The epidemiology of epilepsy in rural Tanzania: prevalence, phenotype, risk factors and treatment gap

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Abstract

Introduction

Epilepsy is especially prevalent in low- and middle-income countries, including those in sub-Saharan Africa (SSA). There are few case-controlled data on epilepsy from SSA, where epilepsy remains largely untreated and highly stigmatized.

Aims

To determine the prevalence of active epilepsy among adults in a rural population in northern Tanzania. To describe the pattern of disease and quantify the epilepsy treatment gap (ETG) in this population.

Methods

People with epilepsy (PWE) were identified through door-to-door screening of the adult study population (n=103,026) using a previously validated screening questionnaire. Controls were recruited from the background population. Odds ratios for risk factors and impacts of epilepsy were calculated using logistic regression. The burden of neurocysticercosis (NCC) was assessed using neuro-imaging in cases and serology. The ETG was estimated according to self-reported antiepileptic drug use.

Results

We identified 291 PWE along with 182 controls. The age-standardised prevalence of active epilepsy was 2.91/1,000. All PWE had convulsive epilepsy, 71.5% being of focal onset. Risk factors for epilepsy were a positive family history (OR 29.0), febrile convulsions in childhood (OR 20.4) and obstetric complications (OR 3.4). Eight cases had NCC; six cases and no controls had antibodies to *Taenia solium* (p=0.036). PWE were less likely to have completed primary education (OR 0.3) and were more likely to be divorced or separated (OR 7.7). The ETG was 68.4%.

Conclusions

This is one of the largest community-based studies of epilepsy from SSA to date. The large proportion of focal-onset epilepsy suggests a considerable burden of acquired epilepsy. The high ETG may reflect the stigma experienced by PWE in this population.

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Statement of candidate's contribution to the work

The study presented in this thesis was conceived, designed and executed by myself, with help from a large number of people, some of whom are mentioned in the acknowledgements. I visited Tanzania on five occasions during the course of the study, including one nine month period spent living and working there. I personally interviewed and examined all of the patients included in the study and was also present at the recruitment and assessment of controls. When not present, I maintained logistical oversight of investigations performed on behalf of the study. All data were entered and analysed by myself. I have thus been responsible for the collection and analysis of all the data presented here.

Aside from data collection I have also been responsible for clinically advising patients and for starting them on drug treatment where necessary or appropriate. In relation to this aspect of the study two Tanzanian nurses received additional training in the UK in the management of epilepsy prior to the main study, and a training workshop on the community-based management of epilepsy was devised and delivered to healthcare workers locally. I maintain contact with the clinical team in Hai, and remain involved in the follow-up and care of patients identified during the study.

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Abbreviations used in the text

ACE	Active convulsive epilepsy
AED	Anti-epileptic drug(s)
AMMP	Adult Morbidity and Mortality Project
AMO	Assistant medical officer
ANOVA	Analysis of variance
CBZ	Carbamazepine
CHMT	Community Health Management Team
CI	Confidence interval
CNS	Central nervous system
CO	Clinical officer
CT	Computed tomography
CVA	Cerebrovascular accident
DSS	Demographic surveillance site
EEG	Electroencephalogram/electroencephalography
EITB	Enzyme-linked immuno-electro transfer blot
ELISA	Enzyme-linked immunosorbent assay
ETG	Epilepsy treatment gap
FGD	Focus group discussion
GBP	Great British Pounds (currency)
GGE	Genetic generalised epilepsy
HDSS	Hai Demographic Surveillance Site
HICs	High income countries
HIV	Human immunodeficiency virus
IGE	Idiopathic generalised epilepsy
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
KCMC	Kilimanjaro Christian Medical Centre
KEMRI	Kenya Medical Research Institute

LMICs	Low- and middle-income countries
LOC	Loss of consciousness
LRT	Likelihood ratio test
MEHATA	Mental Health Association of Tanzania
MNH	Muhimbili National Hospital, Tanzania
NCC	Neurocysticercosis
NCDs	Non-communicable diseases
NGO	Non-governmental organisation
NIMR	National Institute of Medical Research, Tanzania
NPV	Negative predictive value
OR	Odds ratio
PB	Phenobarbital
PD	Parkinson's Disease
PHT	Phenytoin
PPV	Positive predictive value
PWE	Person/people with epilepsy
RD	Research doctor
SE	Status epilepticus
SMR	Standardised mortality ratio
SSA	sub-Saharan Africa
SV	Sodium valproate
Tb	Tuberculosis
TSIP	Tanzanian Stroke Incidence Project
UMN	Upper motor neurone
USD	United States dollars
VA	Verbal autopsy
WHO	World Health Organisation

Chapter 1. Introduction

1.1 Introduction to the thesis

This thesis describes a large community-based epidemiological study of epilepsy conducted in a rural district of northern Tanzania, East Africa. The study consists of two main components: a door-to-door screening survey to establish the prevalence of active epilepsy within the study population, and the comparison of cases with controls to identify the clinical and socio-economic associations with epilepsy in this population. Complementary studies of adult and paediatric populations were conducted in parallel. This thesis describes the adult study; details of the paediatric study can be found in the published literature (Mushi et al., 2012, Burton et al., 2012a, Burton et al., 2012b, Burton et al., 2011). To the best of our knowledge, these are the first studies to have specifically investigated the problem of epilepsy in this population.

The various elements of the adult study are presented here in nine chapters which collectively provide the background, methods, results and discussion of the different research activities. Each chapter has been written, as far as possible, to be self-explanatory within the context of the thesis as a whole.

After briefly summarising the contents of the thesis the remainder of this introductory chapter will define the key terms and concepts which are used throughout and describe the epidemiological context and historical background to the study. As this study is concerned with the prevalence of epilepsy in a Tanzanian population, along with associated findings on phenotype, risk factors and epilepsy treatment gap (ETG), these aspects are explored with reference to other work done in sub-Saharan Africa (SSA) in general, and Tanzania in particular. As the literature from this region remains relatively limited in quantity, and yet heterogeneous in scope, a narrative rather than systematic approach was adopted in writing this review. Initial literature searches using Medline were conducted using the following search terms: epilepsy, epidemiology, prevalence, treatment gap, Africa, sub Saharan Africa, Tanzania. Citations published in English were retrieved and reference lists were scrutinised for any further relevant or useful citations.

Initial searches were repeated following completion of data collection and analysis in order to bring the review up to date at the time of writing the final thesis.

The second chapter, on methods, gives an overview of the general approaches employed in the study. More specific details, where appropriate, are given in the individual chapters which follow. The principal objective of the methods chapter is to provide details of the demographic surveillance site (DSS) in which the study was conducted.

The third and fourth chapters describe in more detail the screening methodology and its development, the pilot study, and the results of the main prevalence survey. The clinical, demographic and socio-economic features of the cases identified during the screening survey are presented in Chapter Five.

Chapter Six describes the recruitment of controls, and the results of comparisons with cases of epilepsy; data collected from cases and controls to specifically examine the issue of neurocysticercosis (NCC) in this population are presented in Chapter Seven.

Details of the current situation with regards to treatment of epilepsy in this population along with an estimate of the ETG are presented in Chapter Eight.

A final brief summary chapter reprises the key findings of the study and presents suggestions for future work.

Details of questionnaires used during field work, ethical approval, consent forms and related publications are given in the appendices. References and are provided at the end of the thesis.

1.2 Context of the study: epilepsy in low income countries

Epilepsy is one of the commonest neurological disorders. It affects up to 65 million people worldwide(Ngugi et al., 2010) and accounts for up to 1% of the global burden of disease (WHO, 2005). An estimated 80% of people with epilepsy (PWE) live in low- or middle-income countries (LMICs)(Diop et al., 2003). While it is generally believed that the incidence, prevalence and mortality associated with epilepsy are higher in LMICs compared with high-income countries (HICs), there have been relatively few large, cross-sectional community-based studies to verify this (Ngugi et al., 2010). Estimates have varied widely and it is often difficult to compare findings from different studies due to differing inclusion criteria, clinical definitions and the difficulties associated with establishing reliable baseline demographic data in resource-limited settings. This is especially true of countries in SSA, including Tanzania.

While the risk factors for developing epilepsy will vary from region to region, detailed observations from populations in LMICs, including data derived from case-control studies, are lacking (Edwards et al., 2008, Preux and Druet-Cabanac, 2005). It is postulated that in SSA acquired brain injuries, through trauma, infections of the central nervous system (CNS) and perinatal or intrauterine insults, are likely to contribute to the increased burden of epilepsy observed in this region (Preux and Druet-Cabanac, 2005).

With regards to incidence, a recent meta-analysis identified nine studies from LMICs, out of 33 studies in total, in which the incidence of epilepsy ranged from 49 to 215/100,000/year (Ngugi et al., 2011). The incidence in LMICs was estimated to be approximately twice that in HICs (81.7 vs. 45.0/100,000/year), reproducing findings from a systematic review of almost a decade previously (Kotsopoulos et al., 2002). In this review of 40 studies, the median incidence in LMICs was 68.7/100,000/year compared to 43.4/100,000/year in HICs. Both studies postulate that higher incidences of head injury and CNS infection may explain these differences, and the latter of these reviews comments that the observed heterogeneity between studies was not explained by methodology and sampling variation alone, and that differences between risk factors locally were likely to play a significant role.

The costs and logistical challenges associated with collecting the longitudinal data required to estimate the incidence of a condition within a population are considerable. For rare conditions there will also be a lack of familiarity with clinical features among health providers to whom new cases may present. In resource-limited settings a paucity of such services and of data-collection systems will make reliable data capture highly problematic. In populations where a demographic surveillance system (DSS) is established, repeated point prevalence estimates over time, coupled with longitudinal tracking of immigration and emigration into and out of the surveillance area along with reliable birth and mortality data would be required. Such undertakings have major cost and human resource implications, hence incidence data being relatively scarce from such settings (Ngugi et al., 2011).

There are considerably more data on the prevalence of epilepsy from all regions of the world, including SSA, although the number of large-scale community-based studies that benefit from reliable baseline demographic data from this region is more limited. A recent meta-analysis of the burden of epilepsy in terms of lifetime prevalence and active prevalence identified 34 studies from LMICs, of which only six were from SSA (Ngugi et al., 2010). The median lifetime prevalence (i.e. ever having suffered from epilepsy) in LMICs was 15.4/1,000 in rural areas and 10.3/1,000 in urban studies. These figures are comparable to the median prevalence of 15/1,000 reported in a review of studies specifically from SSA (Preux and Druet-Cabanac, 2005),and higher than the median prevalence of 5.8/1,000 in studies from HICs. As with incidence, the issue of heterogeneity between studies was addressed, and the higher prevalence of both lifetime and active epilepsy in LMICs was associated with studies conducted in rural populations and smaller study populations (Ngugi et al., 2011).

While the prevalence of epilepsy is higher in LMICs than HICs, estimates available for incidence suggest that it should be higher still (Scott RA et al., 2001, Tomson, 2006). This discrepancy may be due to excess mortality or to spontaneous remission. The mortality rate suffered by PWE in developed countries is two to three times higher than in the general population, with standardised mortality ratios (SMRs) for epilepsy reported at

between 1.6 and 3.0 (Forsgren et al., 2005b). These figures are higher in people with symptomatic epilepsy (i.e. epilepsy secondary to an acquired brain lesion, SMR 2.2 to 6.5), and are highest in people with neurological deficits present from birth (SMR 7.0 to 50.0). Such data are generated through longitudinal studies, which are particularly difficult to perform in LMICs, where the necessary infrastructure is often lacking; death certificates are unreliable or often unavailable altogether, rendering the cause of death difficult to ascertain (Carpio et al., 2005). While there is consequently a general paucity of data on mortality in epilepsy from these regions, the data that do exist support the assumption that mortality is higher than in HICs. In rural China, for example, the SMR for people with convulsive epilepsy has been estimated at 3.9 to 4.9, with seizure-related accidents and drowning being particularly implicated (Mu et al., 2011, Ding et al., 2006). Data on mortality are particularly lacking from SSA (Diop et al., 2003). Only one study, from Uganda, has formally reported SMRs, providing an estimate of 7.2 based on 18 deaths among 51 PWE who were followed up over a period of seven years (Kaiser et al., 2007). A retrospective follow-up of 164 PWE in Tanzania initially identified 30 years previously found that 67.1% had died, which was approximately twice the expected number based on contemporaneous actuarial estimates (Jilek-Aall and Rwiza, 1992). As with more recent data from China, more than 50% of these deaths were considered to be epilepsy-related, including status epilepticus (SE), drowning, burns, and dying during or immediately after a seizure.

Ascertaining the influence of remission, either spontaneous or treatment-induced, on the prevalence of epilepsy in a given population is difficult. Recurrent remissions and relapses may occur within the same individual, and quantification with standard survival techniques is not possible (Berg et al., 2004). It is also difficult to discern whether cases who remain seizure-free after withdrawal of anti-epileptic medication would actually have entered remission spontaneously (Kwan and Sander, 2004). Longitudinal follow-up of an untreated population of PWE in Bolivia over a 10 year period suggested that up to 40% of cases may enter spontaneous remission, with generalised tonic-clonic seizures being a favourable prognostic factor (Nicoletti et al., 2009). To the best of our knowledge, similar formal longitudinal data from SSA are not currently available.

With regards to aetiology, epilepsy may broadly speaking be genetic or acquired (symptomatic). The risk factors of traumatic brain injury and CNS infection, which have a higher incidence in LMICs, are likely to account for the higher incidence and prevalence of epilepsy seen in these countries, particularly in SSA (Preux and Druet-Cabanac, 2005). The particular role of these factors may also explain the differences in age of onset observed between HICs and LMICs, with the bi-modal curve (higher incidences in childhood and in later life) seen in HICs being replaced by a generally higher incidence and prevalence in older children and young adults in LMICs (Hesdorffer et al., 2011, Edwards et al., 2008, Ngugi et al., 2010, Ngugi et al., 2011).

While seizures are recognised as an acute presentation complicating febrile illnesses in children in all populations, the high incidence and sub-optimal management of febrile seizures in early childhood in SSA have been postulated as risk factors in early life contributing to higher rates of epilepsy in this region (Newton, 2009). High rates of obstetric complications have also been implicated (Burton et al., 2012a). With regards to infectious risk factors in later life, epilepsy as a sequela of a variety of specific CNS infections has been extensively studied in LMIC populations, including neurocysticercosis (NCC), cerebral malaria secondary to *Plasmodium falciparum*, bacterial meningitis and encephalitis (Singh and Prabhakar, 2008, Garcia and Del Brutto, 2005, Birbeck et al., 2010, Singhi, 2011).

Epilepsy can carry a good prognosis, given access to appropriate anti-epileptic drug (AED) therapy, with up to 78% of cases becoming seizure-free for two years within five years of initiating treatment (Perucca et al., 2000). This finding holds true of epilepsy due to acquired brain insults, which is considered to account for a considerable amount of the burden of epilepsy in LMICs; it is also true with regards to treatment with older (and cheaper) AEDs, including phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ) and sodium valproate (SV), some or all of which are generally available in LMICs. The annual cost of treatment with PB for an adult with epilepsy may be as low as five US dollars (USD), and mathematical modelling has suggested that if availability of AEDs such as PB could be increased to 50% of active cases, 1,360 disability-adjusted life years (DALYs) per

million population in SSA could be saved (Chisholm and Saxena, 2012). In many parts of the developing world, however, a low degree of awareness regarding correct management coupled with high levels of poverty, illiteracy and stigma mean that the epilepsy remains largely untreated (Radhakrishnan, 2009), and while up to four-fifths of the potential market for AEDs is in LMICs, 90% or more of PWE in these countries may receive no treatment at all (Kale, 2002, Scott et al., 2001, Meinardi et al., 2001). The proportion of cases requiring treatment but who are not receiving it is known as the epilepsy treatment gap (ETG), and this has frequently been estimated at above 80 to 90% in SSA (Meyer et al., 2010).

Epilepsy also remains a highly stigmatised condition worldwide with this being particularly the case in SSA (Baskind and Birbeck, 2005b). PWE in these countries may be excluded from school, work and marriage, with both felt and enacted stigma serving as barriers to treatment above and beyond any social or financial constraints (Mushi et al., 2010).

1.3 Fundamental concepts and definitions

Epilepsy is one of the oldest diseases known to Man, with descriptions of phenomena corresponding to epilepsy or epileptic seizures appearing in Babylonian, Chinese and Indian texts dating as far back as 1,000 years BC (Eadie and Bladin, 2001, Temkin, 1994). While medical historians argue that clear descriptions of distinct seizure types appear in some of these ancient writings, our current understanding of epilepsy rests on concepts first articulated by Hughlings Jackson in the late 19th Century which distinguish isolated epileptic seizures from the abnormal state of the brain and body that gives rise to recurrent epileptic episodes (Eadie and Bladin, 2001).

1.3.1 Epileptic seizures

An epileptic seizure is the clinically recognisable manifestation of a paroxysmal disturbance of brain function originating either in the grey matter of the cerebral cortex or in certain parts of the thalamus and upper brain stem. The electro-chemical events which initiate epileptic seizures arise in or near neurones in these structures; seizures develop when groups of structurally and functionally interconnected neurones act collectively,

suddenly, briefly, excessively, and in a way that serves to disrupt the overall functioning of localised groups of neurones or of the brain as a whole (Fisher et al., 2005). Depending on the normal functions of the neurones involved, a seizure will therefore be manifested as some involuntary alteration in brain function in the affected individual. This alteration may involve any one aspect of normal brain function, including consciousness, behaviour, thought, speech, movement, sensation, or any combination of these (Eadie and Bladin, 2001, Commission on Epidemiology and Prognosis, 1993). Epileptic discharges may arise *de novo*, within particular groups of neurones because of an inherited abnormality present in them(Gutierrez-Delicado E, 2004) or because their biochemical environment is altered by acute systemic illness, toxicity or neurological insults (Banerjeea et al., 2009).

1.3.2 Epilepsy

The diagnosis of epilepsy is reserved for the state characterised by the spontaneous recurrence of epileptic seizures, as opposed to provoked seizures or psychogenic attacks (Sander and Shorvon, 1996, Banerjeea et al., 2009). Distinguishing isolated from spontaneously recurrent seizures is important on clinical grounds, when considering aetiology and treatment, and on epidemiological grounds, when considering the incidence and prevalence of seizure disorders. Up to 5% of individuals in the general population will experience an epileptic seizure at some point during their life, but only a small proportion of these will go on to have recurrent seizures (Sander, 2003, Bell GS and Sander JW, 2001). Similarly, provoked epileptic seizures may be seen in various clinical contexts, including metabolic and biochemical disturbances (e.g. hypoglycaemia or hyponatraemia), acute neurological insults (e.g. traumatic brain injury, brain ischaemia or infarct) and inflammatory processes affecting the brain (e.g. vasculitides, infective processes associated with local inflammation and swelling, or generalised encephalitis). In such cases the risk of spontaneous recurrence of seizures in the future, and hence a diagnosis of epilepsy, will depend on the site and nature of the acute pathology.

The diagnosis of epilepsy therefore remains essentially clinical, and should be based on a thorough history of the clinical episodes in question supported by an eye-witness account wherever possible. While the measurement of various blood markers may be important

in identifying when seizures are due to acute biochemical or metabolic disturbances, and neuro-imaging with computed tomography (CT) or magnetic resonance imaging (MRI) may play a role in diagnosing or excluding intracerebral pathology that may trigger seizures acutely, electroencephalography (EEG) should only be used to support or further characterise a clinical diagnosis of epilepsy (Smith, 2002). Once a clinical diagnosis is made, EEG recording and neuro-imaging may offer useful information when classifying seizures according to seizure type or epilepsy syndrome (Berg et al., 2010).

1.3.3 Classification of seizures and epilepsies

Various schemes for the diagnosis and classification of epileptic seizures and epileptic syndromes have been proposed over the past four decades. These have been developed largely under the auspices of the International League Against Epilepsy (ILAE) in consultation with the international community of practitioners of clinical epileptology (Gastaut, 1970, Commission on Classification and Terminology of the International League Against Epilepsy, 1981, Commission on Classification and Terminology of the International League Against Epilepsy, 1989, Engel, 2001, Engel, 2006, Berg et al., 2010). When considering seizure type, the primary criterion used in these schemes has been the site of epileptogenesis, the secondary criterion being a phenomenological description of the clinical manifestations of seizures. According to the primary criterion, there are three main groups of seizure types: generalised seizures, focal seizures, and seizures of unknown origin.

The most recently revised classification encompasses both seizure types and epileptic syndromes (Berg et al., 2010). With regards to partial seizures, it is now recommended that these are no longer described as either complex or simple (i.e. with or without impairment of consciousness), but simply as 'focal', with an accompanying description of seizure features drawn from the ILAE-endorsed glossary of descriptive terminology for seizures (Blume et al., 2001). This resource encompasses suggestions made by Luders et al who provided a scheme for a purely semiological classification (Lüders et al., 1998), with seizures being described according to their interference with four "spheres": sensorial, consciousness, autonomic and motor.

Frequently occurring patterns of seizure disorder in persons who suffer recurrent epileptic seizures are designated as epileptic syndromes or 'epilepsies'. As with its classification of seizures, the ILAE has also developed and refined a classification of the epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989, Engel, 2001, Engel, 2006, Berg et al., 2010). This syndromic classification was initially built upon the concept of the clinical seizure type, with localisation-related epilepsies (i.e. focal seizure types) and generalised epilepsies being divided into idiopathic, symptomatic and cryptogenic varieties (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Under this classification idiopathic epilepsies were synonymous with inherited syndromes and cryptogenic epilepsies were presumed, although not proven, to be symptomatic of some acquired pathology. In addition to focal and generalised epilepsies a further category of situation-related seizures was proposed; this included febrile convulsions, isolated seizures, and seizures precipitated by acute metabolic or toxic disturbances. The most recent revision of this system replaces the terms "idiopathic"," symptomatic" and "cryptogenic" with "genetic", "structural/metabolic", and "unknown cause"(Berg et al., 2010). Genetic epilepsies are the direct result of known or presumed genetic defects in which seizures are one of the symptoms of the disorder. Epilepsies previously described as "idiopathic" are now included in this group. "Structural/metabolic" epilepsies arise where there is a distinct structural or metabolic disease which is associated with recurrent seizures. Structural lesions may be acquired (e.g. stroke, trauma, infection), or genetic or congenital in origin (e.g. tuberous sclerosis, anomalies of cortical development). Epilepsies previously described as "symptomatic" are now included in this group. The term "unknown cause" is intended to be viewed neutrally, encompassing epilepsies that may ultimately fall under either "genetic" or "structural/metabolic"; epilepsies previously termed "cryptogenic" are now included in this group.

1.3.4 Classification of epilepsy in low income countries

The classification of seizure disorders encountered in LMICs is difficult. In many of these countries the diagnostic tools of cerebral imaging and EEG are simply not available in most clinical settings. For this reason there has been recent interest in developing alternative systems of classification that may be of more pragmatic use in settings where clinical resources are limited (Birbeck, 2012). Winkler et al have developed a pragmatically adjusted clinical classification of seizures for use in rural Africa (Winkler et al., 2008b). This scheme proposes that patients with no obvious focal onset and no evidence of diffuse brain damage should be classified according to age at presentation, with those presenting before six years or after 25 years warranting further investigation where available. For the remainder, those with seizures of clear focal onset or with focal neurology should similarly be investigated further if possible. The authors argue that this approach will help to focus any further investigations on those patients most likely to have underlying brain pathology which may be progressive and which may therefore benefit from specific management beyond controlling seizures with AEDs. Similarly, those patients with diffuse, fixed brain damage are known to present special challenges with regards to treatment and follow-up and may be accorded special attention when planning their management. This system has yet to be widely adopted for either clinical or epidemiological purposes.

1.3.5 Summary of basic concepts

Any meaningful discussion of literature pertaining to epilepsy will depend on a clear and concise application of the concepts summarised above. When comparing populations and study findings it is important to clearly define which definitions are being used, and difficulties may arise when considering clinical and epidemiological studies which may have been performed at different times, using differing descriptive terms and inclusion criteria. The key definitions used in this study are therefore provided here in Box 1.

Epileptic seizure	Any clinical event, provoked or spontaneous, that results from a paroxysmal disturbance of brain function originating in the grey matter of the cerebral cortex or related structures.
Epilepsy	The tendency to suffer recurrent spontaneous (i.e. unprovoked) epileptic seizures, regardless of underlying cause.
Primary generalised seizure	A seizure in which both cerebral hemispheres are involved from the onset of each seizure. Primary generalised seizures are largely synonymous with the idiopathic and genetic generalised epilepsies.
Focal-onset seizure	A seizure arising in a localised neuronal group in one cerebral hemisphere. This definition includes seizures previously referred to as simple partial and complex partial. Epilepsy characterised by focal seizures often arises as a result of an acquired brain insult, and is sometimes referred to as symptomatic epilepsy.
Secondarily generalised seizure	A seizure which has a focal origin, but which then progresses to involve both cerebral hemispheres as a whole. Epilepsy characterised by secondarily generalised seizures would still be considered as focal.

Ref: Thurman et al., 2011, Berg et al., 2010

Box 1: Definitions of key terms as used during this study

1.4 Epidemiology of the epilepsies

Epidemiology is the study of the dynamics of health and disease in terms of their distribution, determinants and effects in any given population. The epidemiology of any particular condition will take into account clinical data on its presentation and natural history along with the socio-demographic context of the disease within the study population. The epidemiology of epilepsy is based largely on descriptive and analytical studies, comprised either purely of clinical observations in PWE, or of attempts to establish associations and determinants of the disease through comparison between individuals with epilepsy and those without (Sander, 2003).

As discussed above, epilepsy is a heterogeneous set of disorders: aetiologies and risk factors vary with age and geographic location, and the differential diagnosis of epilepsy encompasses all causes of transient alteration or impairment of consciousness. Consequently, case ascertainment and diagnostic accuracy represent major challenges to the epidemiology of epilepsy. The majority of PWE do not have permanent physical signs and can be diagnosed only by taking a clinical history. The extent of investigation that is possible in different settings varies widely, and the use of terms such as idiopathic, cryptogenic and generalised are often confused (Sander, 2003, Winkler et al., 2008b). All these factors should be borne in mind when comparing findings from different studies and study populations.

1.4.1 Methods used in low-income countries for studies of epilepsy

In HICs the most common published method of case ascertainment is a review of medical records, usually supplemented by interviews with positively identified cases (Shorvon and Farmer, 1988). Medical records in LMICs are generally much less complete, and this method is generally not appropriate for any comprehensive surveys in regions such as SSA. Other inherent disadvantages of this approach are that those who are incorrectly diagnosed, those who have not sought medical attention for their symptoms and those whose records are not retrieved may be excluded from epidemiological estimates.

Door-to-door studies involve either the direct or indirect contact of all subjects in a sample population, with assessment of all subjects for the relevant disorder. The main

advantage of this approach is the identification of cases that have yet to seek medical attention, and in the case of epilepsy such individuals may represent a significant proportion of the affected population, particularly in LMICs (Mbuba and Newton, 2009, Mbuba et al., 2012b, Mbuba CK et al., 2008, Ngugi et al., 2013a, Mushi D et al., 2010, Birbeck, 2000c, Meinardi H et al., 2001).

Studies of this type in LMICs may be hampered by a lack of accurate diagnostic data, however, with the number of physicians with expertise in clinical neurology working in these countries being limited (Schoenberg, 1982). According to the World Health Organisation (WHO), there are as few as 0.03 neurologists per 100,000 population working in SSA (WHO, 2004). It must also be borne in mind that epilepsy remains a highly stigmatised condition in many countries; PWE are often marginalised or socially excluded, and hence less likely to come forward to be included in studies. With these limitations in mind, the shortcomings of community-based studies of epilepsy may include the exclusion of minor or more subtle seizure types, such as absence or partial seizures, and underreporting because of the stigma associated with epilepsy (Giel, 1970, Senanayake and Roman, 1993). Door-to-door studies are also logistically difficult and expensive to conduct.

These problems notwithstanding, the community-based approach is considered the optimum method to detect cases of active epilepsy in prevalence studies in LMICs (Senanayake and Roman, 1993). It has been suggested that studies of this design require a population of 25 to 50,000 to render age-, sex-, and race-specific prevalence ratios meaningful (Schoenberg, 1982, WHO, 1981).

To maximise efficiency and minimise cost, door-to-door studies for the purposes of neuro-epidemiology are generally conducted using a two-phase approach; lay personnel conduct a screening phase and clinicians with specific expertise make the final diagnoses (Schoenberg, 1982, World Health Organisation Neurosciences Programme, 1981, Ottman R et al., 2010). This approach has been employed successfully in a number of regions around the world including Europe, the United States, Latin America, Africa and Asia (Ottman R et al., 2010).

1.4.2 Screening tools

Any door-to-door population-based study must employ a screening tool with adequate sensitivity and specificity. If the sensitivity of the screening instrument is low, many true positives will be missed: i.e. affected individuals will not be detected. Conversely, a low specificity will lead to the inclusion of large numbers of false positives: i.e. individuals without the disease in question), leading to substantial logistical problems in a survey of any size. Even where validated tools are used, door-to-door studies are likely to have a higher sensitivity for convulsive epilepsies, and more subtle forms of epilepsy will tend to be underestimated (Ngugi et al., 2010). It is also generally the case that the more sensitive a screening questionnaire the less specific it will be (Shorvon and Farmer, 1988). Questionnaires that target symptoms that may represent the presence of a convulsive seizure disorder will therefore tend to have a high sensitivity but at the cost of a lower specificity, with many false positives being identified (Ottman R et al., 2010). This has been seen in practice when screening questionnaires have been used in resource-limited settings; sensitivities in excess of 95% have been reported, but with lower specificities leading to the inclusion of large numbers of false positives among those who have screened positive (Osuntokun et al., 1982, Placencia et al., 1992a).

The positive predictive value (PPV) of a screening test is defined as the proportion of individuals who screen positive who are subsequently confirmed to be affected. Where the background prevalence of a condition being studied is low screening instruments with a low specificity will have a low PPV. In a review of screening questionnaires used in community-based surveys PPVs were as low as 20% due to this effect (Placencia et al., 1992a).

Community-based door-to-door studies conducted in SSA over the past three decades have made use either of screening instruments devised specifically for the individual study or one of a number of validated screening tools, used in whole or in part. These are reviewed in more detail in Section 1.5.2.

The WHO has developed a two-stage protocol for the detection of neurological disability in LMICs (World Health Organisation Neurosciences Programme, 1981). This comprises of

a screening tool, to be used during a population census, followed by individual assessments of positive responders to detect symptoms and signs of a range of neurological diseases. The screening questionnaire contains fifteen questions, of which three relate to epilepsy (Box 2), combined with seven simple tasks. Other conditions that this instrument was designed to detect include cerebrovascular disease, extrapyramidal disorders, peripheral neuropathy, intracranial neoplasia and migraine. Based on contemporary prevalence figures for neurological disorders from HICs it was recommended that a study population of 50,000 or more would be necessary to obtain meaningful rates in four or five age bands across the two sexes (WHO, 1981). Although widely used previously, including in studies from SSA (Tekle-Haimanot et al., 1990a, Osuntokun et al., 1982, Osuntokun et al., 1987, Almu et al., 2006), this instrument is now less favoured, focusing as it does on specific diseases rather than disability, and having been designed without due consideration as to which disease(s) may be of greatest public health importance in LMICs (Bower et al., 2009).

For subjects of seven years of age and older:

1. Have you ever lost consciousness?
2. Have you ever had episodes where you lost contact with your surroundings?
3. Have you ever had any shaking of your arms and legs which you could not control?

For children under seven years of age:

1. Has this child ever lost consciousness
2. Does this child have episodes characterised by vagueness and unawareness of surroundings?
3. Have you ever seen this child shaking and unable to control the arms and legs?

Box 2: Epilepsy questions from WHO screening protocol for LMICs
(WHO, 1981)

More recently a new screening instrument specifically designed for the detection of neurological disability in resource-poor settings has been developed with the aim of improving on the sensitivity and specificity of the original WHO protocol (Bower et al., 2009). A hospital-based pilot study of this tool was conducted in 128 participants in Tanzania; there was a non-significant increase in sensitivity from 98.4% to 100% compared with the WHO protocol, but specificity improved significantly from 29.2 to 62.0% ($p=0.001$). This represents a considerable improvement when contemplating large-scale community-based studies, and initial validation of this instrument in Tanzanian and Ethiopian populations has been promising (Bower et al., 2012)

With regards specifically to epilepsy, it has been argued that the WHO questionnaire was likely to have a poor sensitivity for partial seizures, that its specificity was too low to be logistically acceptable in any large scale epidemiological study, and that for these reasons composite neuro-epidemiological screening questionnaires to detect specific disease entities should be avoided (Placencia et al., 1992a). With this in mind, and for the purposes of a large epidemiologic study of epilepsy in Ecuador, a nine-item screening questionnaire designed specifically to detect partial and generalised seizures was developed (Placencia et al., 1992a). An initial bank of twenty questions derived from the authors' clinical experience was found to have a sensitivity of 100% and specificity of 50.8% when applied to eighty-seven patients and sixty-three controls. After cluster analysis of responses this was refined to a combination of nine questions which collectively had a sensitivity and specificity of 92% and 98% respectively (Box 3). Following comprehensive field-based validation during a population survey of 72,121 people the instrument was found to have a sensitivity of 79.3%, specificity of 92.9%, PPV of 18.8%, and negative predictive value (NPV) of 99.6%. While the final nine questions did not include any that would readily identify absences or myoclonic seizures, this instrument did include a disease-specific question intended to easily detect individuals who may already be aware of their diagnosis; this was not a feature of the WHO questionnaire.

Screening instruments based on modified forms of the Ecuador questionnaire have subsequently been used in community-based studies conducted in SSA. In a study from

Zambia three additional questions were included to exclude individuals that would otherwise screen positive due to febrile or malaria-associated seizures in early childhood (Birbeck and Kalichi, 2004). More recently a large door-to-door study from Tanzania also used a screening questionnaire derived from the Ecuador questionnaire, but with an extended number of questions informed by the work of Birbeck et al in Zambia(Birbeck and Kalichi, 2004) coupled with the authors' own clinical experience of diagnosing and treating epilepsy in Tanzania (Winkler et al., 2009c).

1. Have you ever had attacks of shaking of the arms or legs which you could not control?
2. Have you ever had attacks in which you fall?

Affirmative answers to questions 1 and 2 together render the subject positive.

3. Have you ever lost consciousness?
4. Have you ever had attacks in which you fall with loss of consciousness?
5. Have you ever had attacks in which you fall and bite your tongue?
6. Have you ever had attack in which you fall and lose control of your bladder?
7. Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?
8. Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?
9. Have you ever been told that you have or have had epilepsy or epileptic fits?

Affirmative answers to any of questions 3 to 9 render the subject positive.

Box 3: Nine-item epilepsy screening questionnaire developed in Ecuador (Placencia et al., 1992a)

A number of other screening tools have also been used in studies from countries in SSA. Investigators at the Institute of Neuroepidemiology and Tropical Neurology at the University of Limoges in France, recognising the need for comparable epidemiologic data on epilepsy from tropical countries, have developed a detailed pro-forma designed to collect standardised data when investigating epilepsy in tropical LMICs (Quet et al., 2011). Designed as a comprehensive protocol to be used in two-stage surveys the pro-forma includes a screening questionnaire, consisting of five questions, which has been shown to having a sensitivity and specificity of 95.1% and 65.6% respectively. The full document is available on-line in various translations (Institute of Neurological Epidemiology and Tropical Neurology, 2012). To date this instrument has been employed, in whole or in part, in thirteen epidemiological surveys in twelve African countries (Quet et al., 2011).

The Ten Questions tool is a composite instrument designed to detect severe neurological impairment in children living in resource-poor countries (Mung'ala-Odera et al., 2006). In a study in a rural Kenyan population this questionnaire had a sensitivity of 100% for the detection of active epilepsy in children (Mung'ala-Odera et al., 2004). In a larger community-based study in the same population two questions derived from the Ten Questions Questionnaire were used to detect the presence of seizures with convulsions in all age groups (Edwards et al., 2008). In the latter study children under the age of six years were excluded due to the difficulties in differentiating between febrile seizures and epilepsy in infants.

Finally, in Rwanda, a standardised seven-item tool for the detection of musculoskeletal disorders that included a single question on convulsions was used in a cross sectional community-based survey (Simms et al., 2008). In a validation study conducted in 179 individuals the screening tool performed with a sensitivity of 97.8%, a specificity of 98.8% and had a PPV of 99%, although these were composite scores for all musculoskeletal impairments and no specific discussion of how many individuals with epilepsy were included is offered (Atijosan et al., 2007).

Demonstration projects established by the ILAE to develop models for the management of epilepsy in LMICs have also included community-based screening surveys (Sander, 2002).

These have made use of questionnaires based on the WHO instrument described above (Wang et al., 2003b), include work done in SSA (Ndoye NF et al., 2005), although to the best of our knowledge specific details of the instruments have not been published.

1.4.3 Key informants

Key informants (KI) are defined as long-term residents within a population who occupy positions of trust and respect in their communities (Pal et al., 1998). While KI have been used extensively in LMICs for community health assessments the major criticism of this method has been its lack of sensitivity: in a Jamaican study of childhood disability the sensitivity of KI-based screening for epilepsy was found to be less than 12% (Thorburn et al., 1991), in a Kenyan study of the prevalence of epilepsy KI-based screening yielded a prevalence of 3.6/1,000 compared with 18.2/1,000 estimated by a random cluster sample survey in the same population (Kaamugisha and Feksi, 1988), and a door-to-door screening study conducted in a rural district of West Bengal in India had a sensitivity for the detection of epilepsy of 59% utilising questionnaires compared with 17% when utilising KIs (Pal et al., 1998). The authors of this latter study were however able to demonstrate that when the KI method was used alongside the door-to-door method a number of additional cases of epilepsy were detected that would have been missed by the door-to-door approach alone. While the PPV for seizures was similar for the two methods, the slightly higher value for the KI approach (40% vs. 36%) suggests that this is a useful adjunct to any community-based screening methods. The KI approach has been used in SSA in community-based prevalence surveys of epilepsy (Snow et al., 1994, Debrock et al., 2000), and more recently as an adjunct to a questionnaire-based approach to screening for Parkinson's Disease in Tanzania (Dotchin et al., 2008).

1.4.4 Data-linkage and capture-recapture techniques

Given the limitations and relative costliness of the two-stage screening approach, other methods of estimating the burden of disease in resource-limited settings have been explored.

The technique of electronic data linkage constructs a local register for a given condition using as many data sources as possible (Morris et al., 1997). The capture-recapture technique is a statistical method which analyses multiple patient lists to identify the degree of overlap and allows estimates of the total population, counted and uncounted, to be made (International Working Group for Disease Monitoring and Forecasting, 1995). This technique has been used to assess the undercount of a data linkage approach when attempting to enumerate the number of people with a variety of non-communicable diseases (NCDs), including hypertension, diabetes, asthma and epilepsy, in a rural district of South Africa (Gill et al., 2001). Records from a weekly NCD clinic, satellite health clinics and repeat prescription cards were available for data linkage, with a comparator list being available from the NCD clinic of the local central hospital. There was only overlap between the lists for the hypertension and diabetes groups, however, and consequently little or no adjustment was possible. The authors cite the complex spelling of duplicate names along with duplicate attendances at the same clinic as factors that may complicate data analysis, and also acknowledge the limitation that only enumeration of known, diagnosed disease under healthcare treatment is possible using this approach. The difficulties associated with matching names from different lists have also previously been observed when attempting to use capture-recapture to correct estimates of mortality as part of a long-term study of causes and rates of death in three areas of Tanzania (Kitange HM et al., 1996). Use of capture-recapture in this study was hampered not only by variations in the spelling of names, but also by individuals using completely different names at different times and for different purposes for social, religious and cultural reasons (Black et al., 1994).

1.5 Prevalence of epilepsy

1.5.1 Estimates of prevalence from regions outside sub-Saharan Africa

In systematic review of epidemiological studies of epilepsy from Europe population-based studies came largely from the UK and the Nordic, Baltic and western Mediterranean countries (Forsgren et al., 2005a). Twenty-three sufficiently comparable studies from twelve countries were identified, with active epilepsy being defined as seizures within the previous five years. The median estimated prevalence in these studies was 5.2 /1,000 (range 3.3 to 7.8). Prevalence rates were often higher in males than females, but this was rarely of statistical significance. The overall prevalence was estimated at 4.5 to 5.0 per 1,000.

A review of multiple data sources from the Russian Federation, including records from hospitals, outpatient departments and emergency care units, estimated the prevalence of active epilepsy in the adult population (aged fourteen years or older), with a denominator population of 517,624 people (Guekht A et al., 2010). The prevalence was 3.4/1,000 (95% CI 3.26 to 3.55); epilepsy was significantly more common in men than in women (4.5/1,000 vs. 2.52/1,000; $p<0.0001$), and significantly higher in the Eastern than the Western population of the Federation (4.12/1,000 vs. 2.82/1,000; $p<0.0001$).

A similar review of studies conducted in Latin American countries identified thirty-two studies that provided prevalence estimates (Burneo et al., 2005). Only eleven of these studies made a clear distinction between lifetime and active prevalence, with the median estimated prevalence of active epilepsy being 12.4/1,000 (range 5.1 to 57.0). The majority of the studies utilised a questionnaire plus clinical examination, with additional information from EEG or neuro-imaging being available in seven studies. No overall differences in prevalence were identified between rural and urban studies, or between the males and females.

A systematic review of studies from Asian countries identified twenty-one studies from eleven countries, the majority of which were community-based door-to-door studies (Mac et al., 2007). The median estimated lifetime prevalence was 6/1,000 (range 1.5 to 14.0), with no significant difference between men and women.

The median prevalence of epilepsy in Arab countries, based on five studies from four countries, was 2.3/1,000 (range 0.9 to 6.5) (Benamer and Grosset, 2009). Four of these studies were community-based, with a definition of active epilepsy being provided in three studies and acute symptomatic seizures being specifically excluded in only one.

1.5.2 Prevalence of epilepsy in sub-Saharan Africa

Of the community-based studies that have been performed in Africa over the past two decades, many reflect a model in which lay investigators administer questionnaires and conduct examinations followed by confirmation of cases by neurologists or other trained doctors. As discussed above, while it has been suggested that studies of this design require a population of twenty-five to fifty thousand to render age-, sex-, and race-specific prevalence ratios meaningful (Schoenberg, 1982, World Health Organisation Neurosciences Programme, 1981), and many of the published studies from SSA fall far short of this figure (Bondestam et al., 1990, Dumas et al., 1989, Goudsmit et al., 1983, Osuntokun et al., 1982, Osuntokun et al., 1987, Longe and Osuntokun, 1988, Snow et al., 1994). Estimates of the prevalence of epilepsy in African countries have varied greatly, from 2.2 to 58 per 1,000 (Diop et al., 2003, Preux and Druet-Cabanac, 2005), although differing research protocols and inclusion criteria make the comparison of figures difficult. The lowest rates reported from African countries come from South Africa (2.2/1,000) (Eastman, 2005, Diop et al., 2003). South Africa is usually considered separately from other countries in SSA, however, due its particular combination of economic circumstances which effectively juxtapose conditions associated with both LMICs and HICs (Diop et al., 2003). A review of door-to-door surveys from SSA excluding South Africa identified a median prevalence of 15/1,000, considerably higher than estimates from other regions of the world (Preux and Druet-Cabanac, 2005).

The section that follows briefly discusses some work of historical interest before reviewing by country the community-based studies of epilepsy conducted in SSA over the past four decades. Work from Tanzania is then discussed at the end of this section.

1.5.3 A brief note on sub Saharan Africa

Sub-Saharan Africa is the geographical area of the continent that lies south of the Sahara, and includes all countries which are fully or partially located in this region (United Nations, 2009). Sub-Saharan Africa contrasts with North Africa, which is considered a part of the Arab world. The population of the region is growing by 2.3% per year, and is projected to reach 1.5 billion by the year 2050 (United Nations Department of Economic and Social Affairs, 2012). The region as a whole is characterised by ecological diversity, climactic extremes, poor infrastructure and high poverty indices, including high rates of child and maternal mortality and low adult life-expectancy.

1.6 Review of studies from sub-Saharan Africa

1.6.1 Historical studies

Studies conducted in the 1960s in black South African mine workers reported prevalence rates for epilepsy of 2.2 to 3.7/1,000 (Bird et al., 1962, Hurst et al., 1961). The first of these studies reviewed clinical records relating to mineworkers being repatriated on medical grounds; all cases included were adult males aged fifteen years and above. The second study reviewed local clinic records where registration cards indicated almost complete coverage of local patient population of approximately 60,000 people. Fifty-one patients with seizures were identified (twenty-one male, twenty-nine female), of whom forty-one (80%) were described as having 'grand mal' seizures. Aetiology was identified in fourteen (27.5%) cases, and included perinatal complications (seven), head injury (five), cysticercosis (one), and stroke (one).

In 1964, to complement a hospital-based case series, houses in a reserve near Bulawayo, Zimbabwe, were visited by a local medical officer to seek out cases of epilepsy (Levy, 1964). A prevalence of 7.4/1,000 was estimated, with similar rates in males and females; 56% of cases were under the age of twenty years. Little detail on past history or risk factors is given, although a family history of epilepsy was elicited in 64% of cases. The majority of cases (91%) were described as 'generalised'. Again, few further details are given.

A brief report from Ghana in 1967 describes a study that questioned 3,912 inpatients and outpatients at a hospital in Accra about a history of grand-mal fits beyond infancy (Haddock, 1967). Patients were also asked about a similar history in any full siblings. Combined results provided an estimate of prevalence of 33/1,000, with no significant difference in prevalence between men and women identified. No further assessments are described in this paper, which also appears to use the term incidence in place of prevalence in the main text.

From Ethiopia in 1970, a set of brief observations containing few clinical details describes two morbidity surveys conducted in the south western part of the country that gathered data on the prevalence of epilepsy (Giel, 1970). In an urban sample of one hundred houses (384 people) the prevalence was estimated at 5/1,000; in a rural sample of another one hundred houses (370 people), the prevalence was 8/1,000. No further details of case ascertainment, inclusion criteria or other clinical details are given, and most of the discussion focuses on the various privations suffered by PWE in Ethiopia at that time.

Finally, from Tanzania in 1965, in a descriptive doctoral thesis based on observations made during her time as a mission doctor in the Ulanga district in the Mahenge mountains, Dr Louise Aall-Jilek noted an apparently high prevalence in one tribe in the Wapogoro tribe, with a strong familial tendency among cases being observed (Aall-Jilek, 1965). When local clinic records were interrogated more systematically a minimum estimate of prevalence based on known clinic attendees of 20/1,000 was made (Jilek and Jilek-Aall, 1970). Precise details of case definitions and inclusion criteria are not given, although 85% of cases were reported to be suffering with ‘grand-mal’ fits, and of these nearly half reported prodromal features.

All of the studies described above mention the stigmatising nature of epilepsy in the different communities and settings described. Another common theme is the lack of clearly comparable criteria for the description and classification of seizures, an issue which larger and more systematic studies have subsequently tried to address.

1.6.2 Studies from sub-Saharan Africa since 1982 (excluding Tanzania)

Over the past four decades there have been a number of community-based studies from countries in sub-Saharan Africa that have used a screening approach to identify PWE in order to estimate the prevalence of epilepsy. These have generally been conducted in rural populations and collectively present widely varying estimates of prevalence. Details of twenty studies conducted in eleven countries, excluding Tanzania, are summarised in Table 1. From examining this table it can be seen that comparisons between studies are rendered difficult by a number of factors: wide variations in the size of denominator populations (from less than 200 to greater than 150,000), different inclusion criteria in terms of age groups or active versus lifetime epilepsy (if stated), a general lack of age-standardised figures for prevalence (with different standard populations used when age-standardisation is performed), and differing and non-standardised approaches to screening and case ascertainment. Where details of seizures are given it is often difficult to compare findings as the distinction between seizures and epilepsies is not always clearly elucidated, and very few studies have recourse to further investigations to help further characterise seizures in terms of electro-clinical epilepsy syndromes. Only two of the studies itemised in Table 1 benefitted from EEG investigations (Tekle-Haimanot et al., 1990b, Prischich et al., 2008) and none of them benefit from imaging findings in the form of CT or MRI. The descriptive review of these studies that follows is also intended to illustrate some of the wider issues associated with epilepsy in SSA to have been identified during community-based studies.

Country	Year	Setting	Denom. (n)	Age groups	Screening protocol	LTE/AE*	Prevalence/1,000		M:F	Clinical details	Comments
							Crude	AS†			
Benin (Debrock, 2000)	1997	Rural	3,134	Not stated	Limoges protocol, KIs, medical records, data linkage	LTE	21.1	N/A	None	Yes	Comparison of different screening techniques
Benin (Crepin, 2007)	2005	Rural	11,668	Not stated	Limoges protocol	LTE	12.7	N/A	1.1	Limited	Case-control study of nutrition in epilepsy
Cameroon (Nkwi and Ndonko, 1989)	1986	Rural	500	All	House-to-house survey - no further details	Not stated	70.0	N/A	Not stated	No	Sociological paper. Few clinical details
Cameroon (Kamgno et al., 2003a)	1991	Rural	Not stated	Not stated	KIs	LTE	5.0 to 87.0	N/A	Not stated	Limited	Retrospective estimate as part of mortality study.
Cameroon (Prischich et al., 2008)	2004	Rural	197	All	10-item instrument adapted from Limoges protocol	AE	105.0	134.5 (Cameroon 2000)	1.4	Yes	Case-control study of risk factors
Ethiopia (Tekle-Haimanot, 1990)	1998	Rural	60,820	All	Modified WHO protocol	LTE	5.2	N/A	1.3	Yes	Composite study of neurological disability
Ethiopia (Almu, 2006)	2006	Rural	1,154	Not stated	WHO protocol	AE	29.5	N/A	Not stated	Yes	
Kenya (Edwards, 2008)	2008	Rural	151,408	≥6 years	Two questions from 'Ten Questions' protocol	AE	2.9	N/A		Limited	Screening for ACE only
Kenya (Snow, 1994)	1993	Rural	7,450	≥6 years	KIs	AE	4.0	N/A	2.4	Limited	Part of mortality study
Kenya (Kaamugisha, 1998)	1986	Rural	2,961	All	KIs and cluster sampling	AE	18.2 vs. 3.6	N/A	Not stated	Limited	
Liberia (van der Waals et al., 1983)	1982	Rural	4,436	All	KIs	AE	28.0	N/A	1:1	Yes	

*LTE – lifetime epilepsy/AE – active epilepsy

†Age-standardised (standard population in parentheses)

Table 1: Community-based prevalence studies of epilepsy from SSA (excluding Tanzania)

Country	Year	Setting	Denom. (n)	Age groups	Protocol	LTE/AE*	Prevalence/1,000		M:F	Clinical details	Comments
							Crude	AS†			
Nigeria (Osuntokun, 1982)	1982	Rural	903	All	WHO protocol	AE	37.0	N/A	0.6	No	
Nigeria (Osuntokun, 1987)	1982	Urban	18,954	All	WHO protocol	AE	5.3	5.0 (US 1970)	0.9	Yes	
Nigeria (Longe, 1988)	1986	Rural	2,925	All	Modified WHO protocol	AE	6.2	N/A	0.6	No	
Rwanda (Simms, 2008)	2005	Mixed	6,757	All	Screening tool for musculoskeletal impairments	AE	7.0	6.0 (Europe 1998)	Not stated	No	National survey of musculoskeletal impairments.
Senegal (Ndoye, 2005)	2005	Urban	4,500	All	ILAE protocol	AE	14.2	N/A	Not stated	Yes	
Togo (Dumas, 1989)	1987	Mixed	5,264	>15 years	Random cluster sample, neurological examinations	Not stated	16.7	N/A	2.4	No	Study into relationship between NCC and epilepsy..
Togo (Balogou et al., 2007)	2002	Rural	6,249	All	Limoges protocol	LTE	15.7	N/A	1.3	Yes	Feasibility study for management of epilepsy in LMICs.
Uganda (Kaiser et al., 1996)	1994	Rural	4,743	All	KIs	AE	13.0	11.0 (World)	0.8	No	Study of epilepsy and onchocerciasis.
Zambia (Birbeck and Kalichi, 2004)	2001	Rural	55,000	All	Modified Ecuador protocol	AE	14.5	N/A	Not stated	No	

*LTE – lifetime epilepsy/AE – active epilepsy

†Age-standardised (standard population in parentheses)

Table 1 (cont.): Community-based prevalence studies of epilepsy from SSA (excluding Tanzania)

Benin

A survey in two villages (n=3,134) used the capture-recapture method to estimate the prevalence of epilepsy (Debrock C et al., 2000). Diagnoses of epilepsy obtained through three sources were compared: a door-to-door screening survey, cases identified by key informants in their communities, and a review of medical records in local health centres. The overall crude lifetime prevalence of epilepsy was 21.1/1,000 (15.9/1,000 based on the door-to-door survey alone). Tonic-clonic seizures accounted for 68.1% of cases, and it is implied that these were primary generalised seizures; complex partial seizures with secondary generalisation are described separately and account for 13.6% of cases. The authors suggest that the use of overlapping sources and the application of capture-capture methodology could better depict the frequency of epilepsy in Africa than more traditional cross-sectional methods.

A study examining the relationship between malnutrition and epilepsy in a rural area screened 11,668 people in a door-to-door survey using the Limoges questionnaire (Crepin et al., 2007). Screening was performed by local physicians who had received training in epilepsy as part of the study, with screened-positives being examined by a neurologist. The denominator population was derived from a recent census of the area. The crude lifetime prevalence of epilepsy was 12.7/1,000. Details on seizure type are limited, with "most" subjects having generalised tonic-clonic epilepsy. Details are given on duration of epilepsy, with 82% stating seizure onset before twenty years of age, and on associated clinical findings, with 26% having neurological impairment. The ETG in terms of AED use was 58%. To examine the relationship with malnutrition, 262 controls were recruited and anthropometric measurements along with socio-demographic and nutritional data were collected. The prevalence of malnutrition was found to be higher in PWE than in controls (22.1% vs. 9.2%, p=0.0006).

Cameroon

An anthropological study in one village noted a very high prevalence of 70/1,000 (Nkwi and Ndonko, 1989). No further details of case ascertainment, inclusion criteria or clinical details are given, and it is thus difficult to comment further on this study.

A study to assess the demographic impact of epilepsy in terms of mortality used the results of a community based survey of fourteen village communities as a baseline (Kamgno et al., 2003b). In the initial survey, conducted in 1991, village elders and other key informants were asked to identify and bring forward persons known or suspected to have epilepsy for assessment on given days. Inclusion criteria were consistent with lifetime epilepsy, and the prevalence was reported as ranging from 5 to 87/1,000 among the fourteen communities studied, and exceeded 30/1,000 in four of them. It is not made clear how the figure for the denominator population was arrived at. Details on seizure types and clinical associations are limited, but are based on a follow-up of the original cohort conducted ten years later in 2001, during which only 122 of the original 271 PWE were assessed. Of these, 80.8% had generalised convulsive seizures with no recognised partial onset, 17.6% had partial or secondary generalised seizures with no further distinctions being made, and 1.6% had absence seizures. With regards to mortality, matched controls were retrospectively identified from the original 1991 survey to give 128 pairs. There was a significant excess mortality in PWE (28.9% vs. 4.7%, $p<0.0001$); the OR of dying for PWE compared with controls was estimated at 6.2 (95% CI 2.7 to 14.1). The chief causes of death among PWE were status epilepticus, sudden unexpected death in epilepsy (SUDEP) and drowning during a seizure.

A small door-to-door survey (n=197), conducted in one village in an area known to be hyper-endemic for onchocerciasis reported an age-adjusted prevalence of active epilepsy of 134.5/1,000 (Prischich F et al., 2008). A high prevalence of epilepsy in this population had previously been noted anecdotally, and the authors hypothesised that this may be related to infection with the filarial worm *Onchocerca volvulus* which has been postulated as a possible cause of epilepsy in SSA (Druet-Cabanac et al., 2004). The study had three phases: screening using a ten-item questionnaire derived from the Limoges protocol, clinical evaluation of identified possible cases to establish diagnoses, and a case-control

study to evaluate risk factors and socio-economic factors. Individuals identified as having epilepsy also had an EEG. The endemicity of onchocerciasis was assessed based on the prevalence of cutaneous nodules in adults. The age-standardised prevalence of active epilepsy was very high, at 134.5/1,000. Primary generalised seizures accounted for 52.6% of cases, partial seizures for 47.4%, and 31.5% were described as having partial seizures becoming secondarily generalised. To identify risk factors for epilepsy two matched controls were identified for each case. There was no significant difference in the prevalence of onchocercal nodules (seen in 61% of cases vs. 44.4% of controls), and the reported incidences of cerebral malaria, infectious and parasitic diseases and head injury were similar among cases and controls. A history of febrile convulsions was considerably more frequent in PWE than controls (22.2% vs. 8.3%), although this was also non-significant (OR 3.14; 95% confidence interval 0.4 to 23.8). A family history of epilepsy in a 1st degree relative was, however, more common in cases than in controls (100% vs. 69.4%, p=0.031).

Ethiopia

A community-based study screened a sample of 60,820 individuals in a rural area of Ethiopia for neurological disorders, including epilepsy, utilising the WHO protocol (Tekle-Haimanot R et al., 1990). The crude prevalence of active epilepsy was 5.2/1,000. The study benefited from the availability of EEG, and while generalised tonic-clonic seizures were described clinically in 81% of cases, 68.7% overall were judged to have primary generalised seizures following EEG evaluation. Only 1.6% of PWE had been treated with recognised AEDs prior to the study.

A door-to-door screening study in the Zay society, a small, isolated, endogamous community with a total population of approximately 5,000, sampled 1154 individuals and screened for various conditions including epilepsy (Shitaye A et al., 2006, Almu et al., 2006). The WHO screening protocol was used and the prevalence of active epilepsy was estimated at 29.5/1,000. Although no EEG was available, 82% of cases are described as having primary generalised epilepsy, and the authors postulate that this high proportion may point towards a genetic predisposition in this community. All PWE gave a positive family history of epilepsy, although the criteria for a family history are not defined. The

ETG was lower than in the earlier Ethiopian study (Tekle-Haimanot et al., 1990b), although 44% of PWE were not receiving AED treatment.

Kenya

A study in a semi-urban Kenyan population compared the use of random cluster sampling and the key informant method in determining the prevalence of epilepsy (Kaamugisha and Feksi, 1988). The sampling frames were different for the two techniques, with the denominator for the random cluster technique being based on school attendance registers and for key informants being derived from 1979 census data extrapolated to 1985, the year of the study. Households identified by random cluster sampling were visited by the study team to identify any PWE living within them, while key informants were interviewed to identify any cases of epilepsy known to them. Random cluster sampling gave a prevalence of active epilepsy of 18.2/1,000 compared to 3.6/1,000 for key informants. While no further details of seizure types are provided, the authors do comment that the lower prevalence obtained by the key informant method may be explained by a tendency to report only those cases that are clinically obvious; seizures at night, or partial seizures without secondary generalisation and brief absence seizures may have been frequently missed.

In Kilifi, an established Kenyan DSS, a community-based mortality study noted a high rate of deaths being reported in association with epilepsy (Snow et al., 1994). This prompted a prevalence survey which used key informants to screen 7,450 residents of a pre-defined study area. The sampling frame was a 20% random sample of households drawn from an enumerated population of 51,183. Each household was visited by a field worker and asked about occupants suffering from epilepsy using local terminology. Children under the age of five years were not included in the study in order to exclude repeated febrile convulsions associated with malaria and other infectious diseases. The crude prevalence of active epilepsy was 4/1,000. Seizures were classified based on eye-witness accounts, with 53% being described as generalised tonic-clonic and all remaining cases being either complex partial or unclassified, albeit with loss of consciousness. Ten per cent of cases had never received any form of treatment.

Over a decade later, a much larger community-based study using a three-phase screening protocol was conducted in the same population (Edwards et al., 2008). Initial screening was performed across the whole population aged six years or older (n=151,408) using two questions derived from the Ten Questions composite screening instrument for neurological disability. This instrument had previously been validated in the same population for the detection of convulsive epilepsy in children (Mung'ala-Odera et al., 2006, Mung'ala-Odera et al., 2004). Diagnoses in screened individuals were confirmed by a local physician and reviewed by an international panel of neurologists. The crude prevalence of ACE was 2.9/1,000, rising to 4.5/1,000 after adjustment for non-response and sensitivity. The ETG based on detection of AEDs in blood was 70.3%. Risk factors for ACE were derived from frequency-matched controls identified during the screening phase, with the adjusted odds being significantly increased for all individuals with a family history of either febrile or non-febrile convulsions (ORs 3.3 and 14.6 respectively) and previous head injury (OR 4.1). A multivariable analysis in children under the age of eighteen years also identified adverse perinatal events and the child's mother being widowed as independent associations with epilepsy (ORs 5.7 and 5.1 respectively).

Liberia

A study using key informants screened a population of 4,436 people in a rural population that had previously been noted to have a high prevalence of seizures (van der Waals et al., 1983). The crude prevalence of active epilepsy was 28/1,000, with 37% of cases having generalised seizures, 13% simple partial seizures and 50% complex partial seizures. Historical information on risk factors was collected with an antecedent febrile illness being identified in 38% of cases. Accidents and birth trauma were less frequent associations, being identified in 3.3% and 2.4% of cases respectively. Data from this cohort were further analysed by Goudsmit et al, who postulated that the seizure disorder had been introduced into this population approximately thirty years prior to the study, and that an environmental-genetic interaction my explain the high observed prevalence (Goudsmit et al., 1983).

Nigeria

A pilot study to assess the utility of the WHO research protocol described above was conducted in a rural community of approximately 2,000 people (Osuntokun et al., 1982). The screening protocol, consisting of a questionnaire and simple examination, was designed to detect individuals with stroke, epilepsy, peripheral neuropathy, extra pyramidal disorders, migraine and persistent dysfunction of strength, coordination, sensation, vision or hearing. The crude prevalence of active epilepsy among 903 screened individuals was 37/1,000. No further descriptions of seizure types or any other clinical details are given.

A larger door-to-door study in an urban population subsequently used the same protocol to screen 18,954 subjects (Osuntokun et al., 1987). The prevalence of active epilepsy was 5.0/1,000 after age-standardisation to the 1970 US population. Details of seizures are given, with 25.7% of cases having generalised seizures, including 20.8% overall with tonic-clonic seizures, and 55.4% having partial seizures, with 51.5% overall characterised as complex partial seizures; 18.8% of remained unclassified. Putative causes of epilepsy were identified in 39.6% of cases, including 23.8% with a history of febrile seizures, 5.9% with a history of head injuries, 5.0% with a family history of epilepsy in first- or second-degree relatives, 2.0% with a history of stroke prior to first seizure, and 1.0 % (one patient) identified as having a brain tumour. No details on any overlap between these various groups are provided.

A smaller study in a rural population of 2,925 also used the WHO protocol to screen for neurological disorders (Longe and Osuntokun, 1988). The crude prevalence of active epilepsy was 6.2/1,000. Only very limited clinical details are provided.

Rwanda

A national survey of musculoskeletal impairment used a seven-item screening tool that included a question relating to epilepsy (Simms et al., 2008, Atijosan et al., 2007). Random cluster sampling based on the 2002 Rwandan population census yielded a denominator of 8,400 individuals to be screened, with positive responders being further assessed by a physiotherapist working with the aid of a diagnostic questionnaire. The prevalence of active epilepsy was 6.31/1,000 after age-standardisation to the 1998 standard European population, and details on seizure frequency, age of onset and treatment access are all given. Less than half of PWE identified (41%) were receiving AED treatment at the time of the study with the most commonly cited reason for this being the cost, identified as a barrier to treatment in 74% of untreated individuals. No details of seizure types are provided.

Senegal

A door-to-door community-based study conducted in a sample of 4,500 from a suburban population of Dakar estimated the prevalence of active epilepsy to be 14.2/1,000 (Ndoye NF and et.al., 2005). This study was conducted as part of one of the ILAE demonstration projects (Sander, 2002) and as such, clear definitions of seizures and epilepsies were stipulated. The screening tool used was a local translation of an instrument used in the demonstration project in China (Wang et al., 2003a). Generalised convulsive seizures were identified in 68.8% of cases, generalised non-convulsive seizures in 9.4%, and partial seizures in 21.9%, with 14.1% overall becoming secondarily generalised. Additional impairments in the form of mental retardation plus or minus some form of paralysis were identified in 34.5% of PWE, and 23.4% of cases were not using AEDs at the time of the study. Interviews to ascertain knowledge, attitudes and practice with regards to epilepsy were also conducted in 2,263 randomly selected individuals. Of those that responded, 66.1% had witnessed a person having a seizure while only 35.8% said that they had helped a person during a seizure. Regarding treatment and aetiology, 17.7% felt that epilepsy was best treated with traditional therapy and 35.1% believed that epilepsy was contagious.

Togo

A study in a rural area of Togo where pork consumption is common was conducted to establish the prevalence of epilepsy and to examine the relationship between epilepsy and cysticercosis in the study population (Dumas et al., 1989). Random cluster sampling was used to identify 5,264 individuals aged fifteen years and above who were then screened by way of a questionnaire, for which no details are given, followed by examination of potential cases by a neurologist. The crude prevalence of epilepsy was 16.7/1,000, with epilepsy being over twice as common in men than in women (26.2 vs. 10.7/1,000). It is not clear whether the estimates are of lifetime or active prevalence, the terms 'incidence' and 'prevalence' appear to be used interchangeably, and no details on seizure type are provided. All screened individuals were examined for the presence of subcutaneous cysts suggestive of cysticercosis, and individuals identified as having epilepsy were also examined for the presence of cysticercosis with skull and muscle X-rays and by serological analysis for the presence of antibodies to *Taenia solium,* the causative agent of cysticercosis. While the data presented are somewhat difficult to interpret, it would appear that 12.5% of PWE had cysts typical of cysticercosis compared to 2.1% of individuals without epilepsy. Of the PWE who had cranial X-rays, 7.4% had one or more calcifications typical of NCC, although none of these had positive serology and the one case that consented to biopsy proved to have onchocerciasis rather than NCC.

