3	0.1
Total	2232	100.0

3.4.2.6 *Marital Status*

In the main study population 1103 (49.4%) were married, 1050 (47.0%) were widowed, 32 (1.4%) were separated, 27 (1.2%) were single and 20 (0.9%) were divorced. The main reason for divorce was the woman was perceived to be infertile..

3.4.2.7 *Proportion of the Main Study Population that was Ambulant*

A simple record of ambulance was recorded for each patient in the main study. The great majority (85.8%) of patients remained ambulant. This finding is in keeping with the level of disability in this population group which is described in detail later.

3.4.3 *Analysis of the performance of the screening questionnaire when used in the main study*

This analysis excluded the Pilot village.

3.4.3.1 *Establishing if patients were true negatives or false negatives – the sensitivity check of the main study*

Eight patients were identified to have neurological conditions, during general observation, that had answered negatively to the screening questionnaire, these were recorded as false negatives. There were no cases picked up by alternative methods so all the remaining negatives were recorded as true negatives. All established cases in this population diagnosed in previous disease-specific prevalence studies were correctly recognised by the questionnaire. All patients brought to our attention by family history, and by discussion with the village elders, were also correctly picked up by the screening questionnaire. All these methods reinforced the excellent sensitivity of the questionnaire. We were unable to trace 1 patient who had responded positively to question 12. For purposes of analysis this patient was presumed to be a false positive.

3.4.3.2 *Analysis of sensitivity and specificity of the screening questionnaire in the Main Study*

Again the screening tool had a high sensitivity and specificity. As already described above, the original question 14 was removed after the main study. Presented below is the sensitivity and specificity of the screening tool with and without the question. The final performance of the questionnaire, without the question is: sensitivity 97.0% and specificity 90.4%.

Table 3.17: The overall sensitivity and specificity analysis of the screening questionnaire in the Main Study Population

	True Negative	True Positive	False Negative	False Positive	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Screening tool including original question 14	1519	265	8	163	97.1	90.3	61.9	99.5	91.3
The final screening tool: Screening tool excluding original question 14	1526	259	8	162	97.0	90.4	61.5	99.5	91.3

Table 3.18: Summary of the performance of the screening tool across the pilot and the main study population

	ICD 10 diagnosis of neurological disorder		
	Present	**Absent**	**Total**
Screening instrument diagnosis of Neurological disorders			
Pilot Study			
Present	72	10	82
Absent	10	185	195
Total	82	195	277
K	0.827		
Positive Predictive Value	0.878		
Negative Predictive Value	0.949		
Sensitivity	0.878		
Specificity	0.949		
Accuracy	0.928		
Main Study/Study Extension			
Present	259	162	421
Absent	8	1526	1534
Total	267	1688	1955

K	0.703
Positive Predictive Value	0.615
Negative Predictive Value	0.995
Sensitivity	0.970
Specificity	0.904
Accuracy	0.913

3.4.3.3 *Conditions represented in the Main Study Population that were not represented in the Pilot Population*

Conditions that were not represented in the pilot population, e.g. dyskinesias, motor neurone disease, Myaesthenia gravis, polio and leprosy, were subsequently represented in the main study population and questions dedicated to picking up these conditions did so which is further validation of the tool. However, as this was not a pilot, and every patient did not receive a full neurological history and examination, I cannot say with certainty that no patients with these conditions were missed.

3.5 Description of the cases/true positives from the Main Study

It is important to recognize the WHO ICD 10 for epidemiological studies especially when devising a screening tool as this allows completeness and full inclusion and consideration of all neurological diagnosis. Therefore all patients diagnosed with a neurological condition have been allocated a WHO ICD 10 diagnosis (see appendix 3.1). However for practical reasons description of all the patients and the prevalence rates is often best performed with a more clinically relevant method to divide up the cases. This is done with a combination of the clinical and anatomical pictures that the individual conditions produce. I used a practical combination of clinical classification and the ICD10 criteria (recorded in brackets) to describe the prevalence rates. This is described in the introduction (figure 1.1).

Prevalence rates are presented in table format below, including tables which demonstrate age and sex distributions. Rows are missing in tables where there were no individuals to record

3.5.1 *All cause Neurological Disorders*

There were 384 cases of neurological disorders recorded in the main study population. The crude prevalence (95% confidence intervals (CI)) was 172.04/1000 (156.39 to 187.70). The age adjusted prevalence (95% CI) according to the WHO standard population was 168.94/1000 (153.39 to 184.48)

3.5.1.1 *Age and Sex Distribution*

The age and sex distribution of all the neurological disorders is demonstrated in the table below: 42.7% were female and 57.3% were male.

Table 3.19: Age and Sex distribution of all-cause neurological disorders

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	141	160.8 (136.5 to 185.1)		74	150.1 (118.6 to 181.6)		67	174.5 (136.5 to 212.4)	
75-79	97	155.2 (126.8 to 183.6)		49	144.1 (106.8 to 181.4)		48	168.4 (125.0 to 211.9)	
80-84	60	174.4 (134.3 to 214.5)		33	157.9 (108.5 to 207.3)		27	200.0 (123.5to 267.5)	
85+	86	222.8 (181.3 to 264.3)		46	215.0 (159.9 to 270.0)		40	232.6 (169.4 to 296.0)	
Total	384	172.0 (156.4 to 187.7).	168.9 (153.4 to 184.5)	202	160.8 (140.5 to 181.1)	157.8 (137.7 to 178.0)	182	186.5 (162.0 to 210.9)	183.2 (159.0 to 207.5)

3.5.2 *Total Number of People with a Neurological Disorder*

Some people had more than one neurological disorder so the prevalence of people with a neurological disorder was less than the overall prevalence of neurological disorders. There were 349 people with one or more neurological diagnoses, 314 people with 1 neurological diagnosis and 35 people with 2 neurological diagnoses. The crude prevalence (95% CI) of people with one or more neurological diagnoses was 156.36/1000 (141.29 to 171.43). The age adjusted prevalence (95% CI) according to the WHO standard population was 154.14/1000 (139.16 to 169.12). The crude prevalence (95% CI) of people with one neurological diagnosis was 140.68/1000 (126.26 to 155.11). The age adjusted prevalence (95% CI) according to the WHO standard population was 139.34/1000 (124.97 to 153.71). The crude prevalence (95% CI) of people with two neurological diagnoses was 15.68/1000 (10.53 to 20.84). The age adjusted prevalence (95% CI) according to the WHO standard population was 14.79/1000 (9.79 to 19.81).

3.5.2.1 *Age and Sex Distribution*

The age and sex distribution of all the patients with one or more neurological disorder is shown in the table below: 42.7% were female and 57.3% were male.

Table 3.20: The age and sex distribution of all patients with one or more Neurological Disorders

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	127	144.8 (121.5 to 168.1)	)	68	137.9 (107.5 to 168.4)		59	153.6 (117.6 to 189.7)	
75-79	89	142.4 (115.0 to 169.8)		47	138.2 (101.5 to 174.9)		42	147.4 (106.2 to 188.5)	
80-84	58	168.6 (129.0 to 208.2)		32	153.1 (104.3 to 201.9)		26	192.6 (126.1 to 259.1	
85+	75	194.3 (154.8 to 233.8)		40	186.9 (134.7 to 239.1)		35	203.5 (143.3 to 263.7)	
Total	349	156.4 (141.3 to 171.4).	154.1 (139.2 to 169.1)	187	148.9 (129.2 to 168.6)	146.9 (127.3 to 166.5)	162	166.0 (142.6 to 189.3)	163.5 (140.3 to 186.7)

3.5.3 *Central Nervous System Disorders*

3.5.3.1 *Movement Disorders*

3.5.3.1.1 *Tremor*

3.5.3.1.1.1 *Prevalence and disease subtypes*

There were 110 people in the study population with tremor. The consequent prevalence, age adjusted prevalence and confidence intervals, for tremor and the subtype breakdown are presented in the table below.

Table 3.21: Tremor Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
All Tremors	110	49.28 (40.30 to 58.26)	48.22 (39.34 to 57.11)
Essential Tremor	67	30.02 (22.94 to 37.10)	30.10 (23.01 to 37.18)
Enhanced physiological tremor	16	7.17 (3.67 to 10.67)	6.40 (3.10 to 9.71)
Tremor secondary to Parkinsonism/Parkinson's disease	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
Tremor secondary to cerebellar disease	11	4.93 (2.02 to 7.83)	4.87 (1.98 to 7.76)
Orthostatic tremor	3	1.34 (0 to 2.86)	1.27 (0 to 2.74)
Iatrogenic tremor	1	0.45 (0 to 1.33)	0.46 (0 to 1.35)

3.5.3.1.1.2 *Age and Sex Distribution*

The age and sex distribution of all the patients with tremor is given in the table below: 42.7% were female and 57.3% were male.

Table 3.22: Tremor Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	31	35.3 (23.1 to 47.6)		15	30.4 (15.3 to 45.9)		16	41.7 (21.7 to 61.7)	
75-79	31	49.6 (32.6 to 66.6)		11	32.4 (13.5 to 51.2)		20	70.2 (40.5 to 99.8)	
80-84	22	64.0 (38.1 to 89.8)		11	52.6 (22.4 to 82.9)		11	81.5 (35.3 to 127.6	
85+	26	67.4 (42.4 to 92.4))		10	46.7 (18.5 to 75.0)		16	93.0 (49.6 to 136.4)	
Total	110	49.28 (40.30 to 58.26)	48.22 (39.34 to 57.11)	47	37.42 (26.9 to 47.9)	37.1 (26.6 to 47.5)	63	64.5 (49.1 to 80.0)	62.6 (47.4 to 77.8)

3.5.3.1.1.3 *Description of Essential Tremor patients and follow up*

The average age of the patients with Essential Tremor was 78.8 years: 37 (55.2%) were male and 30 (44.8%) were female.

The Average length of symptoms of tremor that the patients had experienced was 8.3 years with a range of 3 months to 55 years.

The following tables and charts provide the distribution of signs and symptoms

Table 3.23: The anatomical location of tremor on history and examination in patients with essential tremor

	History of Limb Tremor	History of Limb Tremor %	Examination demonstrates Limb tremor	Examination demonstrates Limb tremor %	History of Head tremor	History of Head tremor %	Examination Demonstrates Head tremor	Examination Demonstrates Head tremor %
Y	57	85.1	64	95.5	23	34.3	38	56.7
N	10	14.9	3	4.5	44	65.7	29	43.3

All patients experienced either an action limb tremor or a head tremor for diagnostic purposes. However some patients also had a resting tremor. The percentage of which is given below.

Table 3.24: Presence of atypical features on history and examination of essential tremor patients

	History of Asymmetry of Limb Tremor	History of Asymmetry of Limb Tremor %	Examination demonstrates Asymmetry of Limb tremor	Examination demonstrates Asymmetry of Limb tremor %	History of Resting tremor	History of Resting tremor %	Examination Demonstrates Resting tremor	Examination Demonstrates Resting tremor %
Y	23	34.3	12	17.9	11	16.4	13	19.4
N	44	65.7	55	82.1	56	83.6	54	80.6

Worthy of note is that history and examination findings do not always correlate, this demonstrates the importance of examination in order to make an accurate diagnosis.

16 patients (23.9%) admitted to having a family history of tremor. 24 (35.8%) stated their tremor was alcohol responsive, 13 (19.4%) stated it was not alcohol responsive and 30 (44.8%) said they could not comment as they were Tee-total.

Beta blockers are the1st line treatment (2) and the only recommended treatment routinely available in Tanzania. They were given to 39 (58.2%) patients. The other patients did not want treatment or Beta blockers were contraindicated due to obstructive airways disease, hypotension or heart block. All patients that received medication were made aware of the side effects profile and told to stop the medication if they experienced any ill effects. They had a direct point of contact in the NMI if they had any problems, and the NMI could in turn contact the RD.

3.5.3.1.1.3.1 *Follow up of Essential Tremor Patients*

We attempted to follow up all patients who had been put on Beta blockers to assess their response and to check if they had experienced any side effects. Of the 39 patients we were able to follow up 35 patients. 1 patient had travelled, I had died and the remaining two could not be seen due to their work and social commitments. Of the 35 patients that were followed up, 1 had never taken their medication as he did not feel it would help and did not want to try it. Therefore 34 patients were assessed:

29 (85.3%) patients reported that they had improved on medication. 5 (14.7%) felt that there had been no change as a result of treatment. All patients were asked to give their tremor a mark out of ten when they were on treatment, with 10/10 being the severity of

their tremor prior to the treatment and the subsequent mark being what it was as a severity out of ten whilst they were on treatment. From this we could work out a point score that the patient's tremor had reduced by. The results are shown in table 3.25.

Table 3.25 Tremor Reduction Score in Patients with Essential Tremor treated with Beta Blockers

Mark out of ten on treatment	Number of points score improved by	Number of patients	Percentage of patients
0	10	6	17.6
1	9	0	0.0
2	8	0	0.0
3	7	1	2.9
4	6	2	5.9
5	5	3	8.8
6	4	2	5.9
7	3	7	20.6
8	2	5	14.7
9	1	3	8.8
10	0	5	14.7

Patients were prescribed a variety of propranolol doses for their essential tremor dependent on their blood pressure and level of general frailty. This varied from 10mg TDS to 80mg TDS. Higher doses were utilised if the patient required beta blockers for hypertension as well as tremor. Although beta blockers are not a first line treatment option for hypertension (especially in the black elderly) compliance in this population is an issue and therefore if a medication dose can be optimised for a dual purpose then this was felt to be appropriate. Despite full explanations of how to take the medication patients often took a different dose than what was prescribed, in the majority of cases this was in

order to “spread the tablets out and make them last longer". In other cases the dose taken simply had little correlation to what was prescribed. The variation in dose **taken** is described in the table below along with the average reduction in severity score for that dose group.

Table 3.26: Variation in Beta Blocker dose prescribed and average improvement in tremor severity score

Total dose of Beta blockers taken in 24 hours	**Number of patients**	**Percentage of patients**	**Average improvement in severity score**
1mg to 40mg	6	17.6%	4.5
41mg to 80mg	12	35.3%	4.3
81mg to 120mg	14	41.2%	3.0
>120mg	2	5.9%	8.0

Side effects were only experienced by 2 (5.9%) patients. One patient felt well and experienced a reduction in his symptoms on 10mg TDS but when he increased to 20mg TDS he felt lightheaded. When the dose was reduced back down he had no side effects and felt happy to continue on this dose. One woman experienced “whole body weakness” and did not gain any benefit from the beta blockers. Consequently, she wished to stop the medication, a decision supported by the RD.

Follow up took place at varying times from the initial assessment for logistical reasons related to the completion of the rest of the study. This varied from 1 to 6 months. All patients had received an initial one month supply of beta blockers with a prescription and instruction on how to get more. Only 7 (20.6%) people were still taking beta blockers

when they were reviewed. The remaining 27 (79.4%) had discontinued the medication, for the following reasons; 10 (37.0%) – stated they had no money to get more (despite systems in place for free health care for the over 70s), 5 (18.5%) – had gone to get more but there was no available supply, 5 (18.5%) – had not experienced any improvement on the medication , 2 (7.4%) – had briefly discontinued the medication as they were taking other medication for an alternative problem, 2 (7.4%) – had experienced side effects as detailed above, 1 (3.7%) – was unable to get to the health centre due to leg pain, 1 (3.7%) had forgotten and 1 (3.7%) had lost the prescription.

3.5.3.1.2 *Parkinsonism*

3.5.3.1.2.1 *Prevalence and disease subtypes*

Of the patients with Parkinsonism, 12 (85.7%) had idiopathic PD (IPD), 1 (7.1%) had vascular parkinsonism diagnosed clinically with the Winikates vascular rating scale (3) and 1 (7.1%) had a Parkinson's plus syndrome – progressive supra-nuclear palsy diagnosed clinically with the NINDS-SPSP diagnostic criteria [167]. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for Parkinsonism and the subtype breakdown are given in the table below.

Table 3.27: Parkinsonism Prevalence and Subtype Breakdown

Diagnosis	Frequency	Crude Prevalence per 1000 (95% CI)	Age adjusted prevalence per 1000 (95% CI)
Parkinsonism	**14**	**6.27 (3.00 to 9.55)**	**5.94 (2.75 to 9.12)**
Parkinsonism with tremor	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
Parkinsonism without tremor	2	0.90 (0 to 2.14)	0.81 (0 to 1.99)
Parkinson's Disease	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
Vascular Parkinsonism	1	0.45 (0 to 1.33)	0.31 (0 to 1.04)
Progressive Supra-nuclear palsy	1	0.45 (0 to 1.33)	0.50 (0 to 1.43)

3.5.3.1.2.2 *Age and Sex Distribution*

The age and sex distribution of patients with Parkinsonism is shown in the table below: 42.9% were female and 57.1% were male.

Table 3.28: Parkinsonism Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Crude Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Crude Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Crude Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	2	2.28 (0 to 5.44)		2	4.06 (0 to 9.67)		0	0	0
75-79	2	3.20 (0 to 7.67)		1	2.94 (0 to 8.70)		1	3.51 (0 to 10.37)	
80-84	5	14.52 (1.88 to 27.18)		1	4.78 (0 to 14.14)	)	4	29.63 (1.03 to 58.23)	
85+	5	12.95 (1.67 to 24.23)		2	9.35 (0 to 22.34)		3	17.44 (0 to 37.01)	
Total	14	6.27 (3.00 to 9.55)	5.94 (2.75 to 9.12)	6	4.78 (0.96 to 8.59)	4.51 (0.81 to 8.22)	8	8.20 2.54 to 13.85)	7.77 (2.26 to 13.28)

3.5.3.1.2.3 *Parkinsonism and Idiopathic Parkinson's disease patient data analysis*

The average age of the patients with Parkinsonism was 83.1 years, while the average age of those with IPD was 83.0 years. The duration of symptoms of the patients with Parkinsonism was on average 4.4 years with a range from 1 to 10 years and the patients with IPD had a mean duration of 4.9 years with a range of 1 to 10 years. 1 patient with IPD was unable to comment on how long she had had symptoms for.

The sex breakdown of the patients was as follows;

Table 3.29: Sex representation of Patients with Parkinsonism

Sex	**Parkinsonism – frequency**	**Parkinsonism - percentage**	**PD – frequency**	**PD – percentage**
M	8	57.1	6	50.0
F	6	42.8	6	50.0

The Severity of Parkinsonism is routinely described using the Modified Hoehn and Yahr Scale (5).

Table 3.30: Hoehn and Yahr Score of Patients with all-cause Parkinsonism and Idiopathic Parkinson's disease

Scale	Rating	Parkinsonism – frequency	Parkinsonism - percentage	PD - frequency	PD – percentage
Hoehn and Yahr	2.0	3	21.4	3	25.0
	2.5	1	7.1	1	8.3
	3.0	4	28.6	3	25.0
	4.0	2	14.3	2	16.7
	5.0	4	28.6	3	25.0
Severity	Mild to Moderate (Hoehn and Yahr I-III)	8	57.1	7	58.3
	Severe (Hoehn and Yahr IV-V)	6	42.9	5	41.7

Medication was prescribed initially for 13 out of 14 (92.9%) patients with Parkinsonism including 11 (91.7%) out of 12 patients with PD. The remaining patient stated she did not want to take tablets despite full explanation as to the possible benefits.

The average dose of Levodopa that patients required for relief of their symptoms was 223.2mg/24 hours for Parkinsonism patients and 229.2mg/24 hours for PD patients.

However, some patients had ceased medication as shown in the table below.

Table 3.31: Medication Compliance of patients with Parkinsonism

Still on medication?	Parkinsonism – frequency	Parkinsonism - percentage	PD – frequency	PD – percentage
Yes	8	57.1	7	58.3
No	4	28.6	3	25.0
Not applicable (never started)	1	7.1	1	8.3
Died	1	7.1	1	8.3

Of those that were no longer on medication the following reasons were given; 1 experienced distressing dyskinesias, 2 did not feel the medication made any difference – one of these included the patient with PSP and 1 did not want to take tablets anymore.

The following side effects were experienced by patients; dyskinesias (1), nausea (2), dizziness (2) and vivid dreams (1).

3.5.3.1.3 *Cerebellar Disorders*

3.5.3.1.3.1 *Prevalence and disease subtypes*

There were 11 people in the main study population with cerebellar disorders. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for cerebellar disorders and the subtype breakdown are given in the table below.

Table 3.32: Cerebellar Disorder Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Cerebellar disorders total	**11**	**4.93 (2.02 to 7.83)**	**4.87 (1.98 to 7.76)**
Secondary to alcohol or idiopathic	7	3.14 (0.82 to 5.46)	3.14 (0.82 to 5.46)
Idiopathic	5	2.24 (0.28 to 4.20)	2.20 (0.25 to 4.14)
Secondary to alcohol	2	0.90 (0 to 2.14)	0.94 (0 to 2.21)
Secondary to stroke	4	1.79 (0.04 to 3.55)	1.73 (0.01 to 3.46)

3.5.3.1.3.2 Age and Sex Distribution

The age and sex distribution of patients with cerebellar disorders is given in the table below: 27.3% were female and 72.7% were male.

Table 3.33: Cerebellar Disorder Prevalence and Age and Sex Breakdown

Age Category	Total Frequency	Total Crude Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Crude Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Crude Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	1	1.14 (0 to 3.37)		**0**	**0**	**0**	1	2.60 (0 to 7.70)	
75-79	6	9.60 (1.96 to 17.24)		1	2.94 (0 to 8.70)		5	17.54 (2.30 to 32.79)	
80-84	2	5.81 (0 to 13.85)		1	4.78 (0 to 14.14)		1	7.41 (0 to 21.87)	
85+	2	5.18 (0 to 12.34)		1	4.67 (0 to 13.81)		1	5.81 (0 to 17.18)	
Total	11	4.93 (2.02 to 7.83)	4.87 (1.98 to 7.76)	3	2.39 (0 to 5.09	2.26 (0 to 4.89)	8	8.20 (2.54 to 13.85)	8.23 (2.56 to 13.89)

3.5.3.1.4 *Dyskinesias*

3.5.3.1.4.1 *Prevalence and disease subtypes*

There were 5 people in the main study population with dyskinesias. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for dyskinesias and the subtype breakdown are demonstrated in the table below.

Table 3.34: Dyskinesia Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 100 (95% CI)**
Dyskinesias	**5**	**2.24 (0.28 to 4.20)**	**2.02 (0.16 to 3.88)**
Unspecified chorea	1	0.45 (0 to 1.33)	0.31 (0 to 1.04)
Tardive dyskinesias/ iatrogenic	2	0.90 (0 to 2.14)	0.77 (0 to 1.92)
Orofacial dyskinesias – idiopathic	2	0.90 (0 to 2.14)	0.94 (0 to 2.21)

3.5.3.1.4.2 *Age and Sex Distribution*

The age and sex distribution of patients with dyskinesias is shown in the table below: 60.0% were female and 40.0% were male.

Table 3.35: Dyskinesia Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	1	1.14 (0 to 3.37)		0	0		1	2.60 (0 to 7.70)	
75-79	2	3.20 (0 to 7.63)		1	2.94 (0 to 8.70)		1	3.51 (0 to 10.37)	
85+	2	5.18 (0 to 12.34)		2	9.35 (0 to 22.24)		0	0	0
Total	5	2.24 (0.28 to 4.20)	2.02 (0.16 to 3.88)	3	2.39 (0 to 5.09)	1.92 (0 to 4.34)	2	2.05 (0 to 4.89)	2.15 (0 to 5.05)

3.5.3.2 *Episodic and Paroxysmal Disorders*

3.5.3.2.1 *Headaches*

3.5.3.2.1.1 *Prevalence and disease subtypes*

There were 92 people in the main study population with headaches that affected activities of daily living (ADLs). The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for headaches that affected ADLs and the subtype breakdown are demonstrated in the table below.

Table 3.36: Headache Prevalence and Subtype Breakdown

Diagnosis	Frequency in the Main Study Population/n= 2232	Crude Prevalence per 1000 (95% CI)	Age adjusted prevalence per 1000 (95% CI)
All Headaches	**92**	**41.22 (32.97 to 49.47)**	**41.79 (33.49 to 50.09)**
Primary headaches – total	**44**	**19.71 (13.95 to 25.48)**	**19.86 (14.07 to 25.64)**
Migraine	8	3.58 (1.10 to 6.06)	3.77 (1.22 to 6.31)
Tension Type headaches	36	16.13 (10.90 to 21.36)	16.09 (10.87 to 21.31)
Cluster headaches	0	0	0
Other Primary Headaches	0	0	0
Secondary headaches – total	**48**	**21.50 (15.49 to 27.52)**	**21.93 (15.86 to 28.01)**
Headaches attributed to head and/or neck trauma	3	1.34 (0 to 2.86)	1.40 (0 to 2.95)
Headaches attributed to infection	0	0	0
Headache attributed to arterial hypertension	3	1.34 (0 to 2.86)	1.10 (0 to 2.47)
Headache attributed to hypertensive crisis without hypertensive encephalopathy	0	0	0
Headache attributed to hypertensive encephalopathy	0	0	0

Headache attributed to disorders of the neck	34	15.23 (10.15 to 20.31)	15.53 (10.40 to 20.66)
Headache attributed to disorders of the eyes	4	1.79 (0.04 to 3.55)	1.98 (0.14 to 3.83)
Headache attributed to disorders of the ears	1	0.45 (0 to 1.33)	0.48 (0 to 1.39)
Headache attributed to disorders of the teeth or jaw	2	0.90 (0 to 2.14)	0.98 (0 to 2.28)
Trigeminal neuralgia	1	0.45 (0 to 1.33)	0.46 (0 to 1.35)

3.5.3.2.1.2 *Age and Sex Distributions*

The age and sex distribution of patients with headaches that affect ADLs is given in the table below: 78.3% were female and 21.7% were male.

Table 3.37: Headache Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	40	45.61 (31.80 to 59.42)		32	64.91 (43.16 to 86.65)		8	20.83 (6.55 to 35.12)	
75-79	28	44.8 (25.58 to 61.02)		25	73.53 (45.79 to 101.27)		3	10.53 (0 to 22.38)	
80-84	12	34.88 (15.49 to 54.27)		6	28.71 (6.07 to 51.35)		6	44.44 (9.68 to 79.21)	
85+	12	31.09 (13.77 to 48.40)		9	42.06 (15.16 to 68.95)		3	17.44 (0 to 37.01)	
Total	92	41.22 (32.97 to 49.47)	41.79 (33.49 to 50.09)	72	57.32 (44.47 to 70.18)	58.00 (45.07 to 70.93)	20	20.49 (11.60 to 29.38)	20.93 (11.95 to 29.91)

3.5.3.2.2 *Stroke*

3.5.3.2.2.1 *Prevalence and disease subtypes*

There were 54 people in the main study population with stroke with residual disability (any neurological symptoms or signs). The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for stroke with residual disability, and the subtype breakdown are demonstrated in the table below.

Table 3.38: Stroke Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Prevalence per 1000 (95% CI)**	**Age adjusted prevalence to WHO standard population (95% CI)**
Stroke	**54**	**24.19 (17.82 to 30.57)**	**22.95 (16.74 to 29.17)**
LACS	19	8.51 (4.70 to 12.32)	8.10 (4.38 to 11.82)
PACS	16	7.17 (3.67 to 10.67)	6.62 (3.26 to 9.99)
TACS	12	5.38 (2.34 to 8.41)	5.40 (2.36 to 8.44)
POCS	7	3.14 (0.82 to 5.46)	2.83 (0.63 to 5.04)
POCS cerebellar	4	1.79 (0.04 to 3.55)	1.73 (0.01 to 3.46)
POCS non cerebellar	3	1.34 (0 to 2.86)	1.10 (0 to 2.47)

3.5.3.2.2.2 *Age and Sex Distribution*

The age and sex distribution of patients with stroke with residual deficit is given in the table below: 46.3% were female and 53.7% were male.

Table 3.39: Stroke Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	15	17.10 (8.52 to 25.69)		5	10.14 (1.30 to 18.99)		10	26.04 (10.11 to 41.97)	
75-79	13	20.80 (9.61 to 31.99)		3	8.82 (0 to 18.76)		10	35.09 (13.73 to 56.45)	
80-84	9	26.16 (9.29 to 43.03)		5	23.92 (3.21 to 44.64)		4	29.63 (1.03 to 58.23)	
85+	17	44.04 (23.57 to 64.51)		12	56.07 (25.25 to 86.90)		5	29.07 (3.96 to 54.18)	
Total	54	24.19 (17.82 to 30.57)	22.95 (16.74 to 29.17)	25	19.90 (12.18 to 27.63)(	17.77 (10.47 to 25.08)	29	29.71 (19.06 to 40.37)	29.62 (18.99 to 40.26)

3.5.3.2.3 *Epilepsy*

3.5.3.2.3.1 *Prevalence and disease subtypes*

There were 10 people in the main study population with epilepsy, 9 with Generalised Tonic Clonic Seizures (GTCS) and 1 with partial epilepsy with secondary generalisation. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for epilepsy, and the subtype breakdown, are given in the table below.

Table 3.40: Epilepsy Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Prevalence per 1000 (95% CI)**	**Age adjusted prevalence to WHO standard population (95% CI)**
Epilepsy	**10**	**4.48 (1.71 to 7.25)**	**4.44 (1.69 to 7.20)**
GTCS	9	4.03 (1.40 to 6.66)	3.97 (1.36 to 6.57)
Partial with secondary generalization	1	0.45 (0 to 1.33)	0.48 (0 to 1.39)

3.5.3.2.3.2 *Age and Sex Distribution*

The age and sex distribution of patients with epilepsy is demonstrated in the table below. .

Table 3.41: Epilepsy Prevalence with age and sex breakdown

Age Category	Total Frequency in the Main Study Population/n=2232	Total Crude Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency in the Main Study Population/ n=2232	Female Crude Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency in the Main Study Population/ n=2232	Male Crude Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	8	9.12 (2.83 to 15.41)		4	8.11 (0.19 to 16.03)		4	10.42 (0.26 to 20.57)	)
85+	2	5.18 (0 to 12.34)		1	4.67 (0 to 13.81)		1	5.81 (0 to 17.18)	0.31 (-0.42 to 1.04)
Total	10	4.48 (1.71 to 7.25)	4.44 (1.69 to 7.20)	5	3.98 (0.50 to 7.46)	3.95 (0.48 to 7.42)	5	5.12 (0.64 to 9.60)	5.08 (0.62 to 9.54)

3.5.3.2.3.3 *Description of Epilepsy Patients and Follow up*

All patients with epilepsy were established on antiepileptic medication (phenobarbitone or phenytoin) according to national guidelines. At follow up all patients were still on medication, but 3 had had breaks in medication. All patients had experienced reduced seizure frequency and had had no seizures whilst compliant on medication, while 1 patient had experienced side effects whilst on medication (drowsiness on phenobarbitone). After discussion with the patient the RD found that he was taking an inappropriately large dose which had not been prescribed. He was told to reduce back to an appropriate dose and was given means for local follow up. All patients were aware of local follow up and were aware they should attend. They were also aware that epilepsy medication was free, how to obtain it and the importance of compliance.

3.5.3.3 *Systemic Atrophies/Degenerative Diseases affecting the Central Nervous System*

3.5.3.3.1 *Motor Neuron Disease*

There were 2 people in the main study population with motor neuron disease, a 75 year old man and an 80 year old woman with Barthel indexes of 15 and 16 respectively. The crude prevalence was therefore 0.90/1000, 95% CI (0 to 2.14) and the age adjusted prevalence was 0.96/1000, 95% CI (0 to 2.25). The pattern of disease was that of amyotrophic lateral sclerosis. .

3.5.3.4 *Injury resulting in CNS dysfunction*

3.5.3.4.1 *Spinal Cord lesions*

3.5.3.4.1.1 *Prevalence and disease subtypes*

There were 5 people in the main study population with spinal cord lesions. The consequent prevalence, age adjusted prevalence (based on the WHO standard

population) and confidence intervals for cord lesions and the subtype breakdown are given in the table below.

Table 3.42: Spinal Cord Lesion Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Cord lesions	**5**	**2.24 (0.28 to 4.20)**	**1.89 (0.09 to 3.69)**
Cervical Cord Lesions	**3**	**1.34 (0 to 2.86)**	**1.10 (0 to 2.47)**
Traumatic Cervical Cord lesion	1	0.45 (0 to 1.33)	0.31 (0 to 1.04)
Non-traumatic Cervical Cord Lesion (Arthritic compression or acute lower cervical cord lesion)	2	0.90 (0 to 2.14)	0.79 (0 to 1.95)
Arthritic compression	*1*	0.45 (0 to 1.33)	0.31 (0 to 1.04)
Acute lower cervical cord lesion	*1*	0.45 (0 to 1.33)	0.48 (0 to 1.39)
Thoracic Cord Lesion	**2**	**0.90 (0 to 2.14)**	**0.79 (0 to 1.95)**
Traumatic Thoracic Cord lesion	0	0	0
Non-traumatic Thoracic Cord Lesion	2	0.90 (0 to 2.14)	0.79 (0 to 1.95)

3.5.3.4.1.2 *Age and Sex Distribution*

The age and sex distribution of patients with cord lesions are demonstrated in the table below. 20.0% were female and 80.0% were male.

Table 3.43: Spinal Cord Lesion Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	2	2.28 (0 to 5.44)		0	0	0	2	5.21 (0 to 12.41)	
85+	3	7.77 (0 to 16.53)		1	4.67 (0 to 13.81)		2	11.62 (0 to 27.65)	
Total	5	2.24 (0.28 to 4.20)	1.89 (0.09 to 3.69)	1	0.80 (0 to 2.36)	0.55 (0 to 1.85)	4	4.10 (0.09 to 8.11)	3.60 (0 to 7.36)

3.5.4 *Peripheral Nervous System Disorders*

3.5.4.1 *Polyneuropathy*

3.5.4.1.1 *Prevalence and disease subtypes*

There were 42 people in the main study population with peripheral neuropathy. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for peripheral neuropathy and the subtype breakdown are given in the table below.

Table 3.44: Peripheral Neuropathy Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Peripheral Neuropathy	42	18.82 (13.18 to 24.45)	18.61 (13.01 to 24.22)
Sensory Peripheral Neuropathy	39	17.47 (12.04 to 22.91)	17.36 (11.95 to 22.78)
Sensorimotor Peripheral Neuropathy	3	1.34 (0 to 2.86)	1.25 (0 to 2.71)
Motor Peripheral Neuropathy	0	0	0

3.5.4.1.2 *Age and Sex Distribution*

The age and sex subdivisions of the patients with peripheral neuropathy are demonstrated in the table below. 50.0% were female and 50.0% were male.

Table 3.45: Peripheral Neuropathy Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	17	19.38 (10.26 to 28.51)		11	22.31 (9.27 to 35.35)		6	15.63 (3.22 to 28.03)	
75-79	13	20.80 (9.61 to 31.99)		7	20.59 (5.49 to 35.68)		6	21.05 (4.39 to 37.72)	
80-84	4	11.63 (0.30 to 22.96)		2	9.57 (0 to 22.77)		2	14.81 (0 to 35.19)	
85+	8	20.73 (6.51 to 34.94)		1	4.67 (0 to 13.81))		7	40.70 (11.17 to 70.23)	
Total	42	18.82 (13.18 to 24.45)	18.61 (13.01 to 24.22)	21	16.72 (9.63 to 23.81)	17.42 (10.18 to 24.66)	21	21.52 (12.41 to 30.62)	20.15 (11.33 to 28.96)

3.5.4.2 *Nerve, Nerve Root and Plexus Disorders*

3.5.4.2.1 *Cranial Nerve Pathology*

3.5.4.2.1.1 *Prevalence and disease subtypes*

There were 14 people in the main study population with cranial nerve lesions. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for cranial nerve pathology and the subtype breakdown are shown in the table below.

Table 3.46: Cranial Nerve Pathology Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Cranial Nerve Pathology	14	6.27 (3.00 to 9.55)	5.71 (2.58 to 8.83)
Ptosis	8	3.58 (1.10 to 6.06)	3.34 (0.95 to 5.74)
Ptosis secondary to eye pathology - traumatic	4	1.79 (0.04 to 3.55)	1.58 (0 to 3.22)
Ptosis secondary to eye pathology - non traumatic	2	0.90 (0 to 2.14)	0.98 (0 to 2.28)
Ischaemic 3rd CN palsy	2	0.90 (0 to 2.14)	0.79 (0 to 1.95)
Facial nerve pathology	4	1.79 (0.04 to 3.55)	1.58 (0 to 3.22)
Bells	2	0.90 (0 to 2.14)	0.79 (0 to 1.95)
Traumatic	1	0.45 (0 to 1.33)	0.31 (0 to 1.04)
Hemifacial spasm	2	0.90 (0 to 2.14)	0.79 (0 to 1.95)

3.5.4.2.1.2 *Age and Sex Distribution*

The Age and Sex distribution of patients with cranial nerve lesions are given in the table below: 50.0% were female and 50.0% were male.

Table 3.47: Cranial Nerve Pathology Prevalence and Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	7	7.98 (2.09 to 13.87)		3	6.09 (0 to 12.95)		4	10.42 (0.26 to 20.57)	
80-84	1	2.91 (0 to 8.60)		1	4.78 (0 to 14.14)		0	0	0
85+	6	15.54 (3.20 to 27.88)		3	14.02 (0 to 29.77)		3	17.44 (0 to 37.01)	
Total	14	6.27 (3.00 to 9.55)	5.71 (2.58 to 8.83)	7	5.57 (1.46 to 9.69)	5.09 (1.16 to 9.03)	7	7.17 (1.87 to 12.47)	6.50 (1.46 to 11.54)

3.5.4.2.2 *Upper Limb Mononeuropathies*

3.5.4.2.2.1 *Prevalence and disease subtypes*

There were 15 people in the main study population with upper limb mononeuropathy and polyneuropathy. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for upper limb mononeuropathies and the subtype breakdown are shown in the table below.

