PREVALENCE, INCIDENCE AND MORTALITY OF EPILEPSY IN FOUR HEALTH AND DEMOGRAPHIC SURVEILLANCE SITES IN SUB-SAHARAN AFRICA

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LIST OF ABBREVIATIONS

ACE	Active Convulsive Epilepsy
AE	Active Epilepsy
AED	Anti-Epileptic Drugs
AIDS	Acquired Immune Deficiency Syndrome
CFP	Case Fatality Proportion
CI	Confidence Intervals
CNS	Central Nervous System
DALY	Disability Adjusted Life-Years
FN	False Negative
FP	False Positive
FW	Field Work(er)
GCAE	Global Campaign Against Epilepsy
GPS	Global Positioning System
HDSS	Health and Demographic Surveillance System
HIC	High Income Countries
HIV	Human Immune-deficiency Virus
IBE	International Bureau for Epilepsy
ILAE	International League Against Epilepsy
INDEPTH	International Network of sites involved in Demographic surveillance of Populations and Their Health
IQR	Inter-quartile Range
KDH	Kilifi District Hospital

KEMRI	Kenya Medical Research Institute
LMIC	Low and Middle Income Countries
LTE	Life-time Epilepsy
MeSH	Medical Subject Headings
OR	Odds Ratio
PhD	Doctor of Philosophy
PWE	People With Epilepsy
SBR	Social-Behavioural Research (group within the Kilifi HDSS)
SEEDS	Studies of Epidemiology of Epilepsy in Demographic Surveillance Systems
SMR	Standardized Mortality Rate
SSA	sub-Saharan Africa
SUDEP	Sudden Unexpected Death in Epilepsy
TN	True Negative
TP	True Positive
USD	United States Dollar ($)
WHO	World Health Organization

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Dedication

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Summary

Epilepsy is one of the most prevalent non-communicable conditions and also one of the most common neurological disorders affecting approximately 50 million people in the world, about 80% of who live in low and middle income countries (LMIC). It is characterized by recurrent (two or more) unprovoked seizures, with active epilepsy (AE) being defined as at least one seizure in the last 5 years although in LMIC it is often defined when one of the seizures is within 12 months of identification.

Epilepsy is associated with significant psychosocial co-morbidities that impact on the health-related quality of life of patients and also influence prognosis. In LMIC, the perceptions of causes and consequences of epilepsy may differ from those in the high income countries (HIC) and often lead to stigmatization. The stigma may in turn hide a proportion of the burden of epilepsy since patients are unwilling to seek medical advice, translating into large treatment gaps. Many studies of LMIC have shown that the majority of PWE do not receive appropriate treatment despite the availability of cost effective treatment.

The estimates of the burden of epilepsy in LMIC are based upon little data and between and within country estimates vary considerably. Causes of this heterogeneity have not been established but it is thought to be due to differences in methodological approaches, case definitions and ascertainment and lack of validation of screening instruments, as well as genuine differences in the magnitude of the burden of epilepsy.

In view of the serious health, quality of life and outcome implications of epilepsy, its attendant co-morbidity and inadequacy of data on the burden and outcome, there is need for epidemiological studies of epilepsy in LMIC. These countries have large rural populations with few specialists in neurology, scantily allocated heath care resources and a substantial burden of disease.

These problems have been recognized by the global level with the initiation of The Global Campaign Against Epilepsy (GCAE), a partnership between the International League Against Epilepsy (ILAE), the World Health Organization (WHO) and the International Bureau for Epilepsy (IBE). This campaign aims to bring epilepsy 'out of the shadows' by supporting LMIC to reduce the burden caused by epilepsy through improved acceptability, access to services, prevention and quality of care. The overall goal of GCAE is to improve the identification and management of people with convulsive epilepsies within existing primary health care systems.

The studies reported in this thesis support these efforts by estimating the burden of epilepsy more accurately (particularly patients with Active Epilepsy, who should be on treatment) at the global level. The studies also described the distribution of active convulsive epilepsy (ACE) as well as factors associated with an important component of prognosis (i.e. mortality) in selected regions of LMIC in sub-Saharan Africa (SSA).

Several research methodologies were used in these studies: (*i*) Systematic reviews and meta-analysis of published studies were used to determine the burden and characterize the heterogeneity in the distribution of epilepsy. (*ii*) A three-stage cross-sectional screening

methodology used to identify cases of ACE in LMIC was validated against the gold standard of clinical diagnosis by trained neurologists. (iii) Cross-sectional screening studies in four Health and Demographic Surveillance System (HDSS) sites were used to determine prevalence and heterogeneity of ACE in SSA and, (iv) prospective population-based cohort studies were carried out to determine the incidence, mortality and risk factors associated with mortality in PWE in one of the study sites.

The systematic review reported in chapter 2 indicated that the prevalence of epilepsy (both life-time and active epilepsy) was more than two times higher in LMIC compared to HIC. Within the LMIC, the prevalence in rural areas was twice as high that of urban areas. There was strong evidence of between-study heterogeneity which was associated with age of study participants, study size and rural location. Likewise, the review reported in chapter 3 showed that incidence of epilepsy was about two times higher in LMIC compared to HIC albeit with significant heterogeneity. Population-based studies were associated with higher incidence estimates than hospital-based studies while retrospective study design was associated with lower estimates than prospective studies. This suggested the need for prospective population-based studies to accurately determine the incidence of epilepsy in LMIC.

Chapter 4 provides details of the validation of the three-stage cross-sectional screening methodology used to identify cases of ACE in population-based studies. This study was conducted on a randomly selected sample of participants of the three-stage prevalence census of epilepsy. Clinician diagnosis of ACE was the gold standard. The findings showed that the three-stage methodology had a poor sensitivity of 48.6%, most of which was attributed to the first

stage of the survey. This method however had a specificity of 100% and was 60% cheaper than the clinician-conducted two-stage survey and as such wide-spread use of this method would require careful balancing between the poor sensitivity and the cost savings as well as validation in target populations.

Chapter 5 describes the studies to determine the prevalence and heterogeneity of ACE across four HDSS sites in SSA. The three-stage cross-sectional screening method nested within on-going censuses in the HDSS sites was used to identify people with ACE. The findings showed substantial heterogeneity of prevalence between HDSS sites and between different age groups within and between sites. Site-specific estimates ranged between 7.0/1000 (95% CI: 6.2-7.4) in Agincourt HDSS in South Africa to 14.8/1000 (95% CI: 13.8-15.4) in Ifakara HDSS in Tanzania. Prevalence varied by age in all sites and was highest in the adolescents (13-18 years) in Ifakara HDSS and in the youngest age-group (<=5 years) in Iganga-Mayuge HDSS in Uganda while it was lowest in the youngest age-group (<=5 years) in Agincourt HDSS. There were decreasing and increasing trends of prevalence with age for Iganga-Mayuge and Agincourt HDSSs respectively. Kilifi (Kenya) and Ifakara HDSSs had increasing then decreasing trends of prevalence with age. These findings suggest real heterogeneity that could be related to differences in the distribution and types of risk factors for development of epilepsy across SSA or age-related differences in vulnerability to endemic risk factors within study sites. It may also suggest that risk factors like malaria have varied considerably over time. These results reflect the burden of the people with active epilepsy that should be on treatment in these sites and suggests the need for studies to identify modifiable risk factors that could be targeted in public health interventions.

The incidence study described in chapter 6 demonstrated high incidence of ACE (at 77/100,000/year) in the Kilifi HDSS, with the implication that incidence of life-time epilepsy could be much higher than reported previously. There was strong evidence of association between incidence and age with the lowest incidence occurring in the 29-49 year age group. This finding suggests that the increased risk in the other age groups could be due aetiologies that occur early as well as late in life and preventive interventions should target exposures that occur in these age groups.

In the mortality study reported in chapter 6, people with ACE were more than 6 times more likely to die than people without ACE and mortality was elevated in all ages compared to the reference population. The most important risk factor for mortality was non-adherence to treatment which is amenable to public health intervention.

The studies reported in this thesis have examined the burden, distribution and outcome of epilepsy from a global, regional and a local perspective. They have documented high prevalence, incidence and mortality in people with ACE, suggesting that epilepsy has far reaching effects on the health, welfare and quality of life of patients in the sites in which the studies were conducted and in LMIC more generally. At the global level, these studies show that the burden of epilepsy is much larger than previously thought and have provided estimates of the burden of active epilepsy representing people who should be on treatment.

The findings support prioritization of epilepsy as an important global public health problem and lobby for increased resources, particularly in LMIC, to improve diagnostic, treatment and preventive services.

For local health systems, these findings translate into increased health expenditure in the short term, for treatment services for the patients identified in these studies. In the medium term, the findings suggest a need to increase and sustain capacity to provide more specialized health services to people with epilepsy at the primary care level. In the long term, preventive interventions must be given priority, which means addressing the preventable causes of epilepsy. To conclude, a raft of preventive measures and avenues for further epidemiological inquiry are proposed. These include educating the communities on the causes of epilepsy as well as risk factors of mortality in PWE, improving antenatal and perinatal services, prompt and effective treatment of traumatic head injuries and infections of central nervous system (CNS) as well as vaccinations for vaccine preventable causes of CNS infections. Suggested future work includes case-control studies to identify causes of epilepsy and studies of cause-specific mortality to identify causes of death in PWE.

Chapter 1: General Introduction

Global Burden of Epilepsy

Epilepsy is one of the most prevalent non-communicable conditions and also one of the most common neurological disorders (WHO, 2001). It was thought to affect approximately 50 million people in the world in 2002, about 80% of who lived in low and middle income countries (LMIC). This worldwide proportion of epilepsy represents approximately 0.5% of the global burden of disease, which translates to more than 7 million disability-adjusted life-years (DALY) annually (Leonardi M and Ustan TB, 2002).

Definitions and classification of seizures and epilepsy

Epilepsy is characterized by recurrent (two or more) seizures unprovoked by any immediately identifiable cause and occurring at least 24 hours apart, with active epilepsy (AE) being defined as at least one seizure in the last 5 years (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). In LMIC, AE is often defined when one of seizures is within 12 months of identification (Meinardi et al., 2001), mainly due to poor recall of seizure events that occurred long ago (Snow et al., 1993a), poor documentation of medical records and also because in some countries, anti-epileptic drugs (AED) are recommended for people with at least one seizure per year (Ministry of Health, 2002).

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). These signs or symptoms include sudden and transitory abnormal phenomena such as alterations of

consciousness, or involuntary motor, sensory, autonomic, or psychic events perceived by the patient or an observer (Berg AT et al., 2010; Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993; Thurman et al., 2011).

Epileptic seizures are classified into generalised (both convulsive and non-convulsive), partial (focal) seizures (localised convulsive movements and those that become secondarily generalised) and unclassified. Partial seizures arise from single foci in the brain, while generalized seizures may arise from the central parts of the brain or spread so rapidly that their origin cannot be determined by standard techniques. Unclassified epileptic seizures include all seizures which cannot be classified because of inadequate or incomplete data, or seizures that defy classification in the partial or generalized categories.

The epilepsies can be divided into symptomatic (those with a known or suspected cerebral dysfunction), or idiopathic (epilepsies of unknown aetiology) (ILAE: Commission on Epidemiology and Prognosis, 1993). Recently, the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) proposed a revised terminology and concepts for classifying seizures (Table 1.1) and epilepsies (Table 1.2). This revision recommended that the classification be grouped within categories of "electroclinical syndromes," "constellations," "epilepsies associated with structural or metabolic conditions," and "epilepsies of unknown cause"(Berg AT et al., 2010; Thurman et al., 2011).

Population-based studies from LMIC usually report only convulsive epilepsies since convulsions are easily identified. These epilepsies are associated with higher mortality, stigma and greater resource implications for prevention and control than non-convulsive epilepsies.

Table 1.1: Simplified clinical classification of seizure types

	Generalized	Focal	Undetermined
1) Predominantly motor			
Convulsive	Generalized convulsive[a]	Focal onset with secondary generalization[b]	Convulsive undetermined[c]
Other motor	Generalized other motor[d]	Focal motor[e]	Other motor undetermined[f]
2)Predominantly non-motor			
Impaired responsiveness[g]	Generalized absence[h]	Dyscognitive focal seizures (formerly complex partial)[i]	Impaired responsiveness, undetermined[j]
Other non-motor	Not appropriate	Sensory, psychic, and other, including autonomic[k]	Not appropriate
3) Unknown	Generalized seizure, unspecified	Focal seizure, unspecified	Seizure, unspecified

[a]Seizure onset is manifested by generalized tonic and/or clonic (convulsive) motor activity and unconsciousness. Focal features may occur.
[b]Seizure onset has focal manifestations that evolve to generalized convulsive activity.
[c]Focal or generalized nature of seizure onset is undetermined, but seizures manifest generalized convulsive activity.
[d]Include myoclonic seizures, eyelid myoclonus, epileptic spasms, atonic seizures, other, and unspecified generalized motor seizures with or without impairment of consciousness.
[e]Seizure has focal manifestations (including myoclonic, inhibitory, Jacksonian march, focal asymmetric tonic, hemiclonic, hyperkinetic, and other focal motor seizures) that do not evolve to generalized convulsive activity.
[f]Unspecified motor seizures; includes neonatal and other seizures.
[g]Staring spells, unresponsiveness, or other alteration of consciousness.
[h]Includes typical and atypical absence seizures.
[i]Focal seizure associated with impairment of consciousness (formerly termed "complex partial") without secondary generalization (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).
[j]Seizure manifested by transient decreased responsiveness or "staring," undetermined if absence or dyscognitive ("complex partial") in type.
[k]Includes auras without alteration of consciousness or secondary generalization (including somatosensory and experiential seizures), autonomic, and other nonmotor seizures.

Table 1.2: Classification of epilepsies by causes

Genetic/Presumed genetic	Structural/Metabolic	Unknown or Undetermined
Specific genetic epilepsy syndromes Genetic and chromosomal developmental encephalopathies[a] Other	Infections Traumatic brain injury Stroke Neoplasia Mesial temporal sclerosis[b] Degenerative neurologic diseases Metabolic or toxic insults to brain[c] Perinatal insults Intraventricular hemorrhage Hypoxic–ischemic encephalopathy Other[d] Malformations of cortical or other brain development Neurocutaneous syndromes Inborn errors of metabolism Other	Epilepsy of unknown[a] etiology Epilepsy of undetermined[e] etiology

[a]Without known aetiology despite adequate evaluation (e.g., history, examination, EEG, and other testing determined to be relevant such as neuroimaging or genetic testing).
[b]Where evidence is lacking that the structural pathology precedes the onset of epilepsy, it is not assumed that such pathology causes epilepsy.
[c]With epilepsy as a late effect. For distinction with acute symptomatic seizures.
[d]Includes conditions where underlying etiology is undocumented or available information is limited to terms such as "intellectual disability"/"mental retardation" or "cerebral palsy" when these preceded the onset of seizures.
[e]Without adequate evaluation to determine etiology as defined by investigators.

Causes of epilepsy

Epilepsy is caused by many conditions that result in brain injury such as birth asphyxia, head trauma or cerebral infections. There are also genetically determined epilepsies. However, for most cases of epilepsy an identifiable cause cannot be found. The known aetiological factors for development of epilepsy in LMIC include parasitic infections affecting the brain such as

neurocysticercosis (Newell et al., 1997a; Nicoletti et al., 2002; Nsengiyumva et al., 2003), onchocerciasis (Druet-Cabanac et al., 1999; Newell et al., 1997b) and toxocara (Nicoletti et al., 2002; Nicoletti et al., 2007). Other factors, elicited through clinical history, include family history of both febrile and non-febrile seizures (including epilepsy) (Edwards T et al., 2008; Matuja et al., 2001; Nsengiyumva et al., 2003; Ogunniyi et al., 1987), peri-natal complications (Edwards T et al., 2008; Matuja et al., 2001; Nsengiyumva et al., 2003) traumatic head injuries (Edwards T et al., 2008; Ogunniyi et al., 1987) and history of admission to hospital with cerebral malaria (Carter JA, 2004; Ngoungou et al., 2006). Specific genes have been associated with development of rare sub-types of epilepsy (Tan et al., 2006), with an increasing evidence base for the role of genetics in the generalized epilepsies (Choueiri et al., 2001; Mulley et al., 2005; Ottman et al., 2005; Sander T, 2000). However, there are only a few studies detailing the role of genetic risk factors in LMIC (Kesavan et al., 2011; Kumari et al., 2011), particularly given that a large proportion of all epilepsies do not have an identified cause with suspected genetic aetiology.

Diagnosis of epilepsy

The diagnosis of epilepsy is clinical, usually based on history of epileptic seizures, often reported by the sufferer or an eye witness and should be preferably confirmed by a health professional with expertise in epilepsy using available clinical history and seizure description (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). The neurological examination may point to aetiology e.g. stigmata of neurocutaneous syndromes or the consequence of epilepsy e.g. burns. Electroencephalography may demonstrate epileptic

discharges in less than a third of cases of epilepsy, but is more useful in defining the type of seizures e.g. focal seizures or epileptic syndromes e.g. rolandic epilepsy.

Epidemiology of Epilepsy

Globally, epidemiological studies measuring the burden of epilepsy have been conducted in the last 40 years (Kostopoulos I et al., 2002). However, there are only a few epidemiological studies examining prevalence and incidence of epilepsy in Africa (Sander J W and Shorvon SD, 1996; Sander JW, 2003). The prevalence of epilepsy is higher in LMIC compared to the high income countries (HIC) but the high incidence rates derived from a few studies suggest that prevalence should be much higher than in the HIC (Sander J W and Shorvon SD, 1996). This discrepancy could be caused by increased mortality, spontaneous remission or methodological differences. The few studies that examine the mortality of epilepsy in Africa (Coleman R et al., 2002; Diop AG et al., 2005; Jilek-Aall L and Rwiza HT, 1992) suggest that mortality is higher than in HIC, but by how much is unclear, and the risk factors for death have not been investigated. Epidemiological studies are therefore important to determine the burden of epilepsy and to inform public health initiatives in LMIC.

Many people with epilepsy (PWE) in LMIC have a poor quality of life. In many communities, PWE are ostracized, prevented from employment and/or marriage (Baskind R and Birbeck G L, 2005; Birbeck G L and Kalichi E M, 2003; El Sharkawy G et al., 2006; Nubukpo P et al., 2004). Furthermore, many patients do not receive appropriate treatment, despite the fact that treatment with cost-effective anti-epileptic drugs (AEDs) such as phenobarbital or phenytoin, may control seizures in over 70% of cases (Mbuba CK et al., 2008; Meinardi H et al., 2001; Scott RA et al.,

2001; Wang WZ et al., 2006). The reasons for this treatment gap (i.e. number of people with epilepsy who would benefit from treatment but are not getting AEDs) (Kale R, 2002) vary from one area to another. In some areas stigmatization of PWE interferes with management, whilst in other areas lack of AED or health facilities prevent access to AED. The World Health Organization (WHO) has identified these two as priorities in the management of epilepsy i.e. elimination of stigma and reduction of the treatment gap (ILAE/IBE/WHO, 2003; WHO, 2004). But in order for these problems to be tackled, the burden of epilepsy needs to be estimated.

Comparing estimates form epidemiological studies of epilepsy in LMIC is problematic. These problems include differences in methodological approaches, case definition and ascertainment and lack of validation of screening instruments. Furthermore, there are differences in study sizes (ranging from a few hundred to several thousand participants) and age-groups studied (children only studies versus only adults or all age-groups). These factors are aggravated by resource constraints and logistical difficulties. Subsequently, data from LMIC shows considerable heterogeneity (Leonardi M and Ustan TB, 2002).

While developed countries utilize medical and service records to provide epidemiological data, these records are often not available in LMIC. Single round surveys and key informants have been used in LMIC, but these methods under-report cases (Kaamugisha J and Feksi AT, 1988). Two-phase surveys in which the population is screened with a questionnaire and the diagnosis confirmed by clinical history and assessment have been recommended (Placencia M et al., 1992). These surveys depend on the sensitivity and specificity of the screening questionnaires and they often require piloting and validation in the target populations. These points are frequently

neglected and some published questionnaires are inadequate, which leads to underreporting of cases (Sander JW and Shorvon SD, 1987). Cross sectional survey methods can be improved by capture-recapture methods using other sources of cases such as key-informants (e.g. village elders) and, where available, medical records from hospitals and clinics (Debrock C, 2000 Apr) as part of triangulation of data sources. These methodologies however pose considerable logistical and cost implications when used in large populations.

A cross-sectional study method that has attempted to address these limitations is the three-stage approach. This has been used previously to estimate the prevalence of ACE in the Kilifi HDSS, Kenya (Edwards T et al., 2008). This approach is aimed at screening large populations in HDSS rapidly while simplifying logistics and reducing costs but it has not been validated in the target populations.

Prevalence and incidence

Reported range of prevalence in Africa is 5-74/1000 persons (Preux PM and Druet-Cabanc M, 2005) while in HIC the estimate is 5-10/1000 (Sander J W and Shorvon SD, 1996; Sander JW, 2003). Meta-analyses of the burden of epilepsy conducted as part of this thesis have estimated the prevalence and incidence of epilepsy in LMIC at 13/1000 and 81/100,000 persons per year respectively, albeit with considerable heterogeneity (Ngugi et al., 2010; Ngugi et al., 2011).

A number of studies of epidemiology of epilepsy have been reported from the Kilifi HDSS in Kenya but all used different methodologies or were on different age groups (that were not representative of the general population) thus they yielded varied estimates. A community

survey in 1992, which used key informants in the household to report on any member with epilepsy, estimated the prevalence of active epilepsy to be 4/1000 (Snow RW et al., 1994) in the population above 5 years old. A study based upon histories of epilepsy in relatives of children who acted as controls for study on malaria conducted in 2001/2 reported the prevalence of all types of epilepsy to be 11/1000 (Versteeg AC et al., 2003). In both these studies the diagnoses were not confirmed by clinicians or further assessment, and may either under report the prevalence of epilepsy or include cases that do not have epilepsy or may double count cases. In 2001/2, a survey of neurological impairment and disability in children aged 6-9 years also identified cases of epilepsy and estimated a point prevalence of 11/1000 and a life-time prevalence of 41/1000 (Mung'ala-Odera et al., 2008). A more recent three-stage cross-sectional survey conducted on individuals above 6 years of age and which used clinicians to confirm the diagnosis of active convulsive epilepsy (ACE) estimated a prevalence of 4.5/1000 after adjusting for non-response (Edwards T et al., 2008).

In the HIC the annual incidence of epilepsy is 40-70 per 100,000 per year, whilst in the LMIC annual incidence may be double at >80 per 100,000 per year (Sander J W and Shorvon SD, 1996). There are few studies that have attempted to estimate the incidence of epilepsy in Africa. A study of a small population (18,000 people) in Tanzania over a 10-year period estimated the incidence to be 73/100,000 per year (Rwiza HT et al., 1992 Nov-Dec). A community based study of 61,687 people in Ethiopia estimated the incidence to be 64/100,000 per year (Tekle-Haimanot R et al., 1997 May), while a study of 4,743 people in Uganda estimated an incidence rate of 215/100,000 (Kaiser C et al., May 1998). The Tanzanian study in particular was based upon the recall of seizures over a prolonged period of time while in the Ethiopian study, different methods

were used to identify cases at different time points. The Ugandan study was in an area with high prevalence of Onchocerciasis (suspected to cause epilepsy) implying that this estimate was not representative of the typical Ugandan population.

Mortality

In HIC, mortality is elevated in PWE, compared to the general population, with standardized mortality ratios (SMR) ranging between 1.6-4.1 (Holden EW, 2005 Feb; Kochen S, 2005 Dec; Lindsten H, 2000 Nov; Olafsson E, 1998 Jan) but there is little data from LMIC. The estimates of mortality are predominantly presented as mortality ratios standardized on the age distribution of the study reference populations i.e. the SMR. While this makes it easier to compare mortality between different groups within the same populations, these estimates are difficult to compare across populations that have different age and/or sex profiles. In Africa, only a few population based mortality studies have been conducted, with follow-up ranging between 2-30 years. These studies are based upon a combined total of 186 deaths and show that mortality is higher in people with epilepsy (Coleman R et al., 2002; Jilek-Aall L and Rwiza HT, 1992; Kaiser C et al., 2007; Kamgno J, 2003 Jul; Snow RW et al., 1994). Three of these studies have provided more accurate measures of mortality, with one reporting a rate of 23/1000 person years based upon a selected hospital cohort (Jilek-Aall L and Rwiza HT, 1992), the other a rate of 77/1000/year was based upon only three deaths (Coleman R et al., 2002) and one study reported SMR of 7.2 in an area with high prevalence of Onchocerciasis (Kaiser C et al., 2007). The cause of death in one of these studies was attributed to status epilepticus or accidents (such as drowning or burns) but the risk factors for death were not investigated (Jilek-Aall L and Rwiza HT, 1992).

In the HIC population-based studies, excess mortality is highest in the first few years after diagnosis of the epilepsy and is mainly due to the underlying causes of epilepsy (Cockerell OC et al., 1994). Many studies focus on single epilepsy syndromes or on sub-populations with specific syndromes (Beghi E et al., 2005; Hesdorffer DC and D' Amelio M, 2005; Lorgoscino G et al., 2005; Sperling MR et al., 2005). Death in PWE has been associated with a number of factors, which include: underlying brain disease such as tumor or infection, seizures in dangerous circumstances leading to drowning, burns or head injury, possible respiratory or cardio-respiratory arrest during seizure and suicide and/or unexplained causes (sudden unexpected death in epilepsy (SUDEP)). The importance of SUDEP in Africa is unknown, but in the HIC, it accounts for up to 17% of the epilepsy deaths (Ficker DM, 2000), but is widely variable depending on the populations studies. The incidence of SUDEP ranges between 0.35-2.7/1000 per year in population based studies (Annegers JF and Coan SP, 1999) and can be as high as 6.3/1000 per year in selected epilepsy populations (Tomson et al., 2008) and accounts for more than 50% of mortality in patients with refractory epilepsy/candidates for epilepsy surgery (Sperling et al., 2005). In the HIC, SUDEP is more common in young adults and males, and those with refractory seizures, remote symptomatic epilepsy and non-adherence to treatment (Annegers JF and Coan SP, 1999; Langan Y et al., 2005; Tomson T et al., 2005), all of which are typical features of convulsive epilepsy in sub-Saharan Africa (SSA) and thus may represent important risk factors of mortality in people with epilepsy (PWE) in Africa.

Symptomatic epilepsy carries the greatest risk of death (Beghi E et al., 2005; Cockerell OC et al., 1994; Forsgren L et al., 2005; Lhatoo SD et al., 2001), with the convulsive epilepsies associated with the highest mortality (Lhatoo SD et al., 2001). In the HIC, deaths related directly or

indirectly to epilepsy are infrequent, but these causes may be more frequent in SSA (Caprio A et al., 2005; Diop AG et al., 2005; Kamgno J, 2003 Jul).

Current research

Background to the thesis

The studies described in this thesis were part of a larger study of epidemiology and treatment of epilepsy in SSA namely Studies of Epidemiology of Epilepsy in Demographic Surveillance sites (SEEDS) under the INDEPTH network (http://www.indepth-network.org/). INDEPTH is a network of research sites in LMIC in Africa, Asia, Oceania and Central America that carry out continuous demographic and health surveillance of populations. Activities within these sites are characterized by regular re-enumeration and vital registration of geographically defined populations with maintenance of regularly updated population registers. These provide accurate denominator data and efficient follow-up infrastructure for population-based cross-sectional and longitudinal studies.

The SEEDS studies were nested within on-going demographic re-evaluations in five Health and Demographic Surveillance System (HDSS) sites in SSA. A HDSS setting offers obvious advantages for studies to determine the burden of epilepsy and monitor health, treatment and outcomes in epilepsy patients. These advantages include: coverage of large (mostly rural) populations that provide adequate sampling frames; regular re-enumeration during which large populations can be screened efficiently; census field staff requiring minimal study-specific

training thereby minimizing cost; availability of necessary logistics and follow-up information on individuals e.g. deaths in an epilepsy cohort can be updated during the regular census surveys.

Justification for the research

Epilepsy appears to be common in LMIC, but there are no reliable estimates of prevalence, incidence and mortality on which to base and assess public health interventions. By using similar methodology, definitions and operational procedures across several sites in Africa, the SEEDS studies aimed to determine if the heterogeneity observed in previous prevalence studies in LMIC was methodological or "real" e.g. due to differences in prevalence of risk factors. The other objectives of SEEDS included: i) to determine the association of putative risk factors, particularly parasitic infestations of the brain (Malaria, Neurocystcercosis, Onchocerciasis, Toxocara and Toxoplasma) and HIV infection, with the development of epilepsy using case-control studies, ii) to quantify mortality in PWE, and, iii) to identify modifiable risk factors for death in people with epilepsy in this region.

Further, the studies would enable the establishment of baseline parameters for epilepsy in this region and cohorts of people with epilepsy on which further longitudinal studies of prognosis and interventions can be based.

Study Hypotheses

In this thesis I plan to examine the following null hypotheses:

1) The three-stage prevalence screening is not a valid methodology for detecting cases of ACE in population-based studies.
2) There is no heterogeneity in the prevalence of ACE in SSA.
3) Mortality in people with ACE is not higher than that in people without epilepsy in the Kilifi HDSS.
4) Mortality in people with ACE is not associated with seizure frequency, seizure type, adherence to anti-epileptic drugs (AEDs) and age at onset of seizures.

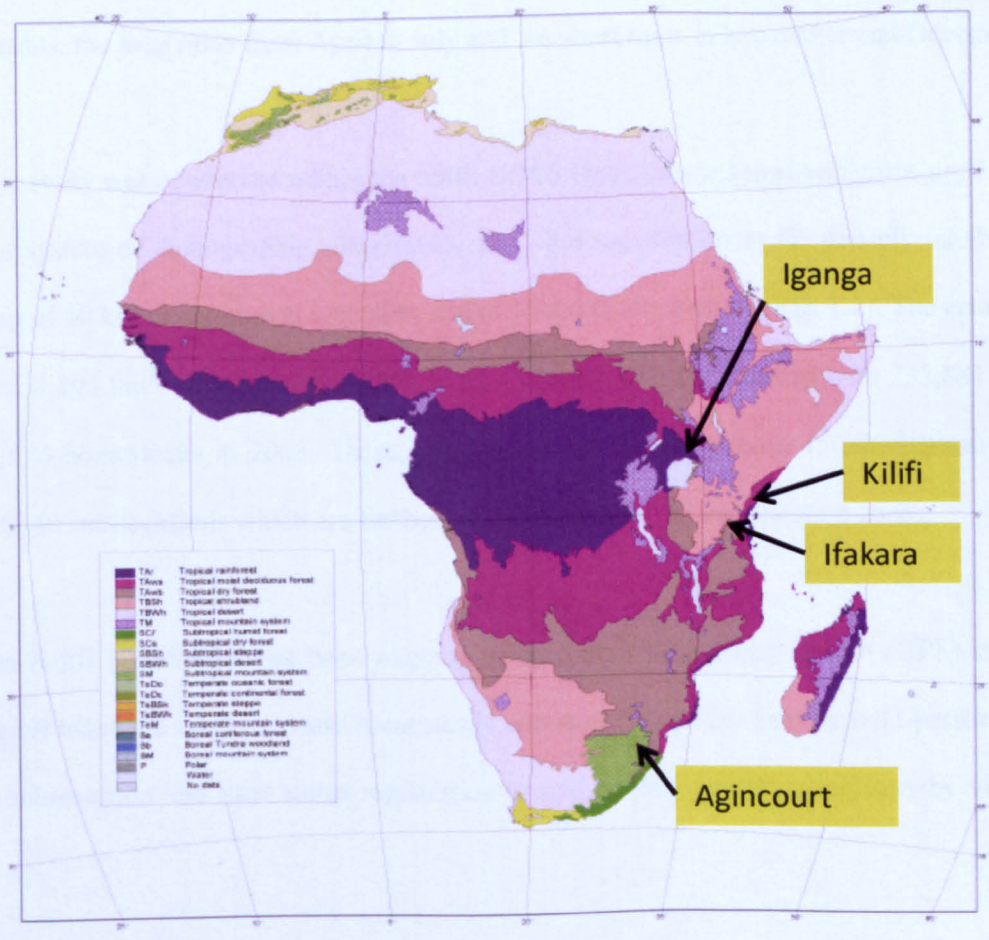
Study objectives

1) To determine the global burden of epilepsy especially AE which should be on treatment and identify study-level factors associated with heterogeneity of estimates.
2) To estimate the global incidence of epilepsy and study-level factors associated with heterogeneity of incidence estimates.
3) To determine the sensitivity and specificity of the three-stage methodology for detecting cases of ACE in population-based epilepsy surveys.
4) To determine the prevalence and heterogeneity of ACE in four HDSS sites in SSA.
5) To determine the incidence of ACE in the Kilifi HDSS.
6) To estimate the mortality ratios and identify risk factors for mortality in a cohort of people with ACE in the Kilifi HDSS.

Study sites

Most of the studies were conducted in the Kilifi HDSS. The HDSS sites in Agincourt in South Africa, Iganga-Mayuge in Uganda and Ifakara in Tanzania (Fig. 1.1) were used to determine prevalence and examine the heterogeneity of the prevalence of ACE in SSA. These sites were selected on the basis of the presence of hospital/clinic within the HDSS to provide support for the clinical aspects and follow-up of ACE patients in the longitudinal studies, availability of laboratory facilities to process the collected samples, operational costs to the study and the endemicity of parasitic diseases that could cause epilepsy.

Figure 1.1: Map of Africa showing the location of the four Health and Demographic Surveillance System study sites



Kilifi HDSS, Kenya

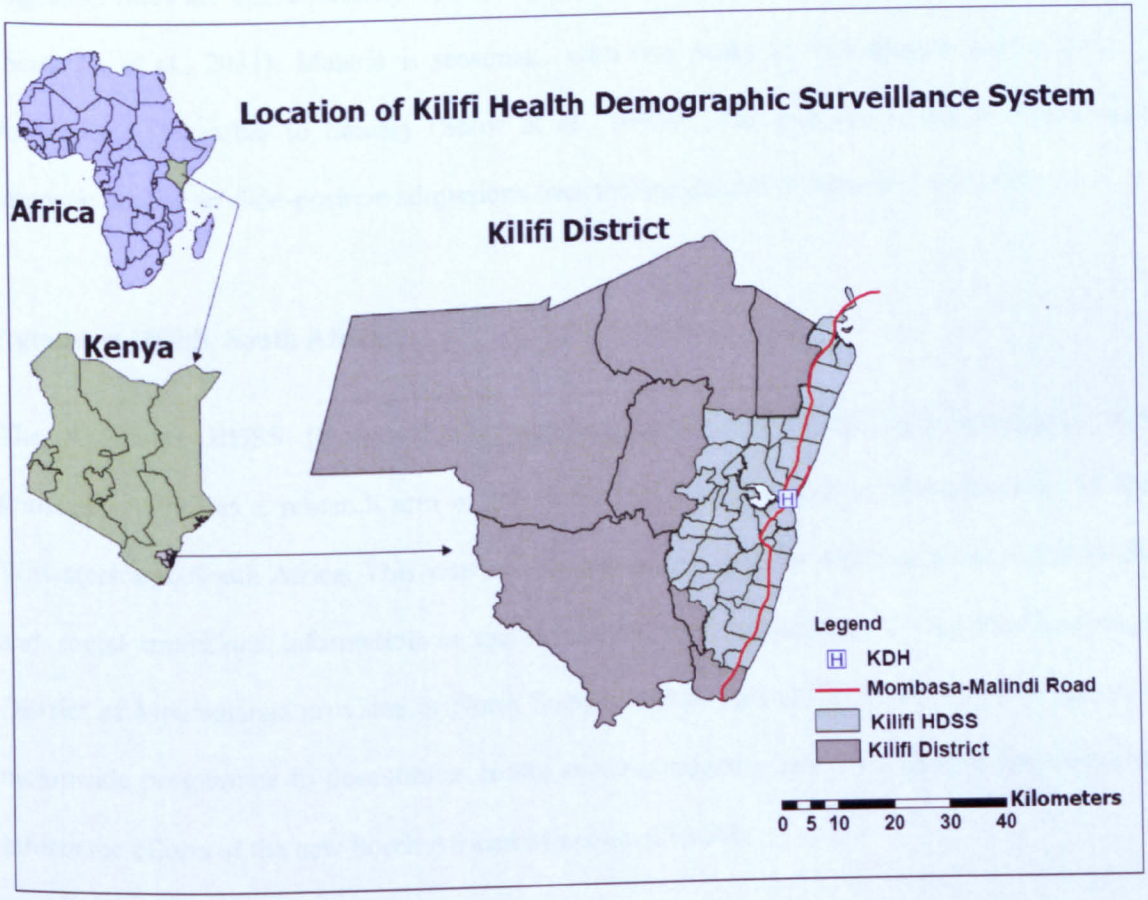
The Kilifi HDSS is in Kilifi District of the Coast province of Kenya, located about 60 kilometres to the north of Mombasa city (Figure 1.1). Kilifi District, with a total area of 4,779 km^2 and a population of 678,702 people includes some of the poorest areas in Kenya (Central Bureau of Statistics (CBS) - Kenya, 2007). It consists of rural and peri-urban communities. There are two urban centres: Mtwapa in the south almost joined to the northern edge of Mombasa has a population of 70,000 and Kilifi town, the district administrative centre with a population of 30,000. Most of the district is rural with subsistence farming. The main crops are maize and tree crops such as coconuts and cashew nuts. Soil fertility is low and variability of rainfall means that in some years crops fail. Average daytime temperatures vary between 28 and 34^{0}C and average annual rainfall is 118cm, though there is considerable year to year variation. There are two rainy seasons, the long rains from April to July and the short rains in November and December.

This study was conducted within the Kilifi HDSS (http://www.kemri-wellcome.org/khdss). This is a system of demographic surveillance and vital registration in the densely inhabited coastal strip of 40 km in length and extending about 15 km in the interior (Fig. 1.2). The estimated study area is 891 km^2, which is about 18% of the total area of Kilifi District with 233,881 residents in 25,526 homesteads in 2008. These homesteads are situated within 15 administrative locations with 40 sub-locations which are further sub-divided into 186 enumeration zones.

The Kilifi HDSS area has been mapped using global positioning system (GPS) receivers and digital maps are used to locate homesteads and study subjects. Census field personnel conduct re-enumeration and vital status registration to update the population registers by visiting every

homestead two-three times per year. Most (80%) of the population uses the Kilifi District Hospital (KDH) as the main hospital for admissions.

Figure 1.2: Map of Africa showing the position of the Kilifi Health and Demographic Surveillance System study area in Kenya.



*KDH: Kilifi District Hospital

Kenya Medical Research Institute (KEMRI) (http://www.kemri-wellcome.org/khdss/) has been running the Kilifi-HDSS in the well demarcated study area in Kilifi District since year 2000. The people are mainly Mijikenda, a Bantu grouping of nine tribes with Girima (45%), Chonyi (33%) and Kauma (11%) being the most common. About 55% of the population is considered

absolutely poor; per capita monthly income is about USD 10. The majority (80%) depend on peasant farming, which is limited by the low productivity of the land (only 19% of the total land is arable). Literacy levels are low: only 45% of people can read and write.

Crude birth and death rates for this area are 35/1,000 and 6/1,000 per year respectively, and migration rates are approximately 100/1,000 per year, most of which is within the study area (Scott JA et al., 2011). Malaria is seasonal, with two peaks in transmission during May to August and December to January (Snow et al., 1993b). The area has however experienced dramatic decline in slide-positive admissions over the last decade (O'Meara et al., 2008).

