Epilepsy in sub-Saharan Africa: Analysis of excess mortality in epilepsy and associated risks factors from cohort studies

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Prof. Dr. Martin Spiess

Dekan Philosophisch-Naturwissenschaftliche Fakultät.

Dedication

…to my wife Rosemary Mbise and son Ethan F Levira

…to my parents Mr & Mrs William Levira

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List of abbreviations

ACE	Active Convulsive Epilepsy
AED	Antiepileptic Drugs
AIDS	Acquired Immune Deficiency Syndrome
AMMP	Adult Morbidity And Mortality Project
Cis	Confidence Intervals
CT	Computerized Tomography
CVR	Civil and Vital Registration
ECG	Electrocardiographic Monitoring with an Implantable
EEG	Electroencephalogram
GBD	Global Burden of Disease
HDSS	Health and Demographic Surveillance System
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD10	International Classification of Disease and Injuries version 10
ILAE	International League Against Epilepsy
INDEPTH	International Network for the Demographic Evaluation of Populations and Their Health
IR-HDSS	Ifakara Rural Health and Demographic Surveillance System
IU-HDSS	Ifakara Urban Health and Demographic Surveillance System
LMIC	Low and Middle-Income Countries
MRI	Magnetic Resonance Imaging
PWE	People With Epilepsy
R-HDSS	Rufiji Health and Demographic Surveillance System
RR	Rate Ratio
SAVVY	SAmple Vital Registration with Verbal autopSY
SEEDS	Studies of Epidemiology of Epilepsy in Demographic Surveillance
SMR	Standardized Mortality Ratio
SSA	sub-Saharan Africa
TB	Tuberculosis
UN	United Nations
VA	Verbal Autopsy
WHO	World Health Organization

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Summary

Epilepsy is a disorder of the brain manifested with the recurrent unprovoked seizures. It affects about 71 million people globally. Epileptic seizures may involve a sudden loss of conscious, rapid muscles rigidity and contractions, violent convulsions and falls if a person is standing or sitting. Epilepsy can be controlled by antiepileptic drugs (AEDs) and adherence to treatment has been shown to improve quality of life, reduce seizure frequency, injuries, and death. Epileptic seizures negatively impact the lives of people with epilepsy (PWE) and those around them especially in LMIC. It is estimated that 80% of PWE live in LMICs. Excess mortality in PWE in developed countries is estimated to be up to 2 times higher than general population. There is scant data on excess mortality in PWE in SSA. Scarcity of evidence on the impact of epilepsy has resulted in PWE being marginalized in health services planning and provision despite having high psychological, economic, morbidity and mortality burden relative to the general population.

This thesis provides needed knowledge on uncertainties of epilepsy in SSA in relation to mortality, risk factors, and causes of death in PWE. The knowledge and evidence were generated from five studies using empirical data from community-based studies.

Systematic review

The first thesis objective was aimed at reviewing and summarizing available evidence on excess mortality in PWE compared to general population in LMIC. Systematic review in Chapter 3 identified only 7 studies in LMIC over the period of 25 years. Estimated excess mortality of ranged from 1.3-7.2 times higher in PWE than general population (median=2.6).

Meta-analysis of this systematic review indicated that up to 80% of total variability's in the estimate of excess mortality (SMR) was only due to differences between studies. These differences may be due to methodological variations between studies or other unknown factors. The estimated excess mortality of 2.6 was median value and not pooled estimate as large variability's between studies could not allow combined estimate of 7 studies.

In conclusion, until this systematic review was done, there were no sufficient data to provide empirical evidence of excess mortality in PWE in LMIC.

SEEDS study: Excess mortality

At the time the systematic review was completed, new data on mortality of PWE were emerging from SEEDS studies. SEEDS studies had already followed PWE for over 8 years and documented deaths in people with and without epilepsy. Chapter 4 of this thesis was dedicated at pooling and generating new evidence of excess mortality in PWE from SEEDS studies.

The pooled excess mortality was 4.8 times higher in PWE than general population (95% CI: 4.2-5.6). SEEDS estimate is higher than summary findings from systematic review in reported in the literature in Chapter 4. SEEDS studies were conducted to account for methodological limitations encountered in most epilepsy studies related to screening, diagnosis, mortality and causes of death assessment, and population representativeness.

SEEDS study: Risk factors

The studies also identified modifiable risk factors potential for intervention programs and mitigating the negative impact of epilepsy.

Causes of death automation

In addition to summarizing excess mortality in PWE, systematic review in Chapter 3 summarized causes of deaths in PWE from different studies. Summary estimates from different studies in LMIC indicated most PWE died of direct causes which are status epilepticus (SE) and sudden death in epilepsy (SUDEP) and indirect (injuries) causes of epilepsy death. These studies compiled causes of death information from variety of sources including physicians, verbal autopsies and death certificates.

In Chapter 5, this thesis assessed the application of automated tools in ascertaining causes of death in PWE. The assessment indicated that, the use of automated tools is potentials, convenient and affordable alternative to post-mortem and physician death certification. Unlike the use of other sources of cause of death information, automated tool estimated lower number of epilepsy-related deaths (27.5%) compared to around 50% when physician make diagnosis of cause of death. Chapter 5 also provides valuable information and recommendation needed for further development and refinement of these tools especially with regards to coding SUDEP, SE, and injuries.

National estimates

Chapter 6 and 7 provides national and community-based estimates of mortality of epilepsy and other neurological disorders from national (SAVVY) and community-based studies (HDSS). The findings indicate epilepsy the second leading cause of death after cerebrovascular disorders. The estimates of mortality rate in the population ranged from 7-8 and 4-8 deaths per 100,000 populations in SAVVY and HDSS respectively.

HDSS data

HDSS sites have become platform for monitoring demographic indicators in most SSA. Analysis of HDSS data was aimed at ascertaining whether there has been declining trends in epilepsy and other neurological disorders over time. In Chapter 7 of this thesis, results of the analysis indicated epilepsy mortality did not change over the past 15 years.

Synthesis

This thesis generated new insights into the epidemiology of epilepsy in SSA. Limited data of studies of burden of epilepsy mortality in SSA point to either lack of interest in the subject, resources limitations from governments and funding bodies, and lack of knowledge of the negative impact of epilepsy. This study provides vigorous evidence of excess mortality needed for advocacy to health care providers, governments, and funding bodies for increased investment in care, preventions and reduction of the negative impact of epilepsy in SSA. The community and health care providers will benefit from evidence on modifiable risk factors for incidence and excess mortality from SEEDS study.

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Lastly, to my wife, Rosemary Mbise and son Ethan Francis for holding on me during my absence from home and to this PhD. I appreciate for your giving and I love you.

Introduction to epilepsy in sub-Saharan Africa

Epilepsy

Epilepsy is a disorder of the brain manifested with the recurrent unprovoked seizures, caused by abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). It affects about 71 million people globally (Ngugi et al., 2010b). Epileptic seizures may involve a sudden loss of conscious, rapid muscles rigidity and contractions, violent convulsions and falls if a person is standing or sitting. Other forms of epileptic seizures may involve impaired responsiveness “staring”, muscles spasms, and cognitive and sensory dysfunction. Epileptic seizures negatively impact the lives of people with epilepsy (PWE) and those around them. Un-employability, poor enrolment and dropout in schools, psychological, injuries due to accidents and deaths are among negative consequence of epilepsy. There is no cure for epilepsy; however antiepileptic drugs (AEDs) are the most effective therapeutic option for managing epileptic seizures. Treatment failure has been reported in 30% and epilepsy-related deaths constitute up to 65% of reported deaths in those under AED prescription (Kwan et al., 2004, Loscher et al., 2011, Radhakrishnan, 2009b). AED are prescribed for the rest of life and adherence to treatment has been shown to improve quality of life, reduce seizure frequency, injuries, and death. There is substantial funding gap in research by both governments and funding bodies thus possibly explaining little progress in the reduction of incidence and mortality of epilepsy (Chin, 2013, Meador et al., 2011).

Epilepsy is a complex disease, not easy to diagnose (specifically non-convulsive) in most sub-Saharan Africa (SSA) countries, and manifested in many different forms. Therefore, standard case definitions and classifications of different types of epilepsy constitute an important component of studies of epidemiology of epilepsy. International League Against Epilepsy (ILAE) published a comprehensive report on standards of

epidemiologic studies and surveillance of epilepsy (Thurman et al., 2011a). The proposed standards define epilepsy, classification of epileptic seizures, and set the basis for future studies and allow meaningful interpretations and comparison over time. In the next sections of this chapter, a comprehensive review of types, causes and diagnosis of epilepsy in SSA in provided prior to the descriptions of the epidemiological profile of epilepsy in SSA.

Types of epileptic seizures

Epilepsy is classified on the basis of the manifestation of seizures and syndromes. 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). Three main seizures types are generalized, focal and those with an undetermined origin (Table 1-1) (Thurman et al., 2011a). Seizures may involve movements of body parts (convulsive) or non-motor. Generalized seizures affect the whole brain. Seizures are thought to originate within bilaterally distributed cortical or cortical-subcortical networks that become rapidly engaged without a specific source of origin and can involve cortical and subcortical structures, but not necessarily the entire cortex. Focal seizures originate within neuronal networks limited to one cerebral hemisphere. Seizures of unknown onset are classified as undetermined. Although many epilepsy syndromes can include both focal and generalized seizure, neurologist always tries to establish whether epilepsy is the result of focal pathology, as it can have implications for treatment especially surgical option (Preux et al., 2005a).

Screening methods employed in many studies in sub-Saharan Africa are capable of detecting convulsive epilepsies which accounts for 50-60% of epilepsy cases,

therefore reported prevalence estimates should always be interpreted with caution as they are likely to underestimate the true burden of epilepsy (Adamolekun, 1995).

Table 1-1: Classification of seizure types

Seizure classification		
Generalised	**Focal**	**Undetermined**
Convulsive and other motor seizures		
Generalized convulsive and other motor seizures	Focal onset with secondary generalization, focal motors	Undetermined
Impaired responsiveness and other non-motor		
Generalized absence	Dyscognitive focal seizures, sensory, psychic, and autonomic	Undetermined impaired responsiveness
Unknown		
Generalized seizure, unspecified	Focal seizure, unspecified	Seizure, unspecified

Causes of epileptic seizures

ILAE proposed three categories for the aetiology/causes of epilepsy: genetic, structural/metabolic, and unknown causes (Table 1-2) (Berg et al., 2010). Disparities in epilepsy prevalence in sub-Saharan Africa and developed countries can be linked to causes/aetiology of epilepsy. Epilepsy cases with no identifiable causes or risk factor (primary/idiopathic epilepsy) are common in both developed and developing countries (Preux et al., 2005a, Adamolekun, 1995). In many cases of primary epilepsy, there is a genetic origin (Weber et al., 2008, Sisodiya et al., 2011, Knoth et al., 2011, Poduri et al., 2011). In SSA, identifiable causes (secondary epilepsy) in children are thought to be identifiable genetic causes or syndromes, perinatal adverse events such as difficulties crying and breathing at birth and head injuries (Ngugi et al., 2013c). Metabolic and structural causes of epilepsy are the major causes of epileptic seizures in adults. Parasites infection with *Plasmodium falciparum*, HIV, *Toxocara canis*, *Toxoplasma gondii*, *Onchocerca volvulus*, and *Taenia solium* has been linked with epilepsy among adults in several studies and reviews (Carter et al., 2004,

Satishchandra et al., 2008, Ngugi et al., 2010b, Pion et al., 2009, Quet et al., 2010). At old ages epilepsy may be related to chronic diseases such as malignancy cancers, stroke and other chronic disease associated with brain dysfunction (Timmons et al., 2002, Brodie et al., 2005).

Table 1-2: Classification of seizure aetiology

Genetic/presumed genetic
Specific genetic epilepsy syndromes, genetic and chromosomal developmental, and encephalopathies.
Structural/Metabolic
Infections, traumatic brain injury, stroke, neoplasia, mesial temporal sclerosis, degenerative neurologic diseases, metabolic or toxic insults to the brain, perinatal insults hypoxic-ischemic, encephalopathy, malformations of cortical or other brain development, neurocutaneous syndromes and inborn errors of metabolism
Unknown or Undetermined
Epilepsy of unknown/undetermined aetiology

Diagnosis

Epilepsy diagnosis is based on the detailed description of the seizure by the patient and witnesses, and may not need any specific investigation (Moshe et al., 2015). Family and personal history, the age onset, seizure type, neurological and cognitive status are key features of initial diagnosis of epilepsy disorder. Epilepsy diagnosis in clinical and research setting uses two different definitions of epilepsy. In a clinical setting, a clinician uses a conceptual definition of epilepsy as a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiology, cognitive, psychological and social consequences of this condition. Researchers, on the other hand; use the operational definition of epilepsy if any of the following conditions are present:

1. At least two unprovoked (or reflex) seizures occurring > 24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years (Fisher et al., 2014).

For practical purposes, the first criterion of at least “two or more unprovoked seizures occurred at least 24 hours apart” in the past 5 years is used as a case definition of active convulsive epilepsy (ACE). Most epilepsy studies conducted in SSA have focused on ACE such as clonic, tonic or clonic-tonic, because non-convulsive epileptic seizures are difficult to diagnose in door-to-door cross-sectional surveys. ACE accounts for approximately less than 50% of epilepsy cases in most studies conducted in SSA, therefore prevalence estimates in SSA should be interpreted with care as they are likely to miss non-convulsive forms of epilepsies.