A feasibility study for a programme of managing epilepsy in a rural setting in Togo included a community-based prevalence survey (Balogou et al., 2007). The Limoges protocol was used to screen 6,249 people yielding a crude prevalence for active epilepsy of 15.7/1,000, with 78.6% of cases having active epilepsy at the time of the study. Details on seizure type are provided, with generalised tonic-clonic seizures being observed in 35.7% of cases. EEG was available, and while 74.5% of cases overall appeared to have generalised seizures, generalised anomalies on EEG were only seen in only 39.8% of these. Suspected or confirmed aetiologies included head injury (10.2%), NCC (14.3%), CNS infections (44.9%) and perinatal morbidity (8.2%). None of the patients identified had previously received AED treatment.

Uganda

A community-based survey in rural western Uganda examined the relationship between epilepsy and of onchocerciasis (Kaiser et al., 1996). A house-to-house survey of a complete parish (n=4,743) used local terminology to ask each household about any occupants with epilepsy living there. Possible cases identified, along with a number who subsequently presented voluntarily, were examined by a physician to confirm diagnoses. The prevalence of active epilepsy was 13/1,000 after age-adjustment to a standard world population. No further details of seizure type are provided and none of the cases identified were treated with AEDs at the time of the study. The prevalence of epilepsy was heterogeneous within the geographical area studied, with areas of higher prevalence being significantly associated with areas where the prevalence of onchocerciasis was also high, based on a skin-snip survey for the presence of microfilariae.

Zambia

A large community-based study conducted in rural Zambia utilised a modified version of the Ecuador questionnaire (Birbeck and Kalichi, 2004). Three additional questions were added to reduce the number of false positives generated by febrile and malaria-associated seizures in children, thus improving the PPV of the questionnaire. A total of 55,000 people were screened with all those responding positively being assessed by a physician; denominator data were derived from a 1999 census conducted under a local insurance scheme. The prevalence of active epilepsy was 12.5/1,000 after an adjustment based on validation of the screening instrument. No details of seizure type are given, although the authors do comment on the predominance of generalised tonic-clonic seizures. There are also no details on treatment.

1.7 Review of studies from Tanzania

This introductory chapter concludes with a review of studies of epilepsy that have been conducted within Tanzania. This encompasses community-based studies of prevalence, hospital-based studies that have examined risk factors, and studies that have addressed wider issues relating to knowledge and practice with regards to epilepsy in Tanzania. Community-based studies of the prevalence of epilepsy that have been conducted in Tanzania are summarised in Table 2.

1.7.1 A brief note on Tanzania

Tanzania is a republic in sub-Saharan East Africa, covering an area 947,300 square kilometres and with an estimated population in July 2011 of 42,746,620 (CIA World Factbook). Forty-five per cent of the population are aged fifteen years and under, and the total population is projected to reach 53.4 million by mid-2025 (World Population Data Sheet, 2010). Tanzania is one of the poorest countries in the world with 36% of the population living below the international poverty income threshold of one USD per day (CIA World Factbook). Life-expectancy is fifty-five years for men and fifty-six years for women, the infant mortality rate is fifty-eight per 1,000 live births, and the prevalence of HIV infection in the general population is 5.6% (World Population Data Sheet, 2010).

1.7.2 Community-based studies

As described in Section 1.6.1, a cohort of PWE in a rural district in the Mahenge mountains of southern Tanzania was initially identified during the latter half of the 1960s when a clinic was set up to treat PWE with phenobarbital (Aall-Jilek, 1965, Jilek and Jilek-Aall, 1970). The area was revisited thirty years later by the clinicians who had first established the clinic by which time only thirty-six (21.9%) of the 164 patients initially identified were known to still be alive (Jilek-Aall and Rwiza, 1992). In those that had died, the cause of death was epilepsy-related in over 50%, including status epilepticus, drowning, burns, and dying during or immediately after a seizure. Extrapolating from contemporary national statistics the mortality among PWE of all age groups was apparently higher than that of the general rural Tanzanian population. While most deaths occurred during the first ten years of follow-up the proportional causes of death seemed to change once AEDs ceased

to become available from the clinic in 1971: prior to this date 42% of deaths were epilepsy-related compared to 72% of deaths thereafter.

The same population has subsequently been further studied and in 1990 a community-based study was conducted in Ulanga, a region which incorporates Mahenge (Rwiza et al., 1992). A population census was conducted during which 18,183 individuals were screened using a modified version of the WHO screening questionnaire (WHO, 1981). The estimated prevalence of active epilepsy was 12.1/1,000 after age-standardisation to the 1970 US population, with a wide variation of between 5.1 and 37.1/1,000 being observed between villages. The prevalence was higher in females than males (11.1 vs. 9.2/1,000), although no statistical analysis of this difference is provided. A peak of prevalence was observed in those between twenty and twenty-nine years old, with a second peak in those over aged over fifty years of age. Fifty-eight per cent of all cases had generalised seizures, 31.9% partial seizures, with 22.2% overall becoming secondarily generalised, and 10.1% remained unclassified. EEG was not available in this study. Possible aetiologies were identified in 25.3% of cases with the commonest being a history of febrile convulsions (13.4%) and unspecified encephalitis (4.7%). Other aetiologies, identified in between 0.5% and 1.9% of cases, were birth trauma, cerebral malaria, meningitis, head trauma, cerebrovascular disease and suspected tumour. Incidence, based on interviews with heads of households during which cases in which epilepsy had developed between 1979 and 1988 were identified, was retrospectively estimated at 73.3/100,000 per year.

PWE identified during this study were subsequently studied in more detail, providing an insight into the lot of PWE in this population (Rwiza et al., 1993b). Although most patients had active epilepsy, with 81.3% having had seizures within the year prior to the initial study, none were on regular treatment. Burns with contractures or disfiguring scars acquired during seizures were seen in 24.1% of cases. Of 181 cases of school age 30.9% had never attended school and 62.9% of those who did attend left school prematurely, presumable as a result of epilepsy. Of 116 individuals of marriageable age, 42.2% remained unmarried and 19.8% were divorced. While more women with epilepsy tended to get married than men, the divorce rates in women were higher (29.9% vs. 4.5%).

Although PWE identified during this study were initially followed up for one year, at the time of publication continued funding for the supply and delivery of AEDs, either through government sources or private donations, was not guaranteed (Rwiza, 1994).

The existence of an epileptogenic genetic disorder peculiar to this population had been postulated at the time of the initial study (Jilek and Jilek-Aall, 1970). To investigate this further, data were collected from more than 1,600 relatives of twenty-six probands drawn from twenty families of PWE identified during the 1990 survey and pedigree analyses were performed to look for evidence of familial clustering (Neuman et al., 1995). While the risks to first- and second-degree relatives were higher than would have been expected with no familial clustering, the mode of Mendelian inheritance, if any, could not be clearly characterised.

A further study in the Mahenge population was subsequently conducted in 2001, using same modified WHO protocol as used previously to screen the population in thirteen villages (Matuja et al., 2001). One hundred and seventy-four PWE were matched with controls in order to ascertain risk factors for epilepsy, and detailed histories and examinations were correlated with corroborative evidence from health records or reliable household or community witnesses where available. Risk factors significantly associated with epilepsy in this population were a family history, defined as first-degree relatives only (OR 3.52), a history of febrile convulsions (OR 2.4), neonatal or intra-partum complications (OR 7.3) and a history of CNS infection (OR 2.4). No details on the denominator population or estimates of prevalence are provided.

In 1988 a survey of mental disorders, including epilepsy, was conducted among 10,776 randomly selected people living on Zanzibar, a large island off the mainland of Tanzania with a predominantly Muslim population (Bondestam et al., 1990). Sampling was based on the ten-cell administrative structure of communities that was introduced throughout Tanzania during Julius Nyerere's initial post-independence presidency (Komba, 1995). The average population of one ten cell unit was estimated at fifty people, and 200 units were randomly selected to give a denominator population of approximately 10,000 people. Nursing students described the symptoms of various mental disorders to the heads of the

selected ten cell units, any individuals identified on the basis of these descriptions were interviewed and examined, and all positive diagnoses were confirmed by a psychiatrist overseeing the study. The crude prevalence of epilepsy was 4.9/1,000. All ages were included, with prevalence in children under four years being highest at 7.7/1,000. No further details of inclusion criteria, classification of seizures or distinction between lifetime and active epilepsy are given.

In 1999 a door-to-door survey in a rural coastal district in the south east of Tanzania was performed (Dent et al., 2005). Using random cluster sampling, 1,047 households containing 4,905 individuals were screened by a senior nursing officer and a final year medical student using the same modified WHO protocol as the Mahenge study described above (Rwiza et al., 1992). All age-groups were included, and possible cases identified during screening were assessed by a neurologist. The prevalence of active epilepsy was estimated at 7.1/1,000 after age-standardisation to the WHO world population. ILAE criteria for seizure classification were applied, with 71.4% of cases having generalised seizures and 28.6% having partial seizures, with half of these (14.3% overall) becoming secondarily generalised. Over one quarter of seizures (26.2%) were strongly suspected to be symptomatic, with putative aetiological factors including trauma, cerebral malaria, meningitis, or other undefined CNS infections. One third of cases had a family history of epilepsy, although EEG was not available to help with further characterisation of possible idiopathic epilepsies. Despite the close proximity of this study population to an established and well-utilised district health centre, only 4.2% of cases were receiving any form of modern anti-epileptic treatment at the time of the study. Furthermore, more than half of PWE identified (56.5%) refused medical advice that was offered. The authors suggest that this emphasizes the underlying socio-cultural stigma associated with epilepsy in Africa.

The final community-based study from Tanzania of which we are aware is a more recent door-to-door study conducted in a remote rural part of northern Tanzania from 2003 to 2004 (Winkler et al., 2009c). Multi-stage random sampling was used to screen 7,399 people for epilepsy. The screening questionnaire used was derived from the Ecuador

questionnaire described earlier in this chapter (Placencia et al., 1992a). Modifications to the original instrument were informed by experience with this instrument in Zambia (Birbeck and Kalichi, 2004) and by the experience of one of the authors in diagnosing and treating epilepsy in the study population over a period of three years. The final screening instrument consisted of fifteen questions, with validation and pilot studies being conducted prior to the main study. Inclusion criteria are clearly defined, and age-standardised estimates are given for the lifetime prevalence (13.2/1,000) and active prevalence (9.1/1,000) of epilepsy. Estimates were age-standardised to the standard WHO population (Ahmad et al., 2001). Seizures were classified according to a set of criteria proposed by the author as an alternative to the standard ILAE classification, designed to be of greater clinical utility in resource limited settings (Winkler et al., 2008b). Generalised epilepsies in otherwise healthy individuals were identified in 44.6% of cases, with 9.6% of these being outside of the age range of between six and twenty-five years old. According to the alternative classification, these individuals should be prioritised for further investigation. Focal epilepsies were identified in cases with generalised seizures and obvious wide-spread brain damage (12.1%), in people with generalised seizures in the presence of focal neurology (9.6%), and in one individual (1.2%) with simple partial seizures. Only one case (1.2%) had a clearly relevant past medical history (cerebral malaria), while 41% mentioned having relatives with epilepsy. At the time of the study, 75.9% of all cases and 85.9% of active cases were not taking or never had taken AEDs.

Region of Tanzania	Year of study	Setting	Denom. (n)	Age groups	Screening protocol	LTE/AE*	Prevalence/1,000 Crude	Prevalence/1,000 AS†	M:F	Clinical details	Comments
Zanzibar (Bondestam et al., 1990)	1988	Not stated	10,776	All	Household screening by psychiatric nursing students, diagnoses validated by psychiatrist		4.9	N/A	1.0	No	Part of composite study of mental disorders.
Ulanga (Rwiza et al., 1992)	1989	Rural	18,183	All	Modified WHO protocol	AE	10.2	12.1 (US 1970)	0.8	Yes	
Lindi (Dent et al., 2005)	1999	Rural	4,905	All	Modified WHO protocol	AE	8.6	7.4 (WHO)	1.2	Yes	
Haidom (Winkler et al., 2009c)	2004	Rural	7,399	All	Modified Ecuador protocol	AE/LTE	8.7/ 11.2	9.1/13.2 (WHO)	0.6	Yes	

*LTE – lifetime epilepsy/AE – active epilepsy

†AS – age-standardised (standard population in parentheses)

Table 2: Community-based prevalence studies of epilepsy from Tanzania

1.7.3 Hospital-based studies

A review of 428 PWE over the age of eight years who were seen at the neurology clinic at Dar es Salaam University Teaching Hospital between 1983 and 1985 presents information on aetiological factors observed in different seizure types and age groups (Matuja, 1989). Aetiological factors were identified in 34% of cases overall, with 46% of these being under fifteen years of age and 24% being over thirty years. The most commonly identified factors among children were febrile seizures and CNS infections (71%), while in adults head injury was the most commonly identified cause (74%). In a related study of similar design, conducted in the same clinic, a high prevalence (60%) of psychiatric or psychological comorbidity requiring intervention was noted among PWE (Matuja, 1990). Psychological disturbance was significantly associated with the presence of a brain lesion, defined as clinically evident focal or diffuse neurology or focal epileptiform abnormalities on EEG ($p<0.05$).

More recently, 8,676 patients admitted to a mission hospital in rural northern Tanzania over a nine month period between 2002 and 2003 were screened for neurological disorders, which were implicated in 747 (8.6%) of all admissions (Winkler et al., 2011). Two hundred and seventy-two of these (3.1%) were accounted for by patients presenting with seizures (Mosser et al., 2007) of which nearly one quarter (24%) were patients with epilepsy, as opposed to febrile seizures or acute provoked seizures. Neurological problems are thus implicated in 8.5% of acute hospital admissions in this part of Tanzania, of which epilepsy accounts for a considerable proportion. This may be reflective of community-held beliefs around epilepsy, such as the 5.2% of people interviewed in a rural Tanzanian population who stated that a person having a seizure should be rushed to hospital (Rwiza et al., 1993a).

1.7.4 Other work on epilepsy from Tanzania

In a parallel with the 1992 prevalence study conducted by Rwiza et al (Rwiza et al., 1992), the need for health education with regards to epilepsy in a rural Tanzanian population was assessed and quantified (Rwiza et al., 1993a). Interviews were held with 3,256 heads of household: 2,953 in the same district as the prevalence study, and a further 302 in a district on the eastern shore of Lake Victoria (it is not made clear how this second population was selected to be included in the study). One third of respondents (33.3%) mentioned a variety of causes for epilepsy, including heredity, witchcraft and spinal infections, while 40.6% believed that epilepsy was infectious through physical contact. Similar perceptions to these were documented in a more recent study from northern Tanzania, with 46.7% of 167 people interviewed (a mix of PWE, their relatives and villagers without epilepsy) ascribing epilepsy to a supernatural cause and 65.3% stating that PWE should not attend school or go to work (Winkler et al., 2010a). Both of these surveys identified the prominent role of traditional healers in the management of epilepsy in Tanzania. The latter of these studies also found that non-biomedical treatment for epilepsy in Tanzania commonly includes the use of Christian prayer, and that a belief in the utility of traditional forms of treatment is more strongly held by PWE and their families than those not affected by epilepsy (Winkler et al., 2010a).

Finally, the stigma associated with epilepsy in SSA that the various studies described above allude to has recently been characterised in a qualitative study conducted as part of the main study presented in this thesis (Mushi et al., 2010). During semi-structured interviews with forty-one PWE, epilepsy was commonly ascribed to witchcraft and curses, with the majority of people interviewed describing discrimination and social exclusion as a result of their epilepsy.

1.8 Summary of introduction

Epilepsy is a common neurological disorder worldwide. The prevalence varies from region to region but is generally considered to be higher in LMICs, including those in SSA. The reasons for this have yet to be accurately characterised in many populations, although are likely to be related to increased incidence of neurological infections along with indices associated with poverty, including higher rates of perinatal morbidity and of head injury. Stigma and aberrant perceptions relating to epilepsy are widespread, particularly in SSA. In SSA in general, including Tanzania, epilepsy remains largely or wholly untreated.

Chapter 2. Aims and methods

2.1 Aims

The primary aim of this study is to determine the age-standardised prevalence of active epilepsy in the Hai demographic surveillance site (HDSS), a rural district in the Kilimanjaro region of northern Tanzania. This study adds to a growing body of knowledge and expertise on the epidemiology of non-communicable diseases (NCDs) in this population as well as contributing novel data on a condition which, to the best of our knowledge, has not been formally studied in the HDSS population previously. This study represents one of the largest and most comprehensive community-based studies of the epidemiology of epilepsy to be conducted in SSA to date, and thus makes a valuable contribution to the understanding of epilepsy in this region.

The execution of a community-based prevalence study and establishing of a prevalent cohort of PWE also allowed a number of subsidiary aims to be pursued, as follows:

- To assess the performance of a previously validated screening questionnaire in a Kiswahili-speaking African population.
- To describe the pattern of epilepsy seen in the HDSS study population with regards to gender, age, age of onset of epilepsy, classification of seizures and of epilepsies, and associated morbidities and impairments.
- To identify risk factors for developing epilepsy in this population through comparison with age- and sex-matched controls.
- To specifically examine the contribution of neurocysticercosis (NCC) to the aetiology of epilepsy in this population, utilising neuro-imaging in cases and comparison of demographic and serological data from age- and sex-matched controls.
- To examine the impact of living with epilepsy on individuals in this population through comparison with age- and sex-matched controls.
- To quantify the ETG in this population.

The study consisted of three main phases. In the first phase, a door-to-door screening survey of the entire adult population within the study area was conducted in order to establish the prevalence of active epilepsy in this population. In the second phase, all PWE that had been identified during the prevalence survey were assessed in more detail in order to establish the pattern of disease, to characterise the socio-demographic profile of PWE, and to evaluate the level of access to treatment for epilepsy in this population. This phase included attendance at a local hospital for further investigation by way of CT head scans and EEG recordings. In the third phase, individuals without epilepsy were recruited from the background population to act as controls, and data were collected in order to characterise the clinical and socio-demographic associations with epilepsy in this population. The case-control component of the study also included analysis of blood samples for antibodies to *Taenia solium*, the causative agent of NCC.

2.1.1 Hypotheses

Prior to the study, we hypothesised the following:

- The prevalence of epilepsy in this population would be higher than that seen in HICs, but lower than the median of 15/1,000 previously reported from SSA (Preux and Druet-Cabanac, 2005). The second assumption was made given that this was a large study with strict inclusion criteria for active epilepsy, both of which are factors previously associated with lower prevalence estimates.
- There would be identifiable risk factors for epilepsy in this population and these were likely to reflect those described elsewhere in SSA: perinatal complications, febrile seizures in childhood, CNS infections and head injuries.
- Cysticercosis would be endemic in the population, with NCC contributing to the burden of acquired epilepsy.
- The ETG in this population would be in excess of 60%.
- There would be evidence of stigmatisation and marginalisation of PWE in this population.

The remainder of this chapter provides a broad overview of the methods employed during the three phases of the study. More specific details are provided, where appropriate, in the individual chapters that follow.

2.2 Study site

2.2.3 Historical background and local context

Hai is a rural district that lies on the slopes of Mount Kilimanjaro, in the Kilimanjaro region of northeast Tanzania (Figure 1). The district was established as a DSS by the Tanzanian Adult Morbidity and Mortality Project (AMMP). This was a large epidemiological programme funded by the United Kingdom Department for International Development and the Tanzanian Ministry for Health, and conducted by Newcastle University (Adult Morbidity and Mortality Project, 2010). AMMP was set up to collect prospective data on various health and social indices in Tanzania, and was operational between 1992 and 2003. Three sentinel sites were established from which to gather data: an urban site in Dar es Salaam, a poor rural area in Morogoro, and a relatively more affluent rural area in Hai (Mswia et al., 2002). The infrastructure of each DSS consisted of a network of village workers, at least one per village in rural sites, all of whom were trained and experienced in collecting census data and administering research questionnaires. These workers, referred to as enumerators, worked closely with community leaders to inform communities of any current research activity and to facilitate access to their communities by visiting researchers.

Since the AMMP finished in 2003, the DSS infrastructure in Hai has been maintained through a series of studies conducted in the district. These have focused on the epidemiology of NCDs, and have included studies on the incidence, mortality and prevalence of morbidity from stroke (Walker et al., 2010, Walker et al., 2000b, Walker et al., 2000a), the prevalence of Parkinson's disease and essential tremor (Dotchin et al., 2008, Dotchin and Walker, 2008) and, more recently, studies of atrial fibrillation (Dewhurst et al., 2012d), disability in the elderly (Dewhurst et al., 2012a, Dewhurst et al., 2012b, Dewhurst et al., 2012c), epilepsy (Burton et al., 2011, Burton et al., 2012a, Burton et al., 2012b, Hunter et al., 2012, Mushi et al., 2012, Mushi et al., 2010), and skeletal fluorosis (Jarvis et al., 2013). As such, the HDSS represents one of only a limited number of sites in SSA that are able to produce robust, community-based epidemiological data.

2.2.4 Geographical Area

The district has an area of 1,300 km^2 and spans three ecological zones, referred to as the lowland, midland and upland areas. The lowland area lies between 750 and 1,000 metres above sea level, receives minimal rainfall (about 325 mm a year), experiences warm to hot temperatures and is sparsely populated (about 70 people per km^2). The midland area lies between 1,000 and 1,600 metres above sea level, receives higher rainfall (about 1,560mm a year), experiences moderate temperatures and has a higher population density (about 150-160 per km^2). The upland area lies above 1,600m, is encompassed within the Kilimanjaro National Park, and is uninhabited. This zone is characterised by heavy rainfall and cool temperatures, with an environment of mountain forests and grasslands. Rainfall and glacial runoff from this zone constitute the principle water sources for the district, with multiple springs and rivers supplying water to lower-lying inhabited areas (Mswia et al., 2004, Mswia et al., 2002). The three zones are illustrated pictorially in Figure 2.

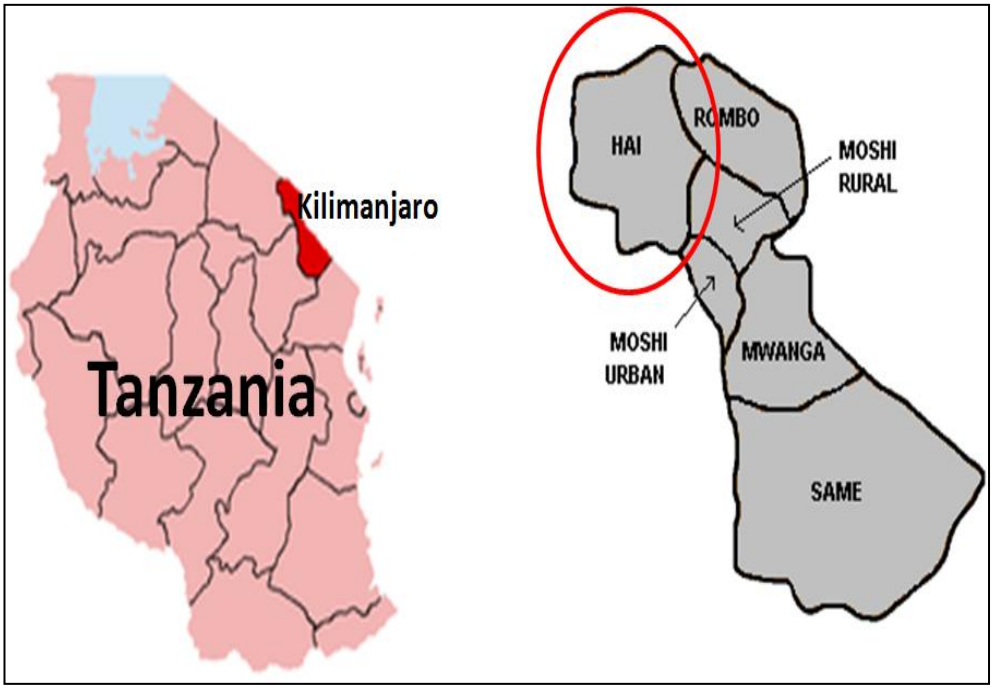

Figure 1: Location of the HDSS in Tanzania

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Figure 2: Ecological zones in Hai
Clockwise from top left: densely forested uplands, fertile mid-zone, semi-arid lowlands

The low- and midland areas of the district are bisected by one paved road, part of one of the Tanzanian national highways, running roughly east to west. There are another three paved roads in the district: one which forms part of the western boundary, one which serves Kilimanjaro International Airport south of the main road, and one which serves Machame, a central town in the district near the boundary with the National Park. Villages in the district are otherwise served by a network of unpaved roads and paths of varying quality.

There are generally two distinct rainy seasons affecting the region: lighter rains during November and December and heavier rains in April and May. During periods of heavy rain many roads in the district become impassable, making access to more remote communities for research purposes problematic.

The nearest large town to Hai is Moshi, which is the administrative centre for Kilimanjaro region. Kilimanjaro Christian Medical Centre (KCMC), a large referral hospital where EEG and CT facilities are available, is located in Moshi.

2.2.5 Administrative divisions and demographic surveillance site

The Hai district is divided administratively into four divisions, eleven wards and sixty-one villages. Each village is further sub-divided into nominal groups of ten households known as cells, or *shinas* in Kiswahili. Each *shina* has an administrative representative known as a ten-cell leader (*balozi* in Kiswahili).

The Hai demographic surveillance site (HDSS) lies within the Hai district, between latitudes 3.13^{o} and 3.46^{o} S, and longitudes 37.11^{o} and 37.36^{o} E. Permanent delineated boundaries including rivers, roads and clearly demarcated administrative boundaries are recognisable on the ground (Figure 3). The HDSS encompasses three of the four administrative divisions in the district: Lyamungo, Machame and Masama. These in turn are comprised of eight wards and fifty-six villages. For the purposes of this study, all references to Hai will be in relation to the HDSS. For practical and enumeration purposes, the fifty-six villages in the HDSS are also divided into three geographical zones: Upland, Lowland and 'Umasaini', comprising thirty-four, fourteen and eight villages respectively. These divisions also roughly correspond to various demographic differences: the Upland

population belong mostly to the Chagga tribal group and is predominantly Christian, while the Lowland and Umasaini populations represent a more cosmopolitan tribal mix, including a greater proportion of people who are Muslims. The Kiswahili term 'Umasaini' roughly translates to 'of the Maasai people', which reflects the historically predominant tribe living in these villages. Seven of the villages in the HDSS are further designated as 'urban' as opposed to 'rural'. The average village population within the HDSS after the 2009 census, conducted for the purposes of this study, was 3,453 persons (median 4,835; range 386 to 7,003).

At the time of the study, the human infrastructure of the HDSS consisted of sixty-one village enumerators coordinated by five supervisors. All of the supervisors have clinical training as clinical officers or assistant medical officers, and are employed as practicing clinicians by the Community Health Management Team (CHMT) of the Hai District Medical Authority. Four of these individuals also spent one year in the UK studying for a Diploma in Primary Health Care Management as part of the original AMMP project. All five supervisors are native Kiswahili speakers and are also fluent in English. In addition, some are also able to speak Kichagga, the predominant local tribal language.

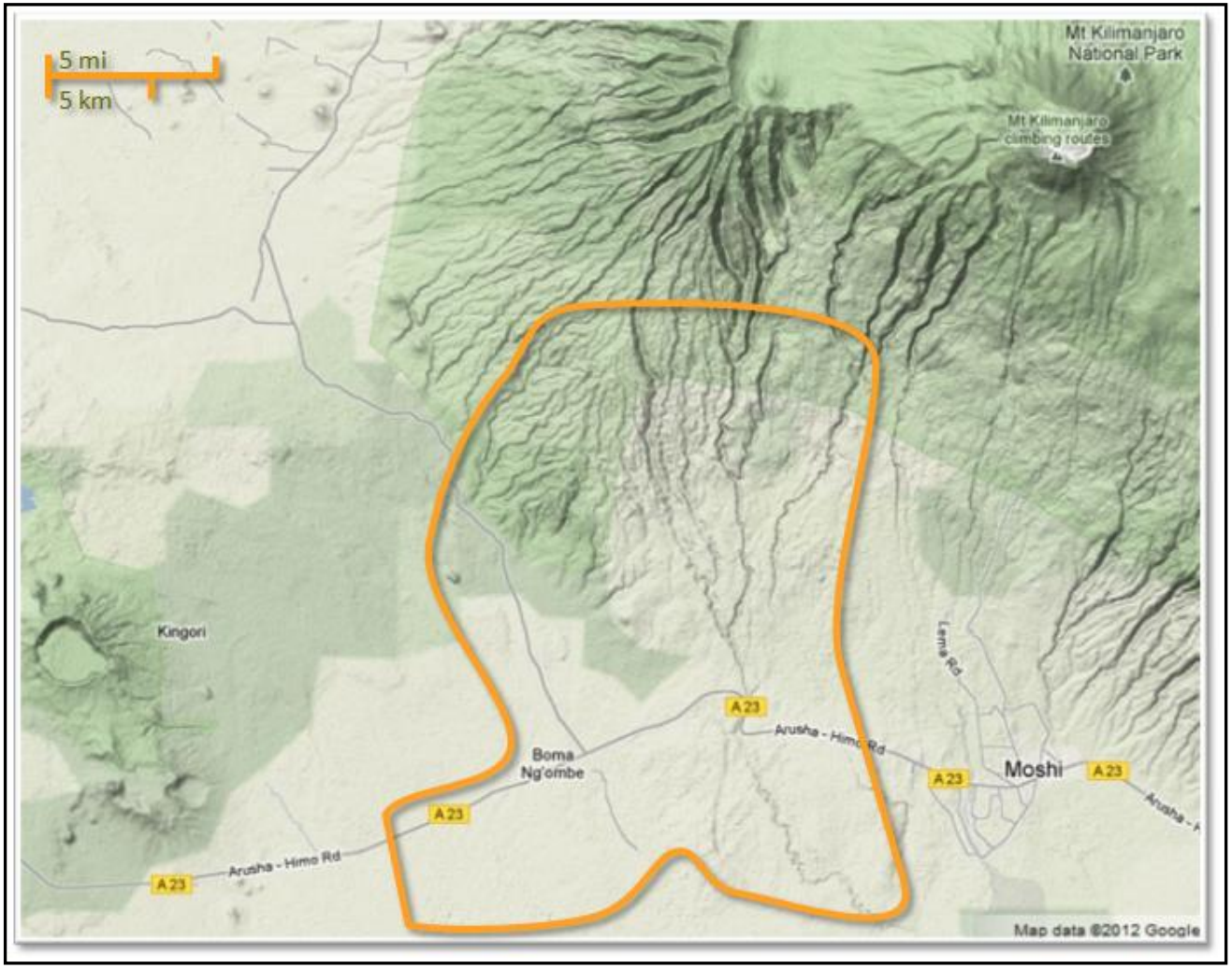


Figure 3: Approximate boundaries of the HDSS
(Google Maps, 2012)

2.3 Prevalence Study

A complete door-to-door census of the HDSS population was conducted between January and April 2009. A census form was completed for each household updating demographic data on household occupants; at the same time a standardised Kiswahili translation of a previously validated screening questionnaire to detect possible cases of epilepsy was asked (Placencia et al., 1992a). In the months prior to the census preparatory workshops were held in the district, the screening instrument was translated and revised, and a pilot study was conducted to establish the sensitivity and utility of the translated screening instrument in a Kiswahili-speaking Tanzanian population.

2.3.1 Census preparations

Prior to the main census an initial one-day training workshop for the HDSS enumerators was held in the district in July 2008. Video demonstrations of different seizure types were used to illustrate the clinical spectrum of epilepsy that might be recognised in the community. These demonstrations were accompanied by explanations relating to the nature of epilepsy as a brain disorder, and to the treatability of the disorder in most patients. At this stage enumerators and other community representatives were asked to inform their communities of the forthcoming census, along with the rationale for seeking to identify patients with epilepsy. This sensitisation work was consolidated later in the year by the distribution of a community newsletter reiterating the nature and rationale of forthcoming research projects to be conducted in the district, including the epilepsy study.

Immediately prior to the census, in January 2009, a further week-long workshop was held for the census enumerators. Materials delivered during the initial workshop the year before were reviewed and additional time was dedicated to group discussions in which questions relating to aetiology, treatment, stigma and safety issues were all answered (Figure 4). The translated screening questionnaire was discussed in detail, with final amendments being agreed upon. These processes are described in more detail in chapters Three and Four.

Figure 4: Pre-census workshops in Hai

Video demonstrations of seizures and discussion of management of epilepsy in the community

2.3.2 Screening instrument and translation

As discussed in Chapter One, a number of different screening protocols for epilepsy have been used in SSA, including in Tanzania. The most recent study of epilepsy in Tanzania made use of a nine-item questionnaire designed for use in LMICs (Winkler et al., 2009c). This questionnaire was originally developed and evaluated in rural Ecuador, with subsequent validation in a rural African population being conducted in Zambia (Placencia et al., 1992a, Birbeck and Kalichi, 2004, Winkler et al., 2009c). When used in Zambia, high rates of false positives were noted during a pilot study, primarily among children with seizures associated with malaria-related fevers (Birbeck and Kalichi, 2004). In the paediatric element of the Hai study, in order to eliminate this problem, only the population aged six years and over was screened (Burton et al., 2012a). This approach mirrors that taken by other studies from SSA for the same reasons (Edwards et al., 2008, Snow et al., 1994). Concerns regarding the unwanted detection of febrile seizures are less relevant to studies in adult populations, such as the one described here, febrile seizures being very uncommon in these age groups.

The screening questionnaire in its original nine-item format was forward- and back-translated between English and Kiswahili following published guidance on the translation of questionnaires for the purposes of epidemiological studies (RAND Corporation, 2013). More details of the translation process and of the final Kiswahili version of the questionnaire are given in the third and fourth chapters, which describe the pilot study and screening and case ascertainment during the main study.

2.3.3 Pilot study

A pilot study to assess the sensitivity and specificity of the screening questionnaire in a Tanzanian population was conducted in patients with and without epilepsy at two sites in Tanzania between July and November 2008. Secondary aims were to detect any linguistic or cultural difficulties with the questionnaire and its translation that could be addressed during further workshop activity, to be held January 2009 prior to conducting the census of the HDSS population. Full details of the design and results of the pilot study are given in Chapter 3.

2.3.4 Census

The AMMP census system is based on door-to-door interviews, with ten-cell leaders (*balozis*) from each village being asked to identify all households within their ten-cell units (*shinas*). Census measures include clear definitions of residence and household and account for migration into and out of the surveillance area. All households and household members are assigned unique identifying numbers which they maintain from census to census. Any new households or migrants into the HDSS have new unique numbers generated for them when detected at census. Ages of individuals are recorded as precisely as possible; a standard list of historical events relevant to the Tanzanian population is used to estimate age when this is not known, a technique that has previously been validated elsewhere in SSA (Paraiso et al., 2010).

A census of the HDSS was conducted annually between 1992 and 2003. Formal AMMP funding ceased in 2003; the census for this final year and another one in 2005 were funded by the Tanzanian Stroke Incidence Project (TSIP) (Walker et al., 2010). The current study employed the same HDSS enumerators and supervisors to conduct a further census in 2009.

Baseline demographic data were updated and the screening questionnaire to detect possible cases of epilepsy living in the HDSS was administered. A single census form was completed for each household, with details of all individuals within each household being captured on each household form. During previous censuses, fields on this form were devoted to various demographic and health indices (e.g. smoking, drinking). Given the number of questions used to screen for epilepsy (nine) during the 2009 census, the number of fields devoted to other information needed to be reduced. The 2009 census form therefore included fields to collect the following demographic information: age, sex, village, occupation, educational level, marital status, religion, whether mother and father alive or dead, relationship to head of household and date of entry into the surveillance area. In addition to the nine questions screening for epilepsy, an additional question was asked to establish the number of households in the district that kept pigs, and questions relevant to two other studies were also included, asking about any previous engagement

with health research and use of insecticide treated bed nets. The 2009 census form is included here in Appendix I.

Completed census forms were transported in batches by road to Dar es Salaam where they were entered onto a dedicated database by a team of data entry clerks hired by the study. This work was overseen by a data manager who had previous training and experience as part of the original AMMP study. Census data were made available to the field team in the form of a Microsoft Excel spreadsheet, with logistical support during case ascertainment provided by the data manager in Dar es Salaam.

The census of the HDSS was conducted from late January through to May 2009, with all census work being completed by 1st June 2009. This date was selected as the prevalence date for the purposes of the prevalence study.

2.3.5 Other case-finding methods

Other than the census-based screening, two other sources were used to detect possible cases of epilepsy in the HDSS population: key informants, and results from other screening studies that may also have detected cases of epilepsy.

Key informants

Village enumerators were asked to approach and bring forward any individuals who they either knew, or suspected, to be suffering from seizure disorders of any kind but who may not have responded to the census screening. This is known as the key informant method, and has been used extensively in rural SSA (Kamgno et al., 2003a, van der Waals et al., 1983, Kaiser et al., 1996), including as an adjunct to population screening (Debrock et al., 2000, Kaamugisha and Feksi, 1988). In studies of mental retardation in LMICs key informants with appropriate training have been shown to have a comparable efficacy to screening questionnaires in detecting cases (Stein et al., 1986). Field work in the villages, including the census and subsequent case-ascertainment, was conducted during four distinct periods between January 2009 and September 2010. The study team also maintained contact with identified PWE between these periods of field work as arrangements were made to bring patients to KCMC for investigations. This meant that the study team was effectively able to maintain a continuous presence in the district for a

period of twenty months. It was stressed to enumerators that any possible additional cases that came to light during this time would also be seen and assessed. As the population became sensitised to the issue of epilepsy, and it became known that PWE were accessing treatment and gaining benefit, it was assumed that some of the more stigmatised and marginalised individuals who may have been hiding their condition or who had otherwise been unaware of the study previously may have been encouraged to come forward.

Cases identified by other studies

Two further studies concerned with neurological disability including epilepsy were conducted in the district during the same time frame: one which screened all ages in a single village only (Bower et al., 2012), and one which screened those aged seventy and over in several villages (Dewhurst et al., 2012a, Dewhurst et al., 2012b). The epilepsy study had access to findings from both of these studies from which possible additional cases were identified (Jim Bower and Felicity Dewhurst, personal communications). In addition to these contemporaneous studies, the records from two recent studies conducted in the district were also made available to the epilepsy study team and scrutinised for possible cases (Walker et al., 2010, Dotchin et al., 2008).

2.3.6 Inclusion criteria

Epilepsy was defined as having previously had two or more afebrile seizures which were unrelated to any acute metabolic disturbance, intoxication, withdrawal from alcohol or drugs or acute neurosurgical insults. Active epilepsy was defined as having satisfied these criteria and having had any seizures in the five years prior to the study. Previous studies have also included individuals who may not meet these criteria but who were taking AEDs at the time of the study. As inclusion in our study was based exclusively on individual assessment by the research doctor we included individuals who were taking AEDs only where it was felt that the initial indication for administering AEDs was consistent with a prior history of epilepsy according to the history available.

In order to be included in the study, patients had to be alive and living within the HDSS area on 1st June 2009, to be aged fifteen years or above on this date, and to have a clinical

diagnosis of active epilepsy confirmed by the research doctor. In cases where the presence of epilepsy was considered possible or probable but in which the diagnosis remained unconfirmed, individuals were kept under observation and offered further assessment at a later stage but were not included in the active prevalence figure unless a clear diagnosis of epilepsy became apparent.

Informed consent was sought from all participants prior to including them in the study. Information sheets and consent forms (English and Kiswahili versions) are provided in Appendix II.

2.3.7 Case ascertainment

All diagnoses were made by a single research doctor (Dr Ewan Hunter), accompanied by a Tanzanian nurse (Sister Jane Rogathe). The research doctor held the MRCP (UK) qualification and had also spent six months prior to the study attending specialist epilepsy clinics in Newcastle-upon-Tyne, UK. The research nurse had previous experience and training in diagnosing and managing epilepsy in Tanzania and had also spent one month in the UK prior to the study gaining further experience of epilepsy services. The research doctor and research nurse were also accompanied during the initial field work, between March and May 2009, by a UK medical student who assisted with interviewing patients. These three individuals were assisted by the five clinical supervisors, at least one of whom was present on any given day in the field.

The large geographical area to be covered and the large anticipated numbers of positive responders to be screened, coupled with concerns about access to certain villages following the onset of the impending rainy season, meant it was deemed necessary to begin clinical assessments prior to completion of the census. Lists of positive responders were compiled locally as the census proceeded; these individuals were assessed for epilepsy and their identities were checked against the final census database when it became available. Cases identified during the initial round of clinical assessments were followed up between June and September 2009, including individuals in whom a final diagnosis had been deferred during the initial assessment. During this time, an attempt was also made to see any additional positive responders to the census that may have

been missed during the initial assessment round. Data entry of the census was complete by early September 2009, and remaining positive responders were traced in two further rounds of field work, conducted in January 2010 and July and August 2010. Once the final case list was complete, controls were generated and recruited in August and September 2010.

All diagnoses of epilepsy were reviewed by Dr Margaret Jackson, a consultant neurologist in the UK with a special interest in epilepsy, between November 2010 and January 2011. Investigations by way of CT head scan and EEG were done in parallel with on going field work, between July 2009 and November 2010.

2.3.8 Interview process

Individuals responding positively to any of the screening questions were approached by their local enumerator and asked to attend a local health facility or other convenient community centre for further assessment by the research team. Individuals who consented to be seen but who were unable to attend their local facility for any reason, such as frailty or distance, were visited at home by the research team (Figure 5). All interviews were conducted in Kiswahili or in Kichagga, with interpretation being provided by the Tanzanian research nurse or by one of the clinical supervisors. All diagnoses, whether epilepsy or otherwise, were ultimately made by the research doctor only, with further clinical examination also being conducted by the research doctor.

All individuals attending were also asked to bring with them a relative or other person that would be able to provide a first-hand collateral history: i.e. an eye-witness account of any events that may represent seizure activity. Where no collateral history was immediately available, permission would be sought to contact witnesses by mobile telephone, to summon witnesses to attend on that day, or to ask witnesses to attend at any future follow-up by the research team.

2.3.9 Validation of diagnoses and classifications

The research doctor had clinical support from Dr William Howlett, a UK-trained consultant neurologist working at KCMC with over 20 years' experience as a physician working in Tanzania. Dr Howlett is a recognised expert on clinical neurology in SSA (Howlett, 2012), and he advised on difficult diagnoses and on management of cases on an on going basis. Following completion of case-ascertainment, all case histories were reviewed in the UK by Dr Margaret Jackson, a consultant neurologist at the Royal Victoria Infirmary, Newcastle, who specialises in epilepsy.

Following assessment, individuals were classified as 'epilepsy', 'probable epilepsy' or 'not epilepsy.' All individuals diagnosed with epilepsy were informed of their diagnosis, were given advice on treatment, and were invited to participate further in the study. Access to further clinical care and follow-up by the research team was not dependent on patients consenting to undergo any investigations on behalf of the study. Those agreeing to participate were invited to KCMC for further investigation by way of EEG, CT head scan and blood sampling.

Individuals were classified as 'probable epilepsy' when they had a history suggestive of a seizure disorder but information available at initial assessment was not sufficient to confirm the diagnosis. These individuals were not included in the final prevalent case series, but have been kept under follow-up by the study team until such time as their diagnoses, epilepsy or otherwise, can be confirmed.

All cases of epilepsy or probably epilepsy were given a simple patient-held seizure diary to aid in follow-up and titration of treatment, or in confirmation of diagnosis where relevant. The seizure diary is included here in Appendix VI.

Any individuals in whom an alternative diagnosis was made were given appropriate advice and referred for management locally where indicated. The sequence of screening and case-ascertainment activities is illustrated schematically in Figure 6. This figure is reproduced in Chapter 4 with final numbers included.

Figure 5: Field work in Hai.
Left: patients attend a village health centre (dispensary) for assessment. Right: assessment interview in patient's own home.

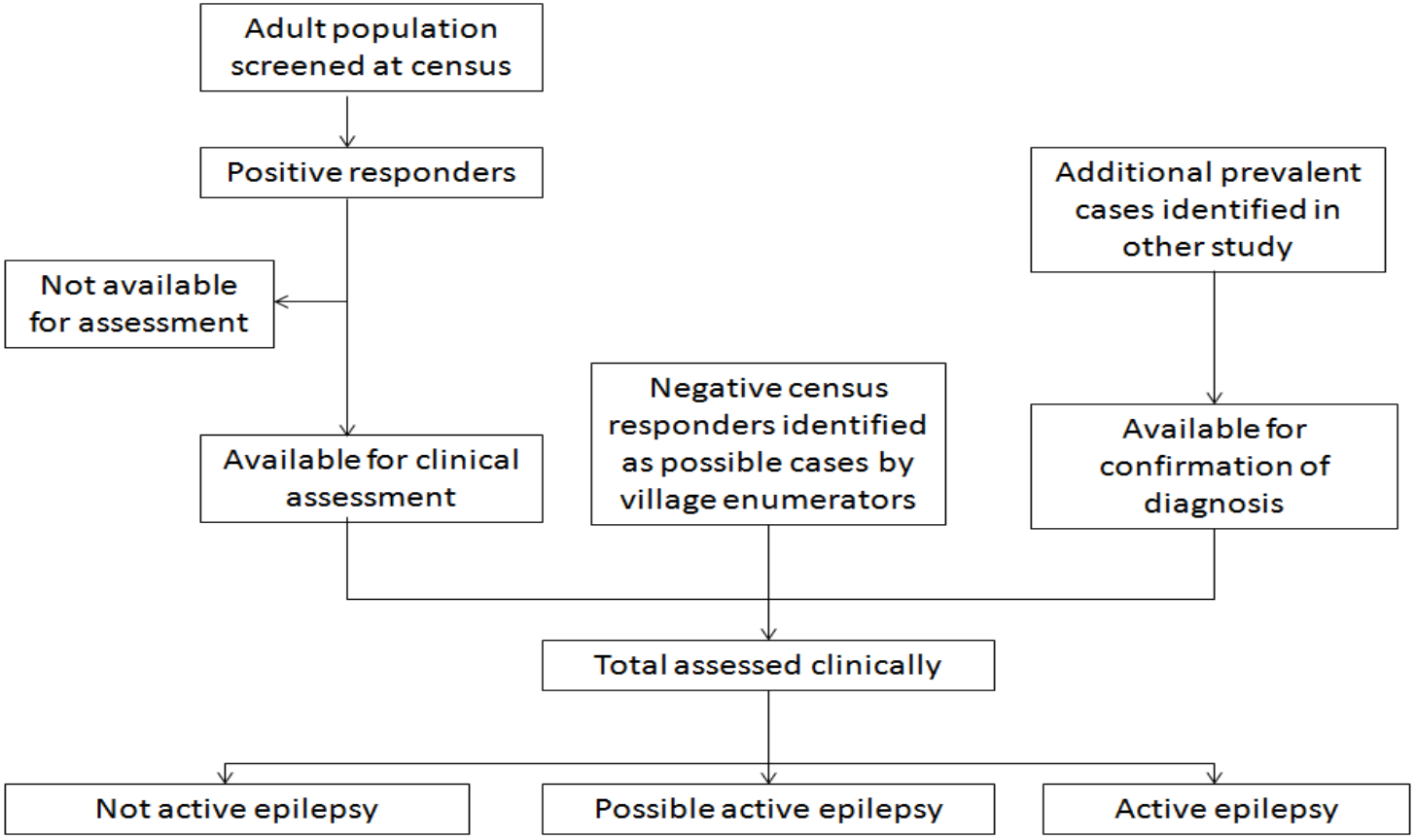


Figure 6: Schematic outline of screening and case ascertainment

2.4 Description of the cohort

2.4.1 Clinical details

Details were collected on onset of epilepsy, seizure frequency and semiology and on any seizure-related injuries, including burns. Where injuries were present they were classed as disabling if any impairment of the activities of daily living were reported.

A full medical history was taken from all cases. This included specifically asking about possible risk factors for epilepsy, including perinatal complications, problems during early development, febrile seizures in childhood, head injury, cerebral infection of any kind, HIV status, brain tumours, strokes, and a family history of seizures in first- or second-degree relatives. Head injuries were classed as significant if there was a history either of loss of consciousness or of hospitalisation as a result of the injury, or of any clearly related sequelae in terms of motor or cognitive deficits.

Treatment history included details of current or previous use of AEDs, and of any traditional medicine or advice from traditional healers. Where cases had previously sought medical attention, details on any services they had previously presented to along with the source of any current AED treatment were collected. We also asked about any diagnoses for their epilepsy that patients had received previously, including from traditional healers. For those taking AED treatment we identified the drug(s) where possible, and asked about dose, timing, compliance, affordability and source(s) of medication. Patients were also asked about any perceived side-effects from their AED treatment, and asked to rate subjectively how efficacious they thought treatment was for them.

Social history included details of tribe, religion, marital status, educational level and occupation. Any patients with incomplete education were asked if this was due to epilepsy. All patients subsequently attending for investigations or followed up in the community were also asked to complete a more detailed socio-economic questionnaire. This included questions on provision of sanitation within the household and meat consumption habits, including pork. This questionnaire was derived from a previously

validated poverty index developed under the original AMMP programme (Adult Morbidity and Mortality Project, 2004). The timing of this questionnaire (i.e. at follow-up rather than at initial assessment) was dictated by the logistics and human-resources available during the field study, with the questions being asked in Kiswahili by enumerators or clinical supervisors. This questionnaire is given here in Appendix IV.

Finally, a brief questionnaire relating to knowledge and attitudes surrounding epilepsy was asked during initial assessment once a diagnosis of epilepsy was established. This was not included as a formal research tool, but rather was intended to further inform the research team of the social context of a diagnosis of epilepsy in this community. The items used were based on a longer questionnaire developed for use at an epilepsy clinic in another region of northern Tanzania (Andrea Winkler, personal communication).

Following the interview all cases received a physical examination, including a detailed neurological assessment. Details of the examination findings are provided in Chapter Five.

2.4.2 Interview pro-forma

The interview pro-forma used in the field was designed to collect clinical and socio-demographic data in a standardised format to facilitate subsequent data entry and analysis. Socio-demographic items in the pro-forma were derived from experience in a previous community-based study in this district (Dotchin et al., 2008, Dotchin, 2007), with categories relating to education and employment being derived from the original AMMP enumeration system (Mswia et al., 2002). Categories for further clinical details were derived from a standardised questionnaire designed to collect comparable epidemiological data on PWE in LMICs, independent of study design (Quet et al., 2011). This questionnaire is in the public domain, and is published on-line in several translations, including English (Institute of Neurological Epidemiology and Tropical Neurology, 2012). The most important part of each interview was an open clinical dialogue between the research doctor and the patient to establish the diagnosis. Hand-written notes were taken in the field, and details for each case or possible case were transcribed into a structured format to facilitate subsequent review and validation of diagnoses by a consultant neurologist in the UK. This portion of the pro-forma was derived from two

previously validated semi-structured questionnaires designed to aid trained interviewers in collecting information to facilitate the classification of seizures (Ottman et al., 1990, Reutens et al., 1992). Both of these instruments performed well in validation studies comparing their performance to direct assessment by a neurologist, although to our knowledge neither has been used previously in either LMICs or in Africa. The field pro-forma is given here in Appendix III.

2.4.3 Investigations

All consenting patients were invited for further investigation by way of CT head scan and EEG, available locally at KCMC. To facilitate these investigations all patients attending the study were registered at the hospital, if not previously registered, and a hospital file opened on their behalf. All associated costs, including administration, investigations, transport and food, were met by the study. When attending for CT and EEG patients were also asked for a blood sample, to be stored and later analysed for the presence of antibodies to *Taenia solium*. Further details of investigations are given in chapters Five and Eight.

2.5 Controls

Controls were recruited into the study once case ascertainment was complete. Using a random number sequence, six age- and sex-matched controls were identified for each case from the census database, providing a broadly matched pool of potential controls from which to recruit. The list of names was compared with the census and field-work databases to ensure that no positive responders or identified PWE had been included, and lists of names of controls found in each village in the district were then distributed to the field team. During August and September 2010 individuals appearing on these lists were approached and invited to participate in the study, and all individuals agreeing to act as controls were clinically assessed by the research doctor to ensure that there were no further cases of epilepsy within this group. Participating controls then completed a questionnaire that mirrored the pro-forma used during case ascertainment and the socio-economic questionnaire completed by cases during follow-up visits. The control interview pro-forma, translated into Kiswahili, was completed by one of the field team (either an enumerator or clinical supervisor).

The case-control portion of the study was designed to answer three principal questions:

- What are the clinical associations with and risk factors for developing epilepsy in this population?
- How important is cysticercosis as a risk factor for epilepsy in this population?
- What are the socio-economic impacts of living with epilepsy in this population?

More details on control recruitment are given in chapter Seven. With regards to cysticercosis, sample size calculations derived from comparable populations in Burundi were made (Prado-Jean et al., 2007, Newell et al., 1997a) and full details are given in Chapter Eight. The questionnaire administered to controls is given in Appendix V.

2.6 Additional activities

During the course of field work some data were collected and work initiated that fall beyond the scope of this thesis. These are briefly detailed below.

2.6.1 Genetics of epilepsy

Whole blood has been stored for future DNA analysis as part of a larger, multi-site study. These samples are currently held at the Wellcome/KEMRI research laboratory at Kilifi, Kenya. Ethical approval for this aspect was sought prior to commencing the study, and prior to collecting any blood samples it was explained to study participants that some of the blood would be stored for analysis in the future and that this would be done anonymously. A statement to this effect was also included in the study information leaflet that was given or read to all participants prior to enrolment in the study (Appendix II).

2.6.2 Qualitative work

An in-depth qualitative study was conducted in parallel with the main study in PWE attending for further investigation. Using purposive sampling, semi-structured interviews and thematic analysis, this study sought to further characterise beliefs about epilepsy and the experience of living with epilepsy in this population. The results of this related study have now been published (Mushi et al., 2010).

2.6.3 Patient follow-up

At the time of the initial interview all PWE were given written information relating to their diagnosis along with a prescription for AEDs to be shown to local dispensing authorities to facilitate continued access to appropriate treatment. Along with this written information patients and their relatives were also instructed in keeping a simple seizure-diary in order to keep a record of seizure frequency from the time of diagnosis. Patients were asked to bring this record with them to any subsequent follow-up with the research team. This patient-held record is included in Appendix VI.

Following the initial phase of clinical assessments of positive responders patients were followed up, either at KCMC or in the community, to assess for sustained access to treatment, treatment response, and any complications or side-effects. Any patients in whom a firm diagnosis had not been initially possible were also followed up in a bid to

confirm or reject a diagnosis of epilepsy, based on reporting of any further events or any additional collateral history that may have become available in the interim. The majority of patients identified received clinical follow-up in this way on at least one occasion during the course of the prevalence and case-control studies. We continue to collect follow-up data on a prospective basis, as well as offering on-going advice and support to the local healthcare team around the clinical care of cases identified. The results of this follow-up, including clinical outcomes and extent of access and response to treatment, are being fed back to the local CHMT on an on-going basis.

2.6.4 Training of local healthcare workers

During the course of the study, the research team was approached by members of the Hai district CHMT and asked to provide input in terms of training for local health workers in the community-based management of epilepsy. In response to this request a one day workshop was delivered on 15th September 2009, during which simple guidelines and an algorithm for the pharmacological management of epilepsy were presented. These were based on guidelines developed by the ILAE (Shorvon et al., 1991) and by the Mental Health Association of Tanzania (MEHATA), a Tanzanian non-governmental organisation concerned with raising awareness and promoting the treatment of mental illness including epilepsy (Mental Health Association of Tanzania, 2012).

2.6.5 Mortality

Data on the mortality associated with epilepsy in SSA are scarce. Having established a prevalent cohort of PWE in a functioning DSS, we are presented with the opportunity of generating robust mortality data in terms of case fatality rates and, by extrapolation from the original AMMP data and from national mortality statistics, standardised mortality ratios for deaths of any cause and proportional mortality ratios for specific causes of death. A verbal autopsy system was established under the AMMP and the current clinical supervisors working in the HDSS are trained in this methodology (Aspray, 2005, United Republic of Tanzania Ministry of Health, 2004).

2.8 Analysis

2.8.1 Data Entry

All data were entered into a Microsoft Excel 2007 spreadsheet as field work progressed. On completion of field work all data were re-entered directly from field notes into a database written specifically for the study (Microsoft Access 2007), with all categorical data coded numerically. All data were therefore double-entered, with data entry carried out exclusively by the research doctor. Corresponding columns from the two databases were compared and any discrepancies were corrected with reference to the original hand-written field notes, thus providing a quality control step prior to final analysis of the data.

2.8.2 Statistical procedures

Statistical analyses were performed using the SPSS 17.0 software package (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test for normality was used for all continuous variables. For continuous variables that were normally distributed, means were compared using Student's independent t-test. For non-normally distributed continuous variables, non-parametric comparisons were made using the Mann-Whitney U test. Variations within groups of continuous variables were assessed using one-way analysis of variance (ANOVA) when distributions were normal, and using the Kruskal-Wallis test when one or more variables were not normally distributed.

Associations between categorical data were assessed using either the chi-square test or Fisher's exact test for small groups where cross-tabulation cells contained counts of less than five. Kappa statistics were used to quantify agreement between data sources.

When comparing cases and controls, categorical predictor variables from both groups were dichotomised according to the presence or absence of the characteristic in question. For ordinal variables where dichotomisation was not appropriate a baseline comparator level was selected. The outcome of interest for each predictor variable was 'epilepsy' or 'not epilepsy', with uni-variable odds ratios (ORs) with 95% confidence intervals being calculated for all predictor variables. Multi-variable logistic regression was used to examine the joint effects of multiple predictors. Regression models were constructed using a backwards stepwise elimination strategy based on the likelihood ratio test (LRT),

with non-significant uni-variable predictor variables with a p-value of 0.1 or greater being excluded at each step. A p-value of 0.05 or less was considered significant for all other statistical tests performed.

Further details of specific statistical procedures are given in the individual chapters, where appropriate.

2.9 Ethics

Ethics committee approval was sought and obtained prior to the start of the study. Given that the study was conducted entirely outside the UK, but that NHS staff were to be involved, a voluntary favourable opinion was offered by the Leeds (West) Research Ethics Committee (Ref: 08/H1307/128). Formal approval in Tanzania was obtained from the National Institute of Medical Research (NIMR), based in Dar es Salaam (Ref. NIMR/HQ/R.8a/Vol IX/786). Documents relating to ethical approval in the UK and Tanzania are provided here in Appendix VII. The research doctor obtained a temporary medical licence from the Tanganyika Medical Council that was valid for the duration of the study, included here in Appendix VIII.

The process of obtaining informed consent may be subject to imbalances when externally sponsored research is conducted in LMICs. In such circumstances, it is recognised that truly informed consent may be compromised by a failure on the part of the research team to take into account the cultural setting of the project, the local beliefs and customs of the study population, and any communication issues that may affect comprehension of information (Tekola et al., 2009). Recognised examples are the inclusion of unfamiliar technical concepts without sufficient culturally appropriate explanation (Molyneux et al., 2004), or the fact that provision of healthcare as part of a research project may represent an undue inducement for participating in research (Tekola et al., 2009). In some settings the norms of decision-making may not lie solely at an autonomous individual level, and it may be culturally inappropriate to seek individual permission in advance of approaching community leaders or elders (Molyneux et al., 2004, Boahen et al., 2013). With due regard to such issues, numerous guidelines have been developed that variously stress the

importance of community-level consultation at an early stage (Dawson and Kass, 2005, Molyneux et al., 2004, Molyneux et al., 2005), using verbal consent in parallel with written consent in communities where literacy rates are low (Dawson and Kass, 2005, Sanchez et al., 2001), and providing information about the study at the correct level of comprehension (Council for International Organisations of Medical Sciences, 2002). We hope that the measures employed during the Hai epilepsy study described here were devised with due regard to these considerations.

All patients identified as having epilepsy were asked to give consent prior to participating further in the study. Written information describing what the study involved, translated into Kiswahili, was given to patients or their carers to read; where patients or carers were illiterate the information was read to them by a member of the local field team. Any patients giving consent but who could not write were asked for a thumb print by way of a signature. Patient information and consent forms are included here in Appendix II. The content of these was developed in consultation with the local field team and their opinions were sought as to the appropriateness and comprehensibility of the content. It was explained to all participants that they were free to withdraw from the study at any stage should they wish to do so. It was also explained that any advice or treatment offered by the study team would not be contingent on their agreeing to either to participate in the study, or to their remaining in the study should they decide to withdraw at a future date. In the months leading up to the main study community consultation exercises were conducted with village elders, local religious leaders and other community leaders, informing them of the study plans and seeking their permission to proceed. Leaflets were distributed in the community, and community leaders were also invited to preparatory workshops held in the district in July 2008 and January 2009. This approach has been employed for a number of years by study teams working in the HDSS, and visiting researchers are well recognised and accepted within the community (Dotchin et al., 2008, Walker et al., 2000b).

Photographic material was collected during the study, including photographs illustrating clinical features of interest. While this activity was not specifically included in the ethics

application, permission was sought on an individual basis for all photographs that were taken. An explanation was given in all cases that images may be used for teaching or research purposes and may appear in medical publications. There were no instances of individuals refusing to have their photographs taken.

Chapter 3. Screening tool and pilot study

Abstract

Background

Community-based door-to-door prevalence studies require sensitive screening instruments to detect possible cases of the disease or condition under investigation. A tool with a very high sensitivity is often compromised by a lower specificity, leading to logistical difficulties in studies of any size. Screening tools should be culturally and linguistically appropriate to the setting in which they are used. We assessed the utility for use in Tanzania of a previously validated screening tool for epilepsy.

Methods

A previously validated screening tool for epilepsy designed for use in community-based studies in resource-poor settings was forward- and back-translated between English and Kiswahili. The sensitivity, specificity and positive predictive value of the translated questionnaire were assessed in volunteers with and without epilepsy recruited at two hospital sites in Tanzania.

Results

The translated instrument performed with a sensitivity of 100% and specificity of 54.5%. Given that the study population of the main study was anticipated to be in excess of 161,000, based on the most recent census of the HDSS in 2005, further statistical modelling was performed to identify optimal combinations of screening items to be used in the advent of a very high response rate. A combination of three of the original nine questions was predicted to perform with an improved specificity of 86.4% while maintaining a sensitivity of 100%.

Conclusions

The translated screening tool had a good sensitivity for the detection of epilepsy in a Kiswahili-speaking Tanzanian population. The low specificity could potentially be improved by using an optimal combination of a reduced number of questions.

3.1 Introduction

Cases of a given condition may be identified in the community utilising a two-stage approach: a simple screening test, such as a questionnaire, followed by more sophisticated diagnostic methods to distinguish true from false positives (Schoenberg, 1982, Senanayake and Roman, 1993). In the case of epilepsy, which is a clinical diagnosis, it is appropriate that the second step consists of a clinical history and examination (Placencia et al., 1992a, Sander and Shorvon, 1987). The sensitivity of a screening test is a measure of the test's ability to detect those individuals who truly have the condition, and is defined as the number of true positives correctly identified divided by the sum of the true positives and false negatives. Conversely, the specificity is a measure of the ability to correctly identify those individuals who do not have the condition, and is defined as the number of true negatives correctly identified divided by the sum of the false positives and true negatives. Both measures are usually expressed as percentages. More sensitive screening tests are generally less specific, with large numbers of false positives which have to be examined and subsequently rejected (Shorvon and Farmer, 1988). The positive predictive value (PPV) of a test is the proportion of individuals who test positive who truly have the condition in question.

Validation of screening tests may be undertaken in clinic-based settings, utilising cases and controls in whom the diagnostic status is known, or in community-based settings where the screening test is applied to a sample of the population followed by formal diagnostic examination of all subjects, regardless of outcome of the screening test. Data extrapolated from the latter method are more powerful, having been obtained in a less biased setting, but are more difficult to obtain due to the expense and logistics of scale (Placencia et al., 1992a). Screening tools previously used in SSA have included both composite instruments, aiming to detect a variety of neurological conditions, and instruments developed specifically for the detection of epilepsy.

The generally accepted method of linguistic translation of screening instruments is the 'forward and backward' approach, whereby anomalies in meaning are detected when the instrument is translated back into its original language from the local language in which it

will be used (RAND Corporation, 2013). Beyond the issues of linguistic translation there may also be ethnographic barriers to case ascertainment, whereby traditional concepts of illness, symptoms and aetiology may be very different from the biomedical model of disease from which screening questions are derived (Sander and Shorvon, 1987). While these issues have been widely discussed, relatively few details of the linguistic or socio-cultural translation of screening instruments have appeared in the published literature (Baskind and Birbeck, 2005b, Senanayake and Roman, 1993, Quet et al., 2011, Andermann, 2008).

For the purposes of this study, we elected to develop a Kiswahili translation of a nine-item screening instrument originally developed in an Ecuadorian population. This instrument was chosen as there are detailed descriptions of its validation and initial application available (Placencia et al., 1992a, Placencia et al., 1992d, Placencia et al., 1992b). It has also recently been used successfully, in modified forms, in published studies from Zambia and Tanzania (Birbeck and Kalichi, 2004, Winkler et al., 2009c). Notable features of this questionnaire are the inclusion of questions intended to detect cases of more subtle seizure types beyond generalised convulsive seizures, and the inclusion of a disease-specific question in order to increase the chances of detecting known or previously diagnosed cases. These elements were initially included to improve on the sensitivity of a questionnaire developed by the WHO for use in studies of neurological disability in LMICs (World Health Organisation Neurosciences Programme, 1981).