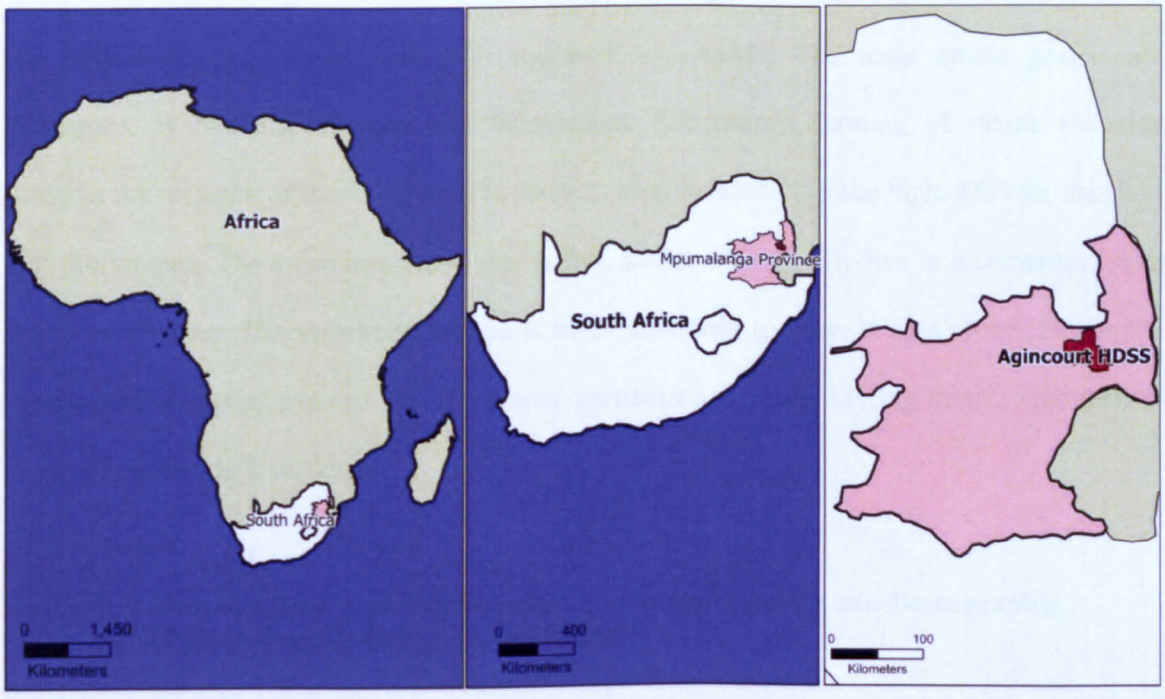
Agincourt HDSS, South Africa

The Agincourt HDSS (http://web.wits.ac.za/Academic/Health/PublicHealth/Agincourt/) was founded in 1992 as a research arm of the School of Public Health of the University of the Witwatersrand, South Africa. This was in response to the need for vital registration and health and social transitions information in the Agincourt rural sub-district of the Bushbuckridge District of Mpumalanga province in North Eastern South Africa (Fig. 1.3). This was part of a nationwide programme to decentralise health systems research and development that aimed to inform the efforts of the new South African Ministry of Health.

The total population then numbered some 58,000 persons, increasing to about 87,000 in 2007 in 14,382 households across 26 villages and covering about 420 sq km. Agincourt HDSS is located alongside the western border of Mozambique, forming part of rural north-eastern South Africa (Fig. 1.3). There are significant numbers of former Mozambican refugees – some 30% of the sub-district population. The Agincourt HDSS includes annual census and special events updates

(systematic recording of all births, deaths and migrations). The overlap between the administrative boundaries of the sub-district and those of the defined population of the HDSS facilitate the transfer and application of research findings to local health and development efforts.

Figure 1.3: Map of Africa showing the position of Agincourt Health and Demographic Surveillance System study area in South Africa.



Reproduced from the INDEPTH website: (http://www.indepth-network.org/)

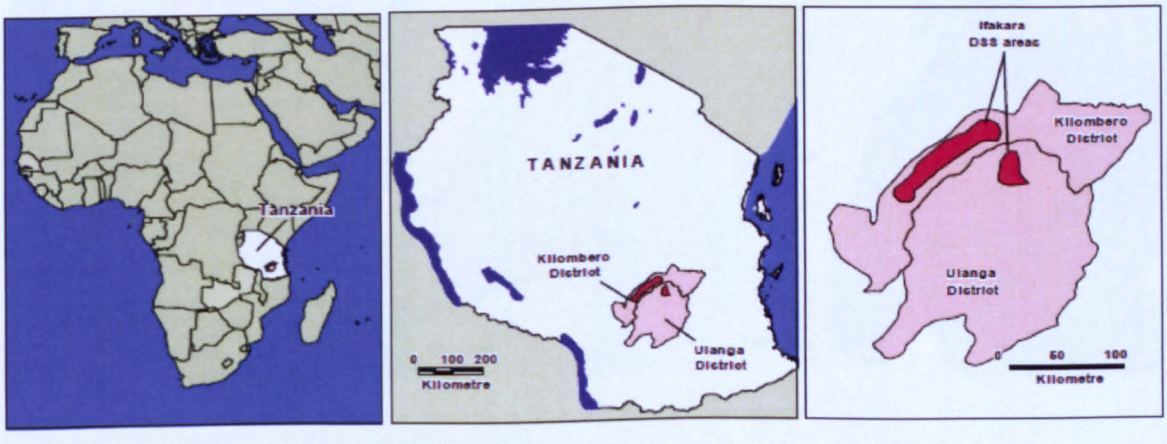
Ifakara HDSS, Tanzania

The Ifakara HDSS (http://www.ihi.or.tz/) study area is located in southern Tanzania and covers parts of two districts, Kilombero and Ulanga both in the Morogoro region (Fig. 1.4). The Ifakara HDSS site was established in September 1996 and the baseline census was conducted between

September and December of the same year. The HDSS covers a total of 25 villages with a population of about 105,000 people in 14,000 households. Since January 1997 each household is visited once every four months (three times in a year) to record births, pregnancies, deaths and migration. In order to document causes of death, verbal autopsies have been conducted since September 2000.

The area is predominately rural with scattered households. The main ethnic groups are Wapogoro, Wandamba, Wabena and Wambunga. Subsistence farming of maize and rice occupies the majority of the villagers. The literacy level in adults is quite high, 88% for men and 69% for women. The mean household size is five people who usually live in a compound with one or two houses. The main rainy season is from November to May. In some years, floods are experienced in several parts of the HDSS area, particularly in April. During floods, accessibility to some households is difficult.

Figure 1.4: Map of Africa showing the position of Ifakara Health and Demographic Surveillance System study area in Tanzania.



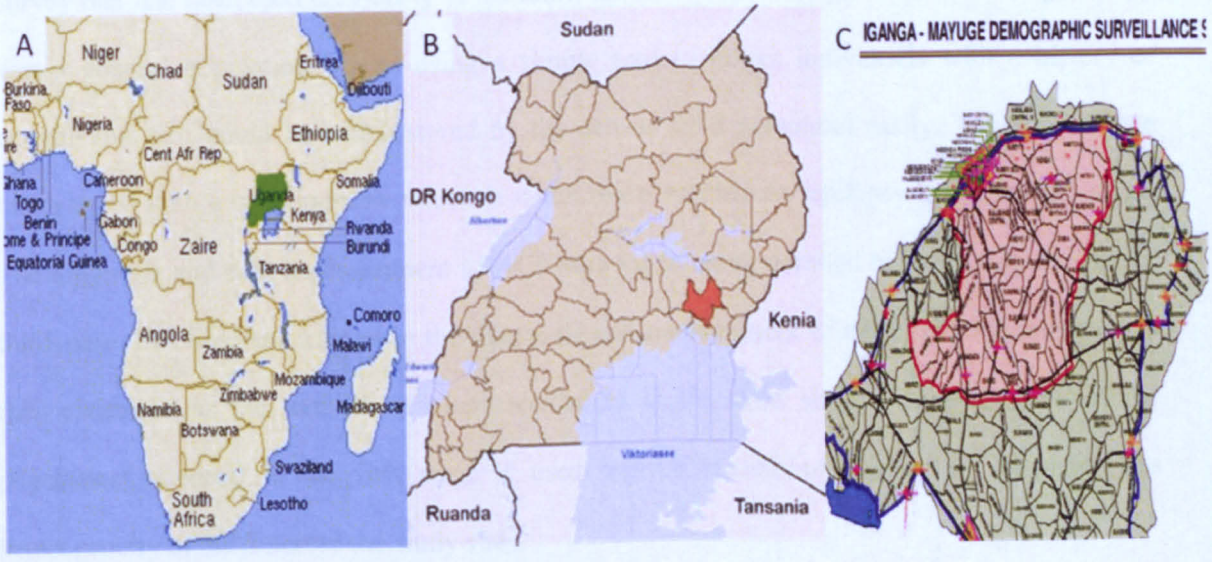
Reproduced from the INDEPTH website: (http://www.indepth-network.org/)

Iganga/Mayuge HDSS, Uganda

Iganga/Mayuge HDSS in Uganda (Fig. 1.5) was established in August 2004. It is located in the eastern part of the country 115km from the capital city, Kampala. According to results from the Baseline Census conducted between March-July 2005, the HDSS had a population of 62,000 people, about 80% living in rural and 20% peri-urban areas. Currently, the population stands at 68,000 people. Data for update rounds is collected 3 times in a year. The Iganga/Mayuge HDSS uses paper based protocol of data collection but has been changing gradually to use of handheld computers (PDAs).

The core demographic events covered are migrations, births, death and verbal autopsies. Other modules collected include pregnancies, education and socio-economic status.

Figure 1.5: Map Africa showing the location of the Iganga-Mayuge Health and Demographic Surveillance System study area in Uganda.



Overview of the methods

I employed various methodologies to collect and analyze data to meet the objectives of these studies. In the second and the third chapters I used formal systematic review procedures to search for and evaluate previously published literature and meta-analysis techniques to analyze the data. To validate the three-stage methodology for detecting cases of ACE in population-based studies, the gold standard method for the identification of cases of epilepsy (i.e. clinical history taken by clinicians with experience in diagnosis and management of epilepsy) was administered on a randomly selected sample of 5,796 Kilifi HDSS residents. The gold standard diagnoses were then compared with those obtained from the three-stage prevalence survey and the sensitivity and specificity were estimated in 2x2 tables.

The prevalence of ACE in all study sites was estimated from the three-stage cross-sectional survey that had been used previously in the Kilifi HDSS. The first stage of the three-stage survey was a general population screen using a simple tool to detect individuals with a history of convulsions that could be administered by the census field personnel easily. These were then interviewed with a questionnaire which is much more specific for epilepsy in the second stage. The diagnosis and case ascertainment of ACE was made using detailed history taken during the third stage by clinicians trained in the diagnosis and management of epilepsy. Prevalence was then estimated as the number of cases confirmed in the third stage as a proportion of the population screened in the first stage. I used logistic regression method to determine the heterogeneity of ACE across the study sites.

The incidence of ACE in the Kilifi HDSS was based on two cross-sectional studies conducted five years apart. The first survey in 2003 determined the ACE status of residents and identified a cohort of individuals without epilepsy. In the second survey in 2008, I re-examined this cohort to determine the number that had developed ACE during the intervening period. Assuming a Poisson distribution for the number of incident cases, the incidence of ACE together with the 95% confidence interval (95%CI) was calculated by dividing the number of incident cases by the person years of observation among the cohort members re-identified in the second survey.

Estimates of mortality ratios and identification of risk factors for death in people with ACE were based on cohorts of people with and without ACE identified in a baseline three-stage population wide prevalence screening within the Kilifi HDSS. These were actively followed-up regularly for three years within the HDSS infrastructure for registration of mortality and within the epilepsy longitudinal study to capture demographic data and putative risk factors for mortality. I calculated the case fatality proportion for the ACE cohort and standardized mortality ratio (SMR) by direct standardization against the population without ACE at baseline. Poisson regression with time-dependent co-variates was used to identify factors associated with mortality in people with ACE.

More detailed descriptions of the methods are presented in each chapter.

Layout of the thesis

This work describes the rationale, methods and findings of my studies of global prevalence and incidence of epilepsy and heterogeneity of ACE in the four HDSS Sites in sub-Saharan Africa, and incidence and mortality of ACE in the Kilifi HDSS.

The first chapter is the general introduction of the basic epidemiology of epilepsy, contrasting LMIC with the HIC, and presenting the rationale and objectives of the thesis. It also describes the study sites and presents a summary of the methods.

The second and the third chapters of the thesis present two systematic reviews and meta-analyses of prevalence and incidence of epilepsy which also compare the burden and heterogeneity of epilepsy in HIC and LMIC. These reviews identify the study-level factors associated with the heterogeneity of the observed estimates, which forms the basis for further inquiry into the types (clinical or methodological) of the heterogeneity in the prevalence chapter.

The fourth chapter of the thesis is a validation study of the three-stage cross-sectional screening methodology that was used to identify cases of ACE to determine prevalence in all four sites.

In the fifth chapter, I describe the methods and results of studies of prevalence and heterogeneity of ACE in the four HDSS sites in sub-Saharan Africa. The sixth chapter describes the estimation of the incidence of ACE, and the seventh describes mortality and risk factors associated with mortality in people living with ACE in the Kilifi HDSS in Kenya.

The eighth chapter includes the general discussion and conclusions which put into context and provide insights into the public health implications of my findings. This chapter also offers recommendations for public health interventions and directions for future research.

Overall, the research reported in this thesis contributes to our broad understanding of the basic epidemiology of epilepsy in resource limited settings. Specifically, it provides a reproducible and data driven estimate of the global burden of epilepsy as well as an estimate of the burden with active epilepsy that should be on treatment. Further, this research provides insights into the causes and type of heterogeneity both globally (in the meta-analysis chapters) and in a resource poor setting (in the prevalence chapter). This aspect of the distribution of ACE has not been evaluated in any previous research. The research also estimates the magnitude of mortality and factors associated with it in people with ACE in the Kilifi HDSS, which are key to informing public health interventions to reduce mortality in PWE. It is hoped that this research will ignite debate and form the basis for studies to collect much needed data on epidemiology of epilepsy in other LMIC and for informing and assessing public health interventions.

Personal statement on my roles in the SEEDS study

Development of SEEDS studies in INDEPTH HDSS sites

The studies reported in this thesis were conducted as a component of SEEDS in 5 HDSS sites in sub-Saharan Africa (SSA). SEEDS was put together through a joint effort of my supervisor Prof. Charles Newton, Dr. Victor Doku (Institute of Psichiatry, King's College, University of London)

and I. I made the initial contact with the site leaders of the sites that are now involved in the SEEDS project during the 6th Annual INDEPTH General Meeting and Scientific Conference in Ouagadougou, Burkina Faso in September 2006. During this meeting, I also presented data from a previous study of prevalence of epilepsy in the Kilifi HDSS and made a call for expression of interest in the SEEDS study that was then in the conceptual stage.

Jointly with Prof. Newton and Dr. Doku, we drafted the concept paper for the SEEDS thereafter (Appendix 1.1) which was circulated within the INDEPTH Network as a call for expression of interest in epilepsy studies. Out of 12 sites that initially expressed interest (3 in Asia and 9 in Africa), 5 sites were selected. Thereafter, I supported the SEEDS study PI (Prof. Charles Newton) during the drafting of the funding proposal by putting together data and some aspects of the analysis that were needed for the proposal development.

I developed the training manuals (Appendix 1.2) for the SEEDS study (based upon the experiences of similar studies in the Kilifi HDSS) and information sheets and consent forms (with the help of the Kilifi Social and Behavioural Research Group) (Appendix 1.3). I conducted the training for the stages I and II field staff and for the study project managers in all sites. Further, I supported and advised the project managers on some logistical aspects during initiation of the studies and continually on all aspects of the study during implementation and monitored data quality using monitoring tools that I developed.

Prevalence surveys in INDEPTH HDSS sites validation of the screening methodology in Kilifi HDSS

I wrote the proposal for the validation of the 3-stage survey methodology in the Kilifi HDSS and was actively involved in managing data collection. Under the supervision and advice from my supervisors Prof. Newton, Dr. Kleinschmidt and Dr Bottomley, I analyzed and wrote-up the validation and prevalence data from these aspects of the study with.

Incidence study in the Kilifi DSS

I conducted the re-evaluation screening of the initial non-epilepsy cohort in 2008, linked study participants in the two surveys and analyzed and wrote up the incidence chapter of this thesis under the supervision and advice of my supervisors.

Mortality studies in the Kilifi DSS

I identified the study participants with ACE in the epilepsy screening of 2008 and conducted the follow-up of the mortality cohort (directing and supervising field work and data handling) for three years. I also analyzed wrote-up the mortality chapter of this thesis with guidance from my supervisors.

The contributions of the authors of the two chapters that have been published so far are detailed at the end of the individual chapters.

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Chapter 2: Estimation of the burden of active and life-time epilepsy: a meta-analytic approach.

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Abstract

Purpose: To estimate the burden of life-time epilepsy (LTE) and active epilepsy (AE) and examine the influence of study characteristics on prevalence estimates.

Methods: We searched online databases and identified articles using pre-specified criteria. Random effects meta-analyses were used to estimate the median prevalence in developed countries and in urban and rural settings in developing countries. The impact of study characteristics on prevalence estimates was determined using meta-regression models.

Results: The median LTE prevalence for developed countries was 5.8/1,000 (5^{th} - 95^{th} percentile range: 2.7-12.4) compared to 15.4/1,000 (4.8-49.6) for rural and 10.3 (2.8-37.7) for urban studies in developing countries. The median prevalence of AE was 4.9/1,000 (2.3-10.3) for developed countries and 12.7/1,000 (3.5-45.5) and 5.9 (3.4-10.2) in rural and urban studies in developing countries. The estimates of burden for LTE and AE in developed countries were 6.8 million (5^{th} - 95^{th} percentile range: 3.2-14.7) and 5.7 million (2.7-12.2), respectively. In developing countries these were: 45 (14-145) million LTE and 17 (10-133) million AE in rural areas and 17 (5-61) million LTE and 10 (5-17) million AE in urban areas. Studies involving all ages or only adults showed higher estimates than paediatric studies. Higher prevalence estimates were also associated with rural location and small study size.

Conclusions: This study estimates the global burden of epilepsy and the proportions with AE, which may benefit from treatment. There are systematic differences in reported prevalence estimates, which are only partially explained by study characteristics.

Introduction

Epilepsy is one of the most common neurological conditions in the world, but the current estimates of 50 million people worldwide (WHO, 2004) lack precision and do not provide an estimate of the proportion with active epilepsy (AE), i.e. who may benefit from treatment.

The epidemiological studies describing the burden of epilepsy in the last 40 years are problematic (Kotsopoulos I et al., 2005; Kotsopoulos et al., 2002). Data on epilepsy are still scarce in many parts of the world, while the available data is inconsistent because of differences in sampling frames, case definitions, measurements (e.g. point versus period or lifetime prevalence), screening tools, diagnostic accuracy and different methodological approaches (Leonardi M and Ustan TB, 2002).

In the developed world where routine medical statistics are available and easily accessible, investigators have used research and hospital databases, rather than population-based studies to estimate the prevalence of epilepsy. This practice, however, discriminates against those who underutilize medical services (Morgan CL et al., 2000 ; Wright J et al., 2000). Community-based surveys are more commonly used in developing countries, but often do not make use of validated tools to screen the population. Even where validated tools are used these studies may have higher sensitivity for convulsive epilepsies and thus more subtle forms of epilepsy are underestimated (da Mota Gomes M et al., 2002; Racoosin JA, 2003).

The prevalence of epilepsy is reported to vary substantially between developed and developing countries: estimated as 4 - 7/1000 persons in the developed countries (Sander JW and Shorvon SD, 1996) and 5 - 74/1000 in developing countries (Preux PM and Druet-Cabanc M, 2005). The wider variations in the estimates of prevalence from resource poor compared to developed countries complicate the use of these data in estimating the number who may benefit from treatment and in informing public health policy.

Heterogeneity in prevalence estimates, though anecdotally referred to, has not been investigated systematically. The heterogeneity could be due to differences in the prevalence of causes, case definitions or case ascertainment. Knowledge of these factors would be useful in the design and implementation of multi-site studies of epilepsy. Further, differences in causes could have implications in resource allocation in public health interventions.

We conducted a systematic review of published literature to determine heterogeneity in prevalence between studies and to provide estimates of the global burden of epilepsy, in particular to provide numbers of those with AE who may benefit from treatment. Furthermore, we modelled the influence of study level covariates on the prevalence estimates.

Methods

Literature searches

Online databases; MEDLINE, EMBASE, PsycINFO, African Index Medicus, Index Medicus for South East Asia, Index Medicus for Eastern Mediterranean Region, BVS Virtual Health Library

(Lilacs, Adolec, Medcarib, PAHO and WHOLIS), SIGLE, Proquest, Wang Fang Database of English and Chinese online journals published in mainland China, SCIELO, CINAHL and Global Health were systematically searched by the first author. Reference lists of identified articles were also searched for relevant titles and these were in turn searched online.

Search strategies

Where applicable, combined text words and Medical Subject Headings (MeSH) terminology were used in addition to the two main search terms [Epilepsy & Prevalence] to identify relevant articles (Appendix 2.1). Boolean operators were used to combine search terms as necessary and the MeSH subheadings tree was used to increase the specificity of the search terms in MEDLINE and EMBASE databases. The review question was broken down into search terms/elemental facets to develop a search strategy (Appendix 2.1). This involved the use of the recommendations of the National Health Service Centre for Reviews and Disseminations (Khan KS et al., 2001).

Study selection

We included retrospective, cross-sectional or prospective population based studies measuring prevalence of epilepsy from anywhere in the world. Hospital based and medical records/research database studies were also examined. The estimate of the prevalence was obtained from papers that met the criteria outlined below, which included the International League Against Epilepsy (ILAE) definition of LTE and AE (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). An additional definition of AE that encompasses seizures

within the previous 12 months was also examined, since this is the criteria used for treatment in many developing countries.

Inclusion and exclusion criteria

A study was included if it: reported prevalence of LTE or AE; collected data using standardized previously validated questionnaires in door-to-door surveys, valid hospital and research databases and general practice records; provided the denominator to allow recalculation of the presented or required estimates; and, included a definition of epilepsy as two or more non-provoked seizures occurring at least 24 hours apart.

A study was excluded if it: examined only acute symptomatic seizures, specific seizure patterns or epileptic syndromes e.g. absence seizures; was published as a review, an editorial, an abstract only, a letter or a comment; was a study on sub-populations e.g. prevalence of epilepsy on patients with a history of head trauma; or, was a part of duplicate populations i.e. those in which the same population overlapped different reports.

Data extraction

We extracted data using a proforma designed for this review. AKN extracted all the data while CRN re-extracted data from a sample of 10% of the studies. From each included study, we obtained information on author, country, study type, study population, data collection and ascertainment method(s), age of study subjects and whether the estimate was point or period prevalence. We used only studies that reported crude prevalence. We calculated the 95%

confidence interval (95%CI) around the estimates where these were not provided. All meta-analyses were carried out in STATA® 10 (College Station, TX, USA).

Analysis

In the summary tables, crude prevalence estimates expressed as the number of cases per 1,000 of the population were presented with their 95%CI. For all meta-analyses, models were fitted to logit-transformed observed prevalences. Estimates of the median, 5^{th} and 95^{th} percentile of the distribution of true prevalences (i.e., the distribution of study prevalences that excludes variation due to sampling error) were obtained by back-transforming estimates on the logit scale to the prevalence scale.

The data were stratified on the World Bank classification of level of economic development of the study country (The World Bank, 2006) but since there were few studies, the countries were classified as developed or developing. Studies from developing countries were stratified further into urban and rural. Studies were also classified by age into those on all age groups (both children and adults), those on adults only (>15 years of age) and those on children only (≤15 years of age). Studies reporting crude LTE and AE prevalence were analyzed separately.

Description of heterogeneity

We used forest plots (Lewis S and Clarke M, 2001) to visualize the heterogeneity among the studies. The standard test for heterogeneity, the Cochrane χ^2 test, was used to examine the null hypothesis that the observed heterogeneity was due to sampling error (Higgins JP and Thompson

SG, 2002). Since heterogeneity was expected *a priori* due to clinical and methodological diversity in the studies, we also quantified the degree of heterogeneity across studies using the statistic I^2 = ((Q – df)/Q) x 100%, where Q is the Cochrane chi-squared statistic and df is its degrees of freedom (Higgins JP and Thompson SG, 2002; Higgins JP et al., 2003). I^2 describes the percentage of the variability in estimates that is due to true heterogeneity (true differences in prevalence) rather than sampling error. A value greater than 50% was considered as substantial heterogeneity.

The median of the logit transformed prevalences was estimated from the random effects model using the command *"meta"* in STATA®. In addition the 5th and 95th percentiles were estimated as $m \pm 1.96\tau$, where τ is the standard deviation of the random effect, i.e. the standard deviation of the true study prevalences on the logit scale. These quantities were then back-transformed to the original prevalence scale. This approach uses information on prevalence and study size (or equivalently standard errors/confidence intervals) and is applicable when there is significant heterogeneity (Goodman SN, 1989). It involves an assumption that the outcomes (such as logit prevalences) being estimated in the different studies are not identical, but follow a normal distribution, allowing for among study variation (Goodman SN, 1989).

Estimation of the number of epilepsy cases

Data on the mid-year population sizes of developed countries were obtained from the U.S. Census Bureau, International Data Base (US Census Bureau, 2007). Rural and urban population sizes in developing countries were obtained from the Columbia University's Global Rural-Urban Mapping Project (GRUMP) database (Center for International Earth Science Information

Network (CIESIN), Accessed 27 July, 2009). The numbers of cases of LTE and AE were estimated by multiplying the estimated median prevalence obtained from the meta-analysis by the average size of the population during the period in which studies in this review were conducted. A range was obtained using the 5^{th} and 95^{th} percentiles.

Investigation of the sources of heterogeneity

The following five study level covariates were investigated for their association with prevalence estimates: level of economic development, age of study participants, method of data collection, type of estimate (point or period prevalence) and study size. The influence of these variables on study prevalence was investigated using random effects meta-regression models. The models were fitted using the *"metareg"* command in STATA®. This approach assumes two additive components of variance, one representing the variance within studies (i.e., error variance), and the other the variance between studies. The regression coefficients represent log odds ratios since the models are fitted to logit-transformed data. The proportion of heterogeneity explained by each of the covariates was estimated by comparing the between studies component of variance in the null model (τ_0^2) with the estimate of τ^2 for the model including covariates $((\tau_0^2 - \tau^2)/ \tau_0^2)$.

Both univariate and multivariable meta-regression were performed. Variables that were significant in the univariate analysis were included in the multivariable model using a forward selection strategy. The order in which variables were introduced into the multivariate model was determined by the size of the p-value in the univariate analysis (starting with the smallest p-value). No further variables were introduced when $p>0.05$ for the introduced variable.

Results

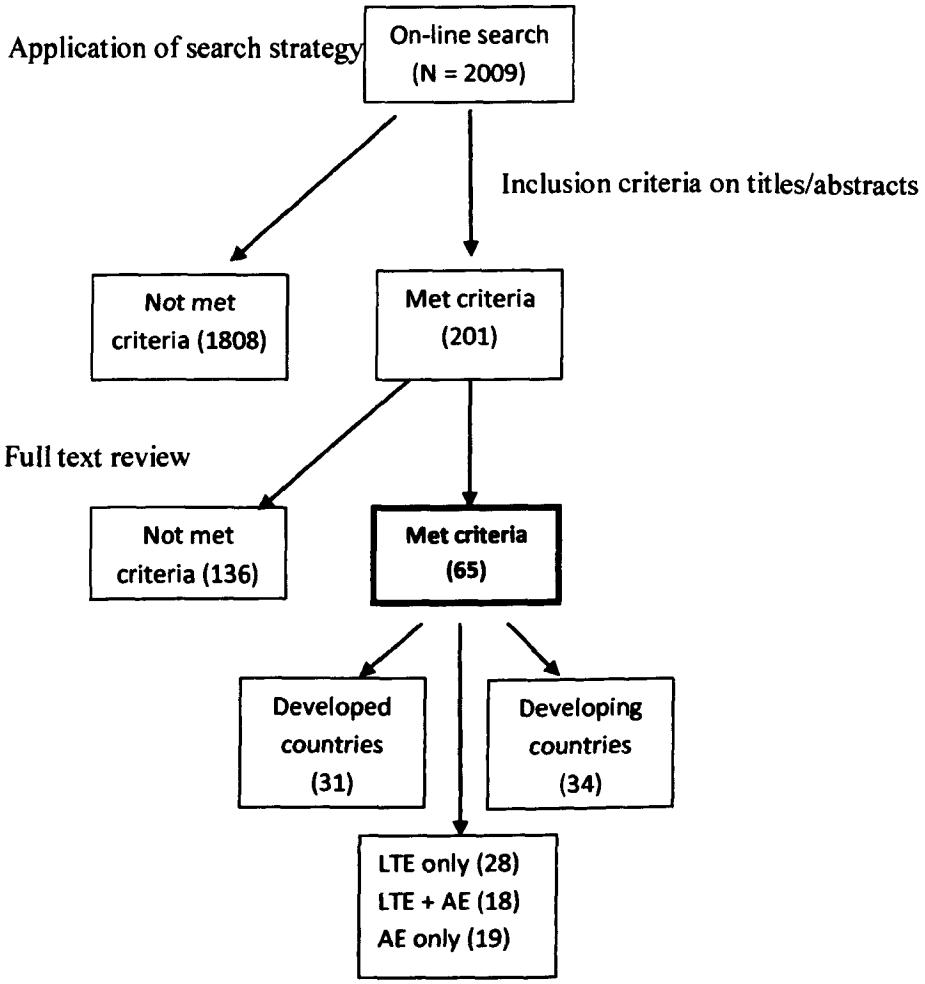
Studies identified

Literature searches from all sources were as displayed in Figure 2.1. Reasons for exclusion of the 136 studies that underwent full text review are displayed in Appendix 2.2. Of the 65 studies included (Appendices 2.3(a) & (b)), 28 reported LTE prevalence only, 18 reported both LTE and AE prevalence while 19 reported prevalence of AE only. Thirty-four were from developing and 31 from developed countries. Among studies from developing countries, LTE was reported in 16 studies from rural areas and nine studies from urban areas. AE was reported in nine studies from rural areas and four from urban areas. Thirty-seven studies were conducted in both adults and children, 17 were in children only and 11 were in adults only.

Period prevalence was estimated in 20 of the studies, while point prevalence was estimated in the rest. The studies did not all use the same methods for data collection: 20 studies used primarily medical records, 35 used questionnaires in cross-sectional field surveys while 10 used medical records to ascertain cases identified through questionnaires. Sixty papers were written in English, four were Spanish and one was in French.

Three studies from developing countries defined AE as epilepsy in which the last seizure occurred in the previous 12 months.

Figure 2.1: Literature search and identification of studies for the meta-analysis.



Description of heterogeneity for studies of LTE

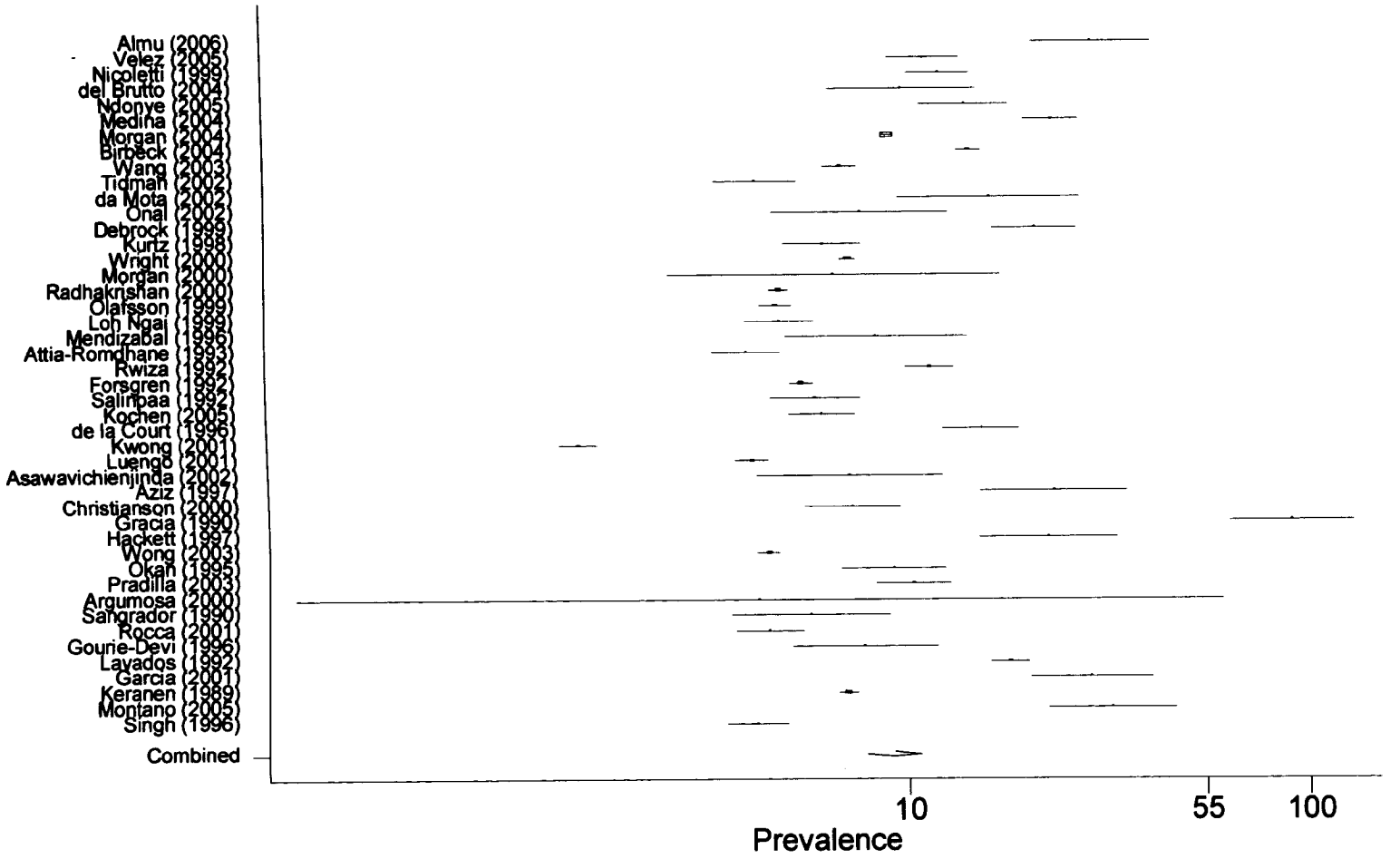
Most of the variability in prevalence estimates was attributable to study heterogeneity (I^2 = 98%, p<0.001) (Figure 2.2), both from developed (I^2 > 99%; P < 0.001) and developing countries (I^2=98%; P < 0.001). The estimates also showed significant heterogeneity (I^2 > 90%) after stratifying on age of study subjects and rural/urban locations for developing countries.

The estimated median prevalence for developed countries was 5.8/1,000 (5^{th} - 95^{th} percentile range: 2.7 – 12.4). In developing countries, the median prevalence and range of LTE was 15.4/1,000 (4.8 – 49.6) in rural areas and 10.3/1,000 (2.8 – 37.7) in urban areas (Table 2.1). On stratification by the age of study subjects, the median prevalence and 5^{th} to 95^{th} range was: 9.7/1,000 (4.6 – 20.5) for all age groups, 11.3/1,000 (4.2 – 30.5) for studies with adults only and 6.7/1,000 (1.6 – 27.2) for studies of children only.

Description of heterogeneity for studies of AE

The estimated median prevalence of AE for developed countries was 4.9/1,000 (5^{th} - 95^{th} percentile range: 2.3 – 10.3). In the developing countries, the median prevalence and range of AE was 12.7/1,000 (3.5 – 45.4) in rural areas and 5.9/1,000 (3.4 – 10.2) in urban areas (Table 1). When stratified on age of study participants, the median prevalence and range was 7.0/1,000 (2.9 – 16.8) for all ages, 7.0/1,000 (2.4 – 20.6) for adults and 4.7/1,000 (3.3 – 6.9) for paediatric studies. There was substantial heterogeneity in the estimates, ($I^2 = 90\%$, $p<0.001$).

Figure 2.2: Forest Plot for the life-time epilepsy prevalence per 1000 persons (all studies).



Estimates of the number of epilepsy cases

The estimated median number of people with LTE in developed countries was 6.8 million (5^{th} - 95^{th} range: 3.2 – 14.7 million) and for AE it was 5.7 million (2.7 – 12.2 million). In the developing countries, the median and range of LTE cases were 45 million (14 – 145 million) in rural areas and 17 million (5 – 61 million) in urban areas. AE constituted 38% of LTE cases in rural and 59% in urban areas (Table 2.1).

Table 2.1: Median prevalence and numbers of cases of life-time and active epilepsy.

Epilepsy Type	Region	Median prevalence/1,000 (5^{th} to 95^{th} percentile range)	Mean Population*	No. of cases in millions median (5^{th} to 95^{th} range)	Percent LTE with AE
LTE	Developed	5.8 (2.7 – 12.4)	1,184,235,962	6.8 (3.2 – 14.7)	84
	Developing	**Rural = 15.4 (4.8 – 49.6) Urban = 10.3 (2.8 – 37.7)	2,929,891,835 1,619,261,754	45 (14 – 145) 17 (10 – 133)	38 59
AE	Developed	4.9 (2.3 – 10.3)	1,184,235,962	5.7 (2.7 – 12.2)	
	Developing	‡Rural = 12.7 (3.5 – 45.4) Urban = 5.9 (3.4 – 10.2)	2,929,891,835 1,619,261,754	17 (5 – 61) 10 (5 – 17)	

*averaged over the period the selected studies were conducted.
** 1 study mixed rural and urban populations (not included in the analysis)
‡ 1 study mixed rural/urban populations and 1 unknown (both not included in the analysis)

Sources of heterogeneity in studies of LTE prevalence

In the univariate analysis, study size explained 45.3% of the observed heterogeneity and studies with fewer than 1,000 subjects were more likely to have higher prevalence estimates than larger studies ($p < 0.001$). The development level of the study country explained 26.4 % of the between study variance. In developing countries, studies from both urban and rural areas had roughly two

times or more the prevalence of those from developed countries (Table 2.2). Age of subjects, method of data collection and type of estimate were not associated with prevalence. In the multivariable regression for all LTE studies, rural areas of developing countries, studies in all age groups and small studies (n <= 20,000) were significantly associated with the prevalence estimates (Appendix 2.4); together, these variables accounted for 52.8% of the observed heterogeneity.

Table 2.2: Random effects meta-regression of prevalence of life-time epilepsy from all studies, univariate analyses (n = 46).

Covariate	Categories (1st listed is reference)	No. studies	Odds Ratio (95% CI)	P value	Heterogeneity (τ^2)	Heterogeneity (%)
Null model	-	46	-	-	0.53	-
Development	Developed	20	1.0	-		
	Developing (Urban)	9	1.8 (1.1– 3.0)	0.03	0.39	(26.4)
	Developing (Rural)	16	2.7 (1.8 – 4.0)	<0.001		
Age	Adult	7	1.0	-		
	Children	11	1.2 (0.7 – 2.2)	0.6	0.52	(2.0)
	All	28	0.7 (0.4 – 1.2)	0.2		
Data collection	Records	11	1.0	-		
	Questionnaires	29	1.6(0.8 – 3.0)	0.2	0.52	(1.7)
	Records & questionnaires	6	1.2 (0.6– 2.4)	0.7		
Study size	>20,000	19	1.0	-	-	-
	1,000-20,000	22	1.9 (1.4 – 2.7)	<0.001	0.29	(45.3)
	<=1,000	5	5.2 (2.9 – 9.5)	<0.001		
Estimate type	Period	15	1.0	-	0.54	(2.3)
	Point	31	1.0 (0.6 – 1.5)	0.9		

Sources of heterogeneity in studies of AE prevalence

In the univariate analysis of all AE studies, country development level and study size were significantly associated with prevalence estimates ($p < 0.05$), explaining 31.7% and 26.4% of the observed heterogeneity respectively. In the developing countries, studies from rural areas had significantly higher prevalence estimates (OR = 2.5 (95% CI; 1.7 – 3.8)) relative to studies from developed countries. Small study size (n<1,000) was also associated with higher prevalence estimates (OR = 3.4 (95%CI; 1.7 – 6.6)). In the multivariable analysis, rural areas and small study size (n<1,000) were significantly associated with prevalence estimates and together accounted for 42% of the observed heterogeneity (Appendix 2.5).

Discussion

This study describes the distribution of prevalence in studies of people with LTE and AE across the world. Numbers of cases of LTE are provided for developed countries as well as for rural and urban locations of developing countries. Combined, these numbers provide a global estimate of cases of LTE which could be much higher than the figure of 50 million estimated by the WHO (WHO, 2004). The number of people with AE who should be considered for treatment in each region is also estimated. The studies included in these analyses however showed considerable heterogeneity, which we quantified using robust meta-analysis (Egger M et al., 1997; Higgins JP and Thompson SG, 2002; Higgins JP et al., 2003). There was substantial variation in the prevalence of both LTE and AE even within studies of similar age group or level of economic development. Other estimates of the prevalence of LTE from developed countries (Sander JW

and Shorvon SD, 1996) and from developing countries (Preux PM and Druet-Cabanc M, 2005) are within the ranges reported in this study.