Table 3.48: Upper Limb Mononeuropathy Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Upper Limb Mononeuropathies	**15**	**6.72 (3.33 to 10.11)**	**6.53 (3.19 to 9.87)**
Traumatic upper limb multiple mononeuropathies	2	0.90 (0 to 2.14)	0.96 (0 to 2.24)
Traumatic damage to Median Nerve	1	0.45 (0 to 1.33)	0.48 (0 to 1.39)
Non-traumatic damage to Median nerve - compression/entrapment	4	1.79 (0.04 to 3.55)	1.58 (0 to 3.22)
Traumatic damage to Radial nerve	2	0.90 (0 to 2.14)	0.94 (0 to 2.21)
Non-traumatic damage to Radial nerve	0	0	0
Traumatic damage to Ulnar nerve	2	0.90 (0 to 2.14)	0.98 (0 to 2.28)
Non-traumatic damage to Ulnar nerve	4	1.79 (0.04 to 3.55)	1.60 (0 to 3.26)

3.5.4.2.2.2 *Age and Sex Distribution*

Age and sex divisions of patients with upper limb mononeuropathies are shown below: 40% were female and 60% were male.

Table 3.49: Upper Limb Mononeuropathy Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	8	9.12 (2.83 to 15.41)		1	2.03 (0 to 6.00)		7	18.23 (4.85 to 31.61)	
75-79	1	1.60 (0 to 4.73)		0	0		1	3.51 (0 to 10.37)	
80-84	2	5.81 (0 to 13.85)		2	9.57 (0 to 22.77)		0	0	
85+	4	10.36 (0.26 to 20.47)		3	14.02 (0 to 29.77)		1	5.81 (0 to 17.18)	
Total	15	6.72 (3.33 to 10.11)	6.53 (3.19 to 9.87)	6	4.78 (0.96 to 8.59)	4.28 (0.67 to 7.90)	9	9.22 (3.22 to 15.22)	9.42 (3.36 to 15.48)

3.5.4.2.3 *Lower Limb Mononeuropathies*

3.5.4.2.3.1 *Prevalence and disease subtypes*

There were 5 people in the main study population with lower limb mononeuropathies. The consequent prevalence, age adjusted prevalence (based on the WHO standard population), confidence intervals and the subtype breakdown are demonstrated in the table below.

Table 3.50: Lower Limb Mononeuropathy Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Lower Limb Mononeuropathies	**5**	**2.24 (0.28 to 4.20)**	**2.38 (0.36 to 4.40)**
Traumatic femoral nerve injury	1	0.45 (0 to 1.33)	0.46 (0 to 1.35)
Sciatic nerve injury from trauma	1	0.45 (0 to 1.33)	0.48 (0 to 1.39)
Sciatic nerve injury from injection site	1	0.45 (0 to 1.33)	0.48 (0 to 1.39)
Common peroneal injury from operation	1	0.45 (0 to 1.33)	0.50 (0 to 1.43)
Traumatic common peroneal nerve injury	1	0.45 (0 to 1.33)	0.46 (0 to 1.35)

3.5.4.2.3.2 *Age Categories*

The age subdivisions of the patients with lower limb mononeuropathies are shown in the table below, all patients were male.

Table 3.51: Lower Limb Mononeuropathy Prevalence with age and sex breakdown

Age Category	Frequency	Crude Prevalence per 1000 (95% CI)	Age adjusted prevalence per 1000 (95% CI)
70-74	2	2.28 (0 to 5.44)	
75-79	2	3.20 (0 to 7.63)	
80-84	1	2.91 (0 to 8.60)	
Total	5	2.24 (0.28 to 4.20)	2.38 (0.36 to 4.40)

3.5.4.2.4 *Plexus Injury*

3.5.4.2.4.1 *Prevalence and disease subtypes*

There were 4 people in the main study population with plexus injury. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for plexus injury and the subtype breakdown are shown in the table below.

Table 3.52: Plexus Injury Prevalence and Subtype Breakdown

Diagnosis	Frequency	Crude Prevalence per 1000 (95% CI)	Age adjusted prevalence per 1000
Plexus Injury	**4**	**1.79 (0.04 to 3.55)**	**1.90**
Brachial-traumatic	2	0.90 (0 to 2.14)	0.94
Lumbosacral-traumatic	2	0.90 (0 to 2.14)	0.96

3.5.4.2.4.2 *Age and Sex Subdivisions*

The age and sex subdivisions of the patients with plexus injury are shown in the table below: 25.0% were female and 75.0% were male.

Table 3.53: Plexus Injury Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	3	3.42 (0 to 7.29)		1	2.03 (0 to 6.00)		2	5.21 (0 to 12.41)	
75-79	1	1.60 (0 to 4.73		0	0		1	3.51 (0 to 10.37)	
Total	4	1.79 (0.04 to 3.55)	1.90 (0.09 to 3.70)	1	0.80 (0 to 2.36)	0.85 (0 to 2.46)	3	3.07 (0 to 6.55)	3.95 (0.02 to 7.89)

3.5.4.2.5 *Root Lesion*

3.5.4.2.5.1 *Prevalence and disease subtypes*

There were 4 people in the main study population with root lesions. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) and confidence intervals for root lesions and the subtype breakdown are shown in the table below.

Table 3.54: Root Lesion Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population/n=2232**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Root Pathology	4	1.79 (0.04 to 3.55)	**1.69 (0 to 3.40)**
Sciatica	3	1.34 (0 to 2.86)	1.23 (0 to 2.69)
C8 root lesion	1	0.45 (0 to 1.33)	0.46 (0 to 1.35)

3.5.4.2.5.2 *Age and Sex Distribution*

The age and sex subdivisions of the patients with root lesions are given in the table below: 25% were female and 75% were male.

Table 3.55: Root Lesion Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
75-79	3	1.60 (0 to 4.73))		1	2.94 (0 to 8.70)		2	7.02 (0 to 16.71)	
85+	1	2.59 (0 to 7.66)		0	0		1	5.81 (0 to 17.18)	
Total	4	1.79 (0.04 to 3.55)	1.69 (-0.01 to 3.40)	1	0.80 (0 to 2.36)	0.82 (0 to 2.40)	3	3.07 (0 to 6.55)	2.81 (0 to 6.14)

3.5.4.3 *Inflammatory/infectious diseases of the peripheral nervous system*

3.5.4.3.1 *Polio*

3.5.4.3.1.1 *Prevalence and disease subtypes*

There were 5 people in the main study population with Polio that had resulted in residual neurological deficit. The crude prevalence was 2.24/1000 95% CI (0.28 to 4.20), the age adjusted prevalence (based on the WHO standard population) was 2.38/1000 95% CI (0.36 to 4.40).

3.5.4.3.1.2 *Age and Sex Distribution*

The age and sex subdivisions of the patients with polio with residual neurological deficit are demonstrated in the table below. 40.0% were female and 60.0% were male.

Table 3.56: Polio Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	2	2.28 (0 to 5.44)		1	2.03 (0 to 6.00)		1	2.60 (0 to 7.70)	
75-79	2	3.20 (0 to 7.63)		1	2.94 (0 to 8.70)		1	3.51 (0 to 10.37)	
80-84	1	2.91 (0 to 8.60)		0	0		1	7.41 (0 to 21.87)	
Total	5	2.24 (0.28 to 4.20)	2.38 (0.36 to 4.40)	2	1.59 (0 to 3.80)	1.67 (0 to 3.93)	3	3.07 (0 to 6.55)	3.30 (0 to 6.89)

3.5.4.3.2 *Leprosy*

There was 1 person in the main study population with leprosy which was not active but was neuropathic, it had resulted in amputation of the right foot to the level of the mid foot. The crude prevalence was therefore 0.45/1000, 95% CI (0 to 1.33) and the age adjusted prevalence was 0.48/1000, 95% CI (0 to 1.39). The patient was a 73 year old man whose Barthel index score was 20.

3.5.4.4 *Diseases of the Myoneural Junction and Muscles*

3.5.4.4.1 *Myaesthenia Gravis*

There was 1 person in the main study population with Myaesthenia Gravis. The crude prevalence was therefore 0.45/1000, 95% CI (0 to 1.33) and the age adjusted prevalence was 0.50/1000, 95% CI (0 to 1.43). The pattern of disease was bilateral ptosis. The patient was an 80 year old woman whose Barthel index score was 20.

3.5.4.4.2 *Muscle Wasting and Atrophy*

3.5.4.4.2.1 *Prevalence and disease subtypes*

There were 17 people in the main study population with muscle wasting and atrophy resulting in weakness caused by disuse. The cause of the disuse was varied and is described below. The consequent prevalence, age adjusted prevalence (based on the WHO standard population) confidence intervals and the subtype breakdown is given in the table below.

Table 3.57: Muscle Wasting and Atrophy Prevalence and Subtype Breakdown

Diagnosis	**Frequency in the Main Study Population**	**Crude Prevalence per 1000 (95% CI)**	**Age adjusted prevalence per 1000 (95% CI)**
Muscle Wasting and Atrophy	**17**	**7.62 (4.01 to 11.22)**	**7.40 (3.84 to 10.95)**
Secondary to primary orthopaedic problem	7	3.14 (0.82 to 5.45)	3.04 (0.76 to 5.33)
Secondary to pain	5	2.24 (0.28 to 4.20)	1.91 (0.10 to 3.72)
Secondary to severe cognitive impairment and consequent immobility	2	0.90 (0 to 2.14)	0.96 (0 to 2.25)
Secondary to soft tissue damage secondary to infection	2	0.90 (0 to 2.14)	0.98 (02 to 2.28)
Secondary to period of ill health and consequent disability	1	0.45 (-0 to 1.33)	0.31 (0 to 1.04)

3.5.4.4.2.2 *Age and Sex Distribution*

The Age and sex distribution of the patients with muscle wasting and atrophy are demonstrated in the table below. 64.7% were female and 35.3% were male.

Table 3.58: Muscle Wasting and Atrophy Prevalence with Age and Sex Breakdown

Age Category	Total Frequency	Total Prevalence per 1000 (95% CI)	Total Age adjusted prevalence per 1000 (95% CI)	Female Frequency	Female Prevalence per 1000 (95% CI)	Female Age adjusted prevalence per 1000 (95% CI)	Male Frequency	Male Prevalence per 1000 (95% CI)	Male Age adjusted prevalence per 1000 (95% CI)
70-74	4	4.56 (0.10 to 9.02)		1	2.03 (0 to 6.00)		3	7.81 (0 to 16.62)	
75-79	2	3.20 (0 to 7.63)		1	2.94 (0 to 8.70)		1	3.51 (0 to 10.37)	
80-84	6	17.44 (3.61 to 31.28)		5	23.92 (3.20 to 44.64)		1	7.41 (0 to 21.87)	
85+	5	12.95 (1.67 to 24.23)		4	18.69 (0.55 to 36.84)		1	5.81 (0 to 17.18)	
Total	17	7.62 (4.01 to 11.22)	7.40 (3.84 to 10.95)	11	8.76 (3.61 to 13.91)	8.33 (3.30 13.36)	6	6.15 (1.24 to 11.05)	6.19 (1.27 to 11.11)

3.6 The patients Identified using the original question 14

One patient was thought to have task specific dystonia. This was described on history although it was never reproduced on examination. Confirmatory investigations were not possible. The condition did not bother the patient and the diagnosis was not certain. The potential crude prevalence was 0.45/1000. This is however not something I can definitely report as a definitive diagnosis was never made. The prevalence is in keeping with other prevalence studies [447, 463].

Eleven patients described symptoms of paramyotonia – muscle contraction or stiffness exacerbated by cold. It was difficult to achieve an accurate account of the symptoms and any associated family history. The signs were not reproduced on examination, it was not possible to reproduce the exacerbating circumstances. Confirmatory investigations were not possible. The condition was "treated" by the patient with simple actions like warming. The main differential diagnosis was musculoskeletal – arthritis. The potential crude prevalence was 4.93/1000. This is however not something I can report as definitive diagnosis was never made. The prevalence is much higher than would be expected from the literature which quotes a prevalence of 1/180-350,000 [446]. However it is possible that in a small community an autosomal condition such as this one could have a high prevalence exacerbated by the lack of population migration. It is worth noting that 5 out of the 11 patients (45.5%) were from the same village – a supportive factor.

As I was unable to confirm diagnosis these patients do not form part of the overall prevalence figures for Neurological Disorders in the Main Study population.

3.7 The Diagnosis and Treatment Gap

There is a large diagnosis and treatment gap for patients with Neurological conditions in the main study population.

The definition of the diagnosis and treatment gap has been fully described and justified in the methods section, in summary;

A correct diagnosis was defined as a diagnosis that corresponded to that made by the research doctor and the expert consultant expressed as a percentage of all of those people with a neurological disorder.

Correct treatment was defined as the treatment that was recommended by the WHO and expert review articles for the condition diagnosed [459], this was expressed as a percentage of all of those people with a neurological disorder.

I felt that to present the diagnosis and treatment gap in only those that had presented for medical care would underestimate the scale of the diagnosis and treatment problem in the region [460].

Of the 349 people with at least one neurological disorders, 64.5% had sought treatment for their symptoms. Of the 384 disorders, only 56 (14.6%) had been diagnosed and only 38 (9.9%) had received appropriate treatment. A breakdown of these figures by sex is presented in Table 3.59 and by specific neurological disorders in Table 3.60. Males with a neurological condition were significantly more likely to be diagnosed than females (OR 2.05, 95% CI 1.15 to 3.68). In cases where treatment was available in Tanzania, males

were more likely to be treated, though the difference was not significant (OR 1.68, 95% CI 0.85 to 3.32). The lack of significance in the latter result is likely to be due in part to the relatively small number of people being treated, representing a Type II error.

Overall, there was no significant difference in levels of disability between those who sought treatment and those who did not. Of 159 who did not seek treatment, 44 (27.7%) had moderate or severe disability, whilst of 225 who sought treatment, 67 (29.8%) had moderate or severe disability, OR 1.10 (95% CI 0.71 to 1.74). Rates of treatment sought and disability for selected neurological disorders are detailed in Table 3.61. For each specific disorder, level of disability was not significantly associated with whether a person sought treatment or not. However, those disorders which were associated with the highest level of disability (epilepsy, stroke and Parkinson's disease) also had the highest levels of treatment sought.

Table 3.59: Treatment seeking behaviour and rates of diagnosis and treatment of people with neurological disorders

	Cases	**Number who previously sought treatment (%)**	**Number with previous diagnosis (%)**	**Number with previous appropriate treatment (%)**	**Number for whom treatment exists (%)**	**Number for whom treatment exists in Tanzania (%)**
Males	182 in 162 males	109 (59.9%)	35 (19.2%)	21 (11.5%)	152 (83.5%)	143 (78.6%)
Females	202 in 187 females	116 (57.4%)	21 (10.4%)	17 (8.4%)	188 (93.1%)	183 (90.6%)
Total	384 (in 349 individuals)	225 (58.6%)	56 (14.6%)	38 (9.9%)	340 (88.5%)	326 (84.9%)

Table 3.60: Treatment seeking behaviour and rates of diagnosis and treatment of people with neurological disorders split into specific disorders

	Cases	Number who previously sought treatment (%)	Number with previous diagnosis (%)	Number with previous appropriate treatment (%)	Number for whom treatment exists (%)	Number for whom treatment exists in Tanzania (%)
CENTRAL NERVOUS SYSTEM DISORDERS						
1. Movement Disorders						
Tremor – all causes including cerebellar disease and Parkinsonism	110*	36 (32.7%)	6 (5.5%)	4 (3.6%)	103 (93.6%)	96 (87.3%)
Parkinsonism	14	10 (71.4%)	4 (28.6%)	3 (21.4%)	14 (100%)	14 (100%)
Cerebellar disorders	11†	5 (45.5%)	2 (18.2%)	1 (9.1%)	4 (36.4%)	4 (36.4%)
Other dyskinesias	5	0	0	0	5 (100%)	2 (20%)
2. Episodic and Paroxysmal Disorders						
Headache disorders	92	62 (67.4%)	4 (4.3%)	12 (13.0%)	92 (100%)	92 (100%)

Stroke	54	44 (81.5%)	36 (68.7%)	16 (29.6%)	54 (100%)	54 (100%)
Epilepsy	10	9 (90.0%)	2 (20.0%)	2 (20.0%)	10 (100%)	10 (100%)
3. Systemic Atrophies/Degenerative Diseases affecting the Central Nervous System						
Motor neuron disease	2	2 (100%)	0	0	2 (100%)	0
4. Injury resulting in CNS dysfunction						
Spinal cord injury	5	4 (80.0%)	0	0	5 (100%)	0
5. Spinal cord dysfunction – other	0	-	-	-	-	-
6. Infection resulting in CNS dysfunction	0	-	-	-	-	-
PERIPHERAL NERVOUS SYSTEM DISORDERS						
1. Polyneuropathies	42	21 (50.0%)	3 (7.1%)	4 (9.5%)	42 (100%)	42 (100%)
2. Nerve, nerve root and plexus disorders						
Cranial nerves	14	14 (100%)	1 (7.1%)	0	4 (28.6%)	3 (21.4%)

Upper limb Mononeuropathies	15	6 (40.0%)	2 (13.3%)	0	8 (53.3%)	8 (53.3%)
Lower limb mononeuropathies	5	4 (80.0%)	0	0	0	0
Plexus pathology	4	4 (100%)	1 (25.0%)	0	0	0
Root pathology	4	3 (75.0%)	0	0	3 (75.0%)	0
3. Inflammatory/infectious diseases of the peripheral nervous system						
Polio	5	5 (100%)	2 (40.0%)	0	0	0
Leprosy	1	1 (100%)	1 (100%)	0	1 (100%)	1 (100%)
4. Diseases of the myoneural junction and muscle						
Myaesthenia gravis	1	0	0	0	1 (100%)	0
Muscle wasting and atrophy	17	11 (64.7%)	0	0	15 (88.2%)	13 (76.5%)

* Including cases of tremor due to parkinsonism/Parkinson's disease (n= 12) and tremor due to cerebellar disorders (n = 11) but not tremor due to stroke affecting the cerebellum (n = 4)

† Including cases of cerebellar disorders secondary to stroke (n = 4)

Table 3.61: Treatment seeking behaviour and level of disability for selected neurological disorders

Disorder	Total number who sought treatment	Number with moderate or severe disability (Barthel index < 15)		Odds ratio (95% CI)
		Treatment sought	No treatment sought	
Epilepsy (n = 10)	9 (90.0%)	8 (88.9%)	1 (100%)	0.52 (0.01 to 20.19)
Stroke (n = 54)	44 (81.5%)	28 (63.6%)	6 (60.0%)	1.17 (0.29 to 4.76)
Parkinson's disease (n = 14)	10 (71.4%)	6 (60.0%)	3 (75.0%)	0.50 (0.04 to 6.68)
Muscle wasting and atrophy (n = 17)	11 (64.7%)	7 (63.6%)	4 (66.6%)	0.95 (0.20 to 4.64)
Headache (n = 62)	32 (51.6%)	5 (15.6%)	9 (30.0%)	0.21 (0.06 to 0.68)
Peripheral polyneuropathy (n = 42)	21 (50.0%)	3 (14.3%)	5 (23.8%)	0.53 (0.11 to 2.59)
Tremor (n = 110)	36 (32.7%)	12 (33.3%)	15 (20.2%)	1.97 (0.80 to 4.81)

3.8 Disability levels

Of 2232 participants aged 70+ (range 70-115), 4.3% (crude prevalence-95% CI 3.4 to 5.1)/3.7%(age-adjusted to WHO world population-95% CI 2.9 to 4.5) were severely disabled (BI <15), 6.9%(crude prevalence – 95% CI 5.8 to 8.0)/6.2%(age-adjusted to WHO world population-95% CI 5.2 to 7.2) were moderately disabled (BI 15-18) and 4.6% of women and 3.6% of men were severely disabled. Disability increased with increasing age[15].

Table 3.62: The relationship of disability and age in the Main Study Population

	Males		**Females**	
	Number	**Mean age (95% CI)**	**Number**	**Mean age (95% CI)**
Barthel Index 0-14	n = 37	85.6 (82.0 to 89.2), Median 84	n = 58	87.0 (84.1 to 90.0), Median 85.5
Barthel Index 15-18	n = 53	82.1 (79.6 to 84.7), Median 80	n = 101	82.9 (81.3 to 84.5), Median 82
Barthel Index 19-20	n = 886	77.3 (76.9 to 77.8), Median 76	n = 1097	76.7 (76.3 to 77.0), Median 75
All cases	n = 976	77.9 (77.5 to 78.4), Median 76	n = 1256	77.6 (77.3 to 78.0), Median 76

		Age Bands				**Total**
		70-74	**75-79**	**80-84**	**85+**	
Barthel Index	0-14	16	12	17	50	95
	15-18	30	30	26	68	154
	19-20	831	583	301	268	1983
Total		877	625	344	386	2232

Across both sexes, those with Barthel index ≤18 are significantly older than those with Barthel index of 19-20.

52.6% of all people with a Barthel index of 0-14 are aged 85 years or over. Only 17.3% of all participants were 85 years and over. For this breakdown χ^2 (6) = 194.3, p < 0.001 demonstrating that the differences between groups is highly significant.

Reducing this table down to dichotomies gives:

Table 3.63: The relationship of disability and age dichotomised

		Age Dichotomised		**Total**
		70-84	**85+**	
Barthel Dichotomised	Severe and Moderate Disability (BI 0-18)	131	118	249
	Mild or No Disability (BI 19-20)	1715	268	1983
Total		1846	386	2232

47.4% of all people with a Barthel index of 0-18 are aged 85 years or over, whilst only 13.5% of those with a Barthel of 19 or 20 are aged 85 years or over. For this breakdown χ^2 (1) = 177.5, p < 0.001, suggesting the differences between groups to be highly significant.

The odds of someone aged 85 years or over having a Barthel index below 19 is 5.76 (95% CI = 4.36 to 7.63) that of someone below 85 years. This odds ratio is highly significant.

Table 3.64: The relationship of disability and sex in the Main Study Population

		Sex Coded		Total
		Male	**Female**	
Barthel Index	Severe Disability (BI 0-14)	37	58	95
	Moderate Disability (BI 15-18)	53	101	154
	Mild or No Disability (BI 19-20)	886	1097	1983
Total		976	1256	2232

4.6% of females and 3.8% of males were severely disabled. 12.7% of females and 9.2% of males had Barthel index below 19. For this breakdown χ^2 (2) = 7.040, p = 0.030, the differences between groups appears significant.

Dichotomising as above:-

Table 3.65 The relationship of disability and sex dichotomised

		Sex Coded		Total
		Male	**Female**	
Barthel Dichotomised	Moderate and Severe Disability (BI 0-18)	90	159	249
	Mild or No Disability (BI 19-20)	886	1097	1983
Total		976	1256	2232

For this breakdown χ^2 (1) = 6.549, p = 0.010, the differences between groups is highly significant. The odds of a female having a Barthel index of below 19 is 1.43 (95% CI = 1.09 to 1.88) times that of a male. This odds ratio is significant and effect is not due to the age structure of the population.

A logistic regression model for predictors of moderate or severe disability was constructed by Dr Keith Gray, the basis and significance of which I understand, as shown in table 3.66. Age, female sex and the presence of a neurological disorder were all identified as significant independent predictors of disability in our population. Sex was the weakest predictor of disability, whilst age was the strongest predictors. Females were generally older than males but even after adjustment, interestingly, female gender was still significantly associated with an increased risk for the presence of disability.

Table 3.66: Regression model for predictors of moderate or severe disability (BI < 19)

	β	S.E.	Wald	df	Sig.	OR/Exp(B)	95% CI for OR	
							Lower	Upper
Gender*	0·458	0·154	10·497	1	0·001	1·645	1·217	2·223
Neurological disorder**	1·649	0·160	106·557	1	<0·001	5·203	3·804	7·116
Age (years)	0·115	0·009	171·509	1	<0·001	1·122	1·103	1·143
Constant	-11·99	0·748	256·955	1	<0·001	0·000	-	-

* Coding: Male = 0, Females = 1** Coding: Absent = 0, Present = 1

3.8.1 *The relationship of disability and Neurological Disorders*

The presence of a neurological disorder is an independent predictor of BI. It is associated with a lower BI. The mean BI of those with a Neurological Disorder is 17.7 in comparison to 19.5 in those people in the main study population without a neurological disorder. 14.3% of people with a neurological disorder were severely disabled in comparison to only 2.39% without a neurological disorder. 14.3% with a neurological disorder were moderately disabled in comparison to 5.5% of people without a neurological disorder. Neurological diagnoses associated with increased disability were as follows;

Cord lesions (mean BI 9.2, 80.0% severely disabled), Muscle Wasting and Atrophy (mean BI 13.6, 52.9% severely disabled), Stroke (mean BI 13.8, 40.7% severely disabled), Dyskinesias (mean BI 15.2, 20.0% severely disabled), MND (mean BI 15.5, all patients moderately disabled), Cerebellar disorders (mean BI 15.9, 27.3% severely disabled) and Parkinsonism (mean BI 16.0, 21.4% severely disabled).

The Neurological disorders least associated with disability were as follows; Leprosy (mean BI 20.0, 0.0% severely disabled), Myaesthenia Gravis (mean BI 20.0, 0.0% severely disabled), Cranial Nerve pathology (mean BI 19.9, 0.0% severely disabled), Root pathology (mean BI 19.8, 0.0% severely disabled), Upper limb mononeuropathies (mean BI 19.3, 6.7% severely disabled), headaches (mean BI 19.2, 3.3% severely disabled) and peripheral neuropathy (mean BI 19.1, 4.8% severely disabled). This is described fully in the following table.

Table 3.67: The relationship of disability and neurological disorders in the Main Study Population

	Mean Barthel Index	Severe Disability (BI 0-14) Frequency	Severe Disability (BI 0-14) Percentage (95% CI)	Moderate Disability (BI 15-18) Frequency	Moderate Disability (BI 15-18) Percentage (95% CI)	No Disability (BI 19-20) Frequency	No Disability (BI 19-20) Percentage (95% CI)
Pilot Study Population	18.73	22	7.9% (4.76 to 11.13)	29	10.5% (6.86 to 14.07)	226	81.6% (77.02 to 86.15)
Main Study Population	19.25	95	4.26% (3.42 to 5.09)	154	6.90% (5.85 to 7.95)	1983	88.8% (87.85 to 90.15)
Main Study Population without neurological Disorders	19.53	45	2.39 (1.70 to 3.08)	104	5.52 (4.49 to 6.55)	1734	92.08 (90.87 to 93.31)
Neurological diagnosis – all	17.71	55	14.32 (10.82 to 17.83)	56	14.58 (11.05 to 18.11)	273	71.09 (66.56 to 75.63)
People with Neurological diagnosis	17.70	50	14.33 (10.65 to 18.00)	50	14.33 (10.65 to 18.00)	249	71.35 (66.60 to 76.09)
Tremor – All	18.43	12	10.9%	12	10.9%	86	78.2%
Parkinsonism	16.00	3	21.4%	5	35.7%	6	42.9%
Cerebellar disorders	15.91	3	27.3%	2	18.2%	6	54.5%

Dyskinesias	15.20	1	20.0%	2	40.0%	2	40.0%
Headaches that affect ADLs	19.17	3	3.3%	11	12.0%	78	84.8%
Stroke – All	13.76	22	40.7%	12	22.2%	20	37.0%
Epilepsy	18.00	1	10.0%	2	20.0%	7	70.0%
Motor Neuron Disease	15.50	0	0.0%	2	100.0%	0	0.0%
Cord Lesions	9.20	4	80.0%	0	0.0%	1	0.0%
Polyneuropathies	19.10	2	4.8%	6	14.3%	34	81.0%
Cranial Nerve Pathology	19.93	0	0.0%	0	0.0%	14	100%
UL Mononeuropathies	19.33	1	6.7%	0	0.0%	14	93.3%
Lower Limb Mononeuropathies	16.60	1	20.0%	2	40.0%	2	40.0%
Plexus disorders	18.50	0	0.0%	2	50.0%	2	50.0%
Root disorders	19.75	0	0.0%	0	0.0%	4	100.0%
Polio	18.40	0	0.0%	1	20.0%	4	80.0%
Leprosy	20.00	0	0.0%	0	0.0%	1	100.0%
Myaesthenia Gravis	20.00	0	0.0%	0	0.0%	1	100.0%
Muscle Wasting and Atrophy	13.59	9	52.9%	2	11.8%	6	35.3%

Table 3.68: The relationship of disability and neurological disorders dichotomised

		Neurological Disorder		Total
		Present	**Absent**	
Barthel Dichotomised	Moderate and Severe Disability (BI 0-18)	100	149	249
	Mild or No Disability (BI 19-20)	249	1734	1983
Total		349	1883	2232

The odds of someone being severely disabled if a neurological disorder is present are 4.67 that of someone who does not have the neurological disorder. This odds ratio was significant (95% CI 3.51to 6.22).This effect is real and is not due to the age structure of the population.

3.9 Walking Aids

391 (17.5%) people used a walking aid regularly; 352 people used 1 stick, 13 people used 2 sticks, 9 people used 2 crutches, 5 people had wheelchairs, 3 people used stools, 3 people used 1 stick and 1 crutch, 3 people used metal zimmer frames, 2 people used chairs and 1 person used a wooden zimmer frame.

The majority of these were felt to be appropriate and advice was given to continue utilising the walking aid. For those whose walking aid was felt to be inappropriate, particularly those using chairs or stools, alternatives were offered. Advice was given to many of the patients about acquiring a stick to help their mobility and reduce their falls risk. These were readily available and cost very little or could be acquired for free. 21 people needed wheelchairs, 25 people needed walking frames and 6 people were thought to need crutches. These were all provided through charitable donations.

3.10 Visual Problems

1047 (46.9%) people stated when asked that they had problems with their vision. 907 (40.6%) denied any problems. 278 people were not asked.

3.11 Diabetes

111 people (5.0%) stated when asked that they had diabetes, the remainder denied the problem.

Chapter 4. Discussion

4.1 Brief Summary of the Main Findings

This thesis demonstrates a high prevalence of neurological morbidity; in 2232 elderly participants, there were 384 neurological diagnoses amongst 349 people. The age-adjusted prevalence of people with neurological diagnoses was 154.1 per 1000 (95% CI 139.2–169.1). The age-adjusted prevalence per 1000 of the most common neurological disorders were tremor (48.2), headache (41.8), stroke (23.0), peripheral polyneuropathy (18.6), upper limb mononeuropathy (6.5) and parkinsonism (5.9). This high prevalence demonstrates the large contribution neurological disorders make to the non-communicable disease epidemic particularly in the elderly population.

This thesis also demonstrates the successful production of a screening instrument for measuring the prevalence of neurological disorders in an elderly population of a developing country. The questionnaire was practical, acceptable to recipients, and easily performed by a NMI. The sensitivity and specificity of the questionnaire were high at 87.8 and 94.9 %, respectively, in the pilot and 97.0 and 90.4 %, respectively, in the extension and supports its feasibility for use in the elderly community population of a developing country.

The research reports rates of patient's: treatment seeking, diagnosis and treatment within the prevalent population. Of 349 people who had neurological disorders, 225 (64.5%) had sought treatment for their symptoms. Of the 384 disorders identified in these 349 people, only 14.6% had been diagnosed and only 9.9% were receiving appropriate treatment. Males were significantly more likely to have been diagnosed and were more likely to have been treated appropriately. Therefore the levels of diagnosis and treatment were low, with some gender inequality.

Finally this thesis demonstrates that the age-adjusted prevalence of severe disability (BI<15) is 3.7% (95% CI: 2.9-4.5) and the age-adjusted prevalence of moderate disability (BI: 15-18) is 6.2% [95% confidence interval (CI): 5.2-7.2] amongst the in 2,232 participants. Increasing age, female gender, memory problems and the presence of neurological disorders were all independent predictors of the presence of disability. In this study, the average disability level was lower than seen in high-income countries.

4.2 Study design

This is one of the most robustly designed epidemiological studies of the prevalence of Neurological Disorders in developing countries. It is the only study that focuses on the elderly in SSA – an important and expanding group. It is the only up to date prevalence study of its kind in SSA.

4.2.1 *The Census*

The census was carried out by experienced NMIs who had carried out censuses in previous years. All of the households in the district agreed to take part in the census, this increased the reliability of the data. The results of the census were handled by experienced data analysts in Dar es Salaam who have previously been employed by the AMMP. There were no data entry discrepancies.

The census completion date was the 1st of June 2009. The prevalence date of the study was the 1st of January 2010. Therefore a proportion of people aged 69 at the time of the census had turned 70 by the prevalence date. This was the major reason for additional inclusions in the study as well as the original 70 and over population identified by the census as detailed previously. A more accurate way of recruiting these patients would have been to obtain an additional list of patients aged 70+ on the prevalence date. This was not done as inaccuracy of dates of birth meant that many people knew their year of

birth but not their exact date of birth so many people had their date of birth recorded as the 1st of January. It was therefore felt that including the additional people who felt they had turned 70 since the census was a more accurate way of inclusion of all patients aged 70 and above. Inaccuracy of date of birth and age meant recruiting patients on the basis of age, although unavoidable in order to focus on the elderly population was difficult.

4.2.2 *The Basic methodology*

I used the previously validated and recommended 2 phased approach to establish the prevalence of Neurological Disorders in developing countries [6, 25].

Phase 1: A screening tool designed to pick up neurological disorders administered by trained interviewers

Phase 2: A full neurological history and examination for those highlighted by screening

This is recommended by the WHO and other high profile investigators as the best practice to accurately establish prevalence in a developing country and its use has been fully justified in the introduction [6, 25]. Hospital based studies do not give a reliable measure of disease burden in this setting as many patients do not present to hospitals and other medical facilities for financial and geographical reasons.

4.2.3 *Research Personnel*

The prevalence study involved local Tanzanian staff with previous experience at such studies. This was beneficial to the study for the following reasons;

1. The majority of the staff were local to the area and in some cases lived in the studied villages. They were known to the patients and therefore this increased the acceptability and consequent uptake of the project.
2. The senior staff of the project were local health workers; they were able to inform me of the processes of referral and the intricacies of the health care system in Tanzania. This was invaluable to ensure best possible care was given to the patients. Additionally they facilitated feedback to the District Medical Officer who in turn was able to feedback to government officials regarding the level of neurological (and other disease) morbidity in the elderly population. Using this process I was able to produce and distribute guidelines for diagnosis and treatment.
3. I provided training for the project staff. Consequently they improved their knowledge of the diagnosis and treatment of neurological disorders. This ensured capacity building in the district and provided a health resource to the community after I had left.
4. Systems were put in place for the maintenance and redistribution of walking aids supplied should one become broken or should a recipient die. The local staff were happy to take responsibility for this when I left.
5. Ongoing follow up for the Parkinson's disease patients will be provided by one of the local clinical officers. He will facilitate free supply of medication to these patients, the cost will be met by a charitable source.

All these factors ensured that the project was beneficial to the local population.

4.2.4 *The age of the population screened*

Determining the exact age of people (particularly the elderly) in developing countries is fraught with difficulty. However, we employed validated methods to determine patient's age [449]. This is one of the first robustly designed neurological prevalence study of its

kind in SSA that has focussed specifically on the elderly population – a group with different and under-recognized needs. Concentration specifically on the elderly has allowed me to reflect on the impact of an ageing population.

4.3 The Screening Questionnaire

The screening instrument was feasible for community screening in SSA, no participant refused to answer any of the questions. Previously in this setting, it has been found that some people are reluctant to answer personal questions with regard to their health [56]. All NMIs found the questionnaire simple and quick to administer and deemed the training straightforward and of a suitable length. The use of NMIs is important, as there are often few medically trained people available to act as interviewers and NMIs can be relatively inexpensive to employ. Furthermore, NMIs often have extensive local knowledge of people and geography. This can make them more acceptable to potential interviewees and so increase participation rates. While it has been demonstrated that the WHO screening instrument can have a higher sensitivity and specificity when neurologists are used as screeners, this is generally financially and logistically unfeasible in resource-poor countries [60, 61]. Many NMIs felt exclusion of an examination section, present in many published instruments[25, 33, 41, 46], ensured the screening instrument was practical, increased their confidence in correctly administering the instrument and the acceptability of the instrument to the local population. In my experience, the elderly in SSA are often unwilling to be examined by an NMI. A published study of a screening instrument demonstrated that the examination section was less reliable when performed by an NMI [26], and the same authors go on to conclude in their more recent paper that an examination section reduces specificity but fails to increase sensitivity [39].

I believe that my instrument is culturally non-specific in content. In designing a screening questionnaire for PD, Sarangmath et al[57] noted that if a questionnaire was culturally specific, it had lower specificity when administered by NMIs rather than medically trained interviewers. The lack of questions that required reading or writing skills ensured it could

be applied to people of all literacy levels. Although the content of the questions is culturally non-specific it is important to note that the wording is culturally specific, ensured through accurate translation and back-translation, this is very important for comprehension within the local population.

4.3.1 *The Sensitivity of the Screening Questionnaire*

My screening tool had a high sensitivity, 87.8% in the pilot population and 97.0% in the main study population. This is comparable to the sensitivity of other published screening tools whose sensitivity vary from 84.0% to 100.0%: Those piloted in SSA 91.0%-100.0% [3, 6, 26, 40] and Those piloted elsewhere 84.0% to 100.0% [31, 33, 37, 41, 43-48, 53, 58].

4.3.1.1 *False Negatives – those patients that reduced the sensitivity*

10 patients with varying neurological diagnoses were not picked up by the screening tool within the Pilot study. None of these patients found their symptoms disabling (in some cases they were merely incidental findings) and therefore the fact that the screening tool failed to bring them to the attention of medical personnel would not have been to their detriment.

4.3.2 *The Specificity of the Screening Questionnaire*

Our screening questionnaire had a very high specificity, 94.9% in the pilot population and 90.4% in the main study population. This is substantially better than other tools used in SSA whose specificity ranges from 29.2% to 85% [3, 6, 26, 40]. It is better or roughly equivalent to screening tools used in non SSA countries whose specificities varied from 80% to 99.9% [31, 33, 37, 41, 43-48, 53, 58]. This high specificity was achieved despite the focus on the elderly, a population group that often presents with multiple co-morbidities. Of previously published screening instruments, only Nicoletti et al[47] have validated their screening instrument in the elderly but this was only for identification of essential tremor and PD rather than all neurological disorders and so it has not been described in more detail in this thesis. In screening populations with high levels of co-morbidity, low

specificity can lead to wasted time and resources. Previous investigators have commented that poor specificity must often be accepted in order to achieve high sensitivity [59]. However, I argue this need not be the case. In my experience, the false-negative cases are often not disabled by their symptoms and a low specificity may make screening unwieldy and financially impractical.