The nine questions included in the original version of the questionnaire were:

1. Have you ever had attacks of shaking of the arms or legs which you could not control?
2. Have you ever had attacks in which you fall and become pale?
3. Have you ever lost consciousness?
4. Have you ever had attacks in which you fall with loss of consciousness?
5. Have you ever had attacks in which you fall and bite your tongue?
6. Have you ever had attacks in which you fall and lose control of your bladder?
7. Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?
8. Have you ever had attacks in which you lose contact with your surroundings and experience abnormal smells?
9. Have you ever been told that you have or have had epilepsy or epileptic fits?

In its original format a positive response was taken either as both questions one and two being answered in the affirmative together, or as an affirmative answer to any of the remaining seven questions. This format was originally arrived at for reasons of balancing specificity with sensitivity (Placencia et al., 1992a, Placencia et al., 1992d).

3.2 Methods

3.2.1 Translation process

The approach used to the translation of the screening questionnaire was based on published guidelines for the translation of health survey tools (RAND Corporation, 2013). Translators were briefed on the socio-demographic characteristics of the target population, the setting for the study and the proposed mode of administration of the survey instrument. Following identification of any terms or concepts likely to present difficulties to translation, an initial forward-translation was made by a professional Tanzanian translator belonging to a pool of translators used by NIMR, Tanzania. These translators are experienced in the translation of materials used in qualitative studies (Plummer et al., 2004). Translations back into English were then performed independently by four individuals. Two were native Kiswahili speakers who are also fluent in English: a Tanzanian doctor trained and working in the UK, and a Tanzanian social-scientist studying for a PhD in the UK. Both of these individuals originally come from the Kilimanjaro Region in Tanzania (of which Hai is a part), and are familiar with the local population. In addition the Tanzanian social scientist had previous experience of community-based studies in the HDSS (Mshana et al., 2008). The third individual was an English statistician who is fluent in Kiswahili who also has extensive prior experience of community-based studies conducted in the HDSS as part of the original AMMP team (Mswia et al., 2004, Mswia et al., 2002). The final person was a German-born paediatrician, fluent in both English and Kiswahili, who has over ten years' experience as a doctor practicing in Kilimanjaro Region with a special interest in neurodevelopmental problems including epilepsy (Oneko et al., 2002, Klingenberg et al., 2003).

Following identification and discussion of anomalies and discrepancies between the three back-translations, a final forward translation into Kiswahili was made. This version was then used in a pilot study to assess for the utility of the questionnaire in translation in terms of sensitivity and specificity.

3.2.2 Pilot study

Subjects were recruited into the pilot study from two sites: KCMC in Moshi, and Muhimbili National Hospital (MNH) in Dar es Salaam. Cases from MNH consisted of individuals with confirmed diagnoses of epilepsy who were attending for EEG over the course of one week in July 2008. Controls were recruited during the same period from out-patients attending the MNH neurology clinic and who did not have epilepsy. The screening questions were asked by a Tanzanian nurse who had been to the UK for training in epilepsy as part of the study. Cases recruited at KCMC also consisted of individuals with epilepsy attending for EEG, with controls being recruited from medical in-patients after medical notes had been examined to exclude anybody with epilepsy or seizures. At KCMC all screening questionnaires were administered by the study research nurse who had also spent time in the UK gaining further experience of epilepsy services as part of the project.

Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated using the clinical diagnosis of epilepsy in known cases as the gold standard. Kappa statistics (κ) were calculated to examine the level of agreement between different combinations of screening questions and a clinical diagnosis of epilepsy. The interpretation of kappa statistics is summarised in Table 3 (Altman, 1991).

Prior to the pilot study a desirable sample size was calculated using the standard error of a proportion. To demonstrate a sensitivity and specificity both of 80%, with a standard error of five per cent, sixty-four cases and sixty-four controls would need to be included in the study. Reducing this number to forty-five cases and forty-five controls would give a standard error of six per cent.

Value of κ	**Strength of agreement**
<0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very good

Table 3: Interpretation of kappa statistics
(Altman, 1991)

3.3 Results

3.3.1 Translation process

During the initial translation process two screening questions in particular presented difficulties, prompting discussion among the translators.

Question two – "Have you ever had attacks in which you fall and become pale?"

The idea of turning pale was anticipated to cause confusion and to be difficult to translate for use in a dark-skinned African population. The initial translation used the term *"kupoteza rangi",* literally translating back to English as "losing colour". On discussion it was felt that this would be confusing and sound bizarre, being taken to refer to a radical change in appearance to resemble a person of Caucasian origin. At the same time it was felt by the native Tanzanian translators that the concept of both pallor, as seen in anaemia or hypovolaemia, and of duskiness of the palms, lips and face, as seen in transient losses of consciousness associated with cyanosis, would be recognised and understood. Consequently it was decided to specifically itemise the colour changes in terms of anatomical location as follows:

"…kubadilika rangi na kuwa mweupe kwenye viganja, midomo na usoni"

(i.e. "changing colour in the palms, lips or face").

Question eight – "Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?"

The initial translation of this question used the term "*kunusa harufu isiyosawa",* which was felt to translate more closely to the active verbal sense of sniffing (*kunusa* – to sniff or to smell), rather than the passive sense of experiencing smells. In the final translation this was changed to *"kusikia"*, which translates more closely to the concept of "sensing" or "being aware of". Furthermore, it was felt that the question could be misinterpreted in both English and Kiswahili as a patient may experience a number of different abnormal sensations in association with an impairment of consciousness, including visual and auditory experiences, or may not experience any abnormal sensations at all. For this reason the "and" was changed to "or" *("na"* to *"au"* in Kiswahili).

There was also some discussion around which version of the past tense would be most appropriate: the past simple tense or the past perfect tense. It was felt that this distinction was important given that in colloquial Kiswahili the past simple tense may more readily be taken to refer to all past events, including those in the more distant past, while the past perfect tense carries a sense of events being more immediately recent: "have you ever….?", i.e. past simple, versus "have you…?", i.e. past perfect. For this reason the past simple tense was chosen for the final translation.

3.3.2 Pilot study: recruitment and demographics

Fifty-two subjects were recruited into the pilot study across the two sites: twenty-eight (53.8%) men and twenty-four (46.2%) women. On reviewing clinical details it became apparent that no formal diagnoses were available for three of the subjects recruited initially, and these individuals were excluded from further analysis. Forty-nine individuals were therefore included in the final analysis: twenty-seven cases of epilepsy and twenty-two controls. The characteristics of these individuals are summarised in Table 44 and Figure 7. No data were available on the background populations from which cases and controls were drawn, other than being native Kiswahili speakers with or without epilepsy; further analysis of the characteristics of cases and controls was therefore not pursued.

The ages of both cases and controls were not normally distributed (Figure 7), with cases being relatively younger than controls (Mann-Whitney U 99.50, $z=-3.95$, $p<0.001$). There was no significant difference in the proportions of the sexes between cases and controls ($\chi^2(1)=0.15$, $p=0.70$). Cases were more likely to come from MNH and controls from KCMC (KCMC) (19 vs. 8; $\chi^2(1)=9.01$, $p=0.003$).

All of the epilepsy cases recruited into the pilot study had a diagnosis of epilepsy recorded in their medical notes, although few further details with regards to seizure semiology or EEG findings were available.

		Cases (n=27)		Controls (n=22)	
		n	(%)	n	(%)
Female, n (% of total)		12	(44.4%)	11	(50.0%)
Male, n (% of total)		15	(55.6%)	11	(50.0%)
Median age in years (inter-quartile range)		13	(8.0)	30.5	(26.5)
Site of recruitment, n (% of total)	**MNH**	19	(70.4%)	6	(27.3%)
	KCMC	8	(29.6%)	16	(72.7%)

Table 4: Summary of recruitment into pilot study

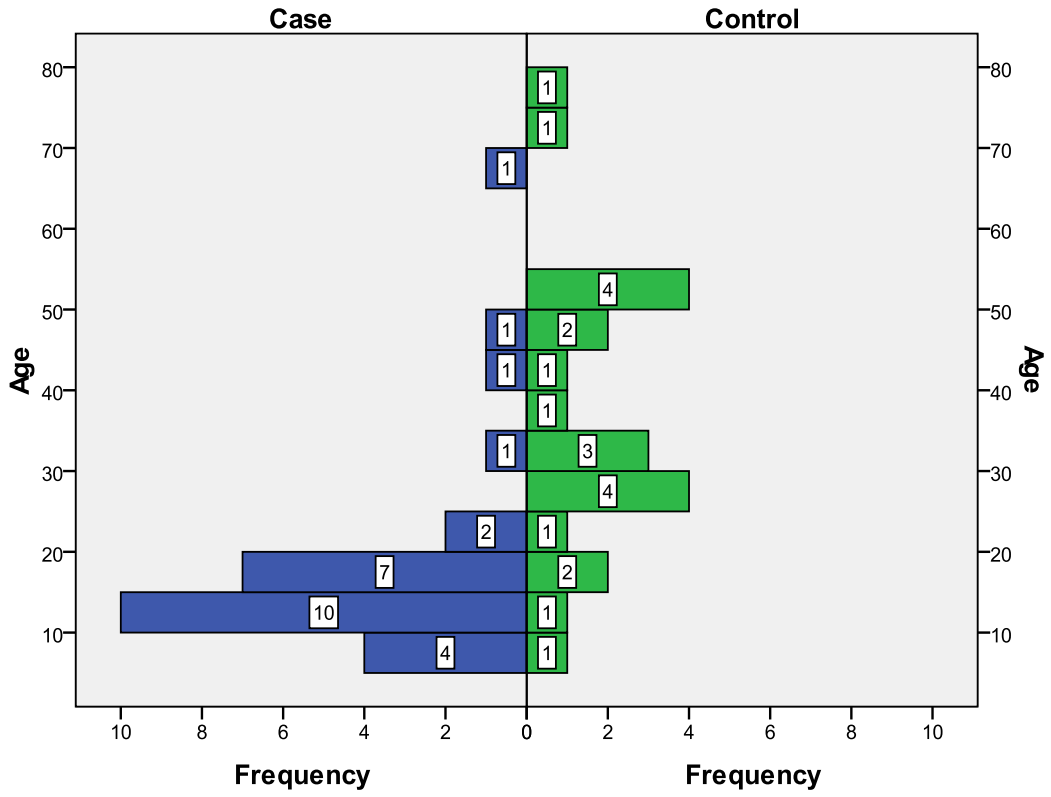


Figure 7: Age distributions of pilot study participants (five year age bands)

3.3.3 Pilot study: response to screening questionnaire

According to the original design of the screening questionnaire, a positive response was defined as either an affirmative answer to questions one and two together, or an affirmative answer to any of questions three to nine. According to these criteria, thirty-seven (75.5%) subjects were identified as possible cases of epilepsy, including all twenty-seven true cases, while twelve (24.5%) were deemed unlikely to have epilepsy. The screening questionnaire thus successfully detected all true cases of epilepsy, with ten people being identified as possibly having epilepsy who did not (Table 5). The sensitivity and specificity of the screening questionnaire were therefore 100% and 54.5% respectively. The PPV of the questionnaire was 73.0% and the NPV was 100.0%. Overall there was a moderate level of agreement between the screening questionnaire and a clinical diagnosis of epilepsy ($\kappa = 0.57$).

	Epilepsy present		
Screening response	**Yes**	**No**	**Total**
Positive	27	10	37
Negative	0	12	12
Total	27	22	49

Table 5: Outcomes of screening questionnaire in pilot study

3.3.4 Pilot study: analysis of individual components

Only three (6.1%) subjects responded positively to both question one and question two, with these three respondents being included in the twenty-seven confirmed cases of epilepsy. With twenty-four (88.9%) cases of epilepsy being missed, the combination of questions One and Two was a poor predictor of epilepsy ($\kappa = 0.10$). Taking these questions individually, twenty (40.8%) subjects answered positively to question one, of whom eighteen had epilepsy and two did not. Six (12.2%) subjects answered positively to question two, of whom five had epilepsy and one did not. Question one was therefore a moderate predictor of epilepsy ($\kappa = 0.56$) and question two was a poor predictor of epilepsy ($\kappa = 0.13$).

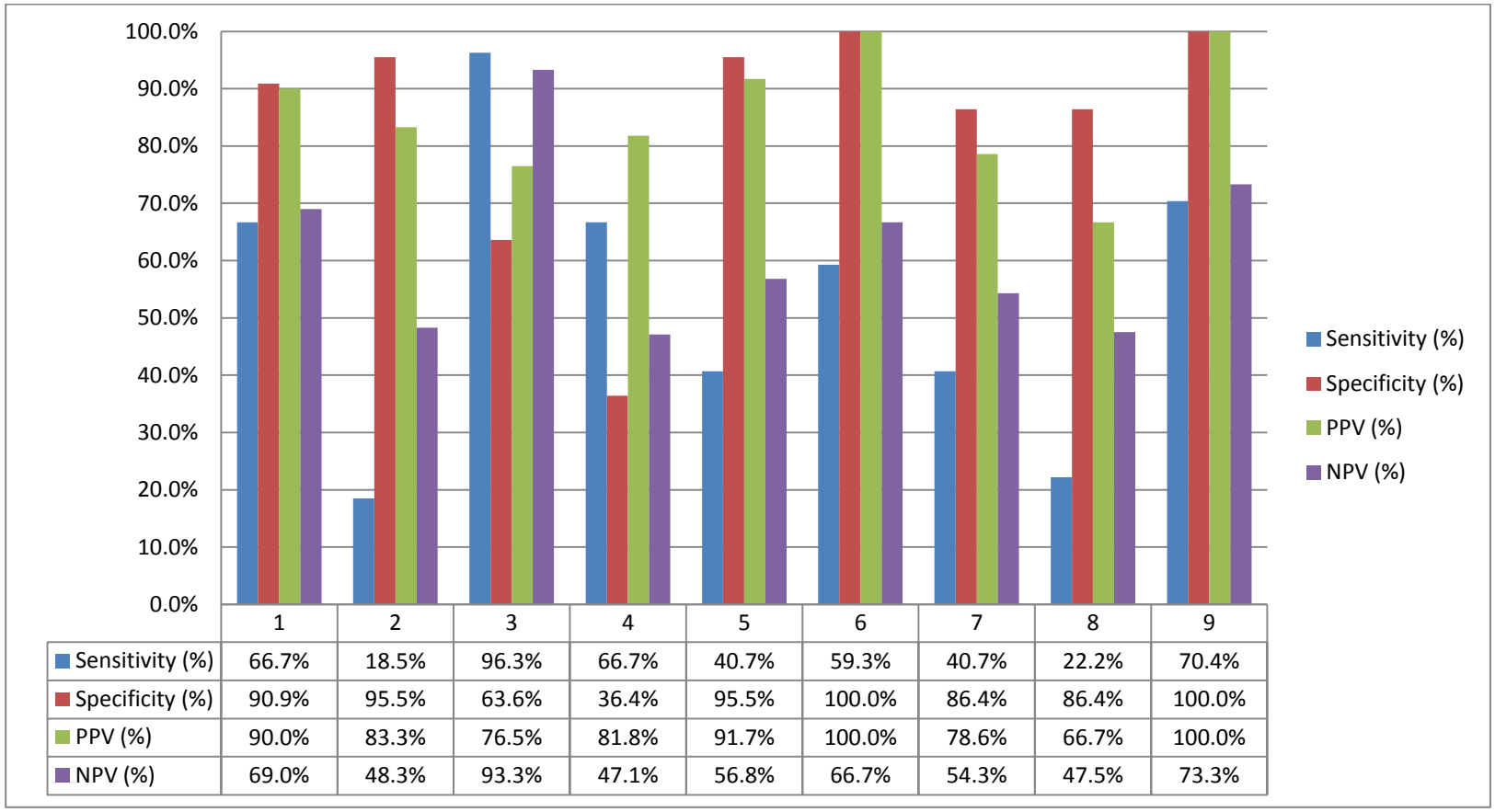
Thirty-seven (75.5%) subjects answered positively to at least one of questions three to nine, twenty-seven of whom had epilepsy and ten of whom did not. All twenty-seven cases of epilepsy were therefore identified by these questions, and questions three to nine collectively were a moderate predictor of epilepsy ($\kappa = 0.57$). All three cases who responded positively to questions one and two were also independently identified as having epilepsy by an affirmative answer to any of questions three to nine. As such, the combination of questions one and two could be considered as being redundant in this study group.

The sensitivity, specificity, PPV and NPV for each of the nine screening questions are illustrated Table 6 and Figure 8, and a summary of the individual analyses for each of questions three to nine is given in Table 7.

	Question	Screened positive Cases (a)	Screened positive Controls (b)	Screened negative Cases (c)	Screened negative Controls (d)	Sensitivity (a/a+c)x100	Specificity (d/b+d)x100	PPV (a/a+b)x100	NPV (d/c+d)x100
1	Have you ever had attacks of shaking of the arms or legs which you could not control?	18	2	9	20	66.7%	90.9%	90.0%	69.0%
2	Have you ever had attacks in which you fall and change colour in the palms, lips or face?	5	1	22	21	18.5%	95.5%	83.3%	48.3%
3	Have you ever lost consciousness?	26	8	1	14	96.3%	63.6%	76.5%	93.3%
4	Have you ever had attacks in which you fall, with loss of consciousness?	18	4	9	8	66.7%	36.4%	81.8%	47.1%
5	Have you ever had attacks in which you fall and bite your tongue?	11	1	16	21	40.7%	95.5%	91.7%	56.8%
6	Have you ever had attacks in which you fall and lose control of your bladder?	16	0	11	22	59.3%	100.0%	100.0%	66.7%
7	Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?	11	3	16	19	40.7%	86.4%	78.6%	54.3%
8	Have you ever had attacks in which you lose contact with the surroundings or experience abnormal smells?	6	3	21	19	22.2%	86.4%	66.7%	47.5%
9	Have you ever been told that you have or have had epilepsy or epileptic fits?	19	0	8	22	70.4%	100.0%	100.0%	73.3%

(N.B. for all rows: a+c = 27 cases, b+d = 22 controls)

Table 6: Pilot study responses to individual screening questions



	1	2	3	4	5	6	7	8	9
Sensitivity (%)	66.7%	18.5%	96.3%	66.7%	40.7%	59.3%	40.7%	22.2%	70.4%
Specificity (%)	90.9%	95.5%	63.6%	36.4%	95.5%	100.0%	86.4%	86.4%	100.0%
PPV (%)	90.0%	83.3%	76.5%	81.8%	91.7%	100.0%	78.6%	66.7%	100.0%
NPV (%)	69.0%	48.3%	93.3%	47.1%	56.8%	66.7%	54.3%	47.5%	73.3%

Figure 8: Performance of individual screening questions in pilot study

Question	Total positive responses (n)	Epilepsy present (n=27) Screening response		Kappa (κ)	Predictive ability
		Positive	Negative		
3	34	26	1	0.62	Good
4	22	18	9	0.48	Moderate
5	12	11	16	0.34	Moderate
6	16	15	11	0.53	Good
7	14	11	16	0.26	Poor
8	9	6	21	0.08	Very poor
9	19	19	8	0.68	Very good

Table 7: Summary of pilot study responses to screening questions 3 to 9

3.3.5 Pilot study: best overall models

Thirty participants (61.2%) responded positively to at least one of questions six, seven or nine, of whom only three did not have epilepsy (Table 8). These three questions picked up all twenty-seven cases of epilepsy, and in combination were therefore a very good predictor of epilepsy ($\kappa = 0.88$). The combined sensitivity of questions six, seven and nine was 100%, the specificity was 86.4%, the PPV was 90% and the NPV was 100%.

The subjects of the pilot study were recruited from hospital neurology departments and the true cases of epilepsy were therefore highly likely to be aware of their diagnoses. This introduces bias to the responses to question nine, and a model that excluded this question was therefore devised. Thirty-six (73.5%) people answered 'yes' to either question one, three or six, including all twenty-seven cases of epilepsy and Nine false positives (Table 9). A positive answer to question One, Three or Six was a good predictor of epilepsy, with $\kappa = 0.61$. The combined sensitivity of questions One, Three and Six was 100% and specificity was 59.1%, with a PPV of 75% and NPV of 100%.

		Epilepsy present		
		Yes	**No**	**Total**
Positive response to questions 6, 7 or 9	**Yes**	27	3	30
	No	0	19	19
	Total	27	22	49

Table 8: Relationship between final diagnoses and questions 6, 7, and 9

		Epilepsy present		
		Yes	**No**	**Total**
Positive response to questions 1, 3 or 6	**Yes**	27	9	36
	No	0	13	13
	Total	27	22	49

Table 9: Relationship between final diagnosis and questions 1, 3 and 6

3.4 Discussion

Various screening questionnaires have been used in a number of epidemiological studies of epilepsy in SSA over the past four decades, most of which have utilised the two-stage door-to-door approach. Of the twenty-four studies summarised in Table 1 and Table 2 in Chapter One, eighteen describe prevalence surveys based on this approach. Only five of these studies provide details of any validation of the screening tool used derived from within the populations being studied, including one study from Tanzania (Winkler et al., 2009c). Outside of Tanzania, validation data are reported in studies from Kenya, Rwanda, Senegal and Zambia (Edwards et al., 2008), (Simms et al., 2008), (Ndoye et al., 2005), (Birbeck and Kalichi, 2004).

In a recent community-based study from Kenya, the second of two screening questions used was found to have a sensitivity for convulsive seizures of 100%, albeit when asked to parents in a study of children only (Mung'ala-Odera et al., 2004). A cross-sectional survey of the prevalence of musculoskeletal impairments performed in Rwanda made use of a composite questionnaire which included a question designed to detect individuals who had fallen as a result of convulsions (Simms et al., 2008). While a pilot feasibility study was performed in Rwanda in a sample of 608 individuals, the questionnaire was originally validated in a sample of 179 individuals in Malawi (Atijosan et al., 2007). In this validation study the diagnoses made by an orthopaedic surgeon and a senior physiotherapist in ninety-three individuals were compared with the results from the screening questionnaire which was administered by technicians in a rehabilitation centre. The overall sensitivity, specificity and PPV are reported as 97.8%, 98.8% and 99% respectively, although no details are offered as to how many of the cases in the validation study had epilepsy, or even as to why epilepsy and seizures should be included in a survey of musculoskeletal impairment. A study from urban Senegal states that a clinic-based validation of the ILAE protocol yielded a sensitivity of 100% and specificity of 78.5%, although no further details are provided (Ndoye et al., 2005). The final study from outside Tanzania to provide validation data is a large study from rural Zambia (Birbeck and Kalichi, 2004). The authors provide details of a clinic-based validation of a modified version of the Ecuador protocol in 100 PWE and fifty controls, quoting a specificity of 86% and PPV of 92%, although no

estimate is given for sensitivity. The authors do comment that while no difficulties with understanding the screening instrument in translation were encountered, large numbers of false positives were initially observed and accounted for by young children who had presented with febrile seizures. This led to a modification of the original screening tool with three questions designed to eliminate seizures in children associated with malaria or fever being added.

Of the four door-to-door studies conducted within Tanzania to date only one has presented validation data of the screening instrument (Winkler et al., 2009c). This study also used a modified version of the Ecuador protocol, and clear details are provided of a clinic-based validation in 106 PWE and 104 others followed by a community-based pilot study in a sample of 400 to assess the feasibility of the screening tool. Sensitivity and specificity of 92.5% and 95% respectively are quoted.

The original validation study of the screening questionnaire piloted here, and previously used in Tanzania and Zambia, was conducted some twenty years ago and involved clinic-based validation followed by extensive validation in the field (Placencia et al., 1992a). An original bank of twenty questions was piloted in eighty-seven PWE with seizures of different types and in sixty-three controls, with a sensitivity of 100% and specificity of 50.8%. A cluster analysis of response rates yielded nine questions with a collective sensitivity of 98% and specificity of 92%. Following a seven-stage field validation in a rural population of 72,121 people, which included examination of screening-negative cases and re-examination of screening-positive cases which had been diagnosed as negative, a sensitivity of 79.3%, specificity of 92.9% and PPV of 18.8% were estimated.

From this brief review it can be seen that the sensitivity of the Ecuador questionnaire and others is generally high regardless of the clinical setting, although specificity is more variable. The results of our pilot study conform to this picture and, to an extent, reflect the experience of the original validation study, albeit in a more limited setting. The translation presented no apparent difficulties in terms of how it was understood, and appeared to be highly sensitive for the detection of epilepsy in a Kiswahili-speaking Tanzanian population. While the low specificity was of concern given the large target

population, it seemed that this could be improved upon if the need arose by selecting a reduced combination of questions without sacrificing sensitivity; i.e. in the advent of a very large response rate during the population census, which would have presented logistic challenges that would be insurmountable with the resources available to the study.

There are important limitations to the pilot study presented here which must be considered. Firstly, the numbers recruited to the study were very small, and fell short of the total sample sizes that would have been needed to confidently report sensitivity and specificity with a standard error of five to six per cent (n=90 to 120). The sample that was included was limited by the number of PWE attending clinics at two hospitals during the time that was available. This number was not easily predictable, and to increase the sample of cases for inclusion in the pilot study would have meant extending the period of the pilot study. This was not possible as the population census, a major logistical exercise, was due to commence in January 2009, and the screening questionnaire needed to be finalised in advance of this in order for census forms to be printed.

Secondly, we had very limited information about the PWE that were included as cases in the pilot study in terms of their seizure history and classification. Medical records often stated simply 'epilepsy', or 'seizures'. On interviewing the nurses who had administered the screening questionnaire during the pilot study it was stated that all of the patients included had described having convulsions. This raised concerns as to the veracity of the 'gold standard' diagnosis on which the validation was based, and also as to how sensitive the translated screening questionnaire would prove to be for the detection of more subtle seizure types.

Without such pressure on time and resources we ideally would have pursued a more rigorous evaluation of the screening instrument, and a larger and better characterised pilot sample would have allowed for exploration of the internal consistency and construct validity of the tool in this setting. Psychometric methods such as the use of Kronbach's alpha statistic are suitable for such work (Cicchetti, 1994, Mbuba et al., 2012a).

While the authors of the original questionnaire acknowledged that there were no questions included that would be likely to detect absence or myoclonic seizures, it was otherwise shown to be effective in detecting focal-onset seizures that did not become secondarily generalised to tonic-clonic seizures (Placencia et al., 1992a), (Placencia et al., 1992c). It is interesting to note that in the two African studies that have used the Ecuador questionnaire, one does not provide details of the types of seizures that were detected (Birbeck and Kalichi, 2004), and the other does not apply the recognised ILAE criteria for classification (Winkler et al., 2009c). In this second study clear details of sixty-one out of eighty-three PWE are given, of whom sixty appear to have generalised seizures of some type, whether primary or secondary, although no details of tonic-clonic activity or otherwise are provided. One case is described as having simple partial seizures and the remainder are described as having two types of seizure, with no further details given.

3.5 Summary and conclusions

The screening questionnaire as a whole had a sensitivity of 100% and a specificity of 54.5%. Using only a positive response to three of the nine questions gave a more accurate screening tool for epilepsy than the full questionnaire, with seven fewer false positives (sensitivity 100%, specificity 86.4%). The pilot study was limited by small numbers and the limited clinical details available, and it was not clear that non-convulsive forms of epilepsy would be detected. Due to limited time and resources no larger field-based validation was possible prior to the population census and screening.

Chapter 4. Census screening, case ascertainment and prevalence

Abstract

Background

Estimates of the prevalence of epilepsy from around the world have varied greatly. Most large studies from low- and middle-income countries including those in SSA have been based on door-to-door screening of rural populations.

Methods

A door-to-door census of the HDSS population was conducted between January and May 2009. During the census a screening questionnaire demonstrated to have 100% sensitivity for known cases of epilepsy in a pilot study was used to detect possible cases of epilepsy in the community. In addition census enumerators were asked to identify possible cases that may not have given a positive response at census screening, and the results of other contemporaneous studies conducted in the HDSS area were scrutinised for additional cases.

Results

The total population of the HDSS was 161,119, including 103,026 people aged fifteen years and above. A total of 291 people with epilepsy were identified from multiple overlapping sources, all of whom were suffering from active epilepsy with convulsive seizures. The age-standardised prevalence of active epilepsy was 2.91/1,000 adults (95% CI 2.58 to 3.24); the crude prevalence adjusted for non-response and deaths was 3.82/1,000 (95% CI 3.45 to 4.20).

Conclusions

The age-standardised prevalence of epilepsy in adults living in the HDSS is lower than the median of 15/1,000 previously reported in SSA, although is in line with a recent large study of comparable design from Kenya. Only cases of epilepsy with convulsive seizures were detected, also in line with the recent Kenyan study.

4.1 Introduction

Most prevalence studies of epilepsy from SSA, including Tanzania, have been conducted in rural populations and have utilised a number of different screening tools. Although most of these tools have been previously validated most studies from SSA have provided only limited details on validation or pilot data from their local study populations. Reviews of prevalence studies have established some important differences in the prevalence of epilepsy when comparing studies from LMICs, including SSA, and studies from HICs. While estimates of prevalence from LMICs tend to be higher there are considerable variations, not all of which can be explained by differences in study design and inclusion criteria (Ngugi et al., 2010, Ngugi et al., 2013b). The median prevalence in SSA has been reported as 15/1,000 (Preux and Druet-Cabanac, 2005), compared to a range of 4.2 to 9.0/1,000 in the UK (Ferro, 2011), and 4.5 to 7.0/1,000 in Europe (Forsgren et al., 2005a). In HICs the prevalence of epilepsy follows a bi-modal pattern, with peaks observed in childhood and then in later life (Cockerell et al., 1995, Hauser et al., 1993). In SSA it is more frequently observed that there is a single peak of prevalence in older children and young adults (Edwards et al., 2008, Winkler et al., 2009c, Rwiza et al., 1992, Simms et al., 2008, Osuntokun et al., 1987, Tekle-Haimanot et al., 1990b, Kaiser et al., 1996, Ndoye et al., 2005). This is not universally the case, however, and some studies have observed a peak prevalence in younger children (Longe and Osuntokun, 1988, Bondestam et al., 1990, Birbeck and Kalichi, 2004), while others have replicated the bi-modal peak seen in HICs (Osuntokun et al., 1982, Dent et al., 2005). Another frequent observation in studies from SSA has been heterogeneity of prevalence and clustering of cases within study populations (Edwards et al., 2008, Rwiza et al., 1992, Kaiser et al., 1996), with variations in prevalence as wide as 5.1 to 37.1/1,000 being observed within one study population (Rwiza et al., 1992).

This chapter describes screening, case ascertainment and estimation of prevalence of epilepsy in adults living in the HDSS.

4.2 Methods

4.2.1 Procedures

A complete door-to-door census of the HDSS population was conducted between mid-January and late May 2009. Prior to the census, a week of preparatory workshops was held in the district. All census enumerators and supervisors were provided with further training on the recognition of seizures and different seizure types. Focus group discussions were held during which the individual components of the translated screening questionnaire were scrutinised and further refinements made to optimise its utility in the field. The census commenced in the week following the workshops on 20th January, and all census work was complete by 1st June 2009. This date was selected as the prevalence date. The procedures used during the census are described in more detail in Chapter Two, section 2.3.4. Given that the specificity of the screening questionnaire was estimated at 54.5% during the pilot study, it was stipulated that a positive response to any of the screening questions should be made known to the study team to allow for further selection. In the event that an unmanageable number of possible cases were yielded, as seemed likely with a specificity of 54.5% and a study population that was anticipated to be in excess of 160,000, only those that had responded to questions six, seven or nine, a combination that had performed with 100% sensitivity and 86.4% specificity in the pilot study (see section 3.3.5). Allowing for public holidays, weekends and the logistics of travelling around the district, it was calculated that up to 2,000 individuals could be assessed clinically between March and September 2009, the time available for initial field work. To optimise the time available for clinical assessments, an initial round was commenced from early March, prior to completion of the census, working from lists of positive responders held locally.

Further possible cases were identified from the results of four other screening studies that have been performed in the district. Two of these were conducted during the same period and made use of baseline demographic data from the same census data set as the epilepsy study. The first of these studies was a field-based validation of a screening instrument designed to measure the prevalence of neurological disability, including epilepsy, in resource-poor settings (Bower et al., 2009, Bower et al., 2012). In this field-

based validation study, the entire population of a single village within the HDSS was screened. The final results of this study were yet to be published at the time of the epilepsy study, although details of cases of epilepsy that had been identified were made available (Jim Bower, personal communication). The second of these studies, a companion study to the epilepsy study with the same clinical supervisor and principle investigators, also screened for neurological disability, this time in all those aged seventy years and above in a selection of twelve villages (Dewhurst et al., 2012a, Dewhurst et al., 2012b). Again, details of cases of epilepsy from within this study cohort were made available to the epilepsy study team prior to publication (Felicity Dewhurst, personal communication). Finally, case records from two recent community-based studies in the district were retrospectively scrutinised for cases of epilepsy: a study of the incidence of stroke in the HDSS population conducted between 2003 and 2006 (Walker et al., 2010), and a door-to-door study of the prevalence of Parkinson's disease (Dotchin et al., 2008). Cohorts from both of these studies remain under follow up (Howitt et al., 2011, Dotchin et al., 2011).

Following completion of case ascertainment, all diagnoses were reviewed and confirmed by Dr Margaret Jackson, a consultant neurologist with a special interest in epilepsy working at the Royal Victoria Infirmary in Newcastle, UK.

4.2.2 Statistics and analysis

Data entry and approaches to continuous and categorical variables are described in Chapter Two, section 2.8. Overlapping sources of cases were used as the basis of a sensitivity analysis of the performance of the screening questionnaire in the field, with sensitivity and PPV being calculated for the screening questionnaire as a whole. Combinations of questions that appeared to perform well in the field were also identified. As no formal field validation with complete examination of a sample of the population was feasible given the time and resources available, it was not possible to calculate specificity or NPV.

Age- and sex-specific prevalence rates for the HDSS adult population were calculated in five-year age-bands. Age-standardisation to the WHO world standard population was

carried out using the direct method, with 95% confidence intervals (CIs) calculated based on a Poisson assumption (Ahmad et al., 2001, Hennekens and Buring, 1987). The WHO standard population was chosen as the reference in order to be in line with the standardisation strategy employed by other studies conducted in the same population (Dewhurst et al., 2012b, Dewhurst et al., 2012d). This study is only concerned with individuals aged fifteen years and above, and both the HDSS and WHO standard populations were therefore weighted accordingly. A crude prevalence estimate adjusted for non-response was calculated using the PPV derived from the field-based sensitivity analysis.

To look for evidence of clustering of cases, prevalence estimates within geographic and administrative divisions within the district were compared parametrically or non-parametrically according to their distribution. To examine for uniformity of case finding the crude prevalence rate per 1,000 was applied to the adult population of each village to generate an expected number of cases. This was then compared to the observed number of cases (observed/expected = rho (ρ)). The distributions of rho statistics within geographic and administrative divisions were then compared parametrically or non-parametrically, as with crude prevalence. For both crude prevalence and rho, the Kolmogorov-Smirnov test was use to identify normal and non-normal distributions. For normally distributed data, one-way ANOVA was used to compare means, and for non-normally distributed data the Kruskal-Wallis test was used. Where only two groups were compared Student's independent t-test was used for normally distributed data, and the Mann-Whitney U test was used for data where at least one variable had a non-normal distribution.

4.3 Results

4.3.1 Screening questionnaire: final refinements

The translation of the questionnaire that had been used in the pilot study was presented to the HDSS enumerators and supervisors for further discussion and clarification, and the following points emerged.

It was felt that the concept of an "attack", which features in questions one, two, and four to eight, was difficult to translate accurately, and that this would be particularly problematic when applied to episodes of falling down. It was decided that the final version for use in the census should have the words *"…ghafla bila sababu yeyote"* ("…suddenly and without any apparent reason") to further qualify this concept. In addition, census enumerators recommended that it should specifically be explained that these questions did not refer to episodes such as intoxication with alcohol, mechanical trips or falls or being knocked down by bicycles, livestock or other traffic. The revised wording for "attack" was applied to all the questions in which it appears.

Question nine – "Have you ever been told that you have, or have had, epilepsy or epileptic fits?"

The usual Kiswahili translation of the word "epilepsy" is *"kifafa"*; this was felt to be a very stigmatising word and was also not felt to capture the various concepts of convulsive activity that the local population may be familiar with. For these reasons two additional terms were added to the final version of the questionnaire used in the census: *"degedege"* (Kiswahili) and "*kiumangungu*" (Kichagga). Both of these terms are used to refer to febrile seizures in children, but are also widely used to refer to convulsions in general in all age groups.

The final version of the screening questionnaire used during the census, and its Kiswahili translation, is included here in Box 4 and in Appendix IX.

1. Have you ever had attacks of shaking of the arms or legs which you could not control?

Je, ulishawahi kupatwa na hali ya kutetemeka mikono au miguu, ghafla bila sababu yeyote, ambayo hukuweza kuizuia?

2. Have you ever had attacks in which you fall suddenly, without any reason, changing colour in the palms, lips or face?

Je, ulishawahi kupatwa na hali ambayo ilikufanya uanguke, ghafla bila sababu yeyote, kubadilika rangi na kuwa mweupe kwenye viganja, midomo na usoni?

3. Have you ever lost consciousness?

Je, ulishawahi kupoteza fahamu?

4. Have you ever had attacks in which you fall with loss of consciousness?

Je, ulishawahi kupatwa na hali ambayo ilisababisha uanguke na kupoteza fahamu, ghafla bila sababu yeyote?

5. Have you ever had attacks in which you fall and bite your tongue?

Je, ulishawahi kupatwa na hali iliyokusababisha uanguke ghafla bila sababu yeyote, na kuuma/kung'ata ulimi wako?

6. Have you ever had attacks in which you fall and lose control of your bladder?

Je, ulishawahi kupatwa na hali ambayo ilikufanya uanguke ghafla bila sababu yeyote na kutoa mkojo?

7. Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?

Je, ulishawahi kupatwa na hali ya muda mfupi ya kutetemeka au kutikisika mkono au mguu mmoja au kwenye uso?

8. Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?

Je, ulishawahi kupatwa na hali ambayo ilikufanya upoteze ufahamu wa mahali ulipo na kusikia harufu zisizo za kawaida?

9. Have you ever been told that you have or have had epilepsy or epileptic fits?

Je, ulishawahi kuelezwa kuwa una au ulishawahi kuwa na kifafa au kuanguka kifafa, au degedege, au kiumangungu?

Box 4: Final screening questionnaire, English and Kiswahili, 2009 HDSS census

4.3.2 Census: population demographics

There were a total of 43,794 households in the HDSS area, with no households refusing to participate in the census. The total population was 161,119 (83,180 female, 77,939 male), of whom 103,026 (63.9%) were aged fifteen years or above (54,386 female, 48,640 male) (Figure 9, Table 10).

4.3.3 Census: door-to-door screening

Of the 103,026 adults in the HDSS population, 568 (0.55%) individuals (286 female, 282 male) responded positively to at least one of the nine screening questions that were asked during the census (Table 11). The response rate was therefore lower than anticipated, and it was deemed feasible to attempt an assessment of all of the positive responders with no further sub-selection based on the modelling of pilot study data described in Chapter Three, section 3.4.5.

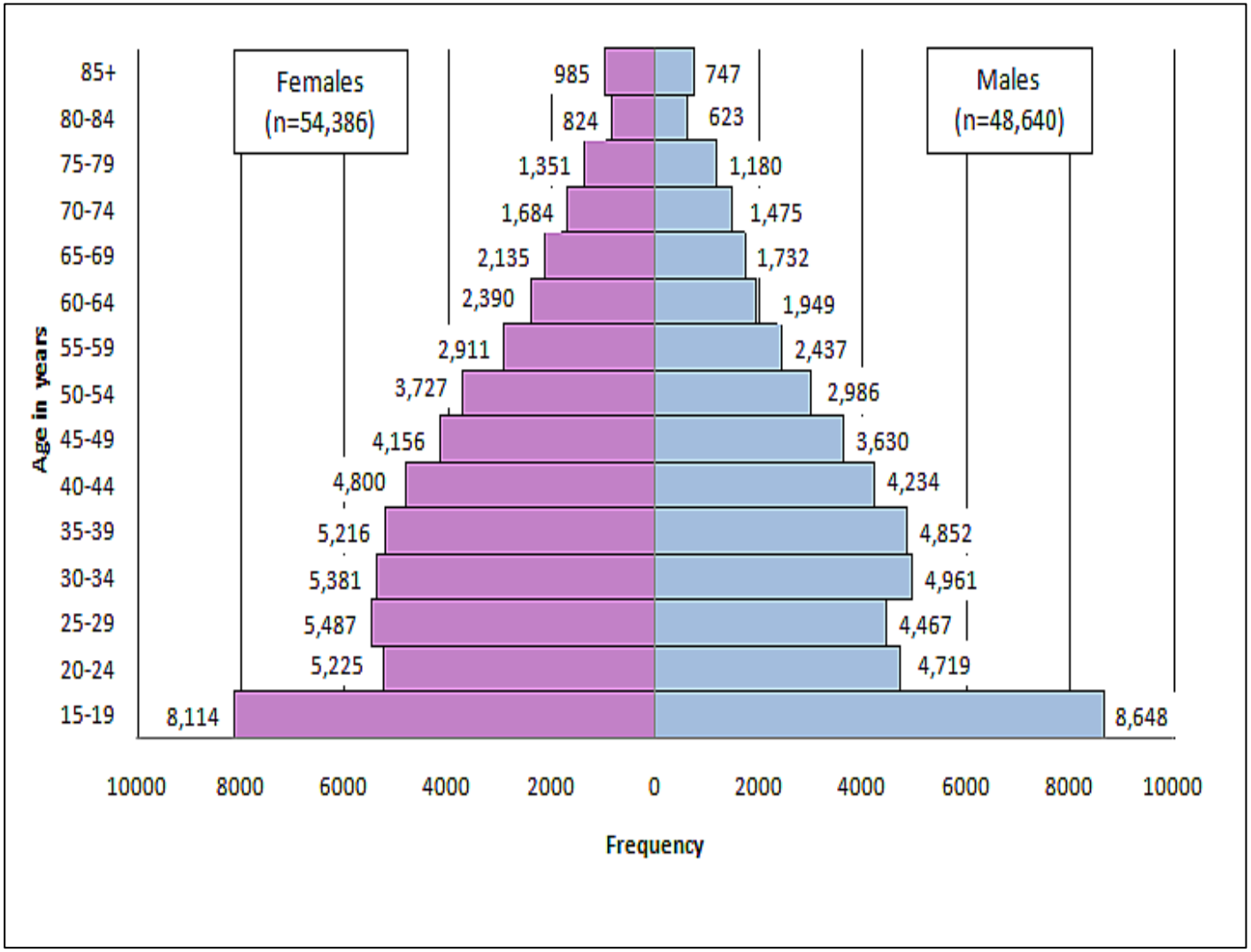


Figure 9: Hai adult population structure (2009 census)

Age-band	Females	(% of females)	Males	(% of males)	Total	(% of total)
0-14*	28,794	(34.6)	29,299	(37.6)	58,093	(36.1)
15-19	8,114	(9.8)	8,648	(11.1)	16,762	(10.4)
20-24	5,225	(6.3)	4,719	(6.1)	99,44	(6.2)
25-29	5,487	(6.6)	4,467	(5.7)	99,54	(6.1)
30-34	5,381	(6.5)	4,961	(6.4)	10,342	(6.4)
35-39	5,216	(6.3)	4,852	(6.2)	10,068	(6.3)
40-44	4,800	(5.8)	4,234	(5.4)	9,034	(5.6)
45-49	4,156	(5.0)	3,630	(4.7)	7,786	(4.8)
50-54	3,727	(4.5)	2,986	(3.8)	6,713	(4.2)
55-59	2,911	(3.5)	2,437	(3.1)	5,348	(3.3)
60-64	2,390	(2.9)	1,949	(2.5)	4,339	(2.7)
65-69	2,135	(2.6)	1,732	(2.2)	3,867	(2.4)
70-74	1,684	(2.0)	1,475	(1.9)	3,159	(2.0)
75-79	1,351	(1.6)	1,180	(1.5)	2,531	(1.6)
80-84	8,24	(1.0)	623	(0.8)	1,447	(0.9)
85+	9,85	(1.1)	747	(1.0)	1,732	(1.1)
Total	**83,180**	**(100.1)****	**77,939**	**(100.0)**	**161,119**	**(100.1)****
Total adults†	**54,386**	**(65.4)**	**48,640**	**(61.6)**	**103,026**	**(64.0)**

*Ages 14 and under not considered further in this study **Totals exceed 100% due to rounding †Defined as aged 15 years and above

Table 10: Hai population structure (2009 census)

	Question	Positive responses (n)	% of all positive responders
1	Have you ever had attacks of shaking of the arms or legs which you could not control?	259	45.6%
2	Have you ever had attacks in which you fall, suddenly and for no reason, and change colour in the palms, lips or face?	363	63.9%
3	Have you ever lost consciousness?	362	63.7%
4	Have you ever had attacks in which you fall with loss of consciousness?	316	55.6%
5	Have you ever had attacks in which you fall and bite your tongue?	213	37.5%
6	Have you ever had attack in which you fall and lose control of your bladder?	177	31.2%
7	Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?	200	35.2%
8	Have you ever had attacks in which you lose contact with the surroundings or experience abnormal smells?	152	26.8%
9	Have you ever been told that you have or have had convulsions, epilepsy or epileptic fits?	173	30.5%

Table 11: Positive response rates to individual screening questions

4.3.4 Case ascertainment: positive responders to door-to-door screening

Clinical assessments were conducted during three separate periods of field work: early March to late June 2009, January 2010, and July to August 2010. Possible cases assessed included positive responders to the census screening, individuals identified by key informants, and cases identified by other studies in the same population.

Of the 568 adult positive responders, 395 (69.5%) were available for assessment. A diagnosis of active epilepsy was made in 209 (52.9%) of those assessed, of whom 101 (48.3%) were female and 108 (51.7%) were male (Table 12). A detailed account of all individuals diagnosed with epilepsy is given in Chapter Five.

Of the 568 positive responders, 173 (30.5%) were not available for clinical assessment. Stringent efforts were made to trace all of the 173 individuals who were not initially available; eighty-nine (51.4%) of these did not attend for assessment on at least two occasions despite, to the best of our knowledge, being aware of the study. All those who refused or who did not attend were visited at home by their local village enumerator to ensure that they were aware of the study and its aims. It also became apparent that four names had been wrongly included in the list of adult positive responders: two duplicate names for individuals already assessed, and two children who had being given the wrong date of birth in the census database. Twelve (2.1%) positive responders had died prior to assessment, with information on the cause or circumstances of death being available for eight of these: one had been admitted to hospital with confusion (male, seventy-four years, died July 2009), one was described as having Parkinson's disease (male, eighty-two years, died on uncertain date in 2009), one died of 'old age' (female, seventy-five years, died July 2010), two died of pneumonia (one female, seventy-six years, died January 2010; one male, forty-six years, died in 2009), one was described as having heart failure and hypertension (male, eighty-seven years, no further details available), one was described as having died unexpectedly during their sleep (male, twenty-five years, died July 2010), and one was described as being a known case of epilepsy who had drowned during a seizure (female, twenty-eight years, died April 2009). The details of the 173 positive responders who were not assessed clinically are summarized in Figure 10.

4.3.5 Case ascertainment: key informants

In addition to those responding positively to the screening questionnaire, a further 130 individuals identified by the village enumerators as possibly suffering from epilepsy were assessed by the research team, and active epilepsy was diagnosed in 80 (61.5%) of these individuals. Final diagnoses made in individuals brought forward by the enumerators are summarised in Table 13.

4.3.6 Case ascertainment: cases identified by other studies

Under the study which aimed to validate a composite screening tool for neurological disability, 4,974 people in one village were screened with five cases of epilepsy being detected (Jim Bower, personal communication). The epilepsy study detected sixteen cases in the same group of screened individuals (eleven from census, five identified by village enumerators), including three of the cases detected by the other study. The two additional cases were not available for clinical assessment by the epilepsy study and have not been included in the final case series.

The second study screened a total of 2,221 individuals aged seventy years and above in twelve villages for neurological disability (Felicity Dewhurst, personal communication). Six cases of epilepsy were detected, including one incident case with first onset of seizures subsequent to 1st June 2009. Of the five prevalent cases, one was detected independently by the epilepsy study and two of the additional four were available for further clinical assessment, with a diagnosis of active epilepsy being confirmed in both of these cases. The two cases that were not available for assessment were discussed with the research doctors involved and although it was apparent that they would qualify for inclusion as cases of active epilepsy, to preserve the uniformity of the method they have not been included in the final case series here.

Examination of the follow-up records of the TSIP study yielded a further three possible cases of epilepsy (Howitt et al., 2011). None of these cases were detected at census by the epilepsy study, and on further assessment a diagnosis of epilepsy was not confirmed in any of these three individuals. Finally, case records of the prevalence survey of

Parkinson's disease did not yield any further possible cases of epilepsy (Catherine Dotchin, personal communication).

In summary, six out of a possible ten additional cases identified by other studies were available for assessment by the epilepsy study, with a diagnosis of epilepsy being confirmed in three of these: one incident case and two prevalent cases. No clear diagnoses were made in the remaining three. The identification of cases from other studies is illustrated schematically in Figure 11.

4.3.7 Case ascertainment: deferred diagnoses

A deferred diagnosis of 'probable epilepsy' was made in fourteen cases (eight identified by census screening, six identified by village enumerators). In these individuals, although the history was in some way suspicious of a seizure disorder, there was insufficient clinical information or corroborative collateral history available to make a firm diagnosis. These individuals have not been included in the final case series, but will be kept under follow-up by the study and have been advised on observing and recording any further episodes and on where to seek help locally.

4.3.8 Case ascertainment: false positives

Diagnoses other than seizures or epilepsy were categorised according to the main problem with which the individual had presented to the study. There were no instances of individuals falling into more than one diagnostic category. The most common diagnosis other than seizures or epilepsy was syncope, accounting for 35.9% of false positives from screening, 47.1% of individuals identified by key informants, and 37.8% of false positives overall. Other neurological problems that were seen included cerebral palsy, cognitive impairment, tremor or Parkinsonism, other movement disorders, muscular dystrophy and stroke. Cardiovascular problems included one case of severe aortic stenosis complicated by syncope. Respiratory problems included asthma and one case of likely lung cancer. Musculoskeletal problems generally consisted of generalised joint pains associated with osteoarthritis in the elderly. Ophthalmological problems included cataract or other causes of reduced visual acuity. Genitourinary presentations included recurrent urinary tract infections, pyelonephritis, urinary retention and chronic loin pain radiating to the scrotum.

Diagnoses related to alcohol included episodes of intoxication where there was no history suggestive of provoked or withdrawal seizures, and instances where individuals were intoxicated with alcohol on the day of assessment rendering objective assessment impossible. In individuals where no diagnosis was possible there was either a history which could not be related to any active problem or clear diagnosis, or the individual concerned denied having any active problems. Diagnoses other than epilepsy are summarised in Table 14 and Figure 12.

4.3.9 Summary of case ascertainment

A total of 527 individuals were assessed clinically, with 291 (55.2%) cases of active epilepsy being identified. Of these, 209 (71.8%) were detected by the screening questionnaire, eighty (27.5%) were identified independently by the village enumerators, and two (0.7%) were identified from other studies. A witness was available to help clarify the diagnosis and to characterise the features of epilepsy in 202 (69.4%) of the confirmed cases. The sources of all the cases identified are illustrated schematically in Figure 13.

Diagnosis	Female (n)	(% of females)	Male (n)	(% of males)	Total (n)	(% of total)
Active epilepsy	101	(49.5%)	108	(56.35)	209	(52.9%)
Probable epilepsy	3	(1.5%)	5	(2.65)	8	(2.0%)
Inactive epilepsy	1	(0.5%)	3	(1.6%)	4	(1.0%)
Provoked seizures	5	(2.5%)	2	(1.0%)	7	(1.8%)
Not seizures	93	(45.6%)	74	(38.5%)	167	(42.3%)
Total	**204**	**(100.0%)**	**192**	**(100.0%)**	**395**	**(100.0%)**

Table 12: Diagnoses in positive census responders

Diagnosis	Female	(% of females)	Male	(% of males)	Total	(% of total)
Active epilepsy	35	(58.3%)	45	(64.3%)	80	(61.5%)
Probable epilepsy	4	(6.7%)	2	(2.9%)	6	(4.6%)
Inactive epilepsy	0	(0.0%)	2	(2.9%)	2	(1.5%)
Incident case	0	(0.0%)	1	(1.4%)	1	(0.8%)
Isolated seizure	0	(0.0%)	1	(1.4%)	1	(0.8%)
Provoked seizures	2	(3.3%)	3	(4.3%)	5	(3.8%)
Resident outside HDSS	1	(1.7%)	0	(0.0%)	1	(0.8%)
Not seizures	18	(30.0%)	16	(22.9%)	34	(26.2%)
Total	**60**	**(100.0%)**	**70**	**(100.0%)**	**130**	**(100.0%)**

Table 13: Diagnoses in individuals identified by key informants

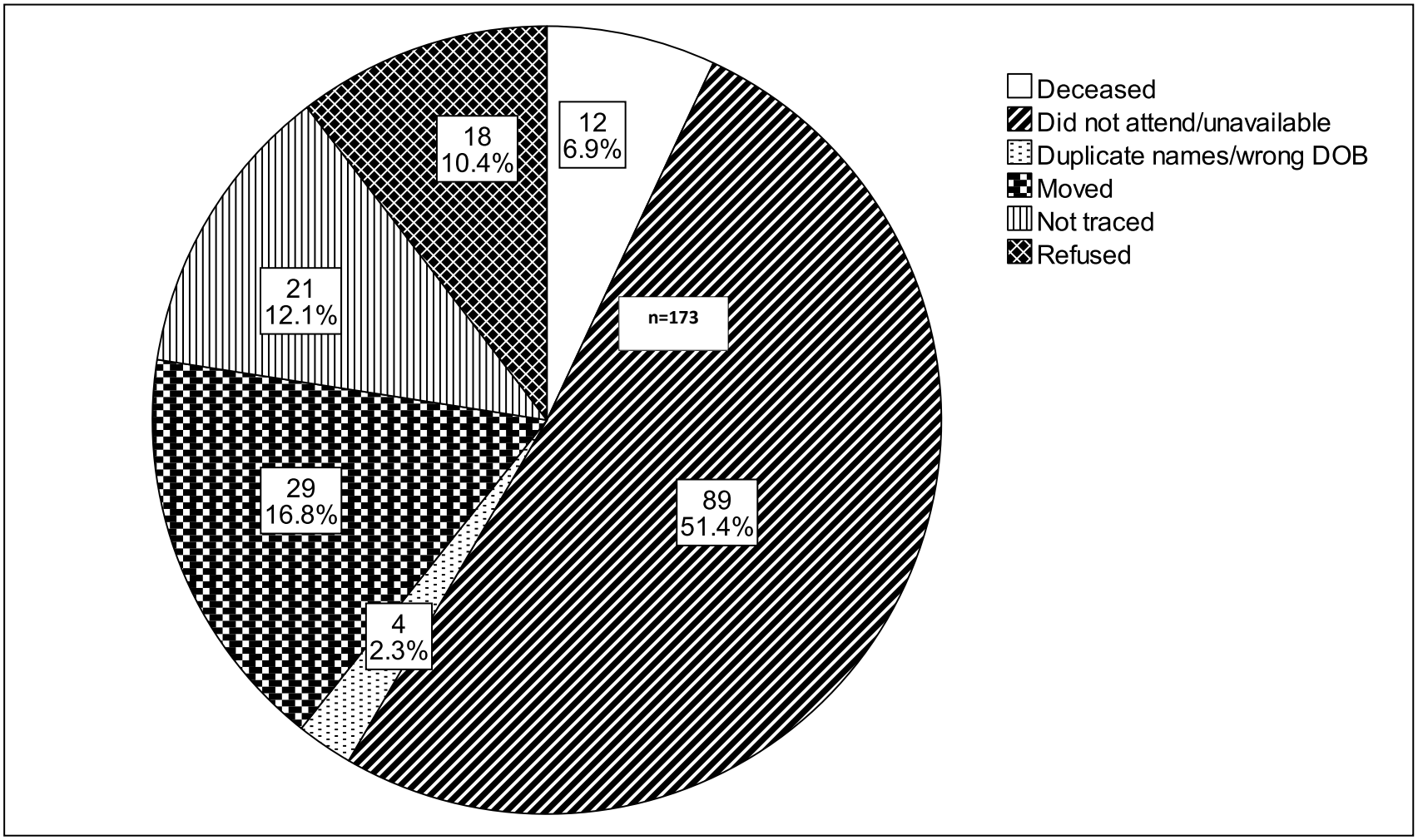


Figure 10: Details of positive responders that were not clinically assessed

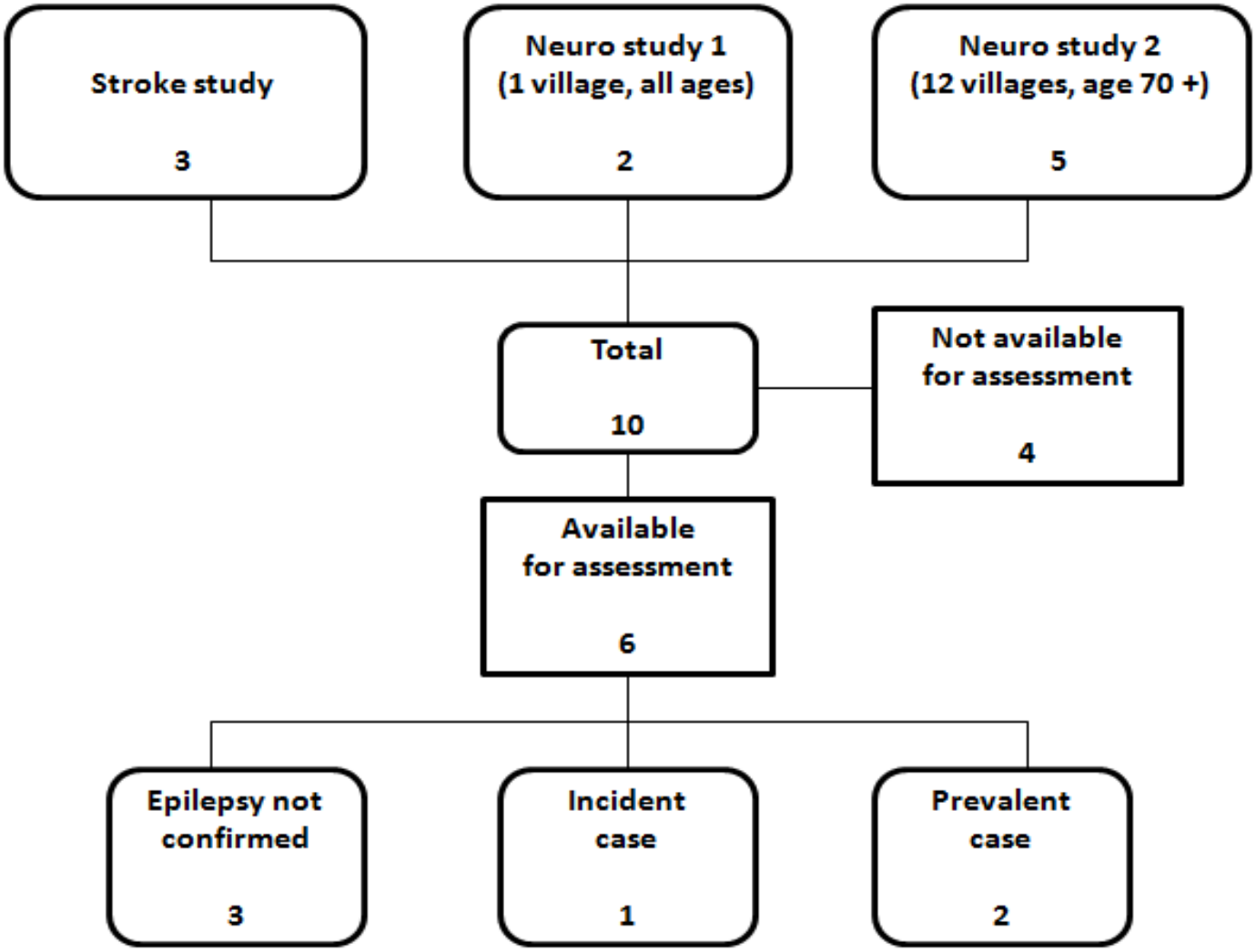


Figure 11: Cases of epilepsy identified by other studies

	Source					
	Census screening		Key informants		Total	
Diagnosis	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Syncope	60	(35.9%)	16	(47.1%)	76	(37.8%)
Neurological	25	(15.0%)	5	(14.7%)	30	(14.9%)
No diagnosis possible	22	(13.2%)	2	(5.9%)	24	(11.9%)
Other miscellaneous	16	(9.6%)	5	(14.7%)	21	(10.4%)
Musculoskeletal problem	17	(10.2%)	2	(5.9%)	19	(9.5%)
Ophthalmological	7	(4.2%)	2	(5.9%)	9	(4.5%)
Respiratory	7	(4.2%)	0	(0.0%)	7	(3.5%)
Alcohol	3	(1.8%)	1	(2.9%)	4	(2.0%)
Cardiovascular	3	(1.8%)	0	(0.0%)	3	(1.5%)
Genitourinary	3	(1.8%)	1	(2.9%)	4	(2.0%)
LOC - non-epileptic	4	(2.4%)	0	(0.0%)	4	(2.0%)
Total	**167**	**(100.0%)**	**34**	**(100.0%)**	**201**	**(100.0%)**

Table 14: Diagnoses other than seizures or epilepsy

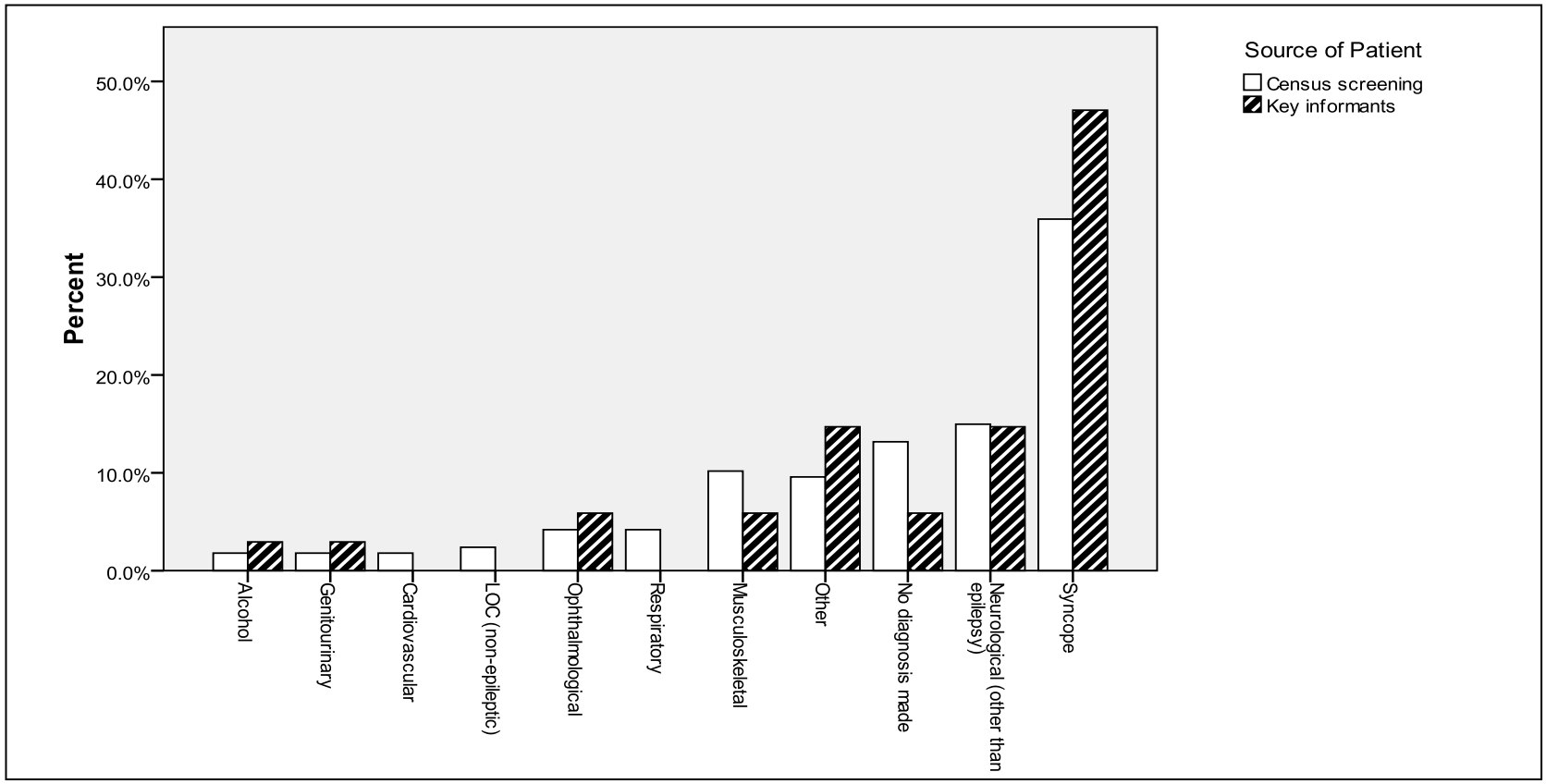


Figure 12: Diagnoses other than seizures or epilepsy, by source

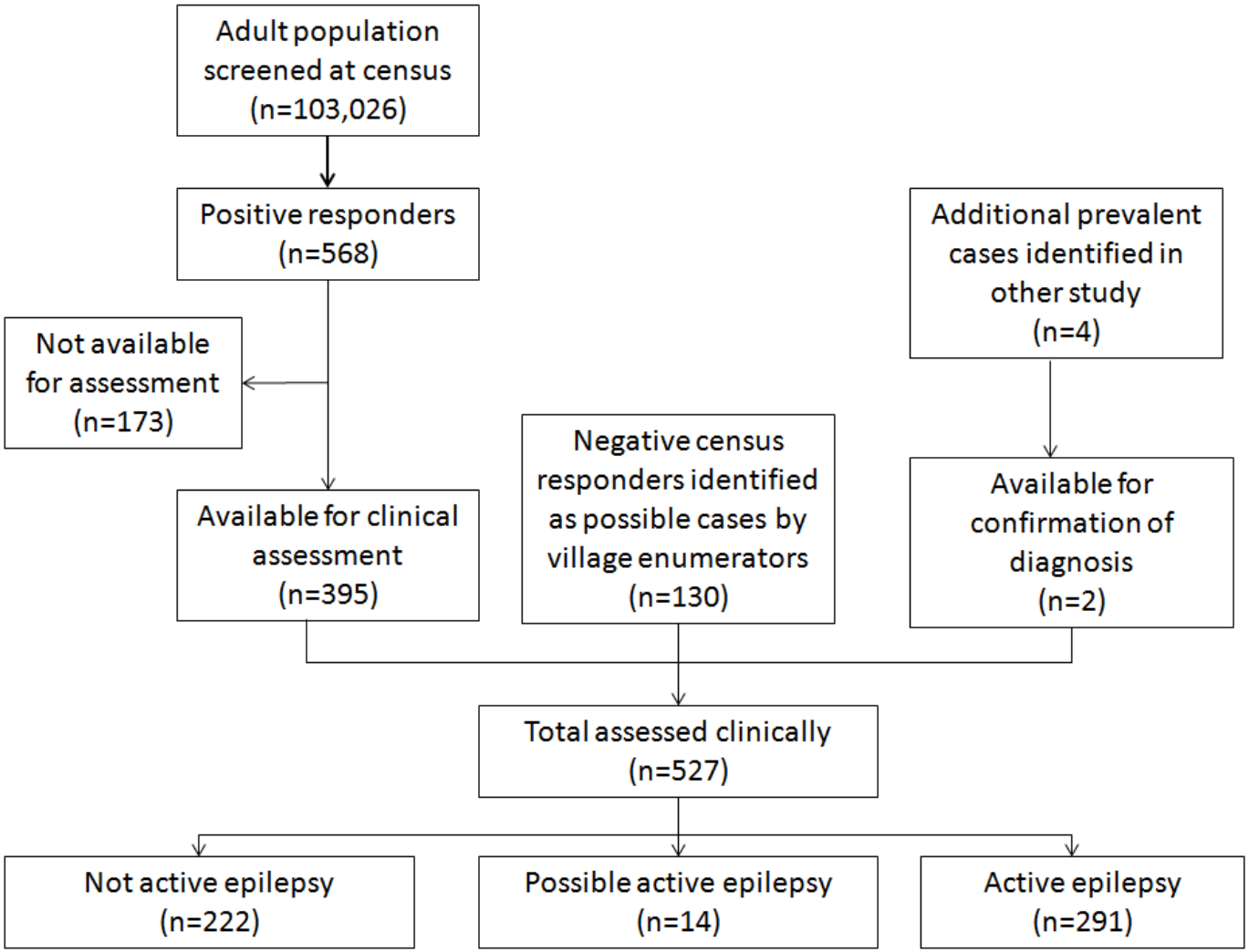


Figure 13: Schematic overview of final case ascertainment

4.3.10 Brief demographic details of cases identified

A total of 291 cases were identified that were alive and resident in the study area on the prevalence date of 1st June 2009: 155 (53.3%) males, 136 (46.7%) females. The age distribution of cases was positively skewed for both sexes (

Figure 14), with a median age for females of twenty-nine years and for males of thirty-one years (Table 15). Age did not differ significantly between the sexes (Mann-Whitney U=9900, z=-0.89, p=0.37).