Comprehensive epilepsy diagnosis demand trained neurologist and neuroimaging equipment for confirming the diagnosis. Diagnosis of underlying epilepsy syndrome can be complex and requires specialized training especially when it is necessary to differentiate epileptic seizures and seizures caused by other disorders [7, 26, 27]. Neurophysiological test with electroencephalogram (EEG) is used to detect unusual brain activities associated with epilepsy. EEG does not always confirm the diagnosis but is helpful for classifying the epileptic seizures and epilepsy syndromes. Magnetic resonance imaging (MRI) may be used to detect the possible cause of epilepsy such as defects or lesion in the structure of brain. Prolonged electrocardiographic (ECG)

monitoring with an implantable ECG recorder is used to rule out cardiac abnormalities related-seizures from epileptic seizures. Computerized tomography (CT) is more accessible in SSA and is used to assess gross pathological changes but cannot be used to diagnose epilepsy. One study in 2007 documented only 75 EEGs and 25 CT scanners in tropical African countries, however, most of these machines were frequently out of order. In the same review of 43 studies of epilepsy aetiology's, only 25 studies used EEG in analysing unusual brain activities associated with epilepsy (Preux et al., 2005b).

Prevalence and incidence

In 2010, epilepsy was estimated to affects 71 million people globally most of whom are living in rural developing countries. In developed countries epilepsy was estimated to affect 6.8 million (5.8 per 1000) while in developing countries, 62 million people were affected. In developing countries, majority of PWE were residing in rural areas 45 million (15.4 per 1000) compared to 17 million (5.9 per 1000) in urban areas (Ngugi et al., 2010b). Paul et al in 2010 estimated epilepsy affected 5.4 million people in SSA (Paul et al., 2012). Studies in SSA were implemented using different epilepsy case definitions and methodology, hence less likely to produce true estimates epilepsy prevalence. In 2013, Studies of Epidemiology of Epilepsy in Demographic Surveillance Sites (SEEDS) estimated prevalence of ACE in five SSA using standardized methods endorsed by ILAE (Ngugi et al., 2013c). The estimated prevalence from SEEDS studies ranged from 7.4-15.5 (median=8.1 cases per 1000 people). Applying estimated prevalence of ACE from SEEDS to the current SSA population, ACE is estimated to affect 8.5milion people using 2018 UN population estimates. Estimates of the incidence of epilepsy are also higher in developing countries with the estimate

of 81.7 cases per 100,000 population than developed countries with an incidence of 45.0 per 100,000 population (Ngugi et al., 2011).

Epilepsy mortality

Mortality statistics are vital in understanding population health and diseases trends (Pakpoor et al., 2017). Several studies have linked higher coverage of civil and vital statistics with improved health outcomes in several countries (Phillips et al., 2015). Few developing countries contribute to World Health Organization's (WHO) Civil and Vital Registration (CVR) database therefore disproportionally represented in most mortality and statistical reports (World Health Organization, 2017). There are also few epidemiological data in developing countries and most available ones are incomplete hospital-based, thus provide little information about the health status in the community (Winkler et al., 2009c). Estimating epilepsy-related mortality requires complete coverage of vital registration and clinical data in the entire community. In most SSA unfortunately, most deaths (>75%) occurs at home, autopsies are not done on routine bases, and death certificates are unreliable hence low coverage of vital registration and cause of death statistics (Carpio et al., 2005). The overall autopsy rate is estimated to probably be <5% in public hospitals and almost none exists in private hospitals. Alternatively, countries have used two approaches in establishing mortality statistics; mortality census survey or continuous mortality surveillance on selected communities. The former also known as Health and Demographic Surveillance System (HDSS) are population-based continuous surveillance of migration, births, deaths and their causes (Network;, 2002). Causes of deaths in HDSS are ascertained using verbal autopsy. Global burden of disease (GBD) analysis uses among other sources cause of death statistics generated from HDSS sites in different parts of

African and Asian countries in producing country and regional estimates of causes of death statistics (IHME, 2016, Lozano et al., 2012, Naghavi et al., 2013). Mortality census surveys are conducted on national representative samples of death identified by key informants or during post-census surveys (Mudenda et al., 2011, Ngo et al., 2010, Statistics; et al., 2012). Demographic Health Surveys (DHS) also capture mortality data, specifically childhood, maternal and adult deaths, however, causes of deaths are normally not ascertained.

Mortality in people with epilepsy

PWE are at increased risk of injuries and death due to the presence of unprovoked seizures. The increased risk is routinely reported as excess or premature mortality. Excess mortality in epilepsy relative to general population measures how much death rate in PWE exceeds that of the general population, estimated as a ratio of mortality rate in PWE to mortality rate in general population. Ratio greater than 1 indicates mortality higher in PWE than general population and ratio less than 1 indicates mortality is higher in general population than in PWE. When the ratio is greater than 1, the multiplicative interpretation is always preferred stated as “times higher in PWE than general population”. In developed countries, systematic reviews provided evidence of excess mortality in PWE compared to general population ranging of the magnitude ranging from 1.6-3 times higher than the general population in community-based studies of substantial good quality. In clinical setting and in symptomatic epilepsy patients, mortality is reported to range from 2.2-6.5 and 7-50 times higher than general population respectively (Nevalainen et al., 2014, Forsgren et al., 2005b, Neligan et al., 2010). Given the fact that, comprehensive individual medical records are almost non-existence in most SSA countries; there are no reliable data on

estimates of mortality rate in cohorts of PWE. In addition, long-term follow-up of PWE is required in order to establish precise estimate of mortality in PWE; unfortunately drop outs are substantial on most cohorts due to household's motilities and migration. Most available data on mortality in epilepsy in SSA are coming from small and short-term population-based cohorts in areas with high epilepsy prevalence, therefore likely to yield to higher estimates mortality in epilepsy (Pion et al., 2009, Terra et al., 2011, Kaiser et al., 2007).

There are limited epidemiological studies SSA, however few studies that have reported mortality of 3 to 7 time higher in PWE than the general population as measured by standardized mortality ratio (SMR). These include those conducted Kilifi in Kenya 6 times, West Uganda 7 times, and Vusai in India 4 times higher than general population (Ngugi et al., 2014c, Kaiser et al., 2007, Carpio et al., 2005). Based on current literature at my exposure, there are no permanent clinical cohorts of PWE in SSA, however, there known three clinical cohorts elsewhere in LMIC which include study in rural Ecuador with mortality estimates in PWE of 6 times and Chile 3 times higher than the general population (Carpio et al., 2005, Devilat Barros et al., 2004).

Causes of death in people with epilepsy

Availability of cause of death in PWE may facilitate effective development of preventive measures aimed to prevent acquired epilepsy and/or reduce premature mortality (Mu et al., 2011a). However, similar to mortality, data on causes of death in epilepsy are not available in most SSA countries due to aforementioned reasons related to coverage of vital statistics. Causes of death in epilepsy are categorized into epilepsy-related/direct, indirect and unrelated. Epilepsy-related causes of epilepsy include status epilepticus and sudden death in epilepsy. Indirect causes are those associated

with events such as falls, burns, drowning and road traffic accidents. Contribution of epilepsy-related causes accounts for majority of death in PWE epilepsy in SSA compared to developed country due to low coverage of interventions aimed at managing seizures. Estimate of epilepsy-related deaths in selected studies from SSA ranges from 30 to 60% (Ngugi et al., 2014c, Carpio et al., 2005, Kamgno et al., 2003b, Kaiser et al., 2007). In developed countries where epileptic seizures are properly managed, epilepsy-related causes of deaths are lower than causes unrelated to epilepsy such as neoplasms, cerebrovascular diseases, and cardiac diseases leading causes of death in PWE (Forsgren et al., 2005b, Cockerell et al., 1994, Nilsson et al., 1997, Lhatoo et al., 2005, Benn et al., 2009). Higher epilepsy-related deaths in developed countries are only reported in clinical cohorts specifically in individual with drug resistance and newly diagnosed epilepsies (Nevalainen et al., 2013).

Epilepsy treatment

Since there is no cure for epilepsy, AEDs has remained the most effective therapeutic option for managing epileptic seizures in both developed and developing countries. Surgical treatment are not routinely done in most SSA countries, however they are effective in treating specific types of epilepsies for which epileptogenic is well established (Cherian et al., 2002, Butler, 2005). Other potential and non-invasive treatment possibly never experimented in SSA is Ketogenic diet, with reported rates of seizure freedom as high as 55% and seizure reduction as high as 85% after three months following diet initiation (Martin et al., 2016). PWE in most SSA countries are not receiving appropriate treatment with AED because epilepsy is not a high priority disease in most countries. Most efforts are directed towards high priority diseases such as malaria, tuberculosis (TB), HIV/AIDS, maternal and newborn health.

Coverage indicator of epilepsy treatment known as “treatment gap” is defined as the number of PWE who have not accessed biomedical services or are not on treatment or are on inadequate treatment, expressed as a percentage of the total number with epilepsy (Meinardi et al., 2001). Treatment gap studies in SSA estimated more than 80% of PWE do not receive appropriate treatment (Amos et al., 2011, Ba-Diop et al., 2014b, Carter et al., 2012, Coleman et al., 2002, Hunter et al., 2016, Mbuba et al., 2012). Global study of treatment gap disparities reported an epilepsy treatment gap of more than 75% in developing countries compared with less than 10% in developed countries.

Intervention programs

Although WHO initiated global efforts on neurology and public health many countries in SSA are still lagging behind in terms of training, diagnosis, treatment and disease management (Janca et al., 1997). Effective intervention in reducing the incidence of epilepsy always target the root causes of preventable epilepsy which include reducing the spread of parasitic infections, brain injuries (accidents and perinatal-related), and chronic diseases (cerebrovascular, neoplasm and neurodegenerative). The negative consequence of epileptic seizures such as road traffic injuries, falls, burns and drowning are effectively managed with increased access to affordable AED. A systematic review of clinical trials of effectiveness and delivery of intervention for epilepsy indicated little evidence of effectiveness towards managing all aspects of epilepsy in both low and high-income countries (Mbuba et al., 2009). With regards to SSA, intervention programs were documented only in Kenya on AED and South Africa on cognitive behavior (Feksi et al., 1991, Lundgren et al., 2006).

Epilepsy in Tanzania

Tanzania as many other SSA lacks morbidity and mortality data on neurological disorders due to insufficient coverage of civil and vital registration systems (Dalal et al., 2011, Dewhurst et al., 2012). Epilepsy was initially documented in scientific literature in Mahenge district in Morogoro region by Dr. Louise Jilek-Aall who was a physician from Canada. Dr. Jilek-Aall documented high prevalence and mortality associated with epilepsy and established a clinic with financial support from abroad to provide AED in PWE. The program supported around 164 of whom, 86 (52.4%) achieved complete seizure suppression and 59 (36.0%) experienced a reduction in seizure frequency.

Head nodding syndrome characterized with head nodding, mental retardation and stunted growth disorder is a rare disorder believed to be possibly a new epilepsy disorder in SSA was also observed to affects a number of people in Mahenge (Winkler et al., 2010, Winkler et al., 2008c, Aalljilek, 1965). Several studies years later have been conducted in different parts of Tanzania in areas with high prevalence of epilepsy and estimated prevalence of epilepsy ranging from 2.9 to 15 cases per 1000. Two studies were conducted in Hai in adults (Hunter et al., 2012) and children (Burton et al., 2012b), Kilombero (Ngugi et al., 2013c), Manyara/Hydom (Winkler et al., 2009b), Nachingwea/Lindi (Dent et al., 2005), Ulanga (Rwiza et al., 1992) (Table 1-3).

Convulsive epileptic seizures (clonic-tonic and clonic) accounts for the majority of epilepsies in Tanzania (Hunter et al., 2012, Rwiza et al., 1992). Most seizures are linked to parasitic infections and perinatal events (Winkler et al., 2008a, Winkler et al., 2009a). National estimate of epilepsy mortality was first published in 2005 in a study of Adult Morbidity and Mortality Project (AMMP) conducted in 1992-1995 that

estimated epilepsy mortality rate of 15 and 5 deaths per 100,000 population in males and females respectively (Aspray, 2005).

Mortality estimates in PWE are limited in Tanzania and many SSA countries. Jilek-Aall et al described mortality in PWE in Mahenge cohort of 164 people diagnosed with epilepsy and observed deaths in 110 (67.1%) deaths in a 30 years follow-up. High treatment gap (>60%) has been reported in most community-based studies (Hunter et al., 2012, Hunter et al., 2016, Jilek-Aall et al., 1992b). Most primary health care facilities and hospitals in Tanzania are not equipped with necessary imaging tools and trained neurologist. Several efforts have been done to improve diagnosis including developing inexpensive tools for screening and classifying neurological disorders in health facilities with limited resources (Feigin et al., 2015, Winkler et al., 2009c).

Table 1-3: Studies of epilepsy prevalence in Tanzania

			Prevalence of ACE (%)	
District/town	**Period**	**Population**	**Crude**	**Age-adjusted**
Hai	2009	15+	3.84(3.45-4.20)	2.91(2.58-3.24)
Hai	2009	2-14	2.91 (2.4–3.5)	
Kilombero	2009	All ages	3·9 (3·5–4·3)	15·5 (14·7–16·3)
Manyara/Hydom	2003	All ages	11.2(8.9-13.9)	9.1
Nachingwea/Lindi	1999	All ages	8.6(6.0–11.1)	7.4
Ulanga	1992	All ages	5.8-37.0	10.2(5.1-37.1)

Knowledge gap and justification for this thesis

Despite improved care and treatment, mortality burden in people with epilepsy is estimated to be up to 3 times higher than general population in HIC. If that is the case, what is the situation in SSA? Conceptual map in Figure 1-1 provide a recap of pathways to mortality impact of epilepsy based on review of epilepsy situation in SSA in the previous sections of this thesis.