In this meta-analysis the prevalence of LTE is higher in studies of adults than studies of all ages (both adults and children), while it is lowest in children. The median prevalence of AE was similar for studies on all ages and adults only, but lower in studies on children. These data also showed that small studies (n < 1000), and studies conducted in less developed regions were associated with a higher prevalence of epilepsy. In developing countries, these data show that the prevalence of LTE is highest in rural areas, with the urban estimates being mid-way between those of rural areas and developed countries. Additionally, the prevalence of AE in urban areas of developing countries is closer to that of developed countries, with that of rural areas being considerably higher.

To the best of our knowledge, this is the first study that comprehensively reviews and analyses available literature to provide robust estimates of the global burden of epilepsy, assesses and quantifies the variability of the estimates and investigates the influence of study level covariates in the observed heterogeneity. The few reviews conducted previously have been regional e.g. Latin America (Burneo JG et al., 2005), exploring incidence and prevalence only (Burneo JG et al., 2005), or incidence only (Kotsopoulos I et al., 2005; Kotsopoulos et al., 2002), or mortality only (Diop et al., 2005; Forsgen L et al., 2005). Furthermore, this is the first study that provides an estimate of the burden of AE that could benefit from treatment.

The difference in heterogeneity of LTE prevalence estimates between developed and resource-poor countries can be explained in part by the fact that medical records, used primarily to ascertain cases in developed countries, are to some extent standardized, and provide consistent, detailed information on patients leading to less variation in recorded data. Where available, medical records are also used to ascertain cases identified through questionnaires. Additionally, the smaller amount of variation in studies from developed countries could be caused by the use of single district, regional and/or national databases that use similar diagnostic codes such as the National General Practice Study of Epilepsy database in the UK. Others include use of the diagnostic record system in Rochester, US (da Mota Gomes M et al., 2002; Hauser WA et al., 1993 ; Racoosin JA, 2003; Tidman L et al., 2003) or the use of the Health Maintenance Organizations' records (Annegers JF et al., 1999 ; Holden EW et al., 2005).

Previously, data from developing countries was thought to vary widely due to differences in methodology (such as the use of non-standard screening tools), differences in definitions, diagnosis and classification (Leonardi M and Ustan TB, 2002; Preux PM and Druet-Cabanc M, 2005). The selection criteria for our meta-analyses and the meta-regression models however suggest that these factors account for an insignificant amount of variation. Rather, age of study participants and sample size are more important causes of the observed heterogeneity. These factors may be further compounded by poor health care, lack of specialized medical personnel and diagnostic equipment. This is particularly evident given that the prevalence estimates for urban areas, with higher concentration of health facilities and specialists, are mid-way between those of rural areas and the developed countries. The higher estimates of LTE prevalence in developing countries are likely to be due to higher incidence of epilepsy (Sander JW and

Shorvon SD, 1996) which could in turn be attributable to infectious aetiology, particularly in rural areas (Matuja et al., 2001; Ogunniyi et al., 1987; Preux PM and Druet-Cabanc M, 2005).

The trend towards a higher prevalence of AE is also apparent in rural areas of developing countries. A much lower prevalence of AE in urban areas that closely approximates estimates from developed countries could be due to better access to health services, diagnosis and management. Rural areas of developing countries have a large burden of untreated epilepsy possibly due to stigma, beliefs and attitudes about causes and consequences of epilepsy and limited access to health services. Further, recall of seizure events over a 5-year period may be poorer in rural areas due to low literacy levels and may lead to underestimation of prevalence (Saha SP et al., 2008).

The proportions of people with AE are higher in developed countries and urban areas of developing countries than in rural areas could also be due to higher mortality in the latter, though few data on epilepsy mortality in developing countries are available and these are not segregated for rural and urban areas (Carpio et al., 2005; Diop et al., 2005). This could imply that people with better controlled seizures live longer on average even though they may continue to experience seizures. We have estimated the prevalence of treatment gap to be 56% (95% CI; 31 – 100%) in developing countries, with higher estimates for rural areas (Mbuba et al., 2008). The better access to healthcare in urban areas of developing countries and in the HIC suggests that not only management of seizures but also management of the less severe life threatening aetiologies improve life-expectancy in PWE.

The higher estimates of heterogeneity observed in rural areas could be due to spatial clustering of risk factors, particularly parasites (Brooker S et al., 2006), associated with development of epilepsy. This observation could be partly due to clustering of genetic risk factors in rural areas, where relatives tend to live in close vicinity.

Small study size (fewer than 20,000 subjects screened) was associated with a higher prevalence of epilepsy possibly because some studies are conducted in communities where the prevalence of epilepsy is suspected to be high. For instance, one was in a small isolated population of Panamanian Indians where apparently a family history of epilepsy was a significant risk factor (risk ratio = 14) (Gracia F et al., 1990).

The prevalence of epilepsy is determined by the rate at which new cases arise and the rate at which existing cases are lost due to death and recovery. The prevalence of LTE increases with age because there is, by definition, no recovery. Thus the older an individual is the more likely they are to have had epilepsy at some point during their lifetime. An association is observed between AE and age because of a low rate of loss of AE cases (due to recovery and death) from the population.

The variables location, age of study participants and study size taken together account for 53% of the variance in prevalence of LTE. Thus much of the variation in study prevalence is attributable to factors not considered in this meta-analysis. For example, variability in the prevalence of genetic or parasitological risk factors or the extent of the treatment gap may be responsible for some of this unexplained variation.

Limitations of the study

The main assumption of estimates of the number of epilepsy cases is that the studies used in the analysis are representative of the populations of both developed and developing countries. However, this is not the case, particularly as there are no data from many parts of the world. The estimates presented in this study therefore need to be interpreted judiciously.

The estimates presented in these analyses are likely to be influenced by different demographic structures, particularly between developed and developing countries. However, it was not possible to derive age-adjusted estimates, mainly because studies presented different age categories, if at all.

Despite the fact that there was no time-limit criterion for inclusion, almost all the selected studies were published after 1990. This was because of the definition criteria of epilepsy used, which was introduced by the ILAE at this time (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). The definition of AE often used in less developed regions is at least two unprovoked seizures one of which should be in the previous 12 months, but this was used in only 3 studies. It would have been interesting to compare the mean prevalence estimate based on this definition from a larger number of studies.

In the meta-regression analysis, the choice of covariates was influenced by the availability of information and therefore heterogeneity could only be explained by factors for which information was available. Ideally future studies should include more appropriate factors, e.g. level of treatment gap, which may influence prevalence.

Conclusions

This study uses a meta-analysis to provide estimates of the burden of epilepsy. We demonstrate substantial heterogeneity in estimates of the prevalence of epilepsy and identify factors responsible for this heterogeneity. This study provides estimates of the burden of AE which can be used as a guide to the number of people who could benefit from treatment.

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Contributors

This study was conceived by AKN, JWAS and CRN. AKN developed the study protocol. Both AKN and CRJCN were involved in extraction of data from the literature. AKN, CB and IM were involved in data analysis. All authors were involved in the preparation of and approved the final manuscript.

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Chapter 3; Incidence of Epilepsy: a systematic review and meta-analysis

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Abstract

Objective: To estimate the pooled incidence of epilepsy from published studies and investigate sources of heterogeneity in the estimates.

Methods: We searched online databases for incidence studies and used meta-analytic methods to analyze the data.

Results: Thirty-three articles met the entry criteria. The median incidence of epilepsy was 50.4/100,000/year (interquartile range (IqR): 33.6-75.6), while it was 45.0 (IqR: 30.3-66.7) for high income countries and 81.7 (IqR: 28.0-239.5) for low and middle income countries. Population-based studies had higher incidence estimates than hospital-based studies (p=0.02) while retrospective study design was associated with lower estimates than prospective studies (p=0.04).

Conclusion: We provide data that could potentially be used to assess the burden and analyze the trends in incidence of epilepsy. Our results support the need for large population-based incidence studies of epilepsy.

Introduction

Epilepsy is one of the most prevalent non-communicable neurological conditions and an important cause of disability and mortality (WHO, 2004). It is estimated to affect almost 70 million people worldwide. The prevalence of epilepsy in Low and Middle Income Countries (LMIC) is more than twice that of High Income Countries (HIC) (Chapter 2). Since mortality is high early in the course of epilepsy and spontaneous remission may occur (Carpio et al., 2005; Diop et al., 2005; Kwan and Sander, 2004; Sander, 1993), prevalence data may significantly underestimate the burden of epilepsy. Thus, incidence of epilepsy, which is not diminished by disease-specific mortality, could be useful in enriching prevalence data in the assessment of the burden of epilepsy.

While many prevalence studies have been reported (Benamer HT and Grosset DG, 2009; Burneo JG et al., 2005; Preux PM and Druet-Cabanc M, 2005) including those presented in chapter 2 of this thesis, there are only a few studies of incidence. Existing studies suggest a higher incidence of epilepsy in LMIC than in HIC, although it is not clear if this difference is real or due to methodological differences (Sander JW, 2003). These estimates are diverse, limiting their utility in informing public health policy and resource allocation for prevention. Reasons for this variability are not clear.

One published review of the incidence of epilepsy did not utilize meta-analytic methods (Kotsopoulos et al., 2002). It did not provide confidence intervals for the aggregate estimates, quantify heterogeneity in incidence rates or identify the reasons for the observed variation.

We conducted a systematic review and meta-analysis of published literature, estimating the median incidence of epilepsy among all the studies as well as within HIC and LMIC separately. We also investigated and quantified the sources of heterogeneity between the studies.

Methods

Data sources and search strategy

We searched all published papers of population studies on the incidence of epilepsy in electronic databases MEDLINE and EMBASE (up to November, 2010), Index Medicus for South East Asia, Index Medicus for Eastern Mediterranean Region, Directorate of Open Access Journals, SCIELO and LILACS. We also searched OpenSIGLE, Proquest and the Wang Fang Database of English and Chinese online journals published in mainland China. In addition, we searched for potentially useful references cited in the key papers and conducted several trial searches to harmonize the final strategy and to increase the sensitivity and specificity of the search. Articles were identified with search terms "epilep*" and "incidence" in all databases and with limits [Humans, Clinical Conference, Journal Article, Multicenter Study, English, French, German, Spanish, Portugese] in MEDLINE and EMBASE (Appendix 3.1). Two authors (AKN & SMK) reviewed the titles and abstracts of articles obtained from on-line searches and reprints of articles eligible for full-text review were obtained. We broke down the review question into search terms/elemental facets to develop a search strategy. This involved using the recommendations of the National Health Service Centre for Reviews and Disseminations (Khan KS et al., 2001).

Inclusion and exclusion criteria

We included all retrospective and prospective population-based studies measuring incidence of epilepsy, and included hospital-based and research database studies if they included a population denominator. We considered studies for inclusion if they included a definition of epilepsy as two or more unprovoked seizures occurring at least 24 hours apart and not acute symptomatic seizures (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). We included studies measuring only cumulative incidence if they provided clear information on duration of follow-up and the numbers at risk at the beginning of the observation period.

We excluded studies if they explored only acute symptomatic seizures or only specific seizure patterns or specific epileptic syndromes. We excluded reviews, editorials, single cases and case series, studies published only as abstracts, letters or commentaries, studies of special groups e.g. incidence of epilepsy in people with a history of head trauma, or if they were part of duplicate populations.

Data extraction

We designed, piloted and revised a standardized data abstraction form to capture all the relevant study-level information required for analysis. AKN and SMK extracted data independently and resolved disagreements by consensus. For included studies, we recorded information on author, year of publication, country, study design, study population (or total person-years of follow-up), duration of follow-up, data collection and ascertainment method (medical records or

questionnaires [with physical examination] in population-based studies), age of subjects, number of people with incident epilepsy and whether the outcome was a crude or an adjusted estimate.

Analysis

We tabulated crude incidence estimates expressed per 100,000 persons per year in summary tables along with their 95% confidence intervals (CI), and we classified studies as coming from HIC or LMIC (The World Bank: 2006). To estimate pooled median incidence rates and assess for heterogeneity, we fitted random effects models to log-transformed observed incidence in STATA v 11 (Stata corp, TX, USA). We obtained estimates of the median incidence, and 25th and 75th percentile of the distribution of true incidence by back-transforming the log estimates to the original incidence scale.

We used the Cochrane χ^2 test to examine the null hypothesis that the observed heterogeneity was random (Higgins JP and Thompson SG, 2002) and calculated the degree of heterogeneity using the statistic $I^2 = ((Q - df)/Q) \times 100\%$, where Q is the Cochrane chi-squared statistic and df is the degrees of freedom (Higgins JP and Thompson SG, 2002; Higgins JP et al., 2003).

To determine the influence of the study-level factors on the observed variability, we used random-effects meta-regression. We estimated the proportion of heterogeneity attributable to each covariate by comparing the between studies component of variance in the null model ($\tau 0^2$) with the estimate of τ^2 for the model with the covariate of interest $((\tau 0^2 - \tau^2)/ \tau 0^2)$.

In these analyses, we investigated only the influence of standardized study-level covariates on the variability of the observed incidence estimates for all studies and for those conducted in HIC.

The small number of studies (n=9) from LMIC would not allow meaningful examination of the influence of these factors for these countries. We performed our analyses on observed crude incidence estimates only, primarily because there were very few studies that reported adjusted estimates only (n=4).

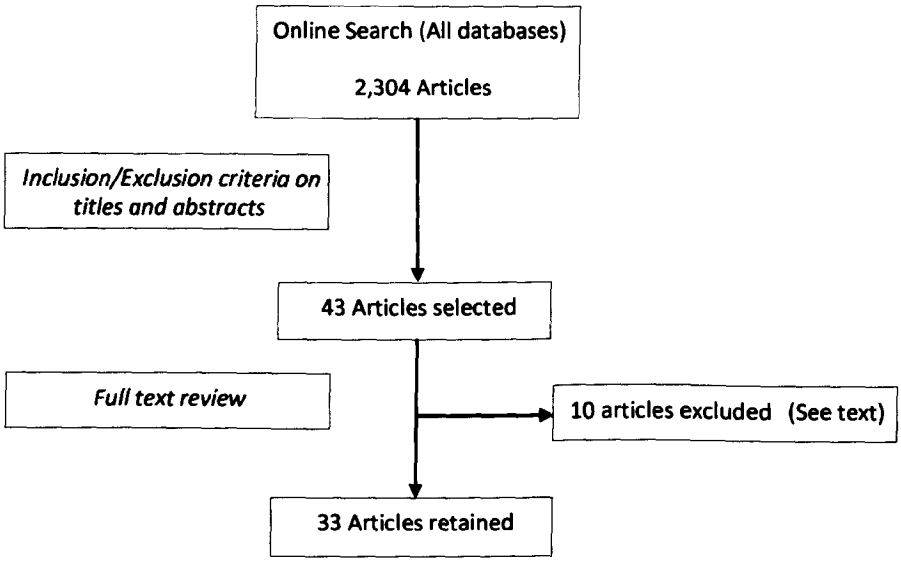
A total of seven study-level covariates were investigated for their influence on incidence estimates for HIC and all countries (HIC and LMIC combined) (Appendix 3.2). We performed both univariate and multivariable meta-regression. Variables that showed evidence of an association at the significance level $p \leq 0.25$ in the univariate analysis were further investigated using multivariable models. Due to the small number of studies (n=33) relative to the number of covariates (n=7) (and following standard recommendations for model size relative to sample size (Altman D, 1991; Robins JM and Greenland S, 1986)), we included only level of development in each multivariable model in addition to the covariate of interest.

Results

Search results

The initial search identified 2,304 articles, of which 43 were retained for full text review after examination of titles and abstracts. The search criteria and the total numbers of articles identified in these steps are shown in Figure 3.1. After full text review, we excluded ten studies: addressed seizures rather than epilepsy (n=1); only age-specific estimates provided (n=1); no definition of epilepsy and/or no denominator data (n=4); duplication (n=1); inappropriate definition of epilepsy (n=1); review (n=1); and no numerator provided (n=1).

Figure 3.1: Search results



Of 33 studies retained, 19 had a prospective and 14 had a retrospective cohort design. In all, 24 studies were from HIC while only 9 were from LMIC. Twelve studies were in children only while 21 were either in adults or all age groups. More than half of the studies (19/33) used solely medical records to identify incident cases in retrospective cohorts and 25/33 had population sizes above 20,000 people. Almost half (15/33) of the studies had follow-up of less than 3 years. All except one Spanish study (Dura et al., 2007) were published in English.

Half (12/24) of the studies from HIC were pediatric studies and the other half included all age groups, whereas in LMIC all studies were in all age groups. Further, 18/24 of the studies from HIC used medical records to ascertain cases while 7/9 from LMIC identified cases using questionnaires with some form of clinical examination in population-based studies. More than

half (5/9) of the studies in LMIC followed cohorts of fewer than 20,000 subjects, and the majority of these (8/9) for less than 5 years. In contrast, 21/24 of the studies in HIC used cohorts of more than 20,000 individuals with 10/21 followed for more than 5 years. (See Appendix 3.3 for details).

Estimates of incidence and heterogeneity among studies

The estimated median incidence of epilepsy for all studies combined was 50.4/100,000 persons/year (interquartile range: 33.6-75.6). The LMIC median incidence rate of 81.7 (28.0-239.5) was higher and the interquartile range was greater than for HIC (45.0 (30.3-66.7)/100,000 persons/year). Most of the variability in the estimates was attributable to unexplained between-study heterogeneity for both HIC (I^2 = 98.5%) and LMIC (I^2 =98.2%).

Sources of heterogeneity of incidence estimates

In the univariate analysis of studies from HIC, age of study participants had a small association with incidence estimates (with pediatric studies associated with slightly higher incidence estimates than studies with both adults and children), accounting for 2.3% of the observed heterogeneity (Table 3.1). Studies with retrospective design were associated with lower incidence estimates, although this was marginal.

Table 3.1: Meta-regression of incidence of epilepsy from HIC, univariate analyses.

Covariate	Categories (1st listed is reference)	No. studies	Rate Ratio (95% CI)	P value	Heterogeneity (τ^2)	Percent Heterogeneity
Null model	-	24	-	-	0.078	-
Age	All	12	1.0	0.18	0.076	2.3
	Children	12	1.2 (0.9 – 1.5)			
Data collection	Records	18	1.0			
	Records & questionnaires	6	1.0 (0.7 – 1.4)	0.86	0.082	Nil
Population size	>100,000	3	1.0			
	20,000-100,000	10	1.0 (0.8 – 1.4)	0.94	0.086	Nil
	<20,000	11	1.0 (0.7 – 1.6)			
Duration (years)	>10	3	1.0			
	5-10	7	0.9 (0.5 – 1.6)	0.36	0.076	2.7
	3-5	3	1.2 (0.8 – 1.9)			
	<3	11	1.3 (0.8 – 2.0)			
Decade	1980	5	1.0			
	1990	9	1.0 (0.7 – 1.4)	0.77	0.083	Nil
	2000	10	1.1 (0.8 – 1.6)			
Study Design	Prospective	13	1.0			
	Retrospective	11	0.9 (0.7 – 1.1)	0.20	0.076	3.3

Univariate analysis of the combined data showed that the level of income in the country was associated with variability of incidence estimates, accounting for 29.6% of the heterogeneity. Studies from LMIC had higher incidence estimates (RR = 1.8) than HIC (Table 3.2). Three other variables also influenced the incidence estimates (Table 3.2): study size (accounting for 14.9% of the observed heterogeneity), method of case identification (48.0%) and study design (10.7%). Studies using screening questionnaires to identify incident cases in population-based studies were associated with higher incidence estimates as were studies with sample sizes ≤ 20,000. Retrospective study designs had lower incidence than prospective designs (Table 3.2).

Table 3.2: Meta-regression of incidence of epilepsy from all countries, univariate analyses (n = 33).

Covariate	Categories (1st listed is reference)	No. studies	Rate Ratio (95% CI)	P value	Heterogeneity (τ^2)	Percent Heterogeneity
Null model	-	33	-	-	0.190	-
Development	HIC	24	1.0			
	LMIC	9	1.8 (1.3 – 2.5)	<0.001	0.134	29.6
Age	All	21	1.0	0.61	0.196	Nil
	Children	12	0.9 (0.7 – 1.3)			
Data collection	Records	19	1.0			
	Questionnaires	7	2.3 (1.7 – 3.2)	<0.001	0.099	48.0
	Records & questionnaires	7	0.9 (0.7 – 1.3)			
Population size	>100,000	11	1.0			
	20,000-100,000	14	1.1 (0.8 – 1.6)	0.02	0.162	14.9
	<20,000	8	1.8 (1.2 – 2.7)			
Duration (years)	>10	3	1.0			
	5-10	8	1.4 (0.7 – 2.7)	0.43	0.200	Nil
	3-5	7	1.7 (0.9 – 3.4)			
	<3	15	1.3 (0.7 – 2.5)			
Decade	1980	6	1.0			
	1990	14	1.4 (0.9 – 2.2)	0.3	0.189	0.5
	2000	13	1.3 (0.8 – 2.1)			
Study Design	Prospective	19	0			
	Retrospective	14	0.7 (0.6 – 0.9)	0.04	0.170	10.7

In the multivariable analysis of the combined data (Table 3.3), studies using only screening questionnaires to identify cases were associated with higher estimates (RR=2.8) and the method of data collection explained 24.7% of the observed heterogeneity (after adjusting for level of development). Study design was also associated with variability of the incidence rates, with retrospective cohort studies reporting lower estimates than prospective studies (RR=0.8) and this accounted for 9% of the heterogeneity.

Table 3.3: Meta-regression of incidence of epilepsy from all countries, multivariable analyses: reported rate ratios are adjusted for level of development (n = 33).

Covariate	Categories (1st listed is reference)	No. studies	Rate Ratio (95% CI)	P value	Heterogeneity (τ^2)	Percent Heterogeneity
Development	HIC	24	1.0			
	LMIC	9	1.8 (1.3 – 2.5)	<0.001	0.134	-
Data collection	Records	19	1.0			
	Questionnaires	7	2.8 (1.5 – 5.3)	0.003	0.101	24.7
	Records & questionnaires	7	1.0 (0.7 – 1.3)			
Population size	>100,000	11	1.0			
	20,000-100,000	14	1.0 (0.7 – 1.4)	0.28	0.134	Nil
	<20,000	8	1.3 (0.9 – 2.1)			
Study Design	Prospective	19	1.0			
	Retrospective	14	0.8 (0.7 – 1.0)	0.05	0.122	8.9

Discussion

Our estimates suggest that the incidence of epilepsy in LMIC is approximately twice that of HIC. A similar finding was made in a previous review, although heterogeneity was not examined[11]. The cause of the higher incidence in resource poor compared to industrialized countries is likely to be multi-factorial. The higher incidence of head trauma and of infections and infestations of the central nervous system such as malaria, neurocysticercosis and invasive bacterial infections may be important causes (Carter JA, 2004; Matuja et al., 2001; Newell et al., 1997; Nicoletti et al., 2002; Nicoletti et al., 2007; Nsengiyumva et al., 2003; Ogunniyi et al., 1987; Preux PM and Druet-Cabanc M, 2005). Several studies have demonstrated important linkages between ion channel polymorphisms and development of seizures (Berkovic SF and Scheffer IE, 2001; Chioza B et al., 2002; ILAE, 2002; Sander T, 2000; Wallace RH et al., 2002), although it is not clear whether there are any differences in these polymorphisms between LMIC and HIC. Further

studies in Africa (Goudsmit J and van der Waals FW, 1983; Jilek-Aall L et al., 1979; Jilek WG and Jilek-Aall LM, 1970; Neuman RJ et al., 1995; Versteeg AC et al., 2003) have demonstrated familial clustering of epilepsy, suggesting that genetic factors could also play an important role in the high incidence of epilepsy. Some studies from LMIC may include people with acute symptomatic seizures in their measurements, thus raising incidence estimates.

There is conflicting evidence regarding the role of socioeconomic deprivation in the development of epilepsy in the HIC where some studies have reported a positive association with level of deprivation while others found no association (Heaney et al., 2002; Hesdorffer et al., 2005; Reading et al., 2006). One study in LMIC (Birbeck et al., 2007) found that people with epilepsy were of lower socio-economic status than people with non-stigmatized medical conditions although the direction of causality in this association was unclear. The difference in incidence could also be accounted for by methodological differences (Sander JW, 2003), although this is less likely (Chapter 2).

The measures of heterogeneity (I^2) for both pooled estimates were above 50%, suggesting that the observed differences were due to between study variability rather than sampling variation (Higgins JP and Thompson SG, 2002; Higgins JP et al., 2003). The tendency towards larger heterogeneity of incidence estimates reflects what was observed in a review of prevalence (Chapter 2). This was documented despite using a standardized selection criteria for our analysis that was based on definitions of epilepsy used and study methodologies. In addition to the study-level covariates that we have investigated, we hypothesize that the observed heterogeneity could,

in part, be attributed to unmeasured factors such as between region differences in epilepsy risk factors, as well as levels and quality of health service provision.

In the univariate analysis of the effect of study-level factors, age of study subjects and retrospective design explained a modest amount of variability in the incidence rates in HIC. The paediatric studies were associated with higher incidence estimates than those involving all age groups. This observation perhaps mirrors the risk factor profiles for these age groups, in which higher incidence in children has been attributed mainly to antenatal, perinatal and postnatal insults and CNS infections, causing cerebral palsy and intellectual disability (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993), which could be prevented. In the combined analysis of data from both HIC and LMIC, the method used to identify incident cases, age of participants and duration of follow-up appeared to explain significant proportions of the observed heterogeneity. Use of screening questionnaires to identify cases in population-based studies was associated with higher estimates than studies using medical records in hospital-based studies. In resource-poor settings with scanty allocation of health care resources and few specialists coupled with poor access to services (WHO/IBE/ILAE, 2005), lack of knowledge and stigma associated with epilepsy (Baskind and Birbeck, 2005; Birbeck and Kalichi, 2003; El Sharkawy et al., 2006; Nubukpo et al., 2004), medical records are unavailable or unreliable and may underestimate the incidence. It is also possible that only people with very severe epilepsy in both HIC and LMIC present to hospital, leading to underestimation of incidence rates in hospital-based studies. Therefore, population-based studies, particularly in LMIC, should be encouraged to ensure valid estimates of incidence of epilepsy.

With regard to the observed association between small sample size (n≤20,000) and high incidence rates, a plausible explanation is that small studies are more likely to be conducted in areas with a higher risk of epilepsy such as a study in Uganda in an area with high prevalence of onchocerciasis, which is a putative risk factor for epilepsy (Kaiser C et al., 1998 May) and others conducted in areas with high prevalence of cysticercosis (Villaran et al., 2009).

Results from multivariable analyses of all studies indicate that level of development, method of incident case identification and study design accounted for moderate proportions of the observed heterogeneity. Retrospective studies were associated with lower incidence estimates, most likely due to incomplete incident case identification in hospital-based records used in these study designs. Factors such as differences in prevalence and distribution of risk factors and patient characteristics could be responsible for most of the unexplained heterogeneity.

Limitations of the study

A major limitation of this study was the relatively small number of studies, particularly from LMIC. This led to wide confidence intervals for the pooled estimates and low power to detect associations between study-level covariates and the incidence estimates, even in the combined data from both HIC and LMIC.

Another limitation was that it was not possible to use narrower age categories since studies provided either overall estimates or age-specific estimates with different age categories. We therefore grouped studies broadly into those that included children only or studies of entire populations. In the regression models, the choice of covariates was limited to the information

provided by the included studies. These covariates were able to explain only a limited amount of the observed study heterogeneity. The residual study heterogeneity is attributable to unmeasured factors such as the prevalence of epilepsy risk factors in the study populations.

Conclusion

We estimated the median incidence of epilepsy as almost twice as high in LMIC as in HIC. There was significant heterogeneity between study estimates but we could identify only a few factors that accounted for a small proportion of this heterogeneity in the studies. The small number of studies with wide variation limits their utility in informing public health policy and allocation of resources for prevention. These results provide baseline information that can be used to monitor future trends in the incidence of epilepsy, particularly in LMIC as they undergo epidemiological transition.

The meta-regression analysis found that region of study (HIC vs. LMIC), field-based questionnaire studies and retrospective study design were associated with heterogeneity of the observed estimates. These findings suggest the need to standardize data collection in future incidence studies to help target interventions to prevent epilepsy.

Our analysis also suggests the need for large population-based incidence studies of epilepsy, particularly in LMIC, to generate more accurate estimates as well as provide a reasonably robust assessment of heterogeneity.

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Contributors

This study was conceived by AKN, JWS and CRN. Both AKN and SMK were involved in literature search and extraction of data. AKN analyzed the data with inputs from CB and IK. AKN wrote the first draft. All authors reviewed all drafts and approved the final submitted manuscript.

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Chapter 4: The validation of a three-stage survey methodology for detecting active convulsive epilepsy in rural Kenya.

NGUGI, A.K., BOTTOMLEY, C., CHENGO, E., KOMBE, M., KAZUNGU, M., BAUNI, E., MBUBA, C.K., KLEINSCHMIDT, I., NEWTON, C.R. (2012). The validation of a three-stage survey methodology for detecting active convulsive epilepsy in rural Kenya. (Prepared for submission to *International Journal of Epidemiology*)

Abstract

Background: There are few studies on the epidemiology of epilepsy in large populations in Low and Middle Income Countries (LMIC). Most studies conducted in these regions use of two-stage population-based screening surveys, but these surveys are time-consuming and costly to implement in large populations required to generate accurate estimates. We examined the sensitivity and specificity of a three-stage cross-sectional screening methodology in detecting active-convulsive epilepsy (ACE), which can be used in large populations in demographic surveillance systems.

Methods: We conducted a population-based validation of the three-stage cross-sectional screening methodology on a randomly selected sample of participants of a three-stage prevalence survey of epilepsy. Diagnosis of ACE by an experienced clinician was used as a 'gold standard'. We further compared the expenditure of this method with the standard two-stage methodology.

Results: We screened 4442 subjects in the validation survey and identified 35 cases of ACE. Of these, 18 were identified as false negatives, most of which (15/18) were missed in the first stage and a few (3/18) in the second stage of the three-stage screening. Overall, this methodology had a sensitivity of 48.6% and a specificity of 100% and was 60% cheaper than a clinician-conducted two-stage survey.

Conclusion: This was the first study to evaluate the performance a multi-stage screening methodology used to detect epilepsy in demographic surveillance sites. Overall, this method had

poor sensitivity, which we attributed mainly to non-response in the first stage. Use of this method needs to take into consideration the poor sensitivity of the first stage and the savings in expenditure and time as well as validation in target populations.

Introduction

Epidemiological studies of rare conditions are difficult and costly to conduct, particularly in Low and Middle Income Countries (LMIC) where majority of the population do not use the health care facilities and medical records and diagnostic facilities are poor (Alam et al., 2010; Bhatia and Cleland, 2001; D'Ambruoso et al., 2010; Mbagaya et al., 2005; Mesfin et al., 2009; Olusanya et al., 2010; Rahman et al., 1998; Shaikh and Hatcher, 2005; Shaikh and Hatcher, 2007). This problem is common for many neurological (including epilepsy) and psychiatric conditions as there are no simple diagnostic tests (e.g. blood measurements), and the diagnosis depends upon history and assessment by experienced specialists. There are relatively few specialists in LMIC and they are expensive to employ for epidemiological surveys (Mung'ala-Odera and Newton, 2007; WHO/IBE/ILAE, 2005).

Studies of neurological and psychiatric conditions are often conducted on high-risk populations e.g. those with high prevalence of putative risk factors (Kaiser C et al., 1998 May; Medina MT et al., 2003; Villaran et al., 2009), leading to high estimates of prevalence that are not representative of wider populations, or in which there still may not be adequate numbers of cases to identify clinically meaningful risk factors in case controls studies (Ruckinger and Boneberger, 2008). Thus, for such conditions, there is need to survey more representative populations or conduct censuses to provide robust estimates of prevalence and incidence using methods that maximise detection of cases with least cost and effort (Ruckinger and Boneberger, 2008). Furthermore, large studies improve the precision of the estimates.

Epilepsy is a common non-communicable neurological condition and a significant cause of disability and mortality (WHO, 2004). It is estimated to affect nearly 70 million people worldwide, 90% of who live in LMIC (Chapter 2). While a large number of studies to determine the prevalence of epilepsy in LMIC have been conducted, these data have yielded a wide range of estimates (Chapter 2), and it is not clear if this is caused by different methods and tools used in the studies, many of which have not been validated in the target populations (Leonardi M and Ustan TB, 2002; Sander JW, 2003; Sander JW and Shorvon SD, 1996).

In High Income Countries (HIC), researchers utilize medical and service records to provide data on epidemiology of epilepsy. In LMIC, single round surveys and key informants have been used, but these methods under-report cases (Kaamugisha J and Feksi AT, 1988). Two-stage surveys in which the population is initially screened with a questionnaire and the diagnoses confirmed by detailed clinical history and neurological assessment have been recommended for detecting convulsive seizures and epilepsies (Placencia M et al., 1992a) and were used in several studies (Borges et al., 2004; Haerer et al., 1987; Melcon et al., 2007; Meneghini et al., 1992; Nicoletti A, 1999 Dec 10; Noronha et al., 2007; Osuntokun et al., 1987; Placencia M et al., 1992b; Schoenberg, 1987). However, these methods are costly to implement in large populations since the first stage often takes considerable time and the second stage requires the use of qualified medical personnel who often have to assess a large number of false positives.

To address these issues in epidemiological studies of epilepsy, we have used a three-stage methodology to survey large populations within Health and Demographic Surveillance Systems (HDSS) (Edwards T et al., 2008), which are part of the INDEPTH network (http://www.indepth-

network.org/). Within the HDSS set-up, censuses are conducted 1-3 times a year, in which non-medical field personnel conduct re-enumeration and vital status registration by interviewing a senior member of the household (usually the house-hold head). The field personnel usually have 3-6 months in which to cover the entire HDSS population. Thus, the epilepsy screen (first stage) needed to be embedded within an on-going census in order to be administered to the entire population using least cost and effort. The first stage of the survey is a general population screen using a simple tool which is intended to have high sensitivity to detect people with a history of convulsions. Those that are positive are then surveyed with a more specific tool to determine possibility of epilepsy. Cases that are likely to have epilepsy in the second stage are then invited for a clinical assessment for confirmation of epilepsy in the third stage. This method is an extension of the two-round surveys in which screening questions were introduced as the first stage of the study and can easily be implemented within on-going census in the HDSS. This stage has symptom-based questions which are designed to maximize sensitivity and be easily administered by non-medical personnel. The second stage is designed to be more specific, thus reducing the number of false positive cases that have to be assessed in the more expensive and logistically difficult third stage. The three-stage method allows rapid and efficient screening of large populations while simplifying the logistics and reducing costs. However, the sensitivity and specificity of this methodology have not been established.

In this paper, we describe a study to assess the sensitivity and specificity of the three-stage method in detecting active convulsive epilepsy (ACE) and compare the expenditure of conducting the two-stage and the three-stage population-based epilepsy surveys.

Methods

The study setting and study population

The study was conducted in Kilifi district of the Coast province of Kenya. It consists of both rural and peri-urban communities. The study area is within a HDSS that covers 15 administrative locations with 40 sub-locations sub-divided into 186 enumeration zones. This subdivision allows study subjects to be easily located using digital maps of homesteads. The demographic surveillance and vital registration is performed 2-3 times a year and covers an area of densely inhabited coastal strip, 40 km in length, and extends about 15 km in the interior, with an area of 891 sq.kms, which is about 18% of the total area of Kilifi District (4840 sq.kms). There were 233,881 residents and 25,526 homesteads in 2008 (Scott JA et al., 2011). The residents are mainly Mijikenda, a Bantu grouping of nine tribes with Girima (45%), Chonyi (33%) and Kauma (11%) being most common. About 55% of the population is considered absolutely poor, per capita income is about USD 10 per month. The majority (80%) are subsistence farmers, which is limited by the low productivity of the land (only 19% of the total land is arable). Literacy levels are low, since only 45% of people can read and write.

Kenya Medical Research Institute (KEMRI) has been running the HDSS in Kilifi District since year 2000. The entire study area has been mapped using global positioning system (GPS) receivers and digital maps derived from these data are used to locate homesteads and follow-up study subjects. The study population consisted of a random sample of 5,796 persons selected from the 16th round of re-enumeration within the HDSS in 2008.

Description of the three-stage cross-sectional survey method (prevalence survey)

Stage 1 (SI): the general population screen

The first stage of the survey is a general population screen using a simple tool, consisting of two questions to detect convulsions. These questions were piloted to maximise their sensitivity to detect individuals with the main symptoms (i.e. convulsions) of convulsive epilepsy. The aim of this stage is to screen large populations rapidly and efficiently, by the HDSS census field staff in their routine re-enumeration and vital registration. The field staffs conduct a door-to-door survey interviewing the head or senior member of each household or an individual who can provide information about each member of their household. It is important that the tool used during this stage is as sensitive as possible to detect all the possible individuals with the disorder even if this entails lower specificity for the first stage. The tool used in this stage of the epilepsy survey is shown in Appendix 4.1.

Stage 2 (SII): the condition-specific screen

In this stage, respondents identified with a positive history of convulsions in SI are followed-up by different interviewers who have more extensive training in epilepsy and more time to identify possible cases. The aim of this stage is to screen those with positive responses in SI, with a more specific tool for the detection of possible ACE so as to minimize the number of false positives by using a tool with higher specificity in order to reduce the cost of diagnosis in the subsequent stage. At the same time it is important that no true cases are lost at this stage (Appendix 4.2).

Stage 3 (SIII): Confirmation of diagnosis

The respondents identified as potential cases of ACE in SII of the survey are invited for assessments and tests by clinicians to confirm the diagnosis. In the epilepsy survey, the diagnosis of ACE consists of taking clinical history by an experienced clinician. ACE was defined as at least two unprovoked convulsions (tonic and/or clonic seizures), of which one occurred in the preceding 12 months (Edwards T et al., 2008; Meinardi et al., 2001).

The three-stage method identified an individual as a case of ACE if they were positive in all the three stages of the prevalence survey.

Assessment of the three-stage methodology using a survey conducted by clinicians (Clinical Survey)

Sampling and follow-up in the Clinical survey

A random sample for the validation of the three-stage survey methodology was selected from the 2008 Kilifi HDSS database. It was calculated that a sample size of 5,796 would be required to estimate the sensitivity of the three-stage method (assumed to be 85%) with a precision of 13% (i.e., half the width of the 95% Confidence Interval (95%CI)) (Burderer NMF, 1996) in a population with a prevalence of 5/1,000 (Edwards T et al., 2008). This sample was interviewed in the three stages of the prevalence survey conducted in 2008. To validate the prevalence survey methodology, everyone in the random sample had the SII questions administered by non-medical fieldworkers, as well as being interviewed by clinicians who received special training in epilepsy and followed the proforma administered in the SIII of the prevalence survey (Clinical Survey or the "gold standard"). The Clinical survey took place after the three-stage prevalence survey

during the period May 2009 to April 2011. Incident cases - those that were negative on the prevalence survey and positive in the Clinical Survey but who developed ACE after the three-stage prevalence survey - were treated as true negatives since they were negative at the time of the prevalence survey. SIII was conducted twice on those that were positive in SII of the prevalence survey (i.e. within the prevalence survey and the validation/clinical survey – because SIII was the clinical survey/"gold" standard) and subjects were classified positive for ACE if they were positive in either of the two SIII assessments.

Analysis

Estimation of Sensitivity

Sensitivities were estimated as: $TP/(TP+FN)$, where TP = True Positive (i.e., positive on prevalence survey and Clinical Survey) and FN = False Negative (i.e., negative on prevalence survey but positive on Clinical Survey). The sensitivities of SI (single stage) and (SI & SII) (two-stage) and the (SI & SII & SIII) (three-stage) methods were evaluated against the Clinical Survey. For example, the sensitivity of the three-stage method was the proportion of individuals who were positive (SI+, SII+, SIII+) in the prevalence survey among those identified as cases of ACE in the Clinical Survey.

Estimation of Specificity

Specificity was estimated as: $TN/(TN+FP)$, where TN = True Negative (i.e., those negative in both the prevalence and Clinical Surveys) and FP = False positive (positive in the prevalence survey but negative in the Clinical Survey). The specificities of single, two and three-stage methods were estimated. For the three stage method the specificity is 100% since there are no false positives because SIII of the prevalence survey is the Clinical Survey. For the single and

two stage methods the specificity may be less than 100%. In addition we estimated the proportion of false positives (1-specificity) and false negatives (1-sensitivity).