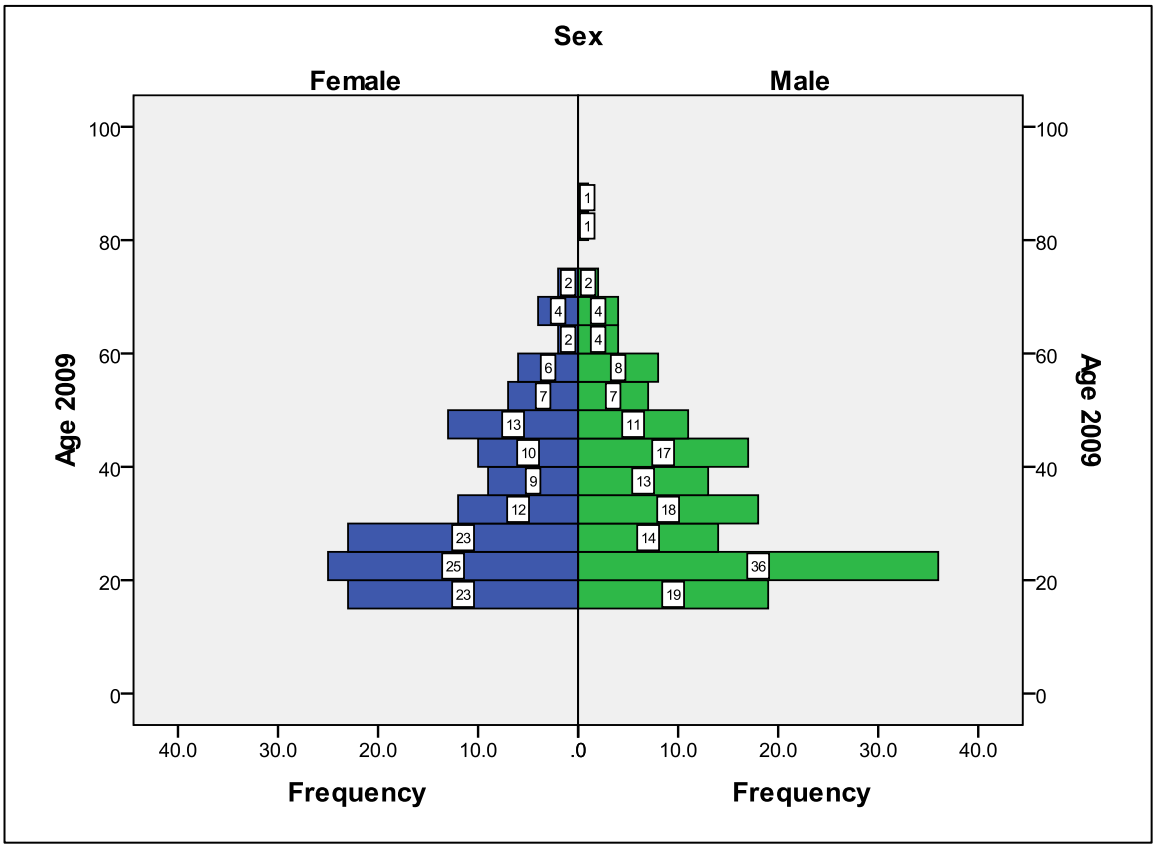


Figure 14: Age distribution of cases

		Age in years			
			Range		
Sex	**n**	**Median**	**Min**	**Max**	**IQR**
Female	136	29.0	15	72	23.0
Male	155	31.0	15	85	21.0
Combined	291	30.0	15	85	21.0

Table 15: Age distributions of cases by sex

4.3.11 Performance of the screening questionnaire in the field

While the diagnosis of active epilepsy in this study was based on strict inclusion criteria (Chapter Two, section 2.3.6), the performance of the screening questionnaire has been analysed on the basis of its ability to detect cases of particular clinical interest; i.e. cases of active epilepsy, seizure diagnoses other than active epilepsy and cases suggestive of epilepsy or seizures in whom a final diagnosis has yet to be reached.

The overall response rate to the screening questionnaire during the census was low, with 568 positive responses from a screened population of 103,026 (0.55%). Of these, 395 (69.5%) were clinically assessed: 209 (52.9%) had active epilepsy, eleven (2.8%) had a history of seizures but not epilepsy, and in eight (2.0%) a final diagnosis was deferred (total 228). For the purpose of assessing the performance of the screening questionnaire this group of 228 positive responders were collectively classed as true positives (57.7% of those assessed). In the remaining 167 (42.3%) of the 395 positive respondents who were clinically assessed there was no history suggestive of seizures and these were classed as being false positives. The total number of negative responses was 102,458, of whom 134 (0.1%) were identified by key informants or by other studies and subsequently assessed. Eighty-two of these (61.2%) were found to have active epilepsy, eight (6.0%) gave a history otherwise consistent with seizures but not active epilepsy and a final diagnosis was deferred in a further six (4.5%). Again, for the purpose of analysing the screening questionnaire, this group of ninety-six were classed as false negatives. The two incident cases identified during the study (one by key informants, one from another study) have been left as true negatives for the purposes of this analysis, as these negative responses would have held true at the time of screening. The combined total of negative responders plus positive responders who were clinically assessed was therefore 102,853 (Table 16). Based on these totals, the sensitivity of the screening questionnaire for a diagnosis consistent with seizures in general, including all those confirmed as having epilepsy, was 70.4% and the PPV was 57.7%. Complete assessment of a population sample was not performed and therefore no gold standard was available for the calculation of specificity or NPV.

The combination of questions one, five, six and nine had a sensitivity of 92.1% and specificity of 53.9%; questions one, five, six, seven and sine collectively had a sensitivity of 94.7% and a specificity of 44.9%. The frequency of positive responses, sensitivity and PPV for each of the individual screening questions are summarised in Table 17 and Figure 15.

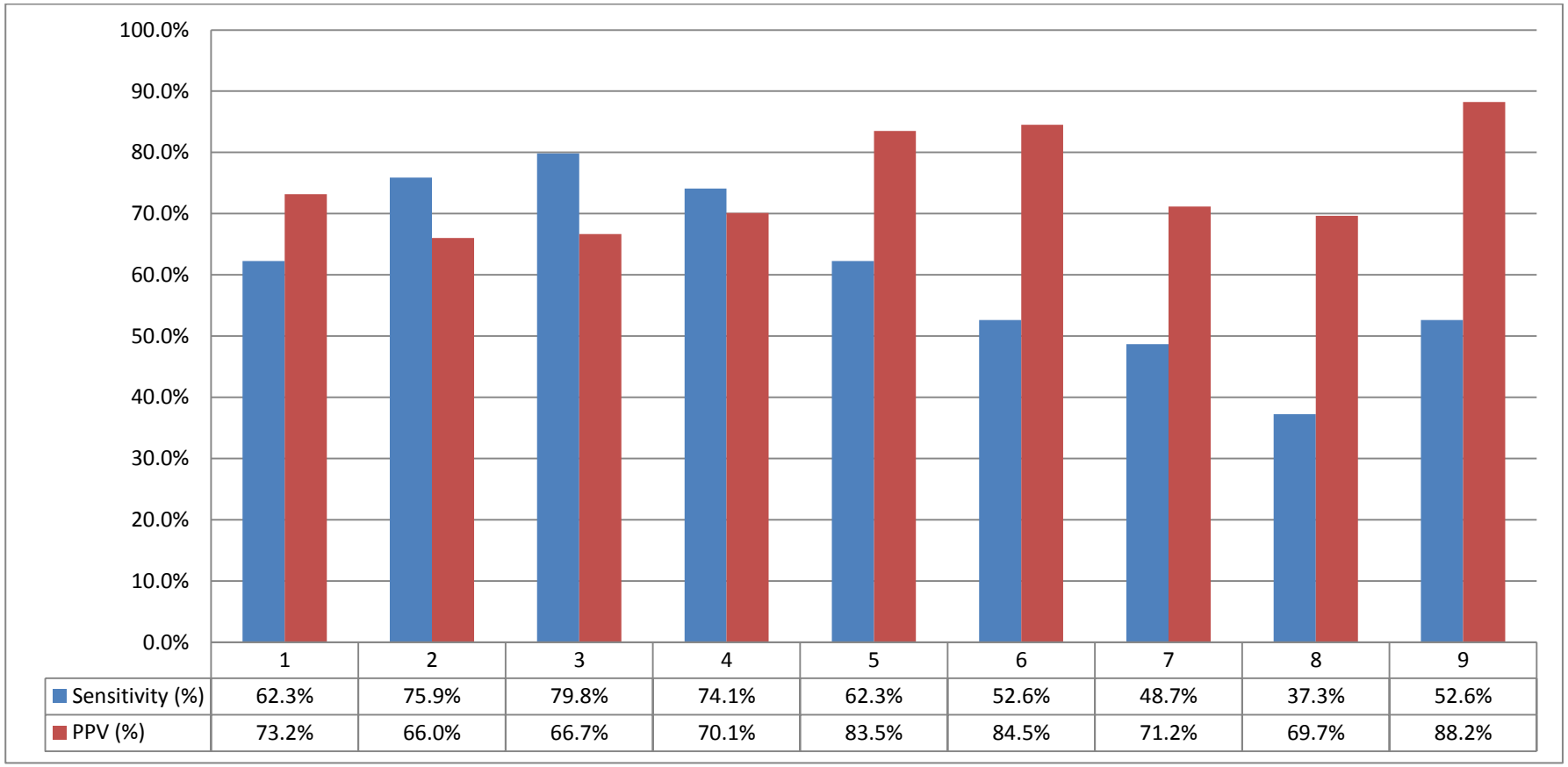
Using data for all 395 individuals (203 female, 192 male) who screened positively for epilepsy during the census, a further analysis similar to that used during the pilot study was performed. The analysis is limited by the inclusion only of false negative responders known to the study. Kappa statistics were calculated for each individual question and combinations of questions as a measure of agreement between the actual diagnosis and the response to the screening questionnaire (Table 18). Using this approach a model based on questions one, five and nine appears to be the most useful, with a sensitivity of 89.0% and a specificity of 59.3%. A model based on questions one and five only has a sensitivity of 84.6% and specificity of 62.3%.

	Diagnosis		
Screening Result	**Seizures**	**Not seizures**	**Total**
Positive	228	167	395
Negative	96	102,362	102, 458
Total	324	102,529	102,853

Table 16: Contingency table for census screening vs. clinical diagnosis

Question		Screened positive		Screened negative		
		True positive (a)	False positive (b)	False negative (c)	Sensitivity (a/a+c)	PPV (a/a+b)
1	Have you ever had attacks of shaking of the arms or legs which you could not control?	142	52	86	62.3%	73.2%
2	Have you ever had attacks in which you fall, changing colour in the palms, lips or face?	173	89	55	75.9%	66.0%
3	Have you ever lost consciousness?	182	91	46	79.8%	66.7%
4	Have you ever had attacks in which you fall with loss of consciousness?	169	72	59	74.1%	70.1%
5	Have you ever had attacks in which you fall and bite your tongue?	142	28	86	62.3%	83.5%
6	Have you ever had attack in which you fall and lose control of your bladder?	120	22	108	52.6%	84.5%
7	Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?	111	45	117	48.7%	71.2%
8	Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?	85	37	143	37.3%	69.7%
9	Have you ever been told that you have or have had convulsions, epilepsy or epileptic fits?	120	16	108	52.6%	88.2%

Table 17: Sensitivity and PPV of individual screening questions during census



	1	2	3	4	5	6	7	8	9
Sensitivity (%)	62.3%	75.9%	79.8%	74.1%	62.3%	52.6%	48.7%	37.3%	52.6%
PPV (%)	73.2%	66.0%	66.7%	70.1%	83.5%	84.5%	71.2%	69.7%	88.2%

Figure 15: Sensitivity and PPV of individual screening questions during census

Question	Positive responders (% of total)	Epilepsy present True positives	False negatives	Kappa statistic (κ)	Predictive ability
1	194 (49.1%)	142	86	0.30	Moderate
2	262 (66.3%)	173	55	0.23	Poor
3	273 (69.1%)	182	46	0.26	Poor
4	241 (61.0%)	169	59	0.31	Moderate
5	170 (43.0%)	142	86	0.44	Moderate
6	142 (35.9%)	120	108	0.37	Moderate
7	156 (39.5%)	111	117	0.21	Poor
8	122 (30.9%)	85	143	0.14	Very poor
9	136 (34.4%)	120	108	0.40	Moderate
1,5,6,9	287 (72.7%)	210	18	0.48	Moderate
5,3	298(75.4%)	203	25	0.34	Moderate
3,5,6	307 (77.7%)	209	19	0.35	Moderate
1,5	256 (64.8%)	193	35	0.48	Moderate
1,5,9	271 (68.6%)	203	25	0.50	Good
1,5,6,7,9	308 (78.0%)	216	12	0.42	Moderate

Table 18: Agreement between diagnoses and screening questions

When considering diagnoses of active epilepsy only, i.e. 209 diagnoses from 395 positive responders assessed and eighty-two known false negatives, the screening questionnaire performed with a sensitivity and PPV of 71.8% and 52.9% respectively.

The low specificity demonstrated in the pilot study raised concerns about the logistics of using this tool in a large population. In the event, a low response rate made an attempt at screening all positive responders feasible. Local key informants involved in the study also made a valuable contribution by identifying additional cases within their communities that had been missed by the census-based screening. A positive response to the screening questionnaire was generally a weaker predictor of a clinical diagnosis of epilepsy during the census than during the pilot study, with a sensitivity for epilepsy of 71.8% compared to 100%, and a PPV of 52.9% compared to 73.0% in the pilot study. On analysis of individual components of the screening questionnaire's performance in the field, no clear model emerged that might guide future studies using this instrument in African populations.

4.3.12 Crude and age-standardised prevalence of active epilepsy

All 291 active cases identified were suffering from convulsive epilepsy. The overall crude prevalence of ACE in the HDSS adult population on 1st June 2009 was therefore 2.82 per 1,000 adults (95% CI 2.50 to 3.15). As this study is concerned with adults only (i.e. aged fifteen years and above), the HDSS and WHO populations were weighted accordingly prior to age-standardisation (Table 19). To accommodate small numbers of cases in the older population, ages of seventy years and above were combined into a single age band. Age- and sex- specific prevalence rates are shown in Table 20 and summarised in Figure 16. While males had a significantly higher prevalence of epilepsy than females (3.19 vs. 2.50; difference in proportions of 0.69/1,000, 95% CI 0.03 to 1.34), this was marginal, and would not have been the case with two fewer male cases or two more female cases. The age-standardised prevalence of epilepsy in the adult HDSS population was 2.91 per 1,000 adults (95% CI 2.58 to 3.24).

Age band	HDSS population n	(%)	HDSS adult-weighted (%)	WHO (%)	WHO adult-weighted (%)
0-14	58,093	(36.1%)	-	26.2%	-
15-19	16,762	(10.4%)	16.3%	8.5%	11.5%
20-24	9,944	(6.2%)	9.7%	8.2%	11.1%
25-29	9,954	(6.2%)	9.7%	7.9%	10.7%
30-34	10,342	(6.4%)	10.0%	7.6%	10.3%
35-39	10,068	(6.3%)	9.8%	7.2%	9.7%
40-44	9,034	(5.6%)	8.8%	6.6%	8.9%
45-49	7,786	(4.8%)	7.6%	6.0%	8.2%
50-54	6,713	(4.2%)	6.5%	5.4%	7.3%
55-59	5,348	(3.3%)	5.2%	4.6%	6.2%
60-64	4,339	(2.7%)	4.2%	3.7%	5.0%
65-69	3,867	(2.4%)	3.8%	3.0%	4.0%
70+	8,869	(5.5%)	8.6%	5.3%	7.2%
All-ages	161,119	(100.1%)*	-	100.2%*	-
Adult population	103,026	-	100.2%*	-	100.1%*

*Totalss may not add up to 100% due to rounding

Table 19: Age distribution of HDSS and WHO populations, adult weighted

Age-band (years)	Female			Male			Total		
	Cases (n)	Denom. pop.* (n)	Prev./1,000 (95% CI)	Cases (n)	Denom. pop.* (n)	Prev/1,000 (95% CI)	Cases (n)	Denom. pop.* (n)	Prev./1,000 (95% CI)
15-19	23	8,114	2.83 (1.68 to 3.99)	19	8,648	2.20 (1.21 to 3.18)	42	16,762	2.51 (1.75 to 3.26)
20-24	25	5,225	4.78 (2.91 to 6.66)	36	4,719	7.63 (5.15 to 10.11)	61	9,944	6.13 (4.60 to 7.67)
25-29	23	5,487	4.19 (2.48 to 5.90)	14	4,467	3.13 (1.49 to 4.77)	37	9,954	3.72 (2.52 to 4.91)
30-34	12	5,381	2.23 (0.97 to 3.49)	18	4,961	3.63 (1.96 to 5.30)	30	10,342	2.90 (1.86 to 3.94)
35-39	9	5,216	1.73 (0.60 to 2.85)	13	4,852	2.68 (1.22 to 4.13)	22	10,068	2.19 (1.27 to 3.10)
40-44	10	4,800	2.08 (0.79 to 3.37)	17	4,234	4.02 (2.11 to 5.92)	27	9,034	2.99 (1.86 to 4.11)
45-49	13	4,156	3.13 (1.43 to 4.83)	11	3,630	3.03 (1.24 to 4.82)	24	7,786	3.02 (1.85 to 4.31)
50-54	7	3,727	1.88 (0.49 to 3.27)	7	2,986	2.34 (0.61 to 4.08)	14	6,713	2.09 (0.99 to 3.18)
55-59	6	2,911	2.06 (0.41 to 3.71)	8	2,437	3.28 (1.01 to 5.55)	14	5,348	2.62 (1.25 to 3.99)
60+	8	9,369	0.85 (0.26 to 1.45)	12	7,706	1.56 (0.68 to 2.44)	20	17,075	1.17 (0.66 to 1.68)
Total	136	54,386	2.50 (2.08 to 2.92)	155	48,640	3.19 (2.69 to 3.69)	291	103,026	2.82 (2.50 to 3.99)

*Denom.pop. – denominator population

Table 20: Age- and sex-specific prevalence of epilepsy in adults in the HDSS

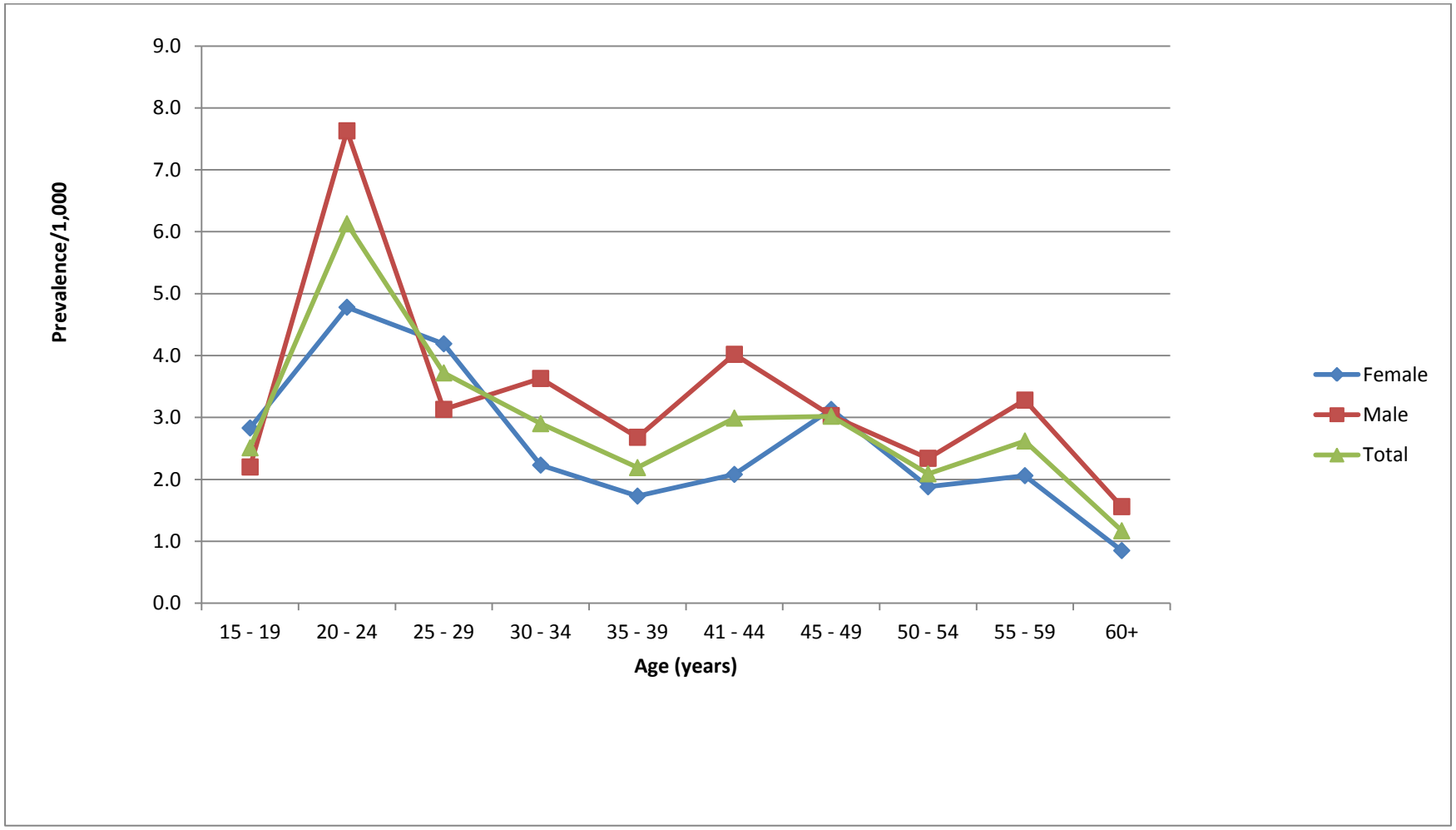


Figure 16: Graphical summary of crude prevalence rates of epilepsy in HDSS
(see Table 21 for 95% confidence intervals)

4.4.13 Crude prevalence adjusted for non-response and deferred diagnoses

There were 173 individuals who responded positively to the screening questionnaire who we were not able to assess clinically for the presence of epilepsy. Four of these were accounted for by data entry errors, one died prior to the prevalence date, and no precise dates of death were available for a further three who had died some time in 2009. The remaining 165 individuals may have been eligible for inclusion in the study had they been assessed, and by applying the PPV of 52.9% calculated for detection of active epilepsy by the screening questionnaire an estimated eighty-seven additional cases may have been missed. This would bring the total number of active cases to 378, giving a crude prevalence of 3.67 per 1,000 (95% CI 3.3 to 4.0).

Diagnoses were deferred in fourteen individuals (eight census positive responders, six identified by key informants), and four cases identified by other studies were not available for assessment by the epilepsy study team. If a diagnosis were also to be confirmed in these eighteen individuals the total case series would be 396, giving a crude prevalence of 3.84 per 1,000 (95% CI 3.47 to 4.22).

4.3.13 Lifetime prevalence

A diagnosis consistent with epilepsy in remission, i.e. no seizures for five years or more without AED treatment, was made in six cases: four census responders and two identified by village enumerators. Adding these to the observed series of 291 active cases would give an estimated crude lifetime prevalence of 2.88 per 1000 (95% CI 2.56 to 3.21). If the adjustments made above are included, the crude lifetime prevalence, based on 402 individuals, would be 3.90 per 1,000 (95% CI 3.52 to 4.27).

4.3.14 Distribution of cases

Prevalence by village had a non-normal distribution for the HDSS as a whole, within the Lowland geographic zone, within the Masama and Lyamungo divisions, within all eight wards, and within the forty-nine rural villages. Normal distributions were observed in the Upland and Umasaini zones, the Machame division and in all seven urban villages. As each grouping variable (division, ward, geographic zone or urban/rural) contained a mix of normal and non-normal distributions of prevalence, variance was therefore assessed non-parametrically. Descriptive and test statistics for prevalence within geographic zones, administrative divisions and urban and rural villages are given in Table 21. There was no significant variance in prevalence within any of these groups, suggesting that clustering of epilepsy is unlikely in the Hai population.

The crude estimated prevalence for epilepsy in the HDSS based on case-ascertainment only (i.e. no adjustment for non-response) was 2.82/1,000. This was applied to the adult population in each village to generate an expected number of cases. This was then used as the denominator to be compared with the observed number of cases for each village to generate rho statistics (ρ). The distribution of ρ was normal within geographic zones, administrative divisions and within urban and rural villages, but not within administrative wards. Means for normally distributed values of ρ were therefore compared parametrically using ANOVA for geographic zones and administrative divisions and Student's independent t-test for urban and rural villages; interpretation of the t-test was based on Levene's test for equality of variance within the two groups (Field, 2009b). Within administrative wards ρ was compared non-parametrically using the Kruskal-Wallis test. Descriptive and test statistics are given in Table 22 and Table 23. As with prevalence, there were no significant differences observed between any divisions within the HDSS, suggesting that case ascertainment had been uniform and proportional to the local study populations. The raw data by for these calculations, by village, are given in Appendix X.

		Villages	Prevalence/1,000				
		(n)	Median	Min	Max	IQR	Test statistic
Geographical zone	Upland	34	2.53	0.00	6.24	1.91	Kruskal Wallis H(2)=0.482; p=0.786
	Lowland	14	2.82	0.00	2.85	0.02	
	Umasaini	8	2.80	2.77	2.83	0.04	
Administrative division	Lyamungo	18	2.82	0.00	6.24	0.85	Kruskal-Wallis H(2)=0.725; p=0.711
	Machame	9	2.91	0.51	5.65	2.02	
	Masama	29	2.81	0.00	60.2	0.39	
Administrative ward	Lyamungo Machame Kusini	9	2.83	0.00	2.85	0.02	Kruskal-Wallis H(7)=4.033; p=0.800
	Machame Kaskazini	4	2.75	2.02	3.75	1.38	
	Machame Magharibi	2	3.08	0.51	5.65	N/A*	
	Machame Mashariki	9	2.26	0.00	6.24	1.85	
	Machame Uroki	3	3.23	2.22	4.53	N/A*	
	Masama Kusini	12	2.82	2.77	2.83	0.03	
	Masama Magharibi	10	2.81	0.57	6.02	3.49	
	Masama Mashariki	7	2.51	0.00	4.11	1.28	
Urban/Rural	Urban	7	2.83	2.81	2.85	0.02	Mann-Whitney U U=1.22, z=-1.226; p=0.233
	Rural	49	2.80	0.00	6.24	0.85	

*n<4 therefore quartiles not calculated

Table 21: Epilepsy distribution by geographical and administrative division of HDSS

		Villages	ρ (observed cases/expected cases)		
		(n)	Mean	Standard deviation	Test statistic
Geographical zone	Upland	34	0.97	0.57	ANOVA F(2,53)=0.766; p=0.470
	Lowland	14	1.04	0.74	
	Umasaini	8	0.72	0.38	
Administrative division	Lyamungo	18	0.93	0.66	ANOVA F(2,53)=0.243; p=0.785
	Machame	9	1.08	0.53	
	Masama	29	0.93	0.58	
Urban/Rural	Urban	7	1.23	0.82	Levene's test. F(1,54)=3.043; p=0.087 Independent t-test (equal variance assumed). t(54)=1.48; p=0.146
	Rural	49	0.91	0.55	

Table 22: Uniformity of case ascertainment: parametric

		Villages	ρ (observed cases/expected cases)				
		(n)	Median	Min	Max	IQR	Test statistic
Administrative ward	Lyamungo Machame Kusini	9	0.92	0.00	1.88	1.46	Kruskal-Wallis F(7)=1.440, p=0.987
	Machame Kaskazini	4	0.98	0.71	1.33	0.49	
	Machame Magharibi	2	1.09	0.18	2.00	N/A*	
	Machame Mashariki	9	0.81	0.00	2.19	0.66	
	Machame Uroki	3	1.15	0.79	1.59	N/A*	
	Masama Kusini	12	0.82	0.00	2.55	0.64	
	Masama Magharibi	10	0.92	0.20	2.12	1.27	
	Masama Mashariki	7	0.89	0.00	1.46	0.45	

* n<4 therefore quartiles not calculated

Table 23: Uniformity of case ascertainment: non-parametric

4.4 Discussion

This study is one of the largest community-based surveys of the prevalence of epilepsy in an adult population to have been conducted in SSA to date. The age-standardised prevalence for active ACE in adults of 2.91/1,000 (95% CI 2.58 to 3.24) and crude prevalence adjusted for non-response of 3.84/1,000 (95% CI 3.47 to 4.22) are considerably lower than both the median prevalence for all epilepsies of 15/1,000 previously reported from SSA (Preux and Druet-Cabanac, 2005), and the range for active prevalence of 8.0 to 10.0/1,000 previously reported from Tanzania (Winkler et al., 2009c, Rwiza et al., 1992, Dent et al., 2005). They are however in line with a recent study of comparable size and design in a rural Kenyan population which found a crude prevalence of 2.9/1,000 (95% CI 2.6 to 3.2), rising to 4.5/1,000 (95% CI 4.1 to 4.9) after adjustment for non-response and sensitivity (Edwards et al., 2008). This latter study sought to identify ACE only, and the lower prevalence figures of both studies may reflect this.

Studies from Europe and the USA have identified peaks in the incidence of epilepsy in young children and in the elderly (Cockerell et al., 1995, Banerjeea et al., 2009, Hauser et al., 1993). We did not find a peak in prevalence in those aged sixty or above, although this age group represents only 10.6% of the total HDSS population and it is difficult to draw comparisons with populations from HICs which have very different population structures. We did find a peak in prevalence of 6.13/1,000 in those aged between twenty and twenty-four years, with a concentration of male cases in this age group (crude prevalence in males 7.63/1,000). This is in keeping with a higher prevalence in adolescents and young adults identified by other studies in rural SSA (Preux and Druet-Cabanac, 2005, Edwards et al., 2008, Dent et al., 2005, Winkler et al., 2009c, Rwiza et al., 1992). Whether the lower prevalence in later adult life points to early mortality or spontaneous remission remains unclear (Edwards et al., 2008). A similar distribution in both the active and lifetime prevalence of epilepsy has been observed elsewhere in Tanzania, suggesting that those in remission may not report their previous seizures (Rwiza, 1994, Rwiza et al., 1992). Conversely there is mounting evidence of early mortality in epilepsy in LMICs in excess of that seen in HICs (Ding et al., 2006). Observational studies suggest that this is likely to be

the case in SSA (Snow et al., 1994, Jilek-Aall and Rwiza, 1992, Diop et al., 2005), although there are presently very few formalised data with comparable standardised mortality ratios to confirm this (Diop et al., 2005).

In community-based studies from SSA heterogeneity of prevalence within study populations has frequently been observed (Preux and Druet-Cabanac, 2005, Edwards et al., 2008, Rwiza et al., 1992). Whether this reflects clustered exposure to environmental or genetic risk factors or a tendency for PWE to live closer to locally available treatment services remains unclear. In our study case ascertainment was grossly uniform across administrative divisions, and there was no observation of clustering based on analyses of variance within geographic and administrative divisions of the HDSS.

We found a higher prevalence in males than in females, although the difference was marginal. A review of nineteen studies of the prevalence in SSA in which data on gender were available found a mean ratio of males to females of 1.4:1, although this difference was significant in only a quarter of studies (Preux and Druet-Cabanac, 2005). While it has been suggested that a higher prevalence of epilepsy in males in Tanzania may reflect a higher risk of cranial trauma through a tendency to engage in more dangerous occupations (Dent et al., 2005), other studies from Tanzania have found higher proportions of females with epilepsy (Rwiza et al., 1992, Winkler et al., 2009c). It has been postulated that this may be accounted for by a higher mortality rate among males, again because of dangerous occupations (Rwiza et al., 1992), although Tanzania is a country with a high maternal mortality rate and the strength of this argument could be questioned (Janson, 2007). It has also been observed that the women in one study population appeared to be more health-conscious then men (Winkler et al., 2009c). The authors suggest that being accustomed to attending maternity and child-care clinics and speaking openly about health issues may contribute to higher ascertainment rates in women. Overall there remains no clear consensus on whether observed differences between the sexes in the prevalence of epilepsy in SSA are due to gender-specific aetiological factors, bias arising through artefact in case-ascertainment or competing mortality risks (Birbeck and Kalichi, 2004).

While our pilot study established the sensitivity of the screening tool in a Kiswahili-speaking Tanzanian population, a field-based validation study with complete ascertainment in a larger sample would have facilitated a sensitivity analysis of the screening questionnaire and would also have allowed us to comment on the likely prevalence of non-convulsive epilepsies, given that these were not detected by our screening protocol. Epilepsy with non-convulsive seizures can account for up to 50% of all epileptic disorders in community-based studies (Cockerell et al., 1995, Banerjeea et al., 2009); only cases of convulsive epilepsy were detected in our study, despite the aim of detecting all seizure types, and the true prevalence of all epilepsies in the Hai population may therefore approach 6/1,000.

Community-based studies from Zambia and Tanzania have used modified versions of the screening instrument used in the Hai study. In Zambia, three additional questions were used to reduce the false-positive rate due to detection of febrile and malaria-associated seizures in children under the age of seven years (Birbeck and Kalichi, 2004). The paediatric study in the HDSS excluded children under the age of six years for this reason (Burton et al., 2012a), and these additional questions were therefore not used in our study. Elsewhere in Tanzania, a fifteen-item instrument based on the Ecuador questionnaire has been used (Winkler et al., 2009c), although results of this study were not available at the time of planning and initiating our population census. In this study only one case of non-convulsive seizures was identified out of a total of eighty-three cases of epilepsy. We anticipated difficulties with at least one of the specific screening questions (Question Eight) which may have picked up non-convulsive seizures, and sought to address these prior to the census through focus group work with the census enumerators (section 4.4.1 of this chapter and 3.4.1 of Chapter 3). The fact that no non-convulsive epilepsy was detected despite these efforts supports the suggestion that screening on this scale in rural SSA should focus on convulsive epilepsies only (Edwards et al., 2008, Ngugi et al., 2013b). The difficulties of identifying focal-onset epilepsies without secondary generalisation in community-based studies in SSA have previously been acknowledged and reflected in study design (Edwards et al., 2008), and our experience in Hai supports this approach.

Nearly one third of individuals (30.5%) who responded positively to the screening questionnaire were not available for clinical assessment. While this decreases the internal validity of our study and must be acknowledged as a limitation, Hai is an established DSS and this high rate of non-attendance may also reflect the degree of stigma associated with epilepsy in this population (Mushi et al., 2010). Such factors may also have contributed to non-response at census by the eighty individuals with epilepsy who were identified by key informants. While an investigation of such factors was not included in the design of this study, further assessment of this group of individuals may yield further insights as to the performance of the screening questionnaire and of the screening methodology as a whole. The use of capture-recapture techniques has previously been used to maximise case-ascertainment of non-communicable diseases in a clinic-based setting in South Africa (Gill et al., 2001), although has been less successful in community-based settings in Tanzania, including Hai (Black et al., 1994), and was not pursued in our study.

We report here on the prevalence of epilepsy in adults only, and the estimate has been age-standardised to facilitate comparison with other studies. The crude prevalence in children over the age of six years in the same population was 2.91 per 1,000 (Burton et al., 2012a).

4.5 Summary and conclusions

Active epilepsy with convulsive seizures has a lower prevalence in this part of Tanzania than elsewhere in SSA. The previously reported high prevalence rates for epilepsy in SSA cannot be generalised, either within Tanzania, or to the region as a whole.

Chapter 5. Convulsive epilepsy in the HDSS

Abstract

Background

Comparison of findings from different study populations of PWE has been difficult due to incompletely described clinical details, and few studies of epilepsy from SSA benefit from investigation with neuro-imaging or electrophysiology. Epilepsy is a highly stigmatised condition in SSA and PWE are known to suffer exclusion across major life domains.

Methods

Clinical, demographic and socio-economic details were collected from 291 adults with active epilepsy in the HDSS. Clinical details were correlated with CT imaging and EEG. Seizures and epilepsies were classified according to internationally recognised criteria.

Results

All PWE identified had convulsive epilepsy: 208 (71.5%) had focal epilepsy and eight (2.7%) had generalised epilepsy; seizures and epilepsies remained unclassified in seventy-five (25.8%) cases. Co-morbidities included cognitive impairment in eighty-nine (30.6%) cases, motor impairment in forty-eight (16.5%) cases, and seizure-related burns in seventy-six (26.1%) cases; disability due to seizure-related injuries was observed in twenty-one (7.2%) cases. One fifth of all cases (20.7%) had no formal education, with this being significantly associated with epilepsy that began before school age. The majority of cases aged nineteen years and above remained unmarried (58.5%), and being single was significantly associated with epilepsy that had started before nineteen years of age. Nearly one quarter of cases (24.1%) were economically inactive due to perceived illness or disability.

Conclusions

CT and EEG aided in the classification of epilepsies in this population. Rates of co-morbidity with neurological impairments and seizure-related injury are high. PWE living in the HDSS are marginalised, and exclusion from education and marriage is correlated with a younger age at onset of epilepsy.

5.1 Introduction

The comparison of epidemiological studies of epilepsy, whether conducted in HICs or LMICs, can be complicated by the application of different definitions of epilepsy or by a lack of clinical details to qualify diagnoses (Thurman et al., 2011), (Sander, 2003, Sander and Shorvon, 1996). This is especially true of studies that have been conducted in SSA (Preux and Druet-Cabanac, 2005). Generalised seizures have been the most commonly reported seizure type worldwide, although it has been suggested that careful application of seizure classifications and the use of EEG may reveal many of these to be focal onset seizures, with or without secondary generalisation (Sander and Shorvon, 1996). While proportions of generalised seizures as high as 88% have been reported (Li et al., 1985), other studies in which routine investigations have been available, such as the United Kingdom National General Practice Study of Epilepsy, have reported partial seizures in 52% of patients and generalised seizures in 39%, with the remainder being unclassifiable (Sander et al., 1990). A recent review of the records of over 2,000 PWE identified in thirteen studies from twelve African countries (Quet et al., 2011). Generalised epilepsy was reported in 65.9% of cases, focal epilepsy in 33.8%, with the remainder being unclassified. The proportion of generalised epilepsy accounted for by focal-onset seizures becoming secondarily generalised is not clearly expressed. Although rates of focal-onset seizures have been higher in African countries, accounting for between 59.4% and 74.3% of all cases, with up to 44.7% of these becoming secondarily generalised (Senanayake and Roman, 1993), community-based studies from SSA have found a predominance of generalised tonic-clonic seizures, accounting for around 60% of all cases (Preux and Druet-Cabanac, 2005). This figure may be biased by the use of screening methodologies based on interviewing undiagnosed cases or their families in the community, which will tend to detect more easily recognised seizure types (Sander and Shorvon, 1987, Ottman et al., 2010, Placencia et al., 1992a).

Three community-based studies from Tanzania over the past twenty years have provided details on seizure classification and aetiology (Dent et al., 2005, Rwiza et al., 1992, Winkler et al., 2009c). In the first of these, conducted in 1989, contemporary ILAE criteria were applied to 207 PWE (Commission on Classification and Terminology of the International

League Against Epilepsy, 1981, Rwiza et al., 1992). Partial seizures accounted for 31.9% of all cases, with seizures becoming secondarily generalised accounting for 22.2% of cases overall. Generalised onset seizures accounted for 58.0% of all seizures, with tonic-clonic seizures accounting for 54.1% of seizures overall. Possible aetiological factors were identified in 25.3% of cases, with febrile convulsions and unspecified encephalitis being the most commonly reported. A study conducted in 1999 applied updated ILAE criteria to forty-two PWE (Dent et al., 2005, Commission on Classification and Terminology of the International League Against Epilepsy, 1989). In this cohort 71.4% of cases had generalised seizures, although further details are limited, and 28.6% had partial seizures. Half of these (14.3% overall) had partial seizures becoming secondarily generalised. In this study a probable aetiology for the epilepsy was identified in 26.2% of cases, including trauma, cerebral malaria, meningitis and other cerebral infections. No EEGs or neuro-imaging were available to aid in diagnosis or classification in either of these studies. Finally, a study from northern Tanzania conducted between 2003 and 2004 identified eighty-three PWE in a remote rural population, of whom sixty-four had active epilepsy (Winkler et al., 2009c). The authors apply their own classification system (Winkler et al., 2008b). This makes comparison with other studies difficult, although it appears that 44.6% of cases had generalised epilepsy and 21.7% cases had generalised seizures with clinical findings suggestive of a focal onset. While no EEGs were performed, some cases from this study were investigated with CT head scans as part of a study of cysticercosis in epilepsy (Winkler et al., 2009b). The findings of this study are discussed in more detail in Chapter Eight. None of these three studies discusses the prevalence of HIV or its possible contribution to the prevalence of seizure disorders within their study populations.

Numerous causes and risk factors for epilepsy peculiar to populations in SSA have been described, with a focus largely on infectious aetiologies (Senanayake and Roman, 1993, Preux and Druet-Cabanac, 2005). Associations between epilepsy and viral encephalitis, meningitis, parasitic infections, cerebral malaria and HIV have all been well described (Misra et al., 2008, Furyk et al., 2011, Garcia and Del Brutto, 2005, Singhi, 2011, Singh and Prabhakar, 2008, Ngoungou and Preux, 2008, Bhigjee, 2005), although given the descriptive nature of most studies from SSA, the relative contribution of any given

aetiological factor is difficult to determine (Preux and Druet-Cabanac, 2005). In such studies risk factors have been identified in around 50% of cases (Preux and Druet-Cabanac, 2005, Quet et al., 2011). In HICs cerebrovascular disease has been identified as the leading cause of epilepsy in older people (Kramer, 2001, Myint et al., 2006), with up to 11.5% of patients with strokes developing seizures within five years (Myint et al., 2006). This issue has yet to be comprehensively studied in SSA, but with ageing populations and a demographic transition towards more urbanised lifestyles this may become more important as an aetiology of epilepsy in this region (Walker et al., 2010, Walker et al., 2000a).

Familial clustering of epilepsy or high rates of PWE giving a family history of epilepsy have been noted in a number studies from Africa (Neuman et al., 1995, Winkler et al., 2009c, Edwards et al., 2008). Genetic epilepsies are thought to have a complex mode of inheritance, and genes identified so far account for only a minority of families and sporadic cases (Gutierrez-Delicado and Serratosa, 2004). A number of neurodevelopmental disorders which do have familial patterns of inheritance, including neuro-cutaneous disorders such as neurofibromatosis and tuberous sclerosis, may feature symptomatic epilepsy as part of their presentation (Kullmann, 2002). While there have been retrospective, hospital-based series of such disorders from Africa (Aiyesimoju et al., 1984, Amir et al., 1993), to the best of our knowledge there are no systematic community-based data on the prevalence of these disorders in SSA. Similarly, we know of no large-scale genetic studies utilising human DNA to examine the inheritance of epilepsy in communities from SSA.

Injuries, including burns and scalds, have long been recognised as a risk for PWE (Hampton et al., 1988), with 16% of 302 PWE in a UK series having reported receiving burns over the course of one year (Buck et al., 1997). In Africa this has been noted as a particular problem, with burns having been described as “an unrecognised epidemic” (Nuss et al., 1974). A hospital-based series from South Africa found that 50% of patients presenting with burns had epilepsy, 40% of whom had presented with burns previously (Allorto et al., 2009).

Epilepsy in SSA is often associated with considerable stigma, particularly in poorer or rural areas (Baskind and Birbeck, 2005b). In spite of a high degree of awareness of epilepsy among people in LMICs, misconceptions abound, meaning that PWE in such communities are less likely to be sent to school, find employment or to marry (Radhakrishnan, 2009), (Birbeck et al., 2007, Birbeck and Kalichi, 2003). While some social limitations experienced by PWE in LMICs may relate to underlying brain disorders which may manifest as cognitive impairments or behavioural disorders as well as seizures, studies of stigma in epilepsy in SSA have nevertheless identified a high level of enacted as opposed to felt stigma (i.e. externally imposed discrimination) (Baskind and Birbeck, 2005b, Winkler et al., 2010b).

5.2 Methods

Cases of active epilepsy identified during the prevalence survey were interviewed and examined in detail, as described in Chapter Four. Data were collected on age of onset and duration of epilepsy, manifestations of seizures including prodromal features, timing of seizures, any reported antecedent history that may constitute a risk factor for acquired epilepsy, and family history of seizures.

Following the interview all cases received a full physical examination including a detailed neurological examination. Formal cognitive testing was not performed, but where any degree of cognitive impairment or learning difficulty was apparent this was classified as mild, moderate or severe as follows:

- *Mild* - some impairment, causing either no or only mild restrictions in daily life; most of the time they are independent.
- *Moderate* – clear restriction in daily life, but only partly depends on relatives/others.
- *Severe* – fully dependent on relatives/others at all times.

This classification was recommended through personal communication with another research team with extensive experience of diagnosing and managing epilepsy in Tanzania, and was developed as part of a proposed alternative classification system for epilepsy designed to be of greater clinical utility in resource-limited settings (Winkler et al., 2008b).

CT head scans were performed with and without contrast on a Philips Tomoscan 4000 machine. All scans were reported locally to exclude any acute pathology that might require urgent further investigation or management. CT films were then transported as hard copy to the UK to be digitised and reported in the UK by Dr Daniel Birchhall, a consultant neuro-radiologist at the Royal Victoria Infirmary in Newcastle. All identified pathologies were reported. Specific details on the radiologic criteria used in the diagnosis of neurocysticercosis are described in Chapter Eight.

EEGs were performed using a Neohen Kohden Neurofax 11000K, a PC-based thirty-six channel system. The project nurse is trained and experienced in the use of this machine. Patients had waking EEGs that included recording during hyperventilation and photo-stimulation. EEGs were recorded over thirty minutes using a standard twenty lead montage. Recordings were stored electronically locally and transferred to compact disc for transport to the UK where they were reported by Dr Roger Whittaker, a consultant neurophysiologist also working at the Royal Victoria Infirmary, Newcastle. EEGs were reported using a standard format (Marson et al., 2007b, Marson et al., 2007a). There were no facilities for reporting EEGs locally.

Following completion of case-ascertainment all case histories were reviewed in the UK by Dr Margaret Jackson, a consultant neurologist who specialises in epilepsy. Cases were initially reviewed on the basis of the recorded clinical history alone and without the benefit of any further investigations that may have been performed. All cases in which a clinical diagnosis of epilepsy was confirmed were classified according to current ILAE recommendations for the clinical classification of seizures. Following clinical classification all cases were reviewed with EEG and CT findings to hand and further classified, as far as possible, according to electro-clinical syndrome and aetiology, again according to current recommendations from the ILAE (Berg et al., 2010, Thurman et al., 2011).

Categorical data on tribal group, religion, and educational, marital and occupational status were collected, as described in Chapter Two, section 2.4.2. Education has been free and compulsory from the age of eight years in Tanzania since 1976. This age was therefore used as a cut-off for being of pre-school age when considering access to education. On discussion with local staff and people in the villages it seemed that young people could traditionally expect to get married from the age of nineteen years onwards, and this was therefore chosen as a cut-off when examining the effect of age of onset of epilepsy and marital status.

Data presented in this chapter are largely descriptive. The chi-square test was used to compare categorical variables, and non-parametric comparisons between non-normally distributed continuous variables were made using the Mann-Whitney U test.

5.3 Results: clinical

5.3.1 Age of onset and duration of epilepsy

Data on age of onset and duration of seizures were available for 284 (97.6%) of 291 cases (Table 24, Figure 17, Figure 18); neither of these variables was normally distributed. There was no significant difference between the sexes for in age of onset (Mann-Whitney U=8986.0, z=-1.516, p=0.129), or duration of epilepsy (Mann-Whitney U=9673.0, z=-0.520, p=0.603).

5.3.2 Manifestations of seizures: prodrome, automatisms and timing

All 291 cases identified gave a history consistent with convulsive epilepsy. Of these, 117 (40.2%) gave a history suggestive of an aura or prodrome of which the patient was subjectively aware (Table 25). The category 'non-specific awareness' refers to cases who clearly recognised stereotypical prodromal events but found these difficult to describe in such a way as could be easily categorised. These include various bodily sensations (e.g. warmth, cold, numbness, headache or nausea), psychological disturbance (e.g. feelings of intense fear, anxiety or elation) or cases where the patient was aware of impending seizures but was unable to further characterise any defining sensations. Cases where the patient was unable to give a history due to cognitive impairment, but where eye witnesses described changes in behaviour prior to a seizure that could be taken to indicate awareness, such as holding on to furniture or other people, were also included in this category. The relative proportions of reported prodromal features are summarised graphically in Figure 19.

Behavioural features possibly suggestive of automatisms were reported in sixty-eight (23.4%) of 291 cases (Table 26). Behavioural features such as smacking lips, chewing, and picking at clothing or unseen objects were classed as mild automatisms, while shouting loudly, undressing or wandering off were classed as being seriously disruptive.

There was a clear diurnal pattern of seizures in 164 (56.4%) of 291 cases, with forty-eight (29.3 %) of these reporting nocturnal seizures only (Table 27).

			Range			
		n	Median	Min	Max	Inter-quartile range
Age of onset (years)	Female	132	11.0	<1	66	16.0
	Male	152	14.0	<1	81	22.0
	Total	284	13.0	<1	81	19.5
Duration epilepsy (years)	Female	132	16.0	1	54	11.0
	Male	152	16.0	<1	51	16.0
	Total	284	16.0	<1	54	13.8

Table 24: Age of onset and duration of epilepsy in years

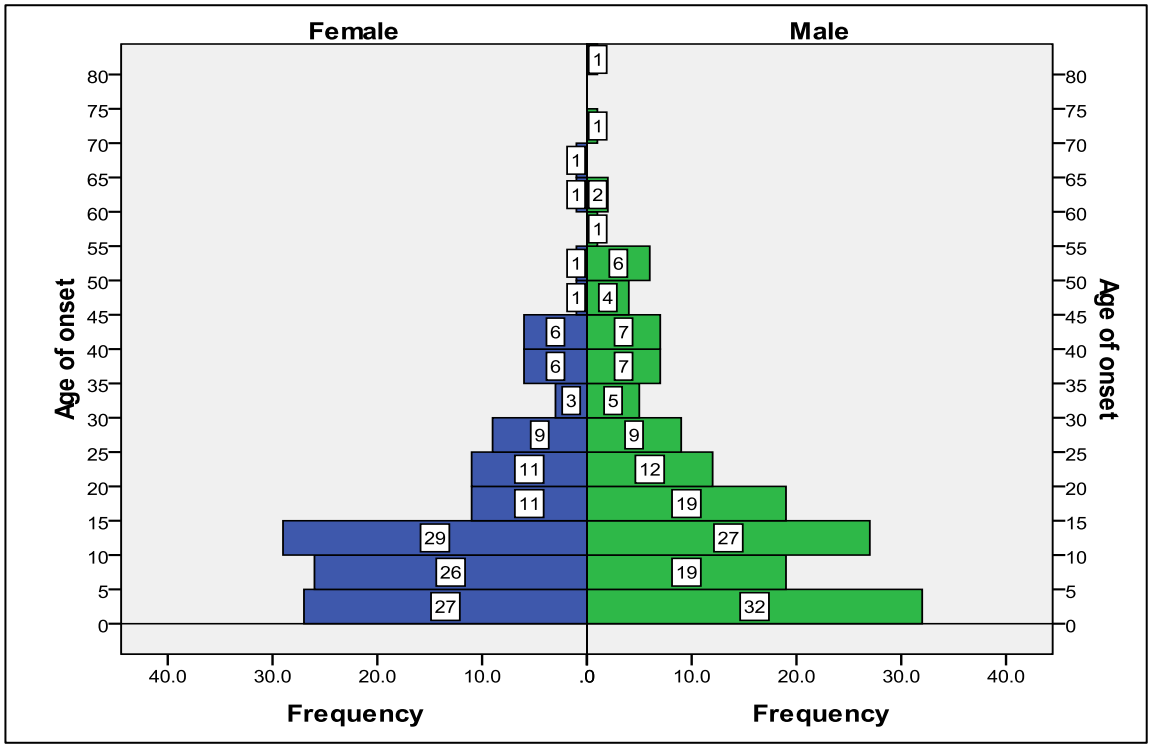


Figure 17: Age of onset of epilepsy

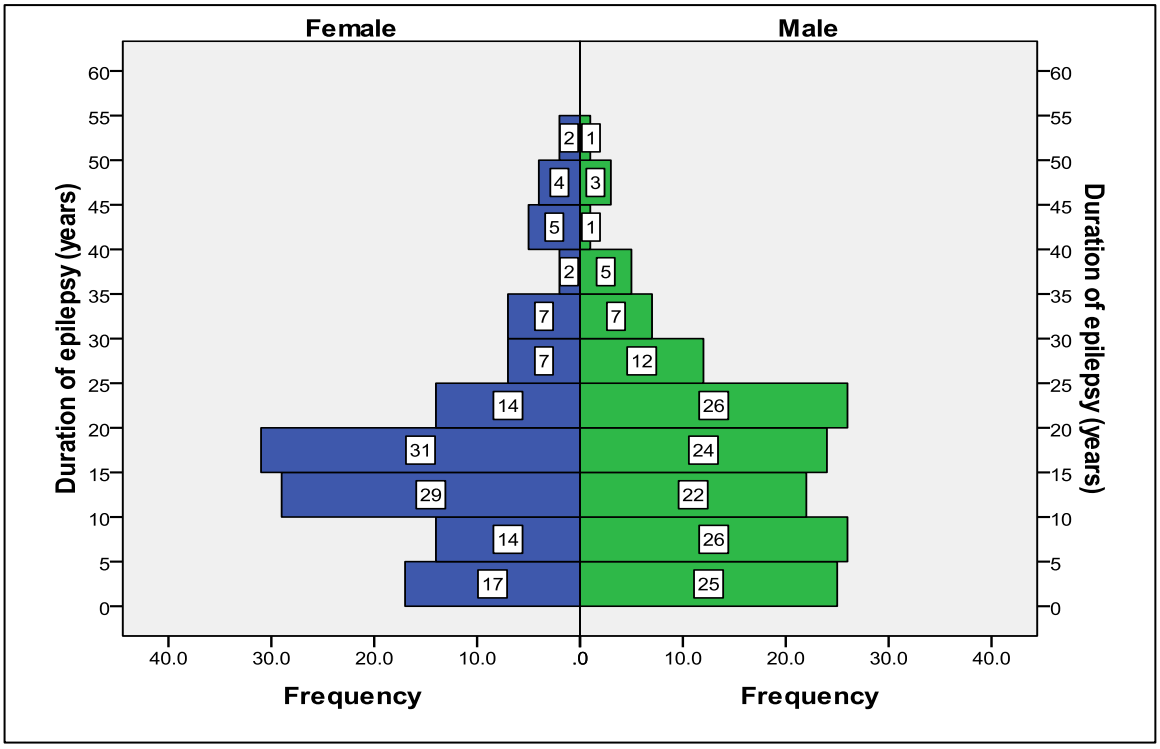


Figure 18: Duration of epilepsy

	Female (n=136)		Male (n=155)		Total (n=291)	
	n	**(% of females)**	**n**	**(% of males**	**n**	**(% of total)**
None reported	87	(64.0%)	87	(56.1%)	174	(59.8%)
Non-specific	26	(19.1%)	33	(21.3%)	59	(20.3%)
Gastric	10	(7.4%)	9	(5.8%)	19	(6.5%)
Visual	3	(2.2%)	9	(5.8%)	12	(4.1%)
Motor onset	3	(2.2%)	7	(4.5%)	10	(3.4%)
Auditory	6	(4.4%)	3	(1.9%)	9	(3.1%)
Olfactory	1	(0.7%)	7	(4.5%)	8	(2.7%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 25: Prodromal events reported by cases

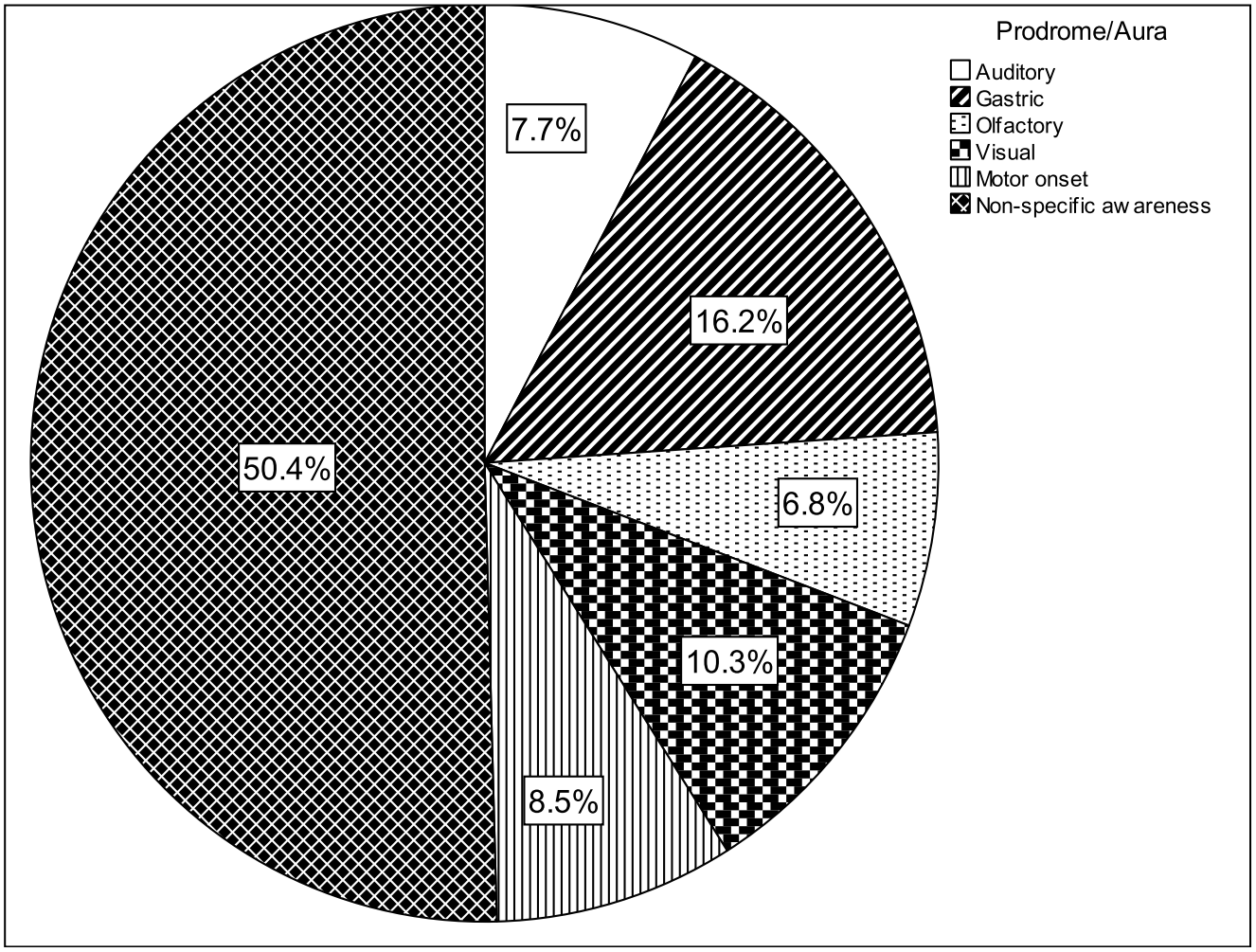


Figure 19: Relative proportions of reported prodromal features

	Female (n=136)		Male (n=155)		Total (n=291)	
Automatisms	**n**	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total)**
None reported	104	(76.5%)	119	(76.8%)	223	(76.6%)
Mild	25	(18.4%)	23	(14.8%)	48	(16.5%)
Seriously disruptive	7	(5.1%)	13	(8.4%)	20	(6.9%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 26: Numbers of cases with history suggestive of automatisms

	Female (n=136)		Male (n=155)		Total (n=291)	
Timing	**n**	**(% of females)**	**n**	**(% of males**	**n**	**(% of total**
Day	40	(29.4%)	76	(49.0%)	116	(39.9%)
Night	24	(17.6%)	24	(15.5%)	48	(16.5%)
Both day and night	72	(52.9%)	55	(35.5%)	127	(43.6%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 27: Timing of seizures

5.3.3 Associated clinical features: cognitive and motor impairments

A degree of cognitive impairment was observed in eighty-nine (30.6%) of 291 cases, and was classed as mild in forty-three (48.3%) individuals, moderate in eighteen (20.2%) and severe in twenty-eight (31.5%). The onset of cognitive impairment could be defined in fifty-nine (66.3%) cases, with forty (67.8%) of these describing cognitive impairment arising either at or subsequent to the onset of seizures. In thirty-five (39.3%) cases with cognitive impairment there was also associated motor impairment. Findings other than motor impairment that were seen in association with cognitive impairment included features consistent with Down's syndrome (two cases), tuberous sclerosis (one case) and neurofibromatosis (one case).

Motor impairment was observed in a total of forty-eight (16.5%) of 291 cases, thirty-five (72.9%) of which presented with an upper motor neurone (UMN) pattern of weakness associated with cognitive impairment. In a further thirteen (27.1%) cases, motor impairment was not associated with cognitive impairment. Seven (53.8%) of these had an UMN hemiparesis only, of which four were apparent from birth or early childhood with no clear cause, one was associated with congenital hydrocephalus, one was presumed secondary to an undefined febrile illness with coma in childhood and one was secondary to a previous traumatic head injury. Three cases had an UMN hemiparesis associated with ipsilateral sensory loss of which two were related to previous traumatic head injury, the other being apparent from early childhood with no clear cause. Of the remaining three cases, one had an UMN hemiparesis and dysphasia secondary to a cerebrovascular accident (CVA) in adulthood, although epilepsy had been present prior to the CVA, one had gross generalised UMN signs presumed secondary to a previous febrile illness associated with coma, and one had a unilateral lower limb lower motor neurone (LMN) weakness secondary to previous trauma sustained in a road traffic accident. This last case had also suffered a traumatic head injury at the same time, but did not manifest any UMN signs, sensory loss or cognitive impairment.