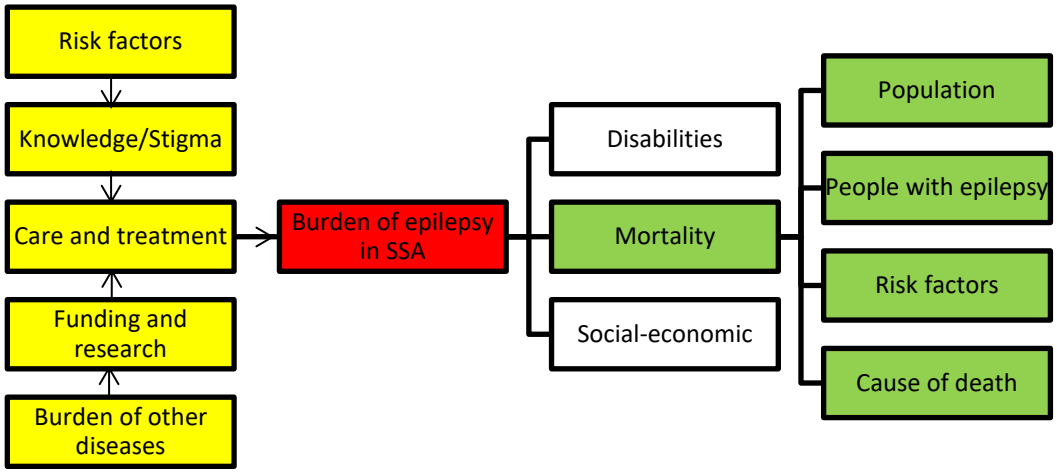

Figure 1-1 Conceptual map of burden of epilepsy in SSA

Multiple factors explain why burden of epilepsy mortality may be higher in SSA compared to high income countries and why it is imperative to conducts mortality studies. Major risk factors common in SSA are infections, brain trauma, adverse perinatal events, and high seizures frequency due to lack of care (up to 90% do not receiving AED. Lastly lack of knowledge on epilepsy in SSA is hampering the uptake of AED, increase informal care through spiritualism and witchcraft, and ultimately increase stigma towards PWE.

Epilepsy studies are underfunded by governments and research agencies and consequently leading to scarcity of data on prevalence, mortality, morbidity and social-economic impact of epilepsy. Substantial funding is directed toward care and management for the three priority diseases, i.e. malaria, HIV/AIDS and tuberculosis and maternal and newborn health. A systematic assessment of available evidence on mortality in PWE in SSA is high needed.

The second reason why epilepsy studies are not easily funded is that they are expensive to conduct in SSA. These studies require expert neurologist, larger

population-based studies and extensive follow-up in order to establish mortality estimates, risk factors, causes of death, and trends. These population-based cohorts are rare in SSA and this thesis is set to evaluate new evidence emerging from these population-based cohorts in SSA countries.

Effective intervention for mitigating the mortality impact of epilepsy require modifiable risk factors be identified and what PWE are dying off. However, it is unfortunate that most SSA lack monitoring and devaluating platform needed to understand causes of death and risk factors. As identified earlier, civil and vital registration and clinical cohorts (medial records) are almost absent in most countries. This thesis is also set to generate evidence on risk factors and causes of death from recently established population-based cohort on SSA.

The focus of this thesis mortality; however, it should be emphasized that epilepsy is associated with high burden of disabilities as well as social and economic impacts that is beyond this thesis. This thesis evaluate mortality rate of epilepsy and secular trend in population; and in PWE to evaluate excess (premature mortality), causes of death and risk factors

Thesis goal and objectives

Thesis aim

The aim of this thesis is to examine the uncertainties of epilepsy in relation to mortality, risk factors and cause of death in people with epilepsy sub-Saharan Africa.

Thesis objectives

The following five objectives are proposed;

1. Conduct a systematic review of premature mortality in people with epilepsy in low- and middle-income countries.
2. Estimate excess mortality in people with epilepsy in SSA and assess associated risk factors.
3. Describe causes of death in people with epilepsy in SSA using automated software's.
4. Estimate cause-specific mortality rate of neurological disorders in Tanzania.
5. Describe secular trends in mortality of neurological disorders mortality in Tanzania from health and demographic surveillance sites in Tanzania.

Structure of the thesis and overview of methods

This thesis is structured towards systematically providing **knowledge and evidence** on the **magnitude of mortality**, **associated risk factors, and causes of deaths in PWE** in SSA countries. The thesis structure and organization is summarized in Figure 2-1. The central ring represents the five target knowledge area as per thesis goal. The outer ring summarizes the approach adopted for each objective and provides a specific chapter for which detailed information can be found.

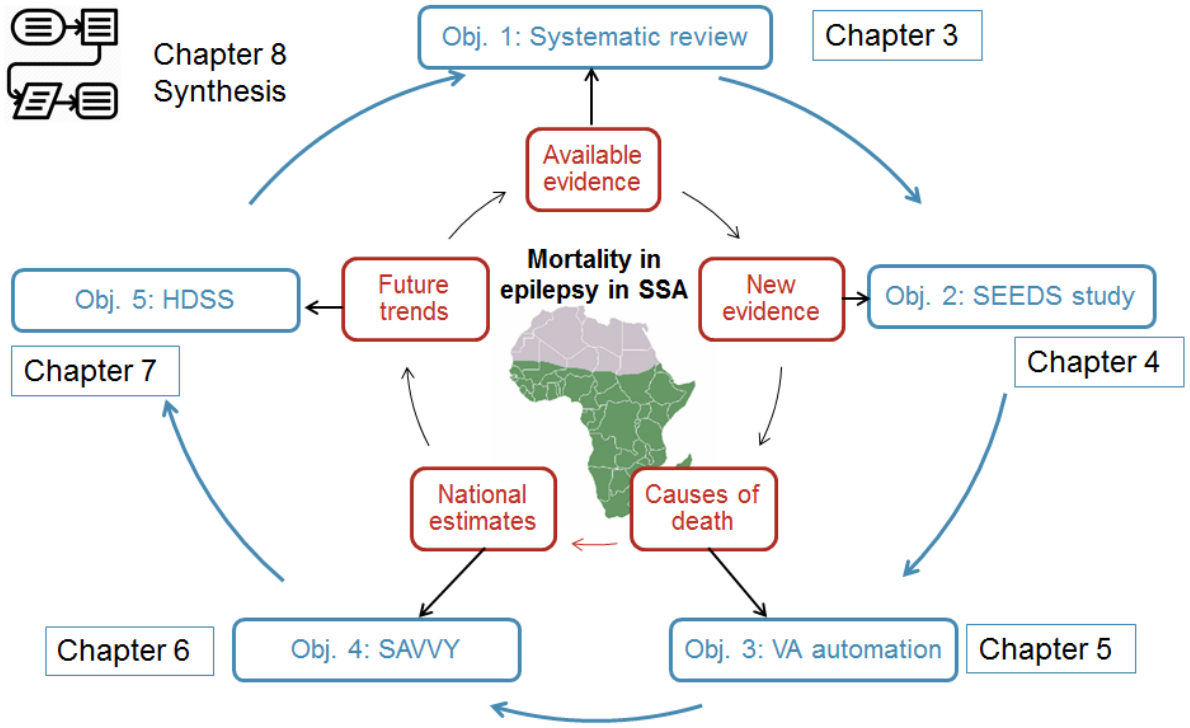

Figure 2-1: Thesis structure summary

Systematic review

Systematic review is the entry point of the thesis aimed at gathering all available evidence on the epidemiological profile of epilepsy in LMIC. The review constitutes a systematic assessment of studies of magnitude of mortality in epilepsy relative to general population, risk factors and causes of death in PWE in LMIC. The study

systematically compiled, reviewed qualities, and summarized measures of epilepsy mortality from peer reviewed and published scientific articles. The study was published in *Epilepsia*; Official Journal of the International League Against Epilepsy is presented in Chapter 3 of this thesis.

SEEDS study

SEEDS study provides new and vigorous evidence of excess mortality in epilepsy in SSA from the large a multi-centre evaluation implemented in five sites of Ifakara in Tanzania, Kilifi in Kenya, Agincourt in South Africa, Iganga-Mayuge in Uganda, and Kintampo in Ghana. SEEDS studies in the first phase estimated prevalence of ACE at 7·8 per 1000 people in Kilifi, 7·0 in Agincourt, 10·3 in Iganga-Mayuge, 14·8 in Ifakara, and 10·1 in Kintampo.

This thesis focuses on the second phase of the SEEDS project aimed to estimate the magnitude of excess mortality in PWE and associated risk factors. The full manuscript of this study is prepared for submission to *Epilepsy & Behavior* and is presented in Chapter 4.

Verbal autopsy automation

Causes of death statistics are valuable public health tools needed in developing effective preventative measures aimed at reducing premature mortality in people with epilepsy. Probabilistic and mathematical-based models have recently emerged as convenient and affordable alternative to physician in assigning causes of death in developing countries.

Verbal autopsy automation study evaluates the use of these models in predicting causes of death in PWE and their implication on the accuracy of causes of death, prevention and control of epilepsy in SSA. The full manuscript for this study is prepared

for submission to *Epilepsia*; an Official Journal of the International League Against Epilepsy and is detailed in Chapter 5.

SAVVY study

SAVVY is an analytical an analytical study focuses on national estimates mortality of neurological disorders in Tanzania. The study explores mortality estimates of neurological disorder and the contribution of epilepsy. The study is based on an analysis of national representative sample of mortality and causes of death survey (SAVVY). The study was published in *Global Health Action* journal. Details of the study are presented in Chapter 6.

HDSS study

Health and Demographic Surveillance Systems (HDSS) provides a platform for monitoring demographic indicators and causes of death statistics in population based study. HDSS study constitute an analytical work on estimating levels and secular trends of neurological disorders (cerebrovascular, epilepsy and meningitis) in HDSS sites in Tanzania. The rationale of this study is to ascertain trend of epilepsy mortality in Tanzania. The full manuscript for this study is prepared for submission to journal of *Stroke and Cerebrovascular Diseases* and is presented in Chapter 7.

The thesis is concluded in Chapter 8 with extensive discussions and synthesis of the findings from five studies in light of strength and methodological limitations. Recommendation and implications for public health are provided as well. All references are provided at the end of the thesis.

Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy

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Abstract

Background

To determine the magnitude, risk factors and causes of premature mortality associated with epilepsy in low and middle income countries (LMIC).

Methods

We conducted a systematic search of the literature reporting mortality and epilepsy in the World Bank-defined LMIC. We assessed the quality of the studies based upon the representativeness, ascertainment of cases, diagnosis, and mortality and extracted data on the standardized mortality ratio (SMR), mortality rate, and incidence of death in epilepsy. We examined the risk factors for death and reviewed the causes of death.

Results

The annual mortality rate was estimated at 19.8 (range 9.7-45.1) deaths per 1000 people with epilepsy (PWE) with a weighted median SMR of 2.6 (range 1.3-7.2) among higher-quality population-based studies. Clinical cohort studies yielded 7.1 (range 1.6-25.1) deaths per 1000 PWE. The weighted median SMRs were 5.0 in males and 4.5 in females; relatively higher SMRs within studies were measured among children and adolescents, those with symptomatic epilepsies, and those reporting less adherence to treatment. The main causes of death in PWE inhabiting LMICs include those directly attributable to epilepsy, which yield a mean proportional mortality ratio (PMR) of 27.3% (range 5%-75.5%) derived from population-based studies. These direct causes comprise status epilepticus, with reported PMRs ranging from 5%-56.6%, and sudden unexpected death in epilepsy, with reported PMRs ranging from 1%-18.9%. Important causes of mortality indirectly related to epilepsy include drowning, head injury, and burns.

Discussions

Epilepsy in LMIC has a significantly greater premature mortality, as in high-income countries, but in LMIC the excess mortality is more likely to be associated with causes attributable to lack of access to medical facilities such as status epilepticus, and preventable causes such as drowning, head injuries and burns. This excess premature mortality could be substantially reduced with education about the risk of death and improved access to treatments, including AEDs.

Keywords: Seizures, convulsions, death, case fatality, developing countries, resource-poor countries, premature mortality

Introduction

Standardized mortality in people with epilepsy (PWE) in high-income countries (HIC) is estimated to be up to 4 to 15 times higher than the general population in community-based studies and selected high-risk populations, respectively (Forsgren et al., 2005a, Nevalainen et al., 2014). Comparable estimates of mortality in epilepsy in low- and middle-income countries (LMIC) are scarce, because vital registration of deaths is incomplete or absent in most countries, and many studies examining mortality in PWE in LMIC have methodological limitations.

Worldwide, approximately 80% of PWE live in LMIC (Newton et al., 2012b, Ngugi et al., 2010a). The high prevalence and incidence of epilepsy in LMIC is most likely associated with higher incidence of adverse perinatal events, head injuries, and parasitic infections (Mbuba et al., Ngugi et al., 2010a, Banerjee et al., 2010, Kochen et al., 2005, Meinardi et al., 2001, Meyer et al., 2010).

Some studies in LMIC (Banerjee et al., 2010, Diop et al., 2005b, Jilek-Aall et al., 1992a) have suggested that mortality in epilepsy is higher than in HIC (Nevalainen et al., 2014). This may be caused by selection bias of studies in areas endemic with specific causes, selection of higher-risk cohorts to follow, or lack of access to comprehensive treatment (Mbuba et al., 2008). The epilepsy treatment gap (defined as the proportion of PWE who either have not accessed biomedical services or are not on treatment with anti-epileptic drugs (AEDs) or are receiving inadequate treatment (Meinardi et al., 2001) is more than 75% in LMIC, compared with less than 10% in HIC (Meyer et al., 2010). The large treatment gap may increase mortality from complications such as status epilepticus, accidents including burns and drowning, and sudden unexpected death in epilepsy (SUDEP).

We conducted a systematic review to estimate the magnitude of premature mortality associated with epilepsy in LMIC, and to identify the risk factors and causes of death among PWE. A companion review focuses on mortality in high-income countries (Thurman et al., 2016a).