Expenditure comparison study

We compared the financial expenditure of conducting a two-stage survey (in which SII is conducted on those that are SI positive by experienced clinicians in the field) and the current three-stage epilepsy survey. Our analyses were based on the SI and SII positive rates and the marginal expenditure incurred in the Kilifi HDSS three-stage survey of 2008 (Tables 2(a) and (b)). In both situations, we assumed that the first stage (SI) would not incur any expenditure since it is nested within on-going re-enumeration in the HDSS study area. For the two-stage survey, we assumed that SII was the definitive stage since it is conducted by clinicians using the clinical history tool used in SIII of the three-stage survey.

All analyses were performed in STATA version 11 (StataCorp, College Station, TX, USA).

Ethical considerations

Written informed consent was obtained from all study participants. Approval for the study was obtained from the Kenya Medical Research Institute/ National Ethical Review Committee.

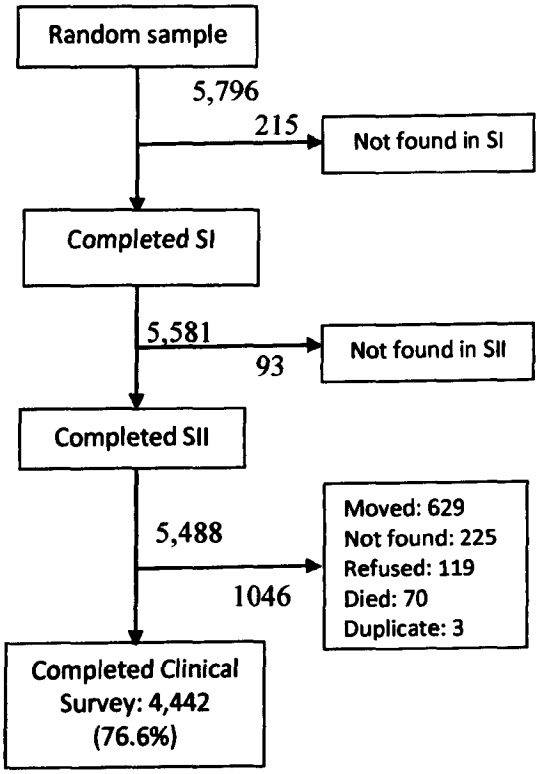
Results

Flow of participants in the Clinical Survey

The Clinical Survey targeted a sample of 5,488 participants who completed both SI and SII of the prevalence survey. Of these, 1,046 (19.1%) were lost to follow-up during the Clinical

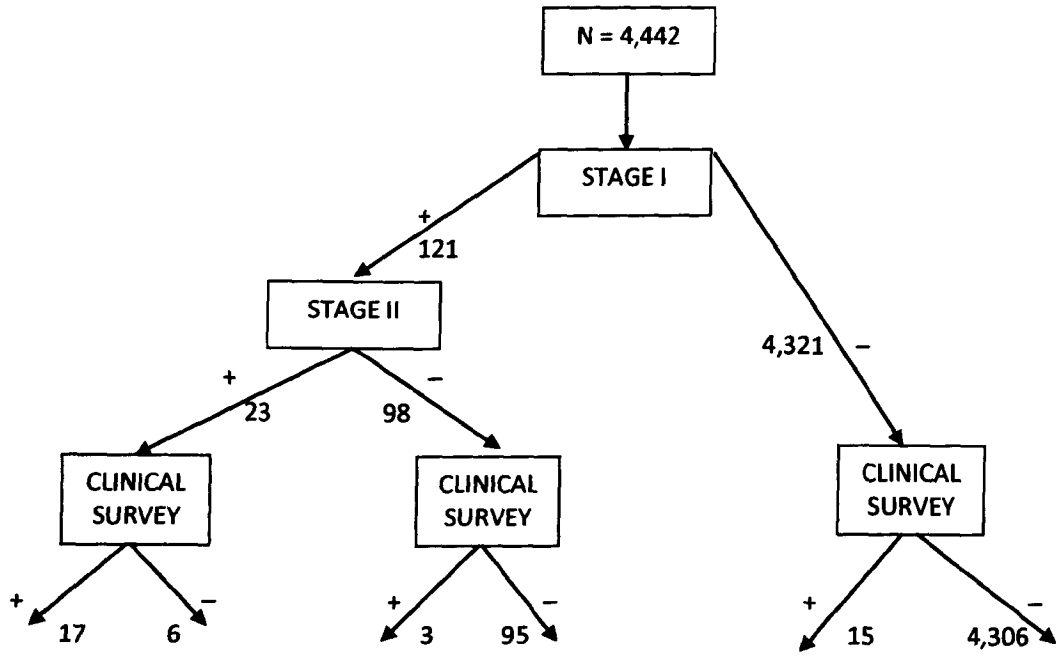
Survey: 629 (60.1%) had moved, 225 (21.5%) could not be traced, 119 (11.4%) refused consent and 70 (6.7%) had died, while 3 (0.3%) were found to have been duplicate records (Figure 4. 1).

Figure 4.1: Flow of subjects in the Clinical Survey



Of 4,442 subjects screened in the Clinical Survey, 18 ACE cases were identified when the Clinical Survey was applied to all the individuals who were negative in the prevalence survey i.e. the 4,321 (SI-) and 98 (SI+, SII-) (Figure 4.2).

Figure 4.2: Response status of subjects within the prevalence and Clinical Surveys



On examination of the reasons for the 18 false negative subjects, 15 were negative in SI (i.e. reported no history of convulsions), but the Clinical Survey documented that the subjects had convulsions that had occurred before the prevalence survey and therefore should have been identified as potential cases. The remaining 3 were positive in SI but were all classified as febrile convulsions in SII.

Sensitivity and Specificity

Sensitivity decreased, with an increase in the number of stages in the survey while specificity increased with the number of stages. The three-stage method (SI & SII &SIII) had a sensitivity of 48.6 % (i.e. 17/35) but with a specificity of 100.0 % (Table 4.1). At 57.1%, sensitivity was

highest for the one-stage (SI) screening method which also had the lowest specificity (97.7 %). Sensitivity and specificity of the various stages of the three-stage cross-sectional methodology are displayed in Table 4.1.

Table 4.1: Estimation of the sensitivity and specificity of the single- and multi-stage survey methodologies using the Clinical Survey as gold standard

Method	Sensitivity (%)	95% CI	Specificity (%)	95% CI	TP	FN	FP	TN
One-stage (SI)	57.1	39.4 – 73.7	97.7	97.2– 98.1	20	15	101	4306
Two-stage (SI & SII)	51.4	32.4 – 67.6	99.9	99.7 – 100.0	18	17	6	4401
Three-stage (SI & SII & SIII)	48.6	31.4 – 66.0	100.0	99.9 – 100.0	† 17	18	† 0	4407

TP=true positive; FP=false positive; FN=false negative; TN=true negative
†TP and FP are derived from 2nd SIII/Clinical Survey on those that were SII+ (i.e. SIII was done twice on the SII+ participants).

Expenditure comparison study

From the proportion of respondents who were positive in SI (2.2%), we estimated that we would require to follow-up 6183 people in SII of the study. In the three-stage method (in which SII is conducted by lay field personnel), this would take 29.4 months to complete at a cost of USD 109,120 (Table 4.2a). In the two-stage method (in which SII is conducted by clinicians), screening the 6183 people positive in SI would take 42.1 months and cost USD 171,922, which is 1.6 times more expensive than the three-stage method (Table 4.2b).

Table 4.2(a): Estimates of the expenditure of the three-stage survey conducted by lay field personnel

Stage II field work					
SI +ve rate (%)	2.2				
SI Population	233,881				
		Duration†		**Expenditure**	
	Follow-up	**FW days**	**FW months**	**Salary (Ksh)**	**Salary (USD)**
No of SI cases	5152.4	515.2	24.5	613,380.80	7667.3
20% Follow-up*	1030.5	103	4.9	122,676.20	1533.5
Sub-total 1	6182.9	618.3	29.4	736,056.90	9200.7
Stage II transport costs					
	Follow-up	**Duration FW days**	**FW months**	**Costs Cost (Ksh)**	**Cost (USD)**
No cases followed up	6182.9	618.3	29.4	7,419,453.70	92,743.20
Sub-total 2		618.3	29.4	7,419,453.70	92,743.20
Stage II cost				8,155,510.70	101,934.90
Stage III					
SII +ve rate (%)	21.8				
No of SII cases	1125.1				
	No screened	**Duration† Clinic days**	**Clinic months**	**Costs Salary (Ksh)**	**Salary (USD)**
No of SII +ve cases	1125.1	160.7	7.7	574,019.20	7175.2
No screened in SII	1125.1	160.7	7.7	574,019.40	7175.2
Total Expenditure				**8,729,529.90**	**109,119.10**

*Assume that at least 20% of the SI positive cases will be followed up in the field at least twice.
† Both SII and SIII run concurrently therefore the total duration is 29.4 months.

Table 4.2(b): Estimates of the expenditure of the two-stage survey conducted by clinicians

Stage II field work					
SI +ve rate (%)	2.2				
SI Population	233,881				
	Follow-up	**Duration FW days**	**FW months**	**Expenditure Salary (Ksh)**	**Salary (USD)**
No of SI cases	5152.4	736.1	35.1	2,628,774.70	32,859.70
20% Follow-up*	1030.5	147.2	7	525,754.90	6571.9
Sub-total 1	6182.9	883.3	42.1	3,154,529.70	39,431.60
Stage II transport costs	**Follow-up**	**Duration FW days**	**FW months**	**Costs Cost (Ksh)**	**Cost (USD)**
No cases followed up	6182.9	883.3	42.1	10,599,219.60	132,490.20
Sub-total 2		883.3	42.1	10,599,219.60	132,490.20
Total Expenditure				**13,753,749.30**	**171,921.90**

*Assume that at least 20% of the SI positive cases will be followed up in the field at least twice.

Notes for Tables 4.2 (a & b):

1) One field worker interviews 10 participants per day on average
2) One working month = 21 working days
3) A fieldworker's salary is Ksh 25,000 per month
4) The study clinician interviews/assesses 7 participants per day
5) A clinician's salary is Ksh 75,000 per month
6) 1 USD = 80 Ksh
7) FW = Field work
8) Transport costs:
   a) Distance/day: estimated at 200km
   b) Cost per = Ksh 60/km (vehicle)

Discussion

The three stage method had a low sensitivity of 48.6%. The savings in expenditure and time compared to the two-stage method have to be weighed up against its poor sensitivity. Sensitivities were slightly higher for the one-stage (57.1%) and two-stage (51.4%) methods. Specificities were marginally lower in single-stage (97.7%) compared to the three-stage method (100%). For this method to be recommended more generally, it will be essential to improve sensitivity of the questions in stage I.

In this study, we examined the entire three-stage system for detecting ACE (in the prevalence survey, a subject was classified as a case if they were positive in all the three stages). Other studies have only validated hospital-based survey methods (Carpio et al., 2006; Melcon et al., 2007; Meneghini et al., 1992) or the validity of a screening tool (within a three-stage method) in detecting epileptic seizures, but not epilepsy (Placencia M et al., 1992a). Generalization of validation parameters obtained from hospital-based studies is limited by selection bias (due to overrepresentation of cases with more severe forms of epilepsy), people who recognise that they have epilepsy and seek treatment, sample size and the fact that it is carried out in a setting that may not represent the situation in the field. This yields less accurate (often inflated) estimates of sensitivity than validation of population-based methods as described by Placencia (Placencia M et al., 1992a). The validation of population-based methods is applied directly to a wider population hence the findings are more generalizable, although this is usually costly. Furthermore, when compared to population-based studies, the validity of hospital-based studies may not be diminished by stigma-related concealment of seizures.

The precision of the validation depends upon the size of the sample. The sample size for our study was statistically determined and was larger than all other validation studies (Carpio et al., 2006; Meneghini et al., 1992; Ottman et al., 2010).

SI of the prevalence survey had the highest false positivity; this is because the SI questions targeted all convulsions (including febrile convulsions). SI as a general population screen is however necessary in order to detect all convulsions to avoid underestimating prevalence of convulsive epilepsies in SII and SIII of the prevalence survey. Even a small FP (1-Specificity) applied to a large population would have considerable logistical and cost implications. For instance, applying the SI false positivity of 2.3% to our study population of 233,881 individuals would have resulted in 5,379 false positive individuals that would otherwise have to be screened in SIII of the prevalence survey. The advantage of adding SII is that it substantially reduces the number of false positives screened in SIII. In our study these declined from 2.3% to 0.1%.

We found that multi-stage methods (SI & SII and SI & SII & SIII) had poor sensitivity. This was observed in another validation study where if only epilepsy specific questions were used, sensitivity was substantially lower and the specificity higher when compared with questions on epilepsy and other seizures (Ottman et al., 2010). Specificity was also observed to be greater if epilepsy specific items were used alone but not when combined with questions on other seizures (Kelvin et al., 2007). These observations suggest that questions about seizures under any circumstances are important in avoiding false negatives.

In our study, stigma-related non-response could have been the main cause of the low sensitivity of the three-stage method. This could partly be attributed to the fact that SI (which contributed the largest proportion of false negatives i.e. 15/18) was conducted by field staff who are usually resident within the community and who were also involved in the regular HDSS re-enumerations within the study area. The Clinical Survey (our validation study) was conducted by clinicians experienced in the diagnosis of epilepsy, of whom PWE or their guardians would perhaps be more trusting (as opposed to non-medical field personnel that conducted SI and SII of the prevalence survey). This implies that the sensitivity of SI may be dependent on the cultural setting and the skills of the field staff in administering culturally sensitive questions. High sensitivity (79.3%) was estimated in a similar field validation which utilized 'rural' doctors in an equivalent of SII of our prevalence survey (Placencia M et al., 1992a). However that study validated a prevalence survey that defined one as a case if they were positive in any of the three stages and included cases from sources other than the survey in the numerator of both the survey and the validation (Placencia M et al., 1992a; Placencia M et al., 1992b). Sensitivity of the three-stage method could be improved further by better training the SII field staff since they were unable to distinguish between febrile and non-febrile convulsions in 3 subjects, misclassifying these as false negatives.

A lack of awareness of convulsions in family members by the household heads could have influenced the low sensitivity of our survey method. These household heads were the primary respondents in the HDSS re-enumeration within which SI was conducted while the actual index respondents (or their caretakers if they were cognitively challenged) were interviewed in the subsequent prevalence survey stages and in the Clinical Survey.

Additionally, increase in awareness of epilepsy in this population following the three-stage prevalence survey could have reduced levels of stigma and increased knowledge of epilepsy and therefore yielded more true positive responses within the Clinical Survey. Indeed, a treatment gap study conducted on the same population after the prevalence survey reported very low levels of perceived stigma (Mbuba et al., in preparation).

The monetary cost and duration of the two-stage clinician conducted epilepsy survey would be higher compared to the three-stage survey by non-medical field personnel. This was attributed to the high salary expenditure of medical trained personnel and lack of field-work experience relative to lay field workers. For this additional expenditure however, the improvement in sensitivity of the two stage method would still be limited to eliminating the false negatives accruing from SII of the prevalence survey and would be thus be equivalent to the sensitivity of SI.

Limitations of the study

A major limitation of this study was the between-stages attrition of subjects over the two years of the Clinical Survey which could have caused non-response bias. These losses were observed despite efforts to rigorously follow-up subjects during the field implementation of the study.

Conclusion

To the best of our knowledge, this is the first study to determine the sensitivity and specificity of a multi-stage survey methodology as a single composite test in field-based validation. We found

that the three-stage method had poor sensitivity to detect ACE in population-based studies, which we could mainly attribute to stigma-related non-response in SI and a lack of awareness and knowledge of epilepsy. This method however has very high specificity (and thus very low false positivity), which reduces study costs. Widespread adoption of this method would require judicious balancing between the poor sensitivity and cost savings and also additional validation in populations with differing levels of stigma.

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Chapter 5: Prevalence and heterogeneity of Active Convulsive Epilepsy in four sites in sub-Saharan Africa: Results from a population-based multi-centre cross-sectional study.

NGUGI, A.K., KLEINSCHMIDT, I., BOTTOMLEY, C., NEWTON, C.R. (2012). On behalf of the INDEPTH SEEDS group. Prevalence and heterogeneity of Active Convulsive Epilepsy in four sites in sub-Saharan Africa: Results from a population-based multi-centre cross-sectional study. (Prepared for submission to *The Lancet Neurology*).

Abstract

Objective: The prevalence of epilepsy in low and middle income countries (LMIC) is estimated to be more than twice that of high income countries (HIC). However, there is considerable heterogeneity in the estimates which could be due to real differences between geographical locations in the prevalence of causal factors, or differences between studies in methodological approaches or case definitions, although this has not been determined. We conducted studies to determine the prevalence and heterogeneity of active convulsive epilepsy (ACE) across four Health and Demographic Surveillance System (HDSS) sites in sub-Saharan Africa (SSA).

Methods: We used three-stage cross-sectional surveys nested within on-going census in the HDSS sites to identify people with ACE. Prevalence was estimated as the ratio of confirmed cases of ACE to the population screened in the first stage of the survey. We adjusted the estimates for attrition between stages of the survey and for the sensitivity of the three-stage screening methodology and used logistic regression to assess for heterogeneity between and within study sites.

Results: There was substantial heterogeneity of prevalence between HDSS sites and between different age groups within and between sites. Site-specific estimates ranged between 7.0/1000 (95% CI: 6.2-7.4) in Agincourt HDSS to 14.8/1000 (95% CI: 13.8-15.4) in Ifakara HDSS. Prevalence varied by age and sex in the Kilifi HDSS and by age in the three other sites. Prevalence was highest in the adolescents (13-18 years) in Ifakara HDSS and in the youngest age-group (<=5 years) in Iganga-Mayuge HDSS while it was lowest in the youngest age-group

(<=5 years) in Agincourt HDSS. There were decreasing and increasing trends of prevalence with age for Iganga-Mayuge and Agincourt HDSSs respectively. Kilifi and Ifakara HDSSs had increasing then decreasing trends of prevalence with age, with the points of inflection being in the 13-18 year age groups.

Conclusion: We used a standardized methodology to identify cases and similar definition of ACE and thus our findings suggest real heterogeneity that could be related to the differences in the distribution and types of risk factors for development of epilepsy across SSA or differences in vulnerability to endemic risk factors within study sites. These results reflect the burden of the people with active epilepsy that should be on treatment in these sites and also suggest the need for studies to identify modifiable risk factors that could be targeted in public health interventions.

Introduction

Epilepsy is one of the most prevalent non-communicable conditions and affects nearly 70 million people in the world (Chapter 2). It represents approximately 0.5% of the global burden of disease and translates to more than 7 million disability-adjusted life-years annually (Leonardi M and Ustan TB, 2002). The prevalence of epilepsy in Low and Middle Income Countries (LMIC) was estimated to be more than twice that in high income countries (HIC) in a review of 46 studies that reported life-time prevalence (Chapter 2). However there was considerable heterogeneity even within similar settings.

Heterogeneity in the prevalence of epilepsy could be due to real differences between geographical locations in the prevalence of causal factors, or differences between studies in methodological approaches, in particular the case definitions, methods of ascertainment and the screening instruments used (Leonardi M and Ustan TB, 2002; Ngugi et al., 2010). It has however not been clarified whether this heterogeneity is real i.e. clinical (e.g. due to differences in patient characteristic or distribution and types of risk factors) or due to differences in methodology.

In 1997, the World Health Organization (WHO), the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) launched the Global Campaign Against Epilepsy (GCAE), aimed at supporting developing countries world-wide to reduce the burden caused by epilepsy through improved acceptability, access to services, prevention and quality of care. The second phase of the GCAE was launched in 2001, with the specific objectives being, among others, to estimate prevalence of untreated active epilepsy in the LMIC. The overall goal

of the campaign was to improve the identification and management of people with convulsive epilepsies, particularly in rural areas, within existing primary health care systems (WHO/IBE/ILAE, 2001).

We conducted large population-based cross-sectional surveys in four Health and Demographic Surveillance System sites (HDSSs) in sub-Saharan Africa (SSA) under the INDEPTH network. The objective of this study was to determine the prevalence of active convulsive epilepsy (ACE), and the heterogeneity in its distribution in a resource-limited setting using standardized tools, definitions and case detection methods. We aimed to generate reliable estimates of prevalence of ACE on which public health interventions and further studies of the aetiology and treatment of the condition can be based.

Methods

Background and study settings

This study was conducted as part of a larger Study of Epidemiology of Epilepsy in Demographic Surveillance Systems (SEEDS) in sub-Saharan Africa. The study sites were Kilifi in Kenya, Agincourt in South Africa, Iganga-Mayuge in Uganda and Ifakara in Tanzania, which are described at the INDEPTH website (http://www.indepth-network.org/) and in chapter 1 of this thesis. These sites were selected on the basis of the availability of health facilities able to provide support to the clinical aspects of the study and follow-up of patients in longitudinal studies, the availability of laboratory facilities to handle biological samples for case-control studies,

operational costs to the study and the endemicity of parasitic diseases putatively associated with the development of epilepsy.

Procedures

The questionnaires used for screening epileptic seizures and epilepsy in the study communities were based upon those used in other studies (Kaamugisha J and Feksi AT, 1988; Osuntokun et al., 1987; Placencia M et al., 1992b; Rwiza HT et al., 1992 Nov-Dec; Tekle-Haimanot R et al., 1990) including previous work in the Kilifi HDSS (Edwards T et al., 2008; Mung'ala-Odera et al., 2008; Snow RW et al., 1994; Versteeg AC et al., 2003). The appropriate terminology for key words in the questions e.g. seizures and epilepsy were derived by consensus in focus group discussions with the local residents and pre-tested in communities outside the study areas. We refined these terminologies during the training of the study field staff who were local residents with at least secondary school level education. The questionnaires underwent forward translation into the local vernacular and independent back translation into English through a well-developed process to remove any ambiguities.

The three-stage survey methodology

Stage I: Screening for convulsions in the community

We conducted the first stage (SI) of the prevalence surveys during the routine re-enumeration and vital registration within the HDSS sites. The census field staff administered 2 questions (Appendix 4.1) to household heads to identify members of their households with histories of convulsions during the door-to-door surveys. Subjects who were positive to any of the questions were considered eligible for a follow-up interview in the second stage.

Stage II: Screening for possible ACE in the community

In the second stage (SII), we interviewed all eligible participants within a week of SI. SII was conducted by a different team, trained to identify possible cases of ACE. A more detailed epilepsy screening questionnaire (Appendix 4.2) based upon an international validated questionnaire (Placencia M et al., 1992a) was used. Respondents considered positive in this stage were eligible for evaluation in the third stage.

Stage III: Confirmation of ACE at the hospital/epilepsy clinic

The diagnosis of ACE was assessed in the third stage (SIII) of the survey within a week of the SII interview, using detailed history taken by clinicians trained in the diagnosis of epilepsy and fluent in the local languages and was supplemented by clinical examination (Appendices 5.1 and 5.2) . ACE was defined as two or more unprovoked convulsions (seizures with tonic and/or clonic movements) occurring at least 24 hours apart with at least one seizure in the preceding 12 months (Meinardi et al., 2001). We further asked individuals if they were currently (or had previously been) on anti-epileptic drugs. Those on medication and had experienced at least two seizures but none in the preceding year were classified as cases (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993). The three-stage method identified individuals as cases of ACE if they were positive in all the three stages of the prevalence survey.

After the surveys, all case notes were reviewed independently by at least two neurologists to confirm the diagnoses and classification assigned by the study clinicians. Where the neurologists disagreed with the study clinician and both independently assigned the same alternative

classification, the subjects were re-classified. Disagreements between the neurologists were resolved by consensus otherwise the subjects were assigned in to the non-classified category.

To enable a comparison between the three-stage methodology of the current survey and the two-stage methodology that has been used in other population-based studies in developing countries (Birbeck GL and Kalichi EM, 2004 Jan; Kaamugisha J and Feksi AT, 1988; Osuntokun et al., 1987; Rwiza HT et al., 1992 Nov-Dec; Tekle-Haimanot R et al., 1990), we selected random population samples of 4,500 to 6,000 individuals from each site's census database. The SII questionnaire of the study was administered (as the first stage) on these random population samples and those that were positive at this stage were assessed in SIII of the survey as was done within the main three-stage survey. .

The prevalence surveys in the four sites were conducted between December 2007 and March 2009: December 2007-July 2008 in Kilifi; August 2008-February 2009 in Agincourt; February-October 2009 in Iganga-Mayuge; and, May-December 2009 in Ifakara.

Analysis

We double entered and verified all data in MySQL Version 5 open source database (Oracle Corporation, Redwood Shores, CA, USA) and all statistical analyses were carried out in STATA Version 11 (StataCorp, College Station, TX, USA). We estimated the unadjusted prevalence of ACE and 95% confidence interval (95%CI) for each site as the number of cases of ACE

confirmed in SIII of the study divided by the total population screened in SI, expressed per 1,000 persons. Age- and sex- specific prevalence of ACE were also estimated.

We used multiple imputation (Rubin DB, 1987; van Buuren S, 2007) to reduce bias due to attrition between stages of the survey. Multiple imputation is a simulation-based technique for handling missing data that uses probability models that are fitted to observed data to predict values for missing observations. In the imputation model, we imputed missing data at each stage of the survey using the outcome of the previous stage. Multiple imputation was carried out using the method of chained equations which was implemented using the "ice" command in STATA. The process of imputation was carried out separately for each country (the highest missing was 36% - between SI and SII in Iganga-Mayuge).[1] Five imputed datasets were created for each site. The technique of multiple imputation involves estimating parameters separately in each of the imputed datasets and then combining the estimates using Rubin's rules (Rubin DB, 1987). Prevalence estimates were divided by 0.486 to account for the sensitivity (48.6%) of the three-stage screening methodology (Chapter 4).

We produced site-specific prevalence estimates adjusted to the age distribution of the mid-2000 United States population (US Census Bureau, 2010) and we used logistic regression to test for heterogeneity of ACE between study sites after adjusting for age and sex.

[1] The theory of multiple imputation (MI) requires that the number of imputations (M) should be infinite but the procedure is also known to have good statistical properties with finite M. The relative efficiency (RE) of the MI procedure with finite M compared with infinite M is roughly 90% with only 2 imputations for a missing data rate as high as 50%. Most literature (Rubin 1987; van Buuren, Boshuzien and Knook 1999) recommend $M = 5$ (corresponding to RE of 95% for a missing data rate of 50%) should be sufficient to obtain valid inference.

The site-specific counts of cases of ACE in the two-stage method (i.e. those identified within the population samples independent of the three-stage method) were generated from the data. Multiple Imputation was used to adjust for loss to follow-up in the comparison of both the two- and three-stage methods. Proportions of cases in the two-stage method not identified (missed) in the three-stage method were also estimated.

Ethics approval was obtained from each of the local Institutional Review Boards (IRB) and the Institute of Child Health, University College London.

Results

The median (IQR) age of the study participants was highest in Agincourt; 21.0 (10.0 – 35.0) years and was lowest in Iganga-Mayuge; 15.0 (8.0 – 29.0). The distribution of sex and age for all sites are displayed in Table 5.1(a) and that of cases of ACE in Table 5.1(b). Age of onset varied between study sites.

SI of the survey was administered to a combined population of 472,788 (96.3 %) residents of the study areas, nearly half (232,176) of whom were from Kilifi. A total of 12,004 were positive in SI. In SII of the study, we screened 82.5% (9,898/12,004) of the eligible subjects in all sites with the site-specific follow-up ranging between 64.0% in Iganga-Mayuge and 100.0% in Agincourt. We further screened 83.0% (2,078/2,505) of the eligible subjects in SIII of the survey, the highest proportion (92.7%) screened at this stage was in Agincourt and the lowest (64.2%) in Iganga-Mayuge (Table 5.2).

The prevalence of convulsive seizures (proportion positive in SI) was highest in Iganga-Mayuge and lowest in Agincourt (Table 5.2). The prevalence of ACE was highest in Ifakara (Tanzania) and was lowest in Iganga-Mayuge (Table 5.2). At 6.8/1000, age-standardized prevalence of ACE was lowest in Iganga-Mayuge and highest (15.5/1000) in Ifakara (Table 5.3). In the combined analysis, there was strong evidence of interaction between study site and age ($p<0.001$), but not with sex.

Table 5.1(a): Age and sex distribution of study populations*

	Kilifi HDSS			Agincourt HDSS			Ifakara HDSS			Iganga-Mayuge HDSS			Total
Age-group	Total	%	Median age† (IQR)	Total	%	Median age† (IQR)	Total	%	Median age† (IQR)	Total	%	Median age† (IQR)	
0-5	41,868	18.0		11,526	13.9		21,027	22.5		11,444	21.2		85,865
6-12	52,248	22.5		13,039	15.7		17,655	18.9		14,972	23.2		97,914
13-18	34,228	14.7	16.0 (7.0-31.0)	12,338	14.9	21.0 (10.0-35.0)	9,381	10.1	17.7 (7.5-34.9)	10,722	15.9	15.0 (8.0-29.0)	66,669
19-28	37,523	16.2		17,765	21.5		13,223	14.2		10,509	15.5		79,020
29-49	42,269	18.2		18,488	22.3		21,865	23.4		11,765	17.3		94,387
50+	24,040	10.4		9,639	11.6		10,272	11.0		4,740	7.0		48,691
Sex													
Female	123,914	53.4		43,053	52.0		46,433	49.7		32,518	50.7		245,918
Male	108,262	46.6		39,742	48.0		46,990	50.3		31,625	49.3		226,619
Sub-total	232,176	100		82,795	100		93,423	100		64,143	100		472,537

*115 female and 123 male missing age information and 13 individuals missing sex information; †All age groups

Table 5.1(b): Age and duration (years) of epilepsy for cases of active convulsive epilepsy in four sites in sub-Sahara Africa.

		Age at survey	Age at onset of seizures†	Duration of Epilepsy‡
Site	Cases	Median (IQR)	Median (IQR)	Median (IQR)
Kilifi HDSS	699	17.0 (9.0-27.0)	3.4 (1.1-12.8)	8.3 (3.2-16.2)
Agincourt HDSS	245	29.0 (17.0-49.0)	13.7 (4.6-30.4)	9.6 (3.4-18.1)
Iganga HDSS	152	11.0 (6.0-19.0)	2.1 (0.8-6.6)	6.0 (3.0-12.0)
Ifakara HDSS	366	17.9 (11.8-30.9)	10.5 (2.6-17.6)	6.3 (2.2-13.9)
Overall	1,462	18.0 (10.0-30.4)	5.1 (1.4-15.4)	8.0 (3.0-15.6)

†Based on 1225 cases that had information on age at onset of seizures; ‡based on 1274 cases that had information on duration of seizures

Table 5.2: Flow of study participants and crude prevalence of active convulsive epilepsy in four sites in sub-Sahara Africa.

Study site	Population	Screened in SI (%)	Positive in SI (%*)	Screened in SII (% of positive in SI)	Positive in SII (%*)	Screened in SIII (% of positive in SII)	Positive in SIII (%*)	Crude Prevalence Per 1000 (95% CI)
Kilifi HDSS	233881	232176 (99.3)	5152 (2.2)	4886 (94.6)	1123 (23.0)	948 (84.4)	699 (73.7)	3.0 (2.8-3.2)
Agincourt HDSS	83121	82795 (99.6)	546 (0.7)	546 (100.0)	354 (64.8)	328 (92.7)	245 (74.7)	3.0 (2.6-3.3)
Iganga HDSS	69186	64172 (92.8)	4917 (7.7)	3145 (64.0)	500 (15.9)	321 (64.2)	152 (47.4)	2.4 (2.0-2.8)
Ifakara HDSS	104889	93645 (89.3)	1389 (1.5)	1321 (95.1)	528 (40.0)	481 (91.1)	366 (76.1)	3.9 (3.5-4.3)
Overall	**490699**	**472788 (96.3)**	**12004 (2.5)**	**9886 (82.4)**	**2505 (25.3)**	**2078 (83.0)**	**1462 (70.4)**	

*Expressed as a percentage of the total screened in the preceding stage

Table 5.3: Site-specific unadjusted and adjusted prevalence of active convulsive epilepsy (per 1000 persons).

Study site	Population	Screened in SI	Unadjusted Prevalence		Adjusted for age†	Adjusted for attrition*	Adjusted for sensitivity§
			Cases	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)‡
Kilifi HDSS	233881	232176	699	3.0 (2.8-3.2)	7.4 (7.1-7.8)	3.8 (3.5-4.0)	7.8 (7.5-8.2)
Agincourt HDSS	83121	82795	245	3.0 (2.6-3.3)	8.1 (7.5-8.7)	3.4 (3.0-3.8)	7.0 (6.2-7.4)
Iganga HDSS	68808	64172	152	2.4 (2.1-2.8)	6.8 (6.2-7.5)	5.0 (4.4-5.6)	10.3 (9.5-11.1)
Ifakara HDSS	104889	93645	366	3.9 (3.5-4.3)	15.5 (14.7-16.3)	7.2 (6.5-7.8)	14.8 (13.8-15.4)
Overall	**490699**	**472788**	**1462**				

†Standardized to the mid-2000 US population; *Adjusted using MI; §Sensitivity was 48.6%; ‡Adjusted for attrition and sensitivity of the 3-stage methodology.

Prevalence of ACE varied by age and sex in Kilifi, being higher in males and in adolescents and young adults (aged 13-28 years). In the other sites, prevalence varied by age (but not by sex); it was lowest in the 0-5 year age group in Agincourt and Ifakara and highest in the same age group in Iganga-Mayuge (Table 5.4).

When we adjusted for attrition between SI/SII and SII/SIII of the survey, there was a 2-fold and 1.5-fold increase in the prevalence of ACE for Iganga-Mayuge and Ifakara, and less at the other sites which were able to follow up more subjects.

In Iganga-Mayuge, prevalence of ACE decreased with age while the reverse was the case for Agincourt where there was a gradual increase. In Kilifi and Ifakara, prevalence initially increased with age reaching a peak among adolescents and young adults (aged 13-28 years). It then declined in middle to late adulthood (29-49 years), increasing again in the fifth decade of life (Figure 5.1).

Prevalence estimates from the two-stage methodology (i.e. the population samples) were higher than the crude estimates from the three-stage methodology for Kilifi, Agincourt and Iganga-Mayuge sites, while there was no difference in the Ifakara HDSS. In the three study sites, between 35% and 64% of the cases of ACE identified within the population sample (two-stage method) had been missed within SI of the three-stage methodology when the data were adjusted for attrition between stages (Table 5.5).

Table 5.4: Age- and sex-specific prevalence of active convulsive epilepsy and prevalence ratios in four sites in sub-Saharan Africa.

Kilifi HDSS					**Unadjusted analysis**			**Adjusted analysis**		
Sex	Screened	Cases†	Prevalence/1000	95% CI	Prevalence Ratio	95% CI	P-value	Prevalence Ratio	95% CI	P-value
Female	123,914	869	7.0	6.6-7.5	1.0	-	<0.001	1.0	-	<0.001
Male	108,262	935	8.6	8.1-9.2	1.3	1.1-1.5		1.3	1.1-1.4	
Age-group										
0-5	41,868	265	6.3	5.6-7.1	1.0	-		1.0	-	
6-12	52,248	389	7.4	6.7-8.2	1.2	1.3-1.8		1.2	0.9-1.5	
13-18	34,228	352	10.3	9.2-11.4	1.6	1.5-1.8	<0.001	1.6	1.3-2.1	<0.001
19-28	37,523	364	9.7	8.7-10.7	1.6	1.4-1.4		1.6	1.3-2.0	
29-49	42,269	254	6.0	5.3-6.8	1.0	0.9-1.1		1.0	0.8-1.3	
50+	24,040	180	7.5	6.4-8.7	1.1	1.0-1.2		1.1	0.8-1.5	
Agincourt HDSS					**Unadjusted analysis**			**Adjusted analysis**		
Sex	Screened	Cases†	Prevalence/1000	95% CI	Prevalence Ratio	95% CI	P-value	Prevalence Ratio	95% CI	P-value
Female	43,053	283	6.6	5.3-7.6	1.0	-	0.4			
Male	39,742	303	7.6	6.2-8.6	1.1	0.9-1.4				
Age-group										
0-5	11,526	24	2.1	0.8-3.3	1.0	-				
6-12	13,039	62	4.7	3.1-6.4	2.4	1.2-4.8				
13-18	12,338	76	6.2	4.3-8.2	3.2	1.7-6.3				
19-28	17,765	113	6.4	4.7-8.2	3.3	1.7-6.3	<0.001			
29-49	18,488	202	10.9	8.8-13.2	5.5	3-10.3				
50+	9,639	91	9.5	7.6-11.5	4.9	2.5-9.5				

Table 5.4: Continued

Ifakara HDSS					**Unadjusted analysis**			**Adjusted analysis**		
Sex	Screened	Cases†	Prevalence/1000	95% CI	Prevalence Ratio	95% CI	P-value	Prevalence Ratio	95% CI	P-value
Female	44,694	629	14.0	12.1-15.8	1.0	-	0.2			
Male	44,245	551	10.9	10.9-14.0	0.9	0.8-1.1				
Age-group										
0-5	21,028	177	8.8	7.6-10.2	1.0					
6-12	17,655	220	13.2	11.5-15.0	1.4	1.1-1.8				
13-18	9,383	176	19.8	17.0-22.9	2.2	1.7-3.0	<0.001			
19-28	13,223	168	13.4	11.4-15.6	1.4	1.0-1.9				
29-49	21,866	274	13.2	11.7-14.8	1.4	1.1-1.8				
50+	10,272	160	16.5	14.0-19.2	1.8	1.4-2.5				
Iganga-Mayuge HDSS					**Unadjusted analysis**			**Adjusted analysis**		
Sex	Screened	Cases†	Prevalence/1000	95% CI	Prevalence Ratio	95% CI	P-value	Prevalence Ratio	95% CI	P-value
Female	32,518	291	8.9	8.0-10.0	1.0	-	0.9			
Male	31,625	303	9.6	8.5-10.7	1.0	0.8-1.3				
Age-group										
0-5	11444	214	18.7	14.4-23.3	1.0	-				
6-12	14972	169	11.3	8.6-14.2	0.5	0.4-0.7				
13-18	10722	77	7.2	4.3-9.9	0.3	0.2-0.5	<0.001			
19-28	10509	65	6.2	3.5-8.8	0.3	0.2-0.5				
29-49	11765	46	3.9	2.1-5.8	0.2	0.1-0.3				
50+	4740	19	3.9	0.8-7.2	0.2	0.1-0.4				

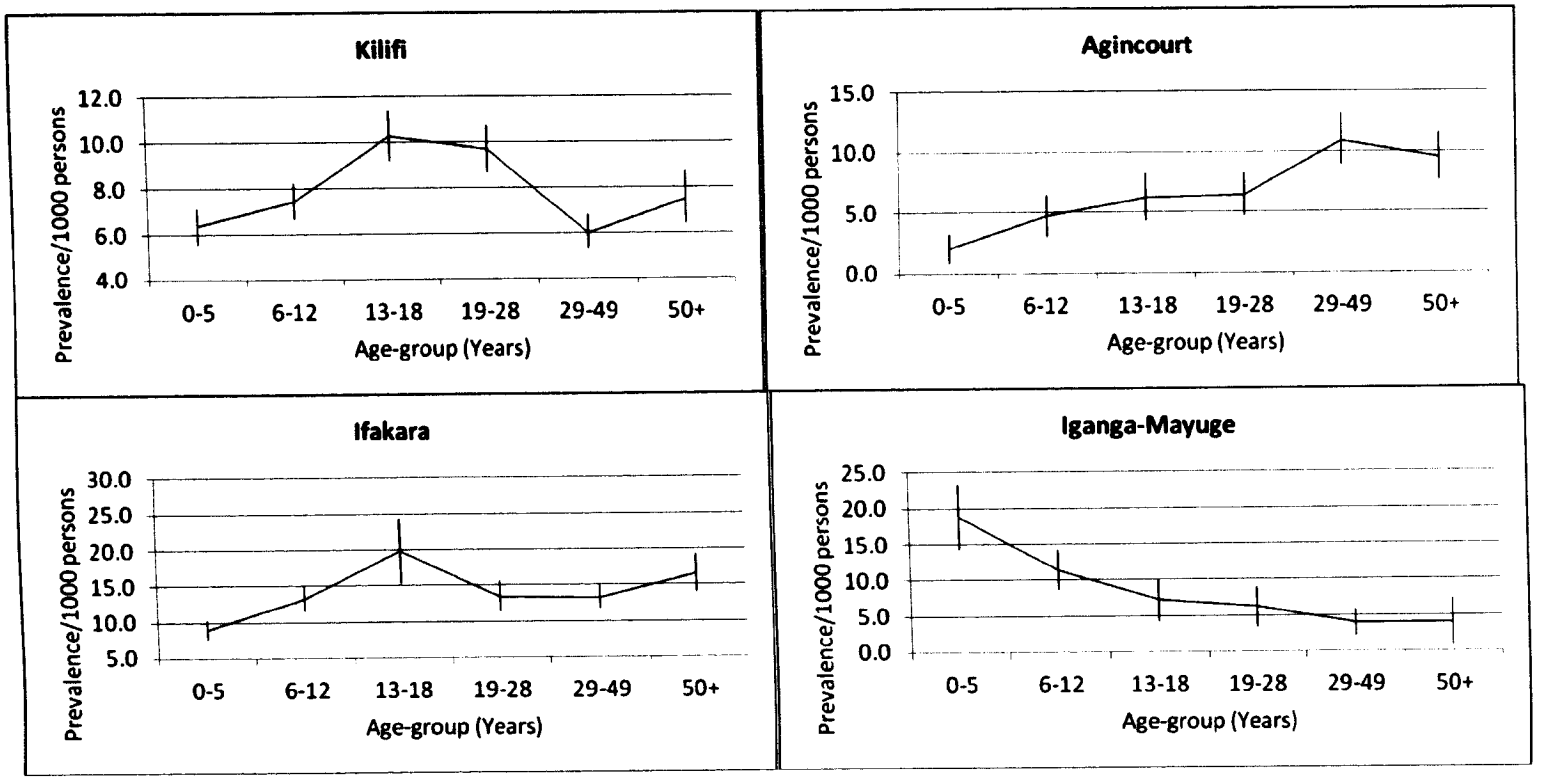
†Based on number of cases estimated after adjustment for loss to follow-up and sensitivity of the screening methodology.