5.3.4 Other associated clinical findings

Relevant examination findings other than cognitive or motor deficits were as follows: evidence of previous traumatic head injury (five cases, Figure 21), bi-temporal hemianopia (one case), dysmorphic features and fused digits consistent with a cranial synostosis such as Apert's syndrome (one case, diagnosis unconfirmed), facial port-wine stain in keeping with Sturge-Weber syndrome (one case, Figure 21), optic atrophy with visual loss secondary to intracerebral neoplasm (one case), Parkinsonian tremor presumed secondary to monthly depot injections with antipsychotic medication used to treat seizures (one case), benign essential tremor (one case), and intraocular calcification (one case). Two female patients were pregnant at the time of assessment.

Two (0.7%) of 291 cases revealed that they were HIV positive. The first of these (female, aged 29 years), had suffered seizures since early childhood and had been diagnosed with HIV at the age of twenty-eight on routine testing. At the time of initial assessment by the epilepsy study she had yet to start anti-retroviral therapy, and manifested no outward clinical features suggestive of advanced immune suppression; she had a recent CD4 count of 261 cells/mm^3 and was maintained on co-trimoxazole prophylaxis. This patient died before she could be followed up at an interval of four months from initial assessment; it was reported locally that she had suffered a diarrhoeal illness, presumed to be HIV-related. The second HIV-positive patient (male, aged thirty-seven years) had also suffered seizures since childhood and had been diagnosed with HIV at the age of thirty-four after presenting for voluntary counselling and testing. At the time of initial assessment by the epilepsy study he was well, with no signs of immune suppression, was on no treatment related to HIV, and had a recent CD4 count of 1,333 cells/mm^3. Given the very high CD4 count his HIV status was re-confirmed at the time of initial assessment by the epilepsy study.

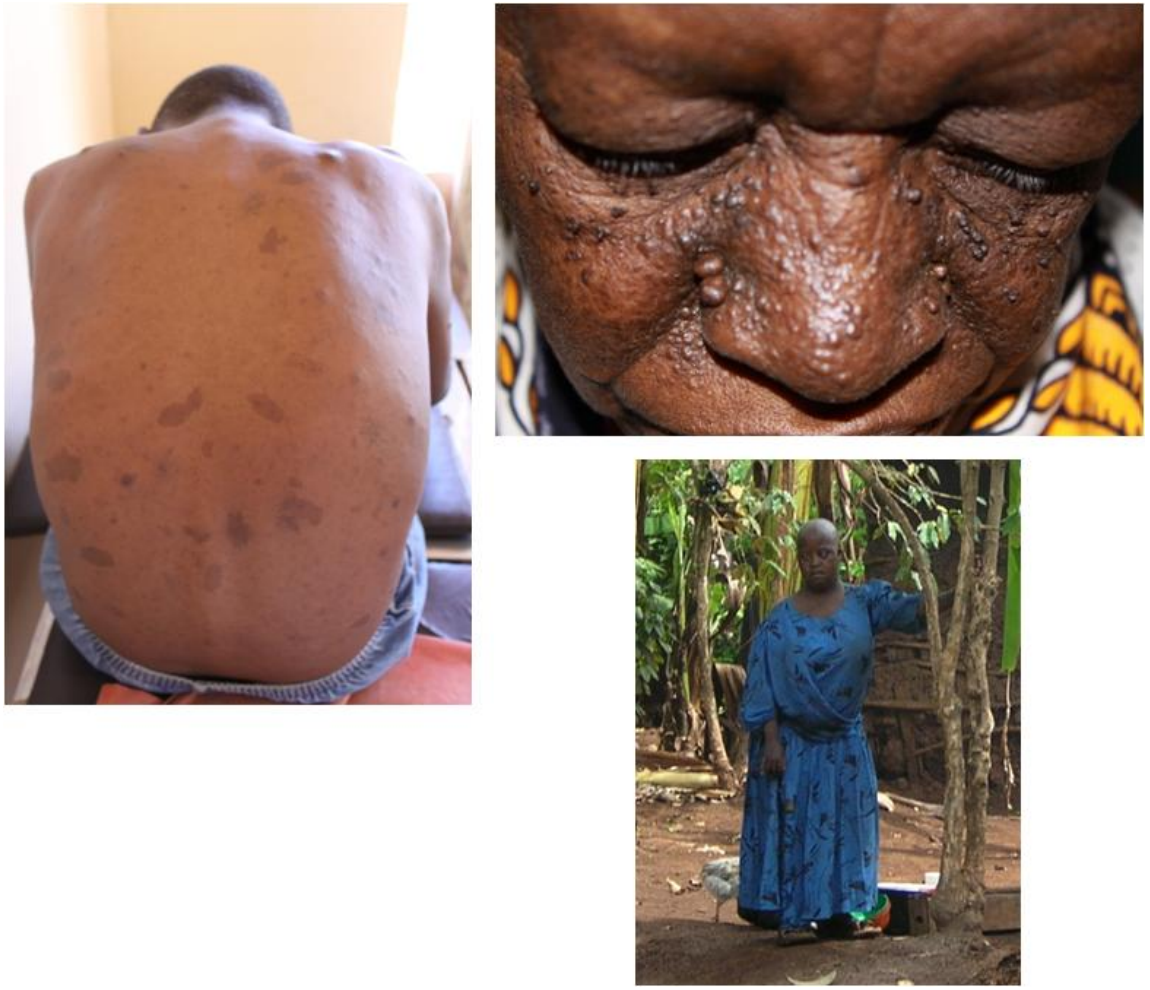


Figure 20: Clinical features in patients with epilepsy and cognitive impairment.

Clockwise from left: dermal fibromas and cafe-au-lait patches suggestive of neurofibromatosis, adenoma sebaceum suggestive of tuberous sclerosis (this patient also had ash leaf macules), typical features of trisomy 21 (Down's syndrome).

Figure 21: Associated clinical findings in epilepsy patients.
Left: Sturge-Weber syndrome.
Right: Childhood head injury from a *jembe* (agricultural hoe)

Figure 22: Congenital abnormalities seen in one epilepsy patient

Note fused digits, left 3rd cranial nerve palsy, dysmorphic facies and cystic swelling lateral left thigh. The patient had no apparent cognitive, motor or sensory deficits.

5.3.5 Seizure-related injuries

Seizure-related injuries were seen or reported in 256 (88.0%) of 291 cases: 123 (90.4%) of 136 females and 133 (85.8%) of 155 males. The slightly higher rate of injuries seen in females was not significant ($\chi^2(1)=1.47$, p=0.225); types of injury are summarised in Table 28. While the high rates of injury reported are largely accounted for by the number of cases reporting tongue-biting during convulsive seizures (84% overall), there was also a considerable number of cases (26.1% overall) who had sustained burns during seizures (32.4% of females, 20.6% of males; ($\chi^2(1)=5.15$, p=0.023). Of the 256 injured patients, twenty-one (9.6%) could be considered in some way disabled from their injuries (fourteen female, seven male; $\chi^2(1)=3.61$, p=0.057). The majority of these were accounted for by seizure-related burns, with disability arising through soft-tissue contractures or the loss of one or more digits from the hands. One case, a twenty-one year old female, had a below-knee amputation after a seizure-related burn to the right lower leg had become infected and then gangrenous. Lack of post-operative physiotherapy had led to a fixed-flexion contracture in the knee, meaning she could not be fitted with a prosthetic leg, and was therefore dependent on crutches for mobility. Seizure type (generalised, focal or unclassified) was not correlated with the overall risk of injury ($\chi^2(2)=1.973$, p=0.373), or with the risk of having sustained burns ($\chi2(2)=0.919$, p=0.631). Details of seizure classifications are given later in this chapter.

	Female (n=136)		Male (n=155)		Total (n=291)	
	n	(% of females	n	(% of males)	n	(% of total)
Tongue bite	102	(75.0%)	113	(72.9%)	215	(73.9%)
Burns	44	(32.4%)	32	(20.6%)	76	(26.1%)
Deep cuts/lacerations	8	(5.9%)	12	(7.7%)	20	(6.9%)
Bruises/superficial cuts	7	(5.1%)	6	(3.9%)	13	(4.5%)
Fractures	4	(2.9%)	10	(6.5%)	14	(4.8%)
Dental injuries	7	(5.1%)	7	(4.5%)	14	(4.8%)

Table 28: Rates of seizure-related injury

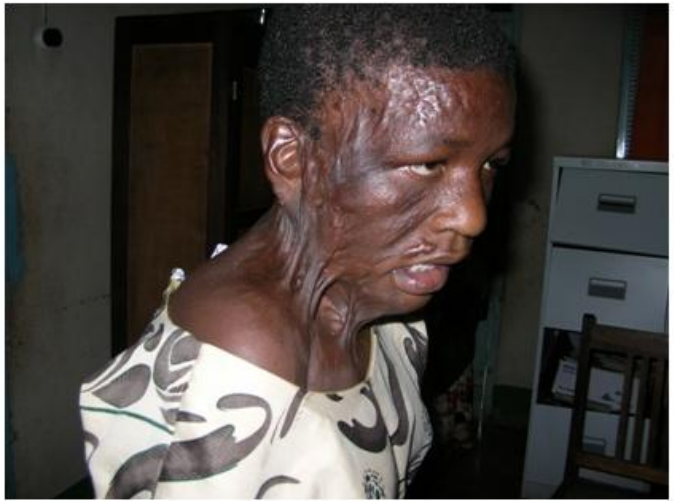


Figure 23: Examples of disabling seizure-related injuries seen in Hai

5.3.6 Risk factors for seizures and epilepsy among PWE in the HDSS

Medical histories that represented possible risk factors for developing epilepsy were established in 127 (43.6%) of 291 cases: fifty-eight (42.6%) of 136 females and seventy-one (45.8%) of 155 males (Table 29,
Figure 24). Eight cases (2.7%) reported two separate risk factors. The most commonly reported acquired risk factors were febrile seizures in childhood (10.7% of all cases), perinatal complications (7.9%), head injury (6.9%), or prior febrile illness associated with loss of consciousness or convulsions (6.9%). A family history of epilepsy was reported by fifty-one (17.5%) of 291 cases: 6.2% in first degree relatives, and 11.3% in second degree relatives (Table 30).

Data on alcohol use were available for all cases, with 238 (81.8%) of 291 cases stating that they did not drink alcohol. Of the fifty-three (18.2%) cases that did drink alcohol, twenty (37.7%) said they drank heavily, defined as four or more days per week or regularly drinking to intoxication (Table 31).

	Female (n=136)		Male (n=155)		Total (n=291)	
	n	(% of females)	n	(% of males)	n	(% of total)
Febrile seizures in childhood	16	(11.8%)	15	(9.7%)	31	(10.7%)
Perinatal complication	11	(8.1%)	12	(7.7%)	23	(7.9%)
Febrile illness with LOC/convulsions	12	(8.8%)	8	(5.2%)	20	(6.9%)
Head injury	6	(4.4%)	14	(9.0%)	20	(6.9%)
Meningitis	4	(2.9%)	2	(1.3%)	6	(2.1%)
Malaria with LOC/convulsions	0	(0.0%)	5	(3.2%)	5	(1.7%)
Stroke	1	(0.7%)	2	(1.3%)	3	(1.0%)
Brain abscess	1	(0.7%)	0	(0.0%)	1	(0.3%)

Table 29: Risk factors for and associations with epilepsy reported by cases

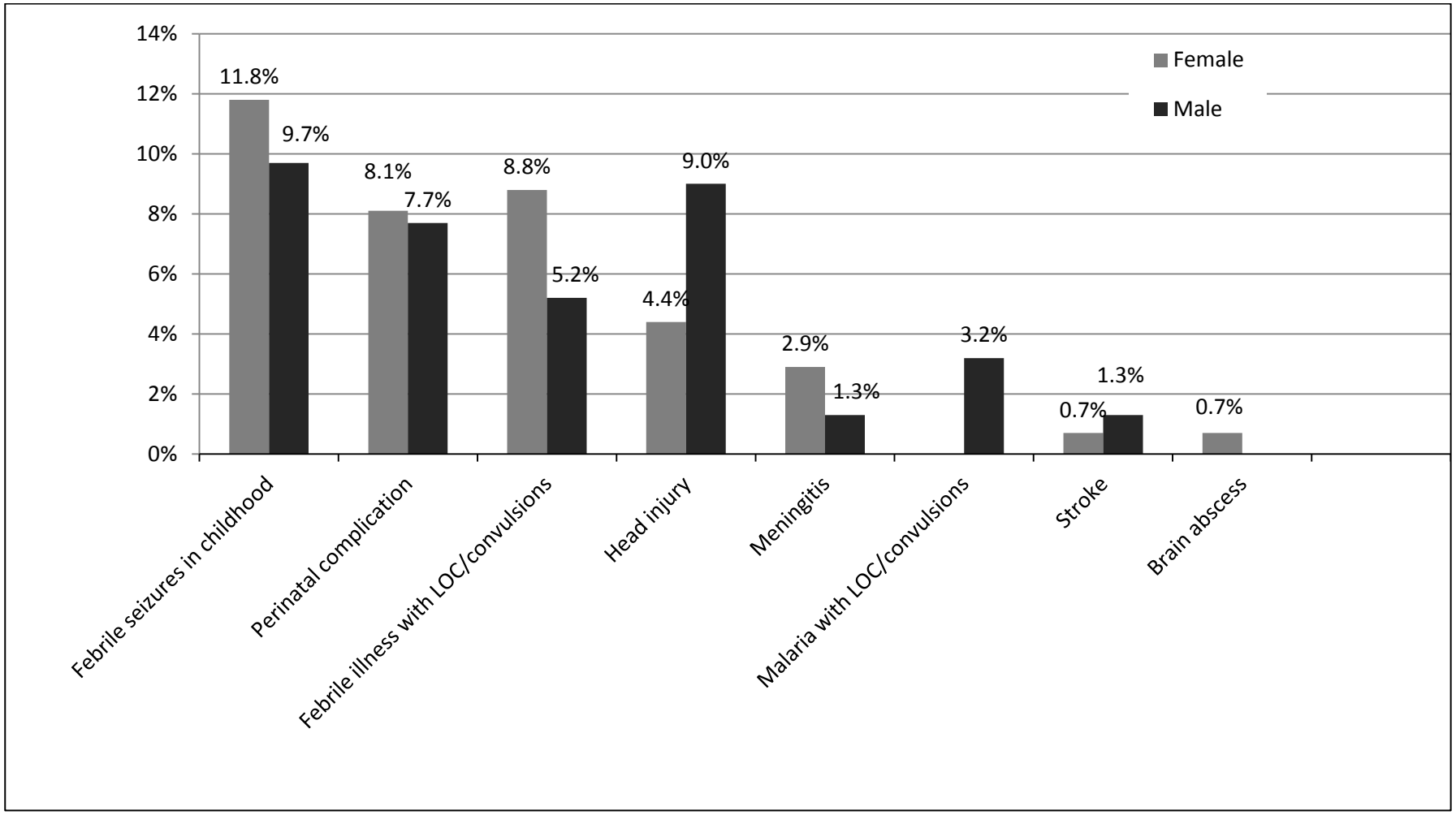


Figure 24: Proportions of cases reporting risk factors for epilepsy (by sex)

	Female (n=136)		*Male (n=155)*		*Total (n=291)*	
	n	***(%of females)***	***n***	***(% of males)***	***n***	***(% of total)***
1st degree relative	*4*	*(2.9%)*	*14*	*(9.0%)*	*18*	*(6.2%)*
2nd degree relative	*12*	*(8.8%)*	*21*	*(13.5%)*	*33*	*(11.3%)*
None reported	*120*	*(88.2%)*	*120*	*(77.4%)*	*240*	*(82.5%)*
Total	*136*	*(100.0%)*	*155*	*(100.0%)*	*291*	*(100.0%)*

Table 30: Cases reporting a family history of epilepsy

	Female (n=136)		**Male (n=155)**		**Total (n=291)**	
	n	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total)**
None	124	(91.2%)	114	(73.5%)	238	(81.8%)
Light	5	(3.7%)	17	(11.0%)	22	(7.6%)
Moderate	4	(2.9%)	7	(4.5%)	11	(3.8%)
Heavy	3	(2.2%)	17	(11.0%)	20	(6.9%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 31: Alcohol intake reported by cases

5.4 Results: investigations

A total of 229 (78.7%) of 291 cases were able to attend KCMC for further investigation with CT head scan, EEG or both. The age- and sex- distributions of cases that did and did not attend for investigation are summarised in Table 32 and Table 33. Attendance and non-attendance for investigation was proportionately distributed between the sexes ($\chi^2(1)=0.321$, p=0.667), although cases that did attend were older than cases that did not (Mann-Whitney U=5808, z=-2.197; p=0.028). When organising patients to attend KCMC for investigations there was some discussion among field staff around which patients might not be appropriate to bring to the hospital, focusing on patients with cognitive impairment or learning disabilities who were perceived to be 'mentally unstable'. This was discouraged, with reassurances and explanations given, and attendance for investigations does not ultimately appear to have been biased by the presence of either cognitive impairment ($\chi^2(1)=3.796$, p=0.061) or motor impairment ($\chi^2(1)=3.390$, p=0.066).

Of the 229 cases that attended for investigation, EEG results were available for 216 (94.3%), and CT results for 200 (87.3%); both CT and EEG findings were available for 187 (81.7%) cases (Table 34). Days on which the CT scanner at KCMC was being serviced or on which the hospital had run out of intravenous contrast medium account for the twenty-nine patients for whom only EEG results are available. Due to technical problems data could not be retrieved from the hard drive of the EEG machine for a further thirteen patients that had both investigations, with CT results only being available for this group of patients.

	Sex					
	Female		Male		Total	
CT and/or EEG available	n	(% of females)	n	(% of males)	n	(% of total)
No	27	(19.9%)	35	(22.6%)	62	(21.3%)
Yes	109	(80.1%)	120	(77.4%)	229	(78.7%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 32: Availability of CT/EEG by sex

	Age (years)				
			Range		
CT and/or EEG available	n	Median	Min	Max	IQR
No	62	25.5	15.0	81.0	20.0
Yes	229	31.0	15.0	85.0	22.0

Table 33: Availability of CT/EEG by age

			CT Scan					
			No	(%)	Yes	(%)	Total	(%)
EEG	No	(%)	62	(21.3)	13	(4.5)	75	(25.8)
	Yes	(%)	29	(10.0)	187	(64.3)	216	(74.2)
	Total	(%)	91	(31.3)	200	(68.7)	291	(100.0)

Table 34: Overall availability of CT/EEG

5.4.1 Computed tomography

A total of 200 (68.7%) of 291 cases had a CT scan: ninety-four (69.1%) of 136 females and 106 (68.4%) of 155 males. CT findings were abnormal in fifty-one (25.5%) of all scans: twenty-three (24.5%) of ninety-four females and twenty-eight (26.4%) of 106 males. CT findings are summarised in Table 35; the category 'other' includes opacification of frontal or maxillary sinuses (two cases), bilateral ocular calcification (one case), and maldevelopment of the frontal and sphenoid sinuses and thickened calvaria, in keeping with fibrous dysplasia with (one case). The findings from eight (4.0%) out of 200 scans were in keeping with neurocysticercosis (NCC): six (6.4%) of ninety-four females and two (1.9%) of 106 males.

5.4.2 Electroencephalography

EEG recordings were available from 216 (74.2%) of 291 cases: 100 (73.5%) of 136 females and 116 (74.8%) of 155 males. EEG abnormalities were reported in a total of eight-four (38.9%) of 216 cases: forty-five (45.0%) of 100 females and thirty-nine (33.6%) of 116 males ($\chi^2(1)=2.987$, $p=0.225$). Seventy-three (33.8%) cases had epileptiform changes: twenty (23.8%) with generalised abnormalities, fifty-three (63.1%) with focal abnormalities (Table 36). Focal abnormalities, when present, were most commonly seen in the temporal lobes, being reported in thirty-four (64.2%) of fifty-three cases (Table 37). The technical quality of the recording due to artefact was very poor in sixteen EEGs: these were classified as normal for the purposes of this analysis. The quality of the recordings obtained was otherwise considered to be excellent by the reporting neurophysiologist.

	Female (n=94)		Male (n=106)		Total (n=200)	
	n	(% of females)	n	(% of males)	n	(% of total)
Normal	71	(75.5%)	78	(73.6%)	149	(74.5%)
Vascular	6	(6.4%)	7	(6.6%)	13	(6.5%)
Discrete calcification	5	(5.3%)	2	(1.9%)	7	(3.5%)
Encephalomalacia	1	(1.1%)	4	(3.8%)	5	(2.5%)
Trauma	1	(1.1%)	4	(3.8%)	5	(2.5%)
Ventricular dilatation	3	(3.2%)	2	(1.9%)	5	(2.5%)
Hemispheric atrophy	2	(2.1%)	2	(1.9%)	4	(2.0%)
Other (non-cerebral)	1	(1.1%)	3	(2.8%)	4	(2.0%)
Hydrocephalus	1	(1.1%)	2	(1.9%)	3	(1.5%)
Lobar atrophy	1	(1.1%)	2	(1.9%)	3	(1.5%)
Cystic changes	1	(1.1%)	1	(0.9%)	2	(1.0 %)
Dural calcification	2	(2.1%)	0	(0.0%)	2	(1.0%)
Tumour	1	(1.1%)	1	(0.9%)	2	(1.0%)
Generalised atrophy	1	(1.1%)	0	(0.0%)	1	(0.5%)
Lobar calcification	0	(0.0%)	1	(0.9%)	1	(0.5%)
Porencephalic cyst	1	(1.1%)	0	(0.0%)	1	(0.5%)
Consistent with NCC	6	(6.4%)	2	(1.9%)	8	(4.0%)

N.B. Categories not exclusive, therefore no column totals given.

Table 35: Abnormal CT findings

	Female (n=45)		Male (n=39)		Total (n=84)	
	n	(% of females)	n	(% of males)	n	(% of total)
Non-specific	6	(13.3%)	5	(12.8%)	11	(13.1%)
Generalised – slow + spike	7	(15.6%)	1	(2.6%)	8	(9.5%)
Generalised – slow, no spike	4	(8.9%)	8	(20.5%)	12	(14.3%)
Focal – slow + spike	28	(62.2%)	25	(64.1%)	53	(63.1%)
Focal - slow, no spike	0	(0.0%)	0	(0.0%)	0	(0.0%)

Table 36: EEG abnormalities seen (SANAD classification)

Site of focal abnormality	n	% of total
Temporal (unilateral)	27	50.9%
Frontal	9	17.0%
Bi-temporal	7	13.2%
Fronto-temporal	4	7.5%
Multi-focal	3	5.7%
Centro-parietal	2	3.8%
Para-sagittal	1	1.9%
Total	**53**	**100.0%**

Table 37: Sites of focal EEG abnormalities

5.4.3 Classification of seizures

All 291 cases identified suffered from generalised convulsive seizures, with no instances of purely focal seizures that did not develop to secondary generalisation being recorded. By considering the clinical case history, including collateral history, in combination with EEG and CT findings where available, the onset of seizures was classified as being either focal, generalised or undefined (Table 38). Focal onset seizures were identified in 208 (71.5%) of 291 cases, and with the benefit of CT and EEG findings, eight cases (2.7%) were diagnosed with primary generalised seizures. The onset of seizures and remained undefined in seventy-five (25.8%) of 291 cases.

The relative contributions of clinical history and examination, CT and EEG to identifying focal onset seizures are illustrated schematically in Figure 25. Of note, in twenty-five (12.0%) of 208 cases with focal -onset seizures the diagnosis was contingent on investigation findings being available: these patients would otherwise have been described as having generalised convulsive seizures with undefined seizure onset, and their epilepsy would ultimately have remained unclassified. In a further 127 (61.1%) cases with focal onset seizures the diagnosis was based on clinical evidence alone: i.e. seizure semiology, the presence of focal neurological deficits or both. Of these, no investigation findings were available for thirty-five cases (27.6%), and EEG and/or CT findings were normal in the remaining ninety-one cases (71.7%). Investigation findings were also available in forty-nine (65.3%) of seventy-five cases in which a distinction between focal or generalised onset could not be made clinically, but did not contribute any additional evidence to aid in making this distinction.

5.4.4 Classification of epilepsies

Six (75%) out of eight cases with a clinical diagnosis of generalised onset seizures were confirmed as having a genetic generalised epilepsy (GGE) based on EEG findings: two cases were specifically identified as juvenile myoclonic epilepsy (JME), with a further four being considered as idiopathic generalised epilepsy (IGE) of some form. The prevalence of GGE within the total cohort of 291 PWE was therefore 2.1% (2.8% of the 216 cases who had EEGs). Based on a combination of CT findings and clinical evidence, sixty-seven

(32.2%) of 208 cases with focal onset seizures were classified as being symptomatic of acquired brain pathology, thus conforming to the currently recommended classification of 'structural/metabolic'. Radiological evidence of specific aetiologies was present in twenty-nine (43.3%) of these, as follows: vascular (thirteen cases), neurocysticercosis (eight), trauma (five), neoplasia (two) and porencephaly (one). In the remaining thirty-eight cases in this group radiological abnormalities were considered likely to be directly related to the presence of seizures although without pathognomic features of any given aetiology (see section 5.4.8, Table 35). No further classification was possible in 141 (67.8%) of 208 focal-onset seizures, in two (25.0%) of eight generalised onset seizures, and in all seventy-five (25.8%) of 291 cases in who the onset of seizures was not defined (Table 39).

	Female (n=136)		Male (n=155)		Total (n=291)	
Seizure type	**n**	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total**
Focal	90	(66.2%)	118	(76.1%)	208	(71.5%)
Generalised	6	(4.4%)	2	(1.3%)	8	(2.7%)
Undefined	40	(29.4%)	35	(22.6%)	75	(25.8%)
Total	136	(100.0%	155	100.0%	291	100.0%

Table 38: Clinical classifications of seizure type

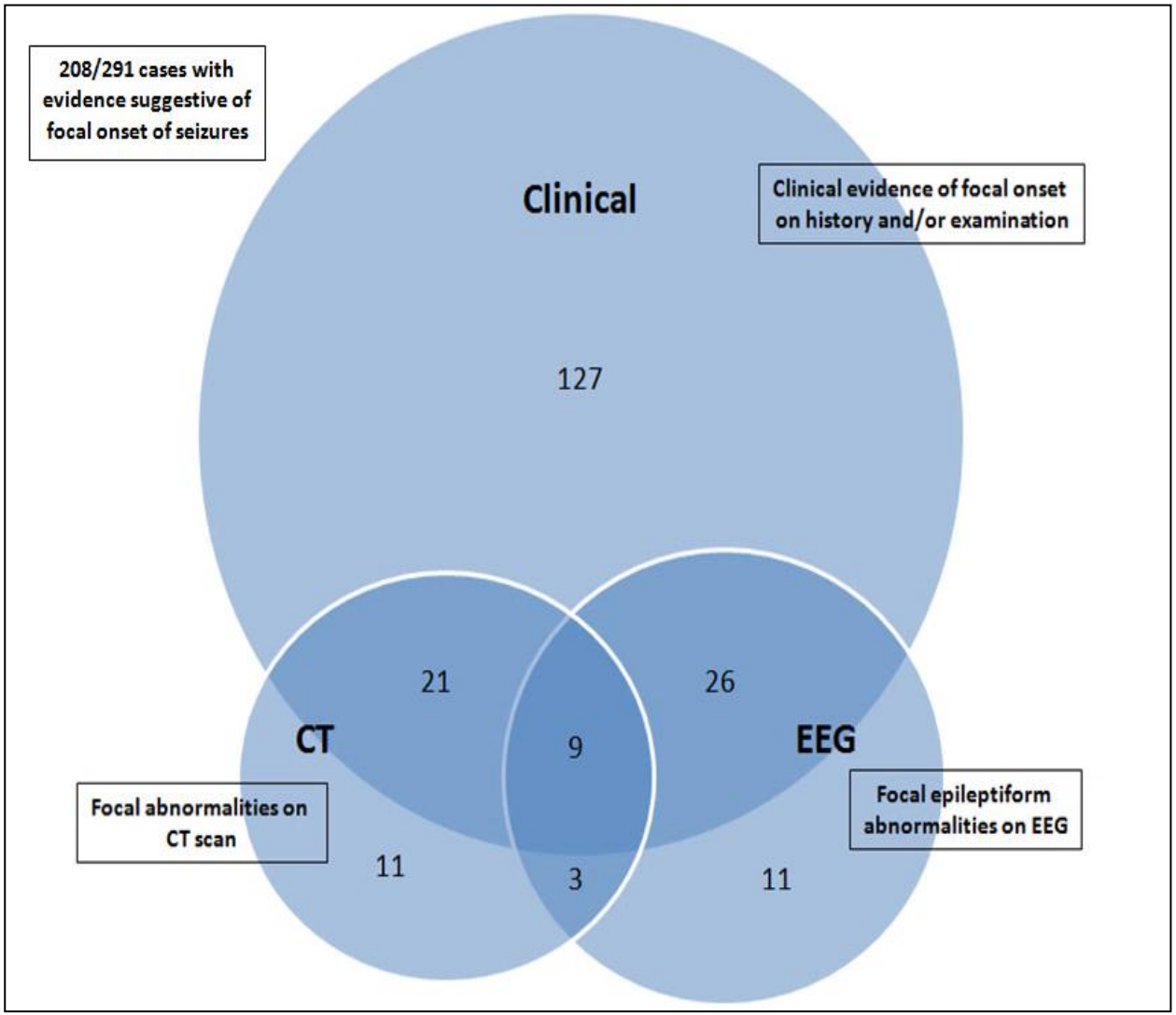


Figure 25: Diagnostic modalities used to identify seizures of focal onset

Final classification	Female (n=136)		Male (n=155)		Total (n=291)	
	n	(% of females)	n	(% of males)	n	% of total
Focal – structural/metabolic	31	(22.8%)	36	(23.2%)	67	(23.0%)
Focal - unclassified	59	(43.4%)	82	(52.9%)	141	(48.5%)
Generalised - IGE	4	(2.9%)	0	(0.0%)	4	(1.4%)
Generalised - JME	2	(1.5%)	0	(0.0%)	2	(0.7%)
Generalised - unclassified	1	(0.7%)	1	(0.6%)	2	(0.7%)
Unclassified	39	(28.7%)	36	(23.2%)	75	(25.8%)
Total	136	(100.0%)	155	(100.0%)	291	(100.0%)

Table 39: Combined classification of seizures and of epilepsies

5.6 Results: socio-demographic

5.6.1 Tribal and religious background

Data on tribal background were available for 275 (94.5%) of 291 cases. The main tribal group within the Hai population are the Chagga, and this is reflected in the tribal background of the cases, with 220 (80.0%) belonging to this group. Other predominant tribal groups were Pare (twenty cases, 7.3%) and Maasai (six cases, 2.2%). The remaining 10.5% of cases belonged to a mix of other tribal groups. Data on religious background were available for 282 (96.9%) of 291 cases, with 223 cases (79.1%) describing themselves as Christian, with the remaining fifty-nine (20.9%) being Muslim.

5.6.2 Education and literacy

Data on the highest educational level attained were available in 275 (94.5%) of 291 cases, including seventeen who were in full-time education at the time of assessment (fourteen at secondary school and three in further education). Of these, fifty-seven (20.7%) had no schooling at all and seventy-five (27.3%) had not completed primary school. Ninety-five (36.8%) of 258 cases who were not in education at the time of the study said that their education had been interrupted directly as a result of epilepsy: fifty (42.4%) of 118 females and forty-five (32.1%) of 140 males ($\chi^2(1)=2.881$, $p=0.090$). As the presence of cognitive impairment could also account for an incomplete education, this analysis was repeated after excluding individuals with any degree of cognitive impairment. Data were available for 191 (94.6%) of 202 individuals with no cognitive impairment, and while the overall proportion of cases with no education fell to 9.9%, the proportions of cases in other categories remained broadly similar.

To further examine the influence of epilepsy on education, analyses relating attendance at school to age of onset of epilepsy were also performed. Data on both age of onset and educational level were available for 269 (92.4%) of 291 cases. Thirty-five (40.2%) of eighty-seven cases in whom epilepsy started pre-school age never went to school, compared to twenty-one (11.5%) of 182 cases in whom epilepsy started over the age of eight years ($\chi^2(1)=29.395$, $p<0.001$). When this analysis was restricted to cases in whom epilepsy had started only under the age of sixteen years, i.e. the years during which

children may be expected to start attending school, the association between age of onset under eight years and non-attendance at school remained significant. Epilepsy started under the age of sixteen years in 175 (61.6%) of 284 cases in which age of onset was available, with data on educational level being available for 169 (96.6%) of these. In this group, thirty-five (40.2%) of eighty-seven cases with an age of onset of under eight years had no education, compared to nine (11.0%) of eighty-two cases in who epilepsy started between the ages of eight and sixteen years ($\chi^2(1)=18.760$, $p<0.001$).

Information on literacy was available from 276 (94.5%) of 291 cases, of whom 135 (48.9%) said they could not read or write: sixty-one (46.9%) of 130 females and seventy-four (50.7%) of 146 males ($\chi^2(1)=0.390$, $p=0.533$). Data on literacy were available in 192 (95.0%) of 202 cases who had no cognitive impairment, with sixty (31.3%) saying that they could not read or write: twenty-seven (29.3%) of ninety-two females and thirty-three (33.0%) of 100 males ($\chi^2(1)=0.298$, $p=0.586$).

	Female (n=129)		Male (n=146)		Total (n=275)	
Educational level	**n**	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total)**
No education	25	(19.4%)	32	21.9%	57	20.7%
Incomplete primary education	35	(27.1%)	40	27.4%	75	27.3%
Completed primary education	50	(38.8%)	61	41.8%	111	40.4%
Any secondary/further education	19	(14.7%)	13	8.9%	32	11.6%
Total	129	(100.0%)	146	100.0%	275	100.0%

Table 40: Highest education level of all cases

5.6.3 Marital status

Two hundred and fifty-eight (88.7%) of 291 cases were aged nineteen or above: 116 (85.3%) of 136 females and 142 (91.6%) of 155 males. Data on marital status were available for 248 (96.1%) of these individuals (Table 41). The majority of cases remained unmarried (58.5% overall), although when seventy-six (30.6%) individuals with cognitive impairment were excluded from this analysis, as these individuals could be considered less likely to get married for this reason, the proportion of unmarried cases fell to 44.8%. When marital status was dichotomized into being single versus ever having married, including cases widowed or divorced, there was a significant association between remaining single and being aged nineteen years or less at onset of epilepsy ($\chi^2(1)=78.816$, $p<0.001$).

Twenty-two (8.9%) individuals were divorced or separated, of whom fourteen (63.6%) provided information on the reason for marital difficulties, with eleven (78.6%) citing their epilepsy as the reason for marital breakdown (nine females, two males). While females were more likely than males to be divorced or separated ($\chi^2(1)=6.724$, $p=0.01$), there was no significant difference between the sexes in the numbers of people citing epilepsy as the cause for their marital difficulties ($\chi^2(1)=0.917$, $p=0.34$).

5.6.4 Occupation

Data on occupation were available from 286 (98.3%) of 291 cases (Table 42). Of note, sixty-nine individuals (24.1%) said that they were not working due to illness or disability. A further forty-seven cases (16.4%) said that they were confined to small domestic tasks or housework with regards to any contribution that they made to the household economy. When all cases with cognitive or motor impairments were excluded the total number of cases not working due to disability was fifteen (5.2%), and the total number describing themselves as being confined to the household was thirty (10.5%).

	Female (n=130)		Male (n=151)		Total (n=281)	
Marital status	**n**	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total)**
Single	64	(58.2%)	81	(58.7%)	145	(58.5%)
Married	24	(21.8%)	50	(36.2%)	74	(29.8%)
Divorced/separated	16	(14.5%)	6	(4.3%)	22	(8.9%)
Widowed	6	(5.5%)	1	(0.7%)	7	(2.8%)
Total	110	(100.0%)	138	(100.0%)	248	(100.0%)

Table 41: Marital status of all cases aged 19 years and over

	Female (n=132)		Male (n=154)		Total (n=286)	
Occupational status	**n**	**(% of females)**	**n**	**(% of males)**	**n**	**(% of total)**
Farming/herding	41	(31.1%)	55	(35.7%)	96	(33.6%)
Sick or disabled	31	(23.5%)	38	(24.7%)	69	(24.1%)
Domestic tasks/housework	31	(23.5%)	16	(10.4%)	47	(16.4%)
Trade/skill	5	(3.8%)	15	(9.7%)	20	(7.0%)
Unemployed	6	(4.5%)	12	(7.8%)	18	(6.3%)
Full-time education	11	(8.3%)	6	(3.9%)	17	(5.9%)
Salaried/business	7	(5.3%)	6	(3.9%)	11	(4.5%)
Retired	0	(0.0%)	3	(1.9%)	3	(1.0%)
Other manual/unskilled	0	(0.0%)	3	(1.9%)	3	(1.0%)
Total	132	(100.0%)	154	(100.0%)	286	(100.0%)

Table 42: Occupational status of cases

5.7 Discussion

All PWE identified in our study had ACE, with focal-onset seizures accounting for 71.5% of all cases. High rates of focal onset seizures were also found in 71% of all cases identified in a recent community-based study of people with ACE in Kenya (Munyoki et al., 2010), and in 55% of all cases in a community-based study from Nigeria, although it is not clear how focal seizures with generalised clonic movements were classified in this latter study (Osuntokun et al., 1987). Conversely, higher rates of generalised-onset seizures have previously been reported from community-based studies in SSA, accounting for between 58% and 82% of diagnoses (Rwiza et al., 1992, Almu et al., 2006, Dent et al., 2005). As discussed in the introduction to this chapter, differing approaches to case-ascertainment, differing diagnostic and classification criteria, and lack of EEG and CT to aid with classification make a strict comparison between studies difficult, although all authors in the above studies comment that focal seizures becoming rapidly generalised may have erroneously been classified as generalised onset seizures.

The proportion of patients with inter-ictal epileptiform EEG findings in the HDSS population was 33.8% overall. This is higher than a rate of 18% in 230 PWE previously reported from Ethiopia (Tekle-Haimanot et al., 1990b), in keeping with a more recent study from Kenya where epileptiform EEG abnormalities were reported in 33.8% of 408 PWE (Munyoki et al., 2010), and lower than a rate of 49.1% reported in fifty-five PWE in western Uganda (Kaiser et al., 2000). It is interesting to compare the influence of the availability of EEG in classifying epilepsy in these studies. In our study investigations were suggestive of a focal onset to seizures in twenty-five cases in whom a clinical diagnosis of generalised seizures had been made: i.e. cases in whom a description of generalised convulsive seizures with no evidence of prodromal or focal-onset features had been obtained. A diagnosis of focal epilepsy was therefore ultimately contingent on the availability of investigations, including EEG, in twenty-five (12.0%) of 208 cases, including eleven (5.3%) in which this distinction depended solely on the EEG. By implication, without the availability of these diagnostic modalities the proportion of PWE diagnosed with focal-onset seizures would have been lower, at 62.9%. This also conforms with

findings from Kenya, where EEG findings of focal abnormalities in 22% of PWE with convulsive epilepsy contributed to 71% of these cases finally being classified as generalised epilepsy with focal onset (Munyoki et al., 2010). Similarly, in a rural area of west Uganda with a high prevalence of epilepsy and onchocerciasis, the addition of EEG findings to a purely clinical classification of seizures led to the proportion of focal epilepsies rising from 24% to 78% (Kaiser et al., 2000). The high rate of focal onset seizures identified in our study suggests that a high proportion of epilepsy in this population may be due to identifiable, and possibly preventable, causes. We know from a companion study that epilepsy in children from Hai is associated with adverse perinatal events (Burton et al., 2012a), while exposure to *Taenia solium*, the parasitic infection responsible for NCC, is associated with epilepsy in a number of African populations (Quet et al., 2010), including in Tanzania (Winkler et al., 2008a, Winkler et al., 2009b).

In our cohort only 2.1% of cases overall had clinical and EEG evidence of a genetic generalised epilepsy (2.7% of cases who had EEG recordings made). This is lower than the 6.6% of PWE with EEGs in a similar population in Kenya (Munyoki et al., 2010), although this may be an underestimate, as no EEG was available in seventy-five cases (25.8%) and sixteen (7.4%) EEG recordings were degraded by artefact, rendering them unreadable.

Clinical associations with or risk factors for epilepsy were identified in nearly half (43.6%) of the patients in this study, with the most commonly reported being febrile seizures in childhood, perinatal complications, febrile illnesses associated with loss of consciousness or convulsions, by implication referring to infections of the CNS, and head injury. A recent review of epidemiologic studies of epilepsy in Africa over a ten year period found that out of 1,379 PWE identified, aetiology was determined in 879 (63.7%) (Quet et al., 2011). Just over half of these (53.5%) were accounted for by symptomatic epilepsies, although the authors point out that most of these data are derived from hospital-based series rather than community-based cross-sectional studies. In a more detailed review of thirty-five studies from SSA, including university theses and articles published in French, head injuries were implicated in between 0.3% and 15.8% of cases, perinatal complications in between 0.1% and 12%, infectious diseases in between 0.5% and 23.0% and a history of

febrile convulsions was ascertained in between 1.0% and 30.9% of cases (Preux and Druet-Cabanac, 2005). These wide variations serve to illustrate the difficulties of comparing and interpreting observational and descriptive data. Case-controlled data on epilepsy from SSA that might further characterise the roles of various aetiologies are very limited. This issue is further addressed in Chapter Six.

In our cohort, a history of febrile convulsions was reported in 10.7% of cases, and one of non-specified febrile illness associated with loss of consciousness or convulsions in 6.9%. As far as possible, the nature of convulsions in the latter was explored in detail to try and exclude patients giving a history more in keeping with chills or rigors as opposed to seizures. Febrile seizures have previously been associated with the subsequent development of epilepsy in Nigeria and Tanzania, with ORs of 2.9 to 11.0 in exposed groups (Ogunniyi et al., 1987, Matuja et al., 2001). What is represented by these illnesses is a matter of much debate. A widely held assumption is that cerebral malaria is responsible for a considerable amount of morbidity (Ngoungou and Preux, 2008), and ORs for developing epilepsy following exposure to cerebral malaria as high as 14.3 have been reported (Ngoungou et al., 2006). In our study a history strongly suggestive of cerebral malaria was given in only 1.7% of PWE (five cases, all male). This rate conforms with that of 1.2% reported from elsewhere in northern Tanzania (Winkler et al., 2009c), and the rate of cerebral malaria identified in our cohort may be an accurate reflection of an altitudinous region, where the transmission rate for malaria is low (Reyburn et al., 2004), although it cannot be discounted that the problem of recall bias in adults for distant events has depressed the reported rate. In a Kenyan study of the clinical characteristics of convulsive seizures in adults and children, recall for febrile seizures and status epilepticus was greater in children, with the assistance of parents, in giving the history (Munyoki et al., 2010).

Two studies from Tanzania have given details of the numbers of cases reporting a family history of epilepsy or seizures, with this being present in 33.3% and 41% of cases (Dent et al., 2005, Winkler et al., 2009c). In our study 17.5% of cases reported a family history of epilepsy or seizures, with this being slightly more common in second-degree than first-

degree relatives (11.3% vs. 6.2%). Whether this points to a complex mode of inheritance is not clear, and would require more detailed further study, although it is interesting to note that in one of the two community-based studies from Tanzania to have reported on family history in epilepsy, this was recorded in up to third degree relatives (Winkler et al., 2009c).

Although our study did not systematically test for HIV, we did ask about HIV when taking a medical history, and a number of bedside tests were done in patients with and without epilepsy presenting with signs or symptoms that may have been markers of immune suppression. Only one HIV test was positive, and this was in a patient who had revealed his status during the clinical interview. Only one other patient was known to be HIV positive, giving a prevalence of 0.7%, which is well below the 5.6% that has previously been documented in a rural population within the Kilimanjaro region (Mmbaga et al., 2007). Up to 11% of patients with untreated HIV presenting with neurological problems may present with seizures (Bhigjee, 2005), and while the HIV positive patients we identified appeared to have acquired HIV subsequent to the development of epilepsy, this issue certainly warrants further study in this population.

Over one-quarter (26.1%) of PWE identified in Hai had sustained burns during seizures: similar to a rate of 24.1% previously documented in a rural Tanzanian population (Rwiza et al., 1993b). This phenomenon is well documented in SSA (Jilek-Aall and Rwiza, 1992, Birbeck, 2000b), and it has been observed that up to 50% of all patients presenting with burns have a history of epilepsy (Allorto et al., 2009). Indeed, it has previously been noted in Malawi that a serious burn, rather than epilepsy itself, would be the event precipitating attendance at medical services, with epilepsy being more frequently diagnosed on surgical wards than in medical clinics (Watts, 1989). In a UK series, burns have been found to be significantly associated with complex partial epilepsy with or without secondary generalisation ($p=0.001$) (Hampton et al., 1988), and with female sex (OR 2.2) (Buck et al., 1997). In our study, burns were more common in women ($p=0.023$), but were not associated with seizure type ($p=0.631$), although this latter distinction perhaps has less meaning as all PWE in this cohort were suffering with generalised convulsive epilepsy of

some description. The determinants of burns in African patients have also been demonstrated to be environmental, being related to the presence of open cooking fires in the home (Rode et al., 2011), and the provision of safety stoves in at risk groups has been proposed as a public health intervention. Further investigation into the risks for injuries and burns among PWE in the Hai population is warranted.

A detailed assessment of the social impact of epilepsy or of associated stigma in this population was beyond the scope of this study, and the brief demographic and socio-economic details presented here were collected for informative purposes and to facilitate later comparison with controls. It is interesting to note, however, that analyses based on relating age of onset of epilepsy to ages at which people in Hai traditionally become eligible for marriage do appear to implicate epilepsy as a limiting factor. These findings mirror those of an earlier study in a different rural population in Tanzania (Rwiza et al., 1993b). In this study 30.9% of 181 PWE of school age or older had never gone to school, and of those who had attended school, 62.9% stopped prematurely. In the same study, 42.2% of cases over the age of nineteen remained unmarried, with this proportion rising to 64.6% in individuals in whom epilepsy had started before this age, a difference that was statistically significant ($p<0.005$). The findings from Hai presented here have since been further explored in a qualitative study of a purposefully selected sample of PWE from this cohort, in which themes of exclusion across major life domains were elaborated (Mushi et al., 2010). In all, it is a sobering finding that these themes appear unaltered from commentary provided over the past two to five decades (Rwiza et al., 1993b), (Giel, 1968). In Chapter Eight of this thesis the issue of treatment for epilepsy and the ETG is considered, and it should be borne in mind that even a brief and crude quantitative assessment as has been presented here hints at the marginalised status of the person with epilepsy living in SSA.

5.8 Summary and conclusions

There is a high prevalence of focal-onset epilepsy among people with convulsive seizures living in the HDSS, suggesting the presence of acquired brain pathology in a considerable proportion of this group of patients. Possible aetiological factors include perinatal complications, febrile seizures in childhood, CNS infections and head injuries. The roles of HIV infection and of family history remain unclear, and warrant further investigation. Over one quarter of PWE living in the HDSS have suffered burns as a result of their epilepsy, and interventions to reduce this morbidity are warranted.

PWE living in the HDSS are socially and economically disadvantaged. The degree to which this relates to their epilepsy should be further explored through comparison with a control population without epilepsy.

Chapter 6. Case-control study of epilepsy in the HDSS

Abstract

Background

There are few case-control data from SSA pertaining to either risk factors for epilepsy or the implications of living with this condition.

Methods

Following completion of case ascertainment of PWE in Hai, control subjects who did not have epilepsy were recruited from the adult population. Clinical, demographic and socio-economic variables were collected for comparison with cases. Multivariable logistic regression models were constructed to look for predictors of epilepsy in this population.

Results

Clinical predictors of epilepsy were a history of febrile convulsions in childhood (OR 16.93; 95% CI 2.14 to 134.26), a family history of epilepsy in second-degree relatives (OR 26.29; 95% CI 3.36 to 205.99), and having cognitive impairment (OR 23.41; 95% CI 5.52 to 99.23) or motor impairment (OR 10.01; 95% CI 1.29 to 77.59). When cognitive and motor impairments were excluded from the regression model a history of perinatal complications was associated with having epilepsy (OR 3.40; 95% CI 1.07 to 10.75). Socio-economic associations with epilepsy were being divorced or separated (OR 15.72; 95% CI 3.15 to 78.61), being less likely to have completed primary education (OR 0.42; 95% CI 0.25 to 0.73), and being less likely to be gaining an income through farming (OR 0.41; 95% CI 0.23 to 0.72).

Conclusions

The association with childhood illness and obstetric complications suggests that a proportion of epilepsy in the HDSS population could be prevented through better health care in early life. PWE are socially and economically disadvantaged compared to people without epilepsy in this population.

6.1 Introduction

The difficulties associated with conducting large-scale community-based studies in SSA have meant that case-controlled data on epilepsy from this region remain sparse. A comprehensive review of the literature from SSA published in 2005 identified only three case-control studies, conducted between 1989 and 2001, that searched for more than one exposure factor (Preux and Druet-Cabanac, 2005). A Nigerian study from 1987 compared 155 PWE identified from a hospital series with an equal number of age- and sex-matched controls with the aim of identifying risk factors for epilepsy (Ogunniyi et al., 1987). Data on childhood immunisations, febrile convulsions, head injury, haemoglobinopathy, venereal diseases, psychotropic drug or alcohol use, and cerebrovascular disease were collected. Of these, febrile convulsions and head injury were identified as predictors of epilepsy (ORs of 11.0 and 13.0 respectively). In 2001, a study in a rural area of Burundi was conducted in 324 PWE and 648 age-matched controls to examine the link between sero-positivity for exposure to cysticercosis and epilepsy in the study population (Nsengiyumva et al., 2003). Data on family history and childhood illness were also collected, and predictors of epilepsy in a multivariable model were sero-positivity for cysticercosis (OR 4.1), a family history of epilepsy (OR 3.3), and severe disease in childhood (OR 1.9). The meaning of 'severe disease in childhood' is not elaborated, and it is not clear whether this should be taken to refer to a history of febrile seizures. This study is discussed in more detail with regards to the issue of cysticercosis in Chapter Eight. In a community-based prevalence study from Tanzania conducted in 1989, a variation in prevalence of between 5.1 and 37/1,000 was observed between wards and divisions within one rural district (Rwiza et al., 1992). To further investigate, 174 cases and an equal number of controls from the division with the highest prevalence were interviewed and examined (Matuja et al., 2001). Controls were matched for age, sex and tribe, and data on family history, febrile convulsions, head trauma, birth complications and CNS infections were collected. Multivariable analysis identified three of these factors as significant predictors of epilepsy: family history (OR 3.34), a history of febrile convulsions (OR 2.9) and a history of intrapartum complications (OR 4.5). In this study, both cases and controls had EEG recordings, with epileptiform abnormalities being found in 22.9% of

cases and no controls (p<0.001), and abnormal background activity being seen in 25.8% of cases versus 11.5% of controls (p<0.001). More recently a study from Kenya compared 445 cases with 633 controls recruited during a large community-based prevalence survey in a rural population (n=151, 408) (Edwards et al., 2008). Controls were frequency-matched for age, data on family history of both febrile and non-febrile seizures and head injury were collected from all participants, and the mothers of children under the age of eighteen years were asked about perinatal complications. Multivariable regression models for adults and children combined and children only were constructed; in adults and children, a family history of both febrile and non-febrile convulsions and previous head injury were both predictors of epilepsy (ORs 7.3 and 4.1 respectively). When the analysis was restricted to children only, head injury was not found to be a predictor of epilepsy, while a history of perinatal complications was (OR 5.7). Finally, and contemporaneous with the study described here, a case-control study of children with epilepsy identified in the HDSS found adverse perinatal events (OR 14.9), a family history of afebrile seizures (OR 5.7) and poor scholastic attainment (OR 8.6) all to be predictors of epilepsy in this population (Burton et al., 2012a).

Other studies from SSA comparing cases with controls have focused on the link between particular infectious diseases and epilepsy rather than the general risk profile in the population, usually triggered by anecdotal observations of high prevalence rates of epilepsy in areas known to be endemic for the infectious disease in question. Such studies have focused on the neuro-helminthoses which are endemic in many LMICs (Winkler et al., 2008a). Studies of the link between exposure to onchocerciasis and epilepsy have been conducted in Cameroon, the Central African Republic and Burundi (Druet-Cabanac et al., 1999, Boussinesq et al., 2002, Newell et al., 1997b), with mixed findings. In Burundi, evidence of onchocerciasis based on the presence of cutaneous nodules or antibody positivity on serological testing was found in 81.8% of 110 cases compared to 68.3% of eighty-two controls (p<0.05) (Newell et al., 1997b). Similar findings were reported from Cameroon, where the prevalence of epilepsy and the community microfilarial load on skin-snip testing were significantly associated (p<0.02), with this being more marked when seventy-two PWE were compared with seventy-two controls for the same measure

(p<0.001) (Boussinesq et al., 2002). A similar study conducted among 187 PWE and 374 controls in the Central African Republic did not find skin-snip microfilarial load to be a predictor of epilepsy (OR 1.21; 95% CI 0.81 to 1.80) (Druet-Cabanac et al., 1999). An association between infection with *Toxocara canis* and epilepsy has also been proposed (Arpino et al., 1990), with this having been supported by work done in Bolivia (Nicoletti et al., 2002). In a study from Burundi, the presence of antibodies to *T.canis* was associated with epilepsy (OR 2.13), although this finding was not reproduced in a Tanzania population, where no association between epilepsy and anti-toxocaral antibodies was found in a small study of forty PWE and twenty controls (p=0.55) (Winkler et al., 2008a). Perhaps the most extensively researched of these conditions is *Taenia solium* infection, the causative agent of neurocysticercosis (NCC), which is well described as a cause of epilepsy in endemic regions of the world (Garcia and Del Brutto, 2005). This issue, including a discussion of studies from SSA, is dealt with in depth in Chapter Seven.

A small number of case-control studies of wider issues relating to epilepsy in SSA have also been performed. In Benin anthropometric data were collected from 131 PWE and 262 controls to look for any link between malnutrition and epilepsy, with the prevalence of malnutrition being higher in cases than controls (p=0.0006) (Crepin et al., 2007). Particular nutritional factors associated with epilepsy included low levels of cereal consumption (OR 4.2), tooth decay (OR 2.9), and food taboos due to perceived health status (OR 16.8). Mean mid-upper-arm circumference was lower in cases than controls (p<0.0001). In a study from Burundi, 352 PWE and 704 controls were compared to assess direct and indirect economic costs associated with epilepsy (Nsengiyumva et al., 2004). While no differences were observed between cases and controls in terms of marital or employment status, mean annual direct healthcare costs were greater in PWE than in controls (p=0.03), as were the mean number of days of disrupted family life (p=0.03). Finally, children with and without epilepsy from the Hai district have been studied with regards to physical and behavioural co-morbidities (Burton et al., 2011, Burton et al., 2012b). In a series of 112 children with epilepsy and 113 controls, one or more of cognitive impairment, behavioural disorder, motor difficulties, burns or other previous injuries were predictors of epilepsy (Burton et al., 2012b). On multivariable regression

analysis factors associated with co-morbidity among cases in this series were age at onset of less than three years (OR 3.1), structural brain disease (OR 4.5) and having epileptiform abnormalities on EEG (OR 4.1).

To summarise, risk factors implicated in the aetiology of epilepsy in populations from SSA have included febrile convulsions, head injuries, a family history of epilepsy or seizures, and a history of perinatal complications. Specific infectious diseases affecting the CNS have also been studied, with mixed results. The wider context of epilepsy also emerges from reading these studies, with malnutrition, reduced educational attainment and increased economic burden all being associated with epilepsy.

In the Hai study, clinical and socio-economic associations with epilepsy identified during case ascertainment were further studied through comparison with controls that were broadly matched for age and sex.

6.2 Methods

6.2.1 Recruitment of controls

Once case ascertainment was complete six age- and sex-matched controls for each case were identified from the census database using a random number sequence, providing a broadly matched pool of potential controls from which to recruit. Names were compared with the census database to ensure that no positive responders had been included. Lists of eligible controls in each HDSS village were then distributed to village enumerators, and during August and September 2010 individuals were approached and invited to participate in the study. Those agreeing to participate were asked to complete a questionnaire pro-forma similar to that used during case ascertainment along with the same socio-economic questionnaire completed by cases during follow-up visits. Prior to inclusion all controls were assessed by the research doctor to confirm that they did not have a history suggestive of epilepsy. The control interview pro-forma translated into Kiswahili was then completed by one of the field team, either enumerator or clinical supervisor.

6.2.2 Statistical analysis

All categorical predictor variables were either ordinal or dichotomous. Dichotomous variables were coded according to the presence or absence of the characteristic in question; for ordinal variables where dichotomisation was not appropriate, a baseline comparator level was selected. The outcome of interest for each predictor variable was 'case' or 'control', with uni-variable odds ratios (ORs) with 95% confidence intervals being calculated for all predictor variables.

Multivariable logistic regression was used to examine the joint effects of multiple predictors. Regression models were constructed using a backwards stepwise elimination strategy based on the likelihood ratio test, with non-significant uni-variable predictor variables with a p-value of 0.1 or greater being excluded at each step. Goodness-of-fit of final models was assessed using the Hosmer and Lemeshow statistic, with values closer to unity indicating a better fit with the data (Field, 2009a). Separate regression models were constructed to examine for significant associations with epilepsy within two domains: clinical associations, including risk factors, and socio-economic outcomes.

6.3 Results

6.3.1 Demographics

By the end of the recruitment period a total of 182 controls had been recruited into the study: ninety-nine females (54.4%) and eighty-three males (45.6%). Although controls were recruited from a pool that was broadly matched to cases for age and sex, they were not recruited on a strict matching basis. Age and sex were therefore compared to assess the degree of match between the two series. The final series of controls was significantly older than cases overall (Mann-Whitney U=21483.0, z=-3.457, p=0.001), with this holding true when the ages of cases and controls were compared by sex: U=5387.5, z=-2.614, p=0.009 for females; U=5238, z=-2.361, p=0.018 for males. Although there were proportionally more male cases than controls (53.3% vs. 45.6%), there was no significant difference between cases and controls in proportions of males and females (OR for male sex and having epilepsy of 1.36, 95% CI 0.94 to 1.97). The age distributions of cases and controls are given in Table 43, Table 44, Figure 26 and Figure 27.

Data on tribal background were available for 275 (94.5%) of 291 cases and 179 (98.4%) of 182 controls. Data on religious background were available for 282 (96.9%) of 291 cases and 181 (99.5%) of 182 controls. These data are summarized in Table 45. There was no significant association with epilepsy in either case (Table 46).

		Age (years)			
			Range		
	n	Median	Min	Max	IQR
Cases	291	30.0	15	85	21
Controls	182	39.0	15	91	25

Table 43: Age distributions of cases and controls

Age band	Females				Males				Total			
	Cases (n=136)		Controls (n=99)		Cases (n=155)		Controls (n=83)		Cases (n=291)		Controls (n=182)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
15-19	23	(16.9%)	10	(10.1%)	19	(12.3%)	8	(9.6%)	42	(14.4%)	18	(9.9%)
20-24	25	(18.4%)	13	(13.1%)	36	(23.2%)	13	(15.7%)	61	(21.0%)	26	(14.3%)
25-29	23	(16.9%)	18	(18.2%)	14	(9.0%)	3	(3.6%)	37	(12.7%)	21	(11.5%)
30-34	12	(8.8%)	5	(5.1%)	18	(11.6%)	9	(10.8%)	30	(10.3%)	14	(7.7%)
35-39	9	(6.6%)	6	(6.1%)	13	(8.4%)	8	(9.6%)	22	(7.6%)	14	(7.7%)
40-44	10	(7.4%)	8	(8.1%)	17	(11.0%)	11	(13.3%)	27	(9.3%)	19	(10.4%)
45-49	13	(9.6%)	11	(11.1%)	11	(7.1%)	10	(12.0%)	24	(8.2%)	21	(11.5%)
50-54	7	(5.1%)	11	(11.1%)	7	(4.5%)	4	(4.8%)	14	(4.8%)	15	(8.2%)
55-59	6	(4.4%)	9	(9.1%)	8	(5.2%)	4	(4.8%)	14	(4.8%)	13	(7.1%)
60-64	2	(1.5%)	3	(3.0%)	4	(2.6%)	5	(6.0%)	6	(2.1%)	8	(4.4%)
65-69	4	(2.9%)	5	(5.1%)	4	(2.6%)	3	(3.6%)	8	(2.7%)	8	(4.4%)
70+	2	(1.5%)	0	(0.0%)	4	(2.6%)	5	(6.0%)	6	(2.1%)	5	(2.7%)
Total	**136**	**(100.0%)**	**99**	**(100.0%)**	**155**	**(100.0%)**	**83**	**(100.0%)**	**291**	**(100.0%)**	**182**	**(100.0%)**

Table 44: Age and sex distributions of cases and controls

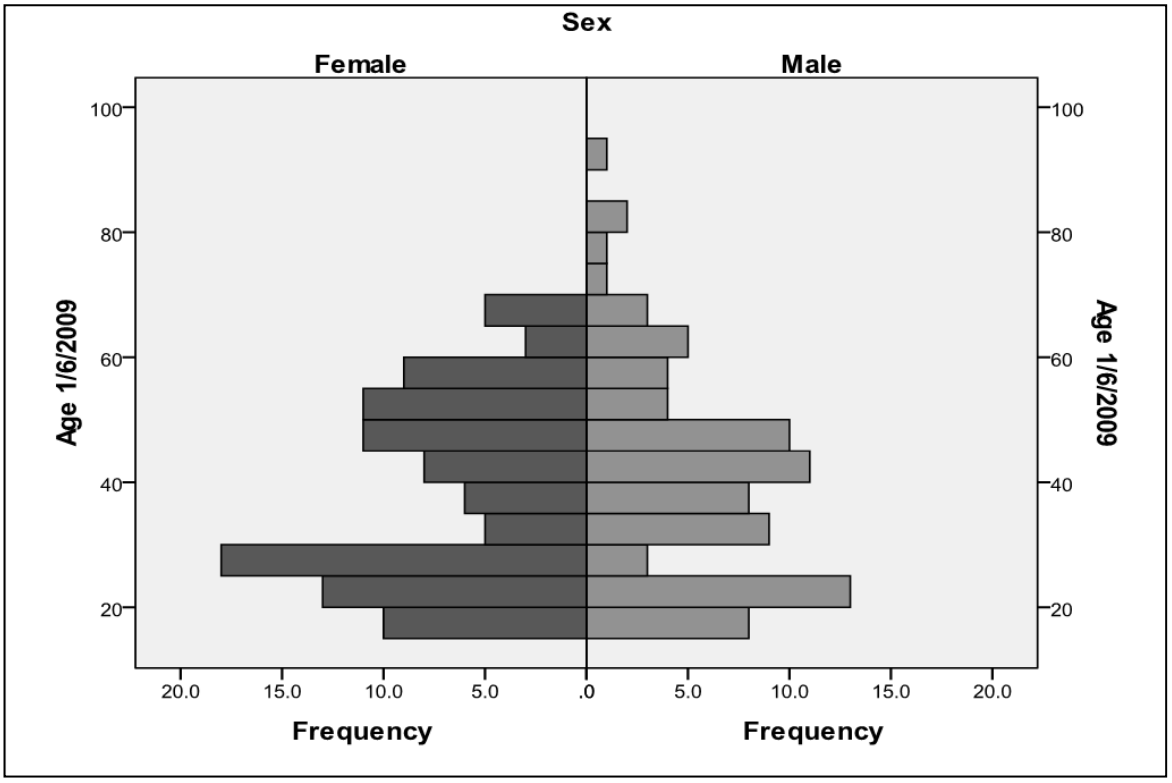


Figure 26: Age distribution of controls

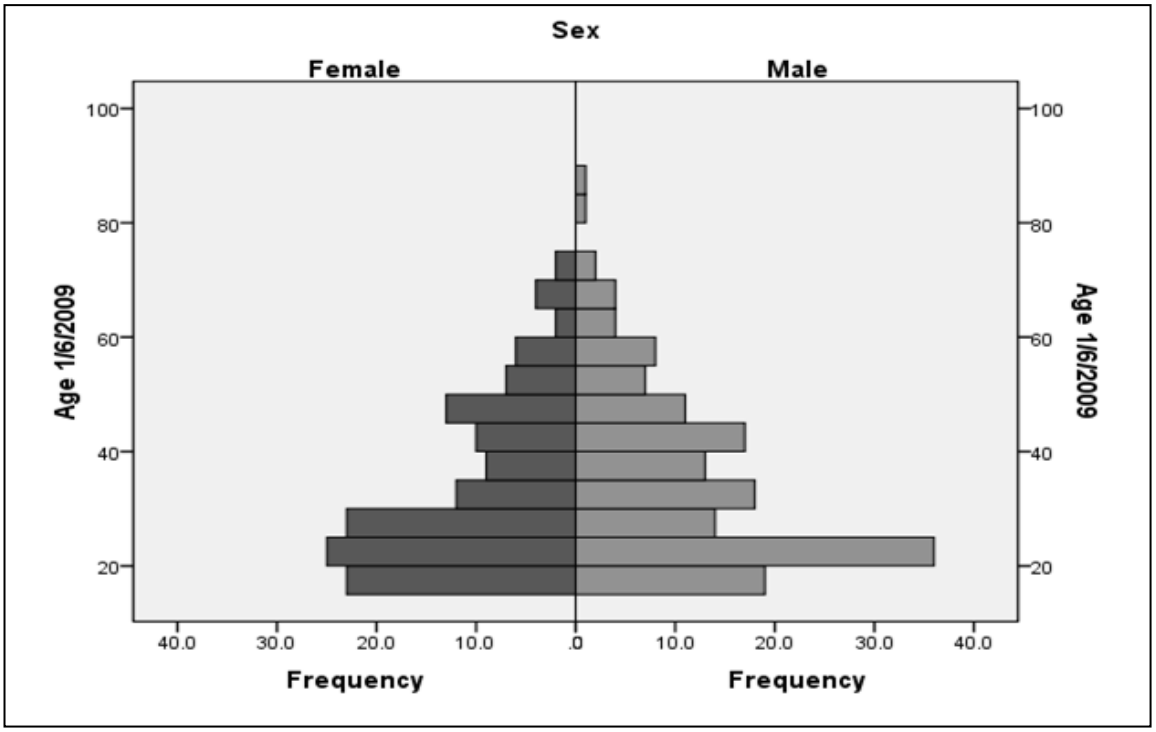


Figure 27: Age distribution of cases

		Designation			
		Cases (n=291)		Controls (n=182)	
		n	(%)	n	(%)
Tribal group	Chagga	220	(75.6%)	148	(81.3%)
	Other	55	(18.9%)	31	(17.0%)
	Not known	16	(5.5%)	3	(1.6%)
Religion	Christian	223	(76.6%)	149	(81.9%)
	Muslim	59	(20.3%)	32	(17.6%)
	Not known	9	(3.1%)	1	(0.5%)

Table 45: Tribal and religious background of cases and controls

Variable	OR	95% CI	*p*-value
Tribal group other than Chagga (vs. Chagga)	1.19	0.73 to 1.94	0.474
Muslim religion (vs. Christian)	1.23	0.76 to 1.98	0.389

Table 46: Tribe and religion: uni-variable odds ratios for association with epilepsy

6.3.2 Risk factors for epilepsy

Data on specific risk factors for epilepsy were available for all cases and controls (Table 47). Factors significantly associated with epilepsy on uni-variable analysis were a history of childhood febrile convulsions and a history of perinatal complications (Table 48). No controls gave a history of meningitis, stroke or brain abscess, and therefore these categories could not be analysed using contingency tables to generate ORs. As these are distinct clinical entities it was not appropriate to include them within any other categories to facilitate any further statistical analysis. No controls reported being HIV +ve.