Methods

Literature search. We searched the Medline, EMBASE, and LILACS databases with terms in the following three categories:

- epilepsy, seizure, or convulsions
- mortality, death, or SUDEP
- low-income countries, middle-income countries, developing countries, resource-poor countries, Africa, Asia, China, India, "Latin America," "Central America," or "South America"

We included only reports indexed with at least one term in each of the three categories, and restricted our search to reports on human subjects from LMIC as defined by the World Bank (World Bank, 2015). Low-income economies in 2014 were those with annual gross national incomes (GNI) per capita of $1,045 or less, while middle-income economies were those with GNI per capita ranging from $1,046 to $12,735. The search period was from 1990 to 28th February 2014. We used the criteria for the diagnosis of epilepsy suggested by the International League Against Epilepsy (ILAE) for epidemiological studies, originally in 1990 (ILAE, 1993) and confirmed in 2011(Thurman et al., 2011b).

Two reviewers (FL and CRN) evaluated the retrieved citations in a two-stage process. In the first stage they independently reviewed the titles and available abstracts to identify potentially relevant reports meriting full review (Figure 3-1). The reviewers compared their selections and resolved the list of publications to arrive at a single list for the second stage of analysis. In the second stage they reviewed the full papers

and assessed whether the articles met the inclusion criteria below. For those meeting these criteria, they extracted the measures of mortality, risk factors, and causes of death.

Inclusion criteria. Original reports of mortality among PWE in LMIC, derived from general populations, clinical cohorts (hospital- or treatment program-based), and case-control studies, were included. Studies that did not report quantitative estimates of mortality in epilepsy were excluded.

Data extraction. Data on the epilepsy were extracted according to the ILAE guidelines, in particular age at onset, seizure type, and the underlying etiology (Thurman et al., 2011b). Age at onset, i.e., first occurrence of unprovoked seizure, helps identify epilepsy syndromes. Three main categories of *seizure type* as classified by ILAE (generalized, focal, and undetermined) were identified (Thurman et al., 2011b). The ILAE proposed three main categories of etiology: genetic, structural/metabolic, and unknown causes (Thurman et al., 2011b). Epilepsy etiology is classified as genetic when genetic defects are the known or presumed to be prime cause of the disease. Structural/metabolic causes (formerly known as symptomatic epilepsies) are considered when a structural lesion or metabolic condition is known to predispose to epilepsy.

Estimates of mortality were extracted from the measures reported in the papers which included case fatality ratio (CFR), proportional mortality ratio (PMR), mortality rate (MR), and standardized mortality ratio (SMR) according to standard definitions (Rothman et al., 2008). Deaths were categorized occurring: (i) as a direct consequence of epilepsy or seizures (i.e. status epilepticus, or SUDEP); (ii) as indirect causes (i.e. accidents due seizures—such as falls, burns, or drowning—or drug

reactions to AEDs); (iii) as a consequence of underlying diseases of which epilepsy is a manifestation; or (iv) unrelated to epilepsy. The definitions and classification of SUDEP are mainly consistent with the earlier recommendations of Nashef (Nashef, 1997) which have been updated since publication of most the studies we reviewed (Nashef et al., 2012).

Quality of studies. The reviewers employed quality assessment criteria for studies of mortality in epilepsy that included the following five elements classified by ILAE's Commission on Epidemiology Task Force on the Burden of Mortality (Supplement Table S1). These address the most important design features of epidemiologic studies of epilepsy, which we employed in preference to less specific conventional evaluation checklists proposed for observational studies (Stroup et al., 2000).

- *Representativeness of the study population.* Provides the basis of generalizability of the study findings. Studies conducted in clinical settings or untreated populations may not be representative of entire populations of PWE.
- *Accuracy of diagnosis of epilepsy.* Evaluates methods employed to diagnose cases of epilepsy; if quantifiable, can be expressed as a positive predictive value. The use of the case definition provided by ILAE and diagnosis by trained neurologists is a reference standard that may reduce the number of false positives and negatives.
- *Epilepsy case ascertainment.* Evaluates completeness (sensitivity) of methods employed to screen the population for cases of epilepsy. This is important in population-based studies of epilepsy prevalence or incidence. A door-to-door survey is thought to generate an optimum number of cases in screening of a community.
- *Mortality ascertainment.* Evaluates the completeness of identifying death occurrence in a cohort or population of PWE. This depends upon the proportion of PWE followed until death or end of the study. Short follow-up of epilepsy individuals, high migration patterns and loss to follow-up are critical issues in establishing mortality rates.

- *Accuracy of cause of death.* Evaluates the validity of cause-of-death determinations, especially for causes of interest associated with epilepsy. Accurate determination of the cause of death is essential to determine the proportion of deaths directly or indirectly related to epilepsy. Autopsies are the reference standard, but are rarely performed in LMICs. Verbal autopsies are most commonly used in LMIC (Aspray, 2005, Baiden et al., 2007, Mateen et al., 2012).

A scale with five items was developed to score the quality of studies with respect to each quality measure listed above. The scoring of each item was generated from 4-5 sub-items, each with 5 points, with a total score ranging from 0 to 20 (Table S1). The total score of the quality was the sum of scores of each quality item, with 100 representing the highest quality.

Statistical analysis. Total, median, and range were used to generate summary measures of mortality across studies. We disaggregated the estimates by study designs (population-based vs. clinical cohort), sex, type of seizure, etiology, and other risk factors. Summary estimates were also identified as reported, whether SMRs, PMRs, or MRs. If not reported as such, we calculated CFRs and MRs when the reports provided sufficient information to allow this.

We also examined heterogeneity statistics, which measure the extent to which SMRs vary between studies, including the I^2 statistic, which is the percentage of between-study heterogeneity that is explained by variability in the treatment epilepsy effect on mortality relative to sampling error (Higgins, 2008).

Results

Search results. Results of the systematic search are described in Figure 3-1. A total of 17 articles met inclusion criteria, of which one reported studies from 4 sites (Carpio et al., 2005) and two reported the follow-up of the same cohort (Ding et al., 2006, Ding et al., 2013). There were 12 population-based studies (Banerjee et al., 2010, Carpio

et al., 2005, Ding et al., 2013, Houinato et al., 2013, Kaiser et al., 2007, Kamgno et al., 2003a, Kochen et al., 2005, Mu et al., 2011b, Ngugi et al., 2014b, Nicoletti et al., 2009) and 8 clinical cohorts (Almeida et al., 2010, Carpio et al., 2005, Devilat et al., 2004, Jilek-Aall et al., 1992a, Terra et al., 2011, Terra et al., 2010, Terra et al., 2009, Thomas et al., 2001) South America provided 8 studies, (Almeida et al., 2010, Carpio et al., 2005, Devilat et al., 2004, Kochen et al., 2005, Nicoletti et al., 2009, Terra et al., 2011, Terra et al., 2010, Terra et al., 2009) Asia 6 studies (Banerjee et al., 2010, Carpio et al., 2005, Ding et al., 2006, Ding et al., 2013, Mu et al., 2011b, Thomas et al., 2001) and Africa 6 studies (Carpio et al., 2005, Houinato et al., 2013, Jilek-Aall et al., 1992a, Kaiser et al., 2007, Kamgno et al., 2003a, Ngugi et al., 2014b).

Nine studies were conducted in rural populations only (Carpio et al., 2005, Ding et al., 2013, Houinato et al., 2013, Jilek-Aall et al., 1992a, Kaiser et al., 2007, Kamgno et al., 2003a, Mu et al., 2011b, Ngugi et al., 2014b, Nicoletti et al., 2009), 6 in urban only (Banerjee et al., 2010, Carpio et al., 2005, Kochen et al., 2005, Terra et al., 2011, Thomas et al., 2001) and 5 in both urban and rural populations (Almeida et al., 2010, Carpio et al., 2005, Devilat et al., 2004, Terra et al., 2010, Terra et al., 2009).

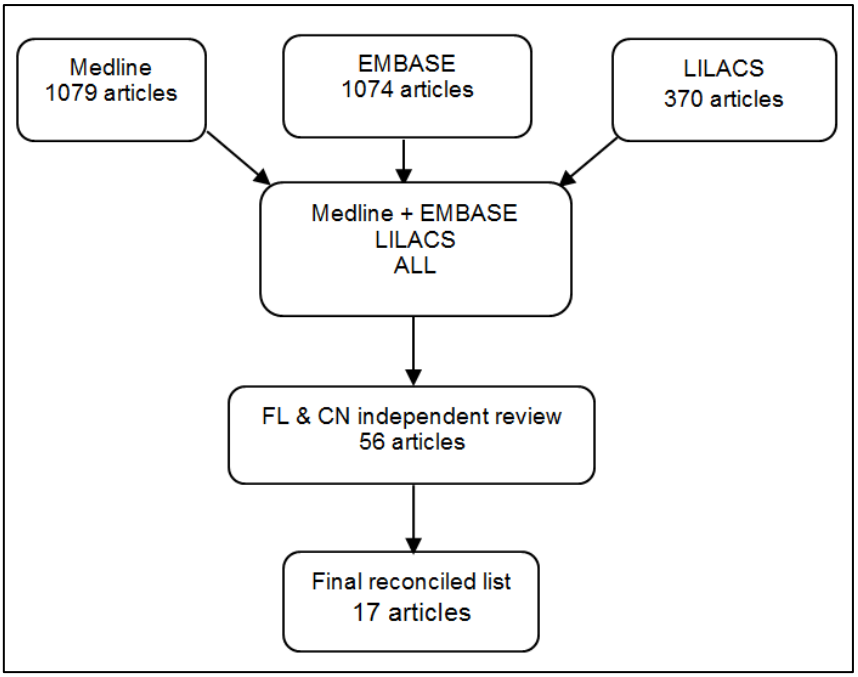


Figure 3-1: Summary results of search strategy

Quality of studies. Supplement Table S2 provides summary characteristics of population-based studies, all of which included all ages. Population-based studies were mainly of good quality, where 7 out of 12 studies had a quality score of ≥80% (Table 3-1) (Banerjee et al., 2010, Kochen et al., 2005, Carpio et al., 2005, Kaiser et al., 2007, Houinato et al., 2013, Ngugi et al., 2014b, Nicoletti et al., 2009). Door-to-door surveys were implemented in most studies, where neurologists made diagnoses of epilepsy. Over 85% of deaths were estimated to be captured in these cohorts and verbal autopsy was used to diagnose causes of death. Most studies used an operational definition of epilepsy as defined by ILAE in the diagnosis of epilepsy, although studies of 3 populations were restricted to active convulsive epilepsies.

Clinical cohort studies were of low quality (≤50%), largely due to poor sample representativeness of the general population (Table S3). There was insufficient information published in most studies to determine the basis of the diagnosis of epilepsy. Individuals in clinical cohorts often had epilepsy described as intractable or

refractory (Almeida et al., 2010, Terra et al., 2011, Terra et al., 2010). Cohorts of children with severe forms of epilepsy were also enrolled in several studies (Terra et al., 2011, Terra et al., 2010, Terra et al., 2009, Devilat et al., 2004). In health care settings, causes of death were available from medical records, death certificates, and verbal autopsy for deaths occurring in the communities.

Mortality. From 7 population-based studies with quality scores ≥80% (Table 3-1) (Banerjee et al., 2010, Kochen et al., 2005, Carpio et al., 2005, Kaiser et al., 2007, Houinato et al., 2013, Ngugi et al., 2014b, Nicoletti et al., 2009), the pooled annual mortality rate was 19.8 deaths per 1000 PWE (range 9.7-45.1), with a weighted median SMR of 2.6 (range 1.3-7.2) and an overall CFR of 8.1% (range 3.3-31.6%). The weighted mean follow-up period was 5.8 years (range 1.5-10), with 6,665 person-years observation.

Eight clinical cohorts (Table 3-2) (Almeida et al., 2010, Carpio et al., 2005, Devilat et al., 2004, Jilek-Aall et al., 1992a, Terra et al., 2011, Terra et al., 2010, Terra et al., 2009, Thomas et al., 2001) in sum enrolled substantially larger numbers of PWE compared to higher-quality population-based studies. There were 3,856 PWE enrolled across these cohorts, of which 88.3% were followed to the end of the studies. The weighted mean follow-up period was 12.4 years, during which 240 deaths were observed, with a pooled annual mortality rate of 7.1 (range 1.6-25.1) deaths per 1000 PWE. Two out of the 8 studies reported SMRs of 3.2 and 6.3 (Carpio et al., 2005, Devilat et al., 2004). The overall CFR in these clinical cohort studies was 7.0% (range 1.3-75.3 %).

Mortality risk by age. Figure 3-2 summarizes 3 population-based studies reporting SMRs among PWE by age of death (Carpio et al., 2005, Ding et al., 2006, Mu et al.,

2011b). Overall, these showed the highest SMRs in the youngest age groups, declining markedly after young adulthood, with a continuing decline with increasing age. We found insufficient data to characterize the risk of mortality by age of epilepsy onset.