4.3.2.1 *False Positives – those patients that reduced the specificity*

The false positives identified by our questionnaire often required simple clarification by the RD (myself) to ascertain that they were not true positives, meaning that although they reduced specificity increasing the time required for the second phase of screening, review of false positive patients was often very quick and easy for the RD. It was felt that in some cases the participants wanted to see the RD for another reason, so answered positively to the screening questionnaire to get medical attention, therefore actual specificity is underestimated. Some of the false positive patients reported a tremor, but when examined no tremor was visible. This may have been due to the tremor only being present intermittently, or they may have misinterpreted the tremor for something else. This has been reported in a study from the UK [464] where 7/20 patients reporting a tremor had none visible at the time of examination, this may be a common problem and was not a result of translation of the questionnaire.

4.3.3 *Identification of all cases of neurological disease*

I have ensured that our screening questionnaire picked up all burdensome neurological disorders. Some published screening instruments, including the WHO protocol (and most published adaptations), only aim to pick up between two and seven major neurological disorders[25, 32, 33, 41, 42, 44, 46, 60].

4.3.4 *Limitations of the screening questionnaire*

There are a number of limitations to our screening tool specifically: I used the ICD-10 criteria to validate our tool. Although the ICD-10 may have some flaws when used in low

and middle-income countries, and some diagnoses may be difficult, it is a recognized international standard and allows direct comparison between studies carried out in different settings. Thus, I felt it was the most appropriate diagnostic criteria to use.

The size of the pilot study limited the accuracy of validation as some target conditions were not present in the population. Therefore, conclusions on sensitivity for these conditions were limited. This highlighted the importance of reflecting on the legitimacy of the screening questionnaire in the study extension where rarer conditions were represented. Questions dedicated to picking up these conditions did so. However, in the study extension as every patient did not receive a full neurological history and examination, we cannot say with certainty that no patients with these conditions were missed. I did not select a random sample of negatives to validate the results. It is possible that the sensitivity level in the main study reflects a rather optimistic extrapolation of results. The prevalence of the majority of Neurological disorders in the Pilot Study were higher than the prevalence in the main study. This might indicate that some cases in the main study were missed and could put the accuracy of the sensitivity of the screening questionnaire in doubt.

However, further robust sensitivity checks were performed through my unique position of having known cases from previous studies namely: stroke (from the TSIP - 1999) [213], Parkinson's disease and Essential Tremor (from the Parkinson's disease and essential tremor prevalence studies -2005) [96, 128] and epilepsy (from the epilepsy prevalence study -2009) [333]within the Main study population. The last follow ups of these patients were performed in 2008, January 2010 and September 2010 respectively. Clearly incident cases have occurred since these studies were performed but the knowledge of cases means that the sensitivity of the screening tool can be checked for these conditions. No patient identified by any of these studies was missed by the screening questionnaire. Of the 12 patients with idiopathic Parkinson's disease 3 were already known from the 2005 study and all of these were found by the screening questionnaire. Of the 67 patients with essential tremor recorded in the main study 8 were already known from the original study

and all 8 were picked up by the screening questionnaire. Of the 10 epilepsy patients, all were found by the screening questionnaire. Of the 54 stroke patients recorded in the main study 8 were already known from the TSIP, and again 100% of these were found by the screening questionnaire. The RD was blinded to all of these diagnoses prior to the study and consequently no bias was introduced when the screening questionnaire was performed.

Additional sensitivity checks in the form of family history search, informal consultation with NMIs, and village elders were also performed; no false-negatives were elucidated., which is a further positive reflection on the accuracy of the sensitivity. Finally, all patients were observed walking, providing consent and holding a conversation by the RD. In total only eight false negatives were identified, all through the brief assessment by the RD.

A further test of sensitivity for rarer neurological conditions would have been to perform an additional pilot in a neurology outpatient clinic. However, I felt that piloting the instrument in the community would be more informative than in a hospital population as this was the proposed area of use. Other tools have only been piloted in hospital settings limiting conclusions that can be drawn in view of higher diagnostic yield in this setting [26, 37, 41, 47].

I could have also performed a medical records search to further check sensitivity however I decided against this for the following reasons: time constraints of the RD**,** previous experience from other prevalence studies carried out in Hai when the medical records search was not informative because most people in this area do not access hospital based care (only 1 additional patient was found in the Parkinson's Disease prevalence study [128]) and informal questioning revealed very few people in the age group studied had attended tertiary referral hospitals. Hospitals and health centres other than tertiary referral hospitals had "hand held" notes kept by the patient, these were requested and reviewed at the time of screening by the NMI to ensure the screen had not missed any neurological disorders.

I have not yet validated our screening instrument in other countries but due to the aforementioned lack of cultural specificity, I do not anticipate any problems with its use. The majority of previously published screening instruments have not been validated for use in SSA and although this is not a criticism as they were not proposed for use in this area it may limit their potential use in future studies in SSA without further validation.

Finally, after the pilot study the PPV fell in the study extension. Nevertheless, sensitivity and specificity were relatively high during both phases and our PPVs bear comparison with previous tools developed for use in low-and middle-income countries [37]. It is interesting that the PPV was higher in the pilot study, when the NMI were supervised. There may be many reasons for this, though it is likely that this may be due to NMI taking extra care not to miss any diagnoses and so included those where there was doubt. Further training of NMI may help to improve the unsupervised PPV.

Neurological diagnosis was based on history and examination alone, while I appreciate that this may limit accuracy, I feel it reflects neurological practice in a resource-poor setting.

In conclusion no previous screening tools have specifically been tested in a pilot study in the community in SSA and purely in an elderly population. This highlights the fact that I have designed a unique screening tool with excellent sensitivity and specificity and the ability to detect a wide range of neurological conditions even in a population with significant co-morbidity. The questionnaire was simple and acceptable to use. I propose the use of the validated questionnaire in the community in SSA for dual epidemiological and clinical purposes. Epidemiologically, documenting prevalence is fundamental to highlight the public health significance of neurological disorders with a background of an ageing population, and an NCD epidemic. Clinically, case identification will reduce the diagnosis and treatment gap and improve the health of individuals [465].

4.4 The Pilot Study

The pilot study village was randomly selected and this to its credibility. As previously pointed out, the number of patients seen in the pilot study may have been inadequate given the low prevalence of some neurological disorders that the screening tool was attempting to detect. It was however the biggest pilot study that could be performed in the time restraints and is comparable with many that have been performed in the literature [26].

It is of benefit that the pilot study was performed in the same type of community and under the same circumstances as the main study was to be performed. As a result, conclusions regarding and modifications to, the screening tool were of direct relevance to the main study population. Under-diagnosis in the community means that it is important not to rely on patients knowing their diagnosis as the sole means of identification. A risk if a pilot is performed in a hospital setting.

4.4.1 *True Positives - The Prevalence figures of the pilot study*

Of those conditions that were represented in the pilot population prevalence rates of the majority were approximately twice as high as those found in the main study. This may have been for the following reasons:

This discrepancy could be down to chance: The 95% CIs overlap in some conditions and therefore it can be argued that there may be no statistical difference between pilot and main study prevalence rates. This is supported by the fact that not all conditions are more prevalent in the pilot population and some are actually more prevalent in the main study population.

Cases were missed in the main study population through systematic bias and false negatives and therefore the sensitivity of the screening tool was not as good as the results of the pilot suggested. The pilot study results are likely to be more accurate (as screening as a source of error has been eliminated) and therefore it may be that proportionately more cases (that would have become false negatives in the main study population) were identified and it is actually the pilot results that are a better estimate.

There is a true difference between the prevalence rates in the pilot population and the main study population. Despite random selection the pilot population may have had an unusually high prevalence of some neurological disorders and therefore the larger population gives a better representation. Indeed the prevalence rates of the main study population seem to be more in keeping with the current literature (this is described in detail for each condition below). Conversely this may be because the methods of case identification were similar in the other studies and subject therefore to the same source of error as outlined above.

I have explored this discrepancy further in the following repeat evaluation and this has demonstrated that the observed difference is highly unlikely to be due to chance. By using the false negatives (10/277-3.6%) from the pilot study one can recalculate the false negative rate for the main study (3.6% of 1955) to be 71. The new prevalence of neurological disorders in the population subsequently becomes 259+71=330/1955=16.9%. As the samples are independent the differences between the two prevalence rates (16.9% versus 29.6%) can be calculated and is -12.7% (95% CI -7.1% to -18.3%, $p<0.0001$).

Therefore in conclusion, the difference in prevalence is potentially multi-faceted; the main contributors are likely to be: geographical variation, sampling error, statistical treatment and missed false negatives. The uncertainty regarding this discrepancy is one of the limitations of the study and is described in the limitation section.

Table 4.1: The Prevalence figures of the Pilot Study and the Main Study Population allowing direct comparison

Neurological Condition	**Number in Pilot Study Population**	**Crude Prevalence in Pilot Study Population per 1000**	**Number in Main Study Population**	**Crude Prevalence in Main Study Population per 1000 (95% CI)**
Total neurological diagnosis	**89**	**321.30**	**384**	**172.04 (156.4-187.7)**
Number of people with a neurological diagnosis	**82**	**296.03**	**349**	**156.36 (141.3-171.4)**
Tremor – All	**23**	**83.03**	**110**	**49.28 (40.3-58.3)**
Essential Tremor	10	36.10	67	30.02
Enhanced physiological tremor	7	25.27	14	6.27
Tremor secondary to Parkinsonism/Parkinson's disease	4	14.44	12	5.38

Tremor secondary to cerebellar disease	0	0	11	4.93
Orthostatic tremor	1	3.61	3	1.34
Tremor secondary to alcohol withdrawal	1	3.61	2	0.90
Iatrogenic tremor	0	0	1	0.45
Parkinsonism	**5**	**18.05**	**14**	**6.27 (3.00-9.55)**
Parkinsonism with tremor	4	14.44	12	5.38
Parkinsonism without tremor	1	3.61	2	0.90
Parkinson's Disease	4	14.44	12	5.38
Vascular Parkinsonism	1	3.61	1	0.45
Parkinsonism secondary to progressive supranuclear palsy	0	0	1	0.45
Cerebellar disorders total	**0**	**0**	**11**	**4.93 (2.02-7.83)**
Cerebellar degeneration secondary to alcohol or idiopathic	0	0	7	3.14
Cerebellar degeneration idiopathic	0	0	5	2.24
Cerebellar degeneration secondary to alcohol	0	0	2	0.90

Cerebellar due to stroke	0	0	4	1.79
Dyskinesias	**0**	**0**	**5**	**2.24 (0.28-4.20)**
Unspecified chorea	0	0	1	0.45
Tardive dyskinesias/ iatrogenic	0	0	2	0.90
Orofacial dyskinesias/ idiopathic/ Meiges syndrome	0	0	2	0.90
Headaches that affect activities of daily living	**22**	**79.42**	**92**	**41.22 (32.97-49.47)**
Primary headaches – total	0	0	44	19.71
Migraine	3	10.83	8	3.58
Tension Type headaches	9	32.49	36	16.13
Cluster headaches	0	0	0	0
Other Primary Headaches	0	0	0	0
Secondary headaches – total	0	0	48	21.51
Headaches attributed to head and/or neck trauma	0	0	3	1.34

Headaches attributed to infection	0	0	0	0
Headaches attributed to disorders of homeostasis/headache attributed to arterial hypertension	0	0	3	1.34
Headache attributed to disorder of homeostasis/headache attributed to hypertensive crisis without hypertensive encephalopathy	0	0	0	0
Headache attributed to disorder of homeostasis/headache attributed to hypertensive encephalopathy	0	0	0	0
Headache or facial pain attributed to disorder of the cranium, neck/headache attributed to disorders of the neck	9	32.49	34	15.23
Headache or facial pain attributed to disorder of the cranium, neck/headache attributed to disorders of the eyes	1	3.61	4	1.79
Headache or facial pain attributed to disorder of the cranium, neck/headache attributed to disorders of the ears	0	0	1	0.45
Headache or facial pain attributed to disorder of the cranium, neck/headache attributed to disorders of the teeth or jaw	0	0	2	0.90
Cranial neuralgias and central causes of facial pain/trigeminal neuralgia	0	0	1	0.45

Stroke	**12**	**43.32**	**54**	**24.19 (17.82-30.57)**
LACS	4	14.44	19	8.51
PACS	3	10.83	16	7.17
TACS	4	14.44	12	5.38
POCS	1	3.61	7	3.14
POCS cerebellar	0	0	4	1.79
POCS non cerebellar	1	3.61	3	1.34
Epilepsy	**1**	**3.61**	**10**	**4.48 (1.71-7.25)**
GTCS	0	0	9	4.03
Partial with secondary generalization	1	3.61	1	0.45
Motor Neuron Disease	**0**	**0**	**2**	**0.90 (0.00-2.14)**
Cord Lesions	**2**	**7.22**	**5**	**2.24 (0.28-4.20)**
Cervical Cord Lesions	2	7.22	3	1.34

Traumatic Cervical Cord lesion	1	3.61	1	0.45
Non-traumatic Cervical Cord Lesion	1	3.61	2	0.90
Arthritic compression	*0*	*0*	*1*	0.45
Acute lower cervical cord lesion	1	3.61	*1*	0.45
Thoracic Cord Lesion	0	0	2	0.90
Traumatic Thoracic Cord lesion	0	0	0	0
Non-traumatic Thoracic Cord Lesion	0	0	2	0.90
Peripheral Neuropathy	**16**	**57.76**	**42**	**18.82 (13.18-24.45)**
Sensory Peripheral Neuropathy	15	54.15	39	17.47
Sensorimotor Peripheral Neuropathy	1	3.61	3	1.34
Motor Peripheral Neuropathy	0	0	0	0
Cranial Nerve Pathology	**2**	**7.22**	**14**	**6.27 (3.00-9.55)**
Ptosis	1	3.61	8	3.58

Ptosis secondary to eye pathology – traumatic	0	0	4	1.79
Ptosis secondary to eye pathology - non traumatic	0	0	2	0.90
Ischaemic 3rd CN palsy	1	3.61	2	0.90
Facial nerve pathology	0	0	4	1.79
Bells	0	0	2	0.90
Traumatic	0	0	1	0.45
Hemifacial spasm	1	3.61	2	0.90
Upper Limb Mononeuropathies	**8**	**28.88**	**15**	**6.72 (3.33-10.11)**
Traumatic upper limb polyneuropathy	1	3.61	2	0.90
Traumatic damage to Median Nerve	1	3.61	1	0.45
Non-traumatic damage to Median nerve - compression/entrapment	1	3.61	4	1.79
Traumatic damage to Radial nerve	2	7.22	2	0.90
Non-traumatic damage to Radial nerve	0	0	0	0
Traumatic damage to Ulnar nerve	0	0	2	0.90

Non-traumatic damage to Ulnar nerve	3	10.83	4	1.79
Lower Limb Mononeuropathy and Polyneuropathy	**1**	**3.61**	**5**	**2.24 (0.28-4.20)**
Traumatic femoral nerve injury	0	0	1	0.45
Sciatic nerve injury from trauma	0	0	1	0.45
Sciatic nerve injury from injection site	0	0	1	0.45
Common peroneal injury from operation	1	3.61	1	0.45
Traumatic common peroneal nerve injury	0	0	1	0.45
Plexus Injury	**0**	**0**	**4**	**1.79 (0.04-3.55)**
Brachial-traumatic	0	0	2	0.90
Lumbosacral-traumatic	0	0	2	0.90
Root Pathology	**1**	**3.61**	**4**	**1.79 (0.04-3.55)**
Sciatica	1	3.61	3	1.34
C8 root lesion	0	0	1	0.45
Polio	**0**	**0**	**5**	**2.24**

				(0.28-4.20)
Leprosy	**0**	**0**	**1**	**0.45 (0.00-1.33)**
Myaesthenia Gravis	**0**	**0**	**1**	**0.45 (0.00-1.33)**
Muscle wasting and atrophy	**0**	**0**	**17**	**7.62 (4.01-11.22)**
secondary to primary orthopaedic problem	0	0	7	3.14
secondary to pain	0	0	5	2.24
secondary to severe cognitive impairment and consequent immobility	0	0	2	0.90
secondary to soft tissue damage secondary to infection	0	0	2	0.90
secondary to period of ill health and consequent disability	0	0	1	0.45

4.5 The workshops

The NMI attended two workshops one week apart to teach them to use the screening questionnaire. This ensured they had time to practice the screening questionnaire on friends and family between sessions and could bring up any queries or problems they had experienced in the second session. They also received a period of training with "real patients" in the field and were observed administering the screening questionnaire until they were confident and competent in its use. All of this improved the validity of the results..

4.5.1 *The enumerators/NMI*

The NMI were experienced in screening for medical conditions as they had been involved in previous prevalence studies in the past. The use of NMI like the enumerators has the following main advantages:

1. They are cost effective to employ and consequently such screening can be used in other resource poor settings.
2. They have optimal geographical knowledge of the area and the households, without which a community based prevalence study in similar remote geographical locations, could not go ahead, or cases, particularly those that need to be seen in their houses, would be missed.
3. Their standing within the village and the fact that they were well known to the villagers and lived in the village ensured that they were acceptable to people within the study and this increased the participation in the study.

Disadvantages of using NMI

1. Their lack of medical knowledge might mean that they produce a higher number of false positives and negatives than medically qualified investigators, decreasing sensitivity and specificity of the screening questionnaire and ultimately underestimating the prevalence of Neurological disorders with an increased number of people required to be seen in the second stage.

2. The lack of an examination section required to enable NMI to screen may reduce the sensitivity of the tool as with a questionnaire alone you rely on the patient to report symptoms and signs which they may feel are stigmatising and are reluctant to disclose.

4.6 The Main Study

The selection of villages was random but ensured the proportion of upland and lowland villages remained representative of the whole Hai District DSS population. The size of the main study was selected due to financial and time constraints. The whole population studied was 40,280 (one quarter of the Hai District DSS population n=161,119). Of this population I only studied the 70 and over population, n=2232. Other community based studies of this nature in SSA have differed in size with no universally accepted optimum, the number of subjects studied have varied from 1113 to 161,071 [3, 5, 34, 96, 99, 128, 131, 187, 191, 204-206, 302, 313, 315, 336, 466, 467].

4.6.1 *False Positives*

The number of false positives (n=163) in the main study remained relatively low, supporting the high specificity of the screening questionnaire. As in the pilot study, in the majority of cases simple questioning revealed that they were false positives and consequently the review of these patients was not time consuming.

The false positives were all reviewed and diagnosed by the RD (myself). The most common false positive diagnosis was osteoarthritis. Some patients when seen and questioned again immediately became negative. It was felt that in the majority of these cases they wanted to see the RD for another reason, so answered positively to the screening questionnaire just to get medical attention. Therefore actual specificity of the screening questionnaire may be underestimated.

4.6.2 *False Negatives*

The potential for missed diagnoses of the 8 false negative patients was relatively unimportant as their symptoms had very little impact on the individual patient. It is possible that some patients may have hidden their symptoms as they believed them to be stigmatising for either themselves or their family. I tried to overcome this problem by simple observation of all the patients in the main study and by education of the enumerators on the nature, causation and potential treatments of neurological disorders. They in turn were able to relay this to each individual patient.

4.6.3 *Description of cases - True positives – The Prevalence estimates*

To the best of my knowledge, this is the first community-based prevalence study of "All-Cause" Neurological Disorders in the Elderly in SSA. Data in this area are sparse and most "up-to-date" data is based on observational studies that assessed hospital populations. Much of the community based data is old and predictive data from the WHO is only speculative. Comparable data on the true prevalence of Neurological disorders in the community is limited but is provided by this study and can inform healthcare planning in this resource-poor setting. The need for such data has been long recognized by the WHO [7]. We can reflect on the prevalence rates that we found by comparing them to available community based prevalence studies that investigated prevalence from SSA. Due to lack of up-to-date data from SSA I have also utilised robust community based epidemiological studies from other developing countries for comparison and worldwide review articles. I have done this with reference to "all-cause" neurological disorders and the most common and public health relevant conditions namely, tremor, parkinsonism, cerebellar disorders, headache, stroke and epilepsy [13, 384, 385]. The prevalence rates of other neurological disorders identified by the study namely; dyskinesias, motor neuron disease, spinal cord dysfunction including injury, infection resulting in CNS dysfunction, polyneuropathies, nerve, nerve root and plexus disorders and inflammatory/infectious diseases of the PNS e.g. polio and leprosy have been briefly discussed. The justification for focussing on literature from SSA has been previously explored in the introduction section.

The elderly in SSA are an important and expanding group with different (from the general adult population) and under-recognised needs and levels of pathology. This study allows reflection on the impact of an ageing population and where possible age related prevalence rates from the literature have been compared.

4.6.3.1 *All Cause Neurological Disorders*

The age adjusted prevalence rate of Neurological disorders in our 70 years and over population was 168.9/1000. The age adjusted prevalence rates of a person with one or more neurological diagnoses were 154.1/1000. The identification of a complete list of neurological disorders as defined by the WHO ICD 10 and the use of standard diagnostic criteria facilitated interpretation of results and increased the quality of the study. In addition I used a two-phased approach to achieve accurate prevalence data. I used my own feasible, valid and specially developed screening questionnaire, utilising findings from previous studies by my research team to help ensure maximal case ascertainment [34, 96, 128, 333]. Finally, extensive training of NMIs added to the reliability of my figures [24].

This study and its conclusions have some important limitations which are discussed in detail below but briefly include inaccuracies of age and interpretation, its small size (consequently the prevalence of rarer conditions are more difficult to interpret), the purely clinical diagnosis. Nevertheless, our methodology is robust, and our estimates are as accurate as possible given the setting of data collection.

4.6.3.1.1 *Comparing our figures to less reliable data sets*

Predictory data from the GBDS has demonstrated neuro-psychiatric disease make up 14.7% of the total global burden of disease and are one of the leading causes of disability[391]. However, these predictions are generally extrapolated from South African data with only limited studies from the rest of SSA.

Winkler et al[394] recently reviewed hospital-based prevalence studies of neurological disorders in rural African settings. They concluded that out of 8676 admissions 740 patients (8.5%) were given a neurologic diagnosis, the most frequent of which were seizures (26.6%) and infectious diseases (18.1%). Other hospital-based studies from SSA estimate that neurological disorders (most commonly stroke and neurological conditions secondary to infection) make up 3.0– 33.1% of all hospital admissions and 4.2–7.5% of out-patient reviews [9, 27, 395, 444, 468].

Mateen et al [396] documented reportable neurologic diseases in refugee camps in 19 countries (13 from SSA). The data presented is difficult to interpret as it is presented in the format of the number of health visits rather than in prevalence format. It does however attribute a high morbidity burden to neurological disorders particularly those that are non-communicable in nature.

The GBDS hospital based and refugee camp studies do emphasise that neurological diseases contribute substantially to morbidity burden. However, their methodology and their conclusions are highly biased and therefore they are difficult to generalise or compare with our dataset [392].

4.6.3.1.2 *Community prevalence studies from SSA*

The only community-based studies from SSA on the prevalence of all cause neurological diseases are from over 20 years ago. The studies were significantly larger than my own, they used robust methodology with little introduction of bias. Osuntokun et al [3] reported a crude prevalence rate of 11.1/1000 or 62.1/1000 if inclusive of lifetime prevalence of headache in Nigeria and Tekle-Haimanot et al [5] found crude prevalence rate of 14.9/1000 in Ethiopia.

These rates are substantially lower than my own, this can be partially explained by the age structure of the population studied. Unfortunately because of rapidly changing population demographics these studies are now out of date and of limited use, even though they were landmark studies of their time. In the Nigerian study 58% of patients

were aged below 20 years and only 2.82% of the population were aged 70 years and over. In the Ethiopian study, 59% of the inhabitants were aged below 20 years, with a median age of 14.5 years. This represented the age distribution of SSA at the time, , by now the ageing of the population will have impacted significantly on the relative contribution of neurological disorders. This population structure, without the means to adjust for age means that prevalence rates reported are difficult to compare with current worldwide prevalence rates, particularly those from our prevalence study which reported on a purely elderly population.

Both studies utilised the WHO neuroepidemiological protocol which was only designed to identify 7 major neurological disorders whereas my study (and screening tool) was designed to identify a more complete list, this could explain the comparatively high prevalence rates in my study.

4.6.3.1.3 *Community based prevalence studies from developing countries other than SSA*

In 1985 Attia Romdhane et al [4] reported the age adjusted prevalence of "all-cause neurological disorders to be 59.5/1000 inclusive of migraine and 25.5/1000 exclusive of headache disorders, this is again substantially lower than my results. The study was well designed but is dated, the population had a very different age structure and it used the WHO neuro-epidemiological protocol which only identified a limited number of neurological disorders.

Dated studies from India include those performed by Razdam et al [137] in Kashmir and Saha et al [61] in West Bengal. Both studies utilised the WHO protocol in the general population. They yielded crude prevalence rates of 9.67/1000 and 29.07/1000 respectively.

Using similar methodology to that used in our study, Gourie-Devi et al. [52] screened a randomly sampled 102,557 urban and rural dwellers from Bangalore, India, and quote an age-adjusted prevalence of 33.6 per 1000 in the general population and 50.1 per 1000 in the >60 years population. Interestingly, they found prevalence rates to be

almost twice as high in rural areas (40.7 per 1000) compared to urban (21.9 per 1000) dwellers and linked this to lower socioeconomic status.

Das et al. [43, 53] quote a crude prevalence of 60.9/1000 in the 60 and over age group in Kolkatar, India and 11.79/1000 in the general population with an age adjusted rate of 15.2/1000, but this was performed to the US 2000 population rather than the WHO World Standard Population.

In both studies a two-phased approach was used with: random sampling, training of interviewers, case verification by neurologists and use of diagnostic criteria to improve the reliability of the results.

The higher prevalence rates in the rural population (found by Das et al) and the ten year age difference (Das studied those aged over 60) may explain the comparatively lower prevalence rates in these two Indian populations. In addition the Indian screening instrument was not specific for use in the elderly and it is possible that neurological disease was mistaken for other co morbidities and therefore was under diagnosed. In the case of Das et al the screening questionnaire used was only designed to pick up stroke, essential tremor, epilepsy, parkinsonism and dementia and therefore the exclusion of other less common neurological disorders may also explain their lower prevalence rates. It is also possible that the prevention and treatment of neurological disease is more advanced in India in comparison to SSA which has resulted in lower levels of disease.

4.6.3.1.4 *Community prevalence studies from developed countries*

Broe et al. [155] quoted the prevalence of neurological disorders as 214.1 per 1000 in the 65 and over age group in the UK. In the general population of developed countries, prevalence rates vary from 68 to 142 per 1000 [398, 399].

We have demonstrated a high level of neurological morbidity in the elderly population of SSA, comparison of this data to other datasets is difficult because of the heterogeneity of study design, population age and the number of neurological

disorders screened. Elderly populations of SSA do however seem to be at increased risk of neurological morbidity than some other populations. They have an equivalent level of neurological morbidity to the elderly from developed countries and therefore healthcare action is urgently required.

4.6.3.2 *Central Nervous System Disorders*

4.6.3.2.1 *Movement Disorders*

4.6.3.2.1.1 *Tremor Disorders*

The most common neurological disorder was tremor, of which 60.9% of cases were essential tremor. My overall prevalence of all cause tremor disorders was 49.3 95% CI (40.3 to 58.3), with an age adjusted prevalence of 48.2 95% CI (39.4 to 57.1).

4.6.3.2.1.1.1 *Essential Tremor*

The world-wide prevalence of ET (limited to community based studies which use a defined and accurate diagnosis of ET) ranges from 4.1–39.2/1000 across whole populations, becoming increasingly common with age, prevalence increased to 13.0-50.5/1000 in persons above 60 years of age [91]. More specifically a recent study from the United States reported the substantial impact of ageing with prevalence rates of 55 per 1000 reported in the over 60 years age group increasing to 217 per 1000 in those aged over 95 years [104].

The prevalence of ET appears to be higher in whites than blacks even within the same geographic location [92].

In SSA, rates of around 0.1 per 1000 have been reported in the general population [3, 5].

The crude prevalence of Essential Tremor (ET) in the studied population was 30.0/1000 95% CI (22.9 to 37.1) and the age adjusted prevalence was 30.1/1000 95% CI (23.0 to 37.2). Using the combined diagnostic criteria detailed in the introduction[86], my

relatively high prevalence rate is likely to reflect the age of our study population. However it may also be due to genetic factors, with some clustering of cases within specific areas[469]. The following section goes on to discuss this in more detail with reference to specific literature.

My ET prevalence figures are reliable because of the robust methodology used, specifically a 2 phased epidemiological survey. Hospital prevalence studies are generally very poor at documenting accurate prevalence data in developing countries and this is particularly the case for the prevalence of ET both in developing countries and the rest of the world. A large number of patients are often undiagnosed in the community and do not seek medical help despite problematic symptoms that substantially effect quality of life. In prevalence studies from Finland [93] and Singapore [94], only 2% and 10%, respectively, had been previously diagnosed. Only 10 cases of ET were identified amongst 2.1 million patients seen in outpatient clinics in a teaching hospital in Nigeria over a 25 year period [95].

As described above estimates of the prevalence of ET vary widely. There are few existing data, from reliable community based studies, on the prevalence of ET in sub-Saharan Africa (SSA) [91].

Early community based studies in SSA investigated all neurological diseases, not just ET and were performed in the 1980s, preceding the ongoing substantial population change which has increased the elderly portion of the population in SSA. Given this and the fact that they focussed on the general population including children, it is not surprising that the prevalence rates found (5-10/100,000) were significantly lower than those found in my study. Unfortunately it is not possible to extrapolate from the data presented in these papers the prevalence rates in older age groups.

There have subsequently been two reliable studies of ET conducted in SSA, one in Tanzania in the same study site as is the subject of this thesis in 2008 and one more recent study from Nigeria, published in 2012.

Dotchin et al's [96] study (also in the Hai district DSS) found similar rates of ET to my own when you allow for the different age of the population studied (Dotchin et al studied all ages). The crude prevalence rate found by this study was 41/100 000 and age standardised prevalence (to the UK population (2001)) was 82/100 000. 61.5% of cases were aged 70 years and over.

My more robust methodology is likely to explain slightly higher prevalence rates (when the rates in the aged population are directly compared). Dotchin et al did use the gold-standard 2 phased approach to perform the epidemiological survey and the denominator population was accurately recorded as part of a census. However, the cases were identified through a questionnaire designed to identify individuals with PD and no effort was made to validate this questionnaire for ET. The poor performance of the questionnaire was highlighted by the 43 individuals identified by other case finding methods which were identical to the ones we used which failed to pick up any additional cases. Standard diagnostic criteria from the MDS were used however validation by a movement disorder expert was not possible. It is important to recognise that Dotchin et al had a much larger sample size than our own 161,071 vs. 2232 and therefore although we may have been able to ensure more robust methodology it may be that our higher figures are a reflection of clustering as discussed above.

Subsequent to the work performed by Dotchin and colleagues, Okubadejo et al [98] performed a multi phased door-to-door survey investigating the prevalence of essential tremor (ET) in an urban Nigerian community. Like our study the sample size of 3000 residents was relatively modest (dictated by logistic constraints and commitment to robust methodology) although selection bias was avoided through

randomisation. Only one of the two screening questionnaires used was validated so sensitivity could be an issue and in consequence there could be uncertainty with regard to the prevalence figures. Diagnosis of ET was positively based on the Movement Disorders Society (MDS) consensus diagnostic criteria for ET. The authors found a crude prevalence of 12 per 1000 (95% CI = 8.1- 15.9). Prevalence was age adjusted according to the "WHO New World population" and found to be 23.78/1000. Gender specific crude prevalence was 10.3 /1000 in males and 14.3/1000 in females. Age specific prevalence increased with advancing age in both sexes. The highest rates were seen in those aged 75-84 where the crude prevalence rate was found to be 473.7/1000.

The whole population was screened which could explain the slightly lower overall prevalence rates than my own. In contrast the prevalence rates in the older age groups were much higher than that found in our study with their peak crude prevalence rate of 473.7/1000 in the 75-84 year old age group compared with the 54.7/1000 found in our population of 70 and over.

It is worth noting that the rates reported by Okubadejo et al are ten times higher than earlier studies based in a rural community in the same ethno-geographical zone [3]. It is likely that the latter more robust studies present much more reliable figures, more applicable to today's SSA society. In addition direct comparison of these data presupposes that the population structures are similar, age adjustment was carried out but there is significant variation in the standard population used and so direct comparison of the results remains difficult.

The crude and age-standardized prevalence data obtained by ourselves and Okubadejo et al [98] fall within the range previously reported from the rest of the world (4.0 – 39.2/1000) indicating that ET is a problem for developing and developed countries alike and likely to become an increasing problem in low-income countries as populations age. A recent study in Sile, Turkey demonstrated a crude prevalence rate of 30/1000 in persons above 18 years of age [100]. A recent study from Italy reported age and sex adjusted prevalence rates of 12/1000 for women and 19/1000 for men [101].

It is important to note that the methodology used in my study as well as those from Dotchin and Okubadejo may underestimate prevalence, as people with mild symptoms may not have responded positively to the screening questions. In an American study, 13 of 46 patients diagnosed with ET had not reported tremor on screening questions [92] and further studies by Louis et al [91] reported that patients with mild tremor may not screen positively, stressing the importance of examining all subjects if possible. However equally it could be argued that those persons with mild tremor may have physiological tremor, or tremor induced by the anxiety of seeing a doctor and therefore examining patients may increase false positives and reduce the specificity of screening. It is also worth noting that in SSA it has been found that patients with tremor suffer from stigma [96]. This may make them less likely to answer questions positively which would result in underestimation of prevalence in my study. Tremor is often thought to be a sign of alcoholism or evil spirits. Social stigma as a result of neurological problems is common in Tanzania and awareness of neurological conditions is low, as in most of SSA.

With direct reference to our prevalence figures other limiting factors include my modest sample size with the potential impact of clustered cases and I used a combination of criteria for diagnosis of ET. This was felt to be pragmatic however using the MDS criteria alone might have facilitated comparison further.

Reasons for varied worldwide prevalence could be differences in exposure to risk and aetiological factors. Different risk factors are explored below with relevance to the literature:

Ageing is the most consistent documented risk factor associated with increased prevalence of ET [102] a finding also corroborated by Okubadejo et al's and Dotchin et al's studies detailed above and obviously specifically relevant to my prevalence rates. There have been various studies that specifically report the crude prevalence of

essential tremor in the elderly (some where the aged population is the only focus of the study, some where the prevalence in this age group is specifically highlighted). Das et al [53]performed a study of 5430 people aged 60 years and older in India and found the crude prevalence of ET to be 13.76/1000. Benito-Leon et al [103] reported a crude prevalence rate of 48/1000 amongst 5278 people aged 65 years and older in a Spanish community study. Gilik et al (2003) reported a crude prevalence of 7.8/1000 in those aged 65 years and older, in a community door to door survey of 900 individuals. Louis et al [104] assessed the prevalence of essential tremor in 1965 people aged 66-102 in Manhattan US, they found that the crude prevalence rate in this whole population was 55/1000. However the prevalence for those aged over 95 was 217/1000 or approximately 1 in 5. Interestingly they found that for each 1 year of advancing age the risk of ET increased by 14%. Our prevalence rate of 30.1/1000 is very much in keeping with these worldwide prevalence rates from elderly populations and together they highlight the impact of ageing on this highly prevalent condition.

Genetics have also been implicated in ET prevalence as demonstrated by clustering of the condition within families [105]. It is estimated that one half of cases of essential tremor are due to a genetic mutation and the pattern of inheritance is most consistent with an autosomal dominant transmission. As yet no genes have been identified but genetic linkage has been established with several chromosomal regions [469-471]. About a third of the participants with ET reported by Okubadejo et al[98] had a positive family history of tremor in a first degree relative and it is possible that undiagnosed ET and recall bias would have lowered the reporting of a positive family history. Dotchin et al's[96] ET patients also reported a family history in approximately one-third of patients (28%). In some cases the first degree relatives had died at a young age, making it possible that they may have developed tremor had they lived long enough. It is difficult to obtain accurate data on family history on ET, Prakash et al [106] report the inaccuracy of family history reporting, with patients tending to under report family members with tremor, especially in mild cases, resulting in a sensitivity of only 43%. However, the specificity of these reports were high (94%), so if a family member is recorded as having a tremor, they probably do have ET. We agree that family history was inconsistently reported, in our population 16 patients (23.9%)

admitted to having a family history of tremor, with one patient denying a positive family history despite the fact that the next patient with ET was her sister,

A gender predilection has previously been reported in some ET studies; several studies have suggested ET is more common in men than in women [92-94, 101], but an older community based study in Papua New Guinea suggested women were more commonly affected than men [108]. Other studies [92, 96, 98], have not found any male to female differences. The basis of a gender predisposition is unproven and there are no strong biological indications that could explain such findings. However, if such a difference does exist it is likely that environmental peculiarities relating to occupational and recreational exposures are possible contributors. We found no significant different in gender; 55.2% of patients were male and 44.8% were female.

Significant ethnic variation have been reported by Louis et al [109] in the US where Caucasians were found to be five times more likely that African Americans to have physician diagnosed ET. It was however unclear from this study whether this reflects inconsistencies in access to medical care and health seeking behaviour of different communities or whether a true difference in prevalence exists. Another study in New York showed higher rates in whites compared with African Americans, with Hispanics having an intermediate prevalence [92]. Reflecting on the rates reported by Okubadejo and ourselves and how comparable they are to worldwide data it seems that under presenting in African Americans (eliminated by community based studies) may explain ethnic variations in hospital studies.