Table 5.5: Site-specific comparison the two- and three-stage methods for detecting cases of active convulsive epilepsy among participants selected in the population samples.

Study site	Sample	Screen SI	Screen SII	Positive SII	Screen SIII	Cases (2-stages)	Cases (MI)	*Prevalence, (95% CI)	Cases (3-stages)	Cases (MI)	†Prevalence, (95% CI)	‡Two- vs. three stages
Kilifi	6000	5883	5594	68	38	23	42	7.5 (4.9-10.1)	17	20	3.4 (1.9-4.9)	22 cases (47.6%) missed in three-stage method
Agincourt	4500	4209	3890	67	58	24	29	7.4 (4.6-10.3)	16	19	4.5 (2.4-6.5)	10 cases (34.5%) missed in three-stage method
Iganga	5000	4436	4053	125	46	22	61	15.0 (9.9-20.1)	15	22	5.0 (2.6-10.1)	39 cases (63.9%) missed in three-stage method
Ifakara	5000	4702	4985	54	49	31	35	7.1 (4.8-9.5)	22	35	7.4 (4.5-10.7)	Equal number of cases identified
Overall	**20500**	**19230**	**18866**	**314**	**191**	**100**	**167**		**70**	**96**		

*(SII+SIII); †(SI+SII+SIII); ‡Based on number of additional cases detected in the two-stages; MI=Multiply imputed; Prevalence estimates and comparisons are based on MI data

Figure 5.1: Age-specific prevalence of active convulsive epilepsy in four sites in sub-Sahara Africa†.



†Estimates adjusted for loss to follow-up and sensitivity of the screening methodology

Discussion

We estimated the prevalence of active convulsive epilepsy (ACE) in four large populations in sub-Saharan Africa to range between 7.0-14.8/1000 persons, when adjusted for loss to follow-up and sensitivity of the screening method. A study in Kilifi which used similar three-stage cross-sectional methodology conducted in 2003 and adjusted for loss to follow up and the sensitivity of SII estimated prevalence of ACE at 4.5/1000 (Edwards T et al., 2008). The crude prevalence estimates were similar in both studies but the study by Edwards and colleagues probably under-estimated the true prevalence because it did not adjust for the sensitivity of the entire three stage methodology.

To our knowledge, these are the largest population-based multi site prevalence surveys of epilepsy anywhere in the LMIC. We utilized standardized tools, methodology and definitions of active epilepsy based on the recommendations by the International League Against Epilepsy (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993) in order to minimize the methodological component of heterogeneity observed in a recent meta-analysis of prevalence studies (Chapter 2). Furthermore, our studies benefited from well established health and demographic surveillance infrastructure which allowed rapid and efficient screening of large populations.

The crude prevalence estimates from the three-stage method were lower in three out of the four sites than estimates obtained from the two-stage methodology. In three of the study sites, between 35% and 64% of the cases identified with the two-stage method had not been detected

as people with histories of convulsions in the first stage (SI) of the three-stage methodology, after adjusting for loss to follow-up. Indeed, SI of the three-stage method contributed >80% of the false negatives in the validation study of the three-stage methodology, with the rest being misclassified as febrile seizures in SII (Chapter 4). It is likely that the false negatives in SI of the three-stage methodology were due to stigma-related concealment of seizures, particularly since the census field staff that conducted SI were usually resident in and had more regular contact with the study communities as opposed to the SII field staff. Lower prevalence estimates in the three-stage methodology could also have been due to lack of awareness of seizure histories in households by household heads who were the primary respondents in SI. This is as opposed to SII in which the respondents were primarily the actual index person eligible for SII or their regular caretakers/guardians (if they were minors or cognitively impaired).

We measured prevalence estimates that showed significant heterogeneity with age and study site. At 14.8/1000 persons, the adjusted site-specific prevalence was highest in Ifakara, and was also slightly higher than the 10.2/1000 reported in the same area in 1992, albeit with significant inter-village heterogeneity (Rwiza HT et al., 1992). The high prevalence of convulsive epilepsies in this region could be attributed to the high prevalence of malaria and onchocerciasis reported in this area of southern Tanzania (Carter JA, 2004; Drakeley et al., 2003; Loewenberg, 2008; Mwaiko et al., 1990; Mweya et al., 2007; Ngoungou et al., 2006; Schellenberg et al., 2003). The second highest prevalence of ACE (after adjusting for loss to follow-up and sensitivity of the screening method) was in Iganga-Mayuge in Uganda, which also had the highest prevalence of convulsions (77/1000) and the lowest median age (2.1 years) of onset of seizures. The combination of these factors is suggestive of acute symptomatic convulsions (particularly

malaria associated) as an important risk factor for development of epilepsy. Iganga-Mayuge HDSS is located along the north-western shores of Lake Victoria, a highland area that has recently been shown to have an increasing malaria transmission intensity (Chaves et al., 2011; Wandiga SO et al., 2010) compared to Kilifi where a decline in malaria admissions and malaria-associated seizures have been observed in the last 10 years (Kariuki et al., 2011; O'Meara et al., 2008). The early age at onset of seizures and epilepsy in the Iganga-Mayuge site could also suggest other important risk factors such as bacterial meningitis and adverse peri-natal events which would need to be investigated in case-control studies. In Kilifi, an important cause of bacterial meningitis (Haemophilus influenza) has been mitigated through a successful introduction of *Haemophilus influenza* type b (Hib) vaccination into routine childhood immunization in Kenya since 2002 (Cowgill et al., 2006), a factor which could partly explain the comparatively lower prevalence in Kilifi, particularly in younger age groups.

The prevalence of ACE in Kilifi was lower than that reported for Ifakara although both sites had a similar age-pattern. Despite the early age at onset of seizures, this could reflect differences in the prevalence of parasitic infections between these sites; for instance, a decline in incidence of slide positive malaria admissions and malaria-associated seizures in Kilifi over the past decade (Kariuki et al., 2011; O'Meara et al., 2008) as well as a decline in the incidence of haemophilus meningitis following the introduction of Hib vaccine (Cowgill et al., 2006). These factors could translate to reduced incidence of epilepsy associated with acute symptomatic seizures, for which the malaria-attributable fraction was estimated at >90% (Kariuki et al., 2011). We estimated a low prevalence of convulsions in SI of this study (22/1000 persons) and history of febrile

convulsions was identified as one of important risk factors of epilepsy in a case-control study in Kilifi (Edwards T et al., 2008).

Compared to the other sites, the prevalence of ACE was significantly lower in the Agincourt HDSS even when the data were adjusted for between-stage attrition of respondents and sensitivity of the screening methodology. South Africa has a high burden of HIV and AIDS which is related to cyclical labour migration, particularly from poor rural areas, with up to 60% of adult males (and ~ 20% of adult females) absent from households most of the time (Collinson MA et al., 2001; Kahn K et al., 2003). HIV seropositivity in Agincourt, based on the SEEDS case-control study, was 20.5% compared to 2.9% in Iganga-Mayuge and 5.1% in Kilifi (SEEDS case-control study – unpublished). This results in reduced life expectancy and high HIV-related mortality at population-level (Adjuik et al., 2006), particularly in rural areas such as Agincourt where infected migrants are thought to return home to die (Clark et al., 2007). It is therefore probable, that high mortality rate in HIV infected people with epilepsy could be the cause of comparatively low prevalence. The other possible reason for lower prevalence of ACE in Agincourt is that the area is hypo-endemic for malaria (Adjuik et al., 2006) and thus low prevalence of malaria-attributable acute symptomatic seizures compared to, for example, Ifakara (Drakeley et al., 2003) and Iganga-Mayuge (Chaves et al., 2011; Wandiga SO et al., 2010). In Agincourt, this explanation is supported by the very low (7/1000) prevalence of convulsions in SI of our study and the highest median age (13.7 years) at onset of seizures, although the Agincourt population and cases of ACE were relatively older. The low prevalence of ACE in Agincourt could also reflect living standards and access to healthcare that are relatively closer to the HIC setting than the other sites.

We observed the highest prevalence of ACE in children aged below 5 years in Iganga-Mayuge which is also reflected in the age at onset of seizures in Iganga-Mayuge and suggests aetiologies that occur early in childhood such as adverse peri-natal events e.g. hypoxic-ischaemic encephalopathy and intra-cranial infections. In contrast, the lowest prevalence in children less than 5 years occurred in Agincourt, where these factors appear to be absent and could perhaps be explained by the relatively better health care system. In Agincourt, the age/prevalence relationship suggests exposures that occur later in life and well into adulthood. These could include traumatic head injuries (mainly due to interpersonal violence particularly amongst males), HIV-related encephalopathies and stroke (Connor et al., 2004; Nell and Brown, 1991).

The decrease in prevalence with age could reflect a decrease in incidence over time in Iganga-Mayuge as older age groups were less exposed to risk factors for epilepsy in the past, than their juvenile counterparts. This could be related to the documented increase in malaria transmission in this area (Chaves et al., 2011; Wandiga SO et al., 2010). Additionally, mortality and/or spontaneous remission could further explain this observation, since most of the epilepsy appears to start at young age.

The age-specific prevalences were similar in Kilifi and Ifakara, being low in childhood, peaking at adolescence, with a dip in early middle-age and a second increase in the late middle-age and old age. This pattern suggests two explanations: i) low prevalence of risk factors associated with early childhood-onset epilepsy (such as febrile illnesses and adverse peri-natal events, which can also cause remote-symptomatic epilepsies in later ages) relative to factors that occur in late

childhood and adolescence e.g. previous head injuries and family history of both febrile and non-febrile seizures and, ii) remote symptomatic epilepsies caused by exposures in early childhood and which manifest as recurrent seizures later in life due to formation of neurological sequelae (if an individual survives the acute phase). Both these scenarios may occur in Kilifi (Carter JA, 2004; Edwards T et al., 2008) although other exposures such as Toxoplasmosis and Onchocerciasis have not been investigated. The observed increase in prevalence of ACE in late middle and old age could imply epilepsy that is associated with progressive encephalopathies such as tumours, stroke and neuro-degenerative conditions (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993), a relationship which needs to be investigated in the context of resource limited settings.

Limitations of the study

We used a three-stage cross-sectional survey methodology that had low sensitivity in identifying potential cases of ACE and in the Iganga-Mayuge site, the study also experienced high attrition rates between survey stages due to logistical difficulties in following up eligible participants. We however adjusted our estimates for these factors in these analyses.

In this study, we have discussed the possible ecological causes of the observed between age and between study site heterogeneity. These associations should be interpreted with caution as they are not informed by the appropriate cases-control data.

Conclusion

We have shown that the prevalence of ACE is heterogeneous across sub-Saharan Africa. We used similar methodologies to identify cases as well as similar definitions of epilepsy and operational procedures across different sites in this region. This was in an effort to systematically minimize the methodological component of the heterogeneity reported in a previous meta-analysis (Chapter 2). Our findings suggest real (clinical) heterogeneity of epilepsy that could be related to the distribution and types of risk factors for development of epilepsy or age differences in vulnerability to endemic risk factors within sites. These results are indicative of the burden of the people with epilepsy that should be on treatment in these sites and also form the basis for case-control studies to identify modifiable risk factors of epilepsy that could be targeted in public health interventions.

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Chapter 6: Incidence of convulsive epilepsy in a rural area in Kenya

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Abstract

Objective: There are only a few studies of incidence of epilepsy in Low and Middle Income Countries (LMIC). These are often small, or in specific age groups, or conducted in areas with high prevalence of risk factors of epilepsy and therefore not representative of the general populations. We aimed to determine the incidence of active convulsive epilepsy (ACE) in a large rural population in Kenya.

Methods: We conducted two cross-sectional surveys five years apart within a health and demographic surveillance system. In the first survey (2003) we identified residents without ACE who were then re-examined in the follow-up survey (2008) to determine the number of new cases. We estimated the overall incidence of ACE as well as incidence rates by age-group, sex and by administrative location. Estimates were adjusted for loss to follow-up during case identification and for the sensitivity of the screening method.

Results: The incidence rate of ACE was 77.0/100,000 persons/year (95% confidence intervals (95%CI): 67.7 – 87.4). There was strong evidence of a U-shaped association between incidence and age with the lowest incidence occurring in the 29-49 year age group (37.4/100,000 persons/year; 95% CI: 25.7 – 54.7).

Conclusion: We estimated a high incidence of convulsive epilepsy in this population. Our findings suggest that the risk of epilepsy was lowest in the middle-aged. The increased risk in the

other age groups is suggestive of aetiologies that occur early as well as late in life and preventive interventions should target exposures that occur in these age groups.

Introduction

Epilepsy is one of the most common neurological conditions in the world and an important cause of disability and mortality, accounting for 1% of days lost to illness globally (Leonardi M and Ustan TB, 2002) and confers a 2-7 fold increased rate of mortality compared with the general population (Carpio et al., 2005; Forsgen L et al., 2005; Kaiser et al., 2007). It is estimated to affect 7 million people in high income countries (HIC) and 61 million people in low and middle income countries (LMIC) (Chapter 2). These estimates are however based on life-time prevalence data, which may underestimate the burden since epilepsy is associated with considerable mortality early after the onset of seizures and may spontaneously remit (Carpio et al., 2005; Diop et al., 2005; Kwan and Sander, 2004; Sander, 1993). Incidence is not affected by either of these factors and may provide a more accurate assessment of the burden of epilepsy.

While a large number of studies have measured the prevalence of epilepsy in LMIC (as described in several reviews) (Benamer HT and Grosset DG, 2009; Burneo JG et al., 2005; Ngugi et al., 2010; Preux PM and Druet-Cabanc M, 2005), there are few estimates of the incidence of epilepsy (Kaiser C et al., 1998 May; Medina MT et al., 2005 Jan; Mung'ala Odera V et al., 2008; Rwiza HT et al., 1992 Nov-Dec; Saha SP et al., 2008; Tekle-Haimanot R et al., 1997 May; Winkler AS et al., 2009). This is mainly due lack of health facility data to identify incident cases and the high cost of continuous surveillance of population-based cohorts required for accurate incidence estimates.

In HIC, incident cases can be identified through medical records (Annegers JF et al., 1999 Apr; Camfield CS, 1996 Jan; Freitag CM, 2001 Aug; Hauser WA et al., 1993 ; Heaney DC, 2002 Nov 2; Kotsopoulos I et al., 2005; Olafsson E et al., 2005 Oct; Oun A et al., 2003 Oct), which are available to researchers. Better and accessible health care systems, specialized personnel and advanced medical technology and diagnostic accuracy further improve case detection in these countries.

In LMIC with poor health-care resources and few specialists in neurology (WHO, 2004), the burden of epilepsy is usually determined using population-based studies. Due to cost, poor infrastructure and other resource constraints, the few studies of incidence that have been conducted in these countries are often small (Kaiser C et al., 1998 May; Medina MT et al., 2005 Jan; Winkler AS et al., 2009) and of short follow-up duration (Kaiser C et al., 1998 May; Medina MT et al., 2005 Jan; Mung'ala Odera V et al., 2008). LMIC studies are also quite often restricted to specific age-groups (Mung'ala Odera V et al., 2008), or are conducted in areas with high prevalence of epilepsy or have used different methods to ascertain cases over the course of the follow-up period (Medina MT et al., 2005 Jan; Tekle-Haimanot R et al., 1997 May). These factors are likely to have contributed to the considerable variability in incidence estimates reported in LMIC (Chapter 3), ranging from 42/100,000 per year in India (Saha SP et al., 2008) to 215/100,000 per year in Uganda (Kaiser C et al., 1998 May).

Our meta-analysis of published incidence studies suggested the need for large population-based studies in LMIC to accurately estimate the incidence of epilepsy (Chapter 2).

In this study we estimate the incidence of active convulsive epilepsy (ACE) in a large population-based cohort in a rural area of Kenya over a five year period.

Methods

Our study consisted of two cross-sectional surveys, separated by five years, nested in a demographic surveillance system. In the first survey we determined the ACE status of residents to identify a cohort of individuals without epilepsy; in the second survey we re-examined this cohort to determine the number that had developed ACE during the intervening period. The incidence of epilepsy was then calculated by dividing the number of incident cases by the person years of observation among cohort members (re-identified in the second survey).

Study setting and study population

We conducted the study within the Kilifi Health and Demographic Surveillance System (KHDSS - http://www.kemri-wellcome.org/khdss/) which covers an area of 891 km^2, in Kilifi District, one of the poorest districts in Kenya comprising of a population of 233,881 persons in 2008 living in 25,526 homesteads (Scott JA et al., 2011). The KHDSS area has been mapped using global positioning system (GPS) receivers, and digital maps derived from these data are used to locate homesteads and follow up study participants. Community based field workers conduct re-enumeration and vital status registration to update the population registers by visiting every homestead two or three times per year. The population is served by the Kilifi District Hospital (KDH) which is located at the centre of the KHDSS area.

Residents of the study area are predominantly Mijikenda, a Bantu grouping of nine tribes with Girima (45%), Chonyi (33%) and Kauma (11%) being the most common. About 55% of the population is considered absolutely poor with per capita monthly income of about USD 10. The majority (80%) depend on subsistence farming, which is constrained by the low agricultural potential of the land (only 19% is arable). Only 45% of people are literate. Crude birth and death rates for this area are approximately 35/1,000 and 6/1,000 per year respectively, and migration rates are approximately 100/1,000 per year, most of which is within the study area (Scott JA et al., 2011). Malaria is seasonal, with two peaks in transmission during May to August and December to January (Snow et al., 1993b). Infectious diseases such as malaria, pneumonia or bacteraemia are common causes of paediatric admission to KDH (Berkley et al., 2003). The area has however experienced dramatic decline in slide-positive malaria admissions over the last decade (O'Meara et al., 2008).

Cohort identification and follow-up

We identified cohorts of people with and without ACE in a baseline cross-sectional survey described by Edwards et al., (Edwards T et al., 2008). The survey was undertaken by door-to-door visits of all residences within the KHDSS between August and November 2003.

The three-stage method used to identify cases has been described elsewhere in detail (Chapters 4 and 5). Briefly, the first stage (SI) involved asking the head of each household two screening questions to identify members of the household with a history of convulsions. Those that were positive were followed-up in Stage II (SII) and were interviewed by a team of field personnel trained to administer a more detailed and specific ACE screening tool (Appendix 4.2).

Respondents positive in SII were then evaluated in the stage III (SIII) where a diagnosis of ACE was made using detailed clinical history taken by a clinician trained in epilepsy and fluent in the local languages (Appendix 5.1). The International League Against Epilepsy (ILAE) definitions of active epilepsy were used (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993; Meinardi et al., 2001), but a cut-off of at least one seizure in the preceding 12 months was used for active epilepsy (Ministry of Health, 2002). Children less than 6 years of age were excluded in SII of the baseline survey due to difficulties of differentiating febrile seizures and epilepsy in younger children.

Deaths and migration were identified during the routine re-numeration within the KHDSS during the follow up period. In the second cross-sectional survey, conducted between December 2007 and June 2008, we attempted to interview every subject in the cohort who had not died and was still a resident in the KHDSS. No attempt was made to find subjects from the first survey who had migrated out of the study area due to logistical and cost implications. The second cross-sectional survey used the same methodology as the first cross-sectional survey to identify new cases of ACE.

In both surveys, we defined ACE as at least two unprovoked convulsions (tonic and/or clonic seizures) of which one occurred in the 12 months preceding the survey (Meinardi et al., 2001). An incident case of ACE was a participant who was found not to have ACE in the first survey but was subsequently detected as a case in the follow-up survey. For an incident case, the first seizure may have occurred days or years before the second survey (Jallon et al., 2001). These cases were included in the analysis because there had been no other diagnosis of epilepsy prior to

presentation in the current study (Hauser et al., 1996; Olafsson E et al., 2005 Oct). We thus defined an incident case on the basis of the date of diagnosis of epilepsy rather than on the date of the second unprovoked seizure (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993) since the recall of dates by the patients and their care-takers was likely to have been poor.

Analysis

We estimated incidence rates (IR) of ACE as the number of new diagnoses of ACE among the subjects that did not have ACE in the baseline cross-sectional survey, divided by the total person years of observation (pyo). Person-observation time lost due to out-migration or death was excluded from the denominator. We estimated an overall incidence rate together with 95% confidence interval (95% CI) assuming a Poisson model for the number of incident cases. Incidence rates were also estimated by age-group, sex and by administrative location.

We used the technique of multiple imputation (MI) with five imputations to reduce bias due to loss to follow-up between stages of the two surveys (Rubin DB, 1987; van Buuren S, 2007). The imputation model used the outcome from SI to impute SII where this was missing, and the outcome from SII to impute SIII. All incidence estimates were adjusted for the low sensitivity (48.6%) of the screening methodology (Chapter 4). Incidence rates were compared between age, sex and administrative area categories using incidence rate ratios (IRR) obtained from Poisson regression models.

All analyses were carried out in STATA version 11 (StataCorp. College Station, TX, USA).

Written informed consent was obtained from all study participants. Where the patient was a child or an adult who could not respond, a caregiver was interviewed. Approval for the study was obtained from the Kenya Medical Research Institute/ National Ethical Review Committee.

Results

In the baseline survey, we identified 448 subjects with ACE and 150,960 subjects without ACE. At the follow up survey, 45,809 (30.3%) participants of the cohort had been lost [42,506 (92.8%) had out-migrated, 2,703 (5.9%) had died and 600 (1.3%) could not be traced]. The baseline characteristics of cohort members who were found and were not found in the 2008 survey are displayed in Table 6.1. We found 194 incident cases of ACE and estimated that there would be 233 incident cases (after adjustment for loss to follow-up) and 479 incident cases (after adjustment for both loss to follow-up and sensitivity of the screening methodology described in chapter 4). The median (IQR) age of incident cases was 19.5 (14-31) years. The proportion of males was 49%.

The total person-years of observation (pyo) for this cohort was 623,004 and the overall incidence rate was 77.0/100,000 pyo (95% CI: 67.7 – 87.4) after adjusting for loss to follow-up and the sensitivity of the three-stage survey methodology.

Table 6.1: Main characteristics of the incidence study completers and those lost to follow-up.

		Recaptured at follow up		Lost at follow up	
Attribute	**Category**	**N**	**%**	**N**	**%**
Sex	Male	47,548	45.2	22,278	48.6
Mean age (years)		26.2		24.6	
Area	Roka-M-M†	14,691	14.0	5,654	12.3
	Ngerenya	6,352	6.0	2,703	5.9
	Tezo	13,590	12.9	5,843	12.8
	Chonyi	21,133	20.1	6,841	14.9
	Sokoke	3,886	3.7	1,691	3.7
	Jarubini-Kauma	6,143	5.8	2,348	5.1
	Junju	17,979	17.1	7,626	16.7
	Takaungu	10,723	10.2	4,454	9.7
	Kilifi Township	10,654	10.13	8,649	18.9
Ethnicity	Giriama	45,310	43.1	20,506	44.8
	Chonyi	36,687	34.9	12,757	27.9
	Kauma	12,133	11.5	4,872	10.6
	Other Mijikendas	5,723	5.4	3,002	6.6
	Luos	593	0.6	856	1.9
	Others	4,702	4.5	3,803	8.3
Stage I status at baseline	Positive	1,425	1.4	475	1.0
All cohort members		105,151		45,809	

†Roka-Matsangoni-Mida

There was strong evidence of variation of incidence of ACE with age and the association appeared to follow a U-shape. The lowest incidence was in the 29-49 year age group (37.4/100,000 persons/year; 95% CI: 25.7 – 54.7) and the highest was in the 6-12 year old age group (96.1/100,000 persons/year; 95% CI: 78.4 – 117.9). The rate ratio for this association was 0.46 (95% CI: 0.31 – 0.71) (Table 6.2). Incidence did not vary by sex, administrative area of residence or ethnicity and there were no incident cases amongst the Luo ethnic group which also had the least person-years of follow-up (Table 6.2).

Table 6.2: Incidence rates and ratios for age, sex, ethnicity and area of residence for active convulsive epilepsy in Kilifi, Kenya.

		Pyo	Cases*	Incidence Rate*	95% CI	Rate ratio	95% CI	P value
Age group								
	6-12	197040	189	96.1	78.4-117.9	1.0		
	13-17	90246	82	91.2	66.9-124.3	0.91	0.62-1.33	
	18-28	102426	84	82.3	60.7-111.9	0.82	0.56-1.20	0.008
	29-49	148020	56	37.4	25.7- 54.7	0.46	0.31-0.71	
	50+	85272	68	79.6	56.6-111.9	0.86	0.57-1.28	
Sex								
	Female	341406	249	72.8	61.1-87.2	1.0		0.3
	Male	281598	230	81.9	67.9-98.6	1.2	0.9-1.5	
Ethnicity								
	Giriama	268206	210	78.2	64.4-95.1	1.0		
	Chonyi	218370	158	72.6	58.0-90.7	0.94	0.69- 1.27	
	Kauma	71814	68	94.7	67.3-132.9	1.35	0.92- 1.98	0.65
	Other Mijikenda	33864	29	85.0	50.4-143.6	0.98	0.54-1.78	
	Luo	3390	0	0	-	0	-	
	Other	27360	14	52.7	25.1-110.5	1.01	0.53- 1.93	
Area								
	Roka-Matsangoni-Mida	86808	93	106.6	79.6-142.8	1.0		
	Ngerenya	37962	29	75.9	44.9-128.2	0.65	0.35-1.20	
	Tezo	80664	56	68.9	47.3-100.4	0.61	0.38-.098	
	Chonyi	126204	93	73.5	54.7-98.4	0.63	0.41-0.95	0.35
	Sokoke	23070	25	107.0	60.7-188.5	0.82	0.41-1.62	
	Jaribuni	36612	33	89.9	55.1-146.7	0.77	0.43-1.38	
	Junju	106938	80	75.1	54.7-102.7	0.67	0.44-1.03	
	Takaungu	63762	43	67.7	44.2-103.9	0.56	0.33-0.96	
	Kilifi Township	60984	29	47.3	28.0-79.8	0.59	0.34-1.00	

*Adjusted for loss to follow-up and sensitivity of the screening methodology

Discussion

In this large-scale study, we estimated an overall incident rate of ACE at 77.0/100,000 persons per year with evidence for variation with age. We used two cross-sectional surveys 5 years apart within an existing HDSS of a rural population in Kenya to identify incident cases of ACE. Cases were identified in three-stage cross-sectional surveys at the beginning and at the end of the follow-up period. ILAE definitions (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993) were used to define cases and non-cases (Edwards T et al., 2008).

Within the KHDSS framework, our study benefited from continuous follow-up for migration and death but was only able to determine the cumulative incidence of new cases from the cross sectional study that was conducted at the end of the study. It was not possible to determine the epilepsy status of residents who migrated away or died, although the demographic profile of these people was similar to that of the cohort members who were found at the second cross-sectional survey. In particular, the proportions of people with histories of convulsions at baseline (i.e., positive in the first stage of the baseline survey and therefore more likely to develop ACE) were similar among those lost and those who remained in the cohort. However, since mortality is typically highest in the first 1-3 years following the onset of seizures (Cockerell et al., 1994; Forsgen L et al., 2005), incidence may have been underestimated because we evaluated our cohort five years apart.

We investigated ACE as opposed to all epilepsies (and life-time epilepsy) for two major reasons. Firstly, convulsive epilepsies are much easier to recognize in community based settings and

hence do not require specialized personnel to identify, reducing cost and enabling us to survey a large HDSS population efficiently. Secondly, convulsive epilepsies are more likely to be associated with disability, mortality and stigma and are also more amenable to prevention and control. We excluded children under six years of age because of difficulties in differentiating between neonatal seizures, febrile seizures and epilepsy in this age group.

At the rate of 77/100,000 pyo, the incidence of ACE was in the 42.1-81.1/100,000 persons/year range reported for both convulsive and non-convulsive epilepsies in other LMIC (Rwiza HT et al., 1992 Nov-Dec; Saha SP et al., 2008; Tekle-Haimanot R et al., 1997 May; Winkler AS et al., 2009), the pooled estimates for LMIC reported in chapter 3 of this thesis and one study in Denmark that reported an incidence rate of 83.8/100,000 persons per year (Christensen et al., 2007). This estimate was however higher than that reported for other HIC (Kotsopoulos I et al., 2005; Ngugi et al., 2011; Olafsson E et al., 2005 Oct). Prevalence studies that have included non-convulsive epilepsies (Birbeck GL, 2004 Jan; Kaamugisha J and Feksi AT, 1988) have reported prevalence estimates that were 2-3 times higher than those that studied convulsive epilepsies only (Rwiza HT et al., 1992 Nov-Dec; Tekle-Haimanot R et al., 1997 May). Assuming similar rates for mortality and remission across studies, these findings would suggest that the incidence of all epilepsies (including focal epilepsies) in our population could be in the range of 154-231/100,000 persons/year, which are higher than those reported from other LMIC (Medina MT et al., 2005 Jan; Rwiza HT et al., 1992 Nov-Dec; Winkler AS et al., 2009). This rate would however be similar to that reported in an Onchocerciasis endemic area of Uganda (Kaiser C et al., 1998 May) and within the range estimated for LMIC in a recent review of incidence of life-time epilepsy (Chapter 3). We used an active epilepsy definition in which the last seizure was

within the previous 12 months as suggested by Meinardi (Meinardi et al., 2001) and because recall of seizures over a year ago is poor (Snow et al., 1993a). Other studies have used a 5-year cut-off (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993) and thus under our definition, the incidence of convulsive epilepsy in this population could be considerably higher.

Overall, the incidence rate was not different between males and females in our study population, which was contrary to findings from other LMIC which reported higher incidence in females (Rwiza HT et al., 1992 Nov-Dec; Winkler AS et al., 2009), or in males (Tekle-Haimanot R et al., 1997).

Age-specific incidence was highest in the children, adolescents and young adults aged 6-28 years and in the old age (50+ years), relative to the 29-49 year age-group. In the 6-28 year age group, onset of recurrent seizures could be related to perinatal insults and infections of the central nervous system particularly in the younger children (Mung'ala-Odera et al., 2008; Preux PM and Druet-Cabanc M, 2005). Many genetically determined epilepsies may also manifest during this period (Edwards T et al., 2008; Goudsmit J and van der Waals FW, 1983; Jilek-Aall L et al., 1979; Jilek WG and Jilek-Aall LM, 1970; Matuja et al., 2001). In the adolescents and young adults, recurrent seizures may develop as a consequence of temporally remote aetiologies that result in static encephalopathies e.g. infectious brain insults earlier in life, cerebral palsy and mental retardation or engaging in activities that increase the risk of head injuries (Edwards T et al., 2008; Nell and Brown, 1991; Ogunniyi et al., 1987).

The age-incidence relationship in our study showed a characteristic U-shape, with lower risk in the young and middle aged adults as has been observed in the HIC (Jallon P et al., 1997 May; Olafsson E et al., 2005 Oct). In this age group (29-49 years), the incidence rate was 54% lower than the 6-12 years age group. This suggests that most of the epilepsy in this community affects the younger population. The incidence rate was also higher in the elderly (50+ years) compared to younger adults, which has also been observed in industrialized countries (Everitt and Sander, 1998; Forsgren L et al., 1996 Mar; Kotsopoulos I et al., 2005; Olafsson E, 1996 Oct; Sander et al., 1990) and in one study in Tanzania (Rwiza HT et al., 1992 Nov-Dec) but not in another study in Ethiopia (Tekle-Haimanot R et al., 1997 May). Although it has not been documented in LMIC, elderly people may experience higher risk of developing epilepsy associated with progressive brain conditions which include tumours, cerebro-vascular accidents and neuro-degenerative conditions such as Alzheimer's disease (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993).

In view of the high incidence of ACE in this population, aetiological studies are necessary in order to elucidate causes, particularly among children, adolescents and the elderly who are at highest risk. Furthermore these age groups should be targeted for preventive public health interventions.

Limitations of the study

We utilized a three-stage survey methodology that had low sensitivity (48.6%) to detect cases of ACE (Chapter 4). Although we were able to adjust estimates for the low sensitivity it is possible that some cases of ACE missed during the baseline survey due to low sensitivity could have been

counted as incident cases in the follow-up survey thus causing an overestimation of incidence rate.

On the other hand, it is also likely that early mortality due to epilepsy and remission may also have led to an underestimate of the number of incident cases, given the duration and the design of follow-up in this study. Future studies would benefit from a more frequent re-evaluation (e.g. every six months) of the cohort to ensure maximum detection of incident cases i.e. follow-up of prospectively identified cohorts of incidence cases, preferably population-based. We also excluded children <=5 years of age from this study, which may have resulted in a further underestimation of incidence in the study population.

Conclusion

We estimated the incidence of ACE in the largest population-based prospective cohort in Africa that was twice as high as that in HIC and within range of estimates reported for LMIC. The risk of epilepsy was highest in children, adolescents and young adults and the elderly and as such, preventive interventions should target exposures that occur early and later in life.

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Chapter 7: Mortality and factors associated with mortality in people living with convulsive epilepsy in a rural area of Kenya

NGUGI, A.K., BOTTOMLEY, C., FEGAN, G., KLEINSCHMIDT, I., NEWTON, C.R. (2012). Mortality and factors associated with mortality in people living with convulsive epilepsy in a rural area of Kenya. (Prepared for submission to *The Lancet*)

Abstract

Objective: Most of the epilepsy mortality studies from Low and Middle Income Countries (LMIC) are based on small cohorts of people with epilepsy (PWE) while some have been conducted in areas where the incidence of epilepsy is very high and thus may not be representative of the general population. Furthermore, there are currently no studies on risk factors associated with mortality PWE in LMICs. We conducted a study to estimate the mortality rate and identify factors associated with mortality in a large cohort of people with active convulsive epilepsy (ACE) in a rural area of Kenya.

Methods:

People with ACE were identified in a cross-sectional population screening and followed up every three months for three years to collect information on putative risk factors of mortality. We estimated, mortality rates (MR), mortality ratios and standardized mortality ratio (SMR) based on age distribution of the Kilifi Health and Demographic Surveillance System (KHDSS) population at the baseline cross-sectional screening. We used Poisson regression analysis to examine the influence of potential risk factors on mortality.

Results:

We registered 61 deaths from among 754 people with ACE, yielding a mortality rate of 33.3/1,000 person/year (95% confidence interval [CI]: 25.9-42.8). The overall SMR was 6.5 (95% CI: 5.0-8.3) and mortality was significantly higher in people with ACE for all age groups.

Non-adherence to anti-epileptic drugs (AEDs) was associated with mortality in this population; the adjusted rate ratio was 4.0 (95% CI: 2.1-7.7).

Conclusion:

We estimated that mortality in people with ACE in the Kilifi HDSS population was more than six fold that of the general population and was increased in all age groups. Mortality is associated with non-adherence to treatment which is amenable to intervention.

Introduction

Epilepsy is one of the most prevalent non-communicable neurological conditions in the world and an important cause of disability and mortality (WHO, 2004). It is estimated to affect approximately 69 million people in the world, with up to 90% living in low and middle income countries (LMIC) (Chapter 2). A large number of mortality studies in people with epilepsy have been carried out in High Income Countries (HIC) (Benn et al., 2009; Cockerell et al., 1994; Forsgen L et al., 2005; Hauser et al., 1980; Holden EW et al., 2005; Kochen S and Melcon MO, 2005 Dec; Lhatoo and Sander, 2005; Lindsten H, 2000 Nov; Mohanraj R, 2006 Jun; Nilsson L, 1997 Oct; Olafsson E, 1998 Jan; Tsai JJ, 2005) and in LMIC (Carpio et al., 2005; Coleman et al., 2002; Ding et al., 2006; Diop et al., 2005; Kaiser et al., 2007; Kamgno J, 2003 Jul; Mu et al., 2011; Snow RW et al., 1994).

Most of the mortality data from LMICs are based on small cohorts of people with epilepsy which register small numbers of mortality events (Coleman et al., 2002; Kaiser et al., 2007; Snow RW et al., 1994), leading to imprecise estimates. Some studies have been conducted in areas where the incidence is very high (Kaiser et al., 2007) and thus may not be representative of this region. This limitation could be attributed to the high cost and requirement for continuous surveillance of large cohorts of patients needed to generate accurate estimates. Furthermore, mortality rates between these studies are difficult to compare since they estimated different epidemiological measures of mortality (mortality rates, proportional mortality, relative risk of death in a case-control study in Cameroon (Kamgno J, 2003 Jul) and standardized mortality ratios).

Cause-specific mortality in epilepsy has been investigated in a number of HIC (Forsgen L et al., 2005; Lhatoo and Sander, 2005) but so far only in China (Ding et al., 2006; Mu et al., 2011) among the LMIC. In HIC, mortality in people with epilepsy has been associated with age at onset of seizures; highest in those developing seizures in childhood (<15 years) or in the elderly (> 65 years) (Hesdorffer et al., 2011; Tomson and Forsgren, 2005; Tomson et al., 2005), and duration of epilepsy (risk being highest in the first 1-2 years following the onset of seizures) (Forsgen L et al., 2005). Other important factors include: 1) seizure frequency (higher in those with more frequent seizures) (Tomson et al., 2005), 2) seizure types (higher in generalized tonic-clonic seizures (Hesdorffer et al., 2011; Langan et al., 2005; Tomson et al., 2005), myoclonic (Forsgen L et al., 2005), and epilepsy syndromes (remote symptomatic epilepsies) (Beghi et al., 2005; Cockerell et al., 1994)and, 3) non-adherence to AED (Langan et al., 2005).

To estimate the rate of mortality and factors associated with mortality among individuals with epilepsy in a resource-limited setting, we conducted a population-based prospective study in a large cohort of people with active convulsive epilepsy (ACE) in a rural area of Kenya.

Methods

Study setting and study population

The study setting and characteristics of the study population have been described previously (Chapters 4 and 5). Briefly, we conducted the study within the KHDSS (http://www.kemri-wellcome.org/khdss/) which is within the Coast province of Kenya. The study area comprised of a population of 233,800 persons in 2008 living in 25,526 homesteads (Scott JA et al., 2011). The

area has been mapped using global positioning system (GPS) receivers, and digital maps are used to locate homesteads and follow up study participants. The KHDSS field personnel conduct re-enumeration and vital status registration to update the population registers by visiting every homestead three times per year. The population is served by the Kilifi District Hospital (KDH) which is located approximately at the centre of the KHDSS area.

Residents of the study area are predominantly Mijikenda, a Bantu grouping of nine tribes with the most common being the Girima (45%), Chonyi (33%) and Kauma (11%). Approximately 55% of the population is considered to be absolutely poor with per capita monthly income of about USD 10. A large proportion of the population (~80%) depend on subsistence farming, which is constrained by the low agricultural potential of the land (only 19% is arable) and the rest are engaged in salaried employment (both casual and formal) or petty trading. Only about 45% of the population is literate. Crude birth and death rates for this area are 35/1,000 and 6/1,000 per year respectively, and migration rates are approximately 100/1,000 per year, most of which is within the study area (Scott JA et al., 2011).