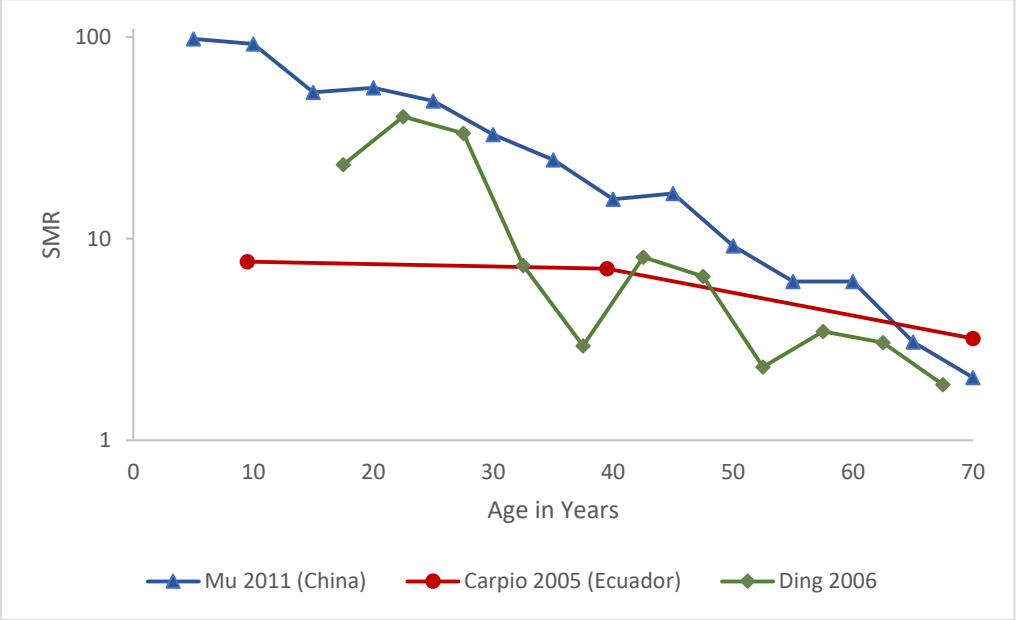


Figure 3-2: Mortality in epilepsy by age at death

Mortality risk by sex. Figure S1 summarizes mortality estimates for males and females from 6 population-based studies and 6 clinical cohorts. Of four studies (Mu et al., 2011b, Banerjee et al., 2010, Kaiser et al., 2007, Kamgno et al., 2003a, Ding et al., 2013) comparing SMRs, two reported higher values among males, with a weighted median SMR of 5.0 for males compared to 4.5 for females. Most studies reporting PMRs showed higher mortality in males.

Table 3-1: Mortality rates estimates from population-based studies

Country-Location	Population	Quality	Cohort size	PWE followed	Duration of FU (years)	Person-years	Deaths in PWE	SMR	95% CI	CFR	95% CI	MR in PWE	95% CI
High quality													
Kenya-Rural	232,164	100	754	754	2.7	2,048	61	6.5	5.00-8.30	8.1	6.1-10	29.8	22.8-38.3
Argentina-Urban	70,000	90	106	96	8	768	8	2.45	1.14-4.65*	8.3	2.8-13.9	10.4	4.5-20.5
Uganda-Rural	4,743	90	61	57	7	399	18	7.2	4.40-11.6	31.6	19.5-43.6	45.1	26.7-71.3
Bolivia-Rural	55,675	85	118	103	10	1,030	10	1.34	0.68–2.39	9.7	4.0-15.4	9.7	4.7-17.9
Benin-Rural	11,688	80	160	150	1.5	225	5			3.3	0.5-6.2	22.2	7.2-51.9
India-Urban	52,377	80	337	337	5	1,685	20	2.58	1.50-4.13	5.9	3.4-8.5	11.9	7.3-18.3
India-Vusai	16,000	80	51	51	10	510	10	3.9		19.6	8.7-30.5	19.6	9.4-36.1
Summary	**442,647**		**1,587**	**1,548**	**5.8†**	**6,665**	**132**	**2.6‡**		**8.1‡**		**19.8**	**16.7-23.5**
Low quality													
India-Persis	14,010	65	109	104	14	1,456	34	0.76	0.51-1.01	32.7	23.7-41.7	23.4	16.2-32.6
Cameroon- Rural	NR	60	271	128	10	1,280	37			28.9	21.1-36.8	28.9	20.4-39.8
China-Rural	5,840,000	50	3,568	2,998	4.5	13,491	106	4.9	4.0-6.1	3.5	2.9-4.2	7.9	6.4-9.5
China-Rural	3,185,000	50	2,455	1,986	6.1	12,114	206	2.9	2.6-3.4	10.4	9.0-11.7	17.0	14.8-19.5
Mali-Urban/Rural	7,158	40	36	31	12	372	13			41.9	24.6-59.3	34.9	18.8-59.8
Summary	**9,112,561+**		**8,894**	**7,233**	**6.0†**	**32,850**	**431**	**2.9‡**		**10.4‡**		**13.1**	**11.9-14.4**

†Mean weighted by study person-years
‡Median weighted by study person-years
§ Follow-up study of cohort described in Ding 2006
PWE: People with epilepsy
FU: Follow-up
SMR: Standardized mortality ratio
CFR: Case fatality ratio
MR: Mortality rate per 1000 PWE

Table 3-2: Mortality rates estimates from clinical cohort studies

Country-Location	Quality	Cohort size	PWE followed	Duration of FU (years)	Person-years	Deaths in PWE	SMR		CFR		Mortality	
							SMR	95% CI	%	95% CI	MR	95% CI
Ecuador- Urban	50	420	379	3	1,137	7	6.3	2.0-10.0	1.8	0.5-3.2	6.2	2.5-12.7
Brazil-Urban/Rural	45	550	550	10	5,500	16			2.9	1.5-4.3	2.9	1.7-4.7
Brazil-Urban	35	1012	987	10	9,870	53			5.4	4.0-6.8	5.4	4.0-7.0
Tanzania, Rural	35	164	146	30	4,380	110			75.3	68.4-82.3	25.1	20.6-30.3
India-Urban	25	447	246	12	2,952	18			7.3	4.1-10.6	6.1	3.6-9.6
Brazil-Urban, Rural	25	267	267	13	3,471	9			3.4	1.2-5.5	2.6	1.2-4.0
Chile-Urban/Rural	5	NR	NR	6	NR	16	3.21	1.5-5.0				
Brazil-Urban/ Rural	5	996	835	8	6,680	11			1.3	0.5-2.1	1.6	0.8-2.9
Summary: all studies		**3856**	**3410**	**12.4†**	**33,990**	**240**	**4.8**				**7.1**	**6.2-8.0**

†Mean weighted by study person-years
‡ Median weighted by study person-years
PWE: People with epilepsy
FU: Follow-up
SMR: Standardized mortality ratio
CFR: Case fatality ratio
MR: Mortality rate per 1000 PWE

Cause-specific mortality in epilepsy. Table 3-3 presents 8 population-based studies that reported cause-specific proportional mortality rates in PWE (Banerjee et al., 2010, Carpio et al., 2005, Ding et al., 2013, Kaiser et al., 2007, Kamgno et al., 2003a, Mu et al., 2011b, Ngugi et al., 2014b, Nicoletti et al., 2009). Among PWE, the weighted median PMR for all causes of death directly or indirectly attributable to epilepsy was 47%. Direct causes comprised status epilepticus (median PMR 13%), and possible or probable SUDEP (median PMR 13%; Table S4). Indirect causes included accidents (falls, road traffic, drowning, and burns; Table S5). Among accidents, the median PMR was 15% (range 3.3%-45%) for drowning, (Banerjee et al., 2010, Ding et al., 2006, Kaiser et al., 2007, Kamgno et al., 2003a, Mu et al., 2011b) and 7.5% for road traffic accidents (Mu et al., 2011b, Banerjee et al., 2010, Ngugi et al., 2014b, Ding et al., 2006); the remaining causes did not have sufficient data for a summary (Table S5). Among these population studies, the median sum of all listed accident-related PMRs was 36% of all deaths in people with epilepsy. Other important causes of death in these populations that were not attributable to epilepsy included cerebrovascular diseases, tuberculosis, malaria, heart disease, and cancer (Table S6).

Six clinical cohort studies reported causes of death as PMRs for individuals with epilepsy (Table 3-3) (Carpio et al., 2005, Terra et al., 2011, Jilek-Aall et al., 1992a, Almeida et al., 2010, Terra et al., 2010, Devilat et al., 2004). The median PMR for direct and indirect causes of death attributable to epilepsy was 39.3% and 24% respectively. Median PMRs for deaths due to status epilepticus and SUDEP in clinical cohorts were 14.8% and 11.1% respectively (Table S4). Data regarding causes of death indirectly attributable to epilepsy and causes not attributable to epilepsy were not sufficiently large to enable generalization.

Mortality risk by seizure type or frequency. Mortality risk by seizure type was reported from two population-based and two clinical cohorts in which median PMRs were consistently higher for focal epilepsy (population-based – 55% and clinical cohort – 73%) than for generalized epilepsy (population-based – 39% and clinical cohort – 26%; Table S7). Two studies reported increased mortality among PWE with a higher frequency of seizures (Kaiser et al., 2007, Terra et al., 2009) (Table S8).

Risk by duration of epilepsy. Two studies reported on mortality by duration of epilepsy (Ngugi et al., 2014b, Kaiser et al., 2007) (Table S9). The study in rural Kenya reported the highest mortality rate (45 per 1000 person-years) for PWE with epilepsy duration of <1 year. In Uganda, SMRs were 8.6 (95% C.I. 4.5-16.5) for PWE of duration <5 years, 3.6 (1.1-11.4) for those of epilepsy duration 5-9 years, and 23.8 (8.9-65.5) for those of epilepsy duration 10-14 years.

Table 3-3: Estimates of proportional mortality ratio by cause

Country-Location	Quality	Number of PWE followed	Number of deaths	Causes of death (%)			
				Direct	Indirect	Unrelated	Undetermined
Population-based							
Kenya-Rural	100	754	61	44.3	11.4	34.3	9.8
Uganda-Rural	90	61	18	33.0	17.0	44.4	5.6
Bolivia-Rural	85	103	10	10	20	50	20
India-Urban	80	337	20	5	30	45	20
Cameroon-Rural	60	271	37	75.5	10.8	13.7	
China, Rural	50	2,998	106	21.6	58.8	19.6	
China, Rural	50	1,986	206	14.1	32.5	39.3	14.1
Mali-Rural & Urban	40	36	13	38.0	NR	62.0	NR
Summary population based		**6,546**	**471**	**27.3***	**20.0***	**41.9***	**14.1***
Ecuador, Urban	50	379	7	42	30	28	
Brazil, Urban-Rural	45	550	16			62.5	
Brazil, Urban	35	987	53	15.1		84.9	
Tanzania, Rural	35	164	110	17.3	18.2	32.7	31.8
Brazil-Urban, Rural	25	267	9	77.8			
Chile, Santiago	5	NR	16	39.3			
Summary: Clinical cohort		>2,347	211	39.3*	24.1*	47.6*	

*Median percentage

Risk by epilepsy etiology. Symptomatic epilepsies appeared to have higher mortality rates compared to cryptogenic epilepsy, (Almeida et al., 2010, Devilat et al., 2004, Kochen et al., 2005, Nicoletti et al., 2009) although only two studies provided direct comparisons (Almeida et al., 2010, Nicoletti et al., 2009) (Table S10).

Risk by treatment adherence. Five population-based studies reported mortality risk by treatment adherence, (Mu et al., 2011b, Kaiser et al., 2007, Ngugi et al., 2014b, Kamgno et al., 2003a, Nicoletti et al., 2009) treatment allocation, (Kamgno et al., 2003a) time since last treatment, (Nicoletti et al., 2009) and dose allocation (Mu et al., 2011b) (Table S11). In Kenya, mortality rates were higher for individuals who did not adhere to AED treatment than for those who adhered to treatment (48 vs. 16 deaths per 1000 person-years) (Ngugi et al., 2014b). In Uganda, the SMR was 7.4 for those with self-reported good AED adherence compared to 8.0 for those with poor adherence (Kaiser et al., 2007). In Cameroon, treatment with AEDs alone was associated with 14% of deaths compared to 27% in those using AEDs and traditional medicine (Kamgno et al., 2003a). In one Chinese study, PWE receiving higher daily doses of phenobarbital (201-240 mg) had a lower mortality of 9% compared to those receiving medium doses (90-180 mg) with 47% mortality and low doses (30-90 mg) with mortality of 50% (Mu et al., 2011b). In a Bolivian study, recent access to AEDs was associated with lower mortality than absence of treatment for an extended period (Nicoletti et al., 2009).

Meta-analysis. Meta-analysis revealed high heterogeneity across population-based studies as well as clinical cohort studies, and among high- and low-quality studies as well as short and long follow-up studies (Figures S2 and S3). Accordingly, a formal meta-analytic synthesis was not attempted.

1.1 Discussion

Limitations. There are substantial limitations to these data. The studies that met our inclusion criteria represented only a small number of communities in Sub-Saharan Africa, Asia, and South America, while other major regions of the world, such as North Africa and the Middle East, were entirely unrepresented. The quality of the studies reviewed varied considerably. The large heterogeneity observed illustrates the high degree of uncertainty in the estimation of the true occurrence of epilepsy-related mortality across LMICs. Ascertainment bias, a major concern in many of the studies, is likely to yield underestimates of the mortality of epilepsy in LMIC. Some population-based studies included only cases with convulsive epilepsies, while others may have incompletely ascertained cases with non-convulsive epilepsies. Most clinical cohorts over-represented people with severe forms of epilepsy, such as one Brazilian study with 72% of enrollees who reported daily seizures (Terra et al., 2011) and another that enrolled people with refractory epilepsy awaiting or having undergone epilepsy surgery (Almeida et al., 2010). The diagnosis of epilepsy in many studies was not made by clinicians with training in the diagnosis of epilepsy; thus the specificity of the estimates and causes of death in epilepsy in some studies should be viewed with caution. Most of the causes of death were ascertained by review of clinical records or verbal autopsy. No studies were identified using post-mortem examination data. The specificity of verbal autopsies varies depending on the other common causes of death in the population, the tool used, and the experience of the person administering the tool (Aspray, 2005).