ET is associated with significant functional disability particularly in persons with an upper limb tremor [114]. Work and productivity can be significantly impacted by ET, in the UK and the US, up to 25% of patients with ET had to change jobs or retire because of their symptoms[105, 115]. The social and emotional burden could be partially relieved with treatment. Non-selective beta blockers are available in SSA. Okubadejo et al[98] reported that only 1 (2.8%) person had a prior diagnosis of ET, and this was

the only individual on treatment. Dotchin et al [96] found that no one they identified was receiving medication for tremor and very few had sought any medical help. Several factors including differing severity and impact of ET on activities of daily living, non-recognition or poor awareness of ET as a neurological or medical disorder amenable to treatment and limited access to care may contribute to the treatment gap, all highlighting that prevalence of ET derived from hospital-based studies will reflect an under estimate of prevalence. Low treatment levels are also seen in developed countries; as many as 75-99% of patients with ET detected through population-based studies are reported to be previously undiagnosed and untreated [92, 117]. No previous studies from SSA have assessed the responsiveness of symptoms to simple drug treatments. We found that 85.3% of patients reported that they had improved on medication which consisted of varying doses of propranolol. To make progress, further consideration of local beliefs behind ET and other neurological conditions is necessary, as is education of the population and community health workers.

In summary ET is a highly prevalent condition in the elderly and this is supported by my data and the more recent studies from SSA and worldwide. It may be that ET is less common in black communities but this is not supported by recent community studies from SSA including this one. It is likely that differences can be attributed to variations in study design and methodology and diagnostic criteria. Improved public awareness and physician education is required to ensure that ET is recognized, and treatment offered where appropriate.

4.6.3.2.1.2 *Cerebellar Disorders*

I found the crude prevalence of all cause cerebellar disorders to be 4.93/1000 95%CI (2.02 to 7.83) with the age adjusted prevalence rate being 4.87/1000 95% CI (1.98 to 7.76). In these patients 45.5% were secondary to idiopathic/unknown cause, 36.4% were secondary to stroke and 18.2% were secondary to alcohol.

According to the recent BMJ best practice guide there is no exact data on the prevalence of cerebellar ataxia of all causes [472]. Epidemiological studies that focus on hereditary types of ataxia have shown a prevalence of approximately 10/100,000, and idiopathic ataxias probably outnumber hereditary cases [473]. Because there are many different types of inherited and degenerative ataxias each individual cause is relatively rare. There are clusters of high incidence and prevalence due to genetic mutations [472].

Osuntokun et al reported a prevalence of 0.10/1000 for primary cerebellar degeneration in Nigeria in 1986 [3]. No other SSA studies comment on the prevalence of cerebellar disorders.

Safe et al [474] performed a retrospective study of 624 elderly patients in the UK referred for gait and balance problems and found 45 (7.2%) of them to have cerebellar ataxia. 37% were secondary to cerebrovascular disease, 20% were due to degenerative cerebellar ataxia, 6.7% were secondary to Normal Pressure Hydrocephalus and 4.4% were secondary to alcohol. They conclude that a significant proportion of elderly people will have cerebellar ataxia due to treatable or reversible causes and therefore it is an important diagnosis to screen for.

Nafissi et al [475] also looked at the different causes of cerebellar ataxia in Iran in all ages (range 6-73). They concluded that 30.4% were secondary to Multiple Sclerosis (MS), 29.6% were secondary to cerebrovascular disease, 3.0% were secondary to a tumour or were paraneoplastic, 7.4% were secondary to inflammation or infection, 11.1% were hereditary ataxias and 14.8% were of unknown origin. This highlights the importance of age specification when looking at the subdivisions of neurological disorders and the possible causes.

4.6.3.2.1.3 *Parkinsonism*

This study found the crude prevalence rate of parkinsonism to be 6.3/1000 95% CI (3.0 to 9.6) and the age adjusted prevalence to be 5.9 95% CI (2.8 to 9.1). The crude prevalence of idiopathic Parkinson's disease was 5.4/1000 95% CI (2.3 to 8.4) and age adjusted prevalence was 5.1 95% CI (2.2 to 8.1).

The prevalence of PD was originally reported to be much less in SSA than the rest of the world. Initial studies from Nigeria [3], Ethiopia [5] and Togo [127] demonstrated prevalence rates of 0.07-0.20/1000. Age adjustment was performed in the Nigerian study to the black population in Copiah, Mississippi [50] allowing direct comparison of the prevalence rates. The age adjusted prevalence rate was 0.67/1000 for those over 39 in Nigeria five times lower than the 3.41/1000 reported from the US. Positively all these African studies were community based. Methodological differences particularly inconsistent diagnostic criteria may still have contributed to inaccuracies and differences in the prevalence rates. It unclear whether all cases of parkinsonism or just idiopathic PD were included. In addition the total number of patients found with parkinsonism were small and limited the conclusions that can be drawn.

In 2006 authors from my research group conducted a prevalence study of PD in the whole population of the Hai district DSS [128]. Strengths of the study included use of an accurate denominator population, standard diagnostic criteria, case verification and multiple sources of case ascertainment. Limitations of the study and possible underestimation of the burden of PD were lack of validation of the screening tool, under reporting due to stigma and use of a surrogate (questioning the head of the household). The age standardised prevalence rate found was 0.40/1000. This figure is more in keeping with the rate of 0.67/1000 reported in African Americans in Manhattan [130] but is still lower than other studies presented in the developed world. Dotchin et al [128]report an age adjusted prevalence rate of 2.07/1000 for those aged 65 and over. Standardised methodology and more comparable diagnostic criteria played a part in detecting more cases of PD in this population than in the aforementioned studies. The rates in a similar age group are still less than half that

detected in my study, I speculate that this is because of improved detection in our study through use of a validated tool and increased awareness of PD brought about through repeated prevalence studies.

Winkler et al [131] reported the prevalence of parkinsonism in a population of northern Tanzania in 2010, however the methodology was significantly flawed and limits the usefulness of the data. A crude prevalence of 1/1000 (n=5) and 0.35/1000 (n=1) was reported for parkinsonism and Parkinson's disease respectively from a hospital population, however this is a highly biased sample and therefore these results are difficult to interpret. None of the community based subjects were diagnosed with parkinsonism or PD, making the prevalence zero. The authors calculate 95% confidence intervals and conclude that prevalence could fall between 0 per 1000 (the best estimate based on their observation) and 2.5/1000.

Indian studies conclude the prevalence of PD varies between 0.06-3.28/1000 with higher prevalence rates being found in Parsi Indians (with rates similar to those found in white Caucasians). The main factor that limits the comparison of my data is the age of the population I studied, however on examining age specific prevalence rates from the Indian data one can conclude that age-specific rates increase from 0.28/1000 (in 4th decade) to 5.73/1000 in ninth decade [58, 145] and that my rates of 5.1/1000 in the over 70 population are comparable. It is also worth noting that in India PD was more prevalent in rural than urban populations [144] potentially another reason why the prevalence rates in my population were slightly higher, and could indicate a causative factor such as pesticides.

A large (n=29 454) cross-sectional prevalence study of Parkinson’s disease in China was undertaken in 1997–98 [133] with robust methodology that included sampling and a one stage standardised diagnostic protocol with good inter-rater reliability. The size of the study and the fact that 277 people with disease were identified means that conclusions drawn are potentially much more accurate than my prevalence figures which are limited by the size of the population studied and the small number of cases identified. The age standardised prevalence of Parkinson’s disease for those aged 65 years and over was 21/1000 (19–23) for both sexes. This is easy to compare to studies

of the same age group in Rotterdam, the Netherlands (22), and in seven European studies (17) and indicates that the prevalence of Parkinson's disease in China is similar to that in developed countries [133] and significantly more than that found in my study (5.1). Standardised estimates for both sexes from a previous Chinese study[147] based on a different age groups (60 years and over) were lower (1-10/1000) than this study from Zhang et al and were more in keeping with my results. The authors attribute this to the fact that their methods corrected several limitations of earlier studies, they surveyed urban and rural populations in diverse regions and reviewed high numbers of participants which yielded statistically precise estimates.

Wickremaratchi et al [134] performed a very large (n=292,637) prevalence study of PD amongst residents in Cardiff. Strengths of the study included multiple case finding methods that included the use of GP databases, prescriptions and neurology clinic notes (robust methods in a developed country).They used standardised diagnostic criteria. The age adjusted prevalence rates for the whole population, those aged 70-79 and those aged 80 and over were 1.42, 7.38 and 12.97/1000 respectively. The authors overall prevalence rates were very similar to previous UK studies where the crude prevalence reported was 1.13-1.64/1000 [148-152, 154, 476]. The authors acknowledge their main limitation is that they only clinically examined one-third of cases, and older cases were less likely to be seen. The authors conclude that there are no major geographical variations in the prevalence of PD in the UK and that the age adjusted prevalence rate has remained relatively stable over the past 40 years. The rates found are higher than found in my study in a similar age group; this may represent a true difference or may represent problems making accurate conclusions on the prevalence of rare conditions in a study with a small sample size such as my own.

The EUROPARKINSON collaborative study [135] represents a huge PD prevalence study (n=14,636) with an unprecedented level of methodological homogeneity from five European populations (France, Italy, The Netherlands and 2 in Spain), it provides reliable prevalence data for people aged 65 years or older. The overall age adjusted prevalence was 23/1000 for parkinsonism and 16/1000 for Parkinson's disease.

In general my study adds to the growing body of evidence that the prevalence is lower in blacks than whites but the difference is not as significant as originally thought. Studies have shown an association of lack of melanin with PD and this may explain racial discrepancies, however more investigation into genetics and the role of melanin and environmental causes of PD are required [130].Those studies that reflect the prevalence in the whole population as opposed to being more specific to the elderly are bound to demonstrate lower prevalence rates, Parkinson's disease, a disease of the ageing brain, becomes more common with increasing age and is one of the many neurological conditions that demonstrate the importance of looking specifically at an elderly population [118].

4.6.3.2.1.4 *Dyskinesias*

The prevalence of chorea in the literature has been reported as 0.05 to 1/1000 of the population, with the higher prevalence rate reflecting the prevalence in an age group aged 65 and over [5, 155]. I found the prevalence of dyskinesias to be 2.2/1000 95% CI (0.3 to 4.2), with an age adjusted prevalence of 2.0/1000 95% CI (0.2 to 3.9). I found the prevalence of chorea to be 0.45/1000 95% CI (0 to 1.33), with an age adjusted prevalence of 0.31/1000 95% CI (0 to 1.04).

4.6.3.2.2 *Episodic and Paroxysmal Disorders*

4.6.3.2.2.1 *Headache Disorders*

The worldwide epidemiology of headache disorders is only partly documented. Many studies have been performed on migraine, but data on tension type headache (TTH), the most frequent, are relatively sparse. In addition, most epidemiological studies have been performed in high income countries in Western Europe and North America. The studies that have come from SSA have variations in methods and diagnostic criteria thus it is difficult to extrapolate meaningful results for comparison.

This study found the prevalence of headache to be 41.2/1000 95% CI (33.0 to 49.6), age adjusted prevalence 41.8/1000 95% CI (33.5 to 50.1). These were subdivided as follows; Migraine; Prevalence 3.6 95% CI (1.1 to 6.1) Age adjusted prevalence 3.8 95% CI (1.2 to 6.3). Tension type headaches; Prevalence 16.1 95% CI (10.9 to 21.4) Age adjusted prevalence 16.1 95% CI (10.9 to 21.3). Headache secondary to disorders of the neck; Prevalence 15.2 95% CI (10.2 to 20.3) Age adjusted prevalence 15.5 95% CI (10.4 to 20.7). Trigeminal Neuralgia; Prevalence 0.45 95% CI (-0.43 to 1.33) Age adjusted prevalence 0.46 95% CI (-0.43 to 1.35).

The IHS ICHD-2[178] is the international gold-standard classification for use in epidemiological studies to allow comparison of findings and is the standard for defining the different types of headaches found in this study. However in order to ensure headaches identified were "disabling neurological disorders" and did not as a group make the second stage of the prevalence study unfeasible, I also added the caveat that headaches had to be recurrent (present in the last year) and had to affect the patient's ability to do their activities of daily living. I therefore did not use the strict definition of when a headache becomes a "headache disorder" as defined by the WHO and IHS;

- "A current or active headache disorder" is one that has been "symptomatic at least once within the last year".
- "A chronic headache disorder" is headaches occurring in patients on 15+ days per month. This is often generally called Chronic Daily Headache (CDH) [174, 178].

Most headache epidemiological studies provide 1-year prevalence estimates, i.e. headache occurring during the last year. In some studies, participants were asked about headache during their whole life (life-time prevalence). Our study does provide 1 year prevalence rates however the additional caveats (although informative about disabling headache) may have led to lower estimates of the prevalence of headache in

this population and as a result complicate comparison with other studies. Diagnoses made were purely clinical and although this is a limitation, it is in keeping with most epidemiological studies of headache and the recommended management of the majority of headache disorders.

Globally, the percentages of the adult population with a current headache disorder are; for general headache 46%-75%, migraine 11% (with male to female ratio 1:3, apparently hormonally driven), TTH 42% (on average but >70% in some populations [181]) and CDH 3% (range 1.0-4%) [174, 180]. Life-time prevalence, are as expected, higher: at 66% for general headache, 14% for migraine, 46% for TTH. There are differences in prevalence rates in different continents with general headache prevalence rates of 50% in Asia, Australia, Europe and North America, but markedly lower (20%) in Africa. Migraine is most prevalent in Europe (15%) and least prevalent in Africa (5%). TTH appears to be much more common in Europe (80%) than in Asia or the Americas (20–30%). CDH has a global prevalence of 3.4% and is most common in Central/South America (5%) and least common in Africa (1.7%). These results represent work from many different studies with great variations in size, methodology and quality and this has not been accounted for [180]. The relative contribution to variations in the results of variations in methodology (compared with variations in age, gender distribution, race and continent) has been estimated at around 30% [188].

4.6.3.2.2.1.1 *Comparing the SSA studies with those from the rest of the world: All headaches*

The prevalence rates of all headaches in SSA vary from 4.7-75%. However the highest values of 75% [192] and 51% [194] represent lifetime prevalence, the former in a biased sample of students and the latter using the AHC diagnostic criteria. 1 year prevalence of 23.7% is reported by Matuja et al [191] but this is in a biased sample of students and workers and used the AHC diagnostic criteria. The lower values 4.7-23.1% represent 1 year prevalence rates from community populations and are therefore more comparable to worldwide epidemiological studies [187, 195, 196]. The prevalence of all headaches in this study was 4.2% (age adjusted), this lower value is likely to be as a direct result of my definition of headache and may therefore

underestimate the morbidity in this area. In Asian and South-American studies with comparable methods gave 1-year prevalence rates of all headaches that ranged from 28.5 to 78.8% [180]. In European and North-American studies, 1-year prevalence rates of headache varied between 13.4 and 87.3% [180]. Headache in general appears to be a highly prevalent disorder worldwide, but seems to be least common in Africa.

4.6.3.2.2.1.2 *Comparing the SSA studies with those from the rest of the world: TTH*

In SSA 6 studies have recorded the prevalence of TTH [187, 189-191, 195, 205]. Overall the prevalence varied from 0.7-35.8%. However there was great variation in the methodology precluding easy comparison. 2 of these studies were from clinic populations and recorded that TTH accounted for 19-22% of consultations in headache clinics [189, 190]. One of the studies was in a pre-selected population observing that TTH has a 1 year prevalence of 35.8% in students and workers aged 20-40 [191]. One of the studies used AHC diagnostic criteria and did not include subjects with rare episodes reported a 1 year prevalence of 0.7% [195]. It is questionable whether reasonable comparison between the two classifications is possible. The most universally comparable results came from the studies performed by Tekle-Haimanot et al. [187] and Winkler et al [205] they reported a 1 year prevalence of TTH of 1.7% and 7.0% respectively using the IHS criteria, although Tekle-Haimanot's results only represented those with CTTH. This study found the prevalence rates of TTH to be 1.6% (age adjusted), it is likely that this also represents CTTH and is therefore directly comparable with Tekle-Haimanot et al's study, however, my interpretation of the IHS criteria complicates comparison and is one of the limitations of my headache data.

South-American and Asian studies have published lifetime and 1-year prevalence rates of TTH using IHS guidelines ranging from 12.9 to 66.2% [180]. In Europe and North America the following prevalence rates for TTH were calculated: Finland 35% [477], Denmark 74% [181], Croatia 34.8% [478], Germany 38.3% (TTH, IHS 2.3: 0.3%; [198] and USA 40.5% (ETTH 38.3%, CTTH 2.2%; [180]. It has to be taken into consideration that in Croatia [478] and Germany [198] lifetime prevalence were calculated, whereas in all other studies 1 year prevalence rates were calculated and this complicates

comparison. The prevalence rates of comparable studies in SSA are lower than those found in Europe and the USA and Asia and South America.

4.6.3.2.2.1.3 *Comparing the SSA studies with those from the rest of the world: Migraine*

Migraine patients are said to make up 34.0-42.4% of clinic patients presenting with headache in SSA [189, 190]. Migraine community prevalence data from SSA reports rates varying from 3.0%-16.7%. However the higher prevalence rates of 7.3, 11.3 and 16.7 are in student and young adult populations [191, 192, 207]. Those from unbiased community populations range from 3.0-6.9%. Those prevalence surveys of migraine headache from African countries applying the IHS criteria reported prevalence rates at a low level ranging from 3.0% in Ethiopia [187] up to 4.3% in northern [205] and 5.0% in southern Tanzania [196].

It is possible to compare the prevalence rates from SSA with those from the rest of the world, however most of the prevalence rates presented from SSA are not age adjusted. Winkler et al [205] did however age adjust their figures to the world standard to allow ease of comparison, this also demonstrates the difference this calculation makes as their rates increased from 4.3% to 6.0% using the WHO world standard [462]. Those studies that calculated 1 year prevalence using the IHS criteria for migraine from Europe and North America had results ranging from 9.5% in the USA to 17.0% in Sweden[199, 479-484]. Even after excluding children and adolescents from the African studies and age adjusting where possible the prevalence rates are still lower in SSA than in the west.

This study found the age adjusted prevalence of migraine to be 0.4%, this is likely to represent the age of the population studied, with the majority of migraineurs possibly dying prior to reaching old age, this is discussed in more detail below. In addition the definition of headache used may underestimate the morbidity migraine represents to our population. However if someone truly suffers from migraine it is likely that it is recurrent and will affect the patient's ability to perform their activities of daily living.

4.6.3.2.2.1.4 *Comparing the SSA studies with those from the rest of the world: Causation*

It is mostly speculation that informs us why rates of headaches in Africa do appear to be lower than the rest of the world, despite methodological differences in epidemiological studies. The following factors appear to play a part;

Stewart et al. [199] performed a meta-analysis of 23 studies and a linear regression model. They found that 70.6% of the variation in headache prevalence could be explained by sex and age**.** Since the highest incidence of migraine is observed in the third and fourth decades of life a substantially younger population is often represented in African studies and a large proportion of 'future migraineurs' might not survive past childhood. Therefore, where possible population structures should be taken into account when comparing migraine prevalence in Africa and western countries, however in very few of the African studies are age adjusted prevalence rates presented [196].

Headaches may be perceived as less important in rural Africa and recall of headaches may be less reliable. This could be the consequence of higher pain thresholds, or the fact that headache is less noticed or perceived as a normal occurrence. In the majority of African studies it was the head of the household who was the main informant of the presence of headaches and to report what might be perceived to be minor ailments to the household head may be deemed unacceptable in this culture. In short it may be in SSA that the socio-economical weight of other diseases makes it culturally unacceptable to mention headaches.

Genetic differences may explain variations, especially with regard to migraine. In western studies racial differences are found in prevalence with higher rates found in Whites compared with African Americans [199, 484, 485]. Stewart et al (1996) compared the prevalence of migraine among Caucasians, African Americans, and Asian Americans in the United States in attempt to determine if differences among races reported in international prevalence studies are as a result of cultural, environmental, or methodological factors or if also present in one standard multi-race population, are

actually due to genetic factors. The authors conducted a large study of 12,328 randomly selected individuals in Baltimore County, Maryland aged 18-65 they used telephone interview only. Migraine diagnoses were assigned using International Headache Society criteria. In women, migraine prevalence was significantly higher in Caucasians (20.4%) than in African (16.2%) or Asian (9.2%) Americans. A similar pattern was observed among men (8.6%, 7.2%, and 4.2%). African Americans were less likely to report nausea or vomiting with their attacks, but more likely to report higher levels of headache pain but less disability. While differences in socioeconomic status, diet, and symptom reporting were not taken into account and may contribute to differences in estimated prevalence (especially if those of African descent are less likely to see their migraine as disabling and are less likely to report classic features to aid diagnosis), the authors suggest that race-related differences in genetic vulnerability to migraine are more likely to predominate as an explanatory factor. It is thought that inherited factors may influence susceptibility to migraine such as variation in neurotransmitter metabolism and receptors [485]. Stewart et al[199] suggested that the higher platelet level of the tyramine conjugating enzyme phenolsulfotransferase in African-Americans compared with Whites may protect against migraine by metabolizing suspected dietary triggers.

Environmental factors may also have a role, the exposure to environmental triggers for migraine, particularly dietary factors may be less in SSA.

It is likely that lifestyle factors have a particular role in the type of headaches found in my study population. There were a significant number of people with headaches secondary to disorders of the neck 1.6% (age adjusted) and this is likely to represent the impact of years of manual labour and carrying heavy objects on their heads. Unfortunately there is no similar data published for comparison.

In summary environmental factors, genetic differences or cultural diversity in the reporting of pain may explain the apparent difference in headache susceptibility in African and Western countries, and should be the topic of future research [205]

Outside these factors prevalence differences could be explained by varying sampling methods and diagnostic criteria.

4.6.3.2.2.1.5 *Gender Specific Prevalence rates*

All headaches and more specifically migraine and TTH have found to be more common in women than men in SSA [191, 195, 196, 205] and the rest of the world[481, 486-492]. The male to female ratio of the prevalence of migraine is 1:3 in studies from both SSA and the rest of the world [196, 205]. Reasons for this are unclear but the influence of hormones has been suggested [181].

4.6.3.2.2.1.6 *Age Specific Prevalence rates*

The age-specific peak prevalence rate of all types of headache was found in the fifth decade of life in 2 studies from Tanzania [196, 205] and one study from Puerto Rico [488]. Other studies have shown peak prevalence rates at younger ages [186, 194, 195, 481, 490, 492].

Looking more specifically at TTH, Rasmussen et al[181], reports a decrease of prevalence rates of TTH with increasing age. A peak of TTH between 20 and 55 years has been reported in other studies [186, 205, 477, 487, 493-496]. I found the prevalence rate of overall TTH increased with increasing age in both genders this is in agreement with studies from Saudi Arabia and Singapore where more TTH was found in elderly people [486, 497]. However, results of these studies refer to lifetime prevalence and could be explained as cumulative effect with increasing age. Winkler et al [205] conclude that in Tanzanian rural communities TTH is a disease of elderly people. This indicates that the prevalence of TTH is potentially underestimated in our study, which is likely due to the diagnostic criteria used.

When considering migraine headache prevalence, rates increase rapidly after puberty with a peak between 30 and 60 years in women and 25 and 40 years in men. Subsequently, migraine prevalence decreases with age. A minimum of migraine sufferers has been reported in children and in the elderly [206]. This is in agreement with the low prevalence rates found in our study.

4.6.3.2.2.1.7 *Difficulty in comparing African studies with the rest of the world's data*

As already discussed it is very difficult to compare prevalence results from the SSA studies with the rest of the world's data. Problems include differences in classification and case definition, variations in time periods for prevalence study methodology and population samples as well as the influence of socio-demographic and psycho-social factors [205].

4.6.3.2.2.1.8 *Limitations of African work in general*

The information recorded above has demonstrated how limited data from SSA is on the prevalence of headaches and how difficult it is to compare prevalence rates with the rest of the world. Firstly there is a very small number of studies carried out in only 6 countries. A major problem inherent to these studies is the use of different headache classifications. Very few series used the Diagnostic Criteria and Classification of the IHS, the established gold-standard [187, 196, 204-206]. Often they have been limited to small and narrowly defined samples, such as students or clinical cases [189-192]. More studies are needed that focus on the general population and use the IHS criteria. My study may have added to the data on headaches from SSA in the elderly, however extension of the diagnostic criteria used does limit easy comparison and potentially underestimates the impact of headache on the elderly population when interpreted at face value.

4.6.3.2.2.1.9 *Headaches in the elderly*

Stovner et al's recent review article highlight's the five prevalence studies that have been performed to describe headaches specifically in the elderly. Two were performed in low income countries in Asia, whereas the remaining 3 were performed in high income countries in Europe and North America. They focussed on the age range of 65 years and over, with the exception of the Thai study which examined the over 60 population [498]. These studies represent the studies performed in the elderly community population worldwide, they contain potentially comparable data to my own. The features of these studies are presented below**;**

Table 4.2: The Prevalence of headaches in the elderly worldwide

Country 1st author year ref	Population	Diagnostic criteria used	Method	N	Age years	Prevalence period	Headache prevalence %	Migraine total %	Classical (with aura) %	Common (without aura)%	TTH %	Chronic headache %
China Wang 1997 [499]	Community rural	his	Personal Interview	1533	65+	1 year	38.0	3.0				3.9
Thailand Srikiatkhacho 1991 [498]	Instituationalised elderly	?	Personal Interview	241	61+	1 year	54.8					
Italy Prencipe 2001 [500]	Community rural	his	Personal Interview	833	65+	1 year	51.0 (some participants had migraine and TTH)	11.0			44.5	4.4

Italy Camarda 2003 [501]	Community rural	IHS	Personal Interview	1031	65+	1 year	21.8	4.6			16.0	
USA Cook 1989 [502]	Community rural	?	Personal Interview	3811	65+	1 year	45.0					

IHS: International Headache Society, All prevalence rates are crude unless otherwise stated

These studies support my conclusions that TTH was more problematic in the elderly population than migraine.

4.6.3.2.2.1.10 *Discussion of the Headache literature in Summary*

At least half of the world's population lives in countries where headache burden is partially or completely unknown. Headache burden is thought to vary considerably worldwide due to genetics, climate, socioeconomics, lifestyle and co morbidities. This is suggested by current studies but methodological problems and variation in cultural attitudes to headaches complicate interpretation. The WHO state it is a priority to document prevalence worldwide accurately using gold-standard methods and the IHS diagnostic criteria. I hope that my study does add to the available data on the prevalence of headache in the elderly population but recognise its limitations particularly with relation to the exact definition of headache used. It does however reinforce that TTH is more problematic than migraine in this age group and that headaches secondary to musculoskeletal pathology need to be considered and managed in populations where manual labour is the predominant occupation.

Headache disorders are prevalent, disabling and largely treatable, but under-recognized, under-diagnosed and under-treated. Headache burdens, both individual and societal, persist with financial costs to society through lost productivity far outweighing any health-care expenditure required to be spent in any country. Health care for headache must be improved, to include supply of medications, improvement of services and very importantly education at multiple levels to achieve this.

4.6.3.2.2.2 *Stroke*

The prevalence of stroke worldwide is said to range from 0.5% to >1% in those aged over 65 years in developed countries. Generally the prevalence in SSA is reported to be half that of developed countries, however with demographic transition this is thought to change [56, 503].

My crude prevalence rate of stroke was 24.2/1000 95% CI (17.8 to 30.6) and the age adjusted prevalence was 23.0 95% CI (16.8 to 29.2). They are lower than in equivalent age groups in developed countries, we can speculate that this is due to an increased mortality rate; the recently updated Global burden of disease study estimated that over 80% of stroke deaths occur in low-income and middle-income countries [215, 216, 389].

My prevalence rates are relatively high for SSA, and I feel to a certain extent this reflects the robust methodology used and the good case ascertainment that resulted. Worthy of note is that I identified all cases previously identified from stroke incidence and prevalence studies in the Hai District DSS [34, 213]. Improved case ascertainment may have also have resulted from the education of the community with regard to stroke this could have resulted from these two previous epidemiological surveys. As a result of these factors it may be that our estimate offers a more accurate reflection of the prevalence of stroke in this setting than some previous studies. It is important to recognise however that the main reason for our higher prevalence rates is likely to be due to the elderly nature of the population studied.

It is worth reflecting that many reported stroke prevalence rates represent previous stroke with or without residual deficit. Our study specifically looked for previous stroke with residual deficit given the notorious inaccuracy of a patient's history in this setting. This does however have the potential to complicate comparison with other studies by underestimating stroke prevalence and the potential short term burden of stroke in those that subsequently recover from their symptoms and signs. It does however reflect the true burden of long term disabling stroke in this community.

My prevalence rates are compared with the current literature in more detail below, specifically population-based studies from SSA that investigated the prevalence of all types of stroke, recent publications specific to stroke in the elderly population and worldwide review articles. Stroke prevalence studies, particularly in demographic

surveillance sites with a known denominator population, have arguably provided the most accurate and up-to-date measures of stroke burden in SSA. It is however important to recognise their limitations which include problematic retrospective diagnosis, underestimation of burden because of case fatalities and confusion with co morbidities such as arthritis and dementia, and methodological differences complicating worldwide comparison. The methodology used in this study is the gold standard for documenting the prevalence of stroke in low income countries and therefore the data is reliable, this is not the case for many studies performed.

Many studies from high income countries now report incidence (methodology that is difficult to perform in SSA) and this further complicates data comparison.

The surveillance of stroke prevalence in SSA began in the 1980s, with landmark studies in Nigeria and Ethiopia. In Nigeria and Ethiopia the prevalence was found to be between 15-68.4/100,000[3, 5, 25, 99]. There were two main limitations of these studies. Firstly their size, which at initial review appear more than adequate, but when one considers that typically 44% of the population in SSA was less than 15 years old [216] then the representation of the older age groups (those predominately affected by stroke) is limited, this particularly complicates any comparison to my data. Secondly the diagnostic criteria or even the types of stroke sought was not detailed, therefore conclusions on the accuracy of diagnoses are difficult to make. The low prevalence rates are likely to reflect, low stroke incidence that results from a young population that died before they were affected by stroke disease and high case fatality from stroke and therefore failure to detect cases.

Walker et al [34] performed the largest study (n=148 135) to date of the prevalence of stroke in SSA in the Hai district DSS (the study population that is the focus of this thesis). The authors limited their study to only detect disabling hemiplegic stroke, which although practical, limits the comparability of the data with the rest of the world and with my data. The crude prevalence of stroke in the whole population was 73/100,000. Age

standardisation was performed to the Segi world population, it gave prevalence of disability resulting from stroke of 154/100 000 in men and 114/100 000 in women over 15 years of age. The crude prevalence rates for those aged 65 and over were 876/100,000 (975/100,000 for men and 786/100,000 for women). My prevalence rates 2300/100,000 were significantly higher, probably because our population were slightly older (aged 70 years and over), Walker et al found the median age of patients was 70 years old and the median age at first stroke was 65, which suggests that studying even a slightly older population would have a significant impact. The difference could also be explained by my methodology that detected all types of stroke. Walker et al concluded that prevalence of disabling hemiplegic stroke was low in comparison to high income countries (age standardised rates for stroke with residual disability was approximately half found by previous studies in high income countries), they felt this was mainly explained by the age structure of the population with <6% of participants being aged 65 and over. Mortality rates may have also been higher.

The Southern Africa Stroke Prevention Initiative (SASPI) team [219]performed a very similar study to Walker et al in rural South Africa. The age adjusted prevalence of hemiplegic stroke was 290/100 000 in people over the age of 15 years. The crude prevalence of those aged 65 years and older was 1490/100,000, more in keeping with my prevalence rates.

Gradual health transition might explain difference in the prevalence of stroke in these most recent robust prevalence studies from SSA, in comparison to each other and in comparison to older studies. Firstly the lifestyle risk factors of South Africans may be higher than Tanzanians, stroke risk factors have recently been shown to be common in all population groups in South Africa [220]. Secondly Tanzanians may have a higher case fatality than South Africans in rural areas.

The age-standardized prevalence of stroke in high-income countries was reported in a recent review to range from 461 to 733/100,000. The largest of these came from

Auckland, New Zealand, where age adjusted prevalence of stroke was found to be 833/100,000 [221].

The prevalence of stroke in Tanzania is half that of South Africa which is in turn a third of that found in Auckland. Methodological differences cannot be excluded as an explanation of the differences. The Auckland Stroke Study followed on from incidence studies and therefore probably recorded mild strokes which would not have been picked up by either of the SSA studies. However both sub-Saharan African countries may have a lower prevalence of stroke when compared with New Zealand, because of a lower incidence of stroke and higher mortality and case mortality [216].

Cossi et al's[223] study from Benin is the most up-to-date well designed stroke prevalence study from SSA. The authors demonstrated age adjusted prevalence rates of 870/100,000, higher than ever previously recorded in SSA which highlighted the increased burden that stroke represents. The mean age of the patients at onset was 56 +/- 13 years.

The prevalence of disabling stroke in sub-Saharan Africa has also been reported by the studies described above and this has been found to be at least as high as in high-income areas. This potentially indicates that the low overall prevalence of stroke (just under half that found in high income regions) may reflect that non-disabling strokes are not identified easily by epidemiological surveys in SSA.

Community based incidence studies with follow-up are required to determine whether the low overall prevalence of stroke results from low incidence or high case fatality or a combination of the two. As risk factors for vascular disease increase, and the populations age, so the burden of vascular disease will certainly increase in SSA. Indeed, without intervention, stroke and heart-disease-related deaths in developing countries are expected to increase from 3 million in 1998 to 5 million in 2020 [216]. The burden of stroke is likely to become epidemic unless interventions are put in place.

4.6.3.2.2.3 *Epilepsy*

This study found the crude prevalence of epilepsy to be 4.5/1000 95% CI (1.7 to 7.3) and the age adjusted prevalence to be 4.4/1000 95% CI (1.7 to 7.2). These rates are lower than the majority of reports from the whole population in low income countries and more in keeping with reports from high income countries. It is likely that this reflects the burden of epilepsy in low income countries which still remains in childhood and early adulthood rather than in the elderly as a result of high mortality. However as the population in developing countries continues to age this part of the community will contribute more to the epilepsy morbidity burden, especially with the increased survival from conditions that predispose to epilepsy, such as stroke disease.

The prevalence of active epilepsy in people of all ages from Europe and North America is 5–8 per 1000 [318]. Higher rates have been reported in studies from Asia, South and Central America and particularly from SSA. The median prevalence of epilepsy in SSA has been reported as 14-15/1000 with an inter-quartile range of 10-21 [294, 295].That is not to say that the rates were consistent, rates were highly varied from 2.9 to 75 per 1000, higher rates were seen in children and young adults, rural areas, and studies with small population sizes and older studies. Therefore, the prevalence of epilepsy in the whole population of sub-Saharan Africa cannot be generalised [294]. Relative contributions of causes of epilepsy are difficult to determine given the limited case-control data, however it is suggested that infections particularly cysticercosis, cause the majority of cases. As populations age non-infective causes such as stroke disease will start to make an impact [294, 295].

Prevalence estimates vary widely from country to country in SSA. This may be false and due to methodological problems or it could be true. I have had to consider these "false factors" when interpreting my results and comparing them with other studies and so the strengths and limitations of my study design are highlighted.

4.6.3.2.2.3.1 *False Factors*

4.6.3.2.2.3.1.1 *Generalised Methodology*

There are many estimates of the burden of epilepsy using hospital based studies, including 2 recently published in northern Tanzania by the same group of authors. They conclude that epileptic seizures account for 3% of all hospital admissions, 27% of neurological diagnoses [299] and febrile seizures and epileptic seizures account for 20.6% and 13.9% of admissions with impairment of consciousness respectively[300]. These cannot however represent true prevalence given the majority of the population in low income countries do not present to hospital for reasons related to geography, finance and health beliefs. Comparison to my prevalence figures is impossible.

Preux and Druet-Cabanac's 2005 review[294], only looked at door-to-door surveys, acknowledging any methodology, other than this gold-standard, will lead to misleading results, the authors observed that studies with data from only medical registries or passive ascertainment systems gave lower estimates and a falsely reassuring picture of the true burden of disease.

My study used mostly the 2 phased epidemiological approach and to add to the robust nature of the prevalence data, multiple other case finding methods were used as suggested by Preux and Druet-Cabanac [294] and Debrock et al [302] when performing epilepsy surveys. Unfortunately it was not possible to perform the capture-recapture method which may have ensured the data was even more complete.

4.6.3.2.2.3.1.2 *Under-reporting due to stigma*

The Stigma related to epilepsy adds an extra complexity to the derivation of accurate prevalence data as this prevents patients coming forwards even when directly questioned. This is particularly true when surrogates are questioned such as the head of the household and therefore this was avoided in my study [295, 319, 320].

4.6.3.2.2.3.1.3 *Screening tools used*

Most studies that have been performed have focussed on convulsive epilepsies[295], given the ease to which surveys can reliably detect them and the increased morbidity that they represent to the patient. Unfortunately as a result there are limited accurate estimates of non-convulsive epilepsies (difficult to accurately detect through simple questioning and clinical examination alone) and reported prevalence rates should be accepted to underestimate the true burden of disease. This exclusion of non-convulsive seizures (along with under-reporting levels secondary to stigma) is said to underestimate the prevalence of epilepsy by two to four times [295, 319, 320].This is true of my study and the majority of studies reported from SSA.

There are standardised questionnaires (the Limoges questionnaire) for the accurate collection of epilepsy prevalence data. However unfortunately given their time consuming nature and that my study focussed on all neurological disorders rather than just epilepsy, it was not possible to use this questionnaire for my study. Unfortunately this limits the comparability of my results with some of the robust studies from SSA, namely those from Benin [302, 308], Burkina-Faso [303], Burundi [304], Cameroon [305], Mali [504], Central African Republic [307].

4.6.3.2.2.3.1.4 *Classifications used*

The use of different terminologies to classify seizures and epilepsy also hinders study comparison and with this in mind my study utilised the standard ILAE classification [294, 295].