6.3.3 Family history

Data on a family history of epilepsy were available for all cases and controls. Proportionally more cases than controls reported a family history of epilepsy in both first- and second-degree relatives. Proportionally more cases than controls reported a family history in a second-degree than in a first degree-relative (Table 49). The uni-variable odds for cases reporting any family history (first- or second-degree relatives) were 5.31 (95% CI 2.36 to 11.99; $p<0.001$). When the categories of family history in either a first- or second-degree relative were compared with the baseline comparator of having no family history there was a significant association between epilepsy and a family history in a second-degree but not in a first-degree relative (Table 50).

6.3.4 Cognitive and motor impairments

The presence of cognitive or motor impairment was recorded for all cases and controls (Table 51). Both were significantly associated with epilepsy, although the small numbers of controls with cognitive or motor impairments led to very wide confidence intervals around the ORs (Table 52).

6.3.5 Alcohol

Information on alcohol consumption was available for all 291 cases and 180 (98.9%) of 182 controls. The overall pattern of alcohol consumption amongst cases and controls is summarised in Table 53. A higher proportion of cases than controls denied alcohol use (81.8% vs. 52.8%) and when this variable was dichotomised (drinks alcohol vs. abstinent from alcohol), this association was found to be significant (OR 0.25, 95% CI 0.16 to 0.38, $p<0.001$). To further explore the pattern of alcohol consumption among those that did drink alcohol, ORs for each category of alcohol use (light, moderate or heavy) were calculated using abstinence as the baseline comparator. A negative association with epilepsy was observed in all three categories (light, moderate and heavy alcohol use) (Table 54).

	Cases (n=291)		Controls (n=182)	
	n	(%)	n	(%)
Febrile convulsions in childhood	31	(10.7%)	1	(0.5%)
Perinatal complication	23	(7.9%)	4	(2.2%)
Head injury	20	(6.9%)	8	(4.4%)
History of febrile illness with LOC/convulsion	20	(6.9%)	9	(4.9%)
Meningitis	6	(2.1%)	0	(0.0%)
History of malaria with LOC/convulsion	5	(1.7%)	3	(1.6%)
Stroke	3	(1.0%)	0	(0.0%)
Brain abscess	1	(0.3%)	0	(0.0%)

Table 47: Risk factors for epilepsy reported by cases and controls

Variable	OR	95% CI	p-value
Febrile convulsions in childhood	21.58	2.92 to 159.52	<0.001
Perinatal complication	3.82	1.30 to 11.23	0.005
Head injury	1.61	0.69 to 3.73	0.258
History of febrile illness with LOC/convulsion	1.42	0.63 to 3.19	0.389
History of malaria with LOC/convulsion	1.04	0.25 to 4.42	0.954

Table 48: Risk factors – uni-variable associations with epilepsy

	Cases		Controls	
Family history	**n**	**(%)**	**n**	**(%)**
1st degree relative	18	(6.2%)	6	(3.3%)0
2nd degree relative	33	(11.3%)	1	(0.5%)
None	240	(82.5%)	175	(96.2%)
Total	291	(100.0%)	182	(100.0%)

Table 49: Family history of epilepsy amongst cases and controls

Variable	**OR**	**95% CI**	***p*-value**
No family history	1.00	-	-
Family history in 2nd degree relative	24.06	3.26 to 177.61	0.002
Family history in 1st degree relative	2.19	0.85 to 5.62	0.104

Table 50: Uni-variable associations between epilepsy and family history

	Cases (n=291)		Controls (n=182)	
	n	(%)	n	(%)
Cognitive impairment	88	(30.2%)	2	(1.1%)
Motor impairment	48	(16.5%)	1	(0.5%)

Table 51: Cognitive and motor impairments in cases and controls

Variable	OR	95% CI	p-value
Cognitive impairment	39.65	9.63 to 163.35	<0.001
Motor impairment	35.75	4.89 to 261.45	<0.001

Table 52: Cognitive and motor impairments: uni-variable associations with epilepsy

	Cases		Controls	
Alcohol intake	**n**	**(%)**	**n**	**(%)**
None	238	(81.8%)	95	(52.8%)
Light	22	(7.6%)	35	(19.4%)
Moderate	11	(3.8%)	33	(18.3%)
Heavy	20	(6.9%)	17	(9.4%)
Total	291	(100.0%)	180	(100.0%)

Table 53: Alcohol use (cases and controls)

Variable	**OR**	**95% CI**	**p-value**
Abstinent from alcohol	1.00	-	-
Light alcohol use	0.25	0.14 to 0.45	<0.001
Moderate use	0.13	0.07 to 0.27	<0.001
Heavy use	0.47	0.24 to 0.94	0.032

Table 54: Uni-variable associations between epilepsy and alcohol use

6.3.6 Marital status

Data on marital status were available for 281 (96.6%) of 291 cases and for all 182 controls (Table 55, Figure 28). PWE were significantly less likely to be married or to be widowed (Table 56).

6.3.7 Educational level

Data on educational level were available for 275 (94.5%) of 291 cases and 180 (98.9%) of 182 controls (Table 57, Figure 29). Three individuals (all PWE with cognitive impairment) had attended non-mainstream education, and for the purposes of analysis were classed as having completed primary education. The category "post-primary education" includes all individuals who were either in full-time secondary or further education at the time of the study or who had any level of prior secondary or further education. Primary education is compulsory in Tanzania from the age of eight years, and access to and completion of primary education were therefore the outcomes of primary interest. To generate uni-variable ORs these data were dichotomised in three ways: any schooling vs. no schooling, completed primary education vs. incomplete or no primary education, and any secondary or further education vs. all lower levels combined. PWE were less likely to have any schooling at all or to have completed their primary education (Table 58).

Data on literacy were available for 276 (94.8%) of 291 cases and 181 (99.5%) of 182 controls, with 48.9% of cases stating they could not read or write compared with 19.9% of controls (OR 3.86, 95% CI 2.50 to 5.96, $p<0.001$).

6.3.8 Occupation

Data on occupation were available for 286 (98.3%) of 291 cases and 181 (99.5%) of 182 controls (Table 59). Epilepsy was significantly associated with not working for health related reasons, and with contributions to the household economy being limited to domestic tasks only (Table 60). Cases were also significantly less likely than controls to be engaged in farming or herding as their main source of income (Table 60). Odds ratios were not calculated for the categories 'other manual' and 'not working-retired/elderly' as no controls fell into either of these categories.

	Cases		Controls	
Marital status	**n**	**(%)**	**n**	**(%)**
Single (never married)	178	(63.3%)	57	(31.3%)
Married	74	(26.3%)	114	(62.6%)
Divorced/separated	22	(7.8%)	2	(1.1%)
Widowed	7	(2.5%)	9	(4.9%)
Total	281	(100.0%)	182	(100.0%)

Table 55: Marital status of cases and controls

Variable	OR	95% CI	p-value
Single (never married)	1.00	-	-
Married	0.21	0.14 to 0.32	<0.001
Divorced/separated	3.52	0.80 to 15.44	0.095
Widowed	0.25	0.09 to 0.70	0.008

Table 56: Marital status: uni-variable associations with epilepsy

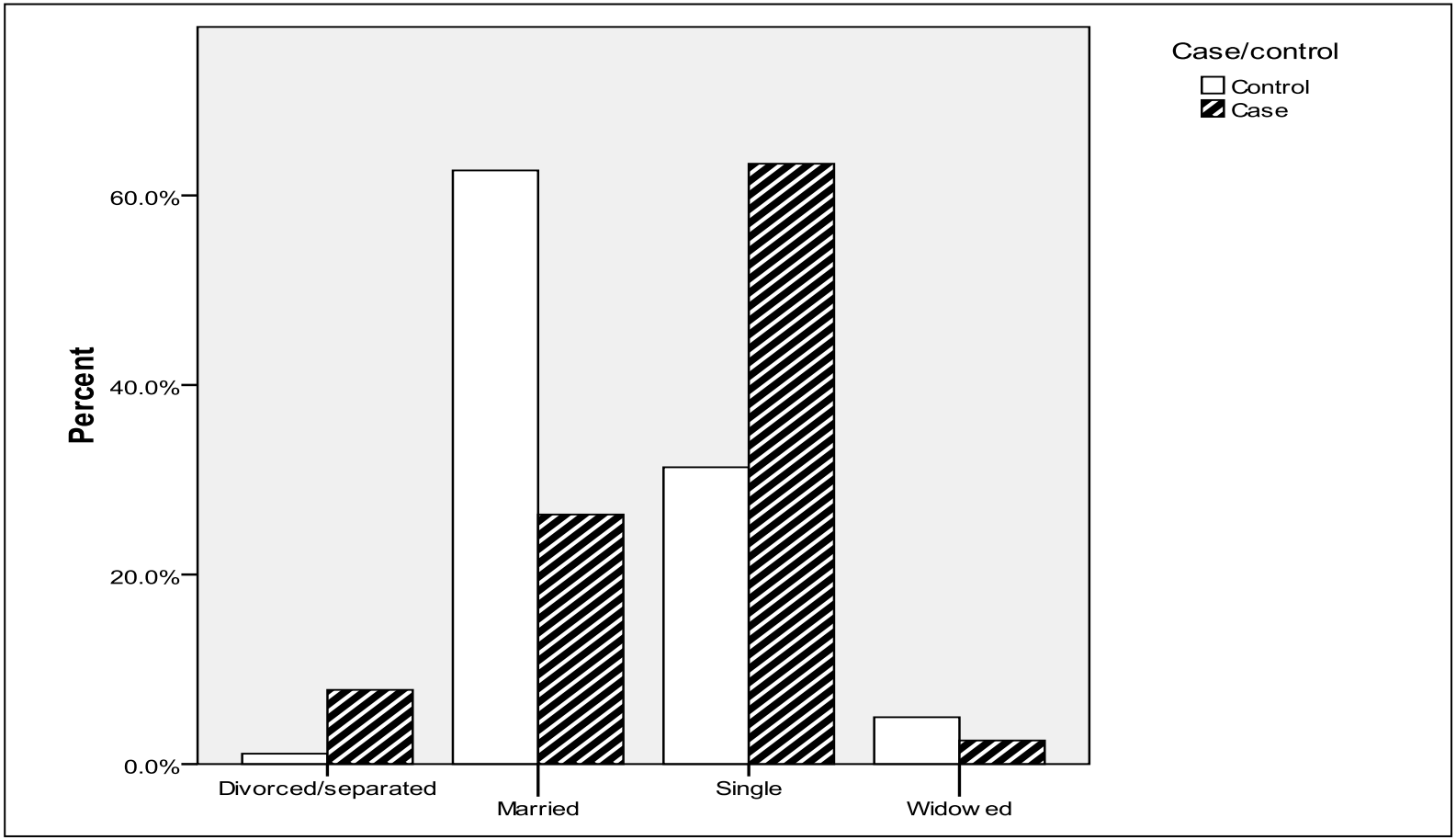


Figure 28: Marital status of cases and controls

	Cases		Controls	
Educational level	**n**	**(%)**	**n**	**(%)**
No schooling	57	(20.7%)	12	(6.7%)
Incomplete primary education	75	(27.3%)	30	(16.7%)
Completed primary education	111	(40.4%)	113	(62.8%)
Any secondary/further education	32	(11.6%)	25	(13.9%)
Total	275	(100.0%)	180	(100.0%)

Table 57: Highest educational level (cases and controls)

Variable	**OR**	**95% CI**	**p-value**
Any schooling (vs. no schooling at all)	0.27	0.14 to 0.53	<0.001
Completed primary education (vs. incomplete primary/no schooling)	0.33	0.22 to 0.50	<0.001
Current or previous post-primary education (vs. lower levels combined)	0.82	0.47 to 1.43	0.48
Illiterate (vs. literate)	3.86	2.50 to 5.96	<0.001

Table 58: Univariable associations between epilepsy and educational level

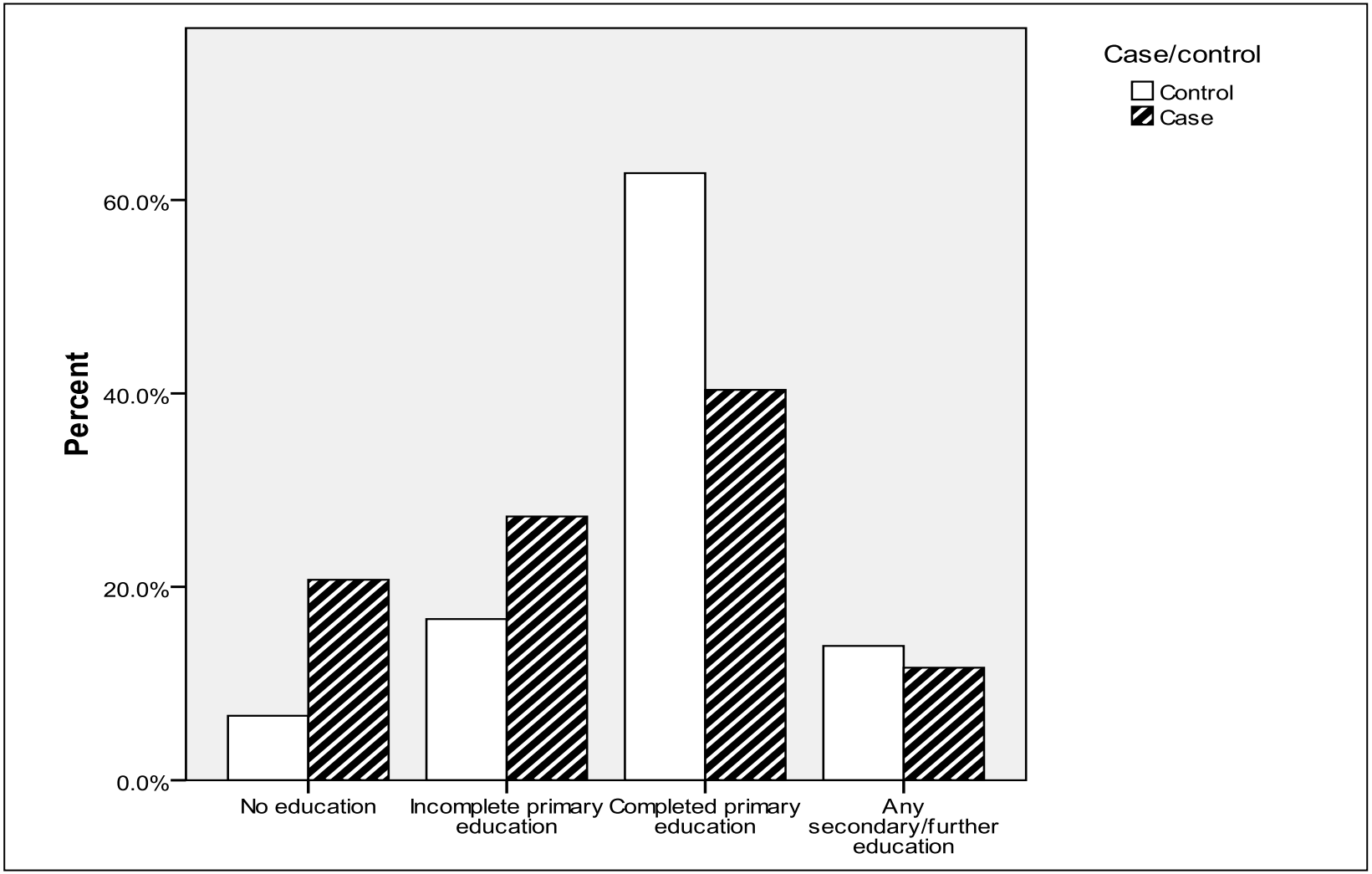


Figure 29: Highest educational level of cases and controls

	Cases		Controls	
Occupation	**n**	**(%)**	**n**	**(%)**
Farming/herding	96	(33.6%)	126	(69.6%)
Not working - sick or disabled	69	(24.1%)	3	(1.7%)
Domestic tasks/housework only	47	(16.4%)	7	(3.9%)
Trade/skill	20	(7.0%)	12	(6.6%)
In full-time secondary/further education	17	(5.9%)	13	(7.2%)
Not working - unemployed	18	(6.3%)	4	(2.2%)
Private business	8	(2.8%)	10	(5.5%)
Salaried employment	5	(1.7%)	6	(3.3%)
Other manual	3	(1.0%)	0	(0.0%)
Not working – retired/elderly	3	(1.0%)	0	(0.0%)
Total	286	(100.0%)	181	(100.0%)

Table 59: Occupations of cases and controls

Occupation	OR	95% CI	*p*-value
Farming/herding	0.22	0.15 to 0.33	<0.001
Not working – sick or disabled	18.87	5.84 to 60.96	<0.001
Domestic tasks/housework only	4.89	2.16 to 11.07	<0.001
Trade/skill	1.10	0.51 to 2.22	0.879
In full-time education	0.82	0.39 to 1.72	0.597
Not working - unemployed	2.97	0.99 to 8.93	0.033
Private business	0.49	0.19 to 1.27	0.142
Salaried employment	0.52	0.16 to 1.73	0.284

Table 60: Univariable associations between epilepsy and occupation

6.4 Multivariable logistic regression analyses

6.4.1 Clinical associations with epilepsy

The uni-variable odds for all clinical associations and risk factors for epilepsy are summarised in Table 61, with the final regression model given in Table 62. As there was incomplete matching for age and sex these variables were also entered into the regression model. Predictors of epilepsy in the final model were a family history of epilepsy in a second-degree relative, presence of cognitive impairment, a history of febrile convulsions in childhood, and presence of motor impairment. Epilepsy was negatively associated with light or moderate alcohol use (Table 62).

Only small numbers of controls had either cognitive or motor impairments (two and one respectively). To assess the effect this had on the sensitivity of the initial model the regression was reiterated with these variables omitted (Table 63). When this was done, a family history of epilepsy in a second-degree relative and a history of febrile convulsions in childhood both remained as predictors of epilepsy, with a history of perinatal complication also now appearing as a predictor of epilepsy, although this model fitted the data less well (Hosmer & Lemeshow 0.82 vs. 0.96). The negative associations with light and moderate alcohol use that were observed in the initial model were reproduced, with similar adjusted ORs as previously.

Variable	OR	95% CI	*p*-value
Demographic features			
Male sex	1.36	0.94 to 1.97	0.105
Tribal group other than Chagga	1.19	0.73 to 1.94	0.474
Muslim religion	1.23	0.76 to 1.98	0.389
Clinical associations			
No family history of epilepsy	1.00	-	-
Family history of epilepsy in 1st degree relative	2.19	0.85 to 5.62	0.104
Family history of epilepsy in 2nd degree relative	24.06	3.26 to 177.61	0.002
Febrile convulsions in childhood	21.6	2.92 to 159.52	<0.001
Perinatal complication	3.82	1.30 to 11.23	0.005
Head injury	1.61	0.69 to 3.73	0.258
History of febrile illness with LOC/convulsion	1.42	0.63 to 3.19	0.389
History of malaria with LOC/convulsion	1.04	0.25 to 4.42	0.954
No alcohol use	1.00	-	-
Light alcohol use (vs. no alcohol use)	0.25	0.14 to 0.45	<0.001
Moderate alcohol use (vs. no alcohol use)	0.13	0.07 to 0.27	<0.001
Heavy alcohol use (vs. no alcohol use)	0.47	0.24 to 0.94	0.032
Cognitive impairment	39.65	9.63 to 163.35	<0.001
Motor impairment	35.75	4.89 to 261.45	<0.001

Table 61: Summary of uni-variable clinical associations with epilepsy

Variable	B	SE	Adjusted OR*	95% CI Lower	95% CI Upper
History of childhood febrile convulsions	2.829	1.057	16.93	2.14	134.26
Family history of epilepsy in 2nd degree relative	3.269	1.050	26.29	3.36	205.99
Cognitive impairment	3.153	0.737	23.41	5.52	99.23
Motor impairment	2.303	1.045	10.01	1.29	77.59
Light alcohol use (vs. none)	-1.351	0.360	0.26	0.13	0.52
Moderate alcohol use (vs. none)	-1.823	0.434	0.16	0.07	0.38

Goodness of fit (Hosmer & Lemeshow)=0.96 ***adjusted for variables summarised in Table 61 and for age**

Table 62: Logistic regression model of clinical associations with epilepsy

Variable	B	S.E.	Adjusted OR*	95% CI Lower	95% CI Upper
Febrile convulsions in childhood	3.017	1.050	20.42	2.61	159.86
History or perinatal complication	1.223	0.588	3.40	1.07	10.75
Family history of epilepsy (2nd degree relative)	3.366	1.067	28.97	3.58	234.73
Light alcohol use	-1.622	0.338	0.20	0.10	0.38
Moderate alcohol use	-2.277	0.429	0.10	0.04	0.24

Goodness of fit (Hosmer & Lemeshow)=0.82 ***adjusted for variables in Table 61 but excluding cognitive and motor impairments, and for age**

Table 63: Logistic regression model (cognitive and motor impairments excluded)

6.4.2 Socio-economic associations with epilepsy

A summary of all socio-economic uni-variable associations with epilepsy is given in Table 64. As for the modelling of clinical associations with epilepsy, age and sex were entered into the regression model as matching for these factors during recruitment had been incomplete. Disability due to cognitive or motor impairments may affect socio-economic status independently of epilepsy, and these were therefore also included in the model as possible confounders. The lower proportion of cases that drink alcohol may also be related to socio-economic status, and alcohol consumption was also included in the model for this reason. Demographic features of tribe and religion were also entered. In the final model, shown in Table 65, being divorced or separated was a predictor of epilepsy, with epilepsy being negatively associated with being engaged in farming or herding as a primary source of income, or having completed primary education. The negative associations with light or moderate alcohol use were also reproduced in this model.

As with the modelling of clinical associations, this model was reiterated to assess the sensitivity with cognitive and motor impairments excluded (Table 66). In the revised model the occupational categories of being sick or disabled and of being limited to domestic tasks only now appeared as additional predictors of epilepsy. The negative association with having completed primary education no longer appeared, while being illiterate now appeared as a predictor of epilepsy. Finally, in addition to being divorced or separated, being currently married now appeared as a negative association with epilepsy. The Hosmer and Lemeshow statistic of 0.19 for this revised model indicates a poorer fit with the data than the model in which cognitive and motor impairments were initially entered, however.

Variable	OR	95% CI	*p*-value
Marital status			
Single	1.00	-	-
Married (vs. single)	0.21	0.14 to 0.32	<0.001
Divorced/separated (vs. single)	7.65	1.78 to 32.92	<0.001
Widowed (vs. single)	3.52	0.80 to 15.44	<0.095
Educational level			
Any schooling (vs. no schooling at all)	0.25	0.09 to 0.70	0.008
Completed primary education (vs. incomplete primary/no education)	0.33	0.22 to 0.50	<0.001
Current or previous post-primary education (vs. all lower levels combined)	0.82	0.47 to 1.43	0.48
Illiterate (vs. literate)	3.86	2.50 to 5.96	<0.001
Occupation			
Farming/herding	0.22	0.15 to 0.33	<0.001
Not working – sick or disabled	18.87	5.84 to 60.96	<0.001
Domestic tasks/housework only	4.89	2.16 to 11.07	<0.001
Trade/skill	1.10	0.51 to 2.22	0.879
In full-time education	0.82	0.39 to 1.72	0.597
Not working - unemployed	2.97	0.99 to 8.93	0.033
Private business	0.49	0.19 to 1.27	0.142
Salaried employment	0.52	0.16 to 1.73	0.284

Table 64: Summary of univariable socio-economic associations with epilepsy

				95% CI	
Variable	**B**	**SE**	**Adjusted OR***	**Lower**	**Upper**
Divorced/separated	2.755	0.821	15.72	3.15	78.61
Light alcohol use	-1.450	0.405	0.24	0.11	0.52
Moderate alcohol use	-1.600	0.472	0.20	0.08	0.51
Farming/herding	-0.903	0.280	0.41	0.23	0.72
Completed primary education	-0.860	0.275	0.42	0.25	0.73

Goodness of fit (Hosmer & Lemeshow)=0.62 ***adjusted for age, sex, tribe, religion, cognitive and motor impairment, and all variables in Table 64**

Table 65: Logistic regression model of socio-economic associations with epilepsy

				95% CI	
Variable	**B**	**S.E.**	**Adjusted OR***	**Lower**	**Upper**
Marital status – married	-0.563	0.271	0.57	0.34	0.97
Marital status - divorced/separated	2.588	0.816	13.30	2.69	65.84
Light alcohol use	-1.401	0.385	0.25	0.12	0.52
Moderate alcohol use	-1.691	0.459	0.18	0.08	0.45
Farming/herding	-0.736	0.288	0.48	0.27	0.84
Sick/disabled	1.871	0.663	6.50	1.77	23.80
Domestic tasks only	1.110	0.496	3.04	1.15	8.02
Illiterate	0.914	0.285	2.49	1.43	4.36

Goodness of fit (Hosmer & Lemeshow)=0.19 ***adjusted for age, sex, tribe, religion and all variables in Table 64**

Table 66: Logistic regression model (cognitive and motor impairments excluded)

6.5 Discussion

After controlling for the demographic features of age, sex and tribal and religious groups, predictors of epilepsy in the HDSS adult population were a history of febrile convulsions, a family history of epilepsy in a second-degree relative, and the presence of cognitive or motor impairments. These findings correlate in part with those of the few other case-control studies from SSA to have used multivariable analyses to control for confounding. In rural Kenya family history was also found to be a predictor of epilepsy (Edwards et al., 2008), and it is interesting to note that in this study a stronger uni-variable association was found with a family history in extended relatives ($p<0.0001$) than in first-degree relatives ($p=0.0332$). A complex, non-Mendelian hereditary pattern for some epilepsy in SSA has previously been proposed (Neuman et al., 1995), and these findings from Hai and elsewhere may lend support to this theory. At the same time, it could be argued that the high rates of focal-onset seizures along with high rates of clinically apparent structural brain disease, as evidenced by cognitive and motor impairments, would point more towards a predominance of environmental causes in the Hai population. Family history has also been identified as a predictor of epilepsy in the two other studies to have used these techniques (Nsengiyumva et al., 2003, Matuja et al., 2001), although details available from the latter of these studies, conducted in Tanzania, implicate first-degree relatives as opposed to extended family members. The authors of the Tanzanian study also comment that the meaning of this finding is not clear, as there was also a high rate of focal-onset epilepsy identified in that study (Matuja et al., 2001). In the recent Kenyan study mentioned above, the authors sought to make the distinction between a family history of febrile and non-febrile seizures, but acknowledge that problems with recall may have limited the power and precision of these observations (Edwards et al., 2008). In our study we did not attempt to make this distinction, and acknowledge that in a study of adults that utilises data derived from reported events problems with recall are likely to be a major limitation.

A childhood history of febrile convulsions and the presence of cognitive and motor impairments were also predictors of epilepsy in the Hai population, also reflecting

observations made elsewhere in SSA (Ogunniyi et al., 1987, Matuja et al., 2001). In two different Tanzanian cohorts of PWE, 9.6% and 22% of cases were described as having mental retardation or of being of impaired intelligence (Winkler et al., 2009c, Matuja et al., 2001). In our study, when the regression model was reiterated with these variables removed it was interesting to note that a history of adverse perinatal events appeared as a predictor of epilepsy. Again, this mirrors case-control data from elsewhere in SSA, including Tanzania (Edwards et al., 2008, Matuja et al., 2001, Nsengiyumva et al., 2003). The issue of obstetric complications and their contribution to the burden of mortality and morbidity is of particular interest in SSA where most children are born at home without professional help, and where maternal and infant mortality rates are generally high (Kitange et al., 1996, Janson, 2007).

Case-control studies from SSA have also previously identified head injury as a significant cause of epilepsy (Ogunniyi et al., 1987, Edwards et al., 2008). While head injury was clearly implicated in a number of cases of epilepsy in Hai, it was not found to be a significant predictor of epilepsy in the HDSS population. This may be a reflection of the rural nature of the district, with few paved roads carrying motorised transport, or possibly of the peaceful nature of the local society, with the prevailing influence on the rates of serious and penetrating head injury of road traffic accidents and civil unrest and conflict that are seen in other parts of SSA not being present (Preux and Druet-Cabanac, 2005, Adamolekun, 1995).

With regards to socio-economic associations with epilepsy, we found that cases were less likely to have completed primary education, and were less likely to be engaged in farming. These predictors were present in the final regression model which adjusted for cognitive and motor impairments, suggesting that these negative associations are reflective of epilepsy, rather than the presence of other disabilities with which epilepsy may be associated. With primary education being compulsory in Tanzania, and subsistence agriculture being the chief economic activity in this population, this finding suggests that any social marginalisation experienced by PWE in this population, as evidenced by a greater likelihood of divorce or marital separation, is further compounded by educational

and economic disadvantage. There are very few case-control data from SSA of which we are aware which specifically examine the degree of association between epilepsy and similar socio-economic outcomes. A study in Burundi compared 352 PWE identified from the general population with 704 controls to ascertain the direct and indirect economic costs of epilepsy (Nsengiyumva et al., 2004). While there was no comparison between cases and controls with regards to the socio-demographic indicators that we have examined here, the authors do state that there were no differences between treated and untreated PWE in terms of marital or employment status. Our findings are consistent, however, with those of a number of observational studies that have documented the experience of PWE living in Tanzania and elsewhere in SSA. In a clinic-based series of 231 PWE from Nigeria, nearly 20% of cases had suffered marital breakdown or had been withdrawn from education as a result of their epilepsy (Nuhu et al., 2010). Observational studies from Nigeria, Zambia and Tanzania have all described children with epilepsy being expelled from school solely because of their seizures (Osuntokun and Odeku, 1970, Birbeck and Kalichi, 2003, Matuja and Rwiza, 1994). In a survey of 276 health care workers in rural Zambia one quarter of respondents stated that they would not allow their child to marry someone with epilepsy and one fifth thought that PWE should not marry or hold employment (Chomba et al., 2007). A survey of 171 teachers drawn from the same population found that between 16.8% and 28.2% of respondents thought that epilepsy was due to possession by spirits, witchcraft or contagion, with aberrant beliefs about epilepsy correlating with stigmatising practices such as excluding children with seizures from school (Birbeck et al., 2006). In a qualitative study conducted in the HDSS epilepsy cohort, forty-one PWE and nineteen relatives or carers were interviewed in depth, with themes of social exclusion across the spheres of marriage, work and education emerging through conversation with both groups (Mushi et al., 2010).

6.6 Summary and conclusions

The identification of febrile seizures, perinatal complications, and evidence of structural brain disease as predictors of epilepsy in the HDSS population points to a considerable burden of acquired epilepsy. By implication, improved obstetric care and improved recognition and management of febrile seizures in childhood may lead to a measurably reduced morbidity with epilepsy in later life in this population. Epilepsy appears to be associated with adverse socio-economic outcomes in this population, indicating that the burden of epilepsy extends beyond the morbidity and costs associated with purely the medical aspects of the disease. The degree to which reduced educational attainment and economic productivity pertains to the physical burden of disease or to enacted stigma warrants further investigation.

Chapter 7. Cysticercosis and epilepsy in Hai

Abstract

Background

Neurocysticercosis (NCC) results from infection with the larval form of the human tapeworm *Taenia solium*. NCC has been described as a major cause of symptomatic epilepsy in endemic regions around the world, including Latin America, India and China. NCC has been postulated as an important cause of epilepsy in SSA, although there have been few comprehensive studies.

Methods

Blood samples from adult PWE and healthy controls living in the HDSS were tested for the presence of antibodies to *T.solium* using an EITB assay to two different cysticercal antigens. All PWE were offered a CT head scan to look for evidence of active or calcified cystic lesions suggestive of NCC. Questionnaire data on pig keeping, household sanitation and pork consumption were collected from cases and controls.

Results

Antibodies to *T.solium* were detected in six out of 218 cases (2.8%) and in none of 174 controls (p=0.036). Lesions suggestive of NCC were seen in eight out of 200 CT scans (4.0%). Taking CT as the gold standard for diagnosis, EITB serology performed with a positive predictive value of 40.0%, sensitivity of 33.3% and specificity of 98.2%. No correlation with household sanitation, pig keeping or pork consumption was identified on comparing either cases and controls, or cases with and without NCC.

Conclusions

NCC is present in Hai, but with very low endemicity. EITB serology does not appear to perform well as a screening test in this context.

7.1 Introduction

7.1.1 Cysticercosis, neurocysticercosis and epilepsy

Taenia solium is a zoonotic human cestode that depends on the pig as an intermediate host. Infection of human tissue with the larval stage of the parasite is known as cysticercosis: the term neurocysticercosis (NCC) specifically refers to infection of the CNS. NCC is the commonest helminthic disease of the CNS worldwide (Winkler et al., 2009a), and is increasingly recognised as a leading cause of epilepsy in endemic countries (de Bittencourt et al., 1996a). Up to fifty million people worldwide may be affected by cysticercosis (World Health Organisation, 2006), which may be implicated in up to 50,000 deaths per year (Roman et al., 2000). The WHO has estimated that up to 30% of all epilepsy worldwide may be associated with NCC, with ten million of these individuals living in Africa (World Health Organisation, 2011).

Humans are the definitive host for *T.solium*, with individuals becoming infected through the consumption of undercooked pork that contains cysticerci, the larval stage of the parasite. Ingested cysticerci become attached to the wall of the small intestine, developing into adult worms of up to three metres in length over a period of approximately two months. Individuals infected in this way will excrete proglottid tapeworm segments in their faeces from which the immediate environment is contaminated with viable *Taenia* eggs. When eggs are ingested by a pig they hatch into active entities known as oncospheres; these are able to cross the gut lumen to become lodged in extra-intestinal tissues where they develop into the cystic larval stage of the parasite. The life-cycle is completed when undercooked encysted pork is consumed and viable cysts develop into adult worms in the gut of the next human host. Human cysticercosis therefore occurs when *Taenia* eggs are accidentally consumed by humans, through faecal-oral transmission or through auto-infection, with human tissue subsequently becoming infected with the encysted larval stage of the tape worm (King, 2005). The tissues most commonly affected in this way include subcutaneous tissue, striated muscle, the eye and the CNS (Winkler et al., 2009a). Four developmental stages in NCC are recognised. In the first stage immature cysts appear in the tissues within one to four weeks (stage 1). Cysts then mature and become viable after approximately two

months (stage 2); this stage is generally asymptomatic and may persist for ten years or more. Loss of host immune control after between two and ten years leads to cyst degeneration and associated inflammation (stage 3); involvement of parenchymal brain tissue at this stage can present with signs and symptoms of raised intracranial pressure and can be associated acutely with seizures and a reduced conscious level. In the final stage there is involution and calcification of the cyst, with eventual resolution of any associated inflammation (stage 4). Calcified parenchymal foci and associated scarring have the potential to act as epileptogenic foci, giving rise to acquired focal-onset epilepsy in affected individuals (King, 2005).

A number of epidemiological insights are gained from this description of the natural history of human *T.solium* infection and human cysticercosis. Firstly, the conditions for the perpetuation of *T.solium* infections in humans depend on two chief factors: there being a pig population that is routinely exposed to human faecal matter, e.g. in water, contaminated vegetable matter or directly from night soil or through defecation in pig pens, and there being insufficient food hygiene standards, in abattoirs or at the food preparation stage, to protect humans from the consumption of undercooked encysted pork. These conditions hold sway in many LMICs, particularly where free-range pig rearing is practiced and where public sanitation is limited, and it is well recognised that cysticercosis is strongly associated with poverty (Willingham III and Engels, 2006). Secondly, the risk factor for human cysticercosis is faecal-oral exposure in an environment where individuals are carrying adult *T.solium* worms in their guts and are excreting eggs into the environment. Each proglottid segment contains between 50,000 and 60,000 eggs, and infected humans may shed a few proglottids per day (Garcia et al., 2003). In this way a single carrier may be responsible for the infection of numerous individuals in a community, and neither pig-rearing nor pork consumption are therefore necessary to the acquisition of cysticercosis (Schantz et al., 1992, Hira et al., 2004).

While post-mortem evidence suggests that NCC may be asymptomatic in up to 80% of infected individuals (Bern et al., 1999), the relationship between NCC and epilepsy has also been clearly established. In Latin-American countries cerebral calcifications are a

common finding in persons with seizures or epilepsy in populations where *T.solium* is endemic (Nash et al., 2004). The prevalence of cerebral calcification consistent with NCC in randomised studies of endemic populations ranges from 9% to 18%, and rates as high as 83% have been documented in selected populations with seizures (Nash et al., 2004). For example, typical calcifications were found in 36% and 35% of persons with seizures in two different villages in Guatemala compared to 15% and 9% in matched controls without a history of seizures (Garcia-Noval et al., 2001). Cysts or degenerating cysts in this study were responsible for about 25% of the seizures in patients with cysticercosis.

An estimated 80 to 90% of people with symptomatic NCC will develop seizures at some point (Bern et al., 1999), although the proportion of people with acute symptomatic seizures associated with NCC who go on to develop epilepsy is unknown (Foyaca-Sibat et al., 2009). While NCC is widely considered to be the leading preventable cause of epilepsy in LMICs (Preux and Druet-Cabanac, 2005, Roman et al., 2000), studies have not always discriminated between acute symptomatic seizures and epilepsy, and some studies have included patients with seizures and positive serology without the support of neuro-imaging (Garcia et al., 1993, Nsengiyumva et al., 2003). In endemic areas many people may be exposed to *T.solium* eggs, including exposure after the onset of epilepsy, leading to high false-positive rates on serological testing (Foyaca-Sibat et al., 2009).

7.1.2 Diagnosing cysticercosis and neurocysticercosis

Although NCC is the most common helminthic infection of the CNS, its diagnosis is rendered difficult by non-specific clinical manifestations, including seizures, headaches, focal neurological deficits, by imaging findings that are often abnormal but seldom pathognomic (Garcia and Del Brutto, 2003, Coyle and Tanowitz, 2009, Martinez et al., 1989), and by the variable sensitivity and specificity of serological tests, particularly in patients with single lesions (Coyle and Tanowitz, 2009, Wilson et al., 1991).

Infection with *T.solium* is associated with specific IgG antibody responses, with multiple antibodies of different specificities appearing at different intervals after infection reflecting the varying antigenic signatures of the different stages of parasitic development (Dorny et al., 2003). Various tests to detect the presence of *T.solium* antibodies have

been developed, making use of either crude antigen preparations or purified glycoproteins (Ito et al., 2003). An enzyme-linked immuno-transfer blot (EITB) of seven purified cysticercal glycoproteins has been shown to have a specificity approaching 100% and sensitivity of between 70% and 90% (Tsang et al., 1989). EITB is an expensive technique, however, and in LMICs the simpler, more affordable and more widely available technique of the enzyme-linked immunosorbent assay (ELISA) is preferable (Rosas et al., 1986). An ELISA using purified glycoproteins obtained from cyst fluid has been shown to have a sensitivity and specificity similar to that of EITB in experimental conditions (Dorny et al., 2003).

Serological tests alone can be difficult to interpret. For example, the utility of antibody-based serological techniques may be limited in cases with small numbers of lesions or solitary cysticerci (Garcia et al., 2003, Dorny et al., 2003), and sensitivities as low as 28% have been reported in cases with single cysts in the brain (Wilson et al., 1991). Conversely, a positive antibody test may merely indicate prior exposure rather than active infection or disease (Garcia et al., 2001), and in endemic populations 10% or more of the general population may have antibodies to *T.solium* (Bern et al., 1999). Reliance on serological tests alone may thus lead to missed diagnoses in individuals truly suffering with NCC or to an overestimation of the extent of disease related to cysticercosis in communities where *T.solium* is endemic. Correlation with clinical details and imaging is therefore imperative wherever possible, although the latter of these modalities is seldom routinely available in resource-limited settings.

Antigen detection has been proposed as a suitable alternative to antibody testing, particularly in the detection of viable cysts that may be amenable to anti-helminthic treatment. Several assays have been developed (Dorny et al., 2003), and a high level of agreement between an antigen ELISA, CT scanning and histological examination have been reported (Erhart et al., 2002). As with antibody serology, however, lower sensitivities have been reported in patients with single viable lesions or enhancing lesions only (Garcia et al., 2000), and the sensitivity and specificity of antigen testing were both found to be

poorer than that of antibody testing in a South African population (Foyaca-Sibat et al., 2009).

A diagnosis of NCC is usually based on neuro-imaging with either CT or magnetic resonance imaging (MRI) (Garcia and Del Brutto, 2005). CT imaging of the brain has a sensitivity and specificity in excess of 95% for the diagnosis of NCC, and although characteristic patterns associated with each stage in the development and subsequent involution of cysts have been described, findings are rarely pathognomonic (Garcia and Del Brutto, 2003), and the differential diagnosis on neuro-imaging in endemic regions includes hydatid disease, tuberculosis and toxoplasmosis (Garcia et al., 2003).

7.1.3 Clinical diagnostic criteria for NCC

To account for these difficulties, and to help clinicians with arriving at a diagnosis, a set of diagnostic criteria comprising four categories has been proposed (Del Brutto et al., 2001). These take into account clinical, imaging and serological findings along with epidemiological factors, as follows:

Absolute criteria: histological demonstration of the parasite, CT imaging demonstrating the scolex, direct visualisation of sub-retinal parasites on fundoscopy.

Major criteria: lesions highly suggestive of NCC on neuro-imaging, positive serum EITB for anti-cysticercal antibodies, resolution of intracranial lesions after specific anti-helminthic therapy, spontaneous resolution of single enhancing lesions.

Minor criteria: lesions compatible with NCC on neuro-imaging, clinical manifestations suggestive of NCC, positive CSF ELISA for anti-cysticercal antibodies or cysticercal antigens, cysticercosis present outside the CNS.

Epidemiologic criteria: evidence of a household contact with *T.solium* infection, individuals coming from or living in endemic areas, and a history of frequent travel to endemic areas.

Diagnoses made using these criteria are accorded one of four degrees of certainty (Table 67).

Diagnostic certainty	**Criteria**
Definitive	1. Presence of one absolute criteria 2. Presence of two major plus one minor and one epidemiologic criterion
Probable	1. Presence of one major plus two minor criteria 2. Presence of one major plus one minor and one epidemiologic criterion 3. Presence of three minor plus one epidemiologic criterion

Table 67: Degrees of certainty for the diagnosis of NCC
(Del Brutto et al., 2001)

7.1.4 Neurocysticercosis and epilepsy in Africa

While NCC is recognised as a leading cause of epilepsy in LMICs worldwide (de Bittencourt et al., 1996b, de Bittencourt et al., 1996a, Roman et al., 2000), there have been relatively few studies of human cysticercosis and NCC from SSA. A recent review identified thirteen studies in eight countries (excluding South Africa) between 1989 and 2009 (Winkler et al., 2009a), with only eleven of these being suitable for inclusion in a meta-analysis that specifically examined the relationship between NCC and epilepsy in SSA (Quet et al., 2010). The sero-prevalence of anti-cysticercal antibodies in PWE has been documented as being as high as 40% in Cameroon (Zoli et al., 2003a), has been shown to be significantly associated with epilepsy in Burundi (Nsengiyumva et al., 2003), and the overall association between cysticercosis and epilepsy in SSA based on serological studies has been estimated to have a significant common odds ratio of 3.4 (95% CI 2.7 to 4.3) (Quet et al., 2010). This picture is not universal, however; in The Gambia cysticercal antigen was detected by ELISA in 1.4% of 210 PWE and 1.9% of 420 controls, with none of the sero-positive individuals demonstrating cysts or other lesions suggestive of NCC on CT imaging (Secka et al., 2010).

Studies of NCC and epilepsy from SSA which benefit from both imaging and serology have been very limited. Outside of South Africa there has been only one set of published studies to date, in a cohort of 212 PWE from northern Tanzania, with only limited data on the sero-prevalence of cysticercosis among controls (Blocher et al., 2011, Winkler et al., 2008a, Winkler et al., 2009b).

To date there have been no systematic studies of which we are aware that have examined the relationship between cysticercosis, NCC and HIV infection.

7.2 Methods

All 291 adult PWE identified during the HDSS prevalence survey were offered CT imaging of the brain and were asked to provide a blood sample. CT scans with contrast were performed as described in Chapter Five and healthy controls were recruited as described in Chapter Six. Controls were also asked to provide a blood sample to be analysed alongside those from cases. Blood samples were collected from cases either when they attended KCMC for investigations or in the community during follow-up visits. All blood samples from controls were collected in the community during the control recruitment phase of the study. Samples were centrifuged in daily batches to separate plasma from serum before storage at -80^{o}C. Plasma samples were shipped to the KEMRI-Wellcome research laboratory in Kilifi, Kenya where they were analysed for the presence of anti-cysticercal antibodies using the EITB method with purified r24 and rES33 *T.solium* antigens. The sensitivity and specificity of this serological method in an endemic area of South Africa have been shown to be 54.5% and 69.2% respectively (Foyaca-Sibat et al., 2009).

Diagnoses of NCC in PWE were made according to clinical, neuro-imaging, serological and epidemiologic diagnostic criteria (Del Brutto et al., 2001). For the purposes of this study the HDSS was considered to be an endemic region for *T.solium* infection, by extrapolation from work done elsewhere in Tanzania (Quet et al., 2010, Winkler et al., 2008a, Mafojane et al., 2003). The number of households in the district that keep pigs was ascertained during the census, and additional demographic data on household occupancy, pork consumption and access to domestic sanitation were collected during the clinical follow-up and control recruitment phases of the study.

Comparisons were made between all cases and controls, and between cases with definitive or probable NCC and those without NCC. Categorical variables were compared using Chi-square and Fisher's exact tests; non-normally distributed continuous variables were compared using the Mann-Whitney U test. A p-value of 0.05 or less was used as the threshold for significance throughout.

With regards to sero-prevalence of antibodies to *T.solium*, sample size calculations were made based on data derived from two case-control studies of cysticercosis in epilepsy performed in Burundi. In a 1997 study, antibodies were detected in 11.7% of 103 PWE versus 2.8% of 72 controls using EITB (Newell et al., 1997a). To detect a similar difference, i.e. least extreme OR of 4.60, with 95% confidence and 80% power using a one-to-one matching stratagem would require a sample of 134 cases and controls (i.e. a total sample size of 268). A more recent study in a population with an apparently higher endemicity of human cysticercosis identified antibodies in 58.7% of 303 PWE compared with 38.3% of 606 controls using an antibody ELISA (Prado-Jean et al., 2007). If such a situation was the case in the HDSS population a similar difference could be detected, again with 95% confidence and 80% power, with one-to-one matching of ninety-five cases and controls, i.e. a total sample size of 190. With a prevalent cohort of 291 PWE willing to participate in the study, we were therefore confident that similar differences could be detected in our study population if present.

7.3 Results

7.3.1 Neuro-imaging

CT head scans were available from 200 (68.7%) of 291 cases. There was no difference in the proportions of males and females among cases who did and did not have a CT scan ($\chi^2(1)=0.18$, p=0.89), although cases who did have scans were older than those who did not (Mann-Whitney U=7733.5, z=-2.054, p=0.040; Table 68). Lesions suggestive of NCC were seen in eight (4.0%) of 200 scans: seven (7.4%) of ninety-four females and one (0.9%) of 106 males (Fisher's Exact Test, p=0.027). A full description of all imaging findings other than NCC is given in Chapter Five, section 5.4.2.

7.3.2 Serology

Blood samples were taken from 231 (79.4%) of 291 cases: 109 (80.1%) of 136 females and 122 (78.7%) of 155 males. There was no difference in gender distribution between cases that did and did not give a blood sample ($\chi2(1)=0.091$, p=0.762), and the ages of these two groups were similar (Mann-Whitney U=6570.50, z=-0.619, p=0.536; Table 69). Blood samples were available from all 182 controls.

When laboratory results became available it was found that twenty-one samples were missing: thirtee n (5.6%) of 231 cases and eight (4.5%) of 182 controls ($\chi2(1)=0.32$, p=0.572; Table 70). A total of 392 samples were therefore analysed: 218 from cases and 174 from controls. The demographic characteristics of these groups are summarised in Table 71 and Table 72. While controls were significantly older than cases (Mann-Whitney U 15833.0, z= -2.812, p=0.005), the proportions of males and females among cases and controls were similar ($\chi2(1)=2.65$, p=0.104).

Antibodies to *T.solium* were identified in six (2.8%) of 218 cases and in none of 174 controls (Table 73). Of the six seropositive cases, three (50%) had antibodies to the T24 antigen only, one (16.7%) had antibodies to the ES33 antigen only, and two (33.3%) had antibodies to both. The overall sero-positivity rate among cases and controls combined was 1.5% (95% CI 0.3 to 2.8), and the sero-positivity rate amongst cases only was 2.8% (95% CI 0.6 to 4.9). Although sero-positivity rates were low, there was a statistically significant association between seropositivity and having epilepsy (Fisher's Exact Test,

p=0.036). There was no association between seropositivity and sex (Fisher's Exact Test, p=1.00).

There were no significant differences between sero-negative and sero-positive cases with regards to either age on prevalence date (Mann-Whitney U 423.5, Z= -1.395; p=0.168), or age at onset of epilepsy (Mann-Whitney U 438.5, Z= -1.255; p=0.216). These data are summarised in Table 74 and Table 75. In addition, no significant associations between sero-status and sex, religion, tribal group or educational status were identified (Table 76).

		Age on prevalence date (years)			
	n	Median	Min	Max	IQR
CT scan	200	31.5	15	85	22
No CT scan	91	26.0	15	81	21
Total	291	30.0	15	85	21

Table 68: Availability of CT scan by age (cases only)

		Age on prevalence date (years)			
	n	Median	Min	Max	IQR
Blood sample taken	231	30.0	15	81	21
No blood sample	60	28.5	15	62	25
Total	291	30.0	15	85	21

Table 69: Availability of blood sample by age (cases only)

	Cases		Controls		Total	
	n	(%)	n	(%)	n	(%)
Not taken	60	(20.6%)	0	(0.0%)	60	(12.7%)
Taken and analysed	218	(74.9%)	174	(95.6%)	392	(82.9%)
Taken but missing	13	(4.5%)	8	(4.4%)	21	(4.4%)
Total	291	(100.0%)	182	(100.0%)	473	(100.0%)

Table 70: Blood samples taken during field work

		Age on prevalence date (years)			
	n	Median	Min	Max	IQR
Case	218	31.0	15	85	22
Control	174	39.0	15	91	25
Total	392	33.5	15	91	23

Table 71: Analysed blood samples, by age (cases and controls)

	Female		Male		Total	
	n	(%)	n	(%)	n	(%)
Case	101	(46.3%)	117	(53.7%)	218	(100.0%)
Control	95	(54.6%)	79	(45.4%)	174	(100.0%)
Total	196	(50.0%)	196	(50.0%)	392	(100.0%)

Table 72: Analysed blood samples by sex (cases and controls)

	Cases		Controls		Total	
	n	(%)	n	(%)	n	(%)
Sero-negative	212	(97.2%)	174	(100.0%)	386	(98.5%)
Sero-positive	6	(2.8%)	0	(0.0%)	6	(1.5%)
Total	218	(100.0%)	174	(100.0%)	392	(100.0%)

Table 73: Outcomes of serological testing

		Age on prevalence date (years)			
	n	Median	Min	Max	IQR
Sero-positive	6	41	22	74	30
Sero-negative	212	34	15	85	21
Total	218	31	15	85	22

Table 74: Age of cases and sero-status for antibodies to *T.solium*

		Age at onset of epilepsy (years)			
	n	Median	Min	Max	IQR
Sero-positive	6	27.5	4	70	41
Sero-negative	209	13	0	81	19
Total	215*	13	0	81	19

*data missing for 3 sero-negative cases

Table 75: Age at onset of epilepsy and sero-status for *T.solium antibodies*

Characteristics			Sero-status			
			Positive	Negative	Total	Fisher's exact
Gender:	Male	n (%)	3 (50.0)	114 (53.8)	117 (53.7)	
	Female	n (%)	3 (50.0)	98 (46.2)	101 (46.3)	n=218; p=1.00
Chagga tribe (vs. other group)		n (%)	5 (83.3)	168 (80.8)	173 (80.8)	n=214; p=1.00
Religion:	Christian	n (%)	6 (100.0)	169 (80.9)	175 (81.4)	
	Muslim	n (%)	0 (0.0)	40 (19.1)	40 (18.6)	n=215; p=0.596
Any education (vs. none)		n (%)	6 (100.0)	165 (96.5)	171 (81.8)	n=209; p=0.595
Completed 1^{o} education (vs. none/incomplete)		n (%)	2 (33.3)	107 (53.5)	109 (52.4)	n=206; p=0.423
Focal onset seizures (vs. generalised/undefined)		n (%)	5 (83.3)	154 (72.6)	159 (72.9)	n=218; p=1.00
Family history of epilepsy		n (%)	0 (0.0)	34 (16.0)	34 (15.6)	n=218: p=0.593
Cognitive impairment		n (%)	2 (33.3)	55 (25.9)	57 (26.1)	n=218; p=0.653
Motor impairment		n (%)	0 (0.0)	28 (13.2)	28 (12.8)	n=218; p=1.00

Table 76: Demographic and clinical characteristics of cases by sero-status

7.3.3 Diagnosis of neurocysticercosis in people with epilepsy

All 291 PWE were considered to have at least one minor diagnostic criterion (i.e. seizures) and one epidemiologic criterion (i.e. coming from an area endemic for cysticercosis). Investigations potentially diagnostic of NCC were available in 252 (86.6%) of 291 cases: 176 (69.8%) with both CT and serology, twenty-four (9.5%) with CT only, and forty-two (16.7%) with serology only. Blood samples were available for six (75%) of eight cases in which lesions suggestive of NCC were seen on CT, of which two (33.3%) were positive for *T.solium* antibodies and therefore fulfilled the criteria for definitive NCC (two major plus one minor criteria and one epidemiologic criterion); both of these cases had multiple lesions on CT. A further four (50%) of eight cases with lesions suggestive of NCC on CT were sero-negative and considered as probable NCC (one major plus one minor and one epidemiologic criterion). Of these, one (25.0%) had a single lesion, one (25.0%) had multiple lesions and two (50.0%) had diffuse calcification. Two cases with CT suggestive of NCC, both with single lesions, from whom no blood sample was available were also considered as probable NCC, with one major plus one minor and one epidemiologic criterion. Finally, three cases who were sero-positive but with no evidence of NCC on CT and one case who was sero-positive but with no CT scan available were also considered as probable NCC, again with one major plus one minor and one epidemiologic criterion. In summary, a total of twelve (4.8%) of 252 PWE in whom appropriate investigations were available were diagnosed with NCC: two with definitive NCC and ten with probable NCC (Table 77). In the absence of a gold standard diagnosis, but taking CT evidence of NCC as a proxy , the PPV of the EITB anticysticercal antibody serology in this setting was 40.0%, the sensitivity was 33.3% and the specificity was 98.2%.

NCC diagnosis	n (%)	Absolute criteria	Major criteria		Minor criteria	Epidemiologic criteria
			CT suggestive	Sero-positive	(seizures)	(endemic region)
Definitive	2 (16.7%)	No	Yes	Yes	Yes	Yes
Probable	4 (33.3%)	No	Yes	No	Yes	Yes
	2 (16.7%)	No	Yes	N/A*	Yes	Yes
	3 (25.0%)	No	No	Yes	Yes	Yes
	1 (8.3%)	N/A*	N/A*	Yes	Yes	Yes
Total	**12 (100%)**	**0**	**8**	**6**	**12**	**12**

*N/A=investigation not available

Table 77: Criteria used in the diagnosis of NCC in PWE from Hai

7.3.4 Neurocysticercosis: demographic and clinical characteristics

Eleven (91.7%) of the twelve PWE with definitive or probable NCC had focal-onset seizures, with the seizure-type remaining undefined in one (8.3%). No significant associations with any demographic or clinical variables were identified among cases with and without NCC (Table 78). In 176 cases for whom both sets of investigations were available, two (33.3%) out of six with CT scans suggestive of NCC were sero-positive, compared to three (1.8%) of 170 in whom NCC was not seen on CT scanning (OR 27.8; 95% CI 3.6 to 215.3; Fisher's Exact p=0.009). With such small numbers involved further examination for confounding and interaction with covariates was unlikely to be meaningful and was therefore not performed.

7.3.5 Risk factors for neurocysticercosis in Hai

Results from the 2009 HDSS census indicated that 2,270 (5.2%) of 43,794 households kept pigs; twenty (8.4%) of 237 PWE for whom there were data and eleven (6.0%) of 182 controls came from households that kept pigs ($\chi2(1)=0.862$, p=0.353). From interviews with cases and controls and visits to households that kept pigs, it became apparent that the predominant pig husbandry technique employed in Hai was that of 'zero grazing', whereby livestock are kept in pens within the homestead and fodder brought to them (Figure 31), with fodder for pigs consisting of a combination of household vegetable waste, night soil and chaff from the fields (this is an anecdotal finding gleaned during field work that we do not have formal data to support).

Data on pork consumption were available from 161 (55.3%) of 291 cases and 178 (97.8%) of 182 controls, with seventy-eight (48.4%) cases and eighty-eight (49.4%) controls stating that they consumed pork at times ($\chi2(1)=0.033$, p=0.855). All cases and controls that were Muslim stated that they never ate pork.

Regarding domestic sanitation, 123 (75.9%) of 162 cases and 128 (73.6%) of 174 controls used piped water as their main domestic water source. The remainder took their water from wells or open sources such as rivers or springs (Table 79). The majority of both cases and controls used pit latrines for domestic sewage: 153 (95.0%) of 161 cases and 166 (93.3%) of 178 controls; a small minority had access to an indoor flushing toilet or had no

formal sewerage within their home (Figure 30, Table 80). While there were no appreciable differences in domestic toilet facilities between cases and controls ($\chi2(2)=1.55$, $p=0.461$), the greater numbers of cases using a well and controls using open water sources was significant ($\chi2(2)=8.74$, $p=0.013$); the clinical significance of this statistical finding is not clear. Possible risk factors for NCC were compared between cases and controls (Table 81), and between cases with and without NCC (Table 82); no significant associations were identified among any groups.

Figure 30: Typical pit latrines in a Hai village

Figure 31: Zero-grazing pig husbandry in Hai
(by permission of Wilbard Mure)

Characteristics			NCC	No NCC	Total	Statistics
Age (years)		n	12	240	252	
		Mean (SD)	34.4 (17.6)	34.5 (15.0)	34.5 (15.1)	
		Median (range)	30 (17 to 74)	30 (15 to 85)	30 (15 to 85)	U=1374.5; p=0.790†
Age at onset (years)		n	12	236	248	
		Mean (SD)	24.4 (20.8)	16.9 (15.3)	17.3 (15.7)	
		Median (range)	15 (1 to 70)	12 (0 to 81)	13.0 (0 to 81)	U=1093.0; p=0.182†
Gender:	Male	n (%)	4 (33.3)	129 (53.8)	133 (52.8)	
	Female	n (%)	8 (66.7)	111 (46.3)	119 (47.2)	$X^2(1)=1.911$; p=0.167
Chagga tribe (vs. other group)		n (%)	9 (75.0)	187 (80.6)	196 (80.3)	n=244; p=0.708*
Religion:	Christian	n (%)	8 (66.7)	192 (81.4)	200 (80.6)	
	Muslim	n (%)	4 (33.3)	44 (18.6)	48 (19.4)	p=0.255*
Any education (vs. none)		n (%)	11 (91.7)	184 (80.7)	195 (81.3)	
Completed 1^o education (vs. none/incomp.)		n (%)	7 (58.3)	116 (51.6)	123 (51.9)	n=237; p=0.647*
Focal-onset seizures (vs. generalised/undef.)		n (%)	11 (91.7)	173 (72.1)	184 (73.0)	n=252; p=0.190*
Family history of epilepsy		n (%)	3 (25%)	41 (17.1)	44 (17.5)	n=252; p=0.445*
Cognitive impairment		n (%)	4 (33.3)	68 (28.3)	72 (28.6)	n=252; p=0.746*
Motor impairment		n (%)	1 (8.3)	36 (15.0)	37 (14.7)	n=252; p=1.000*

*** Fisher's Exact Test** **†Mann-Whitney U Test**

Table 78: Characteristics of PWE with and without NCC

	Main domestic water source							
	Piped water		Well		River/open source		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Case	123	(75.9%)	12	(7.4%)	27	(16.7%)	162	(100.0%)
Control	128	(73.6%)	3	(1.7%)	43	(24.7%)	174	(100.0%)
Total	251	(74.7%)	15	(4.5%)	70	(20.8%)	336	(100.0%)

Table 79: Main domestic water source (cases and controls)

	Domestic toilet arrangements							
	Indoor flushing toilet		Pit latrine		No toilet		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Case	5	(3.1%)	153	(95.0%)	3	(1.9%)	161	(100.0%)
Control	10	(5.6%)	166	(93.3%)	2	(1.1%)	178	(100.0%)
Total	15	(4.4%)	319	(94.1%)	5	(1.5%)	339	(100.0%)

Table 80: Domestic toilet arrangements (cases and controls)

Characteristics		Case	Control	Total	Statistics
No. of household occupants	n	162	180	342	
	Mean (SD)	5.0 (2.1)	5.6 (2.6)	5.3 (2.4)	
	Median (range)	5 (1 to 13)	5 (2 to 18)	5 (1 to 18)	U=13172.5; p=0.119†
Keeps pigs	n (%)	4 (33.3)	129 (53.8)	133 (52.8)	n=419; $X^2(1)=0.862$, p=0.353
Eats pork	n (%)	78 (47.0)	88 (53.0)	166 (49.0)	n=339; $X^2(1)=0.033$, p=0.855
No piped water	n (%)	39 (24.1)	46 (26.4)	85 (25.3)	n=336; $X^2(1)=0.248$, p=0.619
Pit latrine/no domestic toilet	n (%)	11 (91.7)	184 (80.7)	195 (81.3)	n=339; p=0.473*

***Fisher's Exact Test** **†Mann-Whitney U Test**

Table 81: Risk factors for NCC (cases and controls)

Characteristics		NCC	No NCC	Total	Statistics
No. of household occupants	n	162	180	159	
	Mean (SD)	5.3 (2.0)	5.0 (2.1)	5.0 (2.1)	
	Median (range)	5 (3 to 8)	5 (1 to 13)	5 (1 to 13)	U=546.5; p=0.647†
Keeps pigs	n (%)	2 (20.0)	18 (8.8)	20 (9.3)	n=215, p=0.235*
Eats pork	n (%)	2 (25.0)	75 (49.7)	77 (48.4)	n=159; p=0.278*
No piped water	n (%)	0 (0.0)	39 (25.7)	39 (24.4)	n=160; p=0.201*
Pit latrine/ no domestic toilet	n (%)	8 (100.0)	146 (96.7)	154 (96.9)	n=159; p=1.000*

***Fisher's Exact Test** **†Mann-Whitney U**

Table 82: Risk factors for NCC (PWE only)

7.4 Discussion

NCC is recognised as a major cause of both acute seizures and of epilepsy in many LMICs, being demonstrated in up to 80% of PWE in endemic areas (Nash et al., 2004). In SSA there have been few epidemiological studies of NCC in epilepsy, with a recent meta-analysis identifying eleven studies from eight countries in which diagnostic criteria and control groups were described (Quet et al., 2010). Furthermore, while serological testing provides indirect evidence, to date there have been few imaging studies describing the prevalence of NCC in PWE from SSA. Two studies from South Africa presented CT findings without serology in clinic-based series (van As and Joubert, 1991, Cambell and Farrell, 1987), and one more recent study used CT scanning in a random sample of PWE attending a clinic to validate serological findings (Foyaca-Sibat et al., 2009). Outside of South Africa only two studies have presented both CT and serology findings: one, published in French, from Reunion Island (Mignard et al., 1986), and one from northern Tanzania (Blocher et al., 2011, Winkler et al., 2008a, Winkler et al., 2009b). The work from Hai presented here therefore represents only the second study from mainland SSA outside of South Africa to present both neuro-imaging and serological data on NCC in PWE in this region. Furthermore, this is the only study we are aware of to have collected imaging and serological data in parallel from a community-based prevalent cohort.