Interpretation. This is the first systematic review of mortality associated with epilepsy encompassing all LMIC, although previous reviews of mortality in Africa (Diop et al., 2005b) and Latin America (Escalaya et al., 2015) are noteworthy. The incidence of

epilepsy varies substantially across regions comprising LMICs and is higher in regions with high incidence of encephalitis and meningitis and with endemic parasitic infections such as malaria and neurocysticercosis (Kaiser et al., 2007, Nicoletti et al., 2009, Ngugi et al., 2014b). The availability of basic public health services as well as specialized health care for epilepsy also varies considerably among LMICs (World Health Organization, 2015). Both factors may strongly influence epilepsy-related mortality. Thus, any generalizations drawn from the modest number of studies we have reviewed should be applied to other LMIC regions with great caution.

Despite their limitations, these data from LMIC provide clear evidence that the burden of premature mortality, as measured by SMRs, is higher among PWE than in corresponding general populations.

SMRs are especially high in children and young adults with epilepsy. This finding might be explained in part by: (a) the comparatively lower mortality rates in general populations of young age, and (b) the increased mortality of recent-onset epilepsy, given that epilepsy onset is more frequent at young ages.

The burden of premature mortality among PWE in LMICs appears to be somewhat higher in males, as indicated by the PMRs from several studies. This could reflect a higher incidence among males of symptomatic epilepsies (especially from head injury), which have an increased mortality risk. It could also reflect increased mortality from hazardous occupations with an increased risk of drowning, falls, or other fatal injuries occurring consequent to seizures.

These data also indicate that among the most important causes of death in PWE are those directly related to epilepsy, in particular status epilepticus, previously recognized to have a high case fatality ratio in LMICs (Newton et al., 2013). The proportion of

deaths from status epilepticus appears substantially higher in LMICs compared to HICs (Thurman et al., 2016a). This difference might be explained in part by better access to AED treatment, better management of seizures, and better access to prompt treatment for prolonged seizures in HICs compared to LMICs.

SUDEP was identified as another cause directly related to epilepsy in several LMIC studies. The estimated proportions must, however, be viewed with caution as causes of death were seldom diagnosed through post-mortems and diagnoses of SUDEP made by verbal autopsy or clinical history may be inaccurate (Shorvon et al., 2011). Nevertheless, many of the risk factors associated with SUDEP are more common in LMIC than in HIC, e.g., structural causes of the epilepsy and frequent seizures, and thus SUDEP may represent a greater burden in these regions than indicated by some studies. Specific studies to examine SUDEP occurrence in LMIC populations are needed.

In comparison to HIC, a higher proportion of PWE in many LMIC regions also die due to indirect causes, especially accidents. Many of these causes, e.g. drowning and burns, are potentially preventable through education and safety measures. For other causes, e.g., seizure-caused fatal injuries incurred during work or while driving a vehicle, further studies are needed to understand the frequency and circumstances of these injuries and to identify appropriate prevention measures that are specific for different localities.

Comparing Mortality in LMIC and HIC. Overall, the relative premature mortality risk associated with epilepsy in LMIC appears somewhat higher than the risk reported in HICs. In the best quality LMIC studies, the weighted median SMR of 2.6 modestly exceeds the corresponding value of 2.2 in HIC (Thurman et al., 2016a). Such

comparisons of SMRs between studies are, however, fraught with potential error, especially given differing age distributions among study populations (with generally larger proportions of young people in LMIC), problems with case finding (greater in LMIC), and differing overall mortality rates in the study base populations (usually higher in LMIC). Thus, the magnitude of the disparity suggested by SMRs may be deceptive and it appears likely that the actual burden of premature mortality with epilepsy, if this were measured as incidence rates in entire populations, would be much higher in LMIC.

Implications

A limited number of studies demonstrate substantially elevated risks of premature mortality among PWE in LMIC of three continents. Much of this may be attributed to the restricted distribution of healthcare resources in these countries, resources often far more limited than in HIC (World Health Organization, 2015). Thus, lack of access and decreased adherence to medical management with AEDs places PWE at increased risk of fatal medical or injury-related complications of frequent seizures. Lack of access to prompt medical interventions for prolonged seizures places PWE at increased risk of death from status epilepticus. This mortality could be significantly reduced with improved access to health care including AEDs, and with education about the risks of epilepsy and ways to reduce these risks.

The limited existing data on epilepsy-related mortality in LMIC are, however, not sufficient to guide the development of such prevention programs. Too many countries and local regions are not described. The circumstances of fatalities from medical complications, e.g., status epilepticus, are uncertain. What proportion were associated with no AED treatment and in what proportion was AED use interrupted or

reduced because of inability to afford its cost? The types and circumstances of fatal injuries arising from seizures are also uncertain. Where do drownings in PWE occur, how many are occupational, and which occupations are involved? How do fatal burns occur? In how many traffic fatalities are PWE pedestrians, vehicle passengers, or vehicle drivers? How do local laws address motor vehicle driving by PWE? How many injuries involve falls from heights and how many of these are occupational? How do risks vary according to local resources, customs, and industries (e.g., climbing trees to pick fruit)?

More epidemiological studies, involving more LMIC localities, are needed. As with future studies in HIC, studies in LMIC should be performed in conformity with current guidelines for epidemiologic studies (ILAE, 1993, Thurman et al., 2011b). Representative population samples and incident cohorts should be studied, where acute symptomatic seizures are distinguished from single unprovoked seizures and from epilepsy, and where convulsive and non-convulsive forms of epilepsy are also distinguished. Finally, epileptogenic conditions and all risk factors implicated in the mortality of epilepsy should be clearly described. The collection of such higher quality information will enable us to identify many measures necessary to prevent much of the premature mortality in LMIC.

Supporting Information

Table S1 Criteria and grading for assessing qualities of mortality studies

Sensitivity of Epilepsy Case Ascertainment (20/20)

- 20/20 = Screening methods appear likely to ascertain nearly all (≥ 85%) cases in population
- 15/20 = Screening methods appear likely to ascertain most (70 - 84%) cases in population
- 10/20 = Screening methods appear likely to ascertain majority (50 - 69%) of cases in population
- 5/20 = Screening methods appear unlikely to ascertain majority of cases in population OR information published is insufficient to assess
- 0/20 N/A = Not applicable: not a population-based study or sensitivity of methods of epilepsy case ascertainment not relevant to quality of study.

Sensitivity of Mortality Case Ascertainment (20/20)

- 20/20 = Fatalities appear likely to be recorded in nearly all (≥ 85%) cases in study population
- 15/20 = Fatalities appear likely to be recorded in most (70 - 84%) cases in study population
- 10/20 = Fatalities appear likely to be recorded in majority (50 - 69%) of cases in study population
- 5/20 = Fatalities appear unlikely to be recorded in majority of cases in study population OR information published is insufficient to assess

Accuracy of Diagnoses of Epilepsy (20/20)

- 20/20 = Cases are diagnosed (or confirmed) by specialist clinician (i.e., with neurologic training), AND ILAE case definition applied
- 15/20 = Cases are often diagnosed by non-specialist clinician, OR minor deviation from ILAE case definition
- 10/20 = All or substantial proportion of cases diagnosed based on self-report or non-clinical sources with specified criteria judged to have fair positive predictive value
- 5/20 = All or substantial proportion of cases diagnosed with poorly defined criteria from non-clinical sources; positive predictive value judged to be poor OR information published is insufficient to assess

Accuracy of Diagnoses of Cause of Death (20/20)

- 20/20 = Determined mainly from either autopsy, ME/coroner investigation, or other clinical investigation (e.g., review of medical records, structured interview of survivors or “verbal autopsy”)
- 15/20 = Determined largely or wholly from death certificate data, when such data are judged to have good positive predictive value for the specific causes of interest
- 10/20 = Determined largely or wholly from death certificate data, when such data are judged to have only fair positive predictive value for the specific causes of interest
- 5/20 = Other sources of data deemed to have poor positive predictive value for the causes of interest OR information published is insufficient to assess
- 0/20 = Cause of death not studied

Representativeness of the study population (20/20)

- 20/20 = Cohort studies of incident epilepsy whose enrolled cases appear highly representative of the population of interest
- 15/20 = Studies of prevalent epilepsy whose enrolled cases appear highly representative of the population of interest
- 10/20 = Studies of epilepsy whose enrolled cases appear somewhat representative of the population of interest
- 5/20 = Studies of epilepsy whose enrolled cases appear poorly representative of the population of interest or where representativeness cannot be assessed.

Table S2: Summary of characteristics and quality of population-based studies of mortality in epilepsy

Country-Location	Dates	Source	Population (denominator)	Epilepsy cases	Case ascert-ainment (%)	Diagnosis	Mortality captured %	Cause of Death	Represen-tativeness	Quality
Argentina-Urban	1991-1998	PBS	70,000	106	≥85	Neurologist†	≥85	DC	Highly	90
Benin- Rural	2006-2007	PBS + MR+ KI	11,688	160	≥85	Neurologist†	≥85	N/A	Highly	80
Bolivia-Rural	1994-2004	PBS	55,675	118	≥85	ILAE	≥85	NR	Highly	85
Cameroon- Rural	1991-2001	KI	NR	271	50-69	Physicians†	70-84	NR	Somewhat	60
China-Rural	2000-2004	PHC	3,185,000	2455†	N/A	NR	70-84	VA	Somewhat	50
China-Rural		PHC	5,840,000	3568†	N/A	NR	70-84	VA	Somewhat	50
China-Rural	2000-2008	PHC	3,185,000	2455†	N/A	NR	70-84	VA+DC	Somewhat	50
India- Rural	1985-1999	PBS	14,010	109	≥85	Neurologist	≥85	N/A	Poorly	65
India- Urban	2003-2005	PBS	52,377	337	≥85	Neurologist†	≥85	N/A	Highly	80
India- Urban	1989-1994	PBS	16,000	51†	≥85	NR	≥85	VA	Somewhat	80
Kenya- Rural	2007-2010	PBS	232,164	754†	≥85%	Neurologist†	≥85	VA	Highly	100
Mali-Urban, Rural	1988-2000	KI	7,158	36†	50 - 69	NR	70-84	NR	Poorly	40
Uganda- Rural	1994-2001	PBS	4,743	61	≥85	ILAE	≥85	VA	Somewhat	90

Key: DC Clinical Diagnosis; KI: Key informants, MR: Medical records, N/A: Not Available; NR Not Recorded; PBS: Population-based screening, PHC: Primary health care, VA Verbal Autopsy

*These studies describe the same cohort. †Convulsive epilepsy only.

†Using ILAE guideline

Table S3: Summary of characteristics and quality of clinical cohort studies of mortality in epilepsy

Country-Location	Dates	Source of clinical cohort	Epilepsy cases	Case	Diagnosis	Mortality	Cause of Death	Representative ness	Quality
Ecuador-Urban	1997-2000	Tertiary Hospital	420	N/A	ILAE	≥85	N/A	Somewhat	50
Brazil-Both	1992-2002	Tertiary Hospital	550	N/A	Clinical	≥85	N/A	Poor	45
Brazil-Urban	2000-2010	Tertiary Hospital	1012	N/A	N/R	≥85	SR	Poor	35
Tanzania-Rural	1960-1990	District Hospital	164	N/A	N/R	≥85	N/A	Somewhat	35
India-Urban	1985-1997	Tertiary Hospital	447	N/A	N/R	50 - 69	N/A	Somewhat	25
Brazil-Both	1995-2008	Tertiary Hospital	267	N/A	N/R	> 80	N/I	Poor	25
Brazil-Both	2000-2008	Tertiary Hospital	996	N/A	N/R	N/R	N/I	Poor	5
Chile-Both	1996-2002	Tertiary Hospital		N/A	N/R	N/R	N/I	Poor	5

Key: N/A – Not Available; N/R – Not recorded

Table S4: Estimates of proportionate mortality ratio.(PRM) from SUDEP and status epilepticus among people with epilepsy

Country-Location	Quality	PMR (%) SUDEP	SE
Population based studies			
Kenya-Rural	100	6.6[a]	37.7[a]
Uganda-Rural	90	11.1	22.2
India-Urban-Vasai	80	20 [a]	
Bolivia-Rural	85		10
India-Urban	80		5
Cameroon-Rural	60	18.9	56.6
China, Rural	50	14.7[b]	6.9
China, Rural	50	1[b]	13.1
Median All Population Studies		**12.9**	**13.1**
Clinical cohort studies			
Ecuador, Urban	50	14.3 [c]	23
		28.6 [b]	
Brazil, Urban-Rural	45	2.9 [b]	
Brazil, Urban	35	13.2	15.1
Tanzania, Rural	35		14.5
Brazil, Urban-Rural	25	11.1	
Chile-Santiago	5	31.25 [b]	
Urban/Rural		6.25 [c]	
Brazil-Urban, Rural	5	1.38	
Median All clinical cohorts		**11.1**	**14.8**

[a]Cases described as possible.
[b]Cases described as probable.
[c]Cases described as definite.