4.6.3.2.2.3.2 *True Factors*

4.6.3.2.2.3.2.1 *Different samples of populations studied and risk factors*

Consistent findings from epidemiologic studies of epilepsy in developing countries including SSA indicate that the prevalence is higher in rural than urban areas of the same country [323, 324]. The higher prevalence of epilepsy in rural areas might be caused by an increase in the incidence of risk factors. However, many people who develop epilepsy do not migrate to urban areas for work, or if they do develop epilepsy whilst in urban areas, individuals might lose their jobs and return to their rural homes [351].

In some sub-Saharan Africa areas, the consanguinity is reported to be very high e.g. some areas in Mali, 96% [504]. The stigmatization of PWE potentially forces them to intermarry thereby increasing the genetic transmission of epilepsy and prevalence rates in pockets of the community.

Ngugi et al[331] quantify that over 50% of the variation in the global estimates of the lifetime prevalence of epilepsy can be attributed to the differences between studies in rural and urban areas, between children and adults, and in the size of the denominator in the study

The prevalence of epilepsy has been observed to be variable in the same country and ethnic community, even when the same methodology has been utilised. Two Nigerian studies, used the same protocol to investigate two population groups from the same community living 20 km apart. They observed very different results 5.3/1000 in Igbo-Ora [25] and 37/1000 in Aiyété [327]. The researchers felt this highlighted the impact of risk factors on prevalence particularly sanitary conditions, neonatal infections and birth trauma. In contrast the prevalence may be very similar, as observed in Togo [314, 328-330]

The true prevalence of epilepsy in SSA is still hotly debated. A few large-scale studies showed prevalence nearer that found in industrialised countries and this is in line with my own findings. The question is: have these studies underestimated the prevalence because of non-ascertainment of cases or are the smaller scale studies misleading and represent genetic influences of inbreeding and consanguinity, consequences of specific aetiological factors or over inclusion of provoked seizures. There is also the possibility that the discrepancy lies in factors specific to different geographic zones in sub-Saharan Africa. In the case of my study the discrepancy is likely to be purely related to the age of the population studied [294].

The section below discusses the recent prevalence studies in SSA in more detail and demonstrates what meaningful conclusions can be drawn from their data compared to my own:

Edwards et al [319] performed a very robust and large scale study of the prevalence of epilepsy in a poor rural area on the coast of Kenya. They assessed those people aged 6 years and older of which only 3% of the population were aged 65 or older. Thus their population is not directly comparable with the population I studied. Limitations of the data presented include use of a surrogate (the head of the household was questioned) and the lack of validation of the screening questions in adults. Strengths include the robust study design, verification of diagnosis by neurologists and use of the ILAE classification, all which allow direct comparison to my data.

The authors reported the prevalence of active convulsive epilepsy and therefore non-convulsive seizures were excluded from the prevalence figures. Although this is generally a limitation it allows comparison to my prevalence rates which were very similar. The overall crude prevalence of active convulsive epilepsy was 2·9 per 1000 (95% CI 2·6–3·2); after adjustment for non-response and sensitivity of the questionnaire, prevalence was 4·5 per 1000 (4·1–4·9). The prevalence of those aged 50 and over was 2.1 (95% CI 1.7-2.7). Age adjusted prevalence rates were not presented.

Hunter et al [333] present the findings from their very large 2009 community based prevalence study performed in the same demographic surveillance site as is the subject of this thesis. Robust methodology supports their conclusions, although there were a number of limitations that the authors acknowledge; strengths and weaknesses of the study are described below:

The authors utilised a previously validated questionnaire and validated it further in a small Tanzanian hospital population, it achieved a sensitivity of 100% and specificity of 54.5%. A large and unbiased adult population of 103,026 were assessed with the gold standard 2 phased methodology. Additional case finding methodology was also used to pick up cases which adds to the validity of the prevalence rates but calls into question the sensitivity of the questionnaire as a further 82 cases were found in this way.

ILAE classification was used, directly comparable with my data and use of CT, MRI, and verification by neurologists added to the robust nature of each diagnosis.

The age-standardised prevalence (to the WHO standard population allows ease of comparison) of convulsive epilepsy was 2.91/1000 adults (95% CI 2.58–3.24); the crude prevalence adjusted for non-response was 3.84/1000 adults (95% CI 3.45–4.20).
The crude prevalence of those aged 60 years and older was found to be 1.17/1000 (95% CI 0.66-1.68) Unfortunately the authors were not able to assess nearly one third of those who responded positively to the screening questionnaire, an inability to trace these individuals may be related to stigma and may indicate why the prevalence rate presented is lower than the majority of studies from SSA and specifically in the older age groups lower than I found in my study.

Prevalence rates of epilepsy were reported recently from 3 villages in Burkina Faso from a study conducted in 2007 of 888 individuals aged 7 years and over [335]. However due to the rather flawed methodology the results need to be interpreted with caution. The

selection of villages was based on pig rearing practices and hearsay that the villages had a high prevalence of epilepsy and therefore the authors admit that the prevalence rates may not represent that from the rest of the country.

The authors used a previously validated questionnaire (however it was not adapted for or validated in this community) and the ILAE criteria for diagnosis. However diagnoses were not verified by a neurologist. 14/70 people who screened positive were not examined by the physician for various reasons, thus cases may have been missed. The prevalence of epilepsy was 4.5% (95% CI 3.3%-6.0%). The prevalence of active epilepsy was 3.9% (95% CI = 2.8%; 5.4%). The authors acknowledge that their estimates are higher than those reported in Burkina Faso study in 1993 (1.1%; 95% CI 0.9%-1.2%). The methodology of this study was more robust, it involved random selection of 18 villages in 2 provinces and therefore it may be that the former study's prevalence figures are more representative of the entire country. However it may also be that there is a true difference in prevalence of epilepsy between the investigated areas and over the nearly 20-year difference between the studies.

As described above the key limitations of the studies by myself, Edwards et al[319], Hunter et al[333]and Nitiema et al[335] that hamper comparison with other findings are the exclusion of people with non-convulsive epilepsy (non intentionally in the case of Hunter et al). In high income countries partial epilepsies (with focal onset) are more common than generalised onset epileptic disorders or account for at least 50% of all epileptic disorders [320, 334]. If this pattern also applies in Africa an estimated total prevalence would be 6-10 per 1000 population.

Winkler et al [315] performed a study of 7,399 people reporting the prevalence of epilepsy in rural Tanzania, they used unbiased methodology. Strengths included use of a validated questionnaire with high sensitivity and specificity, the use of ILAE criteria and verification of diagnoses by a neurologist. The prevalence rate was age standardised to the WHO standard population and was 13.2/1,000. The prevalence rate of active epilepsy

was 9.1/1,000. The crude prevalence rate of active epilepsy for those aged 55+ was 6.0/1000.

Crepin et al [308] performed a well executed community prevalence study in amongst 11,668 individuals in a rural area of Benin. A questionnaire (the Limoges) validated for epilepsy in tropical countries was used but it was not validated further in this specific population. The entirety of a population was screened with a 94% ascertainment so no bias was produced through sampling errors. The initial screen was performed by trained local physicians and confirmation of cases in the second phase was performed by a neurologist. Final diagnosis was purely clinical but took into account a collateral history and internationally recognised criteria. All types of seizures were included adding to the comparability of their results. The prevalence of epilepsy was found to be 12.7/1000; 95% CI: 10.8 – 14.8. The median number of seizures per year was 12. Both the high number of seizures per year and the fact that the majority of the cases were convulsive indicates that the prevalence of epilepsy may have been underestimated.

4.6.3.2.2.3.2.2 *Age and epilepsy*

There is a marked difference in the age of onset of epilepsy in low income countries in comparison to high. The latter has a bimodal distribution [316] with peaks of incidence in childhood and those aged over 65. In the former it is generally understood that incidence is increased in children and young adults. Age at seizure onset is reported in a few studies but is usually susceptible to recall bias. When available, seizure onset was before age 20 years in more than 60% of cases. This young incidence results from infection and trauma. However it is worth noting especially for this thesis with its focus on the older population, that studies in the older age groups from SSA are limited. As the population of developing countries continues to age and the prevalence of NCDs such as stroke increases as will the burden of epilepsy in these age groups, again demonstrating the impact that the "double burden" of disease will have on SSA [25, 295, 311, 327, 341]. This data explains why my prevalence figures are difficult to compare with other prevalence figures available.

4.6.3.2.2.3.2.3 *Prevalence potentially underestimates burden due to high mortality from epilepsy*

The mortality associated with epilepsy in low-income countries is substantially higher than in high-income countries. Mostly this is felt to be a consequence of untreated epilepsy resulting in falls or status epileptics. However this is another under-researched area [295]. This could explain the relatively low prevalence rates found in my study as the majority of those with epilepsy may have died before reaching old age.

4.6.3.2.2.3.3 Discussion of the epilepsy literature in summary

In conclusion my prevalence rates are similar to those found by other authors in SSA who have performed similar robust studies. The main limiting factor for direct comparison is the age of the individuals I studied along with the identification of only convulsive epilepsies and the small numbers of cases identified in association with the modest sample screened. In general reports of the prevalence of epilepsy are highly varied and need to be interpreted in the context of the methodology used.

4.6.3.2.3 *Systemic Atrophies/Degenerative Diseases affecting the Central Nervous System*

4.6.3.2.3.1 *Motor Neurone Disease*

Studies in developed countries reveal a prevalence of 0.6 to 1.0/1000 [46, 155]. Studies in SSA have demonstrated a prevalence of 0.05 to 0.15/1000 but they are dated and their methodology is questionable [3, 5]. My crude prevalence was 0.90/1000 95% CI (0 to 2.14) and the age adjusted prevalence was 0.96/1000 95% CI (0 to 2.25). This is in keeping with this limited number of studies but the conclusions that can be drawn are limited by the size of the main study population and the fact that there were only 2 patients found.

4.6.3.2.4 *Injury resulting in CNS dysfunction*

4.6.3.2.4.1 *Spinal Cord Pathology*

There are very few community data regarding the prevalence of spinal cord pathology in SSA. Tekle-Haimanot et al report that post traumatic spinal cord pathology has a prevalence of 0.03/1000 but this was published in 1988 [5]. All other studies are hospital based and therefore it is difficult to extrapolate meaningful results that reflect the disease burden in the community. My crude prevalence rate was 2.2/1000 95% CI (0.3 to 4.2) and our age adjusted prevalence rate was 1.9/1000 95% CI (0.1 to 3.7).

4.6.3.3 *Peripheral Nervous System Disorders*

4.6.3.3.1 *Polyneuropathies*

Early prevalence studies from developed countries report rates anywhere between 5.5 to 16.4/1000 [399, 505]. A more up to date review article by Hughes et al in 2001 reports prevalence rates between 24 and 80/1000 and states that prevalence increases with age [506]. Mold et al performed a prevalence study in the US community with general practice records in 2000. They looked specifically at the older age groups stating that the prevalence was 310/1000 in those aged 65 and over. The prevalence did increase with age, with 260/1000 affected between the ages of 65 and 74, 360/1000 between the ages of 75 and 84 and 540/1000 for those aged 85 years and older [507].

The data from developing countries is not as comprehensive. Community studies from Ethiopia and Nigeria are dated but reveal rates of 1.5 and 2.1/1000 respectively [3, 5]. A community based study from India in the 1990s reported a prevalence of 23.84/1000 [508]. Variation may be due to methodological and diagnostic criteria.

Evidently the prevalence rates vary widely. My crude prevalence rate of 18.8/1000 95% CI (13.2 to 24.5) and age adjusted rate of 18.6/1000 95% CI (13.0 to 24.2) is in the middle of these figures. Methodology, diagnostic criteria and causative factors may all explain the wide differences. We did not include patients with “tingling” or paraesthesia alone and stated that they needed to have a loss of at least one modality of sensation for diagnosis. This allowed simple clinical confirmation of the diagnosis using examination techniques. To Include patients with paraesthesia alone relied on histories and was open to error due to translation difficulty. In Swahili there are limited words for symptoms and paraesthesia or tingling can often be reported when the patient actually means pain.

4.6.3.3.2 *Nerve, Nerve root and plexus disorders*

The prevalence of Bells palsy in the literature is reported as between 0.13 and 1.2/1000 [5, 46]. The prevalence of peripheral nerve lesions is reported as anywhere between 0.62 to 144/1000 depending on the diagnostic criteria with the higher figure reflecting even mild symptoms of carpal tunnel syndrome in a community population [3, 46, 155, 509, 510].

The prevalence figures I found are as follows and are in keeping with the current literature. Cranial nerve pathology had a crude prevalence of 6.3/1000 95% CI (3.0 to 9.6) and an age adjusted prevalence of 5.7/1000 95% CI (2.6 to 8.8). Upper limb mononeuropathies and polyneuropathies had a crude prevalence of 6.3/1000 95% CI (3.0 to 9.6) and an age adjusted prevalence of 5.7/1000 95% CI (2.6 to 8.8). Lower limb mononeuropathies and polyneuropathies had a crude prevalence of 2.2/1000 95% CI (0.3 to 4.2) and an age adjusted prevalence of 2.4 95% CI (0.4 to 4.4). Plexus pathology was seen in 1.8/1000 95% CI (0.04 to 3.6) with an age adjusted prevalence of 1.9 95% CI (0.09 to 3.7). Root pathology had a crude prevalence of 1.8/1000 95% CI (0.04 to 3.6) and an age adjusted prevalence of 1.7 95% CI (0.00 to 3.4).

4.6.3.3.3 *Inflammatory/infectious diseases of the peripheral nervous system*

4.6.3.3.3.1 *Polio*

The prevalence of poliomyelitis resulting in disability obviously depends on geographical location and age of the population screened (there is a significant impact from vaccination programmes) but is quoted as between 0.15 to 3.1/1000 [3, 5, 46, 511].

In my population LMN developmental disorders, including polio, had a crude prevalence of 2.2/1000 95% CI (0.3 to 4.2) and an age adjusted prevalence of 2.4 95% CI (0.4 to 4.4).

4.6.3.3.3.2 *Leprosy*

I saw one case of residual neurological deficit as a result of leprosy. The crude prevalence was therefore 0.45/1000 95% CI (0.00 to 1.33) and the age adjusted prevalence was 0.48/1000 95% CI (0.00 to 1.38). Prevalence varies greatly worldwide as a result of eradication programmes that are continuing to be successful. The latest figures from the WHO 2009 global registry quote rates of 0 to 0.2/1000 for Tanzania. These are however for active cases and not residual deficit from cases that have been cured which was the case for my patient [512-514].

4.6.3.3.4 *Diseases of the myoneural junction and muscle*

4.6.3.3.4.1 *Myaesthenia Gravis*

There was 1 person in the main study population with Myaesthenia Gravis. The crude prevalence was therefore 0.45/1000 95% CI (0.00 to 1.33) and the age adjusted prevalence was 0.50/1000 95% CI (0.00 to 1.43). The pattern of disease was bilateral ptosis. Review articles from developed countries quote prevalence rates that vary between 0.015 and 0.18/1000 [515, 516].

4.6.3.3.4.2 *Muscle wasting and atrophy*

It is notoriously difficult to differentiate actual neurological pathology from neurological pathology post fracture and resultant disuse or disuse for another reason, especially when reviewing the patient many years after the primary event. Therefore accurate diagnosis of these patients was difficult and prevalence figures should be interpreted as such. Data from the literature on such patients are lacking.

4.6.4 *Reasons for Variations in prevalence*

4.6.4.1 *Age*

Most published prevalence studies are not specific for the elderly however many neurological conditions are more prevalent in the elderly and an ageing population will further increase their prevalence. This is most notable in Stroke, Parkinson's disease, Essential Tremor and Peripheral Neuropathy. Some conditions, however, are not represented in this age group in developing countries as the mortality rate in this environment preclude sufferers of these conditions from living to old age. Further, if incident cases occur in this age group (in the case of traumatic injury) then subsequent lifespan is short. These include; traumatic spinal injuries, cerebral palsy and hereditary disorders.

4.6.4.2 *Geography-world perspective*

Geographical location does alter the prevalence of Neurological disorders. Some conditions are more prevalent in SSA, e.g. consequences of infectious disease, and some are less prevalent, e.g. Multiple sclerosis. There are limited data on the prevalence of MS in SSA. Data has been reported from the following countries in Africa - South Africa 32/100,000, Egypt 30/100,000, Morocco 20/100,000, Tunisia 15/100,000, Algeria

10/100,000, Nigeria 5/100,000, Cameroon 0.2/100,000, Guinea 0.13/100,000, Senegal 0.05/100,000 and Benin 0/100,000. All the remaining countries in Africa have not reported their prevalence of MS or the data is unknown. This is in comparison to 10 to 150/100,000 in Europe [517]. We found no cases of MS in the Main Study population, this was as expected and we can speculate that this was due to the following reasons;

1. The 70 and over population was studied – if MS had presented in middle age in Africa it is unlikely that a patient will survive to this age
2. MS prevalence is said to be very low in the tropics
3. Diagnostic criteria for MS would make diagnosis in this prevalence study very difficult, histories are often inconsistent and investigation was not available.

4.6.4.3 *Sex*

Headache was found to be more common in women. This is in keeping with the literature [191]. Tremor was less prevalent in women, we can speculate that this is a real difference or is because women are less likely to come forward in the case of tremor as there is a widespread belief that tremor is associated with alcohol excess, a personal attribute looked down upon with respect to women but more readily accepted in men. Additionally any condition that may be thought of as inherited is less likely to be admitted to by women. The mother's and the grandmother's health is judged in this society to be a good predictor of the child's health and ill health will affect affects female offspring's ability to find a husband.

4.6.5. *Cases we may have missed*

148 people refused to take part in the study. No one had the questionnaire performed and then refused to be seen by the RD so no positive responders refused to be seen by the RD. 1 person responded positively then moved out of the area so we were unable to see them; they were consequently recorded as a false positive to ensure that the results of

the screening questionnaire specificity reflected the “worst case scenario” and the prevalence data did not include any cases that could not be accurately confirmed. People with early stage disease may not have answered the screening questionnaire positively. Trying to increase specificity meant asking patients to distinguish pain from weakness this is very difficult and cases may have been missed as a result.

4.6.6. *Accuracy of diagnosis*

The accuracy of our neurological diagnosis was limited due to the fact that there were no available investigations. This does however accurately reflect the majority of clinical encounters in SSA. Validation was performed as much as possible through the use of internationally recognised diagnostic criteria and through discussion of all cases with a consultant neurologist, movement disorder expert or geriatrician, blinding the expert to the provisional diagnosis and where appropriate using scripted video recordings. I do however have to recognise the limitations of purely clinical diagnosis even with recognised diagnostic criteria that are routinely used to make diagnoses without investigation in the UK. This is demonstrated using PD as an example; clinical diagnosis remains the gold standard using the UK PD Society Brain Bank Criteria. However, it still does not confer 100% sensitivity and specificity. Post-mortem remains the conclusive diagnostic test. Previous studies suggest that the best clinical (pre-morbid) diagnostic accuracy of the UK PD Society BBC is around 90% [122].

Further inaccuracies may have resulted from the fact that I did not attempt to undertake either inter or intra-observer reliability studies use of the screening instrument. Each village had one or two NMIs who were based there so that any village differences, if not due to chance, could reflect systematic bias from the use of the tool by the NMI.

Complete blinding of the research doctors was not possible and therefore has the potential to introduce bias. Whilst the RD who assessed patients in the pilot was completely blinded to the results of the tool it was not possible to completely blind the RD in the main study as only those patients that responded positively to the screening tool were seen, however the RD was blinded to which question the participant had responded positively to. In addition it was not possible to blind the consultants who assessed the cases as they were selected on the basis of the presumptive diagnosis.

I therefore acknowledge that there could be some diagnostic inaccuracy and this could in turn result in misdiagnosis in some cases. However I believe that I have taken as many steps as possible to accurately diagnose as many neurological disorders as possible in this population.

4.7 Health seeking behaviour - Level of under diagnosis and the treatment gap in the community

To the best of my knowledge, this is the first published study of rates of diagnosis and treatment for neurological disorders in SSA from within a prevalent population. It reveals that although almost two-thirds of people with neurological disorders had sought treatment for their condition, less than one-tenth were on appropriate treatment.

4.7.1 *Treatment seeking behaviour*

Of the more common disorders, rates of treatment seeking for stroke, epilepsy and Parkinson's disease were high whilst rates for tremor and headache were low. Although the reason why treatment is sought for some conditions but not others are likely to be complex, surprisingly the extent to which a condition is disabling appears not to be a significant factor. Previous researchers who have investigated treatment seeking behaviours in SSA have found that whether people seek medical treatment for their

symptoms depends on a number of factors, such as access to services, financial issues, education level, social networks, intra-household power and health beliefs [5-8]. In the current study, rates of treatment seeking were similar for males and females. There is a growing need for effective interventions for many medical conditions in SSA. Further investigation of the factors which influence treatment seeking will help to inform strategies for the development of healthcare services in SSA.

4.7.2 *Diagnosis and treatment*

The majority of neurological disorders had not been diagnosed prior to the study. This was despite relatively high levels of treatment seeking. When patients sought treatment, it was often not in health centres and hospitals, but via un-registered private pharmacies and traditional healers. In these cases, an appropriate formal diagnosis was rarely made. Of the most prevalent disorders, stroke was the most likely to be diagnosed. Those who had been diagnosed were not necessarily treated, with just over two-thirds of those diagnosed being on appropriate treatment. Those least likely to be on treatment when it was routinely available were patients with tremor disorders, and those most likely to be on treatment (secondary prevention) were those patients with a previous stroke. These generally low rates of diagnosis and treatment may partly reflect patterns of treatment seeking behaviour and health beliefs. However, in this resource poor setting, it may also be due to a lack of access to formal good quality healthcare.

Despite the fact that health seeking behaviour was similar between sexes, the results of this study suggests that men had higher rates of diagnosis and treatment than women. There might be for a number of reasons for this. Firstly, in a society where healthcare is not free at the point of delivery, men are more likely to be the head of the household and have the final decision on financial matters [518, 519]. When the male is the main provider of income, he must keep healthy and the health of a husband and the children is often prioritised over that of the mother. Women have different priorities in the home

with the health of the husband and children coming above their own health [520]. Likewise, money for schooling and food for other family members often comes before the health of the mother[518]. Finally, women often hide symptoms if it reflects badly on their children or grandchildren and their suitability for marriage [521, 522]. Such disparities are likely to be deep rooted in society and are present from early childhood in many cultures [523]. A study published in 2012 of 4822 people aged 18 years and over in Burkina Faso found a significantly higher prevalence of asthma, angina pectoris, back pain and joint disease in women compared to men [524]. Therefore even though women and men were equally likely to seek help for their symptoms in this study, for the reasons explored above men were more likley to recieve a diagnosis and recieve treatment.

Work from this thesis has shown that people with neurological disorders in this population are significantly more likely to be disabled than people without neurological disorders [15]. Low diagnosis and treatment rates are likely to exacerbate the burden of non-communicable disease in SSA, a burden which is predicted to increase substantially as populations age and the infection rates for communicable diseases, such as HIV/AIDS, tuberculosis and malaria, decline [216, 460, 525].

4.8 Disability

Current data estimate 10% of the world's population are disabled [18]. Disability is associated with increasing age and poverty, yet there are few data regarding disability amongst the elderly in developing countries [62].

This study provides a comprehensive picture of the prevalence of disability and its contributory factors, namely increasing age and NCD. We have demonstrated that 3.7% of elderly adults in a developing country are severely disabled and 6.2% are moderately disabled (age adjusted) and that disability is more likely with increasing age, female sex

and the presence of NCD. More specifically it was significantly associated with the presence of neurological disorders, the most detrimental to a person's independence being motor neurone disease, cord lesions, dyskinesias, cerebellar disorders, parkinsonism, disuse weakness and muscle atrophy and stroke.

4.8.1 *Comparison to disability levels in the developed world*

Reported disability prevalence rates around the world vary significantly because of different definitions, study designs, and lack of a universal assessment tool, leading to difficulty making comparisons. I selected the Barthel Index for use because it is widely used and recommended by the RCP and the BGS for routine use in the assessment of older people [426] it is quick and easy to do and it is possible for a wide range of surveyors to perform it consistently. It is culturally and disease non-specific and simple modification allows easy use in Africa. Because it does not need to be highly modified there are fewer requirements for validation in this setting. On saying that it is important to note that actual validation has not been carried out in SSA and therefore caution is required in interpretation of the results. For this study we translated the BI into Swahili and back translated it to ensure accuracy. The use of a simple and commonly used screening tool ensures easy comparison between disability levels in developed and developing countries. The focussed population group allowed direct comparison of our population to a European population studied by Heslin et a l[435] in 2001. They measured BI on 4004 elderly aged 70+. Of the total sample, 9% (10% of women and 7% of men) and 26% were severely and moderately disabled respectively [435]. This is substantially higher than that seen in our population. This may reflect increased mortality from disease that results in disability in developing countries. It also may highlight risk factors for disability within the developed world. Disability levels are likely to increase as the population ages and disease survival increases, thus impacting more on quality of life and requiring urgent attention from healthcare policy makers.

Overall, as generally defined, disabled people represent a significant proportion of the world's population. Data from developed countries and some recent studies in developing countries (Brazil, Ecuador, India, Nicaragua, Vietnam, and Zambia) suggest that an estimate of 10-12%. This estimate is in line with the United Nations' often cited figure of 10%, an informed guess based on data from developed countries [18].

Reported disability prevalence rates around the world do however vary dramatically but in general are lower in developing countries. Rates reported in Kenya [437] and Bangladesh are <1% [438]. Allain et al's Zimbabwean study who found less than 4% of people aged 60 and over experienced difficulty with self maintenance of ADLs [20]. Fitaw et al looked at the prevalence of disability in Ethiopia, they reported the crude disability rate of 3.8% using the WHO international classification functioning disability and health (ICF) when all age groups were studied [21]. Rates in developed countries are substantially higher, 20% in New Zealand [22] and with the Townsend disability scale, The Medical Research Council Cognitive Function and Ageing Study and Resource Implications Study found 11% of men and 19% of women aged 65 and over were disabled in the UK [23]. This variation may be caused by several factors: differing definitions of disability, different methodologies of data collection, and variation in the quality of study design and population group studied [438],[437],[22]. However, my directly comparable study indicates a real difference between disability rates in developed and developing countries in the elderly population at least, comparable data from younger age groups is required to extrapolate this conclusion to the general population.

4.8.2 *Disability levels in the elderly*

I have demonstrated that functional dependence increases with age. The Cognitive Function and Ageing Study supports this conclusion, it reports that 38% of disabled people were aged 85 or over. They concluded that very elderly people make up a large proportion

of those in need of long term care, demonstrating the economic and social burden that an ageing population represents [23].

4.8.3 *Disability levels in NCD*

We have demonstrated the association between NCD, specifically neurological disorders, and disability, this is in agreement with work from the 10/66 dementia research group who concluded that dementia, stroke, limb impairment, arthritis, depression and eyesight problems were in decreasing order associated with disability [62].[62]

4.8.4 *Limitations of the BI*

As a result of its ease of use the BI has one main limitation - it is a measure of physical restriction on daily activities and doesn't look into the social and psychological aspect of disability and should therefore be interpreted as such.

4.9 Ethical issues surrounding the study

Ethical approval was granted by local and regional ethics committees. I felt strongly that this should not just be a prevalence study but it should be of benefit to both the local community under study and more generally the elderly within Tanzania and SSA. We believe this was achieved in the following ways;

4.9.1 *Benefit Afforded to the Local Population*

1. The population studied had neurological disorders diagnosed and fully explained.
2. Those conditions that could be treated were provided with at least 1 month supply of medication and means, financial, logistical and geographical, to get more.

3. One follow up consultation was provided for all tremor patients who wanted, and were amenable to, treatment. If first line treatment was not successful a second line option was suggested and supplied.
4. One follow up consultation was provided for all epilepsy patients to check their level of control and requirement for an increased dose.
5. Parkinson's disease patients were offered and are to receive lifelong follow up and treatment.
6. All patients were made aware of systems for follow up and for financial support for healthcare in their local community.
7. Disabled patients who needed them were all provided with walking aids independent of the underlying cause of their disability. Follow up for these patients, including repairs and redistribution is to be provided as part of this arrangement.
8. Guidelines for treatment were provided for the region.
9. Information on the prevalence of disorders in this age group was fed back to the District Medical Officer and in turn to government officials.

4.9.2 *Benefit Afforded to the elderly Population in Tanzania and SSA*

1. Through feedback to the District Medical Officer it is hoped that the issues raised by this study will be brought to the attention of government officials.
2. It is hoped this study will increase knowledge of the plight of elderly patients in SSA and the substantial contribution that Neurological disorders make to morbidity, mortality and disability in this age group. It is hoped the results will be published in peer review journals, and presented at national and international conferences.

4.9.3 Public health Implications of the study

The WHO document "Neurological disorders: public health challenges" highlights the fact that "unless immediate action is taken globally, the neurological burden is expected to become an even more serious and unmanageable threat to public health"

I have provided evidence on which to base a public health framework for neurological diseases; I believe that the results obtained from this study will facilitate the evidence-based healthcare planning that is needed for neurological disorders and other non communicable diseases in this and other resource-poor settings.

I have demonstrated that the burden is high and increasing further

This study reveals a high prevalence of neurological disorders in the elderly. Neurological morbidity will make a substantial contribution to the non communicable disease epidemic. This, along with the ageing population, constitutes a public health dilemma.

I have demonstrated that neurological disorders can be screened for easily and cheaply

Identification of those with neurological disorders is clearly an important component in reducing the morbidity burden in SSA. I propose the use of the validated questionnaire in the community in low-income countries for dual epidemiological and clinical purposes. Epidemiologically, documenting prevalence is fundamental to highlight the public health significance of neurological disorders on a background of an ageing population, and an NCD epidemic. Clinically, case identification will reduce the diagnosis and treatment gap and improve the health of individuals. Due to the use of NMIs costs will be contained and I believe the screening will then be cost effective.

We know that;

Cost effective interventions are available

Many neurological disorders can be treated readily and inexpensively, the importance of screening for these conditions and their precursors is therefore obvious, these include:

Stroke for secondary prevention (aspirin and antihypertensives) and rehabilitation, Epilepsy with phenobarbitone, Essential Tremor with propranolol, Parkinson's disease with levodopa [161]. Screening for other neurological disorders may be less intuitive but many are amenable to rehabilitation and disability management.

Resources are inadequate and unequally distributed and need addressing

It has recently been reported that African nations have very few neurologists [11], so training of primary caregivers would be important.

4.9.3.1 *Recommendations for Action*

My study not only demonstrates the burden that neurological disorders represent in a specific area in SSA it also offers health professionals and planners the opportunity to assess the burden caused by neurological disorders in their country and to take appropriate action to reduce the mortality, morbidity and disability caused by neurological disorders. One must appreciate that low income countries have limited resources (and multiple problems to tackle), it therefore may be difficult for governments to act alone. I have demonstrated that neurological disorders do need to be prioritised but appreciate that assistance may be required from non government organisations and international agencies

4.9.3.1.1 *Gain commitment from decision-makers*

Political commitment is required to ensure proper funding policies and publicity to subsequently raise awareness and reduce stigma. I have provided solid information on the prevalence, consequences, burden, treatment and prevention of neurological disorders and have fed this back to the district medical officer for Hai who in turn has discussed the problem with government officials.

4.9.3.1.2 *Increase public and professional awareness*

I have also presented and published my work, nationally and internationally, to increase public and professional awareness of public health aspects of neurological disorders. Further actions that need to be taken are global and local campaigns.

4.10.3.1.3 *Minimize stigma and eradicate discrimination*

Stigma and discrimination against people with neurological disorders exist and need to be eradicated with education and global campaigns. If this issue is not addressed disclosure of symptoms will remain low and the poverty of care will remain.

4.9.3.1.4 *Strengthen neurological care within the existing health systems*

I have already stated that African nations have very few neurologists [11], so training of primary caregivers and medical students in neurological disorder recognition and treatment would be fundamental, a recent book "Neurology in Africa" has been written by Dr William Howlett and aims to provide relevant teaching material for this goal [503].

4.9.3.1.5 *Incorporate rehabilitation into the key strategies*

Rehabilitation complements the other key strategies but in addition it may be the only management option for some conditions therefore effective rehabilitation and provision of function aids is fundamental to promote the quality of life of many and their ability to contribute financially to the community. Since community-based rehabilitation programmes are low-cost they need to be encouraged, linked to and supported by institutional and hospital-based rehabilitation services.

4.9.3.1.6 *Develop national capacity and international collaboration*

Many of the problems faced by low income countries with regard to neurological disorders are similar so collaboration with each other, high income countries and non government organisations may be an effective way to address them. The awareness of neurological disorders needs to be increased amongst NGOs and other organisations, to prioritise them on their agenda lists.

4.9.3.1.7 *Establish links to other sectors*

Prevention of neurological disorders needs to involve other sectors for example, road traffic safety, healthy lifestyle campaigns, education and social welfare.

4.9.3.1.8 *Define priorities for research*

The burden of the problem needs to be documented in other communities and that is where our screening tool with its duel epidemiological and clinical purpose needs to be used.

In summary there should be a screening programme resourced by associations and collaboration with government and non government organisations, this would be cost effective because of its cheap nature and the impact of identification and treatment for individuals and societies. Treatment and rehabilitation needs to be available through influencing education and policy. Follow up needs to be provided to ensure benefit is assured to the patients.

4.10 Comparison with previous prevalence studies in SSA

This is the first community-based prevalence study of neurological disorders specifically in the elderly population in SSA. The other community-based studies in Nigeria and Ethiopia looked at the whole population (a heterogeneous group with very different neurological disorders and treatment requirements). In addition they are outdated and use criticized screening tools. I have used well recognized diagnostic criteria which have been used in prevalence studies in other areas of the world to increase comparability, and I have calculated age-standardised rates, again to increase comparability. The diagnosis of the patients has been independently reviewed by specialists in Neurology, Movement Disorders and Geriatrics. Standardised video scripts have been used when appropriate. Diagnosis has been purely clinical which leaves it open to criticism but this accurately reflects the conditions of Neurological practice in the developing world.

Participation rates in the census and the door to door study were 100% and 93.8% respectively, higher than reported from other studies. The screening questionnaire for neurological disorders proved to have an excellent sensitivity and specificity, a challenge in the geriatric age group. It is the only screening tool that focuses on identification of all cause Neurological disorders in the elderly populations. A group that differs from the adult population to such an extent that they warrant an alternative screening tool, in the same way alternative methods of screening are utilized in children.

Detailed information about the nature and prevalence of diseases and their subtypes has been reported, much of which is similar to previous world-wide studies but accurate current data has been lacking in SSA and my data highlights the high level of neurological morbidity in this age group. High rates of previously undiagnosed and untreated cases were detected, re-enforcing the need for a community rather than hospital based search in such areas and the unmet needs of the community in SSA with regard to the treatment and diagnosis of Neurological disorders.

Lower levels of disability have been seen when compared directly to the developed world. This may be falsely reassuring and explained by a higher level of mortality from disabling disease in developing countries. As the population ages and survival from disabling disease increases a public health issue of disability in developing countries may present itself. The disabled adults that are present are not catered for demonstrated by the limited availability of walking aids despite an obvious requirement.

4.11 Study Limitations

My study was limited by a number of factors;

- The use of historical events to determine participants' year of birth gives some uncertainty over ages [443]. However, this is a well recognised problem of research in SSA and the techniques we used are standard practice [449].
- Whilst we had excellent interpreters who were medically trained, it was difficult at times to ascertain the finer points of a patient's symptom burden, given the lack of medically descriptive words in Swahili, and other local tribal languages spoken by village elders.
- The screening questionnaire and the Barthel Index were translated into Swahili and back translated to ensure accuracy, however some of the elderly population only speak tribal languages and therefore translation was performed at the point of interview by the NMI. This may not have been an accurate translation but it was felt to be impractical to formally translate the screening questionnaire into all tribal languages and all dialects.
- There was no attempt to undertake either inter or intra-observer reliability studies using the screening instrument, which constrains reliability estimates.
- Each village had one or two NMIs who were based there so that any village differences, if not due to chance, could reflect systematic bias from the use of the tool by the NMI.
- The size of the main study was selected due to financial and time constraints. The whole population studied was 40,280 (one quarter of the Hai District DSS population n=161,119). Of this population we only looked at the 70 and over population, n=2232. Other community based studies of this nature in SSA have differed in size with no universally accepted optimum, the number of subjects studied have varied from 1113 to 161,071 [3, 5, 34, 96, 99, 128, 131, 187, 191, 204-206, 302, 313, 315, 336, 466, 467]. We must appreciate that our sample population is quite small and that the prevalence of rarer conditions is more difficult to interpret. This is a weakness of our study but is a direct consequence of

the time consuming nature of a robust door to door community study. It was felt robust methodology should be the priority.

- The accuracy of our neurological diagnoses was limited due to the purely clinical nature of our assessments and the lack of investigations available. Although this reflects the majority of medical encounters in SSA some diagnostic inaccuracy is inevitable. Validation was performed as much as possible through the use of internationally recognised diagnostic criteria and through discussion of all cases with a consultant neurologist, or movement disorder expert, where appropriate using video recordings. Unfortunately the consultants who assessed the cases could not be fully blinded to the diagnosis made by the research doctor as they were selected on the basis of the presumptive diagnosis.
- The prevalence rates in the pilot population were approximately twice as high as those in the main study population indicating that prevalence in the main study population may have been underestimated as a result of false negatives.
- The main limitation regarding health seeking, diagnosis and treatment level conclusions relates to the presence of a number of previous epidemiological studies that have been carried out in the Hai district over the last ten years[34, 96, 128, 213, 333]. Consequently, rates of diagnosis and treatment may be higher than would be found otherwise. Specifically, those who had had a stroke were most likely to be on treatment to prevent recurrence. This may be partly a reflection of the educational work done by the Tanzanian Stroke Incidence Project, which ran from 2003-2006[213]. Rates of secondary preventative treatment for stroke in other areas of SSA have been reported to be substantially lower [526][26].