There is a low prevalence of NCC on neuro-imaging among PWE from the Hai district (4.0%), suggesting that this is a population with low-endemicity for *T.solium* infection. This contrasts with findings from elsewhere in northern Tanzania, where 17.9% of 212 PWE were found to have lesions either definitive for, suggestive of or compatible with NCC on CT scanning (Winkler et al., 2009b). In the same study 5.1% of 198 consecutive CT scans done for various clinical indications in people without epilepsy were also found to have evidence of NCC according to the same criteria.

The low prevalence of NCC on neuro-imaging in PWE in Hai correlates with a low seroprevalence, with only 2.8% of PWE and 1.5% of all individuals who were tested being sero-positive for the presence of *T.solium* antibodies (p=0.036). An odds ratio was not

calculated as none of our controls were seropositive. This contrasts to other parts of SSA, where up to one third of all individuals may be seropositive for anti-cysticercal antibodies, rising to nearly 60% in PWE (Quet et al., 2010, Mafojane et al., 2003). A clinic-based study from northern Tanzania found anti-cysticercal antibodies in 30% of twenty PWE who had NCC on and in none of twenty PWE without NCC on CT scanning; the overall sero-prevalence in PWE in this study was 15%, and no antibodies were detected in sera from twenty healthy controls (Winkler et al., 2008a). Commercially available ELISA and Western blot (WB) assays were used initially, but more recently the same samples were re-analysed as part of a larger study using both WB and EITB assays, with serology results being correlated with CT findings (Blocher et al., 2011). The EITB performed with greater sensitivity, identifying 52.2% of twenty-three PWE with NCC on CT scan, although with an apparently lower specificity, giving a positive result in 8.7% of forty PWE with no CT evidence of NCC; no control samples were analysed in this larger study.

Elsewhere in Africa higher rates of seropositivity in PWE and controls have been observed. Two studies from Burundi have examined anti-cysticercal antibody sero-positivity rates in PWE and controls. In the first of these a community-based study examined 103 PWE and seventy-two household controls in three different administrative zones for the presence of cysticercal antigen and anti-cysticercal antibodies (Newell et al., 1997a). Antibodies were detected by EITB in 11.7% of PWE overall and in 2.8% of controls, although the difference that was not statistically significant. Between 10% and 40% of households in the study kept pigs, although no further statistical correlation is offered. In another community-based study of epilepsy in a different province of Burundi, 58.7% of 303 PWE were had anti-cysticercal antibodies on ELISA, compared to 31.4% of controls (OR 3.6; 95% CI 2.5 to 4.9) (Prado-Jean et al., 2007). Controls were recruited from among neighbours of PWE identified during the study. Sero-epidemiological studies of human cysticercosis have also been performed in Cameroon (Zoli et al., 2003a, Nguekam et al., 2003), although only one of these specifically involved PWE (Zoli et al., 2003a). In this study the overall ELISA antibody sero-prevalence in 504 PWE from three rural localities in West Cameroon was 44.6%, rising to 56.2% in cases of late-onset epilepsy (difference not statistically significant) (Zoli et al., 2003a). In a hospital-based matched case-control study from

Madagascar 31.7% of 104 PWE had anticysticercal antibodies on EITB compared to 13.5% of 104 controls (OR 3.4; 95% CI 1.5 to 8.6) (Andriantsimahavandy et al., 1997).

This picture of high seroprevalence rates is by no means uniform, however, with lower rates also having been previously observed in SSA. A study from Togo, in a population where the prevalence of epilepsy was 16.7 per 1,000, used a combination of clinical findings, antibody ELISA, skull and soft tissue X-rays and biopsies of subcutaneous nodules to examine the link between cysticercosis and epilepsy (Dumas et al., 1989). Cysticercosis was diagnosed in 2.7% of the total population, with 9.9% of eighty-one PWE being sero-positive for anti-cysticercal antibodies compared to 6.8% of all 1,527 people who were tested; no statistical comparison between groups is offered. The authors observed that 81% of the study population ate pork, and that this was usually poorly prepared. In a clinic-based series from two areas close to Nairobi in Kenya (rural and urban), anti-cysticercal antibodies were detected in 5% of ninety-nine PWE and 2.4% of controls using an ELISA assay (Macharia et al., 2002).

While these various findings suggest that cysticercosis is indeed important as a cause of epilepsy in parts of SSA, the picture is by no means uniform, and detailed assessments of the socio-economic and environmental circumstances in which different communities live will be necessary to inform any public health interventions designed to tackle this issue.

We combined clinical, serological and imaging findings to arrive at a diagnosis of NCC in PWE from Hai, based on a set of diagnostic criteria that have been used in Africa and elsewhere in the developing world (Del Brutto et al., 2001). All diagnoses of NCC depended on the *a priori* assumption that Hai was a region likely to be endemic for cysticercosis. The prevalence of NCC on imaging was 4.0%, and based on these cases the EITB serology used in our study performed with a sensitivity of only 33.3%, which is considerably lower than that of 54.5% seen with ELISA antibody serology in an endemic area of South Africa, where the prevalence of NCC in PWE on CT imaging was 37% (Foyaca-Sibat et al., 2009). In the only other study outside of South Africa to correlate imaging and serology to diagnose NCC in PWE, the sensitivity was very variable between two different assays: 52.2% for EITB compared with only 13.3% when a commercial

Western Blot was used (Blocher et al., 2011). In this study the overall prevalence of NCC on CT in PWE, either 'definite', 'suggestive' or probable', was 17.9%. It may be that the lower sensitivity of serological testing seen in the Hai district is a reflection of a lower endemicity and prevalence of human cysticercosis in this population. The use of different assays makes the comparison of different studies difficult, with sensitivities and specificities varying according to assay and epidemiological context (Dorny et al., 2003). For example, EITB has performed with sensitivity and specificity as high as 98% and 100% respectively in experimental conditions, compared to lower sensitivities of between 47% and 95% and specificities of between 67% and 100% for ELISAs (Tsang et al., 1989). Differences between different *T.solium* genotypes have also been observed (Ito et al., 2003), and it has been suggested that these may influence both clinical presentation and serological diagnostic accuracy (Quet et al., 2010, Winkler et al., 2009a). While it is difficult to draw any firm conclusions from the limited findings from Hai, it would seem that serological screening is unlikely to be either clinically useful or cost-effective in an area of low-endemicity for *T.solium*. It should also be borne in mind that the mainstay of treatment for NCC is the control of seizures with AEDs; only when viable cysticerci are visualised on CT or MRI should anti-helminthic drugs be given, in combination with steroids to reduce peri-lesional inflammation may confer an improved prognosis (Singh and Prabhakar, 2008, Garcia et al., 2004, Abba et al., 2010). No such lesions were indentified in the Hai study.

The authors of the studies discussed above generally comment that their findings should be seen in the context of exposure to observed risk factors for cysticercosis, such as pig-rearing, pork consumption, poor sanitation, and of the high prevalence of porcine cysticercosis (up to 50%) that is known to exist in much of SSA, including Tanzania (Phiri et al., 2003, Mafojane et al., 2003, Zoli et al., 2003b). While at least some of the potential risk factors for cysticercosis would appear to be present in the Hai district, the reasons for the apparently low prevalence of NCC compared to elsewhere in Tanzania warrant further investigation. Possible factors may be the use of zero-grazing animal husbandry techniques, the quality of meat inspection and food preparation locally, or the source of pork that is consumed within the district. Investigation of these factors is beyond the

scope of this study, although may yield insights important to public health if pursued. With regards to sanitation it has previously been observed that high mortality rates in children under five years in Hai are associated with diarrhoeal disease, unsafe drinking water and poor sanitation (Kissima, 1995). More recently, a contemporaneous cross-sectional study used microscopy to assess the prevalence of enteric pathogens in stool samples from Hai residents (Mziray, 2009). Cysts and parasites were seen in 45.3% of samples taken from 775 individuals in twenty-nine different villages. The most commonly identified organisms were *entamoeba* species, seen in 35% of samples overall and in nearly 50% of samples in the thirty-one to forty years age-group, while the prevalence of eggs from *taenia* species was very low (0.5%). Unfortunately it was not possible to correlate the findings of this study with the epilepsy study more closely.

There are some important limitations in our study. While socio-demographic data were collected from controls in the field during recruitment under supervision from the research doctor, these data were collected from cases independently by field workers during the follow-up phase of the study when patients were attending KCMC for investigations; non-attendance and other operational difficulties meant that these data were missing from nearly half of cases overall (44.3%), reducing the validity of this aspect of comparison with controls. It is also difficult to comment on what biases may have been introduced by this loss of data. Furthermore, there is no control series of CT scans. For ethical reasons controls could not be exposed to CT radiation without a clear clinical indication, and for technical and administrative reasons it proved unfeasible to access a series of consecutive CT images at KCMC from patients attending from the Hai district that might have served as a proxy control series. Finally, the prevalence study in Hai only identified cases with generalised convulsive epilepsy, whether focal or generalised in onset, and more subtle focal-onset seizures without secondary generalisation which were not detected by the study may also be due to acquired brain lesions such as NCC.

7.5 Summary and conclusions

Cysticercosis and NCC appear to be present in Hai but with a low endemicity. In this epidemiological context, while the utility of serological testing with antibody EITB for cysticercosis is not proven, the presence of NCC as an aetiology of epilepsy needs to be considered, especially in the assessment and management of any individual presenting with late-onset epilepsy or incident seizures. The conditions for the ongoing transmission of human and porcine cysticercosis appear to be present in the district, although few households keep pigs, and pigs are generally not free-ranging. Although these aspects have not been formally studied here, a clearer understanding of the social and environmental factors that distinguish Hai from other areas of Tanzania and SSA where NCC is more endemic may help to inform public health initiatives designed to reduce the burden of acquired epilepsy.

Chapter 8. Management of epilepsy in Hai

Abstract

Background

The ETG is high in countries in SSA, including Tanzania, often being close to 100%. Few published studies from SSA have examined patient- and healthcare-related factors associated with lack of treatment or default from follow-up.

Methods

We collected self-reported data on access to treatment for epilepsy from 291 PWE identified during a community-based study in a rural district of northern Tanzania. Multivariable logistic regression analyses were used to identify significant associations with accessing treatment and remaining under follow-up.

Results

The majority (89.0%) of cases had previously presented to medical services. Cases more likely to have presented were those who had completed primary education (OR 2.55; 95% CI 1.09 to 5.98) and those who experienced a prodromal aura with their seizures (OR 2.83; 95% CI 1.12 to 7.12). Cases less likely to have presented were those who drank alcohol (OR 0.32; 95% CI 0.13 to 0.80) and those who had attended a traditional healer (OR 0.36; 95% CI 0.16 to 0.85). 59.8% of cases overall were under follow-up at the time of the study. Predictors of remaining under follow-up were having any education (vs. none) (OR 2.46; 95% CI 1.20 to 5.05) and having previously received a diagnosis of epilepsy (OR 3.09; 95% CI 1.56 to 6.15). The ETG based on AED usage was 68.6% (95% CI 63.6 to 73.7).

Conclusions

The ETG among adult PWE in the HDSS is in line with recent estimates from elsewhere SSA. The protective effects of education and of receiving a formal diagnosis suggest that interventions focusing on these factors may serve to increase levels of sustained access to treatment and care.

8.1 Introduction

An estimated 68.8 million people worldwide have been affected by epilepsy during their lifetimes, with up to sixty-two million (90.1%) of these living LMICs (Ngugi et al., 2010). Although the prevalence of epilepsy in these countries is generally thought to be higher than in HICs, the majority of PWE in LMICs may not receive appropriate treatment for their condition, leading to the concept of the epilepsy treatment gap (ETG), defined as the proportion of PWE with active epilepsy and requiring treatment who are not receiving it (Meinardi et al., 2001, Scott et al., 2001). The concept of the ETG can be applied not just to drug treatment, but also to areas of healthcare on which treatment may be contingent, including failure to diagnose all patients presenting with a given illness (diagnostic gap), or failure to provide the investigations required to diagnose or manage an illness (investigations gap) (Kale, 2002).

The ETG may be measured indirectly, extrapolating from data on prevalence and on total AED acquisition and use at national or population level (Shorvon and Farmer, 1988), or directly during the course of a prevalence study when the number of detected cases who are not receiving treatment can be ascertained (Kale, 2002). The latter of these approaches has been the most frequently employed in studies from LMICs, and has the added advantage that it may also identify the number of PWE who may have been advised on treatment but who either did not take it or discontinued, thus yielding information on the contribution of non-adherence to the ETG. This may be important as it is thought that in LMICs a large proportion of patients who are diagnosed with epilepsy discontinue treatment soon after initiation, and the term 'secondary treatment gap' has been coined to describe this phenomenon (Das et al., 2007). Although the indirect method is crude and relies on data that may not be readily available or robust in many LMICs, it has the advantages of being convenient, of having the potential for validation against direct estimates, and may also be repeated regularly to monitor any reductions in the ETG in response to interventions (Kale, 2002). The direct method is not without its difficulties, however, not least of which is the cost associated with conducting community-based studies. Most studies of ETG that employ the direct method also rely on self-reported use of AEDs, which may not be reliable: for example, a study in rural Kenya that analysed

blood samples for the presence of AEDs reported a sensitivity of 58% and specificity of 87% for self-reported AED use (Edwards et al., 2008).

Studies estimating the ETG in LMICs have consistently identified very high rates, with anecdotal and descriptive estimates reporting gaps in excess of 80% in many countries (Diop et al., 2003), and recent reviews using systematic or meta-analytic approaches have reported rates from 56% to over 75% in most LMICs, albeit with wide confidence intervals and considerable heterogeneity between studies (Mbuba et al., 2008, Meyer et al., 2010). A review of data on treatment from thirteen epidemiological studies of epilepsy conducted in Africa using a standardised questionnaire summarised findings from 2,269 PWE, with the overall ETG from seven community-based studies being 55.7% (95% CI 52.7 to 58.7) (Quet et al., 2011). The most frequently cited reasons for lack or irregularity of treatment were unavailability of drugs (41.3%) and cost (27.2%). A multivariable logistic regression analysis also identified a number factors associated specifically with non-utilisation of phenobarbital: younger age, presence of focal-onset seizures with secondary generalisation, a generally good state of health, age at onset of epilepsy greater than six years, having no family history of epilepsy, and also not having accessed traditional treatment.

Why does the ETG exist to the magnitude that it does? Despite estimates of the ETG being consistently high, there remains a paucity of data examining the causes of or potential solutions to the gap. A recent systematic review of the magnitude and causes of the ETG included studies that met the inclusion criteria of either using direct methods to estimate the gap, presenting observational or qualitative data to identify potential causes, or describing interventions designed to address attributed causes of the ETG (Mbuba et al., 2008). Only eight studies were identified which presented data on possible cause, of which three were from countries in SSA (Preux et al., 2000, El Sharkawy et al., 2006, Elechi, 1991). The most frequently identified contributor to the ETG was the cost associated with seeking epilepsy care, with a lack of medically skilled personnel also correlating to a higher median ETG. Patient-centred factors included non-adherence (Elechi, 1991), and social and cultural beliefs that lead PWE to seek traditional rather than

modern biomedical treatments (Preux et al., 2000, El Sharkawy et al., 2006). This phenomenon is well-described in observational studies from SSA in general, including from Tanzania, and is often associated with considerable costs being incurred to the patient (Birbeck et al., 2007, Winkler et al., 2010b, Shorvon and Farmer, 1988).

The diagnosis of epilepsy is fundamentally a clinical judgement; the accuracy of diagnosis therefore depends on the skill and experience of the physician or other healthcare worker and the quality and reliability of the information provided by the witness. LMICs have an average of one neurologist for every three to five million people, with many countries in Africa having no neurologists at all (WHO, 2005). To put this in context, people with epilepsy have potential access to specialist care in 56% of LMICs compared with 89% of HICs (Dua et al., 2006). Furthermore, two thirds or more of people in LMICs live in rural areas while nearly all the neurologists working in these countries are to be found in urban centres, meaning that most PWE in LMICs rely exclusively on primary care services for diagnosis and treatment (Radhakrishnan, 2009).

In addition to the difficulties associated with accessing effective treatment, epilepsy in SSA is also associated with psychosocial problems, reduced life-expectancy and social isolation (Matuja, 1990, Jilek-Aall and Rwiza, 1992, Mushi et al., 2010). All of these factors may be exacerbated by having uncontrolled seizures, making the condition both more dangerous and more visible. In 2005 the WHO in conjunction with the ILAE published the Atlas of Epilepsy Care, which describes the medical, sociological, psychological and financial consequences of living with epilepsy, highlighting the importance of delivering epilepsy treatment not just to gaining control of seizures, but also to reducing the burden of morbidity and other harms experienced by PWE across these dimensions (WHO, 2005). In the face of these complex issues, resource-poor countries share a number of traits that compound the difficulties associated with addressing these challenges as well as dictating the types of interventions that are appropriate or feasible, with treatment programmes focusing by necessity on primary care and the use of affordable treatments (Radhakrishnan, 2009).

While epilepsy in LMICs may potentially be prevented through public health strategies that tackle identified risk factors such as head injury, CNS infection, febrile seizures and obstetric complications, the primary focus of care for PWE is the control and prevention of further seizures (Kwan and Brodie, 2002). Given access to appropriate and consistent drug therapy, the prognosis of epilepsy can be favourable, with seizure-freedom being achievable in up to 75% of PWE within five years of diagnosis (Feksi et al., 1991, Kale, 1997). It is also important to note that these outcomes are achievable in LMICs as well as HICs (Shorvon and Farmer, 1988, Coleman et al., 2002), and first-line AEDs including phenobarbital (PB), phenytoin (PHT) and, to a lesser extent, carbamazepine (CBZ) are affordable and widely available, appearing on between 86% and 95% of national essential drugs lists (WHO, 2005, Mbuba and Newton, 2009).

The older AEDs, particularly PB, are both affordable and effective, costing as little as five USD a year for an adult in 2005 (Chisholm, 2005). Supply and quality vary, however, and in the case of PB the former of these issues may have been exacerbated by the drug being classified as a controlled drug in some countries (Meyer et al., 2010). Despite these issues, its low cost and widespread availability mean that PB continues to be commonly prescribed in LMICs, while in most HICs it has largely fallen out of use (Kale and Perucca, 2004). Reasons for this, despite its efficacy and broad spectrum of anti-convulsant activity against both focal and generalised tonic-clonic seizures, may relate to documented disadvantages including hepatic enzyme induction and adverse cognitive and behavioural effects, particularly in children (Kwan and Brodie, 2004). Although most of the evidence-base supporting the use of PB comes from observational studies rather than controlled trials, meta-analysis data from four randomised controlled trials comparing PB and PHT, and four trials comparing PB and CBZ are available (Taylor et al., 2001, Tudur Smith et al., 2003). From these studies it is known that while PB is associated with higher discontinuation rates than both PHT and CBZ, efficacy, in terms of time to twelve-month remission and time to first seizure, is similar when comparing PB with either PHT or CBZ. The only trial data on the efficacy of AEDs in SSA come from a large open-label study conducted in Kenya in which 302 untreated children and adults with epilepsy were randomised to receive either PB or CBZ for twelve months (Feksi et al., 1991). No

differences between treatment groups were identified in the proportions of patients remaining seizure-free at six and twelve months, and although the absolute number of patients experiencing side-effects was greater in the PB group, there were no statistically significant differences between treatment groups with regards to this outcome. Observational studies on the use of PB in clinical rather than trial settings are also available, from Mali, Nigeria and Tanzania. In Mali, in a community-based study conducted in a poor and remote rural area, PB was given to ninety-six adults and children with a mix of partial and generalised seizures who were then followed-up for an average of twelve months (Nimaga et al., 2002). High levels of drug adherence and seizure-control were observed, with only 3% of patients reporting adverse effects after one year of treatment and with none of these being severe enough to discontinue treatment. In a clinic-based study from Nigeria complete seizure control was reported in 50.6% of 344 children with epilepsy who were treated with PB (Sykes, 2002). Only two patients discontinued treatment due to side-effects, although nearly one third of patients (27%) were lost to follow-up. Finally, a retrospective study conducted in rural Tanzania reported that 52.4% of 164 PWE who were started on AED therapy (158 of them on PB) between 1959 and 1963 achieved seizure control while maintained on treatment (Jilek-Aall and Rwiza, 1992). Patients were treated for up to ten years until 1971, when the AED supply ended. From these few studies, it would seem that PB appears to be efficacious and well-tolerated as a treatment for epilepsy in SSA populations. It is important to note, however, that these data are not strictly comparable in terms of follow-up duration or approaches to data collection for adverse events, and the low rates of treatment withdrawal may be a reflection of the lack of treatment options rather than tolerability (Kwan and Brodie, 2004); in resource-poor settings the treatment options for PWE generally lie between using the cheapest treatment available or receiving no treatment at all. Given this stark choice it is generally accepted that PB should be used, particularly in adults; a position that is endorsed by the ILAE and encompassed within their demonstration projects (Kale and Perucca, 2004, De Boer, 2002).

Comprehensive interventions at national levels to improve drug supply and increase human and material resources to reduce the ETG would incur significant costs, and

economic assessments of the burden of epilepsy are therefore important. Such assessments have been conducted in the UK, the USA, and in India (Begley et al., 2000, Cockerell et al., 1994, Thomas et al., 2001), although to the best of our knowledge have yet to be conducted in SSA. Where assessments have been performed, the economic implications of epilepsy in terms of health service needs, increased morbidity and mortality, and reduced economic productivity have all been demonstrated. In 2005, in a bid to redress the relative paucity of cost-effectiveness data on epilepsy treatments in LMICs, the WHO estimated the cost-effectiveness of four first-line AEDs (PB, PHT, CBZ and SV) specifically in terms of their potential impact at a primary care level in resource-poor regions of the world (Chisholm, 2005). An economic model was applied to nine WHO developing sub-regions including two African regions encompassing Nigeria, Senegal, Botswana and Kenya. Efficacy of treatment was gauged in terms of reduction in disability, with adjustments for coverage, response and adherence, and treatment costs and cost-effectiveness ratios were measured in international dollars. Only primary or idiopathic were considered for the analysis. The authors concluded that by extending AED treatment coverage to 50% of all cases, up to 40% of the current burden of DALYs could be averted, and that this could be achieved at an annual cost per capita of between 0.20 to 1.33 international dollars, which falls below the average income per capita for these regions. The countries that stood to gain the most were Kenya and Botswana, with 646 DALYs averted per one million people; the cost per DALY specifically associated with PB in these countries was 844 international dollars. These two countries were considered together on the basis of having high mortality rates among children and adults compared to other countries in the analysis.

To summarise, while the prognosis for seizure-freedom given access to regular and adequate AED therapy is good, the majority of PWE in LMICs do not receive treatment. The reasons for this are largely but not solely associated with cost, both to the patient and to the health system providing treatment. Older and more affordable AEDs, in particular PB, are widely available and efficacious, and economic modelling suggests that increasing the availability of PB in LMICs would be a cost-effective means of achieving a considerable reduction in the morbidity and disability associated with epilepsy.

Having established a prevalent cohort of PWE in the HDSS population we sought to quantify the levels of access to treatment for epilepsy in this community and to identify patient-related factors that are associated with failure to access or adhere to AED treatment.

8.2 Methods

8.2.1 Procedures and variables

All 291 cases identified during the prevalence survey were asked about current or previous access to medical care, including any drug treatment for epilepsy. For any cases using AEDs we sought to ascertain the identity, dose and pattern of use of the drug(s), and any side-effects experienced. We also asked about source and cost of treatment and in all cases who had been in contact with medical services because of their seizures we asked about any diagnoses for the problem that had been given previously. In addition to asking about biomedical treatments we also asked about any use of traditional healers or traditional medications, and about the costs of these.

8.2.2 Statistical analyses

Continuous variables with non-normal distributions were compared non-parametrically using the Mann-Whitney U test; distributions of categorical variables were examined using the Chi-square test. The ETG was estimated as a percentage based on self-reported AED use and where the choice of drug, dosage and adherence were considered to be adequate and appropriate. The 95% confidence interval for the ETG was calculated based on a Poisson assumption.

To further explore the data, uni-variable analyses of two binary outcomes were performed: PWE who had previously presented to medical services were compared to those who had never presented; for PWE who had previously presented to services, those remaining under follow-up were compared with those who had defaulted from follow-up. To examine for the joint effects of multiple predictors, logistic regression models were constructed using a backwards stepwise elimination strategy based on the likelihood ratio test (LRT); predictor variables with a p-value of 0.1 or greater were excluded at each step. The goodness of fit to the data of final models was assessed using the Hosmer and Lemeshow statistic, with values closer to unity indicating a better fit (Field, 2009a). A p-value of 0.05 or less was considered significant for all analyses.

8.3 Results

8.3.1 Access to medical care

A total of 253 (86.9%) of 291 cases with active epilepsy had previously sought medical attention for their seizures, with 174 (68.8%) of these remaining under follow-up at the time of initial assessment by the epilepsy study (59.8% of all cases; Table 83). While there was no difference between the sexes in the proportion of individuals seeking medical help at any point ($\chi^2(1)=0.926$; p=0.336), of those who had previously sought help females were more likely than males to remain under follow-up at the time of the study ($\chi^2(1)=5.381$; p=0.02). Thirty-eight (13.1%) of 291 cases denied ever having sought help for their seizures, or ever having been on any form of AED treatment.

The distributions of age at onset of epilepsy and age on prevalence date within these treatment groups are summarised in Table 85 and Table 86. Data on the age of onset of epilepsy were missing in seven (2.4%) of 291 cases overall; five of these had previously sought medical help, of whom four remained under follow-up. There was no significant difference between cases who had previously presented and those who had not in age on the prevalence date (Mann-Whitney U 4424.5, z = -0.791; p=0.43), or in age at first onset of seizures (Mann-Whitney U 3635.0, z = -1.801; p=0.072). Similarly, among cases who had previously presented to medical services there was no significant difference between those remaining under follow-up and those no longer under follow-up in terms of age on the prevalence date (Mann-Whitney U 6541.0, z = -0.616; p = 0.538), or age at first onset of seizures (Mann-Whitney U 5620.5, z = -1.844; p = 0.065).

Data were available on the interval between onset of seizures and presentation to medical services in 225 (88.9%) of 253 cases. Ninety-six (42.7%) of these had presented within a year of seizure onset (forty-four females, fifty-two males), with a further twenty (8.9%) presenting between one and two years of seizure onset (eleven females, nine males). For the 109 (48.4%) of 225 cases that presented more than two years after the onset of seizures, the mean and median times from onset of seizures to presentation to medical services were 9.83 and 7.0 years respectively (Table 84, Figure 32). There was no

significant difference in time to presentation between males and females presenting at more than two years after seizure onset (Mann-Whitney U=1418.5, z=-0.369; p=0.712).

Of the 253 cases that had previously sought medical attention (121 female, 132 male), 156 (61.9%) had presented to a government health facility at district level, 108 (42.9%) had presented to a government hospital (either Mawenzi hospital in Moshi, Kibong'oto National Hospital in the neighbouring Siha district, or Muhimbili National Hospital in Dar es Salaam), and seventy-nine (31.4%) had presented to one of the large mission hospitals in the area, usually KCMC in Moshi, or Machame Hospital within the Hai district (Table 87). One hundred and seven (42.3%) of 253 cases reported seeking help from at least two different sources when initially presenting for advice and treatment (Figure 33).

Of the 174 cases remaining under follow-up at the time of the study, 113 (64.9%) were receiving help from one of the government facilities within the district (Table 88). The plurality of treatment seeking when first presenting was not replicated in cases who remained under follow-up, with 162 (93.1%) of 174 cases stating that they consistently attended one service in particular for treatment. Of the remainder, eleven (6.3%) said that they regularly attended two different services for treatment, and one (0.6%) regularly attended three different services (Figure 33).

8.3.2 Diagnosis

Data on previous diagnosis were available for 250 (99.2%) of 252 cases who had previously sought medical help for their seizures, including 172 (198.9%) of the 174 who remained under follow-up (Table 89). Of all cases seeking medical help for their seizures, eighty-five (34.0%) 250 said that they had been told they had epilepsy. The proportion of cases which remained under follow-up who clearly recalled having been given a diagnosis was 40.1%, compared to 20.5% of those who were not under any kind of follow-up by the time of initial assessment by the study ($\chi^2(1)=9.19$; p=0.002.

	Female (n=136)		Male (n=155)		Total (n=291)	
	n	(%)	n	(%)	n	(%)
Medical help sought previously	121	89.0%	132	85.2%	253	86.9%
Under follow-up at time of study	91	66.9%	83	53.5%	174	59.8%

Table 83: Presentation and follow-up for epilepsy

		Time to presentation (years)			
	n (%)	Median	Min	Max	IQR
Female	51 (46.8)	7.00	2	49	10
Male	58 (53.2)	7.50	2	36	10
Combined	109 (100.0)	7.00	2	49	11

Table 84: Time to presentation at 2+ years after seizure onset

	Age on prevalence date (years)				
	n	Median	Min	Max	IQR
Medical help sought previously	253	30	15	81	22
No medical help sought	38	34	15	85	23
Total	291	30	15	85	21
Under follow-up	174	29	15	81	22
Not under follow-up	79	33	15	71	56
Total	253	30	15	81	22

Table 85: Age distributions of treatment groups

	Age of onset of epilepsy (years)				
	n	Median	Min	Max	IQR
Medical help sought previously	248	12	0	70	18
No medical help sought	36	16	0	81	24
Total	284	13	0	81	20
Under follow-up	171	11	0	70	15
Not under follow-up	77	16	0	63	25
Total	248	12	0	70	18

Table 86: Age at onset of epilepsy among treatment groups

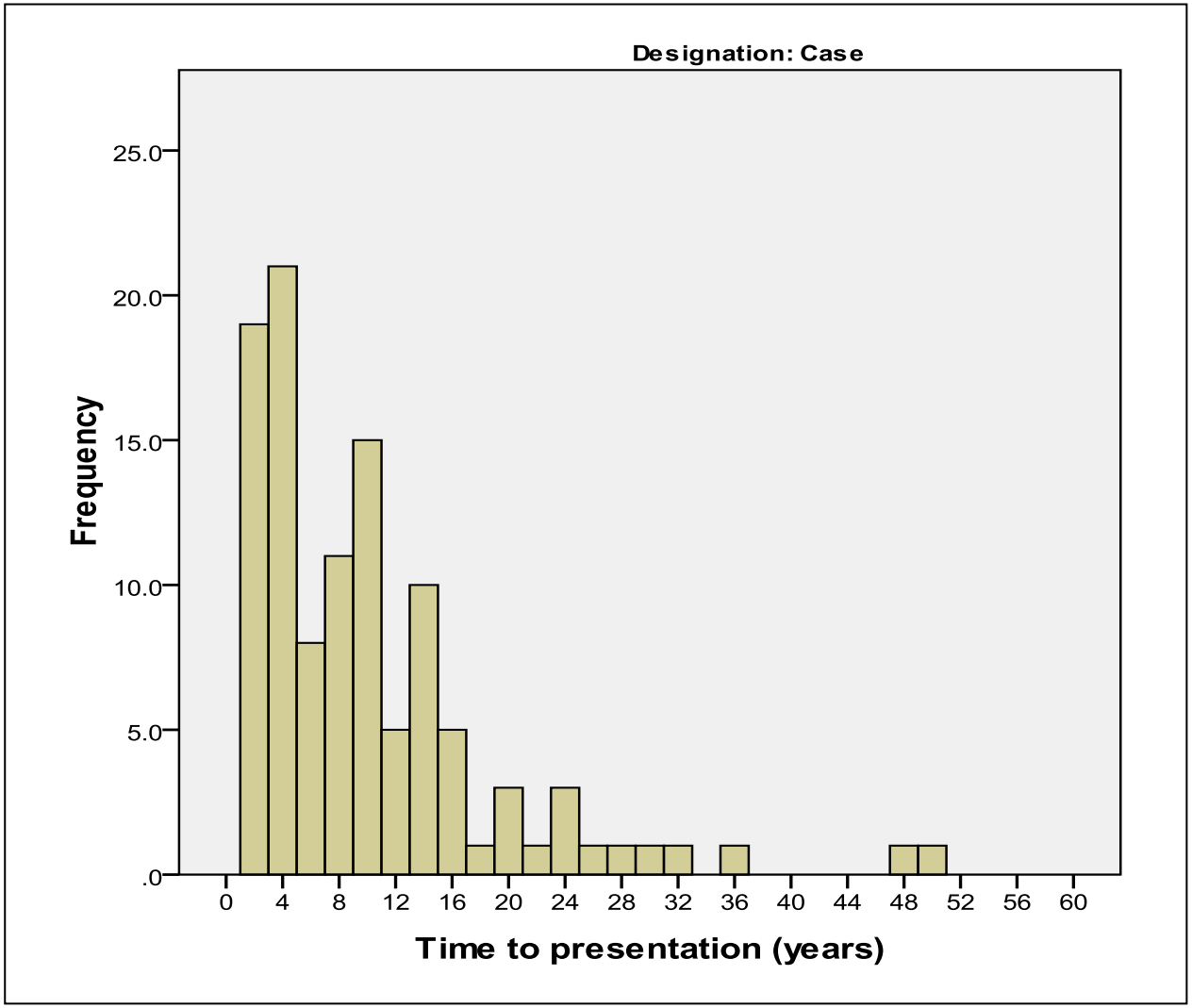


Figure 32: Time to presentation at 2+ years from seizure onset

	Female (n=120)		Male (n=132)		Total (n=252)	
	n	(%)	n	(%)	n	(%)
Govt. district health facility	82	(68.3%)	74	(56.1%)	156	(61.9%)
Govt. hospital	56	(46.7%)	52	(39.4%)	108	(42.9%)
Mission hospital	37	(30.8%)	42	(31.8%)	79	(31.4%)
Private pharmacy	12	(10.0%)	13	(9.8%)	25	(9.9%)
Family/friends/other	7	(5.8%)	7	(5.3%)	14	(5.6%)

N.B. percentage columns total more than 100.0% as categories not exclusive

Table 87: Site(s) of initial presentation

	Female (n=91)		Male (n=83)		Total (n=174)	
Source of follow-up	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Govt. district health facility	65	(71.4%)	48	(57.8%)	113	(64.9%)
Govt. hospital	13	(14.3%)	15	(18.1%)	28	(16.1%)
Mission hospital	13	(14.3%)	14	(16.9%)	27	(15.5%)
Private pharmacy	5	(5.5%)	8	(9.6%)	13	(7.5%)
Family/friends/other	2	(2.2%)	3	(3.6%)	5	(2.9%)

N.B. percentage columns total more than 100.0% as categories not exclusive

Table 88: Sources of on-going care

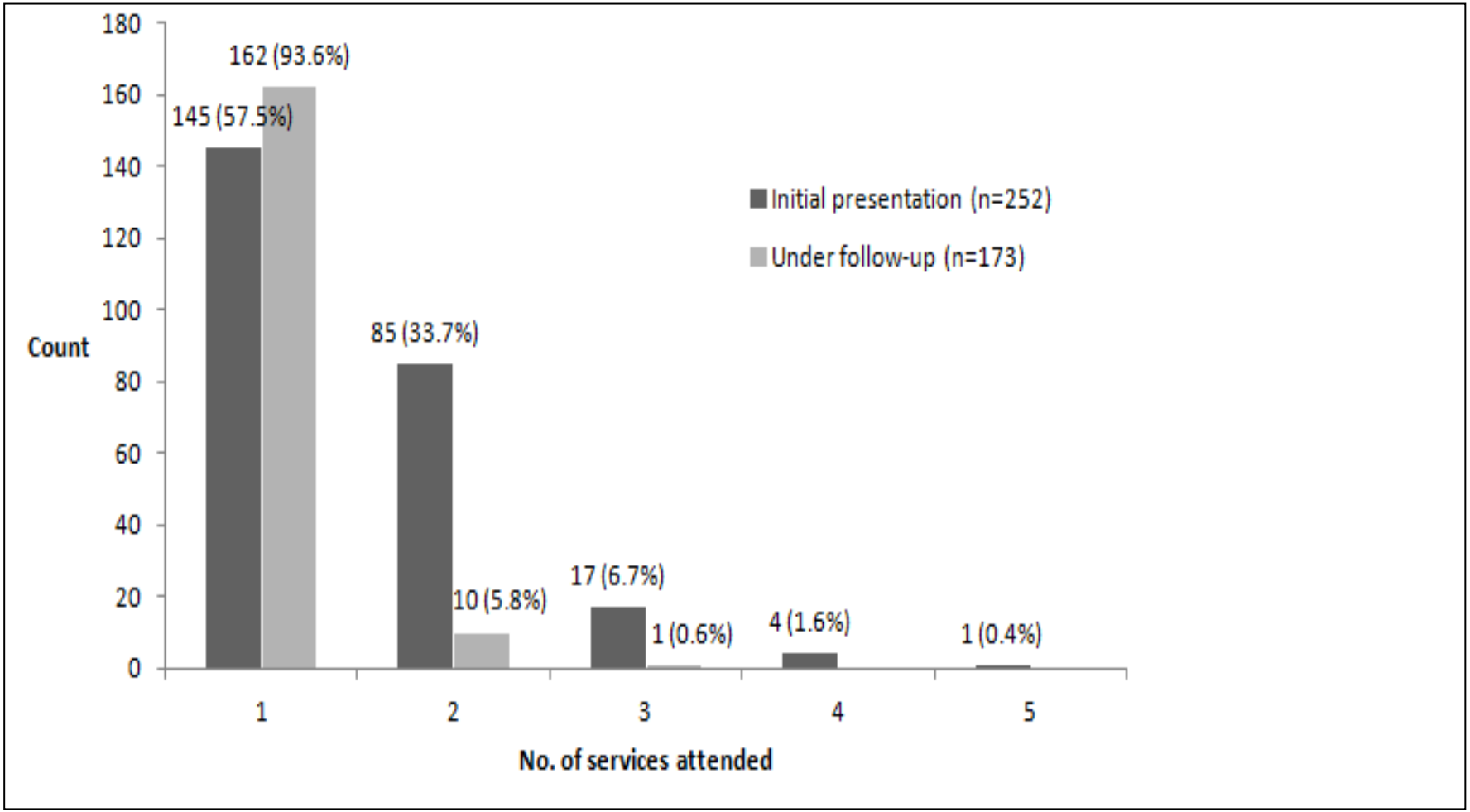


Figure 33: Number of services attended

	Under follow-up					
	Yes (n=172)		No (n=78)		Total (n=250)	
	n	(%)	n	(%)	n	(%)
None given	62	(36.0%)	41	(52.6%)	103	(41.2%)
Kifafa/epilepsy	69	(40.1%)	16	(20.5%)	85	(34.0%)
Other	23	(13.4%)	16	(20.5%)	39	(15.6%)
Degedege/febrile seizures	9	(5.2%)	3	(3.8%)	12	(4.8%)
Unable to recall/unsure	9	(5.2%)	2	(2.6%)	11	(4.4%)
Total	172	(100.0%)	78	(100.0%)	250	(100.0%)

Table 89: Previous diagnoses recalled by PWE presenting to medical services

8.3.3 Drug treatment for epilepsy in Hai

All but one of the 174 cases who remained under follow-up at the time of the study stated that they were regularly taking AED treatment (59.5% of all cases). Of these, 147 (85.0%) were using one AED, and twenty-six (15.0%) were regularly using two AEDs in combination. One case (female, aged thirty years) was maintained on oral haloperidol and diazepam along with AED treatment for a diagnosis of epilepsy with psychosis.

The most commonly prescribed AEDs were PB and PHT. Phenobarbitone was prescribed for 112 (76.2%) of 147 cases on mono-therapy and twenty-three (88.5%) of twenty-six cases on dual therapy (78.0% of treated cases overall); PHT was prescribed for seven (4.8%) of 147 cases on mono-therapy and twenty-one (80.8%) of twenty-six cases on dual therapy (16.2% of cases overall). Other AEDs encountered were CBZ and SV. Carbamazepine was used in sixteen (10.9%) cases of mono-therapy and in six (23.1%) cases of dual therapy (12.7% of cases overall). Sodium valproate was used along with CBZ in two (7.7%) cases of dual therapy (1.2% of cases overall). The patterns of mono- and dual therapy with AEDs are illustrated in Figure 35 and Figure 36. In twelve cases that were using mono-therapy the AED being used could not be clearly identified (Figure 34).

One case (male, aged fifty years) had been given a diagnosis of epilepsy with psychosis. He remained under treatment at district level, but an AED regime of PB and PHT, with previously good seizure control, had been discontinued in favour of a monthly depot injection with flupenthixol; at the time of initial assessment by the study he was suffering significant extra-pyramidal symptoms presumed secondary to this medication.

Figure 34: Difficulties in identifying AEDs and doses in the HDSS.
Clockwise from top left: mislabelled AEDs in government dispensary; improvised container containing unmarked tablets; unmarked and disintegrating tablets; mixed and unlabelled tablets.

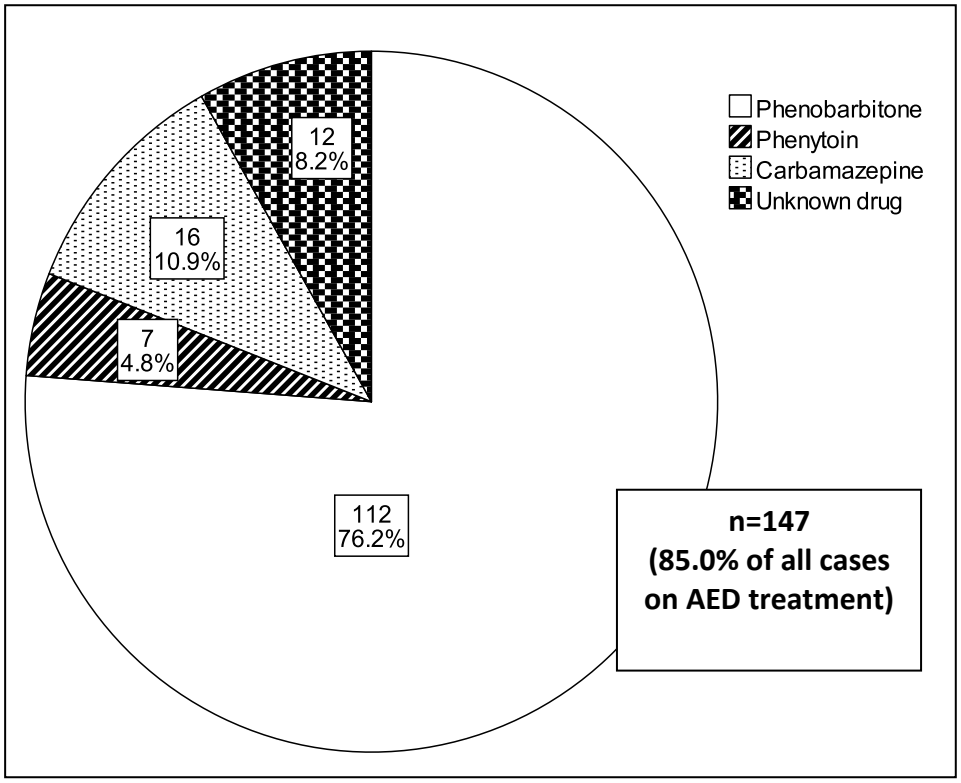


Figure 35: Prescribing pattern in AED mono-therapy

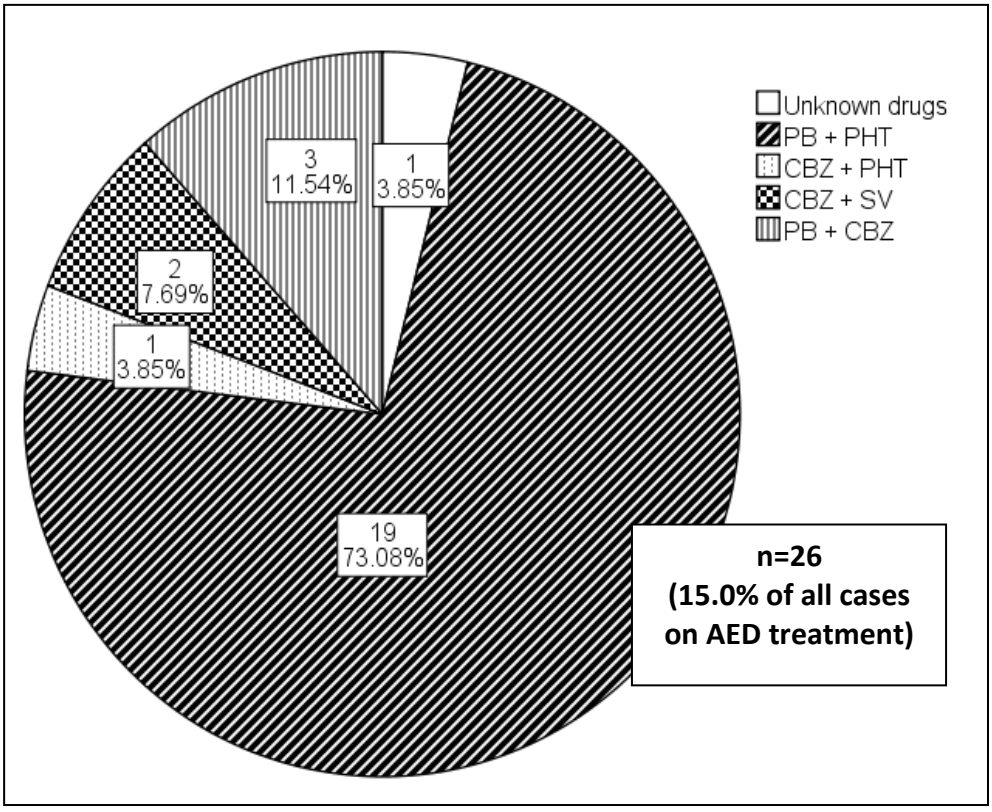


Figure 36: Prescribing pattern in AED dual therapy

8.3.4 Compliance, adequacy and affordability of AEDs in Hai

Data on self-reported compliance were available in 168 (97.1%) of 173 cases using AED therapy at the time of initial assessment (Table 90). One hundred and twenty-two of these (72.6%) reported good compliance, saying that they took their medication either daily or only occasionally forgot. A further forty-six (27.4%) cases were either irregular in their use of AEDs or reported significant problems in obtaining a regular supply of drugs. Four cases reported using AEDs reactively, taking them only after a seizure had occurred.

Data on the affordability of AEDs were available for 147 (85.0%) of the 173 cases on treatment (Table 91). Fifty-one of these (34.7%) stated that their AEDs were provided free by the health facility they were attending, while twenty-six (17.7%) stated that they struggled to afford their drugs on a regular basis. The remainder (47.6%) stated that their drugs were affordable to them.

	Female (n=89)		Male (n=79)		Total (n=168)	
	n	(%)	n	(%)	n	(%)
Daily/occasionally forgets	63	(70.8%)	59	(74.7%)	122	(72.6%)
Irregular/not compliant	26	(29.2%)	20	(25.3%)	46	(27.4%)
Total	89	(100.0%)	79	(100.0%)	168	(100.0%)

Table 90: AED compliance (self-reported)

	Female (n=74)		Male (n=73)		Total (n=147)	
	n	(%)	n	(%)	n	(%)
Provided free	30	(40.5%)	21	(28.8%)	51	(34.7%)
Able to afford	31	(41.9%)	39	(53.4%)	70	(47.6%)
Unable to afford regularly	13	(17.6%)	13	(17.8%)	26	(17.7%)
Total	74	(100.0%)	73	(100.0%)	147	(100.0%)

Table 91: Affordability of AEDs (cases on treatment)

	Female (n=91)		Male (n=82)		Total (n=173)	
	n	(%)	n	(%)	n	(%)
Yes	52	(57.1%)	47	(57.3%)	99	(57.2%)
No	21	(23.1%)	20	(24.4%)	41	(23.7%)
Unknown	18	(19.8%)	15	(18.3%)	33	(19.1%)
Total	91	(100.0%)	82	(100.0%)	173	(100.0%)

Table 92: Adequacy of AED doses in all cases on treatment

	Female (n=63)		Male (n=59)		Total (n=122)	
	n	(%)	n	(%)	n	(%)
Yes	39	(61.9%)	38	(64.4%)	77	(63.1%)
No	16	(25.4%)	14	(23.7%)	30	(24.6%)
Unknown	8	(12.7%)	7	(11.9%)	15	(12.3%)
Total	63	(100.0%)	59	(100.0%)	122	(100.0%)

Table 93: Adequacy of AED doses in cases reporting regular compliance

8.3.5 Adverse effects of AEDs

Data on side-effects from AED treatment were available in 159 (91.9%) of 173 treated cases, with 134 (84.3%) of these reporting no adverse effects. In the twenty-five individuals that did report side effects, the most commonly reported problem was tiredness, identified by seventeen cases: thirteen who were using PB mono-therapy, three using PB and PHT, and one using an unidentified drug. Other adverse effects reported included five cases who complained of dizziness (four on PB mono-therapy, one on an unidentified drug), headache (two cases, both using PB), rash (one case using CBZ and SV), memory problems (one case using PB), and unspecified behavioural disturbance (one case using PB).

8.3.6 Seizure frequency in treated and untreated cases

The majority of cases had little or no seizure control, with only twenty-one (12.1%) of 173 cases taking AEDs reporting to be seizure-free on their treatment (7.2% of all cases). The proportional frequencies of seizures in the 173 cases using AEDS are summarized in Table 94, and the cumulative percentage of seizure frequency in all cases with uncontrolled seizures is illustrated in Figure 37.

	Female (n=91)		Male (n=82)		Total (n=173)	
	n	(%)	n	(%)	n	(%)
Daily - several/day	0	(0.0%)	1	(1.2%)	1	(0.6%)
Seizure(s) most days	1	(1.1%)	3	(3.7%)	4	(2.3%)
Weekly - several/week	11	(12.1%)	5	(6.1%)	16	(9.2%)
Seizure(s) most weeks	14	(15.4%)	11	(13.4%)	25	(14.5%)
Seizure(s) most months	24	(26.4%)	30	(36.6%)	54	(31.2%)
≥1 in past year	28	(30.8%)	20	(24.4%)	48	(27.7%)
≥1 in past 5 years	5	(5.5%)	0	(0.0%)	5	(2.9%)
Seizure-free	8	(8.8%)	12	(14.6%)	20	(11.6%)
Total	91	(100.0%)	82	(100.0%)	173	(100.0%)

Table 94: Seizure frequency among cases taking AED treatment

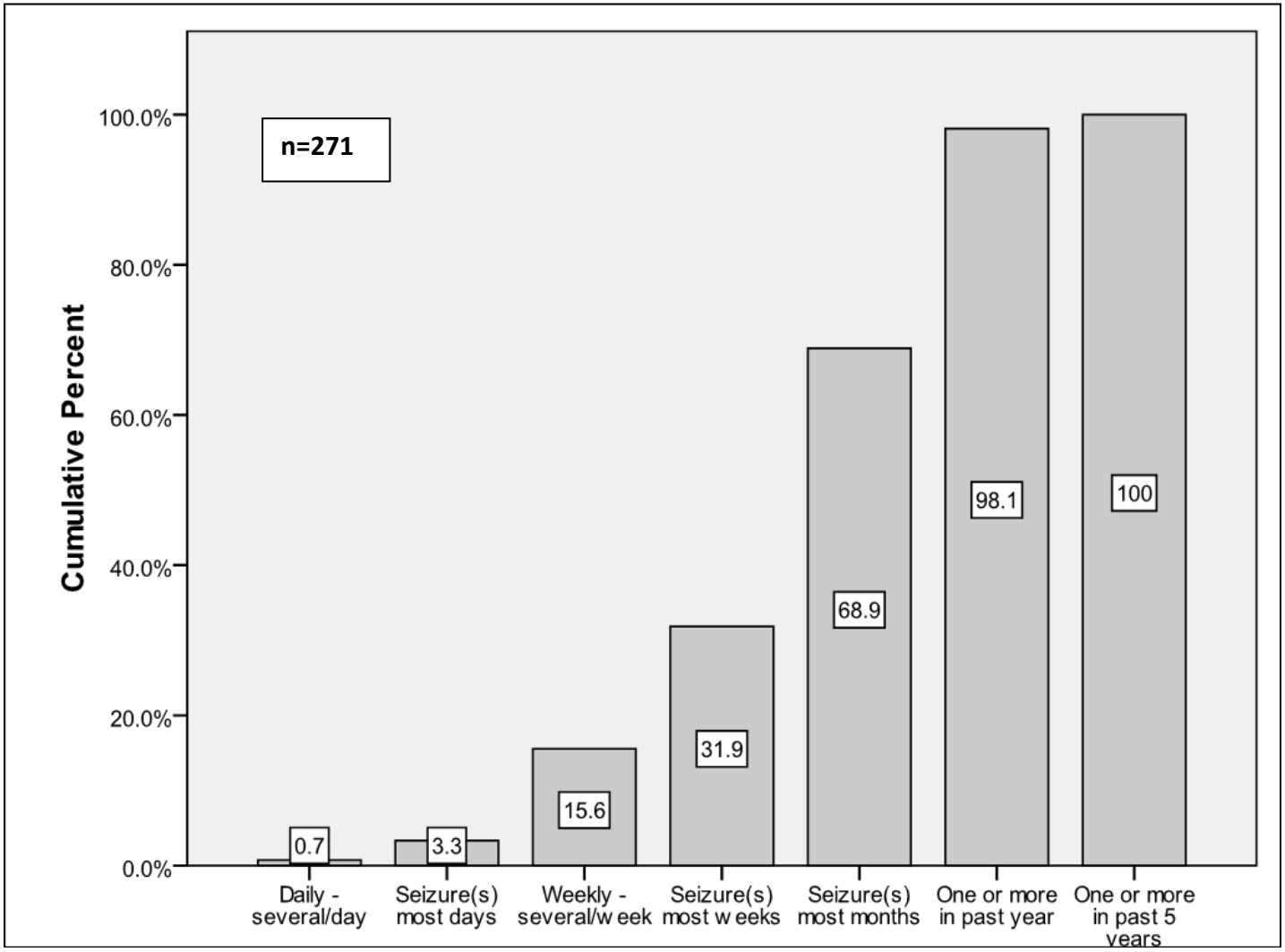


Figure 37: Seizure frequency: cumulative percentage in PWE with active seizures

8.3.7 Previous treatment

Of the seventy-nine individuals who had previously sought help but who were not receiving any treatment at the time of assessment, sixty-four (82.1%) reported having previously received treatment of some description, although the majority of these (thirty-eight cases; 59.4%) were unable to recall the identity or nature of drugs with which they had previously been treated. Thirteen cases (20.3%) had previously received PB, one case (1.6%) had received PHT, another case had received CBZ, and four cases (6.3%) had previously been treated with a combination of PB and PHT. Seven cases (10.9%) described prior treatment with anti-malarial or antipyretic drugs when presenting with convulsive episodes.

Data on the reason for discontinuation of previous treatment were available for fifty-four (84.4%) of the sixty-four previously treated cases: twelve (22.2%) said they had been given an acute prescription only, with no advice that treatment should be continued in the long-term; eleven (20.4%) did not pursue further treatment after a lack of initial efficacy; four (7.4%) reported that they had stopped taking treatment when seizures initially went into remission but had not recommenced treatment when seizures had subsequently relapsed; seven (13.0%) said they stopped due to initial side-effects; seven (13.0%) were unable to afford continued treatment; two (9.3%) said that further treatment had not been readily available. The remaining eleven (20.4%) cases described a range of reasons for stopping treatment that related to various social circumstances, often relating to the death of a relative or other benefactor that had been supplying treatment. Instances of local healthcare workers who had been supplying treatment leaving their posts and treatment not subsequently being continued were also described.

8.3.8 Epilepsy treatment gap

At the time of initial assessment 122 (41.9%) of 291 cases reported using AEDs with good compliance, although thirty (24.6%) of these were identified as using sub-therapeutic doses of AEDs. We therefore identified ninety-two (31.4%) out of 291 cases that could be considered as being adequately and appropriately treated with AEDs at the time of the study. Based on these data, a conservative estimate of the ETG in the adult HDSS population based on self-reported AED use is therefore 68.6% (95% CI 63.0 to 73.7). Given that 92.8% of all cases were suffering from active seizures (including 87.9% of cases using AEDs), the true ETG may be higher still.

8.3.9 Traditional treatment for epilepsy

Data on the use of traditional healers and traditional treatments were available from 276 (94.8%) of 291 cases of whom 133 (48.2%) reported having used traditional treatment of some description. Of the thirty-nine cases who denied having previously sought medical help for their seizures, twenty-two (64.7%) said they had used traditional treatment. Of the 133 cases who had attended traditional healers, ninety (67.7%) were able to recall details of the diagnosis they had been given: no diagnosis was given in thirty-three cases (36.7%), a supernatural explanation for the seizures was used in twenty-three cases (25.6%), thirteen cases (14.4%) were diagnosed as '*degedege*', and ten cases (11.1%) were diagnosed as '*kifafa*'. A further eleven cases (12.2%) described a range of other explanations relating to physical or emotional causes. Of the 121 cases who answered a question on their opinion of the efficacy of traditional treatment, 106 (87.6%) said that they had derived no benefit from their treatment. Eighty-five people provided an estimate of the total they or their family had spent on traditional treatment, and this was often considerable: twenty (23.5%) cases claimed to have spent in excess of 100,000 Tanzanian shillings, with one individual claiming to have spent over two million Tanzanian Shillings (c.700 GBP/1,500 USD). Modes of treatment employed by traditional healers that we encountered included inhalations, purgatives, wearing of amulets and talismen, spiritual ceremonies and scarification (Figure 38).

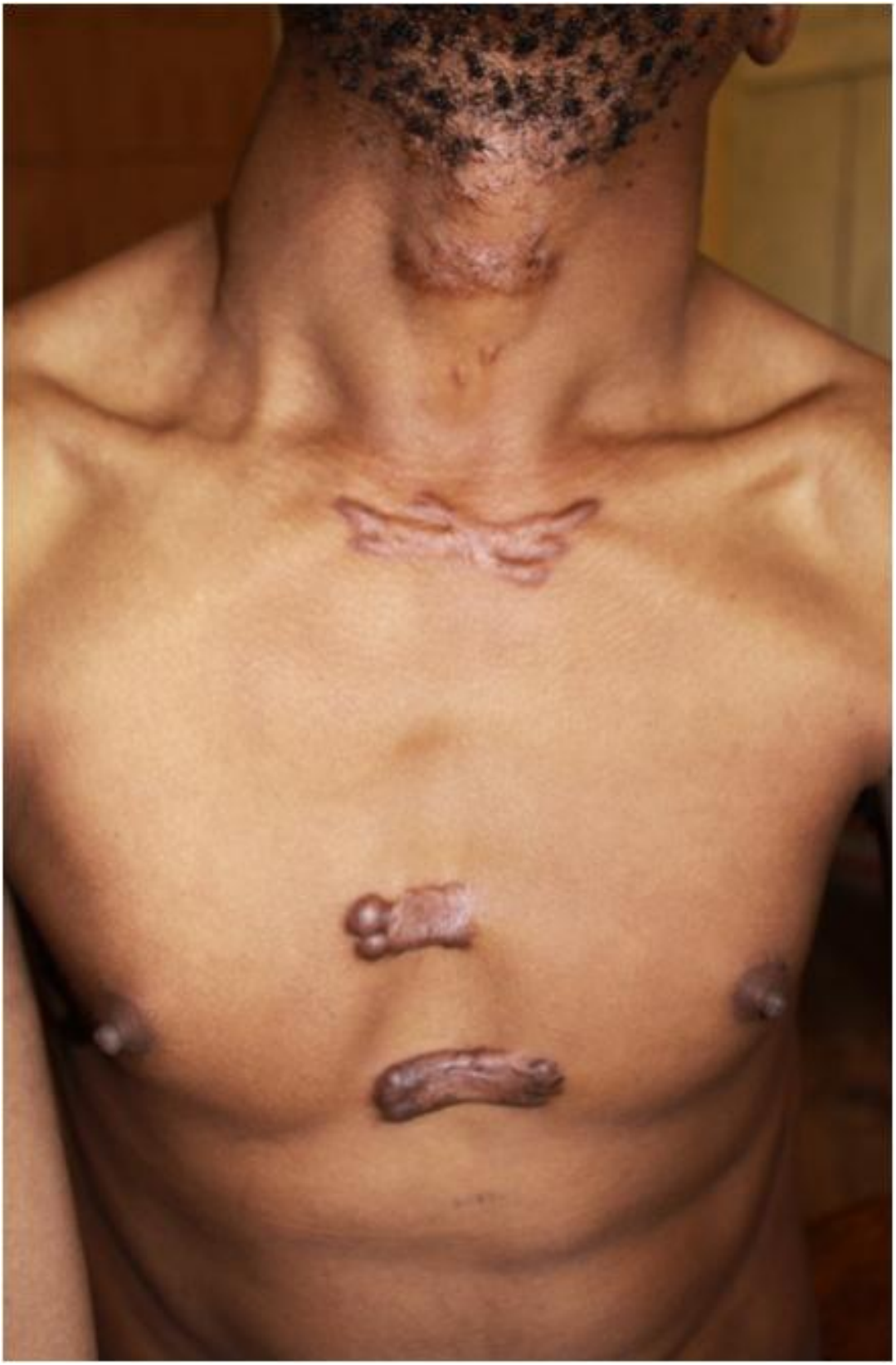


Figure 38: Scarification, used by traditional healers to treat seizures

8.3.10 Analyses of treatment groups: presentation to medical services

Univariable analyses were performed to identify demographic, clinical and social predictors of ever having presented to medical services (Table 95). Cases who were less likely to have presented to medical services previously were those who were Muslim (OR 0.20, 95% CI 0.20 to 0.90; p=0.023), and cases who drank alcohol (OR 0.36, 95% CI 0.17 to 0.77; p=0.006); cases who had completed their primary education, compared with those with either no or incomplete primary education, were more likely to have presented to medical services (OR 2.89, 95% CI 1.28 to 6.53; p=0.008). No other significant uni-variable associations with presentation to medical services were identified.

A binary logistic regression model was constructed to further examine the influence of these predictors and to look for any confounding effects. The adjusted ORs for all variables entered into the model are summarised in Table 96, and the final model is summarised in Table 97. Of note, the positive association with having completed primary education was replicated in the final model (OR 2.55, 95% CI 1.09 to 5.98; p=0.032), as was the negative association with drinking alcohol (OR 0.32 95% CI 0.13 to 0.80; p=0.014). In addition, two further associations with seeking medical treatment were suggested by the final model: a positive association with the presence of an aura as part of the seizure manifestation (OR 2.83, 95% CI 1.12 to 7.12; p=0.028), and a negative association with the use of traditional medicine (OR 0.36, 95% CI 0.16 to 0.85; p=0.020). Thirty-six (12.4%) of 291 cases were excluded from the regression analysis due to missing data.

Variable	OR	95% CI	p-value
Demographic features			
Male sex	0.71	0.36 to 1.43	0.334
Tribe other than Chagga	0.79	0.34 to 1.85	0.583
Muslim religion (vs. Christian)	0.43	0.20 to 0.90	0.023
Cases identified via screening (vs. Key Informants)	1.09	0.51 to 2.31	0.829
Clinical associations			
Seizure-associated injuries	1.13	0.41 to 3.11	0.818
Cognitive impairment present	0.81	0.39 to 1.67	0.568
Motor impairment present	0.59	0.26 to 1.34	0.200
Family history of epilepsy	0.93	0.39 to 2.25	0.876
Aura present	2.05	0.96 to 4.41	0.061
Automatisms present	0.98	0.44 to 2.19	0.961
Daytime seizures (vs. nocturnal only)	1.70	0.75 to 3.87	0.200
Social factors			
Any education (vs. no education)	1.38	0.58 to 3.27	0.466
Completed 1^{o} education (vs. none/incomplete)	2.89	1.28 to 6.53	0.008
Literate	1.21	0.58 to 2.53	0.612
Use of traditional treatment/healers	0.49	0.23 to 1.04	0.058
Drinks alcohol	0.36	0.17 to 0.77	0.006

Table 95: Predictors of previous attendance: uni-variable analyses

Variable	B	S.E.	Sig.	Adj. OR*	95% C.I. Lower	95% C.I. Upper
Demographic features						
Male sex	0.00	0.45	1.000	1.00	0.42	2.41
Tribe other than Chagga	0.04	0.63	0.953	1.04	0.30	3.55
Muslim religion (vs. Christian)	-0.87	0.55	0.112	0.42	0.14	1.23
Cases identified via screening (vs. Key Informants)	0.41	0.47	0.387	1.51	0.60	3.82
Clinical associations						
Seizure-related injuries	0.58	0.65	0.369	1.79	0.50	6.33
Cognitive impairment present	0.16	0.61	0.790	1.18	0.36	3.90
Motor impairment present	-1.02	0.64	0.109	0.36	0.10	1.25
Family history of epilepsy	-0.18	0.57	0.757	0.84	0.27	2.56
Aura present	1.24	0.53	0.020	3.47	1.22	9.85
Automatisms present	-0.06	0.53	0.905	0.94	0.33	2.66
Daytime seizures (vs. nocturnal only)	0.31	0.57	0.588	1.37	0.44	4.20
Social factors						
Any education (vs. no education)	-0.19	0.64	0.767	0.83	0.24	2.91
Completed 1^{o} education (vs. none/incomplete)	1.48	0.61	0.015	4.39	1.33	14.54
Literate	-0.91	0.69	0.183	0.40	0.11	1.54
Traditional treatment/healers	-0.99	0.47	0.034	0.37	0.15	0.93
Drinks alcohol	-1.19	0.53	0.026	0.30	0.11	0.87

***adjusted for variables in Table 95**

Table 96: Predictors of previous attendance: multivariable analysis

Variable	B	S.E.	Sig.	Adj. OR*	95% C.I. Lower	95% C.I. Upper
Drinks alcohol	-1.13	0.46	0.014	0.32	0.13	0.80
Completed primary education (vs. none/incomplete)	0.94	0.44	0.032	2.55	1.09	5.98
Aura present	1.04	0.47	0.028	2.83	1.12	7.12
Use of traditional treatment/healers	-1.01	0.44	0.020	0.36	0.16	0.85

Goodness of fit (Hosmer & Lemeshow)=0.87 ***adjusted for variables in Table 95**

Table 97: Predictors of previous attendance: logistic regression model

8.3.11 Analysis of treatment groups: cases remaining under follow-up

The same set of uni-variable predictor variables were used to compare cases who had previously presented to medical services and remained under follow-up at the time of the study (n=174) with those who were no longer under follow-up (n=79). Within these two groups the cases who were less likely to remain under follow-up were males (OR 0.56, 95% CI 0.32 to 0.96; p=0.035) and those who drank alcohol (OR 0.26, 95% CI 0.13 to 0.53; p<0.001); cases with any level of education compared with non were more likely to remain under follow-up (OR 2.62, 95% CI 1.38 to 4.99; p=0.003). An additional variable of whether patients recalled having previously being given a diagnosis consistent with epilepsy was also included for these groups, and this was also positively associated with remaining under follow-up (OR 2.58, 95% CI 1.42 to 4.69; p=0.002). All variables examined are summarised in Table 98.