Table S5: Estimates of proportionate mortality ratio (PMR) in epilepsy bytype of injury

		PMR by type of injury				
Country-Location	Quality	Falls	Drowning	Traffic injury	Burns	Suicide
Population-based						
Kenya-Rural	100	3.3	3.3	1.6	1.6	
Uganda-Rural	90		5.6		11.1	
Bolivia-Rural	85			10		10
India-Urban	80		15	15		
Cameroon-Rural	60		10.8			
China, Rural	50		37	2.9		
China, Rural	50	5.9	45.1	4.9		2.9
Clinical cohort						
Brazil, Urban	35	1.9	1.9			
Tanzania, Rural	35		12.7		5.5	

Table S6: Estimates of causes of death reported in standardized mortality ratio (SMR) and mortality rate (MR)

Country, Location	**Quality**	**Measure**	**Causes**	**Estimate (95% C.I.)**
China, Rural	50	SMR	Cerebrovascular	1.14 (0.36–3.61)
			Cardiac disease	1.60 (0.50–5.22)
			Influenza and pneumonia	1.05 (0.26–4.32)
			Malignant neoplasm	1.94 (0.90–4.18)
			Other diseases	11.41 (4.03–32.43)
China, Rural	50	SMR	Drowning	39.0 (26.4–55.5)
			Toxic effects	17.0 (6.9–35.7)
			Falls	9.8 (3.6–21.7)
			Suicide	8.2 (4.5–14.0)
			Transport injury	6.0 (2.8–11.4)
			Myocardial infarction	3.6 (1.6–7.2)
			Digestive system diseases	4.4 (2.3–7.7)
			Pneumonia	2.9 (0.7–7.8)
			Cerebrovascular	2.2 (1.5–3.1)
			Neoplasms	1.1 (0.7–1.8)
Brazil	5	MR	Unrelated to epilepsy	22.2

MR: Mortality rate per 1,000 people with epilepsy

Table S7: Proportionate Mortality Ratio (PMR %) by Type of Seizure

	PMR for epilepsy type

Location	Source	Quality	Generalized	Focal	Unknown
Argentina-Urban	Population	90	37.5	50	12.5
Bolivia-Rural	Population	85	40	60	
Brazil, Urban-Rural	Clinical Cohort	45	14.3	85.7	
India, Urban	Clinical Cohort	25	38.9	61.1	

Table S8: Estimates of mortality in epilepsy by seizure frequency

Location	Source	Quality	Measure	Frequency	SMR/MR
Uganda-Rural	Population	90	Standardized mortality ratio	High (>1 per week)	14.7 (8.5—24.8)
				Low (<1 per week)	1.4 (0.4—5.7)
Brazil	Cohort	5	Mortality rate	Daily	0.63
				2-4 per week	0.50
				1 per month	0.13

Table S9: Estimates of mortality in epilepsy by duration of epilepsy in population-based studies

Country-Location	Quality	Measure	Duration of epilepsy (years)	MR/SMR
Kenya-Rural	100	Mortality rate (MR)	<1	45.9(22.9–91.7)
			1–5	30.8(19.1–49.5)
			6–10	35.9(20.4–63.2)
			>10	31.1(20.9–46.4)
Uganda-Rural	90	Standardized mortality ratio (SMR)	0-4	8.6 (4.5-16.5)
			5-9	3.6 (1.1-11.4)
			10-14	23.8 (8.9-65.5)

Table S10: Estimates of proportionate mortality ratios in epilepsy by etiology

			Etiology			
Country-Location	Quality	Measure	Cryptogenic	Sympt-omatic	Remote seizure	Undete-rmined
Brazil, Urban-Rural	45	PMR	21.4	78.6		
Chile-Urban/Rural	5	PMR		81.3		
Argentina-Urban	95	PMR			75	25
Bolivia-Rural	85	PMR			60	
		SMR	0.74(0.2–1.8)*		3(1.2–6.3)	

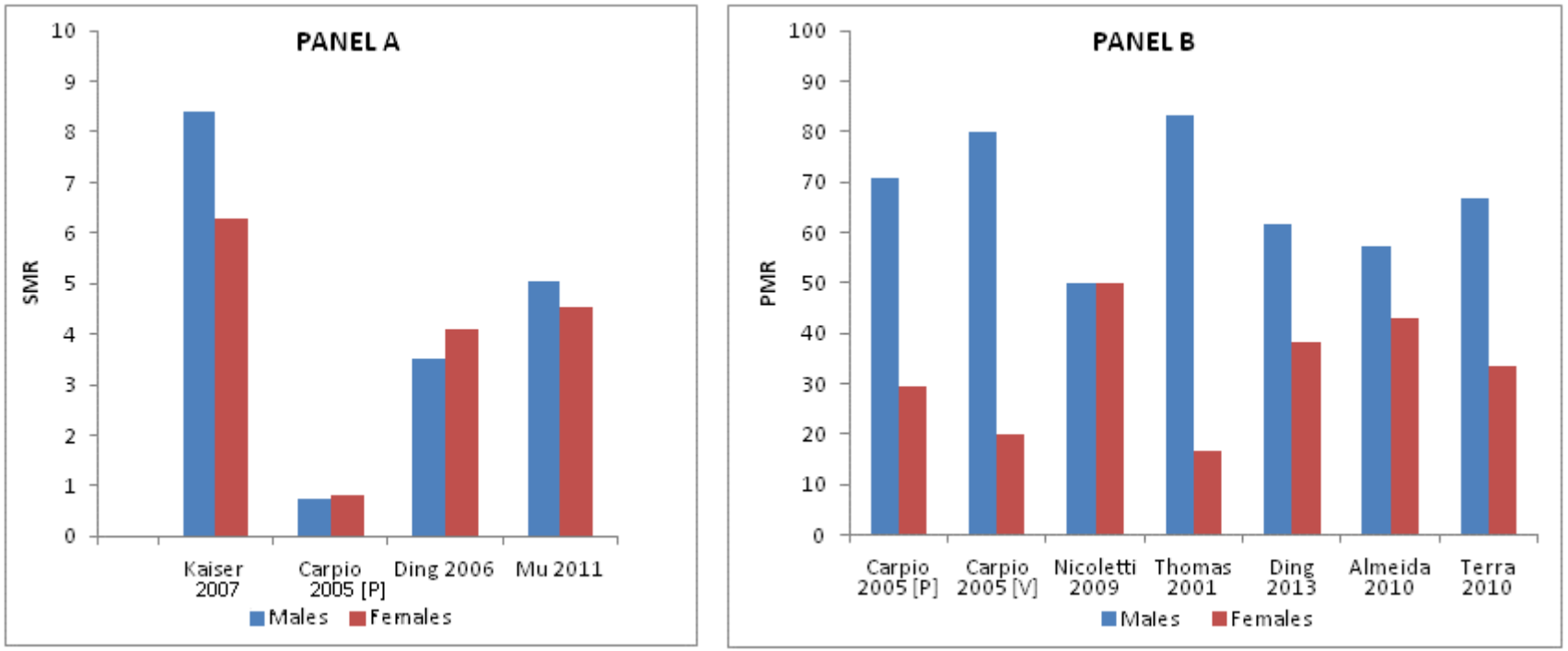
***** Idiopathic, PMR: Proportionate mortality ratio (%), SMR: Standardized mortality ratio

Table S11: Estimates of mortality in epilepsy by treatment

Country-Location	Quality	Measure	Treatment	Result
Kenya-Rural	100	Mortality rate	Adherence	16.1 (9.5–27.2)
			Non adherence	48.8 (36.7–65.0)
Uganda-Rural	90	Standardized mortality ratio	Good adherence	7.4
			Poor adherence	8.0
Cameroon-Rural	60	Proportionate mortality ratio	AED	13.6
			AED + Traditional	27.3

China, Rural	50	Proportionate mortality ratio	Phenobarbital Dose: 30–60 mg.	47.2
			Phenobarbital Dose: 90–180 mg.	44.3
			Phenobarbital Dose: 210–240 mg.	8.5
Bolivia-Rural		Proportionate mortality ratio	Treatment in past year	20
			No treatment in past year	80
			Treatment in last month	20
			No treatment in last month	80

Figure S1: Standardized Mortality Ration and Proportionate Mortality Ratio of epilepsy by sex



SMR: Standardized mortality ratio
PMR: Proportionate mortality ratio (%)

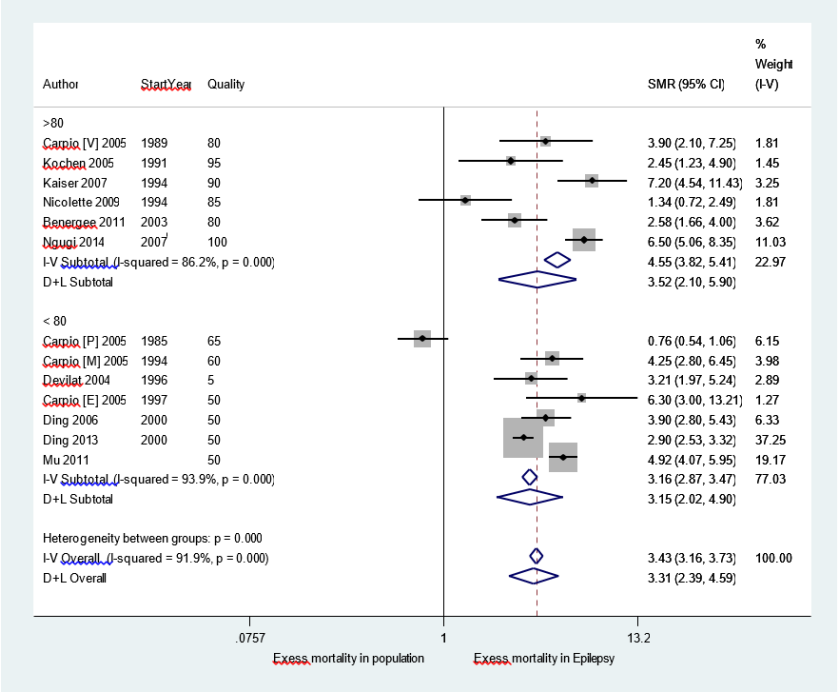


Figure S2: Forest plot of excess mortality in epilepsy by quality of studies

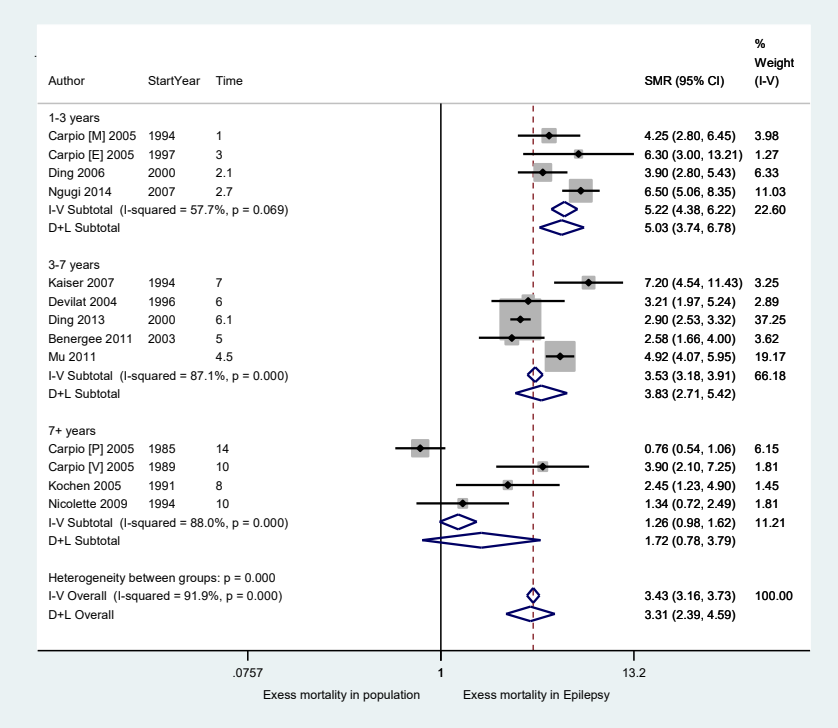


Figure S3: Forest plot of excess mortality in epilepsy by duration of cohort follow-up

Excess mortality in epilepsy in sub-Saharan Africa: Analysis of Studies of Epidemiology of Epilepsy in Demographic Sites (SEEDS)

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Abstract

Objective

To estimated excess mortality in people with epilepsy (PWE) using data from the Studies of Epidemiology of Epilepsy in Demographic Surveillance Sites in three sub-Saharan African countries.

Methods

We followed those with and without epilepsy and documented deaths from three sites; Agincourt (South Africa), Ifakara (Tanzania) and Kilifi (Kenya) for durations (median) of 7, 6 and 8 years respectively. We estimated excess mortality in PWE compared to those without epilepsy using standardized mortality ratio.

Findings

A total of 199 deaths in PWE and 16,801 in general population were observed from the time of diagnosis. Mortality rates in PWE were estimated at 31.5 deaths per 1,000 person years (95%CI: 19.4-43.6) in Agincourt, 23.9 (95%CI: 11.7-36.1) in Ifakara and 24.6 (95%CI: 19.5-29.6) in Kilifi. Pooled estimates of excess mortality, as measured by standardized mortality ratio (SMR), was 4.8 (95% CI: 4.2-5.6) times higher in PWE than in those without epilepsy. Adjusting for age, SMRs were 3.20 (95%CI: 2.41-4.27) in Agincourt, 4.66 (95%CI: 3.46-6.29) in Ifakara and 6.22 (95%CI: 5.15-7.50) in Kilifi.

Conclusions

This study demonstrates evidence of excess mortality in PWE in sub-Saharan African countries. Observed risk factors may be managed by improving access to antiepileptic drugs, preventive measures against accidents, reducing perinatal adverse events at birth, preventing parasite infections with proper management of domesticated animals and hygiene, empowering PWE with education and decent low risk jobs and managing

co-morbidities such as cerebrovascular, cardiovascular, and motor and cognitive impairment.

Introduction

Epilepsy is a neurological disorder that significantly impacts social and economic well-being and survival in people with epilepsy (PWE); this impact is often more pronounced in sub-Saharan African countries when compared with high-income countries (Bhalla et al., 2014, Radhakrishnan, 2009a, Wilmshurst et al., 2014). With poor access to antiepileptic drugs (AED) and health care services, mortality in PWE has been found to be higher than that of general population (Kaiboriboon et al., 2014, Devinsky et al., 2016). Untreated epilepsies are associated with increased seizure frequency and higher mortality rates in status epilepticus, Sudden Death in Epilepsy (SUDEP) and accidents (falls, road traffic, drowning, and burns) (Radhakrishnan, 2009a, Ba-Diop et al., 2014a, Birbeck et al., 2012, Hunter et al., 2016). Seizures are also associated with stigma, which often leads to exclusion from social and economic protective factors of excess mortality such as education, marriage, and employment (Wo et al., 2015, Heersink et al., 2015, Mushi et al., 2011).