Chapter 5. Conclusions

5.1 Study review

This is the first community based prevalence study of "all cause" Neurological Disorders focussing on the elderly population in SSA. A 2009 census provided demographic information on 161,119 people inhabiting the Hai District DSS which allowed me to focus on those of the population aged 70 and over (n=8869). An innovative screening tool, sensitive and specific for picking up a wide range of Neurological Disorders in the Elderly was produced. The Pilot study provided evidence of its excellent sensitivity and specificity in this age group. A two phased approach was utilised. Screening of a quarter of the elderly patients (n=2232) with the screening tool was combined with multiple other case finding strategies to perform a sensitivity check. Positive responders then underwent detailed assessment by the RD (myself). The diagnostic categories used were the widely applicable WHO ICD 10 criteria, which facilitates worldwide comparison of the prevalence figures. For each condition detailed internationally recognised criteria were used for diagnosis. Scripted video recording (where appropriate) and case descriptions of patients confirmed diagnosis which were validated with a Neurologist, Movement disorder expert or geriatrician depending on the nature of the case.

5.1.1 *Study design*

The methodology used in this study, of a community two stage epidemiological survey has been recommended by the WHO as the "gold-standard" way to detect neurological disease in a developing country. The sensitivity of the screening tool used was 87.8-97.0% and it was able to detect previously diagnosed and undiagnosed cases, of all neurological diseases. Multiple case finding methods confirmed the excellent sensitivity as no additional cases were picked up. I am confident therefore that the prevalence estimate is as accurate as could possibly be achieved.

5.1.2 *Main conclusions -Addressing the Main Aim and the Subsidiary Aims of the Study*

5.1.2.1 *The Main Aim – Prevalence estimates*

The main aim of this study was to calculate the age-standardised prevalence of Neurological Disorders in the 70 and over population in the Hai district of northern Tanzania. I report the age standardised figures as summarised in the table below.

Table 5.1: The Prevalence of Neurological Disorders in the 70 and over population of the Hai District of Northern Tanzania

Diagnosis Group	Diagnosis	Sub-diagnosis	Cases	Crude Prevalence/1000 (95% CI)	Age Adjusted Prevalence*/1000 (95% CI)
All Neurological Disorders			384	172.04/1000 (156.39 to 187.70).	168.94/1000 (153.39 to 184.48)
People with Neurological Disorders			349	156.36/1000 (141.29 to 171.43)	154.14/1000 (139.16 to 169.12)
Central Nervous System Disorders					
Movement Disorders	Tremor – total	-	110	49.28 (40.30 to 58.26)	48.22 (39.34 to 57.11)

		Essential Tremor	67	30.02 (22.94 to 37.10)	30.10 (23.01 to 37.18)
		Enhanced physiological tremor	16	7.17 (3.67 to 10.67)	6.40 (3.10 to 9.71)
		Tremor secondary to Parkinsonism/Parkinson's disease	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
		Tremor secondary to cerebellar disease	11	4.93 (2.02 to 7.83)	4.87 (1.98 to 7.76)
		Orthostatic tremor	3	1.34 (0.00 to 2.86)	1.27 (0.00 to 2.74)
		Iatrogenic tremor	1	0.45 (0.00 to 1.33)	0.46 (0.00 to 1.35)
	Parkinsonism	**-**	**14**	**6.27 (3.00 to 9.55)**	**5.94 (2.75 to 9.12)**
		Parkinsonism with tremor	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
		Parkinsonism without tremor	2	0.90 (0.00 to 2.14)	0.81 (0.00 to 1.99)
		Parkinson's Disease	12	5.38 (2.34 to 8.41)	5.13 (2.16 to 8.09)
		Vascular Parkinsonism	1	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)
		Progressive Supra-nuclear palsy	1	0.45 (0.00 to 1.33)	0.50 (0.00 to 1.43)
	Cerebellar disorders total	**-**	**11**	**4.93 (2.02 to 7.83)**	**4.87 (1.98 to 7.76)**
		Secondary to alcohol or idiopathic	7	3.14 (0.82 to 5.46)	3.14 (0.82 to 5.46)
		Idiopathic	5	2.24 (0.28 to 4.20)	2.20 (0.25 to 4.14)
		Secondary to alcohol	2	0.90 (0.00 to 2.14)	0.94 (0.00 to 2.21)
		Secondary to stroke	4	1.79 (0.04 to 3.55)	1.73 (0.01 to 3.46)
	Dyskinesias	**-**	**5**	**2.24 (0.28 to 4.20)**	**2.02 (0.16 to 3.88)**

		Unspecified chorea	1	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)
		Tardive dyskinesias/ iatrogenic	2	0.90 (0.00 to 2.14)	0.77 (0.00 to 1.92)
		Orofacial dyskinesias – idiopathic	2	0.90 (0.00 to 2.14)	0.94 (0.00 to 2.21)
Episodic and Paroxysmal Disorders	**Headaches – total**	**-**	**92**	**41.22 (32.97 to 49.47)**	**41.79 (33.49 to 50.09)**
		Primary headaches – total	**44**	**19.71 (13.95 to 25.48)**	**19.86 (14.07 to 25.64)**
		Migraine	8	3.58 (1.10 to 6.06)	3.77 (1.22 to 6.31)
		Tension Type headaches	36	16.13 (10.90 to 21.36)	16.09 (10.87 to 21.31)
		Cluster headaches	0	0	0
		Other Primary Headaches	0	0	0
		Secondary headaches – total	**48**	**21.50 (15.49 to 27.52)**	**21.93 (15.86 to 28.01)**
		Headaches attributed to head and/or neck trauma	3	1.34 (0.00 to 2.86)	1.40 (0.00 to 2.95)
		Headaches attributed to infection	0	0	0
		Headache attributed to arterial hypertension	3	1.34 (0.00 to 2.86)	1.10 (0.00 to 2.47)
		Headache attributed to hypertensive crisis without hypertensive encephalopathy	0	0	0
		Headache attributed to hypertensive encephalopathy	0	0	0

		Headache attributed to disorders of the neck	34	15.23 (10.15 to 20.31)	15.53 (10.40 to 20.66)
		Headache attributed to disorders of the eyes	4	1.79 (0.04 to 3.55)	1.98 (0.14 to 3.83)
		Headache attributed to disorders of the ears	1	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)
		Headache attributed to disorders of the teeth or jaw	2	0.90 (0.00 to 2.14)	0.98 (0.00 to 2.28)
		Trigeminal neuralgia	1	0.45 (0.00 to 1.33)	0.46 (0.00 to 1.35)
	Stroke	-	**54**	**24.19 (17.82 to 30.57)**	**22.95 (16.74 to 29.17)**
		LACS	19	8.51 (4.70 to 12.32)	8.10 (4.38 to 11.82)
		PACS	16	7.17 (3.67 to 10.67)	6.62 (3.26 to 9.99)
		TACS	12	5.38 (2.34 to 8.41)	5.40 (2.36 to 8.44)
		POCS	7	3.14 (0.82 to 5.46)	2.83 (0.63 to 5.04)
		POCS cerebellar	4	1.79 (0.037 to 3.55)	1.73 (0.01 to 3.46)
		POCS non cerebellar	3	1.34 (0.00 to 2.86)	1.10 (0.00 to 2.47)
	Epilepsy	-	**10**	**4.48 (1.71 to 7.25)**	**4.44 (1.69 to 7.20)**
		GTCS	9	4.03 (1.40 to 6.66)	3.97 (1.36 to 6.57)
		Partial with secondary generalization	1	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)
Degenerative Diseases	**Motor neuron Disease**	-	**2**	**0.90 (0.00 to 2.14)**	**0.96 (0.00 to 2.25)**

Spinal Cord Dysfunction	**Cord lesions**	**-**	**5**	**2.24 (0.28 to 4.20)**	**1.89 (0.09 to 3.69)**
		Cervical Cord Lesions	**3**	**1.34 (0.00 to 2.86)**	**1.10 (0.00 to 2.47)**
		Traumatic Cervical Cord lesion	1	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)
		Non-traumatic Cervical Cord Lesion (Arthritic compression or acute lower cervical cord lesion)	2	0.90 (0.00 to 2.14)	0.79 (0.00 to 1.95)
		Arthritic compression	*1*	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)
		Acute lower cervical cord lesion	*1*	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)
		Thoracic Cord Lesion	**2**	**0.90 (0.00 to 2.14)**	**0.79 (0.00 to 1.95)**
		Traumatic Thoracic Cord lesion	0	0	0
		Non-traumatic Thoracic Cord Lesion	2	0.90 (0.00 to 2.14)	0.79 (0.00 to 1.95)
Peripheral Nervous System Disorders					
	Polyneuropathies	**Peripheral Neuropathy**	**42**	**18.82 (13.18 to 24.45)**	**18.61 (13.01 to 24.22)**
		Sensory Peripheral Neuropathy	39	17.47 (12.04 to 22.91)	17.36 (11.95 to 22.78)
		Sensorimotor Peripheral Neuropathy	3	1.34 (0.00 to 2.86)	1.25 (0.00 to 2.71)

		Motor Peripheral Neuropathy	0	0	0
Nerve, nerve root and plexus disorders	**Cranial Nerve Pathology**	**-**	**14**	**6.27 (3.00 to 9.55)**	**5.71 (2.58 to 8.83)**
		Ptosis	8	3.58 (1.10 to 6.06)	3.34 (0.95 to 5.74)
		Ptosis secondary to eye pathology – traumatic	4	1.79 (0.04 to 3.55)	1.58 (0.00 to 3.22)
		Ptosis secondary to eye pathology - non traumatic	2	0.90 (0.00 to 2.14)	0.98 (0.00 to 2.28)
		Ischaemic 3rd CN palsy	2	0.90 (0.00 to 2.14)	0.79 (0.00 to 1.95)
		Facial nerve pathology	4	1.79 (0.04 to 3.55)	1.58 (0.00 to 3.22)
		Bells	2	0.90 (0.00 to 2.14)	0.79 (0.00 to 1.95)
		Traumatic	1	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)
		Hemifacial spasm	2	0.90 (0.00 to 2.14)	0.79 (0.00 to 1.95)
	Upper Limb Mononeuropathies	**-**	**15**	**6.72 (3.33 to 10.11)**	**6.53 (3.19 to 9.87)**
		Traumatic upper limb multiple mononeuropathies	2	0.90 (0.00 to 2.14)	0.96 (0.00 to 2.24)
		Traumatic damage to Median Nerve	1	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)

		Non-traumatic damage to Median nerve - compression/entrapment	4	1.79 (0.04 to 3.55)	1.58 (0.00 to 3.22)
		Traumatic damage to Radial nerve	2	0.90 (0.00 to 2.14)	0.94 (0.00 to 2.21)
		Non-traumatic damage to Radial nerve	0	0	0
		Traumatic damage to Ulnar nerve	2	0.90 (0.00 to 2.14)	0.98 (0.00 to 2.28)
		Non-traumatic damage to Ulnar nerve	4	1.79 (0.04 to 3.55)	1.60 (0.00 to 3.26)
	Lower Limb Mononeuropathies	**-**	**5**	**2.24 (0.28 to 4.20)**	**2.38 (0.36 to 4.40)**
		Traumatic femoral nerve injury	1	0.45 (0.00 to 1.33)	0.46 (0.00 to 1.35)
		Sciatic nerve injury from trauma	1	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)
		Sciatic nerve injury from injection site	1	0.45 (0.00 to 1.33)	0.48 (0.00 to 1.39)
		Common peroneal injury from operation	1	0.45 (0.00 to 1.33)	0.50 (0.00 to 1.43)
		Traumatic common peroneal nerve injury	1	0.45 (0.00 to 1.33)	0.46 (0.00 to 1.35)
	Plexus Injury	**-**	**4**	**1.79 (0.04 to 3.55)**	**1.89599**
		Brachial-traumatic	2	0.90 (0.00 to 2.14)	0.93965
		Lumbosacral-traumatic	2	0.90 (0.00 to 2.14)	0.95634

	Root Pathology	**-**	**4**	**1.79 (0.04 to 3.55)**	**1.69 (0.00 to 3.40)**
		Sciatica	3	1.34 (0.00 to 2.86)	1.23 (0.00 to 2.69)
		C8 root lesion	1	0.45 (0.00 to 1.33)	0.46 (0.00 to 1.35)
Inflammatory /infectious diseases of the peripheral nervous system	**Polio**	**-**	**5**	**2.24 (0.28 to 4.20)**	**2.38 (0.36 to 4.40)**
	Leprosy	**-**	**1**	**0.45 (0.00 to 1.33**	**0.48 (0.00 to 1.39)**
Diseases of the myoneural junction and muscle	**Myaesthenia Gravis**	**-**	**1**	**0.45 (0.00 to 1.33)**	**0.50 (0.00 to 1.43)**
	Muscle wasting and atrophy	**-**	**17**	**7.62 (4.01 to 11.22)**	**7.40 (3.84 to 10.95)**
		Secondary to primary orthopaedic problem	7	3.14 (0.82 to 5.45)	3.04 (0.76 to 5.33)
		Secondary to pain	5	2.24 (0.28 to 4.20)	1.91 (0.10 to 3.72)
		Secondary to severe cognitive impairment and consequent	2	0.90 (0.00 to 2.14)	0.96 (0.00 to 2.25)

		immobility			
		Secondary to soft tissue damage secondary to infection	2	0.90 (0.00 to 2.14)	0.98 (0.00 to 2.28)
		Secondary to period of ill health and consequent disability	1	0.45 (0.00 to 1.33)	0.31 (0.00 to 1.04)

I report an age-standardised figure of 168.94/1000 for “all cause” neurological disorders in the 70 years and older population, using the WHO population as standard.

This is comparable to the limited number of published studies in developing countries (often hospital based and therefore not a reflection of true prevalence) and more robust studies in developed countries. Specific prevalence data in the elderly in SSA is very limited and differing diagnostic criteria and methodology make results difficult to interpret.

Whilst age standardisation takes into account the difference in the age structure of the population in Hai compared to the UK, I cannot allow for the increased mortality that is likely for those with neurological disease in Hai in comparison to the developed world. The only way to take account of this would be through analysis of an accurate death certification system and more data based on verbal autopsies, both of which are not currently available in this setting.

Given my experience and the data I have presented I feel this community is likely to change over time. The aged population will continue to increase in size and those conditions that are more prevalent in old age such as PD and ET will become more prevalent as a result. Those conditions associated with other NCDs such as stroke (associated with hypertension) and peripheral neuropathy (associated with diabetes) will also become increasingly problematic. Conditions resulting from infections are likely to become less prevalent as treatments and vaccination programmes become widespread however it is likely to be many years before the long term consequences of these conditions are eradicated from the elderly population.

5.1.2.2 *The Subsidiary Aims*

5.1.2.2.1 *The Screening Tool*

The initial subsidiary aim of the study was to produce a screening tool for the detection Neurological Disorders in the 70 and over population of the Hai District DSS. I successfully produced a screening tool with a sensitivity of 87.8-97.0% and specificity of 90.4-94.9%. I demonstrated that it can be effectively and accurately used by NMI with minimal training, this was facilitated by removal of an examination section which complicates many currently available screening tools. Because of the nature of this screening tool (its ease of use and its lack of cultural specificity) I can recommend it for use in other countries throughout the world, particularly developing countries where hospital based prevalence studies are inadequate and there is a limited budget for such screening. The screening questionnaire can also be used to identify cases of neurological disorders for diagnosis and treatment in an attempt to address the large amount of under treatment in the community and the plight of those who remain undiagnosed.

5.1.2.2.2 *Subtypes of Neurological Disease*

A further subsidiary aim was to describe the subtypes of Neurological disease in the prevalent population in Hai. Diagnosis was purely clinical and based on international guidelines and was enhanced through consultation with Neurologists, Geriatricians and Movement disorders experts. Although this was the only practical option in this setting and reflects the practice in SSA it is not (in the case of the majority of the diseases studied) the gold standard. Accuracy of diagnosis may therefore be limited but the training of the RD (myself) and the confirmation of diagnoses by experts helped to validate the conclusions drawn. The prevalence of the subtypes of neurological disorders are described in table 5.1 above. The prevalence rates highlight a high level of neurological morbidity in this age group.

5.1.2.2.3 *The diagnosis gap and treatment Gap*

I have demonstrated low levels of diagnosis and treatment of neurological disorders in the community. Many neurological disorders can be treated readily and inexpensively. However, the reasons for these low rates are likely to be multi-factorial and relate not only to availability and affordability in the broadest sense, but also to accessibility and cultural acceptability [374, 440]. Identification and diagnosis of those with neurological disorders is clearly an important component to reduce the morbidity burden in SSA. It has recently been reported that African nations have very limited numbers of neurologists and geriatricians, with some countries having none [11, 527]. As this situation is unlikely to change in the immediate future, other strategies to manage this burden should be sought. Since diagnosis must precede treatment, screening for neurological disorders by NMI and lay healthcare workers is an important first step to improve treatment rates. Programmes to raise awareness of medical conditions at a community level should be considered. In addition, the training of primary caregivers in the use of non-pharmacological interventions to manage such conditions should be considered. In the absence of initiatives to improve rates of diagnosis and treatment, neurological morbidity will continue to make a substantial, and increasing, contribution to the non-communicable disease epidemic in SSA [524].

5.1.2.2.4 *The level of disability*

The final aim of the study was to record the level of disability in this 70 and over population and see the impact neurological disorders had on this problem. The average level of disability was lower than in a comparable European population. This may reflect increased mortality from disease that would result in disability in developing countries but it may also highlight risk factors for disability within the developed world. Disability levels are likely to increase as the population ages and survival of people with disabling conditions increases, this will impact more on quality of life in older people and requires urgent attention from healthcare policy makers. I have demonstrated the relative ease with which it is possible to identify those that are disabled and to record the level of

disability in an area. This is easily transferrable to many populations worldwide and is a relatively low budget way to identify those in need. I have also demonstrated that disability is associated with the presence of neurological disorders and increased age.

5.2 Recommendations for future

5.2.1 *Future epidemiological studies*

5.2.1.1 *Neurological Disorders*

The two stage approach with a screening tool followed by medical examination is the most accurate approach to identify the true prevalence of neurological disorders in developing countries. Due to health seeking behaviours and the diagnosis and treatment gap other methods will substantially underestimate the prevalence. These methods are recommended to anyone wishing to undertake such a study to allow comparability. The calculation of age-standardised rates, again allows comparability with other studies. The use of well recognised diagnostic criteria further adds to this. I can recommend my screening questionnaire for use in such studies.

Neurological Disorders can significantly impair the quality and span of life. Neurological disorders and other NCD will become increasingly problematic in developing countries as the population ages and therefore the management of these conditions needs to be addressed.

5.2.1.2 *Disability*

This study reports a lower age adjusted prevalence of disability than seen in other parts of the world. This probably reflects a survival bias, where those with disease that results in disability died at a younger age/survived for less time with the disease. If this is the case the impact of improvement in survival rate will substantially increase the burden of

disability. Further community based studies in other developing regions are required to answer this question.

5.2.2 *Training for medical staff*

Healthcare professionals within developing countries have a lack of knowledge of and training on Neurological Disorders as this study demonstrates. This needs to change in order to afford optimal care to elderly patients with neurological disorders. Given the ageing population this training should extend to other NCDs that affect the elderly to improve the quality of life of the aged in developing countries.

5.2.3 *Treatment*

For patients affected by Neurological Disorders, the treatment gap is significant and is the cause of unnecessary morbidity and mortality, it has a substantial effect on the quality and quantity of life of individuals and societies. This needs to be addressed, cost effective medication, rehabilitative techniques and aids to assist function are available and supply of these is fundamental, not just in this highlighted study population but in the elderly in other developing countries who suffer in the same way.

5.3 In Summary

This is the first community-based Neurological Disorder prevalence study specifically in the elderly in SSA. It reveals a high prevalence of Neurological Morbidity and associated disability. I have demonstrated low levels of diagnosis and treatment in the community despite the availability of inexpensive treatments for some conditions. Neurological Morbidity will make a substantial contribution to the non-communicable disease epidemic. This, along with the ageing population constitutes a public health dilemma. I believe that the results obtained will facilitate the evidence based healthcare planning

that is needed for neurological disorders and other NCDs in this resource poor setting, to relieve the aged population of their significant medical and social implications.

I designed a unique screening questionnaire for the detection of Neurological Disorders in the elderly of low income countries. It had a high sensitivity only reduced by incidental findings or non-disabling conditions. It had a very high specificity; a challenging task given the target population. It was designed to be inclusive of all neurological conditions of public health significance in this population and age group. The questionnaire was simple and acceptable to use.

In the future I propose the validated questionnaires use in the community of low income countries for dual epidemiological and clinical purpose. Epidemiologically, documenting prevalence is fundamental to highlight the public health significance of neurological disorders on a background of an Ageing population and a non communicable disease epidemic to allow appropriate allocation of resources in low income settings. Clinically, case identification will reduce the diagnosis and treatment gap and improve the health of individuals. Benefits from a public health perspective are therefore two fold.

This is also the first study demonstrating a directly comparable disability rate to a European population. I have illustrated a lower prevalence of disability in the elderly of low income countries in comparison to high, this is supported by published literature. This may reflect increased mortality from disease that results in disability in developing countries. It also may highlight risk factors for disability within the developed world. Disability levels are likely to increase as the population of developing countries ages and disease survival increases; this is supported by the positive relationship between disability and increasing age and NCD. As studies from developed countries demonstrate, the societal costs of increasing disability are enormous, urgent attention is required from healthcare policy makers of developing countries.

References

1. The World Health Organization, *https://www.who.int/features/factfiles/aging/en/index*. 2007.
2. Heligman, L., N. Chen, and O. Babakol, *Shifts in the structure of population and deaths in less developed regions. Epidemiologic Transitions: Policy and Planning Implications for Developing Countries.* Washington, D.C.: National Academy Press., 1993: p. 9-41.
3. Osuntokun, B.O., et al., *Neurological disorders in Nigerian Africans: a community-based study.* Acta Neurologica Scandinavia, 1987. **75**(1): p. 13-21.
4. Attia Romdhane, N., et al., *Prevalence study of neurologic disorders in Kelibia (Tunisia).* Neuroepidemiology, 1993. **12**(5): p. 285-99.
5. Tekle-Haimanot, R., et al., *Community-based study of neurological disorders in rural central ethiopia.* Neuroepidemiology, 1990. **9**: p. 263-277.
6. The World Health Organization, *World Health Organization Research protocol for measuring the prevalence of neurological disorders in developing countries.* 1981.
7. Murray, C.J.L. and A.D. Lopez, *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020.* Cambridge, MA, Harvard School of Public Health on behalf of the World Health Organisation and the World Bank, 1996 1996. **Global Burden of Disease and Injury Series, Volume 1**.
8. Ojini, F.I. and M. Danesi, *The Pattern of Neurological Admissions At The Lagos University Teaching Hospital* Nigerian. Jrnl of Clin Prac, 2003. **6**: p. 38-44.
9. Emmanuel, C.J., *Neurologic Admissions in the Niger Delta Area of Nigeria - A Ten Year Review.* Afr J of Neuro Sci, 2004. **23**(1): p. 14-20.
10. World Health Organisation. *https://apps.who.int/infobase/mortality.aspx*. 2011.
11. Bower, J.H. and G. Zenebe, *Neurologic services in the nations of africa.* Neurology, 2005. **64**: p. 412-415.
12. World Health Organisation and World Federation of Neurology, *Atlas: Country resources for Neurological Disorders.* Geneva, World Health Organisation and World Federation of Neurology, 2004: p. 1-59.
13. World Health Organisation, *Neurological Disorders: Public Health Challenges.* World Health Organisation Website, 2006.
14. Gupta, M., N. Singh, and S. Verma, *South Asians and Cardiovascular Risk. What Clinicians should know, .* Circulation, 2006. **113**: p. e924-e929.
15. Dewhurst, F., et al., *The prevalence of disability in older people in Hai Tanzania.* Age and Ageing, 2012. **41**(4): p. 517-523.
16. National Bureau of Statistics, *National Bureau of Statistics. Tanzanian Disability Survey Report. Dar es Salaam, Tanzania.* 2010.
17. World Health Organisation, *The International Classification of Functioning Disability and Health.* World Health Organisation Website, 2001.
18. Mont, D., *Measuring Disability Prevalence.* Disability and Development Team, The World bank, 2007.
19. Crepaidl, G., et al., *Reducing disability among the elderly in europe.* The Lancet, 1998. **351**: p. 375.
20. Allain, T.J., et al., *Morbidity and disability in elderly Zimbabweans.* Age and Ageing, 1997. **26**: p. 115-121.
21. Fitaw, Y. and J.M.F. Boersma, *Prevalence and impact of disability in north-western Ethiopia.* Disability and Rehabilitation, 2006. **28**(15): p. 949-953.
22. Statistics New Zealand, *Disability Counts.* 1998.

23. Medical Research Council Cognitive Function and Aging Study (MRC CFAS) and Resource Implications Study (RIS MRC CFAS), et al., *Profile of disability in elderly people: estimates from a longitudinal population study.* British Medical Journal, 1999. **318**: p. 1108-11.
24. Schoenberg, B.S., *Clinical neuroepidemiology in developing countries: neurology with few neurologists.* Neuroepidemiology, 1982. **1**: p. 137-142.
25. Osuntokun, B.O., et al., *Research Protocol for Measuring the Prevalence of Neurologic Disorders in Developing Countries: Results of a Pilot Study in Nigeria.* Neuroepidemiology, 1982. **1**: p. 143-153.
26. Bower, J.H., et al., *A Screening Instrument to Measure the Prevalence of Neurological Disability in Resource-Poor Settings.* Neuroepidemiology, 2009. **32**: p. 313-320.
27. Siddiqi, O.K., et al., *The spectrum of neurological disorders in a Zambian tertiary care hospital.* Journal of the Neurological Sciences, 2010. **290**(1): p. 1-5.
28. Bower, J.H., et al., *The burden of inpatient neurologic disease in two Ethiopian hospitals.* Neurology, 2007. **68**(5): p. 338-334.
29. Casanova-Sotolongo, P., P. Casanova-Carrillo, and J. Rodríguez-Costa, *A neuroepidemiological study in Beira, Mozambigue.* Rev Neurol., 2000. **30**(12): p. 1135-1140.
30. Mathers, C.D. and D. Loncar, *Updated projections of global mortality and burden of disease, 2002-2030: data sources, methods and results. .* Geneva, World Health Organisation (Evidence and Information for Policy Working Paper, 2005.
31. Gutierrez-del-Olmo, A.M.C., B.S. Schoenberg, and A. Portera-Sanchez, *Prevalence of neurological diseases in Madrid, Spain.* Neuroepidemiology, 1989. **8**: p. 43-47.
32. Kapoor, S.K., *Pilot study of the prevalence of major neurologic disorders in a rural population of India.* Neuroepidemiology, 1990(9): p. 287-295.
33. Nicoletti, A., *A neuroepidemiological survey in rural Bolivia: Background and Methods.* Neuroepidemiology, 1998. **17**: p. 273-280.
34. Walker, R.W., et al., *Age specific prevalence of impairment and disability relating to hemiplegic stroke in the Hai district of northern Tanzania.* Journal of Neurology, Neurosurgery and Psychiatry, 2000. **68**: p. 744-749.
35. Anderson, D.W., W.A. Rocca, and J.A. Rosario, *Pitfalls in neuroepidemiologic research.* Neuroepidemiology, 1998. **17**: p. 55-62.
36. Meneghini, F., *Door-to-door prevalence survey of neurological diseases in a Sicilian population.* Neuroepidemiology, 1991. **10**: p. 70-85.
37. Gourie-Devi, M., V.N. Rao, and R. Prakashi, *A protocol to detect neurological disorders in the community.* Indian Journal of Medical Research, 1988: p. 443-449.
38. Morgante, L., et al., *Neuroepidemiological Survey on Sicilian Population. A feasibility study.* Neuroepidemiology, 1989. **8**: p. 214-220.
39. Bower, J., et al., *Validity of a screening instrument for neurologic disability in resource-poor African communities.* Journal of the Neurological Sciences, 2012. **320**: p. 52-55.
40. Tekle-Haimanot, R., M. Abebe, and A. Gebre-Mariam, *Community based study of neurological disorders in Ethiopia: The development of a screening instrument.* Ethiopian Medical Journal, 1990. **3**: p. 123-37.
41. Meneghini, F., et al., *Validating screening instruments for neuroepidemiologic surveys: experience in Sicily. Sicilian Neuro-Epidemiologic Study (SNES) Group.* Journal of clinical epidemiology, 1992. **45**(4): p. 319-31.
42. Meneghini, F., et al., *Screening Instrument for a neuroepidemiological survey in Sicily, Italy (the SNES study): Validation in a hospital population.* Neuroepidemiology, 1990. **9**: p. 169.
43. Das, S.K., et al., *A random sample survey for prevalence of major neurological disorders in Kolkata.* Indian Journal of Medical Research, 2006: p. 163-172.

44. Gourie-Devi, M., et al., *Neuroepidemiological pilot survey of an urban population in a developing country. A study in Bangalore, South India.* Neuroepidemiology, 1996. **15**: p. 313-320.
45. Anderson, D.W., M.O. Melcon, and R.H. Vergara, *Methods for a Prevalence Survey of neurological Disorders in Junin, Buenos Aires, Argentina.* Neuroepidemiology, 1995. **14**: p. 110-122.
46. Vita, G., L. Mortagne, and F. Grigoletto, *Prevalence survey of major neurological disorders in Siciliy.* Journal of Neurology 1989. **236**: p. 315-318.
47. Nicoletti, A., *A screening instrument for a Sicilian neuroepidemiological survey in the elderly.* Archives of Gerontology and Geriatrics, 2004. **38**: p. 37-44.
48. Bharucha, N.E., et al., *Pilot survey of the prevalence of neurologic disorders in the Parsi Community of Bombay.* Am J Prev Med, 1987. **3**: p. 293-299.
49. Meneghini, F., et al., *Door-to-Door Prevalence Survey of Neurological Diseases in a Sicilian Population.* Neuroepidemiology, 1991. **10**: p. 70-85.
50. Haerer, A.F., D.W. Anderson, and B.S. Schoenberg, *Survey of Major Neurologic Disorders in a Biracial United States Population: The Copiah County Study.* Southern Medical Journal, 1987. **80**(3): p. 339-343.
51. Gourie-Devi, M., V.N. Rao, and R. Prakashi, *Neuroepidemiological Study in Semiurban and Rural Areas in South India: Pattern of Neurological Disorders Including Motor Neurone Disease.* Motor Neurone Disease, 1987: p. 11-21.
52. Gourie-Devi, M., et al., *Prevalence of Neurological Disorders in Banglaore, India: A community-based study with a comparison between urban and rural areas.* Neuroepidemiology, 2004. **23**: p. 261-268.
53. Das, S.K., et al., *Prevalence of major neurological disorders among geriatric population in the metropolitan city of kolkata.* Journal of the association of physicians of india, 2008. **56**: p. 175-181.
54. Quet, F., et al., *Determining the burden of neurological disorders in populations living in tropical areas: who would be questioned? Lessons from a Mexican rural community.* Neuroepidemiology, 2011. **36**(3): p. 194-203.
55. Stuck, A.E., *Comprehensive geriatric assessment for older adults.* British Medical Journal, 2011. **343**: p. d6799.
56. Howitt, S.C., et al., *A cross-sectional study of quality of life in incident stroke survivors in rural northern Tanzania.* J Neurol., 2011. **Published online, doi 10.1007/s00415-011-5948-6**: p. accessed online 16th March 2011.
57. Sarangmath, N., *Validity of a modified Parkinson's disease screening questionnaire in India: effects of literacy of participants and medical training of screeners and implications for screening efforts in developing countries.* Movement Disorders, 2005. **20**(12): p. 1550-56.
58. Das, S.K. and K. Sanyal, *Neuroepidemiology of major neurological disorders in rural Bengal.* Neurol India, 1996. **44**: p. 47-58.
59. Twelves, D., K. Perkins, and C. Counsell, *Systematic review of incidence studies of Parkinson's disease.* Movement Disorders, 2003. **18**(1): p. 19-31.
60. Das, S., K. Sanyal, and A. Mitra, *A pilot study of neurepidemiology in urban bengal.* Indian Journal of Public Health, 1998. **42**: p. 34-41.
61. Saha, S.P., et al., *Epidemiological Study of Neurological Disorders in a Rural Population of Eastern India.* Journal of Indian Medical Assocation, 2003. **101**: p. 299-304.
62. Sousa, R.M., et al., *Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey.* The Lancet, 2009. **374**: p. 1823-30.

63. Royal College of Physicians, *Physical Disability in 1986 and beyond. A report of the Royal College of Physicians* Journal of the Royal College of Physicians of London, 1986. **20**(3): p. 160-94.
64. Martin, J., H. Metzer, and D. Elliot, *The prevalence of disability in adults, OPCS surveys of disability in Great Britain. Report 1.* HMSO, 1988.
65. Jette, A.M. and L.G. Branch, *The Framlington Disability Study: II. Physical disability among the aging.* American Journal of Public Health, 1981. **71**(11): p. 1211-6.
66. Pomeranz, B., et al., *Prosthetics and orthotics for the older adult with a physical disability.* Clinical Geriatric Medicine, 2006. **22**(2): p. 377-94.
67. Colin, C., et al., *The Barthel Index: a standard measure of physical disability?* International Disability Study, 1988. **10**(2): p. 64-7.
68. Gosman-Hedstrom, G. and E. Svensson, *Parallel reliability of the Functional Independence Measure and the Barthel ADL index.* 2000. **22**(16): p. 702-715.
69. World Health Organisation, *What are Neurological Disorders.* website: www.who.int/features/qa/55/en/index.html, 2007.
70. World Health Organisation, *International Classification of Disease (ICD).* Website: www.who.int/classifications/icd/en/, 1994.
71. World Health Organisation, *ICD Version 2007 Diseases of the Nervous System.* website: www.who.int/classifications/apps/icd/icd10online/, 2007.
72. National Institute of Neurological Disorders and Stroke, *National Institute of Neurological Disorders and Stroke Disorders A - Z.* Website: www.ninds.nih.gov/disorders/disorder_index.htm.
73. Brucki, S.M. and R. Nitrini, *Subjective memory impairment in a 574 rural population with low education in the Amazon rainforest: an 575 exploratory study.* Int Psychogeriatr, 2009. **21**: p. 164-171.
74. O'Brien, M.D., *Taking a neurological history.* Medicine 2004. **32**(9): p. 1-6.
75. Parry, E., et al., eds. *Principles of Medicine in Africa*. 2004, Cambridge university press: Cambridge.
76. Manji, H., et al., *Oxford Handbook of Neurology*, ed. O.M. Publications. 2007: Oxford Medical Publications.
77. Movement Disorder Society. *www.movementdisorders.org/disorders*. 2012.
78. Medical Research Council, *Aids to the examination of the peripheral nervous system.* Memorandum no. 45, Her Majesty's Stationery Office, London 1981.
79. Kennedy, A. and R. Zakariaa, *Taking a Neurological History.* Medicine, 2008. **36**(10): p. 509-514.
80. www.guardian.co.uk.
81. Cohen, A.B., J.P. Klein, and S. Mukundan, *A guide to imaging for common neurological problems.* British Medical Journal, 2010. **341**: p. 4113.
82. Mallick, A. and A. Weir, *Nerve Conduction Studies: Essentials and Pitfalls in Practice.* Neurology Neurosurgery and Psychiatry, 2005. **76**: p. ii23-ii31.
83. Tripepi, G., et al., *An overview of standard statistical methods for assessing exposure-outcome link in survival analysis (Part I): basic concepts.* Aging-Clinical & Experimental Research, 2012. **2012**(24): p. 109-12.
84. Porta, M., S. Greenland, and J.M. Last, *A Dictionary of Epidemiology*. Vol. 5th Edition. 2008: New York Oxford University Press.
85. Chan, D., *Pilot study of prevalence of Parkinson's disease in Australia.* Neuroepidemiology, 2001. **20**(2): p. 112-117.
86. Deuschl, G., et al., *Consensus Statement of the Movement Disorder Society on Tremor.* Movement Disorders, 1998. **13**(Supplement 3): p. 2-23.
87. National Institute of Health, *NIH Collaborative Genetic Criteria for essential tremor.* 1996.