Identification and follow-up of cohorts of participants with and without ACE

Cohorts of people with and without ACE were identified in a baseline three-stage population wide prevalence screening within the KHDSS between December 2007 and June 2008 as described elsewhere (Chapter 4). Briefly, the first stage (SI) involved asking the head of each household two screening questions to identify members of the household with a history of convulsions. Those that were positive were followed-up in Stage II (SII) and were interviewed

by a team of field personnel trained to administer a more detailed epilepsy screening tool. Those positive in SII were then evaluated in the third stage (SIII) where a diagnosis of ACE was made using detailed clinical history taken by a specialist epilepsy clinician. These diagnoses were further confirmed independently by a panel of neurologists.

We used the International League Against Epilepsy (ILAE) definitions of epilepsy (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993), but defined active epilepsy as at least one seizure in the preceding 12 months (Meinardi et al., 2001), since this is also the criteria for offering anti-epileptic treatment in Kenya (Ministry of Health, 2002).

The ACE cohort identified at the baseline screening was followed up every three months in the study clinic for dose adjustments, assessment of adverse events, monitoring adherence and to replenish supplies of AEDs. Those members of the cohort that failed to attend the clinic appointments were followed up in the community within two weeks by trained epilepsy study field personnel. During each review follow-up, we administered a questionnaire to capture demographic data and information on the risk factors for mortality, which included seizure frequency and types, adherence to AED and age of onset of seizures.

Classification of seizure types for all patients was done by a study clinician using the recommendations of the Commission of the Classification and Terminology of the ILAE (Berg AT et al., 2010). Participants who were not on treatment (i.e. were not on any AED) during any of the follow-ups were classified as non-adherent to medication. This was determined by asking whether they were currently taking AEDs as well as asking to see the medication.

The cohort of people without ACE was followed-up for vital status and migration during the routine (four-monthly) re-enumeration within the KHDSS. Participants were followed-up till death, or censored at out-migration (and during the last clinic contact or withdrawal of consent/refusal for cases of ACE), and at the end of the study in March 2011.

Analyses

The crude mortality rates for the ACE and non-ACE cohorts were estimated as the number of deaths divided by their respective total person years of observation (pyo). To compare mortality between people with and without ACE, mortality among patients with ACE was tabulated in age strata and indirectly standardized against the population without ACE at the baseline survey to estimate the standardized mortality ratio (SMR).

Among the cohort with ACE we examined the influence of 6 putative risk factors on mortality: (i) age (years) at onset of seizures (grouped as 0-5, 6-12, 13-17, 18-28, 29-49 and 50+ year age bands), (ii) sex (male, female), (iii) seizure types (none, focal, generalized tonic-clinic (GTCS), partial becoming secondarily generalized (PBSG) and others), (iv) number of seizure types (none, 1, >=2), (v) seizure frequency per month (<=2, >2) and, (vi) number of AEDs (none, >=1).

To further explore the relationship between AED usage and mortality we used Poisson regression to adjust for the potential confounding effects of number of seizure types, seizure

frequency, and current age (0-5, 6-12, 13-17, 18-28, 29-49 and 50+ years). Each of these potential confounders was included in the Poisson model as a time-dependent covariate.

All analyses were carried out in STATA v. 11 (StataCorp. College Station, TX, USA).

Written informed consent was obtained from all study participants. Where the PWE was a child or an adult who could not respond, a caregiver was interviewed. Approval for the study was obtained from the Kenya Medical Research Institute/ National Ethical Review Committee.

Results

At commencement of the study 232,176 individuals were screened within the Kilifi HDSS (Chapter 5), identifying 762 individuals with ACE. Of the total population 12 participants could not be traced at the start of the study and 232,164 entered follow-up, comprising of 754 individuals with and 231,410 without ACE. The median (IQR) follow-up was 18 (9-24) months. Within the ACE group we recorded a total of 7,331 patient contacts episodes with a mean of 9.7 follow-up contacts per person. During the 39 months of the study, we registered 61 mortality events in people with ACE and 3,291 in people without ACE. Study outcomes of participants by ACE status are displayed in Table 7.1.

Table 7.1: Follow-up of study participants with and without active convulsive epilepsy in Kilifi, Kenya.

Status	Non-ACE	%	ACE	%	Total
Moved	70,339	30.40	49	6.50	70,388
Lost	92	0.04	15	1.99	107
Refused	0	0.00	23	3.05	23
Died	3,291	1.42	61	8.09	3,352
Completed	157,688	68.14	606	80.37	158,294
Total	**231,410**	**100.00**	**754**	**100.00**	**232,164**

The total person-years of observation for the ACE cohort was 1,832.8 and that of the non-ACE group was 540,909.3, yielding crude mortality rate estimates of 33.3/1,000 pyo (95% CI: 25.9-42.8) and 6.1/1,000 pyo (95% CI: 5.9-6.3) respectively.

There was strong evidence that mortality was associated with ACE in this population. The overall SMR for ACE was 6.5 (95% CI: 5.0-8.3). Comparative mortality was highest in the 6-12 year age group in people with ACE: rate ratio was 22.5 (95%CI: 12.4-40.6), and was high in all age groups with ACE (Fig 7.1).

In the univariable analysis, patients who were not adherent to medication had a 3.0 fold the risk of mortality that of patients who were on at least one AED (Table 7.2). In the multivariable analyses (Table 7.3), we adjusted the effect of non-adherence for seizure frequency and number of seizure types since these were likely to confound the relationship between non-adherence and mortality. The multivariable Poisson regression showed that patients not taking AED were at higher risk of death; adjusted rate ratio was 4.0 (95% CI: 2.1-7.7) (Table 7.3).

Figure 7.1: Age-specific mortality rate ratios and standardized mortality ratio (SMR) for active convulsive epilepsy in Kilifi, Kenya.

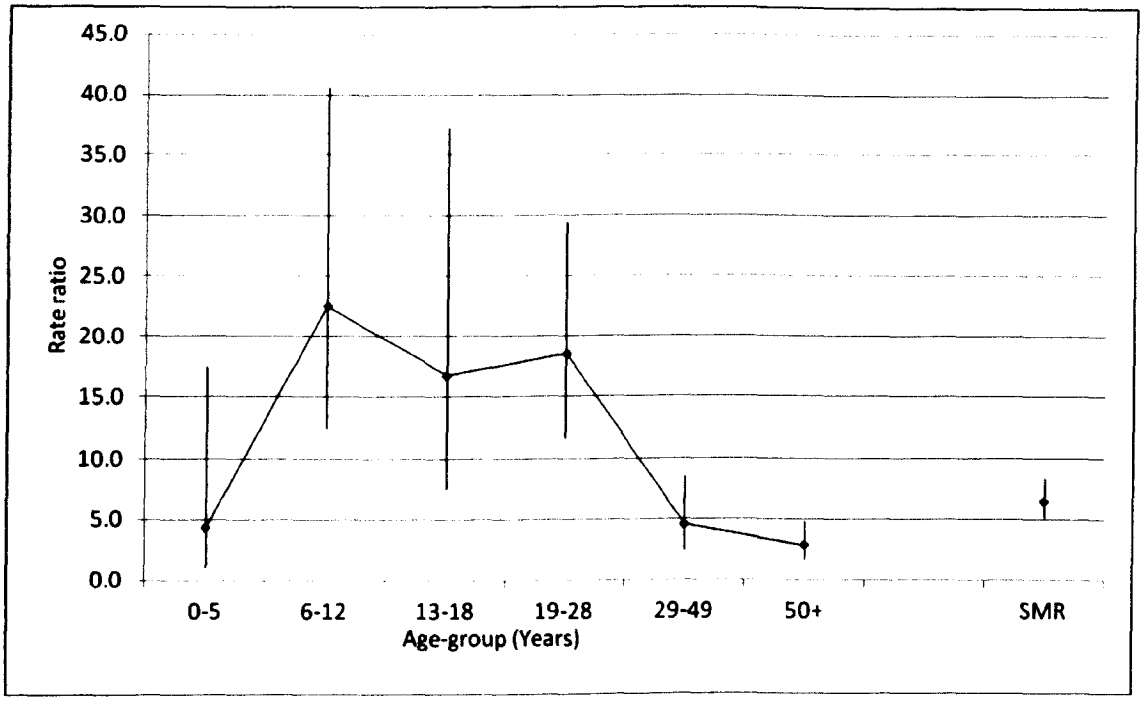

Table 7.2: Univariable analysis of factors associated with mortality in people with active convulsive epilepsy in Kilifi, Kenya.

Factor	Person-time	Deaths	Mortality rate	95% CI	Unadjusted Rate Ratio	95% CI	P-value
Age at Onset							
0-5	1108.7	27	24.4	(16.7-35.5)	1.0		
6-12	278.7	10	35.9	(19.3-66.7)	1.4	(0.7-3.0)	
13-18	165.5	8	48.3	(24.2-96.7)	1.7	(0.7-4.0)	
19-28	111.3	1	9.0	(1.3-63.8)	0.6	(0.1-2.7)	0.2
29-49	76	3	39.5	(12.7-122.4)	1.5	(0.3-6.7)	
50+	92.5	12	129.7	(73.7-228.4)	5.8	(0.9-36.8)	
Sex							
Female	881.7	32	36.3	(25.7-51.3)			
Male	951	29	30.5	(21.2-43.9)	0.9	(0.5-1.5)	0.6
Seizure Type							
None	1176.7	37	31.4	(22.8-43.4)	1.0		
Focal	173.8	3	17.3	(5.6-53.5)	0.6	(0.2-1.9)	
GTCS	256.7	11	42.8	(23.7-77.4)	1.4	(0.7-2.8)	0.5
PBSG	151.3	7	46.3	(22.1-97.1)	1.6	(0.7-3.6)	
Others	74.3	3	40.4	(13.0-125.3)	1.5	(0.5-4.8)	
No. of Seizure types							
none	1176.7	37	31.4	(22.8-43.9)	1.0		
one	623.7	22	35.3	(23.2-53.6)	1.4	(0.8-2.4)	
>=2	32.3	2	62	(12.5-248.0)	2.4	(0.6-9.9)	0.3
Seizure Frequency							
<=2/month	1717.5	55	32	(24.6-41.7)	1.0		
>2/month	115.3	6	52.1	(23.4-115.9)	1.7	(0.7-4.0)	0.2
No. of AEDs							
>=1	870.2	14	16.1	(9.5-27.2)	1.0		
None	962.5	47	48.8	(36.7-65.0)	3.1	(1.7-5.6)	<0.001

Table 7.3: Multivariable analysis of factors associated with mortality in people with active convulsive epilepsy in Kilifi, Kenya.

	Person-time	Deaths	Mortality rate	95% CI	Adjusted Rate Ratio	95% CI	P-value
No. of Seizure types							
none	1176.7	37	31.4	(22.8-43.9)	1.0		
one	623.7	22	35.3	(23.2-53.6)	1.9	(1.0-3.4)	
>=2	32.3	2	62.0	(12.5-248.0)	4.7	(1.0-22.1)	0.06
Seizure Frequency							
<=2/month	1717.5	55	32.0	(24.6-41.7)	1.0		
>2/month	115.3	6	52.1	(23.4-115.9)	1.3	(0.5-3.2)	0.6
No. of AEDs							
>=1	870.2	14	16.1	(9.5-27.2)	1.0		
None	962.5	47	48.8	(36.7-65.0)	4.0	(2.1-7.7)	<0.001

Discussion

To our knowledge, this is the first study to report on factors associated with mortality in people living with epilepsy in LMIC. We used a cross-sectional survey to identify people with and those without ACE and a prospective cohort design to follow-up cases at regular intervals. We minimized attrition within the study by following up people in the community if they failed to attend scheduled clinic appointments. Our study benefitted from an established demographic surveillance system that maintains a regularly updated population register and provides relatively accurate denominator data, for the estimation of mortality rates.

Our findings showed that people with ACE in this area had more than 6-fold risk of death compared to people without ACE. Although mortality was elevated for all ages relative to the

general population, this increase was more marked in the older children, adolescents and young adults aged 6-28 years.

The high mortality rate in our study, relative to other studies that reported mortality rates ranging between 0.024-6.2/1000 person-years (Harvey et al., 1993; Hauser et al., 1996; Sillanpaa et al., 1998; Zielinski JJ, 1974), could partly be due to the fact that we focused on active convulsive epilepsy, which is associated with higher risk of psychosocial co-morbidity and death than life-time and non-convulsive epilepsies (Forsgen L et al., 2005; Lhatoo and Sander, 2005). This finding could also be a reflection of the severity of epilepsy and its underlying causes.

The age-SMR relationship in our study could be due to low mortality in the corresponding age groups in the general population. Indeed, the age-specific mortality rates in people without ACE were lowest in the 6-28 year age-groups which also had the highest SMR. On the other hand the lower SMR in the young children (0-5 years) and older adults and the elderly (29-49 and 50+ years) indicate relatively higher mortality in the general population. Mortality in these age-groups is related to perinatal, nutritional and infectious causes in the very young (Berkley et al., 2003; Moisi et al., 2011) and HIV-related and cardiovascular causes in the older age groups (Bauni et al., 2011).

The higher relative mortality (compared to people without ACE) in older children (6-12 years), adolescents (13-17 years) and young adults (18-28 years) was similar to the observation in a Ugandan study in which mortality was highest in patients aged 10-20 years (Kaiser et al., 2007) and in one study in China (Ding et al., 2006). This finding points to the possibility of epilepsy

related causes of death, either directly or indirectly, such as status epilepticus and drowning (Jilek-Aall and Rwiza, 1992). In our study of incidence of epilepsy in the same population, incidence was highest in the same age groups (Chapter 5), which conforms to the observation that mortality tends to be highest in the first few years following the onset of epilepsy (Cockerell et al., 1994; Forsgen L et al., 2005). In these age groups, it is likely that aetiologies of epilepsy are also important causes of death in people with epilepsy. For example, these age groups are more likely to engage in activities that increase the risk of traumatic head injuries which may cause epilepsy and also increase the risk of accidental death due to occurrence of seizures in dangerous circumstances. Alternatively, it is possible that large proportions of cases in this age group could be remote symptomatic epilepsies that develop as a consequence of temporally remote aetiologies that result in static encephalopathies e.g. cerebral hypoxia at birth, infectious brain insults, cerebral palsy and mental retardation.

In the univariable analysis, patients who were non-adherent to anti-epileptic medication were at a higher risk of mortality. We adjusted for potential confounding of the relationship between this variable and mortality by seizure frequency and number of seizure types in the multivariable analyses since these were associated with non-adherence in this study ($p<0.001$) and have been shown to be important predictors of mortality in other studies. High seizure frequency is a risk factor for epilepsy associated causes of death such as accidents (accidental fall from heights and drowning) and sudden unexpected death in epilepsy (SUDEP) (Lhatoo and Sander, 2005). It is related to poor seizure control in non-adherent patients and in those with refractory epilepsy (Langan et al., 2005). In the adjusted analysis non-adherent patients had a fourfold the risk of mortality compared to those on at least one drug. This finding is important in view of the high

epilepsy treatment gap (75%) estimated in a recent study in Kilifi (Mbuba CK et al., 2012) and concurs with findings of one study from HIC (Langan et al., 2005) but were contrary to another study in LMIC (Kaiser et al., 2007) which did not find higher mortality among non-adherers. Possible reasons for disagreement between our study and that of Kaiser and his co-workers are: (i) the latter study was relatively small (61 patients) and they recorded only 18 deaths in their cohort, (ii) they measured adherence subjectively by constructing an adherence index based on self-reported adherence and assessment of clinical notes, and it has been shown that self-reported adherence has low sensitivity when compared to blood-levels of AEDs in a recent study in Kilifi (Mbuba CK et al., 2012), (iii) self-reported adherence in the study by Kaiser was based on long recall as it was assessed at only two time points over a six year follow-up period, and (iv) Kaiser and colleagues measured adherence in a life-time epilepsy cohort, in which some patients could have entered remission. The possible mechanism through which adherence to AEDs exerts an effect on the risk of mortality is through seizure control. Non-adherence leads to poorly controlled seizures, which increases the severity of epilepsy (with respect to frequency and duration of seizures as well as duration of epilepsy) and thus higher risk of epilepsy-related mortality.

Given the high risk of mortality in people with epilepsy in this area, particularly those not adherent to medication, there is an urgent need for preventive interventions. These could include instituting measures to reduce the incidence of epilepsy (e.g. prevention of trauma through use of head protection when riding motorcycles or bicycles, good prenatal care, including avoiding alcohol and treatment of high blood pressure and infections during pregnancy, reduction of childhood infections by improved public hygiene and immunization to reduce the risk of cerebral

damage, elimination of parasites in the environment that cause diseases such as malaria and cysticercosis and use of bed nets to prevent mosquito bites), educating people with epilepsy and their care-takers on the importance of seeking treatment, strict adherence to medication and identification of epilepsy-related risks of death. Monitoring of people with epilepsy, could mitigate some of the risks associated with epilepsy-related causes of death although this may be difficult to implement. An important factor that is associated with non-adherence in this population is long distances to AED distribution points, due to erratic supply in peripheral health facilities (Mbuba CK et al., 2012). Increasing access to AEDs by ensuring adequate supply at the primary health care level would lead to a significant reduction in mortality in people with epilepsy.

Limitations of the study

Our study suffered large attrition of people without ACE who were followed-up within the regular HDSS census. Due to cost and logistical implications, we did not attempt to determine their vital status and this loss to follow up may not have caused bias in our estimate of the mortality ratios since mortality rate in the non-ACE cohort was similar to what it is was the KHDSS generally.

We used a prevalence cohort of cases which might under-estimate short-term mortality because cases with more severe aetiologies of epilepsy die early in the course of the condition and may not be counted in estimation of mortality over the observation period. In view of this, a prospectively identified population-based cohort of incident cases would be the ideal to study mortality, but is much more expensive and logistically challenging.

There is a need for studies of cause-specific mortality of people with epilepsy to increase the impact of potential interventions aimed at reducing mortality in this population group.

Conclusion

Our study shows that mortality in people with ACE is more than six time that of the general population and was increased in all age groups in the KHDSS. Mortality is associated with non-adherence to treatment which is to a large extent preventable.

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Chapter 8: Summary and Conclusions, Implications for public health and directions for future research

Introduction

The studies in this thesis examine the burden of epilepsy at the global level using systematic review and meta-analysis of existing literature and at the level of LMIC using population-based cross-sectional methods to identify people with ACE for determination of prevalence and incidence. They also assess the methodology used in this and other studies to identify cases, quantify and compare mortality between epilepsy and non-epilepsy populations as well as identify the factors associated with mortality in people with ACE in the Kilifi HDSS.

This chapter summarizes and puts into context the main research findings with reference to the study objectives (Chapter 1), enumerates the public health implications of these findings and proposes some for public health actions and directions for future research.

Background

Epilepsy is an important cause of disability and mortality. It accounts for 0.5-1.0% of the global burden of disease and contributes up to 7 million disability adjusted life-years (DALYs) annually. DALY is a health gap measure that extends the concept of potential years of life lost due to premature death to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability (Leonardi M and Ustan TB, 2002; WHO/IBE/ILAE, 2005). In LMIC, the perceptions of causes and consequences of epilepsy differ from those in the HIC and often lead to stigmatization (Scambler G and Hopkins A, 1986). The stigma may in turn generate a hidden burden of epilepsy in which patients are unwilling to seek medical advice, generating large treatment gaps (Meinardi et al., 2001; Scott et al., 2001).

Epilepsy is associated with significant psychosocial co-morbidities that impact on the quality of life of patients and also influence prognosis. These include social maladjustments due to phobia of the unexpected and uncontrollable nature of epileptic seizures and the stigma (Dilorio C et al., 2003). Cognitive problems such as neuropsychological impairment (including poor memory, language skills, executive functions and motor speed) (Alvarado et al., 1992) and psychiatric conditions (particularly anxiety and depression) (Gaitatzis et al., 2004; Pellock, 2004; Trimble and Krishnamoorthy, 2003) occur with much higher frequency in people with epilepsy (PWE) than the general population, and higher frequency of seizures is associated with greater degree of psychopathology (Gaitatzis et al., 2004).

In 1993, The World Bank declared the control of epilepsy as highly cost-effective, in terms of the DALYs averted per the amount of monetary resources (measured in international dollars) used (World Bank, 1993) since relatively inexpensive AEDs were effective in controlling seizures in the majority of patients (Coleman et al., 2002). In the study by The World Bank, epilepsy was placed in the category of conditions that could be substantially controlled with a cost effective intervention (World Bank, 1993). A more recent study on cost-effectiveness of AEDs by the WHO-CHOICE (Choosing Interventions that are Cost-Effective) programme refined these data and estimated that extending treatment coverage to 50% of the current primary (idiopathic) epilepsy cases would avert 150 – 650 DALYs/million population (about 13 – 40% of the current burden) at an annual cost of 0.2 – 1.3 $ per case. Older first-line AEDs (phenobarbital, phenytoin, carbamazepine and valproic acid) were the most cost effective on account of similar efficacy and lower acquisition cost (800 – 2000 $ /DALY averted) (Chisholm, 2005). Despite the availability of cost-effective treatment, several studies in LMIC have shown

that the majority of PWE do not receive appropriate treatment and hence their epilepsy is uncontrolled (Mbuba et al., 2008; Meinardi et al., 2001; Scott et al., 2001) .

In 1997, The Global Campaign Against Epilepsy (GCAE), was started as a result of a partnership between the International League Against Epilepey (ILAE), the World Health Organisation (WHO) and the International Bureau for Epilepsy (IBE) (WHO/IBE/ILAE, 2001). The theme of this campaign was to bring epilepsy 'out of the shadows' by supporting LMIC to reduce the burden caused by epilepsy through improved acceptability, access to services, prevention and quality of care. In 1999, the WHO gave epilepsy a cabinet level status, in which each WHO regional office pledged to commit personnel and resources to the GCAE. The second phase of the GCAE was launched in 2001 with the initiation of demonstration projects in several countries (China, Argentina, Zimbabwe and Senegal). The specific objectives were to develop models of epilepsy control worldwide. To date more than 90 countries are involved in the campaign whose overall goal is to improve the identification and management of people with convulsive epilepsies within existing primary health care systems (WHO/IBE/ILAE, 2001).

The studies reported in this thesis augment these efforts by estimating the burden of epilepsy (particularly Active Epilepsy, which should be on treatment) through well documented and reproducible methods, describing the distribution of ACE in resource limited settings as well as factors associated with mortality in PWE.

Overview of findings

This research focused on the global, regional and local investigations of burden, distribution and outcomes of epilepsy. The chapters are organized in a sequence that corresponds to the objectives outlined in chapter 1.

The systematic review and meta-analysis of chapter 2 estimates the burden of both life-time (LTE) and active epilepsy (AE) and examines the influence of various study-level factors in the reported heterogeneity of estimates. The prevalence of AE in rural areas (12.7/1000) of LMIC was more than two times higher than that of HIC (4.9/1000) and urban areas of LMIC (5.9/1000). Using average global population estimates for the period in which the reviewed studies were conducted, the estimated number of cases of AE in HIC was 5.7 million, 17 million for rural areas of LMIC and 10 million for urban areas of LMIC. These estimates reflect the global burden of epilepsy that should be on treatment. The data provided evidence of heterogeneity, with studies involving all age groups or only adults, those conducted in rural areas and those with small sample sizes having significantly higher prevalence estimates. In a subsequent multicentre study of prevalence of epilepsy (reported in chapter 5), the component of the heterogeneity in estimates that is related to methodological differences was reduced by including all age groups, studying large populations and using standardized methods of case identification and definitions of ACE.

The third chapter of the thesis is a systematic review and meta-analysis which estimated pooled incidence of epilepsy at the global, HIC and LMIC levels and also investigated sources of heterogeneity of estimates. These analyses were based on the premise that since mortality is high at the onset of epilepsy and spontaneous remission also occurs, prevalence data could potentially grossly underestimate the burden of disease. Estimation of incidence of epilepsy which is not affected by disease-specific mortality could thus be a useful alternative in the assessment of burden. As with prevalence, the incidence of epilepsy in LMIC was approximately twice that of HIC. Compared with hospital-based studies, our results showed that population-based studies reported higher incidence, studies with small sample sizes (<20,000 participants) also reported higher estimates while retrospective studies reported significantly lower estimates than prospective studies. These findings suggested that: (i) hospital-based studies could be missing out on non-severe cases of epilepsy thus the reported low incidence, (ii) researchers, particularly in LMIC, conduct small studies to estimate incidence of epilepsy in areas that are endemic for risk factors for development of epilepsy and thus these are not representative of the general populations and, (iii) retrospective cohort studies do not identify all incident cases. These results emphasized the need for large population-based prospective cohort studies to measure incidence of epilepsy much more accurately, particularly in LMIC. This was attempted in the study of incidence of epilepsy in the Kilifi HDSS, which is reported in chapter 6 of this thesis.

The study reported in chapter 4 was a population-based assessment of the three-stage cross-sectional screening methodology that had been used in a previous study to identify cases of ACE in the Kilifi HDSS and which was also used in the prevalence studies reported in this thesis. The three-stage cross-sectional survey method had poor sensitivity (48.6%) in detecting cases of

ACE in the community. To a large extent, the low sensitivity was attributed to the first stage of the survey which accounted for 15/18 (83.8%) of the false negatives. Given the conspicuous nature of convulsive seizures and the fact that the first stage was conducted by field personnel who resided within the study community, it was likely that the reported low sensitivity was stigma-related. The three-stage method, though 60% cheaper than the more 'traditional' two-stage survey methodology used in many prevalence studies, may not be suitable for identification of people with ACE in LMIC where the condition is stigmatized. However, where it is used e.g. for cost and logistical considerations, the methodology would need to be validated in the target populations and the prevalence estimates adjusted accordingly.

The prevalence studies reported in chapter 5 were conducted in four locations in sub-Saharan Africa that differed with regard to endemicity of factors associated with development of epilepsy. To minimize methodological heterogeneity in these studies, standardized tools, methodologies, definitions of ACE and operational procedures were used. Striking findings from these studies were the between site and within site (by age) heterogeneity in the distribution of ACE. Prevalence of ACE was highest in the Ifakara HDSS in Tanzania and lowest in Agincourt HDSS in South Africa (after adjusting for loss to follow-up and sensitivity of the three-stage survey methodology). Since I focused on ACE (as opposed to life-time and non-convulsive epilepsies), these results reflect the component of the burden of epilepsy that is most vulnerable to stigma and premature mortality and that should be on treatment in these sites. The heterogeneity documented in this chapter (after standardizing the methods and definitions) suggests real heterogeneity (e.g. due to differences in the distribution and types of risk factors or patient vulnerability). This finding implies the need for case-control studies to gain a better

understanding of the factors driving the high prevalence in some of the sites and the between site heterogeneity.

Chapter 6 estimated the incidence of ACE in a large population-based cohort using two cross-sectional surveys five years apart. The incidence rate, estimated at 77/100,000 persons per year, was higher than that reported in most other studies from LMIC. Although the high incidence could have been caused by inclusion of epilepsy cases in the non-epilepsy cohort because of low sensitivity in the baseline survey, it is also possible that this study nevertheless underestimated the incidence due to mortality of incident cases shortly after the onset of seizures. The results showed strong evidence of association between age and development of ACE, with the lowest incidence in the young and middle-aged adults (29-49 years). This was suggestive of higher risk of epilepsy in the young children and adolescents and in the elderly and potential interventions to prevent epilepsy in this community should target these groups.

Chapter 7 documents a study on the magnitude and risk factors associated with mortality in people with ACE in the Kilifi HDSS. The findings of this study show that ACE was associated with a raised mortality rate. When the data were adjusted for age, mortality was more than 6 times higher in people with ACE compared to the general population. Non-adherence to medication was an important epilepsy-related predictor of death in patients and interventions to prevent mortality should target this factor as a matter of priority.

Implications for public health

High prevalence, incidence and mortality in people with ACE are documented in the studies presented in this thesis. These findings suggest that epilepsy is likely to have far reaching effects on the health, welfare and quality of life of patients in the sites in which the studies were conducted and in LMIC more generally.

At the global level, our findings show that the burden of epilepsy is much larger than previously thought and have provided estimates of the burden of active epilepsy representing people who should be on treatment in both HIC and LMIC. These findings should be used to prioritize epilepsy as an important global public health problem and lobby for increased resources, particularly in LMIC, to improve diagnostic, treatment and preventive services and to campaign for the destigmatisation of epilepsy.

For the local health systems, these findings would in the short term translate directly into increased health expenditure in terms of treatment services for the patients identified in these studies. In the medium term, the health systems would need to increase and sustain capacity to provide more appropriate health services to PWE at the primary care level e.g. in terms of training and retaining nurses or clinical officers to diagnose and manage epilepsy as well as provision of counseling services to patients with attendant psychosocial co-morbidities. In the medium to long term, preventive interventions must be given priority and this means identifying the preventable causes of epilepsy. This includes the deployment of measures such as health promotion to educate the communities on causes of epilepsy (as well as risk factors of mortality

in PWE), improved ante-natal and peri-natal services and provision of prompt and effective treatment of traumatic head injuries and infections of the central nervous system (CNS). Additionally, childhood vaccination for vaccine preventable causes of CNS infection (e.g. *Haemophilus meningitis*) could have an important effect on the prevention of epilepsy. However, causes of epilepsy in these communities would need to be identified using formal epidemiological methods.

Directions for future research

Collectively, the studies reported in this thesis suggest a large burden of epilepsy in LMIC, particularly in SSA, and poor prognosis of epilepsy in one of the sites (Kilifi HDSS). There is need to quantify the magnitude of epilepsy mortality in the other study sites in order to assess the effect of epilepsy in these populations as well as to compare the mortality experience in these cohorts given that similar methodology and case definitions were used across these sites. Epilepsy-related risk factors for mortality were also identified only in the Kilifi HDSS and these would need to be identified in the other study sites. Studies of cause-specific mortality (cause of death studies) in PWE would be useful in the quantification of the role of epilepsy related causes of death e.g. status epilepticus, sudden unexpected death in epilepsy (i.e. SUDEP) and accidental injuries. Cause of death as well as mortality risk factor information would form core elements of public health messages aimed at reducing the risk of mortality in PWE in this region.

These studies documented substantial between site heterogeneity in the distribution of ACE. Given that the studies were conducted using similar methodology and case definitions, it is postulated that the observed heterogeneity was due to differences in the distribution and types of risk factors for development of epilepsy between sites and/or in the vulnerability of different segments of populations (particularly age-groups) within sites to endemic risk factors. However, these hypotheses would need to be tested formally in case-control studies. These would identify risk factors that would be key to preventive public health interventions.

The studies reported in chapters 5 and 6 utilized a cohort of prevalent cases to estimate the incidence and mortality of ACE. Mortality is high early in the course of epilepsy and remission is known to occur. Therefore, studies based on prospectively identified cohorts of incident cases would be ideal in estimating more accurately the incidence and mortality of epilepsy, although they would be much more costly and logistically challenging to conduct.

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APPENDICES

Appendix 1.1: A Concept to assess the burden and outcome of epilepsy across INDEPTH sites

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2. Kintampo DSS, Kintampo Health Research Centre, Kintampo, Ghana.

Epilepsy is the most common neurological condition affecting more than 50 million people in the world. However the causes and consequences appear to be different in majority world countries (MWC), and this has implications regards management of epilepsy in these communities.

Epilepsy accounts for 0.5% of the global burden of disease, translating to 7 million disability adjusted life years (DALY's) annually. It is estimated that more than 80% of the global burden of epilepsy is found in the LMIC, with 10 million cases in Africa alone; but these estimates are based upon little data. Epilepsy is associated with behavioural and psychiatric co-morbidities, impairing function within society. Additionally, studies have shown that mortality is increased 2-4 fold in people with epilepsy (PWE) compared to the general population. Active convulsive epilepsy (ACE) is the most reliably detected and is associated with the most severe co-morbidity and increased mortality.

Epilepsy is a treatable condition, with evidence suggesting that up to 75% of the cases that receive appropriate treatment achieve remission in 1 to 5 years of therapy. The World Health Organization has estimated that it costs as little as 15 US $ per person annually to treat. However, up to 90% of people with epilepsy in LMIC do not receive appropriate treatment owing to many different factors including perception of the causes and lack of understanding of the concept of prophylaxis.

Given the serious health and outcome implications of epilepsy, its attendant comorbidities and inadequate data on the burden and outcome of epilepsy, there is a need for good quality epidemiological studies. In LMIC with large rural populations where there are few specialists in neurology, scantily allocated heath-care resources and a substantial burden of disease; epidemiological studies provide information necessary for promoting health to optimize care in epilepsy. Well-planned and coordinated studies in diverse sites would minimize methodological heterogeneity, generate more accurate estimates of disease burden and provide data on co-morbidity and increased mortality. Data from such studies would be used to lobby for appropriate allocation of resources for education and awareness raising, medical care and rehabilitation of PWE and communities in general.

We have recently conducted a survey of >150,000 people in Kilifi DSS in which the prevalence of ACE was estimated at 4.7/1000 after adjustment for non-response. This survey utilized a 3-stage system of diagnosis in which 2 questions were used to screen the entire population for convulsions within the DSS.

With this concept paper, we want to determine the interest of the other InDepth DSS sites to partake in the planning and implementation of a multicentre study. The planning will entail an assessment of resources required at each site, appraisal of available skills and manpower, determination of logistics and co-ordination and development of a substantive funding proposal. We will apply for funds to organize a planning meeting to develop the proposal.

The goal is to obtain data on:

- Prevalence of ACE
- Psychiatric and behavioural co-morbidities associated with ACE;
- Epilepsy treatment gap (proportion of PWE not receiving appropriate treatment);
- Communities' knowledge, attitudes and practices on epilepsy;
- Socio-cultural dimensions of epilepsy, unique care-seeking barriers and how to develop culturally appropriate interventions.

Conducting prospective longitudinal studies to measure:

- Incidence of epilepsy and psychiatric and behavioural co-morbidities associated with ACE;
- Excess mortality due to epilepsy;
- Determine the causes of death in PWE.

Appendix 1.2: Epidemiology and treatment of epilepsy in Sub-Sahara Africa: quality assurance manual

Introduction

Quality assurance (QA) is the total process whereby the quality of research results can be guaranteed. This process consists of systematic actions necessary to demonstrate that a product or service meets specified requirements for quality.

This project quality assurance manual comprises the following sections:

1. Introduction to Epilepsy Surveys
2. Standard operating procedures (SOPs) for pre-analytic processes
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SECTION FOUR: GLOSSARY OF TERMS

SECTION ONE: INTRODUCTION TO EPILEPSY SURVEYS

Epilepsy is a disorder of the brain that is characterized by frequent seizures. Worldwide, it affects almost 50 million people, and it is caused by severe head injury, brain infection, and can be inherited through families.

In developing countries, especially those of Africa, epilepsy remains a misunderstood condition and this is partly due to the existing misconceptions concerning its causes and consequences. Published literature documents a widely held belief among several communities that epilepsy results from bewitchment or possession by evil spirits or the devil, and that the condition is contagious and incurable. It is this conceptualization of epilepsy that is mainly responsible for the socio-cultural and psychological stigma and persistent negative attitudes and discrimination against people with epilepsy. This in turn has resulted to the sufferers being hidden (**This often impacts on the identification of individuals with epilepsy in community settings**) and therefore not seeking medical treatment.

Why is this Study important?

This study is important because it intends to document the number of people with epilepsy in our study communities and also determine its' causes and treatment gap (i.e. number of people with active epilepsy but not on appropriate treatment). This will help us advice about appropriate recommendations geared towards prevention and management of epilepsy.

How will the study be conducted?

This study will be a panel-type survey with 3 stages and will conducted alongside the census, and it will involve visiting all the homesteads in the identified study area to identify individuals with epilepsy. These will be identified upon administration of the following one or two questions about epilepsy/convulsions/seizures/fits on all residents of the study area. The number of questions is determined by which of these are most culturally acceptable. Those answering **Yes** to any of the two questions will be visited by an epilepsy field worker and asked further question to detect epilepsy. Those in whom epilepsy is a possibility (by a **YES** response to any of the 2nd set of questions by the epilepsy team) will be asked to visit **the epilepsy clinic** for further assessment and examination. The two (2) questions to be administered in stage I are:

1. **Do you sometimes have fits or become rigid or experience attacks in which you fall to the ground and lose consciousness.**
2. **Do you have fits or has someone ever told you that you have fits.**

Answers to these questions will be entered on the last two columns of the household census schedule and these can only be a **Y (Yes), N (No) or D (Don't know).**

The census field worker will, in addition to the above, notify the respondent that the epilepsy field team may interview some of the members of the of their household who may not have had convulsions, to enable the study team to determine if the first two (2) questions are detecting possible cases of epilepsy well.

The Survey procedure

This will follow the normal census procedure of going through the list of household members establishing their residential status. This time round, the list will have one or two columns for the one or two epilepsy questions. The questions will be in the last two columns and will be denoted by **Epilepsy 1 and Epilepsy 2.**

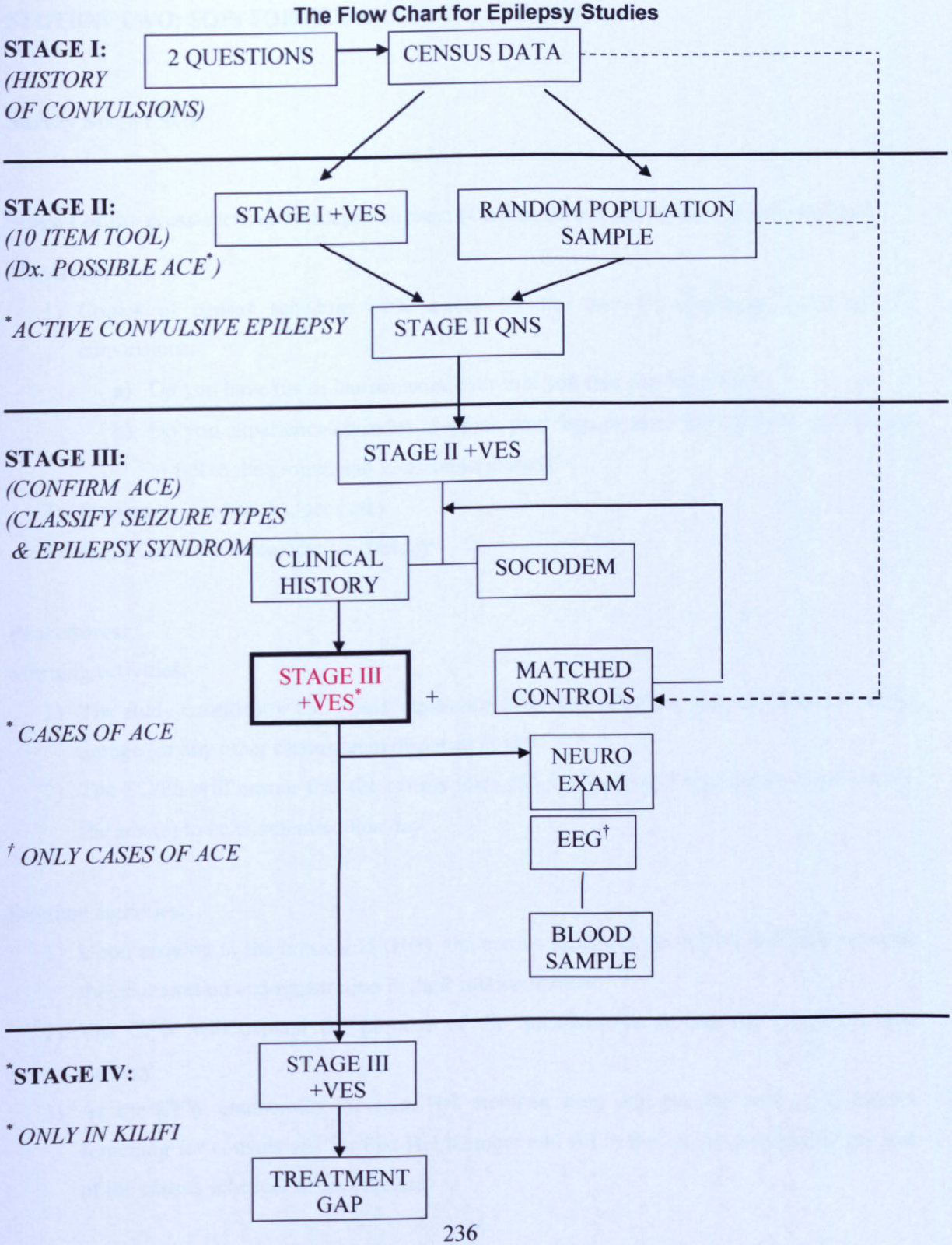
After the normal census of each household member, the above epilepsy questions will be administered to the **household head or any other household member with knowledge of the**

people living in that household. The answers to these should then be entered appropriately in the spaces provided on schedule. This should be repeated for each member of the household and the last one is covered. Before asking these questions, the fieldworker should first introduce the study to the respondent and explain to him why it is important and the procedures involved.