A binary logistic regression model was again used to examine for any confounding effects, and initial and final models are summarised in Table 99 and Table 100. In the final model two protective factors were reproduced as significant associations: ever having received a diagnosis of epilepsy (OR 3.09, 95% CI 1.56 to 6.15; p=0.001) and having any level of education (OR 2.46, 95% CI 1.20 to 5.05; p=0.014). The negative association with alcohol use was also retained (OR 0.32, 95% CI 0.15 to 0.68; p=0.004), although the negative association with being male was not. Twenty-nine (11.5%) of 253 cases who had ever presented to medical services were excluded from regression analysis due to missing data.

Variable	OR	95% CI	p-value
Demographic features			
Male sex	0.56	0.32 to 0.96	0.035
Tribal group other than Chagga	0.91	0.46 to 1.81	0.787
Muslim religion (vs. Christian)	0.81	0.41 to 1.60	0.540
Patients identified by screening (vs. Key Informants)	1.04	0.56 to 1.89	0.890
Clinical associations			
Seizure-associated injuries	0.64	0.26 to 1.56	0.320
Cognitive impairment present	0.73	0.41 to 1.30	0.287
Motor impairment present	0.60	0.30 to 1.21	0.151
Family history of epilepsy	1.26	0.61 to 2.60	0.534
Aura present	1.11	0.65 to 1.91	0.698
Automatisms present	0.85	0.46 to 1.58	0.613
Daytime seizures (vs. nocturnal only)	0.98	0.47 to 2.04	0.947
Diagnosis of epilepsy given previously	2.58	1.42 to 4.69	0.002
Social factors			
Any education (vs. no education)	2.62	1.38 to 4.99	0.003
Completed 1^{o} education (vs. none/incomplete)	1.43	0.83 to 2.48	0.196
Literate	1.19	0.69 to 2.04	0.534
Use of traditional treatment/healers	1.17	0.68 to 2.02	0.573
Drinks alcohol	0.26	0.13 to 0.53	<0.001

Table 98: Predictors for cases remaining under follow-up: uni-variable analyses

Variable	B	S.E.	Sig.	Adj. OR*	95% C.I. Lower	95% C.I. Upper
Demographic features						
Male sex	0.56	0.34	0.095	0.57	0.29	1.10
Tribal group other than Chagga	0.04	0.45	0.931	0.96	0.40	2.33
Muslim religion (vs. Christian)	0.46	0.44	0.303	0.63	0.27	1.51
Cases identified by screening (vs. KIs)	0.20	0.37	0.601	1.22	0.59	2.52
Clinical associations						
Seizure-related injuries	0.21	0.53	0.698	0.81	0.29	2.30
Cognitive impairment present	0.25	0.45	0.587	0.78	0.32	1.89
Motor impairment present	0.30	0.49	0.543	0.74	0.29	1.93
Family history of epilepsy	0.71	0.47	0.130	2.03	0.81	5.04
Aura present	0.14	0.36	0.770	1.11	0.55	2.23
Automatisms present	0.24	0.39	0.538	0.79	0.36	1.70
Daytime seizures (vs. nocturnal only)	0.49	0.51	0.338	0.62	0.23	1.66
Diagnosis of epilepsy given previously	1.15	0.38	0.002	3.15	1.51	6.57
Social factors						
Any education (vs. no education)	0.86	0.53	0.104	2.37	0.84	6.69
Completed 1^{o} education (vs. none)	0.14	0.47	0.764	1.15	0.46	2.88
Literate	0.32	0.51	0.532	0.73	0.27	1.97
Use of traditional treatment/healers	0.11	0.34	0.755	0.90	0.47	1.74
Drinks alcohol	1.14	0.42	0.007	0.32	0.14	0.73

***adjusted for variable in Table 98**

Table 99: Predictors of remaining under follow-up: multivariable analysis

					95% C.I.	
Variable	**B**	**S.E.**	**Sig.**	**Adj. OR***	**Lower**	**Upper**
Diagnosis of epilepsy previously	1.13	0.35	0.001	3.09	1.56	6.15
Any education (vs. none)	0.90	0.37	0.014	2.46	1.20	5.05
Drinks alcohol	-1.16	0.40	0.004	0.32	0.15	0.68

Goodeness of fit (Hosmer & Lemeshow)=0.75 *adjusted for variable in Table 98

Table 100: Predictors of remaining under follow-up: logistic regression model

8.4 Discussion

Although we estimate the ETG in adult PWE living in Hai to be approaching 70%, we also found that a larger proportion (nearly 90%) had previously presented to local health services for advice and treatment at some point. Cases more likely to present to medical services were those who had completed primary education and those experiencing an identifiable aura or prodrome prior to their seizures. Conversely, cases who drank alcohol or who had also used traditional healers were less likely to have presented previously. While being Muslim, compared with being Christian, correlated with a reduced likelihood of seeking medical treatment on uni-variable analysis, this predictor did not appear in the final regression model. Of these factors, lack of education and alcohol use could be interpreted either as socio-economic markers that may predict a lower level of engagement with services in general, or may be factors that are present more frequently as the result of having untreated epilepsy.

Our findings contrast with those of an in-depth cross-sectional study of the risk factors associated with the ETG in 673 PWE in Kilifi, Kenya (Mbuba et al., 2012b). In this study epilepsy-specific factors that were associated with failure to seek treatment were duration of epilepsy of ten years or more and the presence of focal-onset seizures, usually with secondary generalisation. The authors postulate that PWE with a long duration of epilepsy may have learned to cope with their condition, and that the prodromal awareness associated with focal-onset seizures may have made people less likely to seek treatment because of stigma. In Hai there was no association between duration of epilepsy and treatment-seeking, and we found that awareness of an aura or prodrome was positively associated with seeking treatment. It is interesting to note that in the Kenyan study, holding traditional religious beliefs as opposed to being either Christian or Muslim was also associated with failure to seek treatment. In Hai the only religious groups identified on open questioning were Christian and Muslim, with no individuals describing themselves as belonging to traditional religions. It may be that this points to a more modern social milieu, in which stigma may be less prominent than in more traditional societies, which may in turn moderate the influence of epilepsy-specific factors

such as those identified in Kilifi on treatment-seeking behaviours. Elsewhere in Tanzania, both supernatural and more scientific ideas about the causes of epilepsy seem to coexist among PWE and their communities (Winkler et al., 2010b), while in Zambia it has been identified that PWE are disadvantaged with regards to social and economic matters, and social stigma, isolation and lack of knowledge about epilepsy contribute to the fact that only a minority of PWE access health facilities (Birbeck, 2000a, Birbeck et al., 2007). It has been proposed that while quantitative approaches such as those employed here may identify associations with treatment-seeking behaviour, any deeper understanding of the complex influences on the decision to seek care for epilepsy in sub-Saharan communities will need to employ broader ethnographic approaches, taking into account not just patient- and resource-related factors, but also considering treatment providers and the communities in which they work (Kendall-Taylor et al., 2009). Such an approach would certainly seem warranted in Hai, where use of traditional healers is a predictor of not seeking biomedical treatment, which mirrors findings from contemporaneous populations in Kilifi in Kenya as well as elsewhere in Tanzania (Winkler et al., 2010b, Mbuba et al., 2012b).

Among PWE who had previously presented to medical services there was considerable attrition from follow-up, with less than 60% of these cases being in regular contact with treatment services at the time of the study. We have shown that receiving a diagnosis of epilepsy is a protective factor in terms of remaining under follow-up, suggesting that education about epilepsy on the part of both health workers and PWE is a contributory factor to defaulting from follow-up; this is a potentially modifiable barrier to treatment, but one which must be seen in the context of the general absence of specialist neurologists in LMICs (WHO, 2005). It has been suggested that interventions at a local level should address the training of health care workers to diagnose and manage epilepsy, to counsel PWE about their diagnoses, and to make appropriate referrals (Mbuba and Newton, 2009), and such interventions have been shown to be efficacious in improving the diagnosis and management of epilepsy in communities in India, Zimbabwe and Ethiopia (Adamolekun et al., 1999, Gourie-Devi et al., 2003, Berhanu et al., 2009). In Hai, where nearly one third of PWE that initially present to treatment services are not

retained, targeted educational interventions would also be appropriate. This suggestion is further supported by evidence of plurality of treatment seeking behaviour, with 42.5% of those cases initially presenting to services attending two or more different service providers while seeking a diagnosis, implying that treatment approaches and availability are not uniform among the health facilities in the district.

With regards to patient factors, presentation to services from the time of onset of seizures was delayed by two years or more in nearly half of all those who had previously presented (48.4%). Reasons for this are likely to be multi-factorial and educational interventions directly targeting PWE, their carers and their communities to increase awareness and to reduce stigma are therefore also warranted. Support groups for PWE are found in many countries, including Tanzania (Mental Health Association of Tanzania, 2012), and community-based programmes in African countries that have aimed to increase levels of treatment for PWE through education as well as drug supply have reported success, albeit contingent on external support and funding (Feksi et al., 1991, Watts, 1989, Berhanu et al., 2009).

The ETG in the Hai population, based on reported use of adequate and appropriate AED therapy, was 68.4% (95% CI 63.0 to 73.7). This is lower than previous estimates of the ETG in Tanzania of between 76% and 95.8% (Winkler et al., 2009c, Dent et al., 2005), although is in line with more recent systematic reviews of ETG in developing countries worldwide (Mbuba et al., 2008, Meyer et al., 2010). The lower ETG in Hai may be due its proximity to the large towns of Arusha and Moshi, where numerous private clinics and non-governmental healthcare providers are located, and also to a large referral hospital (KCMC), where there is a practicing neurologist. Conversely, we know that there is a high degree of stigma associated with epilepsy in this population (Mushi et al., 2010), and more stigmatised or marginalised individuals may not have presented to the study. It can be assumed that such individuals would be less likely to be treated, and would therefore contribute to the estimate of ETG if they were known.

The utility of self-reporting in estimating the ETG has recently been called into doubt by a study from Kenya (Mbuba et al., 2012b). The overall concordance between self-reported

adherence and detection in blood for the three AEDs known to be prescribed in the study population was only 55%, with reported adherence having a sensitivity of only 38.1% and specificity of 80.8% when verified through detection of AEDs in blood. This would suggest by extrapolation that the true ETG in Hai may be lower than our estimate of 68.6%. In our cohort, however, a low rate of seizure-freedom was observed, being reported in only 11.6% of treated cases. In cases with uncontrolled seizures 68.9% reported seizures on at least a monthly basis and 31.9% on a weekly basis. Retrospective reporting of seizure frequency at up to two months has been shown to be consistent between patients and carers (Wiebe, 2000), and these rates of high seizure frequency among PWE in Hai would suggest that the true level of adequate treatment may be much lower, and the true ETG therefore higher.

Phenobarbital was the most commonly prescribed AED, being used by 78% of all treated cases. The majority of cases using AEDs (84.3%) did not report any side-effects, and none complained of serious side-effects leading to withdrawal of treatment. This finding corresponds with observational studies conducted in resource-poor settings, including SSA, which have consistently demonstrated efficacy and tolerability of PB in everyday clinical use (Nimaga et al., 2002, Feksi et al., 1991, Sykes, 2002). The Hai cohort is now under follow-up, allowing for prospective evaluation of treatment outcomes, including adherence, tolerability and efficacy.

Finally, nearly half (48.2%) of all PWE reported that they had used traditional medicines or healers for their epilepsy. The use of traditional healers has been identified in a number of studies examining access to treatment for epilepsy in LMICs, including SSA. Their influence remains uncertain, with some data suggesting that access to a traditional healer is a positive predictor of subsequent of concurrent access to biomedical treatment (Quet et al., 2011), while observational data have cited a preference for traditional healers as a reason for not attending an epilepsy clinic (Berhanu et al., 2009). In Hai attendance at a traditional healer was associated with a reduced likelihood of presenting to biomedical services (OR 0.44; 95% CI 0.16 to 0.85). What is clear is that traditional healers will provide culturally acceptable explanations for seizures, and may represent a source of

psycho-social support for PWE and their families that is embedded in the community (Baskind and Birbeck, 2005a, Winkler et al., 2010b, Kendall-Taylor et al., 2009). Intervention strategies that incorporate this group of individuals represent an enticing but challenging prospect (Mbuba and Newton, 2009).

8.5 Summary and conclusions

The ETG in adult PWE living in the HDSS is in line with estimates from other countries in SSA, and in LMICs in general. A combination of clinical, socio-economic and cultural factors are associated with the likelihood of seeking treatment. Presentation to medical services is delayed by two years or more in a considerable proportion of patients, and interventions to increase awareness and reduce stigma may serve to encourage PWE to seek treatment sooner. Having presented to services, retention under follow-up is correlated with a higher educational level of the patient and with having received a diagnosis of epilepsy. This latter factor is potentially modifiable through educational interventions targeting healthcare workers. PB is widely available, is the most commonly prescribed drug locally, and appears to be well tolerated in this patient group.

In conclusion, we suggest that low-cost educational interventions targeting both patients and health care workers would serve to reduce the ETG in the HDSS and without recourse to additional external human or material resources. Such efforts should be informed by detailed and nuanced characterisation of the various factors influencing treatment seeking and delivery of care for PWE in this population. Having established a well-characterised prevalent cohort of adult PWE to which we have access for the purposes of clinical follow-up and further study, we are now in a position to pursue these ends. A deeper understanding of these issues in the HDSS population will serve to benefit PWE locally as well as elewhere in Tanzania, and in SSA in general.

Chapter 9. Summary and recommendations

9.1 Introduction

The data presented here are derived from one of the largest community-based epidemiological studies of epilepsy to be conducted in SSA to date and the largest to date in Tanzania. It is also one of only a handful of studies from SSA to correlate clinical data with investigation findings in the context of a cross-sectional prevalent cohort of patients. As such, we hope that these findings will provide valuable insights to those involved in the care of PWE and to those planning further epidemiological, clinical or operational research of epilepsy in this region.

The size of the study coupled with limitations in human and material resources meant that a number of pragmatic decisions were taken as field work progressed that are reflected in the scope and strength of some of the final data.

9.2 Pilot study and screening questionnaire

The chief limitations of the pre-census pilot work were the small numbers included and the paucity of clinical information available regarding epilepsy cases included in the pilot. Accepting this, the screening questionnaire as a whole had a sensitivity of 100% and a specificity of 54.5%. The reason that this apparently low specificity did not lead to a much higher response rate to census-based screening in the Hai population is not clear, and further investigation of this would be informative for any future work seeking to replicate the methods used here.

Due to limited time and resources, no larger field-based validation was possible prior to the population census and screening. Such an exercise would have allowed us to further explore the performance and utility of the screening questionnaire which in turn would have allowed for more precision during analysis of and adjustment of the final prevalence estimates. Field-based validation would also have allowed us to test the utility of statistical modelling of a reduced number of questions that suggested a sensitivity of 100% while maintaining a specificity of 86.4%. As it stood, however, prior to the census

we were confident that the screening instrument was sensitive and culturally acceptable within our study population. We hope that the post-hoc analysis of how the screening questionnaire performed in the field will be of value in the design and planning of any further community-based surveys of epilepsy in SSA, particularly in a Kiswahili-speaking population. Future work may also benefit from further exploration of the screening instrument in a given social context by way of psychometric and linguistic methods to provide measures of internal consistency and construct validity.

9.3 Prevalence and nature of epilepsy in Hai

Only epilepsy with convulsive seizures was detected during this study, and while this renders strict comparisons with studies that have reported on all epilepsy types difficult, active convulsive epilepsy would appear to have a lower prevalence in this part of Tanzania than elsewhere in SSA. We suggest that this should be interpreted as indicating that previously reported high prevalence rates for epilepsy in SSA cannot be generalised, either within Tanzania, or to the region as a whole. Recent large scale multi-site studies that have been published since the completion of the research presented here support this assertion, having found considerable variation in prevalence in different regions that cannot be ascribed to methodology alone (Ngugi et al., 2013b). It should be stressed that these studies have pragmatically chosen from the outset to screen only for active convulsive epilepsy, recognising the difficulties inherent in detecting other seizure types in community-based screening studies.

The high proportion of focal-onset epilepsy among people with ACE living in the HDSS is suggestive of a considerable burden of acquired brain pathology in this patient population. Aetiological factors or associations suggested by this study include perinatal complications and febrile seizures in childhood: findings which are consistent with contemporary and historical studies from elsewhere in SSA. Neurocysticercosis, while present in this population, does not appear to represent a major aetiological burden with regards to epilepsy. The role of family history is unclear, that of HIV is unknown, and both warrant further investigation.

The prevalence of absence seizures or of focal seizures associated with pure motor activity or sensory phenomena only, without secondary generalisation, remains unknown in this population. While further study of these clinical entities is warranted, our experience suggests that alternative methodologies should be used, and any community-based screening approaches to this problem should be developed and piloted on a smaller scale, with complete case ascertainment within a sampling frame rather than a population-wide approach. This would echo the original development work behind the screening questionnaire used here, performed in Ecuador in the 1980s (Placencia et al., 1992a, Placencia et al., 1992d).

The contribution of dissociative or non-epileptic attacks to our prevalence estimate is also unclear. While we have validated our case-finding as best we can, it may be that answers to this question emerge as the cohort is followed up prospectively. While this entity is known to account for up to 15% of cases of apparently refractory epilepsy seen in clinic settings in HICs (Devinsky, 1999), there are presently no data of which we are aware specifically examining this issue in an African setting.

The findings of febrile seizures, perinatal complications and evidence of structural brain disease as predictors of epilepsy in the Hai population point to a considerable burden of acquired epilepsy. By implication, improvements in obstetric care and in the recognition and management of febrile seizures in childhood in this population may lead to a measurably reduced morbidity with epilepsy in those surviving to adulthood.

9.4 Neurocysticercosis

Cysticercosis and NCC appear to be present in Hai, although with a low endemicity. While the utility of serological testing with antibody EITB for cysticercosis is not proven in this epidemiological context, the presence of NCC needs to be considered in the assessment and management of any individual presenting with new-onset epilepsy or seizures, particularly in adulthood. The conditions for the ongoing transmission of human and porcine cysticercosis appear to be present in the district, although few households keep pigs, and these are generally not free-ranging. Although these aspects have not been formally studied here, a clear understanding of the social and environmental factors that distinguish Hai from other areas of Tanzania and SSA where NCC is more highly endemic may help to target public health initiatives to reduce the burden of acquired epilepsy.

9.5 The social burden of epilepsy in Hai

Epilepsy is associated with adverse socio-economic outcomes in Hai, indicating that the burden of epilepsy extends beyond the morbidity and costs associated with the medical aspects of the disease. These aspects should be further explored through more detailed comparison with a control population without epilepsy, utilising appropriate techniques such as psychometric measures and focus-group discussions. The degree to which reduced educational attainment and economic productivity pertains to the physical burden of disease or to enacted stigma also warrants further investigation.

Over one quarter of PWE living in Hai have suffered burns as a result of their epilepsy, and interventions to reduce this morbidity are warranted.

9.5 Treatment

The ETG in adult PWE living in the HDSS is in line with estimates from other countries in SSA, and in LMICs in general. A combination of clinical and socio-economic and cultural factors appear to be associated with the likelihood of seeking treatment. Presentation to medical services is delayed by two years or more in a considerable proportion of patients and interventions to increase awareness and reduce stigma may serve to encourage PWE to seek treatment sooner. Having presented to services, retention under follow-up appears to correlate with educational level of the patient and with having received a diagnosis of epilepsy. This latter factor is potentially modifiable through educational interventions targeting healthcare workers. While phenobarbitone is widely available, is the most commonly prescribed drug locally, and appears to be well tolerated in this patient group, recent systematic work suggests that this and other AEDs remain in limited supply and at increased cost in LMICs, including Tanzania (Cameron et al., 2012).

9.6 Conclusions

W suggest that low-cost educational interventions targeting both patients and health care workers would serve to reduce the ETG in the HDSS without recourse to additional external human or material resources. Such efforts should be informed by detailed and nuanced characterisation of the various factors influencing treatment seeking and delivery of care for PWE in this population, utilising both quantitative and qualitative techniques. Having established a well-characterised prevalent cohort of adult PWE to which we have access for the purposes of clinical follow-up and further study, we are now in a position to pursue these ends. A deeper understanding of these issues in the HDSS population will serve to benefit PWE locally, as well as elewhere in Tanzania and in SSA in general.

Appendix I: Hai DSS census form, 2009

Jamhuri ya Muungano wa Tanzania
Wizara ya Afya

FOMU KWA AJILI YA KAYA MPYA Mfumo wa Taifa wa Ukusanyaji Takwimu za Maradhi na Vifo Katika Jamii
(National Sentinel Surveillance-NSS)

CHF1 ☐ CHF2 ☐

Kijijini anza hapa ⇨ Wilaya__________ Kata__________ Kijiji__________ Kitongoji__________ Shina_____ Mjumbe/Balozi__________
Jina la mmiliki wa /mwenye nyumba__________

						Kazi		Kuingia				Kifafa												
Jina (Anza na jina la mkuu wa kaya)	Terehe ya kuzaliwa	Jinsia	Uhus-iano	Elimu	Dini	Aina ya kazi	Msimbo	Tarehe	Namna	-jifungua /-zaa	Ndoa	Swali la 1	2	3	4	5	6	7	8	9	10	11	Baba hai	Mama hai
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		
												1	2	3	4	5	6	7	8	9	10	11		

Maliza na maswali haya (zungusha 'N'diyo au 'H'apana) ⇨

Je, kuna msiba wowote ulitokea katika kaya hii kwa miezi 12 iliyopita? N H

Je, kuna kifo cho chote cha mtoto mchanga kilichotokea katika kaya hii wa mwezi 1 au mtoto kuzaliwa mfu kwa miezi 12 iliyopita? N H

UTAMBULISHO	BALOZI	NYUMBA	KILA MTU…	UJAUZITO	MAELEZO

Tarehe ya leo__________ Enumerator__________ Entered by__________ Checked by supervisor__________

Appendix II: Patient information leaflets and consent forms (English and Kiswahili)

Study of epilepsy in the Hai District, Kilimanjaro – patient information

You have been invited to take part in a research project studying people with epilepsy in the Hai district. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully, and to discuss it with your friends and relatives. Please ask us if there is anything that is not clear, or if you would like more information.

What is the purpose of the research and what will it involve?
There have been many studies throughout the world to see how common epilepsy is. It is thought that it may be more common in sub-Saharan Africa, including Tanzania, than in other parts of the world. This is not certain, however, and more information is needed. What we do know is that there are good treatments for epilepsy, but that many people who have the condition do not know about it, or are not getting any treatment. We hope that by carrying out this study there will be direct benefits to people with epilepsy in the Hai District.

Why have I been chosen?
You have been chosen because you live in Hai, and because you have epilepsy.

Do I have to take part?
It is your choice whether to take part. If you do decide to, we will ask you to sign a consent form, although you will still be free to withdraw at any time and without giving a reason. If you do not want to take part in the study, the research team will still be happy to offer you advice on how to manage your condition.

What will happen to me if I take part?
You will be asked questions by the research doctor about your medical history, occupation, etc. The doctor will then carry out a physical examination, which may include having a trace of your heart beat made with wires that are attached to your chest with sticky pads (ECG). This is not dangerous and it does not hurt. You will also be invited to come to Kilimanjaro Christian Medical Centre in Moshi to undergo a CT head scan (special X-ray), and a recording of your brain's electrical activity (EEG). This is a little like an ECG, except the wires are attached to your head using tape. It does not hurt, is completely safe, and takes around 15 minutes. The study will pay for all the transport costs and hospital costs. We will also take a blood sample from you that will be analysed to see if you have been exposed to infections that may cause epilepsy. The sample will also be stored to be analysed in the future as part of a study to look at how epilepsy might be inherited.

A file will be opened at the hospital under your name if you do not have one already, and you will be able to use this at any time in the future, should you need to. The results of all these tests will be stored in your hospital file.

If there are particular parts of the study that you do not want to undertake, you are free to decline these but still participate in other parts of the study.

What are the possible disadvantages of taking part in the study?
The process of filling out of the questionnaires, carrying out the examination and taking the blood will take around one hour and will take place either at your local dispensary, or in your own home if you would prefer. If you agree to come to KCMC, it will take a full day, with transport from your village to the hospital and back. Apart from the time that you will spend with us, we do not think there will be any other disadvantages to you.

What are the possible benefits of taking part in the study?
You will undergo an extensive assessment by the research doctor, and the project team will arrange for any problems other than epilepsy that are identified to be addressed.

Will my taking part in this study be kept confidential?
If take part in this study, any information you give will be used by the doctors running the study only to fulfil the objectives of the study, and will be kept completely confidential. The results of any tests that are done at KCMC will be entered into your own personal hospital file, which is also confidential.

Who is organising and funding the research?
The chief investigator for the project is Dr Richard Walker, Consultant Physician at North Tyneside General Hospital in the UK. Dr Eric Aris, Consultant Neurologist, Muhimbili, Dar-es-Salaam, will be assisting with the research project. A research doctor from the UK, Dr Ewan Hunter, will be carrying out the project in the Hai district.

The study is funded by Northumbria Healthcare NHS Foundation Trust in the UK.

Who has approved the study?
The study has been given approval by the National Institute for Medical Research (NIMR), Dar-es-Salaam, Tanzania. The District Medical Officer (DMO) for Hai has also been informed, and has given his approval.

Contact for further Information?
If you require further information, please contact any member of the local Adult Mortality and Morbidity Project (AMMP) team. There will be an AMMP enumerator in your village who can arrange to put you in contact with the relevant person.

The AMMP supervisor mobile phone contacts are as follows:

Addess F Moshi	0744 86 71 72
John Massame	0744 62 72 04
Dr Richard Amarro	0744 48 98 62
Dr John Kisima	0744 57 07 33
Ali Mhina	0744 50 78 42

Thank you for your time.

Hai District Epilepsy Study
Consent form for person with epilepsy

Name:
Balozi:
Village:

Have you read the information sheet? Yes No

Have you had the opportunity to ask questions and discuss the study? Yes No

Have you had all your questions answered to your satisfaction? Yes No

Who have you spoken to?_____

I understand that I can withdraw from the study:

- at any time,
- without having to give a reason,
- and without affecting my future care. Yes No

Do you agree to take part in the Epilepsy study for the Hai District? Yes No

Signature of person consenting: _____

Print name: _____ Date...../...../.....

Signature of doctor/supervisor_____

Print name _____ Date...../...../.....

Hai district/adult epilepsy study/patient.consent.form

FOMU YA RIDHAA – Mtu mwenye kifafa

Utafiti wa ugonjwa wa kifafa katika wilaya ya Hai

Jina:
Balozi:
Kijiji:

Je, umesoma karatasi ya maelezo? **Ndiyo** **Hapana**

Je, umepata nafasi ya kuuliza maswali na kujadili utafiti huu? **Ndiyo** **Hapana**

Je, maswali yote uliyokuwa nayo yamejibiwa kwa ufasaha? **Ndiyo** **Hapana**

Je, umezungumza na nani?_____

Je, unafahamu kuwa unaweza kujitoa kushiriki kwenye utafiti:

- wakati wowote,
- bila kutoa sababu,
- bila kuathiri huduma yako siku zijazo. **Ndiyo** **Hapana**

Je, unakubali kushiriki kwenye utafiti wa ugonjwa wa kifafa katika wilaya ya Hai? **Ndiyo** **Hapana**
Sahihi ya mwenye kutoa ridhaa

Andika jina _____ Tarehe...../...../.....

Sahihi ya daktari/mganga msaidizi_____

Andika jina _____ Tarehe...../...../.....

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |

CLINICAL ASSESSMENT

Date of assessment: __ __/ __ __/ __ __ Assessment site: _____

Name: **Age/YOB:** **Sex:** **M** **F**

Witness present? **Yes** **No** Details: _____

Village: _____ Balozi : _____

HoH: _____

Tribe |____|

1. Zaramo
2. Ndengereko
3. Chagga
4. Masai
5. Pare
6. Nyamwezi
7. Sukuma
8. Other (state) _____

Religion |____|

1. Christian
2. Muslim
3. Hindu
4. Pagan
5. Other (state) _____

Marital status |____|

1. Married
2. Widowed
3. Divorced
4. Single (never married)
5. Separated

Age when married |__|__| Number of children |__|__|

Patient born in Hai? **Yes** **No** Details: _____

Working Diagnosis

Epilepsy **Not Epilepsy**

Plan for management/referral/follow-up (if not epilepsy)

1

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |

C: DETAILS OF SEIZURES

Loss of consciousness: **Yes** **No** **Noct. Only** 1. From beginning 2. After motor signs start

Focal signs before LOC? **Yes** **No** Description:_____

_____

Falls to the ground? **Yes** **No**
1. Occasionally
2. Often
3. Nearly always or always
[___]

If no LOC, description: _____

_____

Motor activity: 0. None 1. Tonic 2. Clonic 3. Both 4. No limb movement, rolling eyes/grinding teeth

Side of limb movements: 1. Only left side 2. Only right side 3. Both

Supportive signs: **Yes** **No** Froth from mouth Tongue/lip bite Urine/faecal incont.

If incontinent of urine during their seizures:
1. Occasionally
2. Often
3. Nearly always or always
[___]

Prodrome/Aura: **Yes** **No** Description:_____

_____

Does the warning ever occur on its own, without a seizure? **Yes** **No**

If LOC, warning long enough for patient to protect him/herself?
1. Never
2. Sometimes
3. Nearly always/always
[___]

Automatisms? **Yes** **No**
1. Seriously disruptive
2. Mild automatisms/focal jerking
[___]

Details:_____

Reorientation phase present? **Yes** **No** Description:_____

Time to recovery?

1. Less than one minute
2. 10 minutes to 1 hour
3. 1 to 3 hours
4. More than 3 hours
[___]

Time to return to work/activity:

1. 1 to 10 minutes
2. Within 1 hour
3. Half day
4. Full day
5. >Full day
[___]

Days lost/month: [___][___]

Injuries? **Yes** **No**
1. Milder injuries or mild headaches
2. Bitten tongue or severe headaches
3. Burns, scalds, deep cuts, fractures
[___]

Details:_____

Timing of seizures: 1. Daytime 2. Nocturnal 3. Both

Precipitants? **Yes** **No** Details:_____

Year/age of first seizure:_____ Last fit:_____

Initial frequency:_____ Current frequency:_____

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |

D: TREATMENT HISTORY

Help sought for seizures?: **Yes** **No** Year/age of **first** Rx:_____

Self-medication using modern drug	☐	Government hospital	☐
Family members or friends	☐	Private dispensary	☐
Traditional healers/medicines	☐	Private health centre	☐
Village health worker	☐	Private hospital	☐
Government dispensary	☐	Private Pharmacy, shop	☐
Government health centre	☐		

Details:_____

_____

Have you ever been given a reason/diagnosis for the seizures? **Yes** **No**

Details:_____

Present follow-up/attendance:_____

Treatment	AED	Dose/Timing	From who? Since when?
Current Known?: **Y** **N**			

Advised to continue treatment? **Yes** **No** Afford regularly? **Yes** **No** **Free**

Has the frequency of seizures ever relapsed since starting treatment? **Yes** **No**

Details:_____

Compliance:
1. Daily
2. Occasionally forgets
2. Following a seizure
3. From time to time
4. When available ☐

How effective is treatment?
1. Very good
2. Good
3. No effect
4. Bad
5. Very bad ☐

Side effects? **Yes** **No**

Dizziness	☐	Nausea	☐
Tiredness	☐	Rash	☐
Headache	☐	Other (state)	☐ _____

Previous Rx (inc.dates and source):_____

_____

Why stopped?: 1. Financial ☐
2. Lack of efficacy
3. Lack of availability
4. Seizures stopped
5. Other (state) _____

Compliance?: 1. Daily ☐
2. Following a seizure
3. From time to time
4. When available

Side effects? **Yes** **No**

Dizziness	☐	Nausea	☐
Tiredness	☐	Rash	☐
Headache	☐	Other (state)	☐ _____

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |

Traditional Healer Intervention?: **Yes** **No** Length of trad. healer treatment:

Oral medication ☐
Bath ☐
Inhalation ☐
Topical ☐
Roots/leaves (state type if known) ☐
Scarification ☐
Prayer ☐
Other: _____ ☐

1. Less than one week
2. 1 – 2 weeks ☐
3. 2 weeks – 1 month
4. More than one month

Details: _____

Explanation/diagnosis? _____

Cost? _____ Effective? **Yes** **No**

D: PAST MEDICAL HISTORY

Ante-natal/perinatal problems? **Yes** **No** _____

Illness/event prior to first fit? **Yes** **No** _____

Any history of the following: **Yes** **No**

TB	☐	Cerebral malaria (malaria with coma)	☐
Head injury	☐	HIV	☐
Stroke	☐	Brain abscess	☐
Meningitis	☐	Febrile illness with convulsion	☐
Psychiatric problem	☐	Febrile illness with coma	☐

Details: _____

Other PMHx: _____

Present treatment other than AEDs? **Yes** **No**

Details: _____

In the previous twelve months, for any reason other than collecting AEDs:

Admitted to hospital? **Yes** **No**

1. Once ☐
2. Twice
3. More than twice (state) _____

Attended health centre/dispensary? **Yes** **No**

1. Once ☐
2. Twice
3. More than twice (state) _____

Details/diagnosis: _____

Cognitive impairment? **Yes** **No**

1. mild
2. moderate ☐
3. severe

1. Before seizures started? ☐
2. Since seizures started?

Motor impairment? **Yes** **No** Details: _____

_____

Alcohol? **Yes** **No**

1. Local brew
2. Bottled beer ☐
3. Mainly spirits

1. Light (weekends/holidays)
2. Average (<4 days/week) ☐
3. Heavy(4 + days/week)

More heavily in the past? **Yes** **No**

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. STUDY NO: | | - | | | |

E: FAMILY HISTORY

Is there a family history of epilepsy/seizures? **Yes** **No**

Brother	☐	Son	☐	Maternal Aunt	☐
Sister	☐	Daughter	☐	Paternal Aunt	☐
Father	☐	Grandmother	☐	Maternal Uncle	☐
Mother	☐	Grandfather	☐	Paternal Uncle	☐

Is there a family history of febrile seizures? **Yes** **No**

Brother	☐	Son	☐	Maternal Aunt	☐
Sister	☐	Daughter	☐	Paternal Aunt	☐
Father	☐	Grandmother	☐	Maternal Uncle	☐
Mother	☐	Grandfather	☐	Paternal Uncle	☐

Details:_____

F: SOCIAL HISTORY

Occupation:_____

Does patient keep animals? **Yes** **No**

Cows	☐		
Pigs	☐	Roam freely	Zero grazing
Goats	☐		
Cats	☐		
Dogs	☐		

Did/does pt. go to school? **Yes** **No** If no, reason:_____

Highest level achieved:_____

Regular attendance? **Yes** **No** If No:1. epilepsy 2. financial 3. social 4. other ☐

Details: _____

Able to read and write? **Yes** **No**

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |

G: KNOWLEDGE AND ATTITUDES

Why do you think somebody gets 'kifafa'?_____

_____

Heriditary/genetic	☐	Natural forces	☐	Doesn't know	☐
Mental illness	☐	Food/drink	☐	Lunar phases	☐
Physical illness	☐	Alcohol	☐	Problem in the brain	☐
Infections	☐	Hunger/poverty	☐	Emotions	☐

Spiritual reason? **Yes** **No** **DK**

Will of god/allah	☐	Witchcraft / sorcery	☐
Punishment	☐	Other	☐
Possession by spirits	☐		

Details:_____

Does the person believe that seizures are contagious ? **Yes** **No** **Don't know**

Physical contact during a fit	☐	Flatus	☐	
"Normal" physical contact	☐	Other excretions (state)	☐	_____
Saliva	☐	Sharing food	☐	
Blood	☐	Sexual contact	☐	
Breath	☐	Other (state)	☐	_____

Details:_____

What should be done for a person who gets a seizure?_____

_____

Has the patient's relationship with others been affected by seizures? **Yes** **No**
(e.g. avoidance, rejection, indifference, acceptance, no change):

_____

other family members / clan members	☐	friends	☐
spouse/partner	☐	others in village/community	☐
teacher / employer	☐		

If the patient is unmarried/separated, is this due to seizures? **Yes** **No**

Details:_____

Are you aware of the MEHATA service? **Yes** **No**

Have you ever copied anyone else's treatment? **Yes** **No**

If yes, why? _____

Have you ever advised anyone to take the same treatment that you have taken? **Yes** **No**

If yes, how many and over what period of time? _____

Do you know anyone that has had seizures and died? **Yes** **No**

If yes: How old were they? _____ Do you know what treatment they took? **Yes** **No**

Details:

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. STUDY NO: | | - | | | |

Summary of History and Examination

Classification of seizures:

Likely aetiology:

Associated problems:

Plan for management/referral/follow-up
(Drug Rx to include date started, starting dose and schedule for each drug)

Picture no.:_____

Hai Epilepsy Study 2009, Northumbria Healthcare, UK. **STUDY NO:** | | - | | | |
Clinical Follow-up Proforma

Patient name:_____

Socio-Demographic Questions

Date of assessment:_ _/_ _/_ _ Assessment Site:_____

Assessed by: **Enumerator** **Supervisor** **EH** **JK** **Other**

Details: _____

Witness present? **Yes** **No** Details:_____

How many people live in your household? |___|___|

How many people sleep in the same room as yourself? |___|___|

Is the head of your household male or female? **Male** **Female**

Are there any salaried workers in your household? **None** **One or more**

Do you or anyone in your household possess any of the following:
(please read entire list and circle all that apply)

Mobile Phone	**Sofa**	**Bicycle**	**Iron**
Radio	**Bed**	**Motorbike**	**Electric Stove**
Television	**Wardrobe**	**Car**	**Washing machine**
Computer			**Refrigerator**

Is your house owned by your family or rented? **owned** **rented**

What is the main water supply for you house? **piped inside** **piped outside/well** **river**

What type of toilet does your house have? **indoor toilet** **pit latrine** **no toilet**

Is your house connected to the electricity supply? **Yes** **No**

What kind of fuel do you use for cooking? **Charcoal/firewood** **Solar/gas/kerosene** **Electricity**

What materials is the roof of your house made of? **Not modern** **Modern**

What material are the walls of your house made of? **Not modern** **Modern**

Do you have any land for farming? **None/<1 acre** **1 – 5 acres** **5 or more acres**

What type of crops do you grow? **Cash crops** **Food crops for sale** **Food crops for self**

In the past one week have you eaten any of the following? **Meat** **Fish** **Milk/dairy**

Do you ever eat any of these types of meat?:

Beef **Goat** **Pork** **Sheep** **Fish** **Chicken**

1

Hai Epilepsy Study 2009-10, Northumbria Healthcare, UK. STUDY NO: | | - | | | |

Socio-Demographic Questions

Jina la mgonjwa:_____ Tarehe ya uchunguzi:_ _/_ _/_ _

Familia yenu ina watu wangapi? |___|___|

Mnalala watu wangapi chumbani kwako? |___|___|

Kiongozi wa numba/familia ni mama au baba ai mlezi? **Mama** **Baba** **Mlezi**

Kuna watu ambao ni wafanyakazi na wanalipwa mshahara nyumbani kewnu? **Hapana** **Ndio**

Kuna mtu katika nyumba yako anavitu vifuatavyo:

Simu ya mkononi	**Makochi ya sofa**	**Baiskeli**	**Pasi**
Radio	**Kitanda**	**Pikipiki**	**Jiko la umeme**
Televisheni	**Kabati la nguo**	**Gari**	**Jiko la gas**
Computer		**Mashine ya kufulia**	**Jokofu**

Nyumba mnayoishi ni yakwenu au mmepanga? **Ya kwenu** **Ya kupanga**

Maji mnayotumia nyumbani? **Ya bomba** **Ya kisima** **Mto**

Aina ya choo mnachotumia nyumbani? **Cha ndani ya nyumba** **Cha shimo** **Hakuna choo**

Nyumba yenu imewekwa umeme? **Ndio** **Hapana**

Unatumia nishati gani katika kupika? **Kuni/mkaa** **Nishati ya jua/gas/mafuata ya taa** **Umeme**

Nyumba yenu imeezekwa kwa? **Mabati** **Vigae** **Majani**

Nyumba yenu imejengwa kwa? **Matofali ya simenti** **Matofali ya udongo** **Miti na udongo**

Una mahali/eneo la kulima? **Hapan/chini ya hekari 1** **1 – 5 hekari** **5 na zaidi hekari**

Aina gani ya mazoa unalima? **Ya biashara** **Ya chakula na kuuza** **Ya chakula**

Wiki moja iliyopita umekula moja kati ya hivi? **Nyama** **Samaki** **Mazwa**

Umeshawahi kula chochote kati ya aina hii ya nyama?:

Ng'ombe **Mbuzi** **Nguruwe** **Kondoo** **Samaki** **Kuku**

1

Hai Epilepsy Study 2009/10, Northumbria Healthcare, UK. **Control No:** |_|_| - |_|_|_|_|

CONTROL PROFORMA

Date of assessment: __ __/ __ __/ __ __

Name: **Year of birth:** **Sex: M F**

Tawai:

Tribe		**Religion**		**Marital Status**	
Chagga	|___|	Christian	|___|	Married	|___|
Masaai	|___|	Muslim	|___|	Divorced/Separated	|___|
Pare	|___|			Single	|___|
				Widowed	|___|
Other	_____	Other	_____		

Number of children |__|__|

MEDICAL HISTORY

Any history of ante-natal/perinatal problems? **Yes** **No** **Don't Know**

Details:_____

Any history of the following (please indicate which):

Head injury	|___|	Hypertension	|___|
Stroke	|___|	Malaria with coma	|___|
Meningitis	|___|	Febrile seizures	|___|
Febrile illness with coma	|___|	Other	|___|

Details:_____

_____

Admitted to hospital or attended dispensary in past 12 months? **Yes** **No**

Once	|___|
Twice	|___|
More than twice (state)	|___|

Details:_____

Do you ever drink alcohol? **Yes** **No**

Local brew	|___|	Light (weekends/holidays)	|___|
Bottled beer	|___|	Average (less than 4 days/week)	|___|
Spirits	|___|	Heavy (4 or more days/week)	|___|

1

Hai Epilepsy Study 2009/10, Northumbria Healthcare, UK. Control No: |_|_| - |_|_|_|_|

FAMILY HISTORY

Is there anyone in your family with epilepsy? **Yes** **No** **Don't Know**

Brother	|_|	Son	|_|
Sister	|_|	Daughter	|_|
Father	|_|	Grandmother	|_|
Mother	|_|	Grandfather	|_|

Other |_|

Details:_____

Is there one in your family who has had febrile seizures? **Yes** **No** **Don't Know**

Brother	|_|	Son	|_|
Sister	|_|	Daughter	|_|

Other |_|

Details:_____

Hai Epilepsy Study 2009/10, Northumbria Healthcare, UK. CONTROL PROFORMA

Control No: 141 - ____ **Census ID:**_____

Tarehe ya uchunguzi: __ __/ __ __/ __ __ Tawi:_____

Jina: **Mwaka wa kuzaliwa:** **Jinsia: Me Ke**

Umezaliwa wilaya ya Hai? **Ndio Hapana**

Kama "hapana", umezaliwa wapi, na umhamia wilaya ya hai mwaka gani?

_____

Kabila		**Dini**		**Ndoa**	
Mchaga	|____|	Mkristo	|____|	Ameoa/kuolewa	|____|
Mmasai	|____|	Muislamu	|____|	Ameachana/ametengana	|____|
Mpare	|____|			Hajaolewa	|____|
				Mjane	|____|
Mengineyo	_____	Mengineyo	_____		
				Idadi ya watoto	|___|___|

HISTORIA YA KITABIBU/AFYA

Matatizo ya ujauzito/na kujifungua? **Ndio** **Hapana** **Sijiu**

Eleza:_____

Una historia yeyote kati ya yafuatayoa? (N = Ndio, H = Hapana)

Kuvunjika au kupata ajali kichwani	N	H	Shinikizo la damu	N	H
Kiharusi	N	H	Malaria na kupoteza fahamu	N	H
Ugonjwa wa uti wa mgongo	N	H	Homa na mitetemo	N	H
Homa kali na kupotesa fahamu	N	H	Mengineyo	N	H

Eleza:_____

_____

1

Hai Epilepsy Study 2009/10, Northumbria Healthcare, UK. **CONTROL PROFORMA**

Ulishawahi kulazwa hospitali au kuhudhuria zahanati miezi 12 iliyopita?

Hapana	|___|
Mara Moja	|___|
Mara mbili	|___|
Zaidi ya mara mbili	|___|

Eleza:_____

Ulishawahi kunywa pombe?	**Ndio**	**Hapana**	
Pombe ya kienyeji	|___|	Kidogo (mwisho wa wiki/wakati wa sherehe)	|___|
Bia	|___|	Wastani (chini ya siku nne kwa wiki	|___|
Gongo	|___|	Mara nne au zaidi kwenye wiki	|___|

HISTORIA YA FAMILIA

Kuna mtu yeyote katika familia ana kifafa?			**Ndio**	**Hapana**	**Sijui**
Kaka	|___|	Mtoto wa kiume	|___|	Mengineyo	|___|
Dada	|___|	Mtoto wa kike	|___|		
Baba	|___|	Bibi	|___|		
Mama	|___|	Babu	|___|		

Eleza:_____

Kuna mtu yeyote katika familia alishawahi kupata homa kali na miteteмo?			**Ndio**	**Hapana**	**Sijui**
Kaka	|___|	Mtoto wa kiume	|___|	Mengineyo	|___|
Dada	|___|	Mtoto wa kike	|___|		

Eleza:_____

Hai Epilepsy Study, 2009/2010
Northumbria Healthcare, UK.

STUDY NO: ⊥⊥ - ⊥⊥

PATIENT RECORD

Name:

DOB: ___/___/__ Age: |__|__|__| Yrs Sex: **Male** **Female**

Summary of History and Examination

Diagnosis:

Associated problems:

Plan for management/referral/follow-up
(Drug Rx to include date started, starting dose and schedule for each drug)

Signed:_____ **Date:**_____

1

Hai Epilepsy Study, 2009/2010
Northumbria Healthcare, UK.

STUDY NO: ⊥⊥ - ⊥⊥

Date/Tarehe	Date/Tarehe	Date/Tarehe

NHS

National Research Ethics Service

Leeds (West) Research Ethics Committee
A/B Floor, Old Site
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Telephone: 0113 2065637
Facsimile: 0113 2066772

22 October 2008

Dr Richard Walker
Consultant Physician and Honorary Clinical Senior Lecturer
Department of Medicine
North Tyneside General Hospital,
North Shields, Tyne and Wear
NE29 8NH

Dear Dr Walker

Full title of study: **The prevalence, and phenotype, of epilepsy in the Hai district of northern Tanzania**

REC reference number: **08/H1307/128**

The Research Ethics Committee reviewed the above application at the meeting held on 10 October 2008.

It was noted that as this research will not be taking place within the NHS, and is not a clinical trial of a medicinal product for human use, it falls outside the remit of Research Ethics Committees as set out in the Governance Arrangements for NHS Research Ethics Committees (GAfREC).

However, the Committee was happy to review the ethics of the research on a voluntary basis and to offer the following opinion.

Ethical opinion

The Committee would draw your attention to the guidelines for importing tissue into the UK and remind you that the samples should be stored under license from the Human Tissue Authority.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Participant Consent Form: Parent/Guardian/Carer	1	02 September 2008
Participant Consent Form: Person with epilepsy	1	02 September 2008
Participant Information Sheet: 2	1	02 September 2008
Participant Information Sheet: 1	1	02 September 2008
Questionnaire		
Summary/Synopsis	1	02 September 2008

This Research Ethics Committee is an advisory committee to Yorkshire and The Humber Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Protocol	1	02 September 2008
Investigator CV		
Application		02 September 2008

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1307/128 **Please quote this number on all correspondence**

Yours sincerely

Mr Jon Silcock
Chair

Enclosures:

Attendance at Committee meeting on 10 October 2008

THE UNITED REPUBLIC OF
TANZANIA

National Institute for Medical Research
P.O. Box 9653
Dar es Salaam
Tel. 255 22 2124400/390
Fax: 255 22 2122808/2121360
E-mail: headquarters@nimr.or.tz

Ministry of Health and Social Welfare
P.O. Box 9083
Dar es Salaam
Tel. 255 22 2150261-7
Fax: 255 22 2110986

NIMR/HQ/R.8a/Vol. IX/756

10th February 2009

Dr Richard Walker
Consultant Physician and Honorary Clinical Senior Lecturer
Department of Medicine
North Tyneside General Hospital
North Shields, Tyne and Wear
NE29 8NH

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: The prevalence and phenotype of epilepsy in Hai district, Tanzania, (Walker R. et al), whose local investigator is Dr Eric Aris, Muhimbili National Hospital, has been granted ethics clearance to be conducted in Tanzania

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is made available to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research
3. Copies of final publications are made available to the Ministry of Health and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine.
5. Approval is for one year (9th February 2009 to 8th February 2010.

Name: Dr Andrew Y Kihwa

Signature

CHAIRMAN
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Dr Deo M Mtasiwa

Signature

CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL
WELFARE

CC: RMO
DMO

Appendix VIII: Tanzanian Medical License

MFA 42

OFFICE OF THE REGISTRAR
P.O. BOX 9083,
DAR ES SALAAM.

Date 11th February, 2009

MEDICAL COUNCIL OF TANGANYIKA

The Medical Practitioners and Dentists Ordinance
(No. 1 of 1968)

CERTIFICATE OF TEMPORARY REGISTRATION AS A MEDICAL PRACTITIONER

I hereby certify that the following is a true extract from entry in the Register relating to the medical practitioner named below:-

NO.	FULL NAME	QUALIFICATION	DATE OF REGISTRATION	EMPLOYMENT TO WHICH REGISTRATION APPLIES
4563	HUNTER Ewan Robert	MB., BS. (2005) University of Newcastle Upon Tyne, UK	11th February 2009	Muhimbili National Hospital P.O. Box 65000 Dar es Salaam

NOTES:

1. This certificate is given to afford immediate evidence of the registration which it attests. In due course the name of the practitioner will appear in the list of Fully Registered Medical Practitioners published annually by the Medical Council of Tanganyika and reference should be made to the CURRENT published list for evidence of the continued registration of the practitioner.

2. This certificate is not evidence of the IDENTITY of its holder with the person named above and must not be used as such.

REGISTRAR
MEDICAL COUNCIL OF TANGANYIKA

THIS CERTIFICATE IS VALID FOR TWO YEARS ONLY FROM THE DATE OF ISSUE.

Appendix IX: Epilepsy screening questionnaire

1. Have you ever had attacks of shaking of the arms or legs which you could not control?

   Je, ulishawahi kupatwa na hali ya kutetemeka mikono au miguu, ghafla bila sababu yeyote, ambayo hukuweza kuizuia?

2. Have you ever had attacks in which you fall suddenly, without any reason, changing colour in the palms, lips or face?

   Je, ulishawahi kupatwa na hali ambayo ilikufanya uanguke, ghafla bila sababu yeyote, kubadilika rangi na kuwa mweupe kwenye viganja, midomo na usoni??

3. Have you ever lost consciousness?

   Je, ulishawahi kupoteza fahamu?

4. Have you ever had attacks in which you fall with loss of consciousness?

   Je, ulishawahi kupatwa na hali ambayo ilisababisha uanguke na kupoteza fahamu, ghafla bila sababu yeyote?

5. Have you ever had attacks in which you fall and bite your tongue?

   Je, ulishawahi kupatwa na hali iliyokusababisha uanguke ghafla bila sababu yeyote, na kuuma/kung'ata ulimi wako?

6. Have you ever had attacks in which you fall and lose control of your bladder?

   Je, ulishawahi kupatwa na hali ambayo ilikufanya uanguke ghafla bila sababu yeyote na kutoa mkojo?

7. Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?

   Je, ulishawahi kupatwa na hali ya muda mfupi ya kutetemeka au kutikisika mkono au mguu mmoja au kwenye uso?

8. Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?

Je, ulishawahi kupatwa na hali ambayo ilikufanya upoteze ufahamu wa mahali ulipo na kusikia harufu zisizo za kawaida?

9. Have you ever been told that you have or have had epilepsy or epileptic fits?

   Je, ulishawahi kuelezwa kuwa una au ulishawahi kuwa na kifafa au kuanguka kifafa, au degedege, au kiumangungu?

Appendix X: Geographic distribution of cases and case finding (by village)

Village	Zone	Division	Ward	Urban/ rural	Adult population (n)	% HDSS adult population	Expected cases (n)	Observed cases (n)	Observed/expected (P)	Prevalence/ 1,000
Bomang'ombe	Umasaini	Masama	Masama Kusini	Urban	7004	6.8	19.8	16	0.81	2.83
Foo	Upland	Machame	Machame Kaskazini	Rural	2699	2.6	7.6	7	0.92	2.59
Isuki	Upland	Masama	Masama Magharibi	Rural	1195	1.2	3.4	1	0.29	0.84
Kawaya	Umasaini	Masama	Masama Kusini	Rural	1570	1.5	4.4	2	0.45	2.80
KIA	Lowland	Masama	Masama Kusini	Rural	923	0.9	2.6	1	0.38	2.82
Kikavu Chini	Lowland	Lyamungo	Lyamungo Machame Kusini	Rural	2197	2.1	6.2	8	1.29	2.82
Kilanya	Upland	Lyamungo	Machame Mashariki	Rural	1175	1.1	3.3	3	0.91	2.55
Kimashuku	Lowland	Lyamungo	Lyamungo Machame Kusini	Urban	1761	1.7	5	1	0.2	2.84
Kware	Lowland	Masama	Masama Kusini	Rural	2164	2.1	6.1	6	0.98	2.82
Kwasadala	Lowland	Masama	Masama Kusini	Urban	2090	2	5.9	15	2.55	2.82
Kwatito	Lowland	Lyamungo	Lyamungo Machame Kusini	Urban	667	0.7	1.9	1	0.53	2.85
Kyeeri	Upland	Machame	Machame Magharibi	Rural	1963	1.9	5.5	1	0.18	0.51
Kyuu	Upland	Masama	Masama Magharibi	Rural	1162	1.1	3.3	7	2.12	6.02
Lemira Kati	Lowland	Masama	Masama Magharibi	Rural	1079	1.1	3	2	0.66	2.78
Lengoi	Lowland	Lyamungo	Lyamungo Machame Kusini	Rural	1134	1.1	3.2	6	1.88	2.82
Losaa	Upland	Masama	Masama Magharibi	Rural	840	0.8	2.4	2	0.83	2.38

Village	Zone	Division	Ward	Urban/ rural	Adult population (n)	% HDSS adult population	Expected cases (n)	Observed cases (n)	Observed/expected (P)	Prevalence/ 1,000
Lukani	Upland	Masama	Masama Magharibi	Rural	865	0.8	2.4	4	1.67	4.62
Lyamungo Kati	Upland	Lyamungo	Machame Mashariki	Rural	1514	1.5	4.3	0	0	0.00
Lyamungo Side	Upland	Lyamungo	Machame Mashariki	Rural	1328	1.3	3.7	3	0.81	2.26
Mamba	Upland	Machame	Machame Uroki	Rural	1349	1.3	3.8	3	0.79	2.22
Mashua	Upland	Masama	Masama Magharibi	Rural	1766	1.7	5	1	0.2	0.57
Mbatakero	Lowland	Lyamungo	Lyamungo Machame Kusini	Rural	386	0.4	1.1	1	0.92	2.85
Mboreni	Upland	Masama	Masama Masariki	Rural	889	0.9	2.5	0	0	0.00
Mbosho	Upland	Masama	Masama Magharibi	Rural	1186	1.2	3.3	5	1.52	4.22
Mbweera	Upland	Masama	Masama Masariki	Rural	2291	2.2	6.5	8	1.23	3.49
Mijongweni	Lowland	Lyamungo	Lyamungo Machame Kusini	Rural	2407	2.3	6.8	3	0.44	2.83
Mkalama	Umasaini	Masama	Masama Kusini	Rural	1787	1.7	5	3	0.6	2.80
Mtaa Wa Shabaha	Umasaini	Masama	Masama Kusini	Rural	542	0.5	1.5	0	0	2.77
Mtakuja	Umasaini	Masama	Masama Kusini	Rural	897	0.9	2.5	2	0.79	2.79
Mudio	Upland	Masama	Masama Masariki	Rural	3610	3.5	10.2	8	0.78	2.22
Mulama	Upland	Lyamungo	Machame Mashariki	Rural	1122	1.1	3.2	7	2.19	6.24
Mungushi	Lowland	Masama	Masama Kusini	Urban	4974	4.8	14	16	1.14	2.81

Village	Zone	Division	Ward	Urban/ rural	Adult population (n)	% HDSS adult population	Expected cases (n)	Observed cases (n)	Observed/expected (P)	Prevalence/ 1,000
Muroma	Upland	Masama	Masama Magharibi	Rural	1260	1.2	3.6	1	0.28	0.79
Ng'ira	Upland	Masama	Masama Masariki	Rural	1486	1.4	4.2	4	0.95	2.83
Ng'uni	Upland	Masama	Masama Magharibi	Rural	1607	1.6	4.5	6	1.33	3.73
Ngosero	Lowland	Lyamungo	Lyamungo Machame Kusini	Rural	534	0.5	1.5	0	0	0.00
Nkuu Ndoo	Upland	Lyamungo	Machame Mashariki	Rural	1363	1.3	3.8	3	0.79	2.20
Nkuu Sinde	Upland	Lyamungo	Machame Mashariki	Rural	1457	1.4	4.1	2	0.49	1.37
Nkwansera	Upland	Masama	Masama Magharibi	Rural	1409	1.4	4	4	1	2.84
Nronga	Upland	Machame	Machame Magharibi	Rural	1593	1.6	4.5	9	2	5.65
Nshara	Upland	Machame	Machame Kaskazini	Rural	5153	5	14.5	15	1.03	2.91
Nkuu Ndoo	Upland	Lyamungo	Machame Mashariki	Rural	1363	1.3	3.8	3	0.79	2.20
Nkuu Sinde	Upland	Lyamungo	Machame Mashariki	Rural	1457	1.4	4.1	2	0.49	1.37
Nkwansera	Upland	Masama	Masama Magharibi	Rural	1409	1.4	4	4	1	2.84
Nronga	Upland	Machame	Machame Magharibi	Rural	1593	1.6	4.5	9	2	5.65
Nshara	Upland	Machame	Machame Kaskazini	Rural	5153	5	14.5	15	1.03	2.91
Roo	Upland	Masama	Masama Masariki	Rural	3405	3.3	9.6	14	1.46	4.11
Rundugai	Umasaini	Masama	Masama Kusini	Rural	4170	4.1	11.8	14	1.19	2.83
Saawe	Upland	Masama	Masama Masariki	Rural	1722	1.7	4.9	4	0.82	2.32
Sanya Station	Umasaini	Masama	Masama Kusini	Rural	1731	1.7	4.9	4	0.82	2.83

Village	Zone	Division	Ward	Urban/ rural	Adult population (n)	% HDSS adult population	Expected cases (n)	Observed cases (n)	Observed/expected (P)	Prevalence/ 1,000
Shari	Upland	Machame	Machame Uroki	Rural	2428	2.4	6.9	11	1.59	4.53
Shiri Mgungani	Lowland	Lyamungo	Lyamungo Machame Kusini	Urban	1831	1.8	5.2	9	1.74	2.84
Shiri Njoro	Lowland	Lyamungo	Lyamungo Machame Kusini	Urban	1951	1.9	5.5	10	1.82	2.82
Sonu	Upland	Masama	Masama Masariki	Rural	1991	1.9	5.6	5	0.89	2.51
Tella	Upland	Lyamungo	Machame Mashariki	Rural	1573	1.5	4.4	6	1.36	3.81
Tindigani	Umasaini	Masama	Masama Kusini	Rural	644	0.6	1.8	2	1.1	2.80
Uduru	Upland	Machame	Machame Kaskazini	Rural	1488	1.4	4.2	3	0.71	2.02
Urori	Upland	Lyamungo	Machame Mashariki	Rural	1539	1.5	4.3	2	0.47	1.30
Usari	Upland	Lyamungo	Machame Mashariki	Rural	1323	1.3	3.7	3	0.81	2.27
Uswaa	Upland	Machame	Machame Uroki	Rural	2165	2.1	6.1	7	1.15	3.23
Wari	Upland	Machame	Machame Kaskazini	Rural	2667	2.6	7.5	10	1.33	3.75

Appendix XI: Related publications, abstracts and presentations

Peer-reviewed publications

Hunter E, Rogathi J, Chigudu S, Jusabani A, Jackson M, McNally R, et al. Prevalence of active epilepsy in rural Tanzania: A large community-based survey in an adult population. *Seizure*. 2012 Nov;21(9):691-8

Burton, K., Rogathe, J., Whittaker, R., Mankad, K., Hunter, E., Burton, M., Todd, J., Neville, B., Walder, R. & Newton, C. 2012. Epilepsy in Tanzanian children: Association with perinatal events and other risk factors. *Epilepsia,* 53**,** 752-760.

Burton, K., Rogathe, J., Whittaker, R. G., Mankad, K., Hunter, E., Burton. J., Todd, J., Neville, B. G., Walker, R. & Newton, C. R. 2012. Co-morbidity of epilepsy in Tanzanian children: a community-based case-control study. *Seizure,* 21**,** 169-74.

Mushi, D., Burton, K., Mtuya, C., Gona, J. K., Walker, R. & Newton, C. R. 2012. Perceptions, social life, treatment and education gap of Tanzanian children with epilepsy: a community-based study. *Epilepsy Behav,* 23**,** 224-9.

Burton, K., Rogathe, J., Hunter, E., Burton, M., Swai, M., Todd, J., Neville, B., Walder, R. & Newton, C. 2011. Behavioural comorbidity in Tanzanian children with epilepsy: a community-based case-control study. *Dev Med Child Neurol,* 53**,** 1135-42.

Mushi D, Hunter E, Mtuya C, Mshana G, Aris E, Walker R. Social-cultural aspects of epilepsy in Kilimanjaro Region, Tanzania: knowledge and experience among patients and carers. *Epilepsy Behav*. 2010;20(2):338-43.

ELSEVIER

Editor's Choice

Title

Prevalence of active epilepsy in rural Tanzania: a large community-based survey in an adult population

Authors

Ewan Hunter, Jane Rogathi, Simukai Chigudu, Ahmed Jusabani, Margaret Jackson, Richard McNally, William Gray, Roger G. Whittaker, Ahmed Iqbal, Eric Aris, Richard Walker

Selected as

Editor's Choice in *Seizure: European Journal of Epilepsy*[1] Volume 21, Issue 9,

Pages 691-698, November 2012

[1] *Seizure* is the official journal of Epilepsy Action and published by Elsevier Ltd.

epilepsy action

Abstracts and presentations

Hunter E, Epilepsy treatment in rural Tanzania: a low treatment gap does not correspond to high levels of seizure control (Oral presentation at World Federation fo Neurology, 20th World Congress, Marrakech Morocco, November 2011).

E Hunter, et al. Convulsive epilepsy in a rural district of northern Tanzania: risk factors and classification, *J Neurol Neurosurg Psychiatry* 2012;83:e1 doi:10.1136/jnnp-2011-301993.89 (Poster presentation at the Association of British Neurologists Annual Meeting, Newcastle UK,. September 2011).

Hunter E, Epilepsy in rural Tanzania: prevalence, phenotype, risk factors and treatment gap (Invited speaker at Society of Neuroscientists of Africa 1st East African regional conference, Nairobi, September 2010).

Hunter E, Chigudu S, Kibiki J, Jusabani A, Aris E, Walker R. The prevalence, phenotype and treatment gap, for epilepsy in rural Tanzania: Initial findings of a large door-to-door survey. *Epilepsia*. 2010; 51 (suppl 4):54 (Poster presentation at 9th European Congress on Epileptology, Rhodes, Greece).

Hunter E, et al. The role of neurocysticercosis in the aetiology of epilepsy in a rural district of Northern Tanzania, Royal Society of Tropical Medicine and Hygiene Research in Progress, London, 16th December 2009 (Poster presentation).

Other publications

Hunter E, et al. Epilepsy in Africa: an update from rural Tanzania. *Epilepsy Care* 2010; 2 (9): 8-12

Hunter E, et al. Supporting epilepsy services in Tanzania through international links with North-East England, *Epilepsy Care* 2009; 2 (7): 8-12.

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