88. Fahn, S., E. Tolosa, and C. Martin, *Clinical rating scale for tremor* Parkinson's Disease and Movement Disorders, 1993: p. 271-280.
89. Deuschl, G., et al., *Physiologic classification of essential tremor* Handbook of Tremor Disorders. New York, 1995: p. 195-208.
90. Louis, E.D., et al., *Diagnostic Criteria for Essential Tremor.* Archives of Neurology, 1998. **55**: p. 823-828.
91. Louis, E.D., R. Ottman, and W.A. Hauser, *How common is the most common adult movement disorder? estimates of the prevalence of essential tremor throughout the world.* Movement Disorders, 1998. **13**(1): p. 5-10.
92. Louis, E., K. Marder, and L. Cote, *Differences in the prevalence of essential tremor among elderly African Americans, whites and Hispanics in Northern Manhattan, NY.* Arch Neurol, 1995. **52**: p. 1201-1205.
93. Rautakorpi, I., J. Takala, and R. Marttila, *Essential tremor in a Finnish population. .* Acta Neurol Scand, 1982. **66**: p. 58-67.
94. Tan, L., N. Venketasubramanian, and V. Ramasamy, *Prevalence of essential tremor in Singapore: a study of three races in an Asian country.* Parkinsonism Relat Disorders, 2005: p. 233-239.
95. Aiyesimoju, A., B. Osuntokun, and O. Bademosi, *Hereditary neurodegenerative disorders in Nigerian Africans.* Neurology 1984. **34**: p. 361-362.
96. Dotchin, C.L. and R.W. Walker, *The prevalence of essential tremor in rural northern Tanzania.* Journal of Neurology Neurosurgery Psychiatry 2008. **79**: p. 1107-1109.
97. Louis, E.D., B. Ford, and H. Lee, *Does a screening questionnaire for essential tremor agree with the physician's examination?* Neurology, 1998. **50**: p. 1351-1357.
98. Okubadejo, N., et al., *Prevalence of essential tremor in urban Lagos, Nigeria: a door-to-door community-based study.* BMC Neurology, 2012. **12**: p. 110.
99. Longe, A.C. and B.O. Osuntokun, *Prevalence of neurological disorders in Udo, a rural community in southern Nigeria.* Tropical and Geographical Medicine, 1989. **41**(1): p. 36-40.
100. Sur, H., et al., *Prevalence of essential tremor: a door-to-door survey in Sile, Istanbul, Turkey.* Parkinsonism Relat Disord 2009. **15**: p. 101-104.
101. Mancini, M., F. Stracci, and N. Tambasco, *Prevelance of essential tremor in the territory of Lake Trasimeno, Italy: results of a population-based study.* Mov Disord, 2007. **22**: p. 540-545.
102. Dogu, O., et al., *Essential tremor in Rochester, Minnesota: a 45-year study.* J Neurol Neurosurg Psychiatry, 1984. **47**: p. 466-470.
103. Benito-León, J., et al., *Prevalence of essential tremor in three elderly populations of central Spain.* Movement Disorders, 2003. **18**(4): p. 389-394.
104. Louis, E.D., S.P. Thawani, and H.F. Andrews, *Prevalence of Essential Tremor in a Multiethnic, Community-Based Study in Northern Manhattan, New York, N.Y.* Neuroepidemiology, 2009. **32**: p. 208-214.
105. Louis, E.D., et al., *Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community- based family study.* Ann Neurol 2001. **49**(6).
106. Prakash, K. and E. Tan, *Validity of family history in essential tremor.* Parkinsonism Relat Disorders, 2008. **14**: p. 151-153.
107. Tan, E., et al., *Non-motor manifestations in essential tremor: use of a validated instrument to evaluate a wide spectrum of symptoms. .* Parkinsonism Relat Disorders, 2005. **11**(6): p. 375-380.
108. Hornabrook, R. and J. Nagurney, *Essential tremor in Papua New Guinea. .* Brain, 1976. **99**: p. 659-672.

109. Louis, E.D., L. Fried, and A. Fitzpatrick, *Regional and racial differences in the prevalence of physician-diagnosed essential tremor in the United States.* Mov Disord 2003. **18**: p. 1035-1040.
110. Hubble, J., K. Busenbark, and R. Pahwa, *Clinical expression of essential tremor: effects of gender and age.* Mov Disord, 1997. **12**: p. 969-972.
111. Hardesty, D., D. Maraganore, and J. Matsumoto, *Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester epidemiology project.* Mov Disord, 2004. **19**: p. 529-533.
112. Cohen, O., S. Pullman, and E. Jurewicz, *Rest tremor in patients with essential tremor: prevalence, clinical correlates and electrophysiologic characteristics.* Arch Neurol, 2003. **60**: p. 405-410.
113. Louis, E., K. Wendt, and S. Pullman, *Is essential tremor symmetric?* Arch Neurol, 1998. **55**: p. 1553-1559.
114. Rajput, A., C. Robinson, and A. Rajput, *Essential tremor course and disability: a clinicopathologic study of 20 cases.* Neurology, 2004. **62**: p. 932-936.
115. Bain, P.G., L. Findley, and P. Thompson, *A study of hereditary essential tremor.* Brain 1994. **117**: p. 805-824.
116. Bain, P.G., *The Management of Tremor.* Journal of Neurology Neurosurgery and Psychiatry, 2002. **72**: p. Suppl i3-i9.
117. Benito-Leon, J., F. Bermejo-Pareja, and E.D. Louis, *Neurological disorders in central Spain (NEDICES) study group. Incidence of essential tremor in three elderly populations of central Spain.* Neurology, 2005. **64**: p. 1721-1725.
118. National Institute of Clinical Excellence, *Parkinson's Disease diagnosis and management in primary and secondary care.* www.nice.org.uk, 2006.
119. Rajput, A.H., B. Rozdilsky, and A. Rajput, *Accuracy of clinical diagnosis in Parkinsonism - A prospective study.* Canadian Journal of Neurological Sciences., 1991. **18**(3): p. 275-278.
120. Hughes, A.J., S.E. Daniel, and L. Kilford, *Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases.* Journal of Neurology, Neurosurgery & Psychiatry., 1992. **55**(3): p. 181-184.
121. Hughes, A.J., S.E. Daniel, and Y. Ben Shlomo, *The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service.* Brain, 2002. **125**: p. 4-70.
122. Hughes, A.J., S.E. Daniel, and A.J. Lees, *Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease.* Neurology, 2001. **57**(8): p. 1479-9.
123. Schrag, A., Y. Ben-Shlomo, and N. Quinn, *How valid is the clinical diagnosis of Parkinson's disease in the community?* J Neurol Neurosurg Psychiatry, 2002. **73**: p. 529-534.
124. Marras, C. and C. Tanner, *The Epidemiology of Parkinson's Disease." In Movement Disorders Neurologic Principles and Practice*, ed. K.W.C. Watts R.L. 2002, New York: McGraw-Hill.
125. Tanner, C. and S. Goldman, *Epidemiology of Parkinson's Disease.* Neurology Clinics, 1996. **14**: p. 317-35.
126. Ascherio, A., et al., *Prospective Study of Caffeine Consumption and Risk of Parkinson's Disease in Men and Women.* Annals of Neurology, 2001. **50**(1): p. 56-63.
127. Balogou, A.A.K., A. Doh, and K.E. Grunitzky, *Affectations neurologiques et endemie goitreuse: analyse comparative de deux provinces du Togo.* Bull Bull Soc Pathol Exot, , 2001. **94**(5): p. 406-410.
128. Dotchin, C.L., *The Prevalence of Parkinson's disease in rural Tanzania.* 2008. **23**(11): p. 1567-1572.
129. Anderson, D.W., et al., *Case ascertainment uncertainties in prevalence surveys in Parkinson's disease. .* Movement disorders 1998. **46**: p. 1052-1060.

130. Mayeux, R., *The frequency of idiopathic Parkinson's disease by age, ethnic group and sex in Northern Manhatten, 1988-1993.* American Journal of Epidemiology, , 1995. **142**(8): p. 820-827.
131. Winkler, A.S., et al., *Parkinsonism in a population of northern Tanzania: a community-based door-to-door study in combination with a prospective hospital-based evaluation.* Neurology, 2010. **257**(5): p. 799-805.
132. Bharucha, N.E., et al., *Prevalence of Parkinson's disease in the Parsi community of Bombay, India. .* Arch Neurol, 1988. **45**: p. 1321-1323.
133. Zhang, Z., et al., *Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai.* Lancet, 2005. **365**: p. 595-597.
134. Wickremaratchi, M., et al., *Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis.* J Neurol Neurosurg Psychiatry, 2009. **80**: p. 805-807.
135. de Rijk, C.M., et al., *Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study.* Journal of Neurology, Neurosurgery, and Psychiatry, 1997. **62**: p. 10-15.
136. Leonardi, M., *Neurology and Public Health in Developing Countries.* Recent Advances in Tropical Neurology, 1995: p. 1-6.
137. Razdan, S., et al., *Epidemiology of Neurological disorders in Kashmir.* Neuroepidemiology, 1994. **13**: p. 113-119.
138. Gourie-Devi, M., G. Gururaj, and P. Satishchandra, *Neuroepidemiology in developing countries. A manual for descriptive studies. .* Prism Books Pvt. Ltd.,Bangalore, 1997.
139. Gourie-Devi, M., G. Gururaj, and P. Satishchandra, *Bangalore Urban and Rural Neurological Survey. Report to Indian Council of Medical Research,.* 1995.
140. Anand, K.S. and M.M. Singh, *Pattern of neurological disorders above the middle aged population in JIPMER, Pondicherry.* Neurology India, 1993. **41**: p. 165-168.
141. Ragothaman, M., et al., *High occurrence and low recognition of Parkinson's disease in Elderly Homes in Bangalore, India: Implications for healthcare of elderly.* Movement Disorders., 2006.
142. Wadia, N.H. and R.K. Swami, *A new form of heredo-familial spinocerebellar degeneration with slow eye movements (nine families).* Brain, 1971. **94**: p. 359-374.
143. Wadia, N.H. and K. Bhatia, *Multiple Sclerosis is prevalent in the Zoroastrians (Parsis) of India.* Ann Neurol, 1990. **28**: p. 177-179.
144. Muthane, U.B., M. Ragothaman, and G. Gururaj, *Epidemiology of Parkinson's Disease and Movement Disorders in India: Problems and Possibilities* JAPI, 2007. **55**: p. 719-724.
145. Gourie-Devi, M., et al., *Prevalence of Parkinson's disease in Bangalore. A door to door survey of urban and rural population.* Neurology India, 1999. **47**: p. 73.
146. Calne, D.B., B.J. Snow, and C. Lee, *Criteria for diagnosing Parkinson's disease.* Ann Neurol, 1992. **32**: p. S125-S127.
147. Zhang, Z.X., D.W. Anderson, and J.B. Huang, *Prevalence of Parkinson's disease and related disorders in the elderly population of greater Beijing, China.* Mov Disord 2003. **18**: p. 764-772.
148. Porter, B., et al., *The Prevalence of Parkinson's Disease in an Area of North Tyneside in the North-East of England.* Neuroepidemiology, 2006. **26**(3): p. 156-161.
149. Hobson, P., J. Gallacher, and J. Meara, *Cross-sectional survey of Parkinson's disease and parkinsonism in a rural area of the United Kingdom.* Mov Disord, 2005. **20**: p. 995-998.
150. Schrag, A., Y. Ben-Shlomo, and N.P. Quinn, *Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. .* BMJ, 2000. **321**: p. 21-2.
151. MacDonald, B.K., et al., *The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK.* Brain, 2000. **123**: p. 665-676.

152. Mutch, W.J., I. Dingwall-Fordyce, and A.W. Downie, *Parkinson's disease in a Scottish city.* BMJ, 1986. **292**: p. 534-536.
153. Sutcliffe, R.L., R. Prior, and B. Mawby, *Parkinson's disease in the district of the Northampton Health Authority, United Kingdom. A study of prevalence and disability.* Acta Neurol Scand, 1985. **72**: p. 363-379.
154. Brewis, M., D.C. Poskanzer, and C. Rolland, *Neurological disease in an English city.* Acta Neurol Scand, 1966. **42 (Suppl 24)**: p. 1-89.
155. Broe, G.A., A.J. Akhtar, and G.R. Andrews, *Neurological disorders in the elderly at home.* Journal of Neurology Neurosurgery and Psychiatry, 1976 **39**: p. 362-366.
156. Schoenberg, B.S., D.W. Anderson, and A.F. Haerer, *Prevalence of Parkinson's disease in the biracial population of Copiah county, Mississippi.* Neurology, 1985. **35**: p. 841-845.
157. Van Den Eeden, S.K., et al., *Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity.* American Journal of Epidemiology, 2003. **157**(11): p. 1015-22.
158. Berger, K.M., et al., *Prognosis with Parkinson's Disease in Europe: A Collaborative Study of Population-Based Cohorts: Neurologic Diseases in the Elderly Research Group.* Neurology, 2000. **54**(11 Suppl 5): p. S24-27.
159. Mathers, C.D., *Global burden of disease in 2002:data sources, methods and results.* GPE Discussion Paper, 2004. **54**.
160. Dotchin, C.L., O. Msuya, and R.W. Walker, *The challenge of Parkinson's disease management in Africa.* Age Ageing, 2007. **36**(2): p. 122-127.
161. Dotchin, C.L., J. A., and W. R.W., *Three year follow up of Levodopa plus Carbidopa treatment in a prevalent cohort of patients with Parkinson's disease in Hai, Tanzania.* J Neurol., 2011: p. (in press).
162. Cilia, R., et al., *Parkinson's disease in sub-Saharan Africa: step-by-step into the challenge.* Neurodegenerative Disease Management, 2011. **1**(3): p. 193-202.
163. Litvan, I., et al., *Movement Disorders Society Scientific Issues Committee Report SIC Task Force Appraisal of Clinical Diagnostic Criteria for Parkinsonian Disorders.* Movement Disorders, 2003. **18**(5): p. 467-486.
164. Grosset, D., *Differential Diagnosis ofParkinsonism and Tremor*, in *Birmingham Movement Disorders Course*. 2010: Birmingham. p. 39-54.
165. Nath, U., et al., *Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study.* Neurology, 2003. **2003**(60): p. 910-6.
166. Osaki, Y., Y. Ben-Shlomo, and A.J. Lees, *Accuracy of clinical diagnosis of progressive supranuclear palsy.* Movement Disorders, 2003. **19**: p. 181-9.
167. Litvan, I., G. Campbell, and C.A. Mangone, *Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steel-Richardson-Olszewski syndrome): report of the NINDS-SPS international workshop.* Neurology, 1996. **1996**(47): p. 1-9.
168. Gilman, S., G.K. Wenning, and P.A. Low, *Second consensus statement on the diagnosis of multiple system atrophy.* Neurology, 2008. **26**(71): p. 9.
169. Mahapatra, R.K., et al., *Corticobasal degeneration.* Lancet Neurology 2004. **3**: p. 736-43.
170. Thanvi, B., N. Lo, and T. Robinson, *Vascular parkinsonism—an important cause of parkinsonism in older people.* Age and Ageing, 2005. **34**: p. 114-119.
171. Winikates, J. and J. Jankovic, *Clinical correlates of vascular parkinsonism.* Arch Neurol, 1999. **56**: p. 98-102.
172. Hirose, G., *Drug Induced Parkinsonism. A Review. .* Journal of Neurology 2006. **253**(Supplement 3): p. 3004-8.
173. Hebb, A.O. and M.D. Cusimano, *Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome.* Neurosurgery, 2001. **49**(5): p. 1166-1186.

174. World Health Organisation, *Atlas of headache disorders and resources in the world 2011. A collaborative project of the World Health Organisation and Lifting The Burden. .* http://www.who.int/mental_health/management/who_atlas_headache_disorders.pdf.
175. Steiner, T.J., *Lifting the burden: the global campaign against headache.* Lancet Neurol, 2004. **3**: p. 204-5.
176. Headache Classification Committee of the International Headache Society, *Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain.* Cephalalgia, 1988. **8**(Suppl. 7): p. 1-96.
177. International Headache Society, *ICD-10 Guide for Headaches.* Cephalalgia, 1997. **17**: p. 1-91.
178. Headache Classification Subcommittee of the International Headache Society, *The International Classification of Headache Disorders, 2nd Edition.* Cephalalgia, 2004. **24**: p. 1-160.
179. International Headache Society, *International classification of headache disorders - Second edition.* International headache society website www.ihs-classification.org, 2003.
180. Stovner, L.J., et al., *The global burden of headache: a documentation of headache prevalence and disability worldwide* Cephalalgia, 2007. **27**: p. 193-210.
181. Rasmussen, B.K., *Epidemiology of headache.* Cephalalgia, 1995. **15**: p. 45-68.
182. World Health Organisation, *Factsheet 277* *http://www.who.int/mediacentre/factsheets/fs277/en/index.html* *http://www.who.int/mental_health/neurology/headache/en/index.html.* 2012.
183. Castillo, J., *Epidemiology of chronic daily headache in the general population.* Headache, 1999. **39**: p. 190-196.
184. Srikiatkhachorn, A. and K. Phanthumchinda, *Prevalence and clinical features of chronic daily headache in a headache clinic. .* Headache 1997. **37**: p. 277-280.
185. Fischera, M., et al., *The incidence and prevalence of cluster headache: a meta-analysis of population based studies.*
186. Alders, E.E., A. Hentzen, and C.T. Tan, *A community-based prevalence study on headache in Malaysia.* Headache 1996. **36**: p. 379-384.
187. Tekle-Haimanot, R., B. Seraw, and L. Forsgren, *Migraine, chronic tension-type headache, and cluster headache in an ethiopian rural community.* Cephalalgia, 1995. **15**: p. 482-488.
188. Scher, A.I., W.F. Stewart, and R.B. Lipton, *Migraine and headache: a meta-analytic approach.* Epidemiology of pain., 1999: p. 159-170.
189. Lisk, D.R., *Severe headache in the African. report on 250 cases from Sierra Leone, West Africa.* Headache, 1987. **27**: p. 477-483.
190. Matuja, W.B., *Headache: pattern and features as experienced in a neurology clinic in Tanzania.* East Afr Med J 1991. **68**: p. 935-943.
191. Matuja, W.B., I.B. Meteza, and H.T. Rwiza, *Headache in a nonclinical population in Dar es Salam, Tanzania.* Headache, 1995. **35**: p. 273-276.
192. Adoukonou, T., et al., *Migraine Among University Students in Cotonou (Benin)* Headache, 2009. **49**: p. 887-893.
193. Osuntokun, B.O., et al., *Migraine Headache in a Rural Community in Nigeria: Results of a Pilot Study.* Neuroepidemiology, 1982. **1**: p. 31-39.
194. Osuntokun, B.O., et al., *Prevalence of headache and migrainous headache in Nigerian Africans: a community based study.* East Afr Med J, 1992. **69**: p. 196-199.
195. Levy, L.M., *An epidemiological study of headache in an urban population in Zimbabwe.* Headache, 1983. **23**: p. 2-9.
196. Dent, W., et al., *Prevalence of migraine in a rural area of South Tanzania: a door to door survey.* Cephalgia, 2004. **24**: p. 960-966.
197. Ba´nk, J. and S. Ma´ rton, *Hungarian migraine epidemiology.* Headache, 2000. **40**: p. 164-9.

198. Göbel, H., M. Petersen-Braun, and D. Soyka, *The epidemiology of headache in Germany: a nationwide survey of a representative sample on the basis of the headache classification of the International Headache Society.* Cephalalgia, 1994. **14**: p. 97-106.
199. Stewart, W.F., et al., *Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors.* JAMA 1992. **267**: p. 64-9.
200. O'Brien, B., R. Goeree, and D. Steiner, *Prevalence of migraine headache in Canada: a population-based survey.* Int J Epidemiology, 1994. **23**: p. 1020-6.
201. Wong, T.W., et al., *Prevalence of migraine and other headaches in Hong Kong.* Neuroepidemiology 1995. **14**: p. 82-91.
202. Zaho, F., et al., *Epidemiology of migraine: a survey in 21 provinces of the People's Republic of China,.* Headache, 1988. **28**: p. 558-65.
203. Cheng, X.M., et al., *An epidemiologic survey of migraine in six cities in China. .* Chin J Neurol 1990. **23**: p. 44-6.
204. Houinato, D., et al., *Prevalence of Migraine in a Rural Community in South Benin* Cephalalgia, 2010. **30**(1): p. 62-67.
205. Winkler, A.S., et al., *The Prevalence of Headache With Emphasis on Tension-Type Headache in Rural Tanzania: A Community-Based Study* Cephalalgia, 2009 **29**(12): p. 1317-1325.
206. Winkler, A.S., et al., *Prevalence of migraine headache in a rural area of northern Tanzania: a community-based door-to-door survey.* Cephalalgia, 2010. **30**(5): p. 582-592.
207. Ogunyemi, A.O., *Prevalence of headache among Nigeria University students. .* Headache, 1984. **24**: p. 127-30.
208. Friedman, A.P., et al., *Classification of headache (Ad Hoc committee on classification of headache).* JAMA, 1962. **179**: p. 717-8.
209. The World Health Organization, *WHO MONICA project (monitoring trends and determinanats in cardiovascualr disease) a major international collaberation* Journal of clinical epidemiology, 1988. **41**: p. 105-114.
210. Poungvarin, N., A. Viriyavejakul, and C. Komontri, *Siriraj Stroke Score and Validation Study to Distinguish Supratentorial Intracerebral Haemorrhage from infarction.* British Medical Journal, 1991. **302**: p. 1565-1567.
211. Celani, M.G., E. Righetti, and R. Migliacci, *Comparibility and validity of two clinical scores in the early differential diagnosis of acute stroke* British Medical Journal, 1994 **308**: p. 1674-1676.
212. Bamford, J., et al., *Classification and natural history of clinically identifiable subtypes of cerebral infarction.* Lancet, 1991. **337**(8756): p. 1521-1526.
213. Walker, R., et al., *Stroke incidence in rural and urban Tanzania: a prospective, community-based study.* Lancet Neurology, 2010. **9**(8): p. 786-792.
214. Lopez, A.D., et al., *Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data.* Lancet, 2006. **367**: p. 1747-57.
215. Mathers, C.D., et al., *The burden of disease and mortality by condition: data, methods and results for 2001.* Global burden of disease and risk factors.New York Oxford University Press, 2006: p. 45-240.
216. Connor, M.D., et al., *Burden of stroke in black populations in sub-Saharan Africa.* Lancet Neurology, 2007. **6**(3): p. 269-278.
217. Mahony, P.G., et al., *Validation of a population screening questionnaire to assess prevalence of stroke.* Stroke, 1995. **26**: p. 1334-37.
218. Geddes, J.M., et al., *Prevalence of self reported stroke in a population in northern England.* J Epidemiol Community Health 1996. **50**: p. 140-43.

219. Connor, M.D., et al., *Prevalence of stroke survivors in rural South Africa: results from the Southern Africa Stroke Prevention Initiative (SASPI) Agincourt field site.* Stroke, 2004. **35**: p. 627-32.
220. Connor, M.D., et al., *The South African Stroke Risk in General Practice Study.* SAMJ, 2005. **95**: p. 334-338.
221. Bonita, R., N. Solomon, and J.B. Broad, *Prevalence of Stroke and Stroke-Related Disability Estimates From the Auckland Stroke Studies* Stroke, 1997. **28**: p. 1898-1902.
222. Danesi, M., N. Okubadejo, and F. Ojini, *Prevalence of stroke in an urban, mixed-income community in Lagos, Nigeria.* Neuroepidemiology, 2007. **28**(4): p. 216-223.
223. Cossi, M.J., et al., *Stroke: prevalence and disability in Cotonou, Benin.* Cerebrovascular Diseases., 2012. **33**(2): p. 166-72.
224. Sudlow, C.L.M. and C.P. Warlow, *Comparing stroke incidence worldwide.* Stroke, 1996. **27**: p. 550-558.
225. Feigin, V.L., et al., *Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review.* Lancet Neurol, 2009. **8**: p. 355-69.
226. Lavados, P.M., C. Sacks, and L. Prina, *Incidence, 30-day case-fatality rate, and prognosis of stroke in Iquique, Chile: a 2-year community-based prospective study (PISCIS project).* Lancet, 2005. **365**: p. 2206-15.
227. Corbin, D.O.C., V. Poddar, and A. Hennis, *Incidence and case fatality rates of fi rst-ever stroke in a black Caribbean population: the Barbados register of strokes. .* Stroke, 2004. **35**: p. 1254-58.
228. Minelli, C., L.F. Fen, and D.P.C. Minelli, *Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matao, Brazil: a population-based prospective study.* Stroke, 2007. **38**: p. 2906-11.
229. Dalal, P.M., S. Malik, and M. Bhattacharjee, *Population-based stroke survey in Mumbai, India: incidence and 28-day case fatality.* Neuroepidemiology, 2008. **31**: p. 254-61.
230. Wang, W.Z., B. Jiang, and S.P. Wu, *Change in stroke incidence from a population-based intervention trial in three urban communities in China.* Neuroepidemiology, 2007. **28**: p. 155-61.
231. Edwards, R., N. Unwin, and F. Mugusi, *Hypertension prevalence and care in an urban and rural area of Tanzania.* J Hypertens, 2000. **18**: p. 145-52.
232. Aspray, T.J., F. Mugusi, and S. Rashid, *Rural and urban differences in diabetes prevalence in Tanzania: the role of obesity, physical inactivity and urban living. .* Trans R Soc Trop Med Hyg, 2000. **94**: p. 637-44.
233. Osuntokun, B.O., et al., *Incidence of stroke in an African city: results from the stroke registry at Ibadan, Nigeria, 1973–1975. .* Stroke 1979. **10**: p. 205-07.
234. Matenga, J., *Stroke incidence rates among black residents of Harare: a prospective community-based study. .* S Afr Med J 1997. **87**: p. 606-09.
235. Rosman, K.D., *The epidemiology of stroke in an urban black population.* Stroke, 1986. **17**: p. 667-69.
236. Walker, R.W., et al., *Stroke Mortality in Urban and Rural Tanzania: Adult Morbidity and Mortality Project.* The Lancet, 2000. **335**(9216): p. 1684-1687.
237. Sacco, R.L., B. Boden-Albala, and R. Gan, *Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. .* Am J Epidemiol 1998. **147**: p. 259-68.
238. Feigin, V.L., et al., *Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century.* Lancet Neurol 2003. **2**: p. 43-53.
239. Razum, O., *Monitoring cardiovascular disease in Zimbabwe: a review of needs and options. .* Cent Afr J Med 1996. **42**: p. 120-24.

240. Bradshaw, D., et al., *South African cause-of-death profi le in transition—1996 and future trends.* S Afr Med J, 2002. **92**: p. 618-23.
241. Dennis, M.S., et al., *Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain.* BMJ, 1987. **295**: p. 379-81.
242. Dennis, M.S., J.M. Bamford, and C.P. Warlow, *Strokes among black people in Harare, Zimbabwe [letter]. .* BMJ ClinRes, 1994: p. 134.
243. Warlow, C.P., *Epidemiology of stroke.* Lancet 1998. **352**: p. 1-4.
244. Murray, C.J.L. and A.D. Lopez, *Mortality by cause for eight regions of the world: global burden of disease study.* Lancet 1997. **249**: p. 1269-76.
245. Lisk, D.R. and E.K. McEwen, *The significance and trend of hypertension related deaths in urban Sierra Leonean Africans.* J Hum Hypertens, 1996. **10**: p. 215-18.
246. INDEPTH network, *Population and health in developing countries. Ottawa: International Development Research Centre,.* 2002.
247. Kahn, K. and S.M. Tollman, *Stroke in rural South Africa-contributing to the little known about a big problem.* South African Medical Journal,, 1999. **77**: p. 248-251.
248. Office for National Statistics, *Mortality statistics—cause: review of the Registrar General on deaths by cause, sex, and age, in England and Wales, 1993 (revised) and 1994.* Office of National Statistics: United Kingdom,, 1996.
249. Kahn, K., et al., *Validation and application of verbal autopsies in a rural area of South Africa.* Trop Med Int Health, 2000. **5**: p. 824-31.
250. Chukwumeka, A.C., J.O.M. Pobee, and E. Larbi, *Are cardiovascular diseases important causes of mortality in Africa? Results of a WHO/UGMS cardiovascular disease follow-up study over a five year period in a suburb of Accra. .* Trop Cardiol, 1982. **8**: p. 105-09.
251. Walker, A.R. and H. Grusin, *Coronary heart disease and cerebral vascular disease in the South African Bantu: examination and discussion of crude and age-specific death rates. .* Am J Clin Nutr, 1959. **7**: p. 264-70.
252. Walker, A.R., *Mortality from coronary heart disease and from cerebral vascular disease in the different racial populations in South Africa.* S Afr Med J, 1963. **37**: p. 1155-59.
253. Wyndham, C.H., *Mortality from cardiovascular diseases in the various population groups in the Republic of South Africa. .* S Afr Med J, 1979. **56**: p. 1023-30.
254. Wyndham, C.H., *Trends with time of cardiovascular mortality rates in the populations of the RSA for the period 1968–1977. .* S Afr Med J 1982. **61**: p. 987-93.
255. Botha, J.L. and D. Bradshaw, *African vital statistics—a black hole?* S Afr Med J, 1985. **67**: p. 977-81.
256. Unwin, N., *Non-communicable disease and priorities for health policy in sub-Saharan Africa.* Health Policy Plan, 2001. **16**: p. 351-52.
257. Caldwell, J.C., *Population health in transition.* Bull World Health Organ, 2001. **79**: p. 159-60.
258. Walker, R.W., N. Unwin, and K.G. Alberti, *Hypertension treatment and control in Sub-saharan Africa. Burden of cerebrovascular disease will increase as more people survive to old age. .* BMJ, 1998. **317**: p. 76-77.
259. Obiako, O.R., S.K. Oparah, and A. Ogunniyi, *Prognosis and outcome of acute stroke in the University College Hospital Ibadan, Nigeria.* Nigerian Journal of Clinical Practice, 2011. **14**(3).
260. Joubert, J., *The MEDUNSA stroke data bank: an analysis of 304 patients seen between 1986 and 1987.* S Afr Med J, 1991. **80**: p. 567-70.
261. Walker, R.W., et al., *Mortality and recovery after stroke in the Gambia.* Stroke, 2003. **34**: p. 1604-09.
262. Sene Diouf, F., A.M. Basse, and K. Toure, *Prognosis of stroke in department of neurology of Dakar.* Dakar Medical, 2006. **51**: p. 17-21.

263. Sene Diouf, F., A.M. Basse, and A.K. Ndao, *Pronostic fonctionnel des accidents vasculaires cerebraux dans les pays en voie de developpement : Senegal.* Ann Readapt Med Phys, 2006. **49**: p. 100-04.
264. Keir, S.L., J.M. Wardlaw, and C.P. Warlow, *Stroke epidemiology studies have underestimated the frequency of intracerebral haemorrhage: a systematic review of imaging in epidemiological studies.* J Neurol, 2002. **249**: p. 1226-31.
265. Wardlaw, J.M., S.L. Keir, and J. Seymour, *What is the best imaging strategy for acute stroke? .* Health Technol Assess 2004. **8**: p. 1-180.
266. Wiredu, E.K. and P.K. Nyame, *Stroke-related mortality at Korle Bu Teaching Hospital, Accra, Ghana.* East Afr Med J., 2001. **78**(4): p. 180-4.
267. Mensah, G.A., *Global burden of cardiovascular disease, Epidemiology of stroke and high blood pressure in Africa.* Heart 2008. **94**.
268. Mating, J., I. Kitai, and L. Levy, *Strokes among black people in Harare, Zimbabwe: results of computed tomography and associated risk factors.* BMJ (Clin Res Ed), 1986. **292**: p. 1649-51.
269. Connor, M.D. and C. Warlow, *Stroke in Sub-Saharan Africa: a systematic review (abstract). .* Stroke, 2000. **31**: p. 2793.
270. Marmot, M.G. and N.R. Poulter, *Primary prevention of stroke.* Lancet, 1992. **339**: p. 344-7.
271. Connor, M.D., G. Modi, and C.P. Warlow, *Accuracy of the Siriraj and Guy's Hospital Stroke Scores in urban South Africans.* Stroke, 2007. **38**: p. 62-68.
272. Nyame, P.K., K.B. Jumah, and S. Adjei, *Computerised tomographic scan of the head in evaluation of stroke in Ghanaians.* East Afr Med J, 1998. **75**: p. 637-39.
273. Kolapo, K.O., et al., *Validation study of the Siriraj Stroke score in African Nigerians and evaluation of the discriminant values of its parameters: a preliminary prospective CT scan study.* Stroke, 2006. **37**: p. 1997-2000.
274. Sandercock, P., A. Molyneux, and C. Warlow, *Value of computerised tomography in patients with stroke: the Oxfordshire Community Stroke Project.* BMJ 1985. **290**: p. 193-207.
275. National Stroke Association, *Recovery and Rehabilitation* National Stroke Association, Englewood www.stroke.org/homepage, 2002.
276. Chandra, V., et al., eds. *Disease control priorities in developing countries*. second ed., ed. e.a. Jamison D.T. 2006.
277. Thorvaldsen, P.K., et al., *Stroke Incidence, Case Fatality, and Mortality in the WHO MONICA Project: World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease.* Stroke, 1995. **26**(3): p. 361-367.
278. Smaha, L.A., *The American Heart Association Get with the Guidelines Program.* American Heart Journal, 2004. **148**(suppl 5): p. S46-48.
279. Chinese Acute Stroke Trial Collaborative Group, *CAST: Randomised Placebo-Controlled Trial of Early Aspirin Use in 20,000 Patients with Acute Ischaemic Stroke: CAST (Chinese Acute Stroke Trial) Collaborative Group.* The Lancet, 1997. **349**(9066): p. 1641-49.
280. International Stroke Trial Collaborative Group, *The International Stroke Trial (IST): A Randomised Trial of Aspirin, Subcutaneous Heparin, Both, or Neither among 19,435 Patients with Acute Ischaemic Stroke: International Stroke Trial Collaborative Group.* The Lancet, 1997. **349**(9065): p. 1569-81.
281. Antithrombotic Trialists' Collaboration, *Collaborative Meta-Analysis of Randomised Trials of Antiplatelet Therapy for Prevention of Death, Myocardial Infarction, and Stroke in High Risk Patients.* British Medical Journal, 2002. **324**(7329): p. 71-86.
282. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, *Tissue Plasminogen Activator for Acute Ischemic Stroke:The National Institute of Neurological*

Disorders and Stroke rt-PA Stroke Study Group. New England Journal of Medicine, 1995. **333**(24): p. 1581-87.
283. Sacco, R., J. Sivenius, and H.C. Diener, *Efficacy of Aspirin Plus Extended-Release Dipyridamole in Preventing Recurrent Stroke in High-Risk Populations.* Archives of Neurology, 2005. **62**: p. 403-8.
284. Diener, H.C., et al., *Aspirin and Clopidogrel Compared with Clopidogrel Alone after Recent Ischaemic Stroke or Transient Ischaemic Attack in High-Risk Patients (MATCH): Randomised, Double-Blind, Placebo-Controlled Trial.* The Lancet, 2004. **364**(9431): p. 301-7.
285. European Atrial Fibrillation Trial Study Group, *Secondary Prevention in Non-Rheumatic Atrial Fibrillation after Transient Ischaemic Attack or Minor Stroke.* The Lancet, 1993. **342**(8882): p. 1255-62.
286. Mohr, J.P., et al., *A Comparison of Warfarin and Aspirin for the Prevention of Recurrent Ischemic Stroke.* New England Journal of Medicine, 2001. **345**(20): p. 1444-51.
287. Asymptomatic Carotid Surgery Trial Collaborative Group, *Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients without Recent Neurological Symptoms: Randomised Controlled Trial.* The Lancet, 2004. **363**: p. 1491-502.
288. Asymptomatic Carotid Atherosclerosis Study, *Endarterectomy for Asymptomatic Carotid Artery Stenosis.* Journal of the American Medical Association, 1995. **273**(18): p. 1421-28.
289. North American Symptomatic Carotid Endarterectomy Trial Collaborators, *Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial Collaborators.* New England Journal of Medicine, 1991. **325**(7): p. 445-53.
290. Outpatient Service Trialists, *Therapy-Based Rehabilitation Services for Stroke Patients at Home.* Cochrane Database of Systematic Reviews (2) CD002925., 2002.
291. Commission on epidemiology and prognosis International league against epilepsy (ILAE), *Guidelines for epidemiological studies on epilepsy.* Epilepsia, 1993. **34**: p. 592-596.
292. Commision on classification and terminology of the international league against epilepsy, *Proposal for the revised clinical and electroencephalographic classification of epileptic seizures.* Epilepsia, 1981. **22**: p. 489-501.
293. Berg, A.T., et al., *Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009.* Epilepsia, 2010. **51**(4): p. 676–685.
294. Preux, P.M. and M. Druet Cabanac, *Epidemiology and aetiology of epilepsy in sub-Saharan Africa.* Lancet Neurol 2005. **4**: p. 21-31.
295. Newton, C.R. and H.H. Garcia, *Epilepsy in poor regions of the world.* Lancet, 2012. **380**(9848): p. 1193 - 1201.
296. World Health Organisation, *Epilepsy: an historical overview. Fact Sheet 168.* Geneva: WHO, 2001.
297. World Health Organisation and E.H. Reynolds, *The ILAE/IBE/WHO Global Campaign against Epilepsy: Bringing Epilepsy "Out of the Shadows". .* Epilepsy Behav, 2000. **1**: p. S3-S8.
298. World Health Organisation, *WHO Epigraph: The newsletter of the International League against Epilepsy.* Geneva 1999. **1**: p. 5-6.
299. Mosser, P., E. Schmutzhard, and A.S. Winkler, *The pattern of epileptic seizures in rural Tanzania. .* J Neurol Sci, 2007. **258**: p. 33-8.
300. Winkler, A.S., A. Tluway, and E. Schmutzhard, *Aetiologies of altered states of consciousness: A prospective hospital-based study in a series of 464 patients of northern Tanzania,.* Journal of the Neurological Sciences, 2011. **300**: p. 47-51.