At the end of the day, all the census schedules should follow the procedures normal to the routine census. The epilepsy team will get this data and then prepare a list of all the people with a history of convulsions identified on that particular day for subsequent follow-up (**These will also be entered in the epilepsy register, maintained by Data Manager**). The follow-ups will be within one or two weeks of identification and the epilepsy team fieldworkers shall perform it.

In stage II of the survey, those identified to have a possible diagnosis of epilepsy will be referred to stage III whereby they will be assessed by a clinician who will confirm a diagnosis of epilepsy. This will involve detailed medical history taking (in local language) and neurological examination. The diagnosis of ACE will be made on the basis of clinical history. Those who are positive at this stage will undergo EEG examination to enable classification of seizure types and epilepsy syndromes. The people identified to have ACE will be asked to be part of long-term studies into risk factors and causes of mortality in people with epilepsy.

Concomitant with survey will be a case-control study in which cases of ACE will be matched to and compared to randomly selected population controls at a ratio of 1:1. Matched controls will be recruited from the community by the administration of the stage II tool by the epilepsy field workers and those turning negative will be referred to stage III for assessments similar to those done on cases. These assessments will also include detailed socio-demographic questionnaire administered by a field worker unaware of the case/control status of the respondent and a blood sample to evaluate parasitic risk factors of epilepsy, HIV status and anti-epileptic drug levels to determine the prevalence of epilepsy treatment gap.


The Flow Chart for Epilepsy Studies
STAGE I:
(HISTORY OF CONVULSIONS)
2 QUESTIONS
CENSUS DATA
STAGE II:
(10 ITEM TOOL)
(Dx. POSSIBLE ACE*)
*ACTIVE CONVULSIVE EPILEPSY
STAGE I +VES
RANDOM POPULATION SAMPLE
STAGE II QNS
STAGE II +VES
STAGE III:
(CONFIRM ACE)
(CLASSIFY SEIZURE TYPES & EPILEPSY SYNDROM
CLINICAL HISTORY
SOCIODEM
STAGE III +VES*
+
MATCHED CONTROLS
* CASES OF ACE
NEURO EXAM
EEG†
† ONLY CASES OF ACE
BLOOD SAMPLE
*STAGE IV:
* ONLY IN KILIFI
STAGE III +VES
TREATMENT GAP

SECTION TWO: SOPs FOR PRE-ANALYTIC PROCESSES

Survey Stage I SOP

Stage I of the cross-sectional epilepsy survey: (Census screen for history of convulsions)

Materials;

1) Copies of census schedule with spaces for the two (2) questions screening for convulsions:
    a) Do you have fits or has someone ever told you that you have fits?
    b) Do you experience episodes in which your legs or arms have jerking movements or fall to the ground and lose consciousness?
2) Stationary (note books, pens etc)
3) Copies of the communication strategy

Procedures;

Morning activities;

1) The study coordinator (SC)/field supervisor (FS) will assemble daily at 08:00 hrs at the garage (or any other census team dispersal point)
2) The SC/FS will ensure that the census team has adequate and appropriate materials for the area(s) to be enumerated that day

Daytime activities;

1) Upon arriving at the household (HH), the census field worker (CFW) will proceed with the enumeration and registration in their routine manner
2) The CFW will explain the purpose of the questionnaire as per the communication strategy
3) As the CFW enumerates for each HH member, they will ask the two (2) questions screening for convulsions for that HH member and fill in the spaces provided at the end of the census schedule as appropriate

4) The CFW will complete all parts of the questionnaire. If there is no information or response, the FW will fill in "no response" for that question.
DO NOT LEAVE ANY BLANK SECTIONS

Evening activities;

1) At the end of the day, the CFWs will place all the completed census schedules in an envelope with their name, location and date on the cover
2) The CFW will, upon arrival at unit hand all the completed census schedules to the FS
3) The FS will then prepare a list of all the people with convulsions identified on that particular day for subsequent follow-up
4) The FS will then enter this information into a convulsions register/study control sheet and hand them over to the SC for verification and consultation the following day
5) The SC will keep an updated copy of the control sheet and transmit the data to the data manager (DM) for entry into the database
6) The SC and FS will solve all logistical issues as they arise and where these require higher-level input, they will seek advice from the overall supervisor (*name of person in-charge of study at the site*)
7) The SC, DM and FS will solve all data/information issues as they arise

Information the CFW may convey to the community:

What the study will do for the patients identified in Stage II of the survey:

1) The study will identify people with possible epilepsy.
2) The study will invite these people to the Epilepsy Clinic for further investigations.
3) The study will provide fares to and from clinic for the index case and an accompanying responsible person.
4) The study will provide lunch on the day of appointment for the index case and the accompanying responsible person.
5) If after clinical examination the index case is found to have epilepsy, s/he will be started on anti-epileptic drugs provided for free by the study on this occasion.

6) The index case may then be given a review appointment by the study clinician. Fares to and from the Epilepsy Clinic and lunches will also be provided for on this occasion.
7) The study, unless otherwise on the advice of the study clinician, will from the second appointment onwards consider the index to be stabilized on medication upon which s/he will be referred to the district hospital epilepsy clinic for future appointments.
8) The study will from henceforth cease to provide fares and lunches for subsequent appointments.
9) The study will give back individual results of examinations, tests and samples taken during the 1st survey to the people with epilepsy at the earliest opportunity identified then if found during the 2nd survey.
10) For people with epilepsy identified in the 1st survey but not found during the 2nd survey, the study will make every attempt to trace them and give these results individually.
11) The study will, during the 2nd survey give provisional results for examinations, tests and samples taken to patients, preferably on the day of examination for diagnosis and come for sample results at the earliest possible opportunity.

What the study will NOT do for the patients identified in Stage II of the survey:

1) The study will NOT provide free medication to index cases throughout their illness or for appointments beyond the study duration (six months).
2) The study will NOT provide free lunches or transport to and from clinic throughout their illness or for appointments beyond the study duration (six months).
3) For patients identified to have epilepsy during the 2nd survey and for whom examination, tests and samples are taken, the study will NOT follow them up in their homes to give individual results.

Survey Stage II SOP

Stage II of the cross-sectional epilepsy survey: Screening for Active Convulsive Epilepsy (ACE)

Materials;

1) Pre-printed list of the households (HH) for the area to be surveyed for the day.

2) Stationary (note books, pens, ink pads, petty cash vouchers etc) for the field workers.
3) Case report forms (CRFs) pre-printed with the HH's name and PID numbers.
4) A set of blank CRFs.
5) Copies of the communication strategy.
6) Copies of consent form.

Procedures;

1) The data manager (DM)/study coordinator (SC) will give the pre-printed list of HH, CRFs and consent forms to the Epilepsy field workers (EFWs).
2) Only one EFW will each HH at a time.
3) On arriving at the HH, the EFW will seek out the person identified on their list, and if they are found to have cognitive impairment the EFW will seek out a responsible close family member/relative to the index.
    a. If in case of mental disability none of the alternates is available at that time, the EFW will arrange to visit the HH the following day and leave a request that a senior/responsible member of the HH be around at specified a time.
    b. If on the following day this is not possible, the EFW will request for an appropriate appointment with the identified respondent and arrange the 2nd visit accordingly.
4) The EFW will introduce themselves and the study to the appropriate respondent as in the COMMUNICATION STRATEGY (PARAGRAPHS 1 & 2).
5) The EFW will then proceed to administer the questionnaire. If there is no information or response, the EFW will fill in "no response" for that question but DO NOT leave any blank sections.
6) If the respondent is classified as a case, the EFW will read the communication strategy (PARAGRAPHS 3 – 7) to the respondent and invite them to sign two (2) copies of the consent form (PARAGRAPHS 8 – LAST).
7) If the respondent is unwilling to sign, the EFW will elicit the reasons for the decline and indicate these in the pre-printed CRF for that respondent, thank the respondent and move to the next HH on their list.

8) The EFW will invite those who fulfill the criteria of active convulsive epilepsy (ACE) to come to the Epilepsy Clinic for further assessments at an appropriate date, preferably accompanied by relative/care giver.
9) S/he will give an invitation/appointment tag with the name, other identification details and the date of appointment among other relevant information. (The EFW will emphasize that the person brings the appointment tag to the clinic. This will enable the study to track the appointments and to identify those not in the preceding stage of the study and those not recruited as controls).
10) The EFW will provide fare for the subjects who fulfill the criteria and agreed to come for assessments and a relative to attend the clinic.
11) The EFW will leave one copy of the signed communication/consent form with the respondent and bring the other copy back to the office.
12) For the respondents turning negative to the stage II questions, the EFW will read the communication strategy for the controls (as detailed in PARAGRAPHS 8 – LAST, EMPHASIZING THAT THEY MAY NOT HAVE EPILEPSY).
13) S/he will notify the negatives of the possibility of coming back to recruit them as controls for the study.
14) S/he will explain the concept of a control and request if the negative respondent is willing to participate as such, including giving a teaspoonful of blood for appropriate tests. This information will also be entered in the appropriate sections of the questionnaire.

Activity flow;

Morning activities;

1) The driver will be available everyday at 8.00 am
2) The EFWs will assemble at the assessment centre each day at 8.00 am
3) The SC will see to it that all the necessary materials for the day are availed to the field team.
4) The SC, with the assistance of the DM together with the EFWs will review all the outstanding issues from the previous day's CRFs (missing data, inconsistent data, HH not available, HH to be revisited etc).

5) The drivers will ferry the EFWs to the field at 8.30 am.

Daytime activities;

1) Ideally, the actual field work will be carried out between 9.00 am and 4.30 pm, with a one hour lunch break between 1.00 pm and 2.00pm. This will translate to 6 ½ hours of actual work hours in the field*.
2) The SC and DM will check the previous day's CRFs for any problems/queries and come up with remedial measures.
3) The drivers will move around in the field, ferrying the EFWs between homesteads as they administer the interviews.
4) Two days every week, the SC will visit the field and use the vehicle to make spot checks and address issues as they arise in the field

*Assuming maximum questionnaire administration duration of 20 minutes per HH and an inter-HH movement duration of 15 minutes, we will have a questionnaire administration cycle of 35 minutes per EFW. Thus, given an average of 6 ½ hours (390 minutes) of actual field work time per day, each EFW will be able to interview an average of eleven (11) subjects per day (~ 10 subjects/EFW/day).

Evening activities;

1) At the end of the day, the EFWs will hand all the completed CRFs to the FS.
2) The FS will scrutinize the CRFs for errors, omissions etc and refer back to the responsible EFW for correction
3) The unused CRFs will also be handed to the FS at the end of the day for re-issuing for follow-up the following morning/as appropriate.
4) The driver will begin to collect the EFWs from their last positions of the day at 4.30pm.
5) The SC will be at hand at 5.00 pm to receive the CRFs from the FS.
6) The SC will discuss with the FS and note down a summary of issues arising for the day in the study log.

7) The SC will then check and verify the CRFs, update the daily study register/control sheet and forward all the day's CRFs to the DM for entry into the database (most likely the following day).

Survey Stage III SOP

Stage II of the cross-sectional epilepsy survey: Assessment, Examination, Sampling and Diagnosis of ACE

Materials;

1) Pre-printed list of all the patients referred for assessments for that day
2) Stationary (note books, pens etc) for the assessors/clinicians
3) Copies of assessment tools (questionnaires) pre-printed with the patient's name and PID number among other ID details. These include:
4) Socio-demography, birth & medical history form (both adult and child)
5) Epilepsy screening and medical history form
6) Neurological examination form
7) Epilepsy examination summary form
8) EEG classification form
9) Blood withdrawal form/consent
10) Copies of the communication strategy
11) Copies of consent form
12) Patient examinations/assessment log files (front sheet)

Procedures;

Reception, consent and socio-demographic assessment;

1) Patients referred for the day will be received at the reception of the assessment centre.
2) Assessors on a first come first served basis will see patients at the reception area.
3) S/he will request the patient/guardian to produce the assessment appointment tag given by the EFW during phase II of the study.

4) S/he will then explain the study to the individual patient (read the communication strategy) and administer the consent.
5) If the patient/guardian is unwilling to sign, the assessor will elicit the reasons for the decline and indicate these in the space provided in the sociodemography questionnaire, thank the respondent and move to the next person on the queue.
6) If the patient/guardian consents to the study, the assessor will guide them to sign two (2) copies of the consent form, one copy will remain with the assessor and the respondent will keep the other copy.
7) The assessor will then administer the sociodemography & birth history questionnaire.
8) The assessor will ensure to complete all sections of the questionnaire. If there is no information or response, s/he will fill in "no response" for that question but do not leave any blank sections.
9) S/he will log the patient details in the assessment check list upon completion of the socio-demographic form.
10) The assessor will then usher into the study clinician-1's office the patient for whom the socio-demography questionnaire is satisfactorily completed and logged.

History and epilepsy screening

1) The study clinician-1 will take complete history of the patient as detailed in the Epilepsy screening form.
2) S/he will ensure to take all details of history provided for in this form.
3) If there is no information or response, s/he will fill in "no response" for that question but do not leave any blank sections.
4) S/he will then forward the patient to the study clinician-2's office.
5) S/he will log the patient details in the assessment check list upon completion of the history and epilepsy screening form.
6) S/he will give history and diagnosis details for that patient to study clinician-2.

Neurological evaluation and EEG examination;

1) The study clinician-2 will administer a full neurological examination to the patient.

2) S/he will to record all the examination findings in the Neurological examination form and ensure not to leave any blank sections on the form.
3) The study clinician-2 will then refer for EEG examination ONLY those patients with a positive diagnosis of active convulsive epilepsy (ACE) as per the study clinician-1's findings.
4) The study clinician-2 will then record his/her findings on the EEG classification form, ensuring to fill in all the details.
5) S/he will log the ID details for the patient upon completion of the neurological examination form.
6) The EEG technician will perform the EEG examination on all patients referred by the clinicians and summarize his/her findings as provided for in the EEG summary form.
7) S/he will then log the patient details and refer the patient to clinician 1 or 2 for blood drawing.

Blood drawing;

1) The study clinician 1 or 2 will administer consent for blood drawing very carefully, explaining the intention and need for HIV testing and emphasizing on confidentiality and options for getting results. The clinician will then invite the patient to sign the consent.
2) The study clinician will draw 2ml of heparinized blood from the patients who have given consent.
3) The clinician will label the sample appropriately and place it in a cool box.
4) S/he will then fill in all the details in the appropriate form and log.

The sociodemographics assessors will provide money for lunches and fares back home to patients who have been fully assessed and have them sign the petty cash voucher.
They will identify cases at this point and notify them of the treatment gap follow-up to be done within a week of assessment.

Evening activities/day's audit;

1) At the close of business each day, each assessor/clinician will reconcile their completed forms with the details logged in the assessments checklist/front sheet, note and explain any discrepancies.
2) The study clinicians will ensure that all the blood samples have been transmitted to the lab and the handover verified and signed for.
3) Each assessor will then hand his or her completed set questionnaires to the study clinicians to use in the summary examination form.
4) The clinicians, on completing summary will hand over the forms to the SC who will go over the forms and the log checklist and raise any queries.
5) The SC will then summarize the important issues in a master log.
6) S/he will then use the data to update the study control sheet, and transmit the forms to the DM for data every 3 days.

Survey Stage II forms reception, checking and follow-up

SOP for Stage II screening forms reception and checking.

1. The field supervisor (FS) (Name: _____will collect and check that all the forms are filled in appropriately at the end of each day.
2. At the end of a field day, the study co-ordinator (SC) will receive the verified forms from the field supervisor (FS);
3. The SC will count and verify the number of forms with the FS;
4. The SC will discuss with the FS and note down in the Stage II log the field issues arising on that day;
5. The SC/FS will allocate the study numbers (EPISURVNO) to all the forms in the order in which they are received from the field, continuing from the last number of the previous day;
6. The SC will check each individual form (or a sample thereof) and note in the study log issues such as wrong entries, missing data, inconsistent data, lack of adequate explanation for no consent etc. S/he will note against these details the FW code, PID, EZ HM. These will be raised with team the following morning and remedial action taken;

7. The SC will then update the study register (obtained earlier from the data manager – DM) by indicating those found on that day or otherwise as provided for in the register;
8. The SC will then update the study control sheet with a summary of the days' data and check for any important trends.
9. The SC will then prepare a list of follow-ups (FU) of those respondents not found on that day;
10. The SC, in consultation with the DM will allocate FU dates for the FUs identified. This will be given to the FS for implementation;
11. The SC will then hand over the forms to the DM for data entry.

SOP for Stage II follow-up (FU) of individuals not screened on a particular day.

1. The 1st FU for all individuals (cases and controls) not seen on a particular day will be carried out by the epilepsy field team (EFT) on the date allocated by the SC;
2. The 2nd FU for all individuals not seen on the 1st FU will be carried out by the EFT if screening in that area/EZ on that particular day; otherwise it will be carried out by the 'mop-up' field workers (MFW);
3. The 3rd FU for all individuals not seen in the 2nd FU will be by the MFW. They will at this time request for an appointment at the most appropriate date/time for the respondent i.e. when the respondent is most likely to be available. Those for who appointments are not given by the 3rd FU will be considered missing;
4. The 4th FU for all individuals not seen in the 3rd FU and who have scheduled appointments will be by the MFW;
5. Those **CASES** that had appointments but still not found by the 4th FU will be classified as missing observations;
6. The **replacement** of controls will be carried out by the MFW and will follow the same procedure as follows;
7. Those **CONTROLS** that had appointments but still not seen by the 4th FU will be replaced with an individual from the age-band who is topmost in the list of randomly selected replacements;

8. This will proceed to the 2nd topmost person in that list and that age-band if the 1st person in the replacement list is not found after two visits, the 2nd of which will be by appointment;
9. The FU for replacements will stop with the 3rd person in the list of replacements for that age-band.

Survey Stage II – Selection of population sample

Materials

1. Population dataset from the most current census. This will be the denominator dataset.

Procedure

1. The number of people in the population sample determined for each site will be selected randomly from the census dataset using the Random command (in which software?).

Survey Stage III – Selection of matched controls

Materials

1. A list of cases of ACE determined from stage III of the study
2. The most current census dataset.

Procedure

1. Remove the determined ACE cases from the census dataset.
2. Remove from the census dataset the stage II respondents who had refused consent to participate in stage III as matched controls i.e. when being interviewed as part of the population sample.
3. Create an age band field in census and ACE cases datasets, and populate it with data in relation to the age of the person as below:-

Age groups (years)	Age band
a. 0 – 5	-1
b. 6 – 12	- 2
c. 13 – 18	- 3
d. 19 – 28	- 4
e. 29 – 49	- 5
f. 50 and Above	- 6

4. Match the ACE cases to the census dataset resulting from steps 1 and 2 of this procedure ensuring to match by the age bands.
5. While matching limit the selection to five controls for each ACE case and ensure that a control is not selected more than once.
6. Those selected as controls are the eliminated from the denominator census dataset in readiness for the next round of matching.
7. When the follow-up list of controls is exhausted, i.e. all controls in the list are either found, missed, refuse to participate or do not satisfy the control selection criteria e.g. they have had seizures in past, the un-matched cases will be re-matched again to the census dataset resulting from step 6 of this procedure.

Survey (All Stages) – Data entry SOPs

Procedures

Data forms reception;

1. The forms are brought to DM section after the SC has gone through.
2. The DM notes down the date when received and the list of forms received.
3. DM goes through the forms and avails them for data entry if everything is in order, but in case there are queries refers back to the appropriate person.

Data entry;

1. The 1st entry is done as the files are received. Any anomalies noted and taken for clarification by the person who filled the form.
2. The 2nd entry is done by a different person for the forms that 1st entry has been done.
3. During 2nd entry interactive verification is done where the second entry operator resolves discrepancies between first and second entry and is aware of the first entered values.
4. A third person could resolve any discrepancies between first and second entry when both entries are completed.
5. The entry screens are with same format as the data collection forms to enable ensuring entry are done in the appropriate variables.

SECTION FOUR: GLOSSARY OF TERMS

PID:	Personal identification (number) – a unique number assigned to each resident of the DSS study area
EZ:	Enumeration zone – used to refer to a mapped cluster of homesteads delineated on the basis of some geographical feature?
EZHHID:	A unique homestead identifier which is a composite of EZ number and homestead number
ACE:	Active convulsive epilepsy – two or more unprovoked generalized tonic clonic seizures (GTCS) with (or without) other types of seizures and in which one seizure was in the previous one year
SOP:	Standard operating procedure(s) - a set of instructions detailing systematic actions to be taken in achieving a stated objective and having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness

SC:	Study co-ordinator – person charged with the responsibility of overseeing the study in each site on a daily basis
HH:	Household (or homestead)
CFW:	Census field worker – any person who, in the context of this study is involved in the administration of the Stage I tool
EFW:	Epilepsy field worker - any person who, in the context of this study is involved in the administration of the Stage II tool
DM:	Data manager
EEG:	Electroencephalography
EPISURVNO:	Epilepsy survey number – a unique study number assigned to all study participants who respond to the stage II tool of the survey and is used in the subsequent stages of the study
HM:	Homestead (number)
FU:	Follow-up
EFT:	Epilepsy field team – a group of epilepsy field workers as defined previously
MFW:	"Mop-up" field worker(s) – a stage II field worker involved in FU of respondents missed by the core EFT after a stipulated number of visits
SCC:	Scientific steering committee
CCC:	Consent and communication committee
ERC:	Ethical review committee (board)
ICF:	Informed consent form
IC:	Informed consent (process)

Appendix 1.3: Communication and consent materials: epilepsy studies SOP for informed consent

1.0 Introduction

This study will be a panel-type survey carried out in three stages, and will comprise of four communications and consent taking processes, one of which will be for blood sample collection.

1.1. Stage I: Census screen for convulsions

The first stage of the study will be embedded within an on-going census survey and will be carried out by the census teams in their regular re-enumeration and registration exercises within the DSS. It will involve screening for convulsions by asking each household head (or any responsible adult with knowledge of people in the homestead) about the history of convulsions for each member of the household. This stage will involve introducing the study to the community and no consent will be sought for the two question interview.

1.2. Stage II: Interview of Stage I positives and Stage III matched controls

This stage of the study will involve administering a ten item questionnaire to people with a history of convulsions identified in stage I and the matched controls randomly selected for stage III of the study. This will be conducted by a team of epilepsy field workers and the communication and consent taking process will be as follows;

a) Communication and consent for interview of individuals with a history of convulsions identified in stage I
b) Further information and invitation for clinical assessments of individuals with possible epilepsy identified in stage II
c) Communication and consent for interview of individuals selected as matched controls for stage III of the study
d) Further information and invitation for clinical assessment of individuals eligible to be matched controls for stage III of the study
e) Information for individuals with a history of convulsions but not meeting the study criteria for epilepsy

1.3. Stage III: Clinical assessment, examination and sample taking

The third stage of the study will involve socio-demographic and clinical interviews of individual in groups in stage II (b) and (d), above, clinical assessment/examination and blood sample taking. The participants in the stage of the study will first undergo a socio-demography and medical history interview by a field worker unaware of their case/control status who will give information pertaining to this stage of the study and take consent for the same. S/he will then take the participant to a clinician who will take detailed clinical history and take a blood sample for which s/he will give information and also take consent.

2.0 Background

We aim for our Studies to conform to the following principles for informed consent;

- The subject/guardian must be COMPETENT in the language of communication
- The research team must DISCLOSE all relevant information to the subject
- The subject must COMPREHEND the information and understand how their involvement in the study differs from normal clinical care.
- The subject must AGREE to the proposed intervention/procedures in the research study
- The subject's agreement must be VOLUNTARY and free from coercion
- The subject must be informed that, even after voluntarily agreeing to take part, they may WITHDRAW their agreement at any time without penalty

*In Kenya, children below the age of 18 years are not allowed to give consent, and informed consent for them to take part in studies is sought from their parents or legal guardians. If the parent or guardian is unable to read the informed consent documentation, the consent process must be witnessed. An exception to this occurs for emancipated minors[2], defined in Kenya as those aged under 18 years who are married, pregnant, have children or are in the armed forces, and who are able to give consent on their own (and their children's) behalf.

3.0. The study

This SOP describes the process to be followed for obtaining written informed consent from subjects/guardians taking part in the research study to ensure compliance with the above principles

STUDY TITLE: EPIDEMIOLOGY AND TREATMENT OF EPILEPSY IN SUB-SAHARAN AFRICA

The PI(s) for this study is/are (Name PIs in the site) and the sponsor is (WELLCOME TRUST)

Name .....
Name .....
Name .....
Name .....
Name .....

4.0. SCOPE/ RESPONSIBILITY

This SOP applies to study staff involved in obtaining informed consent from participants in this study. These will be:

1) Epilepsy Field Workers
2) Epilepsy Clinician/Nurse

5.0. Development of ICF

i. The English versions are written and submitted with this SOP to the SCC for approval. They are then submitted to (City) and any other ethics committees as required. This version is numbered 1 and dated.
ii. Any amendments will be made following protocol review and the new version (with new number and date) is created.

iii. All translated versions are now generated in local languages by ----------

iv. In the event of a revision of the ICF:

- Where the ICF is amended (any change that affect the study participants or the data analysis) the amended ICF will be submitted to Consent & Communication Committee (CCC) prior to forwarding to SSC and ERC for approval before its use is instituted.
- Where the ICF is modified (a non substantive change to the wording of an ICF) the modified ICF will be submitted to CCC for review, prior to forwarding to SSC and ERC for notification. Use will be instituted following CCC approval and forwarding.

6.0 Training of staff involved in the informed consent process

The overall study coordinator, **Anthony Ngugi**, is responsible for training the study coordinators, clinicians/nurses and field staff involved in the IC process in all the 4 sites.

i) The training objectives: the training on the IC process will be built-in to the training on the survey methodology to ensure that the staff are conversant with the study background, methodologies and SOPs; ii) The study communication/consent forms and study SOPs will be used in the training; iii) the total duration of trainings in each site will be one week; iv) the training will be evaluated using role plays; v) over time, the trainees will be monitored through continuous checking of the consent forms filed in an overall built-in study control and monitoring mechanism.

7.0 Administration of Informed Consent

When and where will consent be taken?

The communication material used in stage I will be administered at the homesteads by the census field workers during the census process. In stage II, these will be administered at home by the epilepsy field workers.

Individuals diagnosed with Active convulsive Epilepsy (ACE) in stage III will be provided with anti-epilepsy drugs (AEDs) free of charge for the duration of the study and requested to be part

of a long-term cohort study into risk factors and causes of death in people with epilepsy. It is not envisaged that these individuals will form part of other studies within this project.

Who gives and witnesses consent?

- Consent will be sought from all respondents identified in Stage I of the study as having a history of convulsions or their guardians if they are minors or cognitively challenged and from cases and controls identified for Stage III assessment. In the event that a witness is required, the witness shall be a responsible literate adult in the household or neighbourhood.

How will it be sought? :

- The consent forms and all the questionnaires will be translated in to the local languages and the ability of the respondents to read will be determined by asking them of their literacy status and on whether or not they prefer to print their name and sign or append their thumb print on the consent forms. The need for a witness will be determined if the respondent is deemed to be illiterate or cognitively challenged.
- The person administering the consent will READ slowly and systematically the information as printed on the consent form to the respondent, pausing from time to time to assess the respondent's reactions/body language for cues to understanding/comprehending the information.
- The subject/guardian will be made aware that they are free to ask questions or seek clarification at any stages of the consenting process or questionnaire administration. The person administering the consent/questionnaire will attempt to respond to all the queries to the best of their abilities. If they are unable to respond to some of the information needs, they will refer the subject to the people named for such queries at the bottom of the consent forms.

  The subject/guardian will be invited to make a free choice to participate in the study once the interviewer has given them all information as detailed in the consent form, has responded to all the queries and is satisfied that the respondent has understood the information given.

Signing the consent form

If the consent giver can read (so no need for a witness)

- The investigator/designee to ask the subject/guardian to print their name, sign and date the ICF
- The investigator/designee to sign and date the ICF
- A copy of the ICF is given to the subject/guardian by *(YES)*
- The giving of informed consent is recorded in the source document by *(THE INTERVIEWER)*
- The signed ICF will be filed in (A FOLDER TOGETHER WITH OTHER CRFs BY THE SAME RESPONDENT)
- Describe where the outcome (e.g. refusal) of all ICF processes are filed *(IN A* SEPARATE FOLDER SET ASIDE FOR ALL REFUSALS)

If the consent giver cannot read then a witness is needed;

- To print the name of the subject/guardian on the ICF; and sign and date the ICF confirming that the information has been provided and that they have understood fully.
- The subject/guardian to make their mark (e.g. thumb print) on the ICF

8.0 Ensuring the quality of the consent process

i. The study team will ensure that the consent process is being adhered to by SPOT-CHECKS AND DOCUMENTATION REVIEW.

ii. The quality assurance mechanisms of the Epilepsy study will ensure that the procedures described in this document are adhered to by checking adherence to this SOP during the monitoring process

iii. Understanding of the participant will be checked by inviting the consent giver to seek further clarification and ask questions and confirming their understanding that they are in the study.

iv. Detail any external monitoring that may be planned. (NONE)

SURVEY STAGE I – CENSUS INTRODUCTION

My name is....., and I'm from (Organisation). I am here for the normal census exercise we conduct in every ___ months/year (i.e. Updates for births, deaths, in-migrants etc).

Besides that we will ask you 1-2 extra questions regarding to the history of convulsions for each member of your household. (Organisation) is interested in knowing the extent of epilepsy in this community, to enable them to come up with better ways of treating and managing the condition now and in the future.

If your responses to any one of the 2 questions for you/any member of your household is YES, you/they will be visited by another group of (Organisation) workers within 2 weeks to establish if you/they may have epilepsy. Further to this, the 2nd group of (Organisation) workers may also be interested in asking the same questions to some members of your household even if your responses for them is NO. This will enable us to find out those with epilepsy who may have been left out in this round. Those found to have epilepsy and currently not on medication will be started on anti-epilepsy drugs.

STAGE II: STAGE I POSITIVE CASES INTERVIEWED IN STAGE II

What is (Name of Research Organisation)?

KEMRI is a Government organisation that carries out health research to learn more about diseases that affect children and adults in Kenya. Sometimes research only involves asking questions of patients, their parents, community members or health providers about what they know, feel or do. All research at KEMRI, including those involving only interviews, are approved by committees in Kilifi, and by national independent expert committees in Nairobi to make sure that participants' safety and rights are respected.

What is this research about?

As you may have heard from your community leaders, one of (organization's) current interests is to learn more about the causes, distribution and effects of epilepsy among the different age groups in this community. This is important because although epilepsy is known to be an important problem for citizens, developing appropriate interventions for the country needs far better information about how many people suffer and why.

In order to do this, we would like to talk to people individually in their homes.

Why do you want to talk to me and what does it involve?

A few weeks ago, an individual from (Organisation) on their regular registration and enumeration exercise asked you two questions regarding your (child's) history of convulsions. Given the responses you gave to these 2 questions, I/We would like, with your permission, to ask you a few more questions regarding your (child's) history of epilepsy. If you do not want to answer any of the questions you may say so and I will move on to the next question. Our discussion will take place in here in your home. No-one else but you and I will be present unless you would like someone else here. The discussion should take approximately *15 minutes.*

On the basis of your responses to these questions, we are inviting the people who we think may have epilepsy to (Organisation's) epilepsy clinic for further assessments including blood sample taking.

CONSENT FORM – INTERVIEWS

STAGE III - CASE-CONTROL STUDY: ICF FOR INTERVIEWING AND INVITING CONTROLS

NB: Verbal consent can be obtained for interviews in which the information being sought is non-sensitive. In such situations the person giving consent will not sign but the person seeking consent can sign as below to document that informed consent was obtained.

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I change my mind at any stage [and it will not affect the benefits due to me/my child].

☐*please tick* **I agree to be interviewed**

Signature: _____ **Date** _____

Participant/guardian Name _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to explain this study to the [participant/guardian], and that s/he understands the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Signature: _____ **Date** _____

Designee/investigator's Name _____ **Time:** _____
(please print name)

Thumbprint of the parent as named above if they cannot write: _____

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

STAGE II: STAGE II POSITIVES INVITED FOR STAGE III ASSESSMENT

On the basis of the questions that we have just asked, I/we believe that you (your child) might have epilepsy. We are therefore asking you to assist us in learning about the disease by coming/bringing your child to (Clinic) where;

1) A clinician will first see you to ask various questions to confirm that there is a possibility that you have epilepsy.

2) If you are suspected to have epilepsy, you will also be examined and a recording will be done from your head using an EEG (show picture of EEG), a machine that diagnoses and classifies epilepsy and does not cause any discomfort.
3) A blood sample (5mls) equivalent to one teaspoonful may be taken from you/from your child. There is no harm in taking this amount of blood. This blood sample will be used to look for the causes of epilepsy.

Also, we may request a sub-group of those found to have and not have epilepsy to be involved in a more detailed and long-term study on that visit to the hospital.

You will be provided with breakfast, lunch and travel expenses.

Are there any disadvantages or advantages involved in taking part?

If you (your child) are (is) found to be suffering from epilepsy, you (your child) would be given medication at no cost for the duration of the study; and an epilepsy clinic has been (will be) established at (the hospital) for the purpose of dispensing drugs at a minimal cost after the study. This study is intended to provide a better understanding of the problem of epilepsy in this community and Africa in general.

You will be given more information when you come (bring your child) to the epilepsy clinic for further assessments.

Who will have access to the information I give?

We will not share individual information about you or other participants with anyone beyond a few people who are closely concerned with the research. All of our documents are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research will be shared in summary form, without revealing individuals' identities, with other researchers in the field. Participants will get their individual results.

What will happen if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time.

What if I have any questions?

For information about this study, you can contact the researchers who are responsible:

[PI's name(s) and contacts]

KEMRI- Wellcome Trust [Kilifi District Hospital,]

P.O.Box. 230, Kilifi. Telephone: 041 522 063

If you want to ask someone independent anything about this research please contact

Dorcas Kamuya , at KEMRI – Wellcome Trust

P.O.Box 230, Kilifi. Telephone: 041 522 063 ***Or***

Mr. Ambrose Rachier, Chairman - KEMRI/National Ethics Review Committee

P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0723342780 or 0738472281

STAGE II: COMMUNICATION TO RESPONDENTS WITH A HISTORY OF CONVULSIONS BUT WHO DO NOT MEET THE MINIMUM CRITERIA FOR ACE.

These are people who do not qualify to be either cases or controls and include:

1. Respondents who have had only one fit/seizure/convulsion in their life-time.

2. Respondents who have had more than one fit/seizure/convulsion in their life time whereby the last one was not within the 12 months preceding the survey interview.

3. Those who have had fits but only during febrile illnesses when aged 6 months to 6 years only.

The epilepsy field workers (EFW) will elicit whether such respondents have any health concerns given their history of fits. If they respond in the affirmative, the EFW will state that they are not doctors but advice the respondent to seek medical attention from their local health facility, particularly if they experienced more fits.

The interview should go as follows;

EFW: According to your responses to the questions I just asked, and to the training I have been given by (Organisation), I believe you may not have epilepsy, even though you have had fits in the past. However, if:

- you are worried about your health now or in the future, OR
- you have any further fits;

You should seek advice from a trained health worker (since I am not a doctor).

STAGE II - CASE-CONTROL STUDY: ICF FOR INTERVIEWING MATCHED CONTROLS

What is (Name of Research Organisation)?

KEMRI is a Government organisation that carries out health research to learn more about diseases that affect children and adults in Kenya. Sometimes research only involves asking questions of patients, their parents, community members or health providers about what they know, feel or do. All research at KEMRI, including those involving only interviews, are approved by committees in Kilifi, and by national independent expert committees in Nairobi to make sure that participants' safety and rights are respected.

What is this research about?

A few weeks ago, a team from (Organisation) visited your household to ask the normal enumeration and registration questions asked every ____ months/year. At this last visit, 2 extra questions were asked of everybody about fits. These questions were a first step to teaching us how common epilepsy is in this community.

You/your head of household answered NO to the two convulsion questions, suggesting no possibility of epilepsy. Although we are now mostly following up those who answered YES, we have also randomly selected some who answered NO to visit. This is because we can learn more about epilepsy when we compare the characteristics of those who do and do not have epilepsy.
If you are willing to take part, we would like to ask you some additional questions just to check that we have not missed any possibility of epilepsy. Assuming that your answers confirm no epilepsy, we would then like to invite you (your child) to our clinic. At the clinic we will be seeing both those suspected of suffering from epilepsy and those who are not.

If you do not want to answer any of the questions you may say so and the interviewer will move on to the next question. The discussion will take place in here in your home. No-one else but you and I will be present unless you would like someone else there. The discussion should take approximately *15 minutes*.

CONSENT FORM – INTERVIEWS

STAGE II - CASE-CONTROL STUDY: ICF FOR INTERVIEWING MATCHED CONTROLS

NB: Verbal consent can be obtained for interviews in which the information being sought is non-sensitive. In such situations the person giving consent will not sign but the person seeking consent can sign as below to document that informed consent was obtained.

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I change my mind at any stage [and it will not affect the benefits due to me/my child].

☐*please tick* I agree to be interviewed

Signature: _____ **Date** _____

Participant/guardian Name _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to explain this study to the [participant/guardian], and that s/he understands the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Signature: _____ **Date** _____

Designee/investigator's Name _____ **Time:** _____
(please print name)

Thumbprint of the parent as named above if they cannot write: _____

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

STAGE II: CONTROLS INVITED FOR STAGE III ASSESSMENT

Given your (child's) responses to the questions I just asked, I believe you/they may not have epilepsy. We are therefore requesting you/your child to become involved in this study by allowing us to compare your (child's) characteristics to those of a person with epilepsy to help us learn more about factors that are associated with development of epilepsy in some people and not in others.

We are requesting you to come (bring your child) to the Epilepsy clinic for a full medical examination, including blood tests. This will enable us to find out those characteristics that are different between people with and without epilepsy.

You will be provided with breakfast, lunch and travel expenses.

At the clinic:

1) A clinician will first see you (your child) to ask various questions to confirm that you do not have epilepsy.
2) A blood sample (5mls) equivalent to one teaspoonful may be taken from you/from your child. There is no harm in taking this amount of blood. This blood sample will be used to look for the causes of epilepsy.

You will be given more information when you come (bring your child) to the epilepsy clinic for further assessments.

Are there any disadvantages or advantages involved in taking part?

By participating in this project, you/your child will get a full medical examination by a qualified clinician and any medical conditions that you/your child may have will be diagnosed and you will be advised accordingly. For instance, if you/your child are found to have anaemia (less blood in the body) or if you/they have worms in the stomach, you will be advised accordingly and put on medication.

At the community level, you will be assisting in efforts to find out factors associated with epilepsy in this community and in Africa in general, some of which may be preventable and which will enable us to come up with preventive strategies.

Who will have access to the information I give?

We will not share individual information about you or other participants with anyone beyond a few people who are closely concerned with the research. All of our documents are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research will be shared in summary form, without revealing individuals' identities, with other researchers in the field. Participants will get their individual results.

What will happen if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time.

What if I have any questions?

For information about this study, you can contact the researchers who are responsible:

[PI's name(s) and contacts]

KEMRI- Wellcome Trust [Kilifi District Hospital,]

P.O.Box. 230, Kilifi. Telephone: 041 522 063

If you want to ask someone independent anything about this research please contact

Dorcas Kamuya , at KEMRI – Wellcome Trust

P.O.Box 230, Kilifi. Telephone: 041 522 063 *Or*

Mr. Ambrose Rachier, Chairman - KEMRI/National Ethics Review Committee

P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0723342780 or 0738472281

STAGE III - CASE-CONTROL STUDY: ICF FOR INTERVIEWING CASES AND CONTROLS

What is (Research Organisation)?

KEMRI is a Government organisation that carries out health research to learn more about diseases that affect children and adults in Kenya. Sometimes research only involves asking questions of patients, their parents, community members or health providers about what they know, feel or do. All research at KEMRI, including those involving only interviews, are approved by committees in Kilifi, and by national independent expert committees in Nairobi to make sure that participants' safety and rights are respected.

What is this research about?

A few weeks ago, an individual from (Organisation) visited your household to ask you some questions regarding your (child's) history of epilepsy and then you were invited to come to this clinic for further examination by a clinician. This is still part of the study to teach us how common epilepsy is in this community.

I will first ask you some questions regarding your (child's) social background and medical history and then I will take you to the doctor who will ask you a few more questions, carry out a medical examinations and take a sample of your (child's) blood. The doctor will explain to you why we would like to take a sample of your (child's) blood and request your consent/permission to do so. You may decline to give a sample of your (child's) blood but still take part in this study. Further, we are requesting those individuals found to have epilepsy to participate in a long-term study to help us identify some of the causes of mortality in people with epilepsy. This will involve collecting information from you regarding the frequency of seizures and use of anti-epileptic drugs on a regular basis (every 3 – 6 months) during your (child's) routine clinic visit or in your home. This will also involve administering a questionnaire (verbal autopsy – VA) the relatives of the person with epilepsy when they die to probe the factors immediately associated with the death.

I would now like, with your permission, to ask you the questions I just mentioned. If you do not want to answer any of the questions you may say so and I will move on to the next question. The discussion will take place in here at the clinic. No-one else but I and you (and your child) will be present unless you would like someone else here. The discussions should take approximately *15 minutes.*

CONSENT FORM – INTERVIEWS

STAGE III - CASE-CONTROL STUDY: ICF FOR INTERVIEWING CASES AND CONTROLS

NB: Verbal consent can be obtained for interviews in which the information being sought is non-sensitive. In such situations the person giving consent will not sign but the person seeking consent can sign as below to document that informed consent was obtained.

I have had the study explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I change my mind at any stage [and it will not affect the benefits due to me/my child].

☐ *please tick* **I agree to be interviewed**

☐ *please tick* **I agree to be in a long-term study of causes of death among people with epilepsy**

Signature: _____ **Date** _____

Participant/guardian Name _____ **Time:** _____
(please print name)

I certify that I have followed the study SOP to explain this study to the [participant/guardian], and that s/he understands the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Signature: _____ **Date** _____

Designee/investigator's Name _____ **Time:** _____
(please print name)

Thumbprint of the parent as named above if they cannot write: _____

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

STAGE III - CASE-CONTROL STUDY: ICF FOR BLOOD SAMPLE TAKING

What is (Research Organisation)?

KEMRI is a government organisation that carries out medical research. Research is different from normal treatment because research aims to find better ways of preventing and treating illness in the future for everybody's benefit. You have come to the hospital/clinic because you/your child were/was invited to take part in the ongoing epilepsy research. We would like to ask for your help in our research by allowing us to take a blood sample. The rest of your treatment and care will be as normal. We are asking this of several people in this community; those with and those without epilepsy.

Why am I requested to give blood in this research?

Besides finding out how many people have epilepsy in this community, we are interested in learning what some of the causes of epilepsy might be. We are therefore asking you to assist us further learn more about the disease by allowing us do some detailed blood tests to help us understand what causes epilepsy in this community. Causes that we are interested in include inheritance (genetic factors i.e. characteristics that you inherit from your parents e.g. shape of your ear). There are other factors that may explain why people develop epilepsy including infections like cerebral malaria, meningitis and HIV. All these factors can be assessed by doing some blood tests and will be compared between those with epilepsy and those without.

What will it involve for me/my child?

We will take a small sample of blood (about 1 teaspoonful – 5ml) from your (child's) arm.

The procedure for testing for HIV will be as follows:

If you agree to participate in this study a trained professional will offer you the opportunity to have counselling for an HIV test if you are not sure you want the test. If after the counselling you decide you want the results of the test then we will arrange for it to take place here at the research centre, and for your results to be given to you soonest possible. Those who want their test results given to them, and who test positive will be seen regularly in the hospital/clinic to try and treat and prevent illnesses that might arise in future. If you decide that you do not want to know the HIV test result your decision will be respected. In this case we would like to use the

result of the test to help our research project but nobody except the doctor in charge of the study will know the result. If you do not want an HIV test to be done at all on your blood you can still be in the study. You can make your wishes known at the end of this form or after counselling.

Are there any risks or advantages to me or my child of participating?

Taking blood from the arm causes a small amount of pain where the needle enters the skin, but this does not last. The amount of blood taken will be too small to affect your/your child's health. By participating in this project, you/your child will get a full medical examination by a qualified clinician and any medical conditions that you/your child may have will be diagnosed and you will be advised accordingly. For instance, if you/your child are found to have anaemia (less blood in the body) or worms in the stomach, you will be advised accordingly and put on medication.

If you (your child) are diagnosed to have epilepsy, you/they will be put on medication free of charge for the duration of this project.

At the community level, you will be assisting in efforts to find out factors associated with epilepsy in this community and in Africa in general, some of which may be preventable and which will enable us to come up with preventive strategies.

What happens if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want (your child) to give a blood sample. You/your child will have the same level of care whether you/they give a sample or not. This will not affect you/your child's care now or in the future.

What happens to the samples?

Some of the tests that are needed as part of this research cannot be done in this country at the moment, so part of the samples will be sent to laboratories abroad for these tests.

After the research has been done, a small portion of the blood will be stored. In the future, new research may be done on these samples about [*illness, or indicate if any illness*]. Future research must first be approved by a national independent expert committee in (Capital city) to ensure that

participants' safety and rights are respected. Individual names will be removed and replaced by codes, so that information cannot be linked to the participants.

Who will have access to information about me/my child in this research?

All our research records are stored securely in locked cabinets and password protected computers. Only a few people who are closely concerned with the research will be able to view information from participants.

Who has allowed this research to take place?

An independent committee in (Country) that is run by the Government and a committee in (Local town) have looked carefully at this and agreed that the research is important, that it should be safe to take part in and will be conducted properly.

What if I have any questions?

You may ask any of our staff questions at any time. You can also contact those who are responsible for the care of your child and this research:

PI's name(s) and contacts

Dr. _____

KEMRI- Wellcome Trust [Kilifi District Hospital,]

P.O.Box. 230, Kenya. Telephone: 041 522 063

If you want to ask someone independent anything about this research please contact

Dorcas Kamuya , at KEMRI – Wellcome Trust

P.O.Box 230, Kilifi. Telephone: 0723342780 or 041 522 063

Or

Mr. Ambrose Rachier, Chairman - KEMRI/National Ethics Review Committee

P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722205901 or 0733400003

STAGE III - CASE-CONTROL STUDY: ICF FOR BLOOD SAMPLE TAKING

I, [being a guardian of _____ (name of child)], have had the research explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I can change my mind at any stage and it will not affect the benefits due to me/my child.

Please insert the boxes below where relevant:

☐ **Yes** ☐ **No** *please tick* **I agree to take part/allow my child to take part in this research**

☐ **Yes** ☐ **No** *please tick* **I agree to samples being stored**

☐ **Yes** ☐ **No** *please tick* **I agree to samples being exported**

☐ **Yes** ☐ **No** *please tick* **I agree to a HIV test**

☐ **Yes** ☐ **No** *please tick* **I agree to a HIV test only after counseling**

Subject/Parent/guardian's signature: _____ **Date** _____

Subject/Parent/guardian's name: _____ **Time** _____

(Please print name)

I certify that I have followed all the study specific procedures in the SOP for obtaining informed consent.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name : _____ **Time** _____

(Please print name)

Only necessary if the parent/guardian cannot read:

I *attest that the information concerning this research was accurately explained to and apparently understood by the parent/guardian and that informed consent was freely given by the parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

(Please print name)

***A witness is a person who is independent from the study or a member of staff who was not involved in gaining the consent.**

Thumbprint of the parent as named above if they cannot write: _____

THE SUBJECT/PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP.

Appendix 2.1: Description of search strategy for studies of prevalence of epilepsy.

Search Element	MEDLINE/ EMBASE/ PsycINFO	Other Databases
Epilepsy **(AND)**	*Thesaurus Exploded* Epilepsy Epilepsy, Tonic-Clonic Epilepsy, Frontal Lobe Epilepsy, Rolandic Epilepsy, Generalized Epilepsy, Absence Epilepsy, Complex Partial Myoclonic Epilepsy, Juvenile Epilepsy, Benign Neonatal Epilepsy, Temporal Lobe Epilepsy, Partial, Motor Epilepsy, Partial, Sensory Epilepsy, Post-Traumatic Epilepsies, Myoclonic Epilepsies, Partial Myoclonic Epilepsies, Progressive	*Epilepsy* (kw, ti, ab) **(AND)** *Prevalence* (kw, ti, ab)
Epidemiology **(OR)**	Epidemiology +subheading "epidemiology"	
Morbidity **(OR)**	Morbidity	
Prevalence	Prevalence Data collection Cross-sectional studies	

Appendix 2.2: Reasons for exclusion from meta-analysis of prevalence studies.

Reason	**No of studies**
Lack of/inadequate definition of epilepsy (2 or more non-provoked seizures occurring at least 24 hours apart)	52
Study on subpopulation with epilepsy e.g. prevalence in patients with a history of head trauma	6
Published as a review article	15
Study on single epilepsy syndromes	23
Published as correspondence/letter/editorial/abstract only	15
Study on single seizure syndromes	5
Study of epilepsy as a risk factor to other conditions e.g. fractures	9
Duplicate study	4
Study did not provide denominator data	3
Study not on prevalence of epilepsy	4
Total	**136**

Appendix 2.3(a): Summary of prevalence of epilepsy from the studies included in the meta-analysis.

Reference	Country	Econ. Dev	Population	Ascertain*	Age	Type	Follow-up	Prevalence/1000	U95%CI	L95%CI
(Almu et al., 2006)	Ethiopia	Developing	1154	Q, E	All	LT	Point	29.5	40.9	20.5
(Velez , 2006)	Colombia	Developing	8910	Q, E, T	All	LT, AE	Period	11.3	13.8	9.2
(Nicoletti et al., 2005)	Bolivia	Developing	9955	Q, E	All	LT	Point	12.3	14.8	10.4
(Del Brutto et al., 2005)	Ecuador	Developing	2415	Q, E	All	LT	Point	9.94	13.9	5.98
(Ndoye et al., 2005)	Senegal	Developing	4500	Q, E, T	All	LT	Point	14.2	17.7	10.7
(Medina, 2005)	Honduras	Developing	6437	Q, E, T	All	LT, AE	Point	23.3	27	19.6
(Morgan &Kerr, 2004)	UK	Developed	424000	MR	All	LT	Period	9.2	9.4	8.9
(Birbeck & Kalichi, 2004)	Zambia	Developing	55000	Q	All	AE	Point	14.5	15.6	13.5
(Wang et al., 2003)	China	Developing	55616	Q, E	All	LT, AE	Point	7	7.7	6.3
(Tidman et al., 2003)	UK	Developed	15907	MR	Children	LT	Period	4.3	5.5	3.4
(da Mota et al., 2002)	Brazil	Developing	982	Q, E	All	LT, AE	Point	16.3	26.3	9.3
(Onal et al., 2002)	Turkey	Developed	2187	Q, E, T	All	LT, AE	Period	7.8	12.4	4.5
(Debrock et al., 2000)	Benin	Developing	3134	Q, MR	All	LT	Point	21.1	26.7	16.3
(Kurtz et al., 1998)	UK	Developed	17414	Q, MR	Children	LT	Period	6.3	7.7	4.9
(Wright et al., 2000)	UK	Developed	225439	MR, E	All	LT, AE	Period	7.3	7.6	6.9
(Morgan et al., 2000)	UK	Developed	434000	MR	All	LT	Period	6.7	13.4	2
(Radhakrishnan et al., 2000)	India	Developing	238102	Q, E, T	All	LT	Point	4.9	5.19	4.62
(Olafsson & Hauser, 1999)	Iceland	Developed	89656	MR	All	LT	Point	4.8	5.27	4.35
(Kun et al., 1999)	Singapore	Developed	20542	Q, MR	Adult	LT	Point	4.9	6	4
(Mendizabal & Salguero, 1996)	Guatemala	Developing	1882	Q, E	All	LT, AE	Point	8.5	13.8	4.9
(Attia-Romdhane et al., 1993)	Tunisia	Developing	25000	Q, E	All	LT	Point	4.04	4.91	3.29
(Rwiza, 1992)	Tanzania	Developing	18183	Q, E	All	LT, AE	Point	11.5	13.15	9.99

Appendix 2.3(a): Continued

Reference	Country	Econ. Dev	Population	Ascertain*	Age	Type	Follow-up	Prevalence/1000	U95%CI	L95%CI
(Forsgre, 1992)	Sweden	Developed	129005	MR	Adult	LT	Point	5.53	5.93	5.13
(Salinpaa, 1992)	Finland	Developed	21104	Q	Children	LT	Point	6.8	5.97	4.03
(Kochen & Melcon, 2005)	Argentina	Developing	17049	Q, E	All	LT, AE	Point	6.2	7.5	5.1
(de la Court et al., 1996)	Netherlands	Developed	5559	Q, MR, T	Adult	LT, AE	Point	15.3	12.2	18.9
(Kwong et al., 2001)	Hong Kong	Developed	203499	Q, MR, T	Children	LT	Point	1.52	1.35	1.69
(Luengo et al., 2001)	Spain	Developed	98405	Q, E, T	Adult	LT	Point	4.12	3.7	4.5
(Beilmann et al., 1999)	Estonia	Developed	157449	MR, E, T	Children	AE	Point	3.6	3.3	3.9
(Asawavichienjinda et al., 2002)	Thailand	Developing	2069	Q, E	All	LT	Point	7.2	11.9	4.1
(Aziz, 1997 Jun)	Pakistan	Developing	994	Q, E, T	Children	LT	Point	23	34.5	14.7
(Christianson et al., 2000)	S. Africa	Developed	6692	Q, E	Children	LT, AE	Point	7.3	5.4	9.4
(Gracia et al., 1990)	Panama	Developing	337	Q, E	Adult	LT, AE	Point	90	60.9	124.6
(Hackett et al., 1997)	India	Developing	1172	Q, E	Children	LT	Period	22.2	14.5	32.3
(Wong, 2003)	Hong Kong	Developed	245340	MR	Children	LT	Period	4.5	4.2	4.8
(Okan et al., 1995)	Turkey	Developing	5002	Q, E	Children	LT	Point	9.2	6.7	12.2
(Kraagac et al., 1999)	Turkey	Developing	4803	Q	All	LT	Point	10.2	13.5	7.6
(Rocca et al., 2001)	Italy	Developed	24496	Q, E	All	LT, AE	Point	4.53	5.5	3.7
(Gourie-Devi et al., 1996)	India	Developing	3040	Q	All	LT	Period	7.8	11.7	5.1
(Lavados et al., 1992)	Chile	Developing	17694	MR	All	LT	Point	17.8	19.9	15.9
(Argumosa & Herranz, 2000)	Spain	Developed	225	Q	Children	LT	Point	4.24	24.4	0.12
(Oun et al., 2002)	Estonia	Developed	72245	MR, E	Adult	AE	Period	5.3	5.8	4.8
(Al Rajeh et al., 2001)	S. Arabia	Developed	22630	Q, E, T	All	AE	Point	6.54	7.6	5.5
(Dent et al., 2005)	Tanzania	Developing	4905	Q, E	Children	AE	Period	8.6	11	6

Continued

Appendix 2.3(a): Continued

Reference	Country	Econ. Dev	Population	Ascertain*	Age	Type	Follow-up	Prevalence/1000	U95%CI	L95%CI
(Gallitto et al., 2005)	Italy	Developed	13431	MR, E, T	All	AE	Point	3.13	4.2	2.2
(Waaler et al., 2000)	Norway	Developed	38593	MR	Children	AE	Point	5.13	5.8	4.4
(Jacoby et al., 1998)	UK	Developed	177703	Q, MR	All	AE	Point	7.6	7.8	7.2
(Eriksson & Koivikko, 1997)	Finland	Developed	83464	MR	Children	AE	Point	3.94	4.39	3.53
(Aziz et al., 1997(a))	Pakistan	Developing	24130	Q, MR	All	AE	Point	9.98	11.3	8.8
(Aziz et al., 1997(b))	Turkey	Developing	11497	Q, MR	All	AE	Point	7.0	5.5	8.65
(Sidenvall et al., 1996)	Sweden	Developed	36524	Q, MR, T	Children	AE	Point	4.2	5.0	3.6
(Hauser et al., 1991)	US	Developed	56447	MR	All	AE	Point	6.8	7.5	6.1
(Cornaggia et al., 1990)	Italy	Developed	54520	Q, E, T	Adult	AE	Period	4.7	4.2	5.3
(Tran et al., 2006)	Lao PDR	Developing	4310	Q, E	All	AE	Point	7.7	5.3	10.7
(Fong et al., 2003)	Hong Kong	Developed	475900	MR, E, T	Adult	AE	Point	1.54	1.7	1.4
(Garcia-Noval et al., 2001)	Guatemala	Developing	1183	Q	Adult	LT,AE	Period	28.5	39	19.3
(Endziniene et al., 1997)	Lithunia	Developing	88871	MR, E, T	Children	AE	Point	4.25	4.7	3.8
(Keranen et al., 1989)	Finland	Developed	194282	MR, E	Adult	LT,AE	Period	7.1	7.5	6.7
(Cowan et al., 1989)	US	Developed	246047	MR	Adult	AE	Period	4.71	5	4.4
(al Rajeh et al., 1993)	S. Arabia	Developed	22630	Q	All	AE	Period	6.5	7.7	5.5
(Montano et al., 2005)	Peru	Developing	903	MR, E	All	LT,AE	Period	32	46	22
(Singh & Kaur, 1997)	India	Developing	30000	Q,E	All	LT	Point	4.2	3.5	5

*Q = questionnaire; E = neurological examination; T = neuro-imaging tool (EEG, CT scan or MRI); MR = medical records; AE = active epilepsy; LT = life-time epilepsy

Appendix 2.3(b): List of prevalence studies included in the meta-analysis

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Almu S, Tadesse Z, Cooper P & Hackett R. (2006 Apr) The prevalence of epilepsy in the Zay Society, Ethiopia--an area of high prevalence. Seizure 15: 211-213.

Argumosa A & Herranz JL. (2000) The economic cost of childhood epilepsy in Spain. Rev Neurol. 30: 104-108.

Asawavichienjinda T, Sitthir-Amon C & Tanyanont W. (2002) Prevalence of epilepsy in rural Thailand: A population based study. J Med Assoc Thai 85: 1066-1073.

Attia-Romdhane N, Mrabet A & Ben Hamida M. (1993 Nov-Dec) Prevalence of epilepsy in Kelibia, Tunisia. Epilepsia 34: 1028-1032.

Aziz H, Guvener A, Akhtar SW & Hasan KZ. (1997(b)) Comparative epidemiology of epilepsy in Pakistan and Turkey: population-based studies using identical protocols. Epilepsia 36: 716-722.

Aziz H, Guvener A, Akhtar SW & Hasan KZ. (1997(a)) Comparative epidemiology of epilepsy in Pakistan and Turkey: population-based studies using identical protocols. Epilepsia 38: 716-722.

Beilmann A, Napa A, Soot A, Talvik I & Talvik T. (1999 Jul) Prevalence of childhood epilepsy in Estonia. Epilepsia 40: 1011-1019.

Birbeck GL & Kalichi EM. (2004 Jan) Epilepsy prevalence in rural Zambia: a door-to-door survey. Trop Med Int Health 9: 92-95.

Christianson AL, Zwane ME, Manga P, Rosen E, Venter A & Kromberg JGR. (2000) Epilepsy in rural South African children: Prevalence, associated disability and management. South African Medical Journal 90: 262-266.

Appendix 2.3(b): Continued

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De la court A, Breteler MM, Meinardi H, Hauser WA & Hofman A. (1996) Prevalence of epilepsy in the elderly: the Rotterdam Study. Epilepsia 37: 141-147.

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Del Brutto OH, Santibanez R, Idrovo L, Rodriguez S, Diaz-Calderon E, Navas C, Gilman RH, Cuesta F, Mosquera A, Gonzalez AE, Tsang VC & Garcia HH. (2005 Apr) Epilepsy and neurocysticercosis in Atahualpa: a door-to-door survey in rural coastal Ecuador. Epilepsia 46: (4) 583-587.

Dent W, Helbok R, Matuja WB, Scheunemann S & Schmutzhard E. (2005 Dec) Prevalence of active epilepsy in a rural area in South Tanzania: a door-to-door survey. Epilepsia 46: 1963-1969.

Endziniene M, Pauza V & Micevisiene I. (1997) Prevalence of childhood epilepsy in Kaunas, Lithuania. Brain & Development 19: 379-387.

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Appendix 2.3(b): Continued

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Garcia F, de Lao S & Castillo L. (1990) Epidemiology of epilepsy in Guaymi Indians of Bocas del Toro province, republic of Panama. Epilepsia 31: 718-723.

Hackett RJ, Hackett L & Bhakta P. (1997) The prevalence and associated factors of epilepsy in children in Calicut District, Kerala, India. Acta Paediatr. 86: 1257-1260.

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Hauser WA, Annergers JF & Kurkland LT. (1991) Prevalence of epilepsy in Rochester, Minnesotta: 1940 - 1980. Epilepsia 32: 429-445.

Kochen S & Melcon MO. (2005 Dec) Prognosis of epilepsy in a community-based study: 8 years of follow-up in an Argentine community. Acta Neurol Scand. 112: 370-374.

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Appendix 2.3(b): Continued

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Appendix 2.3(b): Continued

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Velez A. (2006) Epilepsy in Colombia: epidemiologic profile and classification of epileptic seizures and syndromes. Epilepsia 47: 193-201.

Waaler PE, Blom BH, Skeidsvoll H & Mykletun A. (2000 Jul) Prevalence, classification, and severity of epilepsy in children in western Norway. Epilepsia 41: 802-810.

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Appendix 2.4: Results of random effects meta-regression of prevalence of life-time epilepsy from all studies, multivariate analyses

Covariate	Categories	No. of studies	Odds Ratio	95% CI	P value
Development	Developed	20	1.0	-	-
	Developing	26	1.6	1.06 – 2.3	<0.02
Age	Adult	7	1.0	-	-
	Children	11	0.7	0.4 – 1.1	0.08
	All	28	0.5	0.3 – 0.8	0.004
Study size	>20,000	19	1.0	-	-
	1,000-20,000	22	1.8	1.2 – 2.5	0.001
	<=1,000	5	4.1	2.3 – 7.5	<0.0001

Amount of heterogeneity explained = 52.8%

Appendix 2.5: Results of random effects meta-regression of prevalence of active epilepsy from all studies, multivariate analyses

Covariate	Categories	No. of studies	Odds Ratio	95% CI	P value
Development	Developed	18	1.0	-	-
	Developing	19	1.4	1.0 – 2.1	0.055
Age	Adult	8	1.0	-	-
	Children	7	0.9	0.6 – 1.4	0.7
	All	22	0.8	0.5 – 1.3	0.3
Study size	>20,000	20	1.0	-	-
	1,000-20,000	14	1.3	0.9 – 1.9	0.2
	<=1,000	3	2.9	1.4 – 61.	0.004

Amount of heterogeneity explained = 40.0%

Appendix 3.1: Description of search strategy and search results of meta-analysis of incident studies.

Database	Search strategy	Limits	Number of articles	No of articles after [Ti & Ab] review
1) Medline	epilep*[Title/Abstract]) AND incidence[Title/Abstract]) NOT review[Title/Abstract]) NOT letter[Title/Abstract]) NOT comment[Title/Abstract]) NOT editorial[Title/Abstract];	"(Humans, English, French, German, Spanish, Portugese)" AND "(Clinical Conference OR Journal Article OR Multicenter Study)"	1,841	41
2) EMBASE	epilep*[Title/Abstract]) AND incidence [Title/Abstract])	"(Human , EMBASE, English, French, German , Spanish, Portuguese)" AND "(Article OR Conference abstract OR Conference paper OR "Conference review" OR Journal))"	374	0
3) SCIELO	[Epilepsy & Incidence/Ti & Ab]	None	3	1
4) Index Medicus for South East Asia	[Epilepsy AND Incidence/All Indices]	None	35	0
5) Directorate of Open Access Journals	[Epilepsy AND Incidence/All Indices]	None	14	0
6) Arquivos de Neuro-Psiquiatria	[Epilepsy AND Incidence/All Indices]	None	8	0
7) Index Medicus for Eastern Mediterrenean Region	[Epilepsy AND Incidence/KW]	None	23	0
8) LILACS	[Epilepsy AND Incidence/Ti]	None	1	0
9) Others	[Epilepsy AND Incidence/Ti/Ab/Kw]	None	2	1
10) Reference lists			3	0
Legend: Ti = Title; Ab = Abstract; Kw = Key word				

Appendix 3.2: Description of study-level covariates in the meta-analysis of incidence studies.

	Covariates						
	Development	**Case ascertainment**	**Decade of study**	**Age group**	**Duration of follow-up**	**Population size**	**Study design**
Levels	HIC	Medical Records (MR)	< 1990	Adults	<3 years	≤20,000	Prospective
	LMIC	Questionnaires (Q)	1990 – 1999	Children	3-5 years	20,000-100,000	Retrospective
		MR+Q	≤2000	Adults and Children	5-10 years	>100,000)	

Appendix 3.3: Studies included in the meta-analysis of incidence

Study*	Design	Country	Study size category (thousands)	Case ascertainment	Age category	Incidence rate/100,000	Follow-up (years)	Economic status
1	Prospective	Sweden	20-100	Q+MR	Child	82.3	<3	HIC
2	Retrospective	Italy	20-100	Q+MR	All	33.1	>10	HIC
3	Retrospective	China	20-100	Q+MR	All	25	<3	LMIC
4	Retrospective	Denmark	20-100	MR	All	42	5-10	HIC
5	Prospective	Japan	≤20	MR	Child	55.3	5-10	HIC
6	Retrospective	Finland	>100	MR	Adult	24	3-5	HIC
7	Prospective	UK	≤20	Q+MR	Child	43	5-10	HIC
8	Prospective	Ecuador	20-100	Q	All	122	<3	LMIC
9	Retrospective	US	>100	MR	All	44	>10	HIC
10	Prospective	Sweden	20-100	MR	Child	53	<3	HIC
11	Retrospective	Iceland	20-100	MR	All	47	<3	HIC
12	Retrospective	Canada	>100	MR	Child	41	5-10	HIC
13	Prospective	Ethiopia	20-100	Q	All	64	3-5	LMIC
14	Prospective	India	20-100	MR	All	49.3	<3	LMIC
15	Prospective	UK	≤20	MR	Child	36.6	>10	HIC
16	Prospective	Uganda	≤20	Q	All	215	3-5	LMIC
17	Retrospective	Tanzania	≤20	Q	All	73.3	5-10	LMIC
18	Retrospective	US	20-100	MR	All	52.3	3-5	HIC
19	Prospective	Estonia	>100	MR	Child	45	<3	HIC
20	Retrospective	US	20-100	MR	All	35.5	5-10	HIC
21	Prospective	UK	>100	MR	All	46	<3	HIC
22	Prospective	Germany	>100	Q+MR	Child	60.7	<3	HIC
23	Retrospective	Estonia	20-100	Q+MR	Adult	35.4	<3	HIC
24	Prospective	Iceland	>100	Q+MR	All	33.3	<3	HIC
25	Prospective	Honduras	≤20	Q	All	92.7	<3	LMIC

26	*Prospective*	*Netherlands*	>100	MR	*Child*	*30.3*	<3	HIC
27	Prospective	Canada	>100	MR	*Child*	*63*	*5-10*	*HIC*
28	Retrospective	Sweden	20-100	MR	Child	40	3-5	*HIC*
29	Retrospective	Denmark	>100	MR	All	83.3	5-10	HIC
30	Prospective	Spain	20-100	MR	Child	62.1	<3	HIC
31	Prospective	US	>100	MR	All	38.6	<3	HIC
32	Prospective	Peru	≤20	Q	All	162.4	3-5	LMIC
33	Retrospective	Tanzania	≤20	Q	All	81.1	3-5	LMIC

Key: Q=questionnaire, MR=medical records, HIC=High Income Country, LMIC=Low and Middle Income Country,
*references as organized in the e-references

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Appendix 4.1: Stage I (SI) of the cross-sectional survey: (Census screen for convulsions)

Q1: Do you have fits or has someone ever told you that you have fits?

Q2: Do you experience episodes in which your legs or arms have jerking movements or fall to the ground and lose consciousness?

Appendix 4.2: Stage II (SII) screening questions

Q1. Have you ever had a fit?

Q2. Has someone ever told you that you have fits?

Q3. Have you ever been told that you have epilepsy or epileptic fits?

Q4. Have you ever had attacks in which you fall to the ground with loss of consciousness?

Q5. Have you ever fallen to the ground without a reason and experienced:

a) Twitching?

b) Shaking of the arms or legs without control?

c) Wetting yourself?

d) Biting of the tongue?

Q6. Have you ever been told by a doctor that you have epilepsy or epileptic fits?

Appendix 5.1: Clinical History Form

Name: [_____] [_____] [_____]

EPISURV Number: [_A_]_G]_N_]_0_]_8_[_]_]_]_]_]

Sex: [ ]

DOB: [ ][ ]/[ ][ ]/[ ][ ][ ][ ]

Date of assessment: [ ][ ]/[ ][ ]/[ ][ ][ ][ ]

Summary

Does s/he have epilepsy? **Yes/ No** [ ] **(HE)**
If Yes is it Active Epilepsy? **Yes/ No** [ ] **(AE)**
Does this s/he need an EEG? **Yes/ No** [ ] **(EEG)**
If Yes, when done? [ ][ ]/[ ][ ]/[ ][ ][ ][ ] **(EEGDATE)**

Does s/he have any sickle cell disease? **Yes/ No** [ ] **(SCD)** Diabetes mellitus **Yes/ No** [ ] **(DM)**
Hypertension **Yes/ No** [ ] **(HYP)**
Stroke **Yes/ No** [ ] **(STK)**
Others, specify_____

EPILEPSY RECORD

Answer Yes (Y) or No (N) or Unknown (U)

Has s/he ever had a fit	[ ] **(CF)**
Has s/he ever had episodes when s/he loses consciousness	[ ] **(CLC)**
Has s/he ever fallen to the ground without a reason	[ ] **(CFG)**
and the arms or legs twitch/shake	[ ] **(ALT)**
and bites the tongue	[ ] **(BT)**
and wets him/herself	[ ] **(WH)**
Have you ever noticed that s/he has episodes of	
shaking, trembling of one arm or one leg or the face	[ ] **(ST)**
becoming stiff	[ ] **(BS)**
loses contact with the surroundings	[ ] **(LCS)**
frequent loss memory from a short period of time	[ ] **(FLM)**
jerkings which move up your arm, leg or body	[ ]**(JALB)**
Has s/he had episodes when s/he appears dazed	[ ] **(CD)**
complains of tummy aches	[ ] **(TA)**
smells an odd smell	[ ] **(OS)**
sees something strange	[ ] **(SS)**
Have you ever been told that s/he has had a fit	[ ] **(TCF)**

If response to any of the above questions is Yes, please fill the next section and table on the next page:

Date of onset of seizures:	[	][	]/[	][	]/[	][	][	][	**](DOS)**
Number of different seizure types								[	**](NST)**
When was the last seizure	[	][	]/[	][	]/[	][	][	][	**](LS)**
How many seizures in the last year							[	][	**](SY)**

When does s/he have seizures? **Daytime / Sleeping/ Both**	[ ] **(WS)**
How many seizures has s/he ever had? **0 – 9** or **Frequent** (>9)	[ ] **(NS)**
How many times per month? **0 – 9** or **Frequent** (>9)	[ ] **(PM)**
How many times per week? **0 – 9** or **Frequent** (>9)	
How many times per day? **0 – 9** or **Frequent** (>9)	
Is the seizure provoked?	
If **Yes** is it by fever?	
If **No** what are the precipitating factors	

Description of seizures:

Current anti-epileptic drugs:
Any Medication ? **Y/N** [ ] **(AM)**

If Yes which one/s; Phenobarbitone (**PB**); Phenytoin (**PH**); Carbamazepine (**CB**); Sodium valproate (**NN**)

First drug taken: [ ][ ] **(AE1)** Second drug taken: [ ][ ] **(AE2)**
Dose per day [ ][ ][ ] **(AED1)** [ ][ ][ ] **(AED2)**

Previous anti-epileptic drug history:
First drug taken: [ ][ ] **(AEP1)** Second drug taken: [ ][ ] **(AEP2)**
Dose per day

Drug reactions or unacceptable side effects from anti-epileptic **drugs**

(Y/N).....[ ]**DR**

Describe_____

Traditional medicine? [ ] **(PTRM)**

Description of seizure types:	1st		2nd	
Before the episode				
Does s/he know it is going to occur eg. goes to another person		**(KO1)**		**(KO2)**
Abnormal behaviour		**(AB1)**		**(AB2)**
During the episode				
Becomes unresponsive (not answer questions, disobey commands)		**(BU1)**		**(BU2)**
Fall to the ground		**(FG1)**		**(FG2)**
Talks nonsense		**(TN1)**		**(TN2)**
Does not know where s/he is		**(DW1)**		**(DW2)**
Hallucinations; paraesthesiae		**(HP1)**		**(HP2)**
Automatisms: swallowing/grimacing/fiddling/gestures/vocalizations/walking		**(AM1)**		**(AM2)**
Other phenomena: fear/weeping/abdominal/déjà vu,		**(OP1)**		**(OP2)**
Convulsive movements				
Which side: **B**oth; **R**ight; **L**eft; one **S**ide (unsure which)		**(CS1)**		**(CS2)**
Which limb: **B**oth; **A**rms; **L**egs		**(CM1)**		**(CM2)**
Partial: **F**ace; **L**ips; **H**and		**(CP1)**		**(CP2)**

Eyes involved:				
Blank look		(BK1)		(BK2)
Stares ahead		(SA1)		(SA2)
Deviate: **U**pwards; **R**ight; **L**eft; **D**eviate (unsure to which side)		(ED1)		(ED2)
Jerking movements		(JM1)		(JM2)
Lips involved: **N**o, **S**macking, **L**icking		(LI1)		(LI2)
Bites tongue		(BG1)		(BG2)
Wets self		(WE1)		(WE2)
Soils self		(SO1)		(SO2)
Duration (minutes)		(DU1)		(DU2)
After the episode				
Drowsy		(DY1)		(DY2)
Sleeps		(SP1)		(SP2)
Headache		(HE1)		(HE2)
Abnormal behaviour		(AN1)		(AN2)
Paralysis		(PA1)		(PA2)
Disturbance of sleep		(DS1)		(DS2)
Speech and language difficulties (aphasia)		(SL1)		(SL2)
Does s/he remember the episode		(RE1)		(RE2)
Number per day		(NU1)		(NU2)
per month		(NM1)		(NM2)
Age when started (months)		(AS1)		(AS2)

Sign if you have checked that the form is complete_____

Appendix 5.2: Neurological Examination Form

Name: [_____] [_____] [_____]

EPISURV Number: [_A_]_G_]_N]_0_]_8_[_]_]_]_]_]

Sex: [ ]

DOB: [ ][ ]/[ ][ ]/[ ][ ][ ][ ]

Date of assessment: [ ][ ]/[ ][ ]/[ ][ ][ ][ ]

Nutritional Measurements:

Weight |__|__|.|_| Kg **(WT)**
OFC |__|__|.|_| cm **(HC)**
MUAC |__|__|.|_| cm **(MUAC)**
Height |__|__|__|.|_| cm **(HT)**

Handedness: **Right Left Undetermined** [ ]**(HD)**
Skull shape; Normal/ Abnormal / /***(SKS)***
Facial Appearance: Normal; Dysmorphic / /***(FA)***

_____

_____

Skin: Any features of neurofibromatosis **(Y/N)** [ ]**(NCF)**
Any features of tuberous sclerosis **(Y/N)** [ ]**(NCT)**
Any scratch marks **(Y/N)** [ ]**(NCS)**
Any nodules **(Y/N)** [ ]**(NCN)**

Hands and feet: Normal; Abnormal [ ]**(HF)**
Blood pressure(BP): (mmHg). [_]_]_]/[_]_]_] **(BP)**
Respiratory system: Normal; Abnormal [ ]**(RPS)**
Cardiovascular system: Normal; Abornomal [ ]**(CDS)**

Mental State exam: Is he oriented to: Person **(Y/N)** [ ]**(ORP)**
Place **(Y/N)** [ ]**(ORPL)**
Time **(Y/N)** [ ]**(ORT)**

Does s/he have any burn marks? **(Y/N)** [ ]**(ABM)**

If yes, where _____

Examination of Cranial Nerves

Cranial Nerve II

Ptosis	Yes/ No	[ ] **(PT)**
Pupils	Normal/ Abnormal	[ ] **(PU)**

Cranial nerves III, IV and VI; V and VII

Eye movements	**Cranial nerves III, IV and VI**	
Squint?	Yes/ No	[ ] **(SQ)**
Which eye?	Right /Left/ Both	[ ] **(SWE)**
Nystagmus?	Yes/ No	[ ] **(NY)**

The face	**Cranial nerve VII**	
Muscles of facial expression		
Facial weakness?	Yes/ No	[ ] **(FW)**
Forehead stronger than lower face	Yes/ No	[ ] **(FS)**

Cranial nerves IX and X; XII

The mouth, pharynx and larynx	**Cranial nerves IX, X, XII**	
Pharynx and larynx		
Uvula: is central?	Yes/ No	[ ] **(UMC)**
Deviates to:	Right/ Left/ None	[ ] **(UD)**

Tongue

Deviation?	Yes/ No	[ ] **(TD)**

Motor system:

Arms:

Wasting?	Yes/ No	[ ] **(AW)**
Where?_____		
Tone	Normal Increased or Decreased?	[ ] **(AT)**
Contractures?	Yes/ No	[ ] **(AC)**
Where?_____		
Power (MRC 0-5)	Normal/ Abnormal/ Grossly Abnormal	[ ] **(AP)**
	Right	**Left**

Upper arm	—	—
Lower arm	—	—
Hand	—	—

Legs:

Wasting?	Yes/ No	[ ] (LW)	
Where?_____			
Tone	Normal Increased or Decreased?	[ ] (LT)	
Contractures?	Yes/ No	[ ] (LC)	
Where?_____			
Power (MRC 0-5)	Normal/ Abnormal/ Grossly abnormal		[ ] (LP)
		Right	**Left** Upper leg
		—	—
Lower leg		—	—
Foot		—	—

Reflexes:

	Right	Left
Biceps	[ ] (BR)	[ ] (BL)
Knee	[ ] **(KR)**	[ ] **(KL)**
Ankle	[ ] **(AR)**	[ ] **(AL)**
Plantar	[ ] **(PR)**	[ ] **(PL)**

(Decreased Normal Increased)

Co-ordination:

Finger-nose	Normal/ Abnormal	[ ] **(FN)** Piano-
playing	Normal/Abnormal	[ ] **(PP)**
Dysdiadochokinesia?	Yes/ No	[ ] **(DDK)**

Gait:

Normal/ Abnormal [ ] **(GN)**

Describe gait abnormality

Ears

Auroscope examination:	Right	Normal/Abnormal/Wax	[ ] **(UR)**
	Left	Normal/Abnormal/Wax	[ ] **(UL)**
Otitis Media	Right	Yes/No/Wax	[ ] **(OMR)**
	Left	Yes/No/Wax	[ ] **(OML)**
Otitis Externa	Right	Yes/No/Wax	[ ] **(OER)**
	Left	Yes/No/Wax	[ ] **(OEL)**

Eyes

Cataracts	Yes/No	[ ] **(CT)**
Which eye?	Right /Left/ Both/None	[ ]**(CWE)**
Other abnormality	Yes/No	[ ] **(EAB)**

Describe_____

_____

Fundoscope examination:	Fundi seen (Y/N):	[ ] **(FE)**
Right	Normal/Abnormal/Impossible[ ] **(FR)**	
	Left Normal/Abnormal/Impossible[ ] **(FL)**	
Any toxocara nodules (Y/N):		[ ] **(TN)**

Any other Observations and medical history (Y/N)..... [ ](AOM)

Has consent been given for the blood sample Y/N ..... [ ] (CBS)
Has the blood sample been taken Y/N ..... [ ] (BST)

Summary

Does s/he have evidence of learning difficulties [ ]**(ELD)**

Does s/he have any neurological deficits? **(Y/N)** [ ]**(EXND)**

Does s/he need a CT scan? **(Y/N)** [ ]**(EXCT)**

Sign if you have checked that the form is complete_____