301. Quet, F., et al., *Investigating epilepsy in Africa: 10 years of data collection using a standardized questionnaire in 2,269 peoples with epilepsy.* Epilepsia,, 2011. **52**(10): p. 1868-1876.
302. Debrock, C., et al., *Estimation of the prevalence of epilepsy in the Benin region of Zinvie using the capture-recapture method.* International Journal of Epidemiology, 2000. **29**: p. 330-335.
303. Kabre, D., *Epidemiologie de l'epilepsie dans le foyer d'Onchocercose du bassin de la Bougouriba (Burkina Faso).* These de Doctorat en Medecine Ouagadougou, 1998.
304. Nsengiyumva, G., M. Druet-Cabanac, and B. Ramanankandrasana, *Cysticercosis as a major risk factor towards epilepsy in Burundi, East Africa.* Epilepsia, 2003. **44**: p. 950-55.
305. Dongmo, L., et al., *Cysticercosis and epilepsy: a case–control study in Mbam Valley, Cameroon.* Bull Soc Pathol Exot, 2004. **97**: p. 105-108.
306. Farnarier, G., et al., *Onchocerciasis and epilepsy. Epidemiological survey in Mali.* Med Trop, 2000. **60**: p. 151-155.
307. Druet-Cabanac, M., P.M. Preux, and B. Bouteille, *Onchocerciasis and epilepsy: a matched case-control study in Central African Republic.* Am J Epidemiol 1999. **149**: p. 565-70.
308. Crepin, S., et al., *Link between Epilepsy and Malnutrition in a Rural Area of Benin.* Epilepsia,, 2007. **48**(10): p. 1926-1933.
309. Ngugi, A.K., et al., *Incidence of epilepsy: a systematic review and meta-analysis.* Neurology 2011. **77**: p. 1005-12.
310. Kaiser, C., G. Asaba, and M. Leichsenring, *High incidence of epilepsy related to onchocerciasis in West Uganda.* Epilepsy Res, 1998. **30**: p. 247-51.
311. Tekle-Haimanot, R., L. Forsgren, and J. Ekstedt, *Incidence of epilepsy in rural central Ethiopia. .* Epilepsia, 1997. **38**: p. 541-46.
312. Debouverie, M., et al., *Epidémiologie de l'épilepsie au Burkina-Faso* Neurologie Tropicale, Paris: John Libbey Eurotext, 1993: p. 57-61.
313. Rwiza, H.T., et al., *Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community-based study.* Epilepsia, 1992. **33**(6): p. 1051-1056.
314. Grunitzky, E.K., M. Dumas, and E.M. Mbella, *Les épilepsies au Togo.* Epilepsies, 1991. **3**: p. 295-303.
315. Winkler, A.S., et al., *Prevalence, incidence, and clinical characteristics of epilepsy--a community-based door-to-door study in northern Tanzania.* Epilepsia, 2009. **50**(10): p. 2310-2313.
316. Sander, J.W.A.S. and S.D. Shorvon, *Epidemiology of the epilepsies.* J Neurol Neurosurg Psychiatry, 1996. **61**: p. 433-43.
317. Forsgren, L., E.O. Beghi, and A. Sillanpa, *The epidemiology of epilepsy in Europe – a systematic review.* European Journal of Neurology, 2005. **12**: p. 245-253.
318. Forsgren, L., et al., *Epidemiology and prognosis of epilepsy and its treatment.* The treatment of epilepsy. Oxford: Blackwell Science, , 2004: p. 21-42.
319. Edwards, T., A.G. Scott, and G. Munyoki, *Active convulsive epilepsy in a rural district of Kenya: a study of prevalence and possible risk factors. .* Lancet Neurol, 2008. **7**: p. 50-56.
320. Cockerell, O.C., et al., *Epilepsy in a population of 6000 re-examined: secular trends in first attendance rates, prevalence, and prognosis.* J Neurol Neurosurg Psychiatry 1995. **58**: p. 570-76.
321. Mac, T.L., et al., *Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. .* Lancet Neurol, 2007. **6**: p. 533-43.
322. World Health Organisation, *Atlas: epilepsy care in the world.* Geneva: World Health Organization,, 2005.
323. Jallon, P., *Geographical distribution of epilepsy in the world.* Presse Med, 1996: p. 1876-1880.

324. Jallon, P., *Epilepsy in developing countries. .* Epilepsia 1997. **38**.
325. Mielke, J., M. Sebit, and B. Adamolekun, *The impact of epilepsy on the quality of life of people with epilepsy in Zimbabwe: A pilot study. .* Seizure, 2000. **9**: p. 259-264.
326. Birbeck, G.L., *Epilepsy Curr* Epilepsy care in developing countries: part I of II. , 2010. **10**: p. 75-79.
327. Osuntokun, B.O., A.O. Adeuja, and V.A. Nottidge, *Prevalence of the epilepsies in Nigerian Africans: a community-based study.* Epilepsia, 1987. **28**: p. 272-79.
328. Grunitzky, E.K., A.K. Balogou, and K. Agboli, *Cartographie des épilepsies au Togo.* Communication presented to the 12th Congress of the Pan-African Association of Neurological Sciences, Durban (South Africa), , 1996: p. 19-23.
329. Dumas, M., K. Grunitzky, and M. Deniau, *Epidemiological study of neurocysticercosis in Northern Togo (West Africa).* Acta Leidensia, 1989. **57**: p. 191-96.
330. Balogou, A.A.K., K.E. Grunitzky, and K.A. Beketi, *Cysticercose et épilepsie au nord du Togo dans le Tone. .* Rev Neurol 2000. **156**: p. 270-73.
331. Ngugi, A.K., et al., *Estimation of the burden of active and life-time epilepsy: a meta-analytic approach.* Epilepsia 2010. **51**: p. 883-90.
332. Munyoki, G., et al., *Clinical and neurophysiologic features of active convulsive epilepsy in rural Kenya: A population-based study.* Epilepsia, 2010. **51**(12): p. 2370-2376.
333. Hunter, E., et al., *Prevalence of active epilepsy in rural Tanzania: A large community-based survey in an adult population.* Seizure, 2012. **21**: p. 691-698.
334. Banerjeea, P.N., D. Filippi, and W.A. Hauser, *The descriptive epidemiology of epilepsy –a review. .* Epilepsy Research, 2009. **85**: p. 31-45.
335. Nitiéma, P., et al., *Prevalence case-control study of epilepsy in three Burkina Faso villages. .* Acta Neurol Scand, 2012. **126**: p. 270-278.
336. Simms, V., et al., *Prevalence of epilepsy in Rwanda: a national cross-sectional survey.* Tropical Medicine and International Health, 2008. **13**(8): p. 1047-1053.
337. Gbenou, H.D., *Contribution à l'étude de l'association onchocercoseépilepsie: résultats préliminaires d'une enquête neuroépidémiologique à Agbogbomé—commune de Paouignan, Sous-Préfecture de Dassa, Zoumé, au Bénin. Medical Thesis, Cotonou, Benin,.* 1995.
338. Avodé, D.G., O.B. Capo-Chichi, and P. Gandaho, *Epilepsie provoquée par la cysticercose: a propos d'une enquête sociologique et culturelle réalisée à Savalou au Bénin.* Bull Soc Pathol Exot 1996. **89**: p. 45–47.
339. Nkwi, P.N. and F.T. Ndonko, *The epileptic among the bamilékés of Maham in the Nde division, West Province of Cameroon. .* Cult Med Psychiatry, 1989. **13**: p. 437-48.
340. Dongmo, L., D. Ndo, and G. Atchou, *Epilepsie au Sud-Cameroun: enquête préliminaire dans le village de Bilomo.* Bull Soc Pathol Exot, 2000. **93**: p. 266-67.
341. Tekle-Haimanot, R., L. Forsgren, and M. Abebe, *Clinical and electroencephalographic characteristics of epilepsy in rural Ethiopia: a community-based study. .* Epilepsy Res, 1990. **7**: p. 230-39.
342. Kouassi B, K.J., Diarra JA, et al. .1988; 89: 25–30., *Prévalence de l'épilepsie en milieu rural ivoirien: étude pilote.* Pub Méd Afr 1988. **89**: p. 25-30.
343. Kouadjo, Y., *Génétique et épilepsie : à propos d'un foyer d'épilepsie observé dans un village ivoirien.* Medical Thesis, Abidjan, Cote d'Ivoire, 1990.
344. Kaudjhis, P.J.R., *Les agrégats de l'épilepsie de M'brou : approche électro-clinique et étiologique.* Medical Thesis, Abidjan, Cote d'Ivoire, 1995.
345. Kaamugisha, J. and A.T. Feksi, *Determining the prevalence of epilepsy in the semi-urban population of Nakuru, Kenya, comparing two independent methods not apparently used before in epilepsy studies.* Neuroepidemiology., 1988. **7**(3): p. 115-21.

346. Goudsmit, J., F.W. Van Der Waals, and D.C. Gajdusek, *Epilepsy in the Gbawein and Wroughbarh clan of Grand Bassa County, Liberia: the endemic occurrence of "See-ee" in the native population.* Neuroepidemiology, 1983. **2**: p. 24-34.
347. Andriantseheno, L.M. and D. Dalaizandriny, *Prévalence communautaire de l'épilepsie chez les malgaches.* Epilepsies, 2004. **16**: p. 83-86.
348. Ndiaye, I.P., J.B. Mauferon, and M. Diagne, *Epidémiologie de l'épilepsie au Sénégal.* Communication presented to the 7th Congress of the Pan-African Association of Neurological Sciences, Abidjan, (Cote d'Ivoire),, 1986.
349. Diop, A.G., O.L. Agbohous, and M. Ndiaye, *Prévalence de l'épilepsie en milieu scolaire sénégalais.* Communication presented to the 12th Congress of the Pan-African Association of Neurological Sciences, Durban (South Africa), 1996.
350. Kaiser, C., W. Kipp, and G. Asaba, *The prevalence of epilepsy follows the distribution of onchocerciasis in a West Ugandan focus.* Bull WHO, 1996. **74**: p. 361-67.
351. Birbeck, G.L. and E.M.N. Kalichi, *Epilepsy prevalence in rural Zambia: a door-to-door survey.* Trop Med Intern Health, 2004. **9**: p. 92-95.
352. Forsgren, L., et al., *Mortality of epilepsy in developed countries: a review.* Epilepsia 2005. **46**(suppl 11): p. 18-27.
353. Kaiser, C., et al., *Mortality from epilepsy in an onchocerciasis-endemic area in west Uganda. .* Trans R Soc Trop Med Hyg 2007(101): p. 48-55.
354. Jilek-Aall, L. and H.T. Rwiza, *Prognosis of epilepsy in a rural African community: a 30-year follow-up of 164 patients in an outpatient clinic in rural Tanzania.* Epilepsia, 1992. **33**: p. 645-50.
355. Kamgno, J., S.D.S. Pion, and M. Boussinesq, *Demographic impact of epilepsy in Africa: results of a 10-year cohort study in a rural area of Cameroon.* Epilepsia, 2003. **44**: p. 956-63.
356. Herman, S.T., *Where in the World Are We? Generalizing the Results of Status Epilepticus Trials.* Epilepsy Curr, 2009. **9**(2): p. 38-40.
357. Ogunniyi, A., B.O. Osuntokun, and O. Bademosi, *Risk factors for epilepsy: case control study in Nigeria.* Epilepsia, 1987. **28**: p. 280-85.
358. Bademosi, O., A. Ogunniyi, and B.O. Osuntokun, *Febrile convulsion as a risk factor for epilepsy in Nigerians: a case control study.* Afr J Neurol Sci 1989. **8**: p. 20-23.
359. Matuja, W.B., G. Kilonzo, and P. Mbena, *Risk factors for epilepsy in a rural area in Tanzania. A community-based case-control study. .* Neuroepidemiology 2001. **20**: p. 242-47.
360. Newell, E.D., F. Vyungimana, and J.E. Bradley, *Epilepsy, retarded growth and onchocerciasis, in two areas of different endemicity of onchocerciasis in Burundi. .* Trans R Soc Trop Med Hyg 1997. **91**: p. 525-27.
361. Winkler, A.S., et al., *Epilepsy and neurocysticercosis in sub-Saharan Africa, .* Wien Klin Wochenschr 2009. **121**(suppl 3): p. 3-12.
362. Pal, D.K., A. Carpio, and J.W.A.S. Sander, *Neurocystercerscosis in developing countries, .* J Neurol Neurosurg Psychiatry, 2000. **68**: p. 137-143.
363. Singhi, P., et al., *Clinical spectrum of 500 children with neurocysticercosis and response to albendazole therapy.* J Child Neurol 2000. **15**: p. 207-213.
364. Mbuba, C.K., et al., *The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies.* Epilepsia 2008. **49**: p. 1491-503.
365. Scott, R.A., S.D. Lhatoo, and J.W.A.S. Sander, *The treatment of epilepsy in developing countries: where do we go from here?* Bulletin of the World Health Organization 2001. **79**(344-51).

366. Meyer, A.C., T. Dua, and J. Ma, *Global disparities in the epilepsy treatment gap: a systematic review.* Bull World Health Organ 2010. **88**: p. 260-66.
367. Kale, R., *Global campaign against epilepsy: the treatment gap. .* Epilepsia, 2002. **43**(Suppl. 6): p. 31-3.
368. Meinardi, H.R., et al., *The Treatment Gap in Epilepsy: The Current Situation and Ways Forward.* Epilepsia, 2001. **42**(1): p. 136-49.
369. Coleman, R., L. Loppy, and G. Walgraven, *The treatment gap and primary health care for people with epilepsy in rural Gambia.* Bull World Health Organ, 2002. **80**: p. 378-83.
370. Mbuba, C.K., A.K. Ngugi, and G. Fegan, *Risk factors associated with the epilepsy treatment gap in Kilfi , Kenya: a cross-sectional study.* Lancet Neurology, 2012. **11**(8): p. 688-696.
371. Ndoye, N.F., A.D. Sow, and A.G. Diop, *Prevalence of epilepsy, its treatment gap and knowledge, attitude and practice of its population in sub-urban Senegal, an ILAE/IBE/WHO study.* Seizure, 2005. **14**: p. 106-11.
372. Ogunniyi, A., O.S.A. Oluwole, and B.O. Osuntokun, *Two-year remission in Nigerian epileptics. .* East Afr Med J, 1998. **75**: p. 392-95.
373. Bruckner, T.A., R.M. Scheffler, and G. Shen, *The mental health workforce gap in low- and middle-income countries: a needs-based approach.* Bull World Health Organ 2011. **89**: p. 184-94.
374. Mushi, D., et al., *Social-cultural aspects of epilepsy in Kilimanjaro Region, Tanzania: Knowledge and experience among patients and carers.* Epilepsy & Behavior 2011: p. 338-343.
375. Sander, J.W., *The use of antiepileptic drugs—principles and practice. .* Epilepsia, 2004. **45**(suppl 6): p. 28-34.
376. Zaccara, G., *Neurological comorbidity and epilepsy: implications for treatment.* Acta Neurol Scand, 2009. **120**: p. 1-15.
377. International League Against Epilepsy, *Evidence based guideline: Antiepileptic drug selection for people with HIV/AIDS: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the AdHoc Task Force of the Comission on Therapeutic Strategies of the International League Against Epilepsy, .* Neurology, 2012. **78**(2): p. 139-145.
378. Chisholm, D. and S. Saxena, *Cost effectiveness of strategies to combat neuropsychiatric conditions in sub-Saharan Africa and South East Asia: mathematical modelling study.* BMJ 2012. **344**: p. 609.
379. Janca, A., L. Prilipko, and J.A. Costa e Silva, *The World Health Organisation's global iniitiative on neurology and public health.* Journal of the Neurological Sciences, 1997. **145**: p. 1-2.
380. Gwatkin, D.R., M. Guillot, and P. Heuveline, *The burden of disease among the global poor.* Lancet, 1999. **354**: p. 586-589.
381. Janca, A., L. Prilipko, and J.A. Costa e Silva, *The World Health Organisation's work on public health aspects of neurology.* Journal of Neurology, Neurosurgery and Psychiatry, 1997. **63(Suppl 1)**: p. S6-7.
382. Janca, A., L. Prilipko, and B. Saraceno, *A World health Organisation perspective on neurology and neuroscience. .* Archives of Neurology, 2000. **57**: p. 1786-1788.
383. Owolabi, M.O., J.H. Bower, and A. Ogunniyi, *Mapping Africa's way into prominence in the field of neurology.* Arch Neurol, 2007. **64**(12): p. 1696-1700.
384. Janca, A., *WHO/WFN survey on neurological services: a world-wide perspective.* Journal of the Neurological Sciences, 2006. **247**: p. 29-34.
385. World Health Organisation, *Atlas: Country resources for neurological disorders* Geneva: World Health Organisation, 2004.

386. Murray, C.J.L., A.D. Lopez, ., and D.T. Jamison, *The global burden of disease in 1990: summary results, sensitivity analyses, and future directions.* Bulletin of the World Health Organisation, 1994. **72**: p. 495-508.
387. Lopez, A.D. and C.J.L. Murray, *The global burden of disease, 1990-2020.* Nature Medicine, 1998. **4**: p. 1241-1243.
388. Barendregt, l.J.J., *A generic model for the assessment of disease epidemiology: the computational basis of DisMod II.* Population Health Metrics, 2003. **1**: p. e4.
389. Lopez, A.D., et al., *Global and regional burden of disease and risk factors, 2001: systematic analysis of population data.* Lancet, 2006. **367**(9524): p. 1747-1757.
390. Bergen, D.C., *The world-wide burden of neurologic disease.* Neurology, 1996. **47**(1): p. 21-25.
391. Bergen, D.C. and D. Silberberg, *Nervous system disorders: a global epidemic.* Arch Neurol, 2002. **59**(7).
392. Coleman, R., *Disease Burden in sub-Saharan Africa.* Lancet, 1998. **351**: p. 1208-1209.
393. Mathers, C.D., *Sensitivity and uncertainty analyses for burden of disease and risk factor estimates In Lopez AD et al., eds. Global burden of disease and risk factors.* The World Bank and Oxford University Press, 2006.
394. Winkler, A.S., P. Mosser, and E. Schmutzhard, *Neurological disorders in rural Africa: a systematic approach.* Tropical doctor, 2009. **39**(2): p. 102-104.
395. Kwasa, T., *The pattern of neurological disease at Kenyatta National Hospital.* East Africa Medical journal, 1992. **69**: p. 236-239.
396. Mateen, F.J., et al., *Reportable neurologic diseases in refugee camps in 19 countries.* Neurology, 2012. **79**(9): p. 937-40.
397. Attia Romdhane, N., *Prevalence study of neurologic disorders in Kelibia (Tunisia).* Neuroepidemiology, 1993. **12**: p. 285-299.
398. Munoz, M., et al., *Prevalence of Neurological Disorders in Haute-Vienne Department (Limousin Region – France)* Neuroepidemiology, 1995. **14**: p. 193-198.
399. Nakashimaa, K., et al., *Prevalence of Neurological Disorders in a Japanese Town.* Neuroepidemiology, 1996. **15**: p. 208-213.
400. Perkin, D.G., *The impact of neurological illness and disability. The likely impact of demographic changes on the incidence and prevalence of neurological disease: demography in the United Kingdom.* J Neurol Neurosurg Psychiatry 1997. **63**: p. S8-S10.
401. Aarli, J.A., A. Gallo Diop, and H. Lochmuller, *Neurology in sub-Saharan Africa. A challenge for World Federation of Neurology. .* Neurology 2007. **69**: p. 1715-1718.
402. Association of British Neurologists, *Neurology in the United Kingdom towards 2000 and beyond.* London: ABN, 1997.
403. Larner, A.J. and S.F. Farmer, *Clinical Review. Recent Advances. Neurology.* British Medical Journal, 1999. **319**: p. 362-366.
404. Zarocostas, J., *WHO launches programme to extend treatment of mental and neurological disorders.* British Medical Journal, 2008. **337**: p. 2090.
405. Al-Shahi, R., R.G. Will, and C.P. Warlow, *Amount of research interest in rare and common neurological conditions: bibliometric study.* British Medical Journal, 2001. **323**: p. 1461-2.
406. Gross, C.P., G.F. Anderson, and N.R. Powe, *The relation between funding by the national institutes of health and the burden of disease.* New England Journal of Medicine, 1999. **340**: p. 1881-7.
407. Global Forum for Health Research, *The 10/90 report on health research.* Geneva: Global forum for health research, 2000.
408. 2010, W.P.d.s. *World Population data sheet. 2010*. 2010; www.prb.org/pdf10/10WorldDataSheet.pdf.].
409. www.geology.com.

410. Nordberg, E. and African Medical and Research Foundation, *Health and the elderly in developing countries with special reference to sub-Saharan Africa.* East African Medical Journal, 1997. **74**(10): p. 629-33.
411. The Royal College of Nursing, *Report. Ensuring equity and quality for care of elderly people.* London: RCN 1994.
412. Hacker, C., *Health care for an aging population. .* New York: State University of New York Press, 1976.
413. Kinsella, K., *Aging in the Third World..* Washington, DC: Bureau of the Census, US Department of Commerce, 1988.
414. Fuchs, V.R., *New Priorities for Future Biomedical Innovations.* New England Journal of Medicine, 2010. **363**: p. 706.
415. Dworkin, R., *Life's dominion, an argument about abortion and euthanasia.* Harper Collins, 1993: p. 219-20.
416. Rivlin, M., *Protecting elderly people: flaws in ageist arguments.* British Medical Journal, 1995. **310**: p. 1179.
417. Africa's population and development bulletin, *A Note on Aging* Africa's population and development bulletin, 1999.
418. Social Administration Unit, University of Ghana, and Legon., *International models. Health care of the elderly in Africa: focus on Ghana.* Caring, 1995. **14**(1): p. 42-45 47-49.
419. Stuck, A.E., J.C. Beck, and M. Egger, *Preventing disability in elderly people.* The Lancet, 2004. **364**: p. 1641-1642.
420. Awofeso, N. and A. Rammohan, *Elderly Africans have AIDS too.* British Medical Journal, 2010. **341**: p. 4169.
421. Centers for disease control and prevention, *HIV/AIDS surveillance report: cases of HIV infection and AIDS in the United States and dependent areas.* 2007.
422. Kassu, A., et al., *HIV and syphilis infection among elderly people in Northwest Ethiopia.* Journal of Infectious Diseases, 2004. **57**: p. 264-7.
423. Mmbaga, E.J., et al., *Trends in HIV-1 prevalence and risk behaivours over 15 years in a rural populaiton in kilimanjaro region of Tanzania.* AIDS research and therapy, 2007. **4**: p. 23.
424. Altschuler, J., A.P. Katz, and M. Tynan, *Developing and implementing an HIV/AIDS educational curriculum for older adults.* Gerontologist, 2004. **44**: p. 121-6.
425. Kautz, T., et al., *AIDS and the declining support for dependent elderly people in Africa: retrospective analysis using demographic and health surveys.* British Medical Journal, 2010. **340**: p. 2841.
426. British Geriatric Society, *Rehabilitation of Older People.* BGS Best Practice Guide, 2009.
427. Mahoney, F. and D. Barthel, *Functional Evaluation: The Barthel Index.* Maryland State Medical Journal, 1965. **14**: p. 56-61.
428. Colin, C., et al., *The Barthel ADL Index: a reliability study.* International Disability Study, 1988. **10**(2): p. 61-3.
429. Research Unit of the Royal College of Physicians and British Geriatric Society, *Standardised assessment scales for elderly people SAFE.* Royal College of Physicians 1992.
430. Royal College of Physicians, *Report of joint workshops of the Royal College of Physicians and the British Geriatrics Society. Standardised assessment scales for elderly people.* Royal College of Physicians, 1992.
431. Sainsbury, A., et al., *Reliability of the Barthel Index when used with older people.* Age and Aging, 2005. **34**: p. 228-232.
432. Uyttenboogaart, M., et al., *Optimizing Cutoff Scores for the Barthel Index and the Modified Rankin Scale for Defining Outcome in Acute Stroke Trials.* Stroke, 2005. **36**: p. 1984-1987.
433. Celani, M., et al., *Different measures for assessing stroke outcome: an analysis from the international stroke trial in Italy.* Stroke, 2002. **33**(218-223).

434. Kay, R., et al., *Dichotomizing stroke outcomes based on self-reported dependency.* Neurology, 1997. **49**: p. 1694-1696.
435. Heslin, J.M., et al., *Health status and service utilisation of older people in different European countries.* Scandanavian Journal of Primary Health Care 2001. **19**: p. 218-22.
436. The World Health Organization, *Developing the World Health Organisation Disability Assessment Schedule 2.0* The World Health Organisation Bulletin, 2010.
437. Central Bureau of Statistics, *Kenya population census.* 1989.
438. Bangladesh Bureau of Statistics, *Disabled population of Bangladesh, evidence from a demographic sample survey.* 1987.
439. Jacoby, A., D. Snape, and G.A. Baker, *Epilepsy and social identity: the stigma of a chronic neurological disorder.* Lancet Neurology, 2005. **4**: p. 171-178.
440. Mshana, G., et al., *Urban-rural contrasts in explanatory models and treatment-seeking behaivours for stroke in Tanzania.* Journal of Biosocial Science, 2008. **40**(1): p. 35-52.
441. Jilek-Aall, L., *Psychological study of epilepsy in Africa.* Social Science and Medicine, 1997. **45**: p. 783-795.
442. Butler, R.N., *Why Survive? Being old in America.* New York: Harper and Row, 1975: p. 11-12.
443. Adult Morbidity and Mortality Project (AMMP), *Policy Implications of Adult Morbidity and Mortality; final report. Dar-es-Salaam:.* Tanzanian Ministry of Health 2004. **http://research.ncl.ac.uk/ammp/finrep/**
444. Talabi, O.A., *A 3-year review of neurologic admissions in University College Hospital Ibadan, Nigeria.* West African Journal of Medicine, 2003. **22**: p. 150-1.
445. Marsden, C.D. and N.P. Quinn, *The dystonias.* British Medical Journal, 1990. **300**: p. 139-144.
446. Jarman, P.R. and T.T. Warner, *The Dystonias.* Journal of Medical Genetics, 1998. **35**: p. 314-318.
447. Torres-Russottoa, D. and J.S. Perlmuttera, *Task-specific dystonia.* Ann N Y Acad Sci. , 2008. **1142**: p. 179-199.
448. National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR), *www.rarediseases.info.nih.gov.* 2011.
449. Paraïso, M.N., et al., *Validation of the Use of Historical Events to Estimate the Age of Subjects Aged 65 Years and Over in Cotonou (Benin).* Neuroepidemiology, 2010. **35**: p. 12-16.
450. Findley, L.J. and W.C. Koller, *Handbook of Tremor Disorders.* New York, 1995.
451. American Psychiatric Association Task Force on Tardive Dyskinesia, *"Tardive Dyskinesia" summary of a task force report of the American Psychiatric Association by the Task Force on Late Neurological Effects of Antipsychotic drugs.* American Journal of Psychiatry, 1980. **137**: p. 1163-1172.
452. National Institute of Neurological Disorders and Stroke. *Motor Neuron Disease Fact Sheet*. 2011.
453. American Spinal Injury Association, *International Standards for Neurological Classifications of Spinal Cord Injury. revised ed.* Chicago, Ill: American Spinal Injury Association; , 2000: p. 1-23.
454. Ditunno, J.F.J., et al., *The international standards booklet for neurological and functional classification of spinal cord injury. .* Paraplegia. , 1994. **32**(2): p. 70-80.
455. Jaretzki, A., et al., *Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America.* Annals of Thoracic Surgery, 2000. **70**(1): p. 327-34.
456. Kjeldsen, S.E., et al., *Hypertension Optimal Treatment (HOT) Study: Home Blood Pressure in Treated Hypertensive Subjects.* Hypertension., 1998. **31**: p. 1014-1020.

457. Sherwin, R., et al., *The Multiple Risk Factor Intervention Trial (MRFIT): II. The development of the protocol.* Prey Med, 1981. **10**: p. 402-25.
458. Bassey, E., *Demi-span as a measure of skeletal size.* Annals of Human Biology 1986. **13**(5): p. 499-502.
459. World Health Organisation, *WHO Model List of Essential Medicines.* http://www.who.int/medicines/publications/essentialmedicines/en/index.html, 2011.
460. Dewhurst, F., et al., *Rates of diagnosis and treatment of neurological disorders within a prevalent population of community-dwelling elderly people in sub-Saharan Africa.* Journal of Epidemiology and Global Health, 2012. **2**(4): p. 207-214.
461. Walker, R., et al., *Aetiology of stroke in an incident stroke population in Tanzania: first two year data for the Tanzania Stroke Incidence Project in the Hai district* Age and Ageing, 2006. **35**(Suppl 3): p. 59.
462. Ahmad, O.B., et al., *Age standardisation of rates. A new WHO standard (GPE discussion paper series: No 31).* Geneva: World Health Organisation, 2001.
463. Dystonia in Europe Collaborative Group, *A prevalence study of primary dystonia in eight European countries. Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group.* J Neurol. , 2000. **247**(10): p. 787-92.
464. Racette, B.A., *A rapid method for mass screening for parkinsonsim. .* Movement Disorders, 2004. **19 (Suppl 9)**: p. S186.
465. Dewhurst, F., et al., *Neurological disorder screening in the elderly in low-income countries.* J Neurol., 2012. **259**(10): p. 2189-97.
466. Kaamungisha, J. and A.T. Feksi, *Determining the prevalence of epilepsy in the semi-urban population of Nakuru, Kenya, comparing two independent methods not apparently used before in epilepsy studies.* Neuroepidemiology, 1998. **7**: p. 115-121.
467. Patel, V., et al., *Prevalence of severe mental and neurological disorders in Mozambique: a population-based survey.* The Lancet, 2007. **370**: p. 1055-1060.
468. Matuja, W.B.P. and W.J. Makene, *Neurological disease pattern in adults admitted to the medical wards at Muhimbili Medical Centre.* Tanzanian Medical Journal, 1989. **4**: p. 18-21.
469. Deng, H., W. Le, and J. Jankovic, *Genetics of essential tremor.* Brain, 2007. **130**: p. 1456-1464.
470. Higgins, J.J., L.T. Pho, and L.E. Nee, *A gene (ETM) for essential tremor maps to chromosome 2p22-p25.* Movement Disorders, 1997. **12**: p. 859-864.
471. Gulcher, J.R., P. Jonsson, and A. Kong, *Mapping of a familial essential tremor gene, FET1, to chromosome 3q13.* Nature Genetics, 1997. **17**: p. 84-87.
472. British Medical Journal, *Assessment of Ataxia.* http://bestpractice.bmj.com/best-practice/monograph/1097.html.
473. Muzaimi, M.B., J. Thomas, and S. Palmer-Smith, *Population based study of late onset cerebellar ataxia in south east Wales.* Journal of Neurology Neurosurgery and Psychiatry, 2004. **75**: p. 1129-1134.
474. Safe, A.F., S. Cooper, and A.C. Windsor, *Cerebellar ataxia in the elderly.* Journal of the Royal Society of Medicine, 1992. **85**(8): p. 449-51.
475. Nafissi, S., et al., *Epidemiology of Cerebellar Ataxia on the Etiological Basis: A Cross Sectional Study.* Acta Medica Iranica, 2009. **47**(6): p. 465-468.
476. Sutcliffe, R.L. and J.R. Meara, *Parkinson's disease epidemiology in the Northampton District, England, 1992.* Acta Neurol Scand, 1995. **92**: p. 443-450.
477. Nikiforow, T., *Headache in a random sample of 200 persons: a clinical study of a population in northern Finland. .* Cephalalgia, 1981. **1**: p. 99-107.
478. Zivadinov, R., et al., *Migraine and tension type headache in Croatia: a population-based survey of precipitating factors.* Cephalalgia, 2003. **23**: p. 336-343.

479. Lipton, R.B., et al., *Migraine in the United States: epidemiology and patterns of health care use.* Neurology, 2002. **58**: p. 885-894.
480. Henry, P., et al., *A nationwide survey of migraine in France: prevalence and clinical features in adults. GRIM. .* Cephalalgia, 1992. **12**: p. 229186–37.
481. Hagen, K., et al., *Prevalence of migraine and non-migrainous headache—head-HUNT, a large population-based study.* Cephalalgia, 2000. **20**: p. 900-6.
482. Rozen, T.D., et al., *Incidence of medically recognized migraine: a 1989–1990 study in Olmsted County, Minnesota.* Headache, 2000. **40**: p. 216-223.
483. Dahlo, F.C. and M. Linde, *One-year prevalence of migraine in Sweden: a population-based study in adults.* Cephalalgia, 2001. **21**: p. 664-71.
484. Steiner, T.J., et al., *The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity.* Cephalalgia, 2003. **23**: p. 519-27.
485. Stewart, W.F., R.B. Lipton, and J. Liberman, *Variation in migraine prevalence by race.* Neurology, 1996. **47**: p. 52-59.
486. Abduljabbar, M., et al., *Prevalence of primary headache syndrome in adults in the Qassim Region of Saudi Arabia.* Headache, 1996. **36**: p. 385-388.
487. Deleu, D., M.A. Khan, and T.A. Al Shehab, *Prevalence and clinical characteristics of headache in a rural community in Oman.* Headache 2002. **42**: p. 963-973.
488. Miranda, H., et al., *Prevalence of headache in Puerto Rico. .* Headache 2003. **43**: p. 774778.
489. Garcia-Pedroza, F., et al., *Prevalence survey of headache in a rural Mexican village.* Neuroepidemiology, 1991(10).
490. Boardman, H.F., et al., *Epidemiology of headache in an English district.* Cephalalgia, 2003. **23**: p. 129-137.
491. Waters, W.E., *The Pontypridd headache survey.* Headache, 1974: p. 81-90.
492. Queiroz, L.P., L.M. Barea, and N. Blank, *An epidemiological study of headache in Florianopoli, Brazil. .* Cephalalgia 2006. **26**: p. 122-7.
493. Cheung, R., *Prevalence of migraine, tension-type headache, and other headaches in Hong Kong. .* Headache 2000. **40**: p. 473-9.
494. Takeshima, T., et al., *Population-based door-to-door survey of migraine in Japan: the Daisen Study.* Headache, 2004. **44**: p. 8-19.
495. Lavados, P.M. and E. Tenhamm, *Epidemiology of tension-type headache in Santiago, Chile: a prevalence study.* Cephalalgia, 1998. **18**: p. 552-558.
496. Roh, J.K., J.S. Kim, and Y.O. Ahn, *Epidemiologic and clinical characteristics of migraine and tension-type headache in Korea.* Headache 1998. **38**: p. 356-365.
497. Ho, K.H. and B.K.C. Ong, *A community-based study of headache diagnosis and prevalence in Singapore. .* Cephalalgia, 2003. **23**: p. 6-13.
498. Srikiatkhachorn, A., *Epidemiology of headache in the Thai elderly: a study in the Bangkae Home for the Aged.* Headache, 1991. **31**: p. 677-81.
499. Wang, S.J., et al., *Prevalence of headaches in a Chinese elderly population in Kinmen: age and gender effect and cross cultural comparisons.* Neurology, 1997. **49**: p. 195-200.
500. Prencipe, M., et al., *Prevalence of headache in an elderly population: attack frequency, disability, and use of medication.* J Neurol Neurosurg Psychiatry, 2001. **70**: p. 377-381.
501. Camarda, R. and R. Monastero, *Prevalence of primary headaches in Italian elderly: preliminary data from the Zabut Aging Project.* Neurolog Sci, 2003. **24**((Suppl. 2)): p. S122-S124.
502. Cook, N.R., et al., *Correlates of headache in a population-based cohort of elderly. .* Arch Neurol, 1989. **46**: p. 1338-44.
503. Howlett, W., *Neurology in Africa*. 2012, Bergen, Norway: BRIC.
504. Farnarier, G., S. Diop, and B. Coulibaly, *Onchocercose et épilepsie. Enquête épidémiologique au Mali.* Méd Trop, 2000. **60**: p. 151-55.

505. Munoz, M., et al., *Prevalence of Neurological Disorders in Haute-Vienne Department (Limousin Region-France).* Neuroepidemiology, 1995. **14**: p. 193-198.
506. Hughes, R., *Peripheral Neuropathy Review.* British Medical Journal, 2002. **324**: p. 466-469.
507. Mold, J.W., et al., *The Prevalence, Predictors, and Consequences of Peripheral Sensory Neuropathy in Older Patients.* Journal of the American Board of Family Practice, 2004. **17**: p. 309-318.
508. Bharucha, N.E., A.E. Bharucha, and E.P. Bharucha, *Prevalence of peripheral neuropathy in the Parsi community of Bombay.* Neurology, 1991. **41**(8): p. 1315-1317.
509. Atroshi, I., et al., *Prevalence of carpal tunnel syndrome in a general population.* JAMA, 1999. **282**: p. 153-158.
510. Fuller, G., *Diagnosing and managing mononeuropathies.* CME Neurology, 2004. **4**(2): p. 113-117.
511. Lambert, M.L., et al., *Household survey of locomotor disability caused by poliomyelitis and landmines in Afghanistan.* British Medical Journal, 1997. **315**: p. 1424.
512. Wallace, R.B., ed. *Public health and Preventative Medicine*. 2008.
513. World Health Organisation. *Prevalence of Leprosy*. http://www.who.int/lep/situation/prevalence/en/index.html 2009.
514. World health Organisation, *Leprosy-Global situation.* Wkly Epidemiol Rec, 2000. **28**: p. 226-231.
515. Carr, A.S., et al., *A systematic review of population based epidemiological studies of myaesthenia gravis.* BMC Neurology 2010, 2010. **10**(46): p. 10-46.
516. Awwad, S., R. Ma'luf, and N. Hamush, *Myaethenia Gravis.* http://emedicine.medscape.com/article/1216417-overview, 2010.
517. MS Society, *www.atlasofms.org.* 2008.
518. Vlassoff, C., *Gender inequalities in health in the third world: uncharted ground.* Soc Sci Med 1994. **39**: p. 1249-59.
519. Ojanuga, D.N. and C. Gilbert, *Womens access to health care in developing countries.* Soc Sci Med, 1992. **35**: p. 613-7.
520. Vlassoff, C. and C. Garcia Moreno, *Placing gender at the centre of health programming: challenges and limitations.* Soc Sci Med, 2002. **54**: p. 1713-23.
521. Sen, G. and P. Ostlin, *Gender inequity in health: why it exists and how we can change it. .* Glob Public Health, 2008. **3**: p. Suppl 1-12.
522. Bates, L.M., O. Hankivsky, and K.W. Springer, *Gender and health inequities: a comment on the Final Report of the WHO Commission on the Social Determinants of Health.* Soc Sci Med 2009. **69**: p. 1002-4.
523. United Nations Childrens Fund, *Boys and girls in the life cycle: sex-disaggregated data on a selection of well-being indicators, from early childhood to young adulthood.* 2011.
524. Miszkurka, M., et al., *Heavy burden of non-communicable diseases at early age and gender disparities in an adult population of Burkina Faso: World Health Survey.* BMC Public Health, 2012. **12**: p. 24.
525. Elbaz, A., *Validity of family history data on PD: evidence for a family information bias.* Neurology, 2003. **61**(1): p. 11-17.
526. Thorogood, M., et al., *Secondary prevention of stroke-results from the Southern Africa Stroke Prevention Initiative (SASPI) study.* Bull World Health Organ, 2004. **82**: p. 503-8.
527. Dotchin, C.L., et al., *Geriatric medicine: services and training in Africa. .* Age Ageing, 2012. **471**: p. 119.