In sub-Saharan Africa, there is a paucity of evidence for understanding the magnitude of excess mortality in PWE and risk factors for deaths (Diop et al., 2005a). Recent systematic review highlighted the limited number of studies that estimate mortality in PWE (Levira et al., 2017). The review also revealed considerably large heterogeneity between studies, illustrating the high degree of uncertainty in the estimation of the true occurrence of epilepsy-related mortality across Low and Middle Income countries (LMICs).

Studies of Epidemiology of Epilepsy in Demographic Surveillance (SEEDS) were designed to systematically collect comparable data on the prevalence and mortality in PWE in population-based house-to-house surveys in 5 sub-Saharan African countries

(Tanzania, South Africa, Uganda, Kenya and Ghana) (Ngugi et al., 2013a). This study, using data from SEEDS sites, aims to estimate country-specific and overall excess mortality in PWE and assess risk factors associated with excess mortality.

Methods

Study settings and populations

The initial SEEDS study was conducted in Health and Demographic Surveillance System (HDSS) in Agincourt, South Africa, Ifakara, Tanzania and Kilifi, Kenya (Geubbels et al., 2015, Kahn et al., 2012, Scott et al., 2012). HDSS sites were established by enumerating the entire population (households and residents) in selected area. Following the establishment, continuous updates of residency status and vital events (migration, birth and deaths and their causes) have been conducted on a regular basis ranging from 1 to 3 visits in every enumerated household per year. Total populations at the start of the study in three HDSS were 83,121, 104,889 and 233,881 residents in Agincourt, Ifakara and Kilifi, respectively (Ngugi et al., 2013a).

People with ACE were identified in a three stages screening process of the entire population (Ngugi et al., 2012). ACE was defined as presence of at least “two or more unprovoked seizures occurred at least 24 hours apart” in the past 12 months (Thurman et al., 2011a). Estimates of prevalence of ACE in three sites have been published elsewhere in the literature (Ngugi et al., 2013a). After screening cohorts of people with ACE were established and followed as part of normal HDSS updates.

Baseline census and risk factors

Data on risk factors for ACE and mortality in PWE were collected by trained clinicians and field workers during baseline epilepsy surveys. General and adult specific (such as alcohol consumption) data on social and demographic, historical and clinical factors

were directly collected from individuals aged 18 years and older. For study participants younger than 18 years of age, or with cognitive impairment, the mother or caregiver was interviewed. Child and mother's specific data were collected including questions about antenatal (such as severe abdominal pain, vaginal bleeding, or infection during pregnancy) and perinatal events (difficulties breathing, feeding, or crying after birth, as recalled by the mother).

Clinical classification of seizures on the basis of electroencephalography (EEG) features of ACE in SEEDS cohorts has been published elsewhere (Kariuki et al., 2013, Kariuki et al., 2014, Kariuki et al., 2016). In summary, EEGs were performed on all participant diagnosed with ACE using 16 channel digital recording system (Grass Technologies, Warwick, RI, USA) according to the 10–20 international system with hyperventilation and photic stimulation. EEG activities were coded and classified in four categories of normal, mild, moderate or severe excess of generalized/diffused slow of cerebral function. Binary classification was recorded as normal and abnormal (mild, moderate and severe). Identification of origin of epileptic seizures in the brain was done by analyzing waves, spikes, polyspike, and burst of interictal epileptiform discharges (IEDs). IEDs were classified as generalized (involving the entire brain), focal (involving a region of the brain) or multifocal (involving 3 or more discrete brain regions). An EEG summary indicator was categorized as abnormal if there was evidence of an abnormal background, focal changes, interictal epileptiform activity or an abnormal response to hyperventilation and photic stimulation.

Nutritional status was defined using body mass index (BMI; weight/height^2) and categorized using the standard World Health Organization categories <18 (underweight), 18-24 (normal), 25-30 (over weight), and 30+ (obese). Detailed

information on definitions and categories of risk factors have been published previously (Kariuki et al., 2014).

Follow-up of ACE and general population

Both people diagnosed with ACE and the general population of the HDSS remained under continuous surveillance. Median follow-up durations were 7, 6 and 8 years in Agincourt, Ifakara and Kilifi, respectively (Table 4-1). Deaths in those diagnosed with ACE were compared with the general population. These were documented in longitudinal databases and extracted for analysis from all sites.

Statistical analysis

Mortalities from ACE were estimated using survival analysis models. Exposure time was estimated from individual's residence episodes started at the study start date in each site and ended at out-migration, death or at the end of analysis period. Mortality rate estimates were stratified by risk factors and rate ratio compared over different levels of factors. Mortality rate ratios were estimated using the Mantel-Haenszel method. Standardized Mortality Ratios (SMRs) were estimated to assess excess mortality in ACE compared to general population. The INDEPTH standard life table was used as standard population in comparing mortality between the three sites (Sankoh et al., 2014b) Stata software version 13 (StataCorp LP, College Station, Texas) was used for descriptive statistics and statistical analysis (Boston et al., 2003).

Standard Protocol Approvals, Registrations, and Patient

The study protocol was approved by Ifakara Health Institute's Institution Internal Review Board and National Institute of Health Research and Commission of Science and Technology, Tanzania. All participants were enrolled through written consent.

Data Availability Statement

SEEDS baseline data is available through INDEPTH Network's data sharing policy. Site specific mortality status is available with prior permission from respective HDSS site Manager\Leaders.

Results

A total of 199 deaths were observed in the cohort of 1,268 individuals with ACE from the three sites. These deaths occurred between the time of diagnosis to the most recent HDSS survey for which data were available. In the general population, 16,801 deaths occurred in the total population of 506,813 residents in the sites (Table 1). Mortality rates in general population were 9.7deaths per 1000 person years (95%CI: 9.6-10.1) in Agincourt, 7.7 (95%CI: 7.5-7.9) in Ifakara and 5.0 (4.9-5.1) in Kilifi. Mortality rates in PWE were similar across the sites when adjusted for INDEPTH standard population. Estimated mortality rates were 31.5 deaths per 1000 person years (95%CI: 19.4-43.6) in Agincourt, 23.9 (95%CI: 11.7-36.1) in Ifakara and 24.6 (95%CI: 19.5-29.6) in Kilifi. Mortality rate stratified by site and risk factors are presented in Supplement Table S1.

Table 4-1: Key summary findings by population

	Agincourt		Ifakara		Kilifi		Total	
	GP	PWE	GP	PWE	GP*	PWE	GP	PWE
Initial cohort size	83,121	245	104,889	366	233,881	697	21,891	1,308
Lost to follow-up		2		4		27		33
Final cohort								
Sex								
Males	38,961	128	103,980	171	98,889	340	241,830	639
Females	42,052	115	108,443	191	113,697	327	264,192	633
Age								
0-5	9,634	9	55,150	20	12,668	22	77,452	51
6-18	9,240	43	55,416	113	85,393	233	160,049	389
19-49	39,961	138	80,691	190	83,910	344	04,562	672
50+	2,183	53	21,166	39	31,449	71	64,798	163
Total	**81,018**	**243**	**212,423**	**362**	**213,420**	**670**	**506,861**	**1,275**
Residency status								
Alive	59,924	166	126,676	222	115,855	369	302,455	757
Out-migration	17,892	41	80,096	97	91,157	192	89,145	330
Deaths	3,202	36	5,651	43	6,409	109	15,262	188
Follow-up (years)	7.4	7.4	3.3	6.3	8.1	8.6		
Mortality rate								
Crude	8.8	34.4	7.7	23.8	5.0	26.0		
Adjusted	7.5	32.7	7.9	23.9	4.7	24.6		
95% CI Lower	7.2	20.7	7.7	11.7	4.6	19.5		
95% CI Upper	7.8	44.6	8.1	36.1	4.8	29.6		

GP:General Population ;PWE: People with Epilepsy; CI: Confidence interval

In analysis of risk factors for mortality in PWE, controlling for site, high mortality rates were observed for those who ate soil (RR=1.70, 95% CI:1.27-2.26), snored more than 3 nights per week (RR=1.42, 95% CI: 1.04-1.93), adults who were divorced/separated/widowed (RR=2.30, 95%CI: 1.46-3.63), adults who were illiterate (RR=1.69, 95%CI: 1.21-2.36), those with onset of epilepsy at ages between 29-49 years (RR=1.88, 95% CI: 1.01-3.50) or 50 years and above (RR=4.67, 95% CI: 2.71-8.05), those with daily seizures (RR=1.54, 95%CI: 1.03-2.28), those with seizures that occurred both day and night (RR=1.80,95%CI: 1.05-3.09), those with severe general EEG diagnosis (excessive slow cerebral function) (RR=2.27, 95% CI: 1.34-3.83), those with burn marks (RR=1.46, 95%CI: 1.05-2.02), those with systolic blood pressure above 140mmHg (RR=2.58, 95%CI: 1.82-3.66) or a diastolic blood pressure greater than 90mmHG (RR=2.78, 95%CI: 1.90-4.06), those with pre-existing neurologic deficits (RR=1.78, 95%CI:1.31-2.43) or cognitive impairment (RR=2.11, 95%CI:1.57-2.84). The observed overall estimates were similar across sites based on test of unequal RR controlling for site (Table 4-2).

Table 4-2: Rate ratio and (95% CI) of mortality in epilepsy by site and risk factors

Risk factor	Agincourt	Ifakara	Kilifi	Overall	chi	p-value
Males	2.12 (1.15-3.92)†	1.22 (0.67-2.22)	1.09 (0.75-1.58)	1.29 (0.98-1.71)	3.42	0.181
Head injury	4.03 (2.09-7.79)†	2.48 (0.89-6.96)	1.23 (0.72-2.09)	1.84 (1.26-2.69)†	8.29	0.016
Eat soil	1.23 (0.68-2.23)	1.74 (0.95-3.19)	1.93 (1.31-2.85)†	1.70 (1.27-2.26)†	1.57	0.455
Snore > 3 nights a week	1.00 (0.54-1.86)	1.38 (0.76-2.52)	1.70 (1.09-2.66)†	1.42 (1.04-1.93)†	1.88	0.391
Marital status-Single	Ref	1	1	1		
Marital status-Married	3.35 (1.50-7.52)†	0.42 (0.16-1.08)	1.04 (0.61-1.78)	1.16 (0.79-1.70)	2.3	0.002
Marital status-Previous married	3.58 (1.55-8.26)†	1.28 (0.42-3.84)	2.16 (1.14-4.07)†	2.30 (1.46-3.63)†	2.26	0.324
Illiterate adult	2.88 (1.54-5.41)†	2.15 (0.98-4.71)	1.22 (0.76-1.95)	1.69 (1.21-2.36)†	5.07	0.079
Adult consuming alcohol	3.15 (1.57-6.31)†	0.73 (0.25-2.16)	1.09 (0.54-2.20)	1.42 (0.92-2.21)	7.35	0.025
Difficulties crying after birth	1.84 (0.22-5.77)	3.34 (1.09-0.25)†	1.16 (0.36-3.77)	1.84 (0.87-3.89)	1.72	0.424
Age onset 6-12	Ref	1	1	1		
Age onset 29-49	3.47 (1.22-9.85)†	1.21 (0.24-5.98)	1.25 (0.49-3.19)	1.88 (1.01-3.50)†	2.42	0.299
Sickle cell disease			7.51 (1.86-0.44)†	3.54 (0.88-4.26)	2.22	0.33
> 12 seizure per year	0.73 (0.36-1.49)	2.42 (1.12-5.21)†	1.08 (0.64-1.82)	1.16 (0.81-1.66)	5.39	0.068
Seizure frequency-Monthly	Ref	1	1	1		
Seizure frequency-Daily	0.71 (0.22-2.36)	1.55 (0.77-3.11)	1.87 (1.10-3.17)†	1.54 (1.03-2.28)†	2.18	0.336
Seizure time-Night						
Seizure time-Day & Night	1.67 (0.65-4.33)	1.41 (0.59-3.35)	2.47 (0.91-6.74)	1.80 (1.05-3.09)†	0.71	0.7
EEG GB-Severe	3.12 (1.17-8.32)†	1.45 (0.19-1.26)	2.12 (1.10-4.08)†	2.27 (1.34-3.83)†	0.63	0.728
No BCG vaccine scar	0.81 (0.39-1.68)	0.69 (0.21-2.22)	1.69 (1.13-2.54)†	1.28 (0.91-1.79)	4.45	0.108
Burn marks	1.88 (0.97-3.63)	1.26 (0.56-2.83)	1.39 (0.91-2.12)	1.46 (1.05-2.02)†	0.75	0.686
Systolic blood pressure: > 140	2.32 (1.23-4.36)†	3.17 (1.25-8.08)	2.65 (1.66-4.23)†	2.58 (1.82-3.66)†	0.31	0.857
Diastolic blood pressure: > 90	2.29 (1.21-4.35)†	2.51 (0.90-7.04)	3.39 (2.01-5.72)†	2.78 (1.90-4.06)†	0.95	0.623
Pre-existing neurological	1.19 (0.66-2.17)	2.74 (1.33-5.66)	1.98 (1.30-3.00)†	1.78 (1.31-2.43)†	3.36	0.186
Cognitive impairment	1.53 (0.84-2.78)	2.25 (1.04-4.86)	2.41 (1.64-3.54)†	2.11 (1.57-2.84)†	1.61	0.448
Motor impairment	0.75 (0.32-1.77)	4.07 (1.57-0.54)	2.75 (1.87-4.07)†	2.16 (1.56-2.99)†	9.63	0.008

Ref: Reference category, EEG: Electroencephalogram, BCG: Bacillus Calmette–Guérin
CI: Confidence interval, GB: General background, †: Statistically significant (P-value < 5%)

Site specific analysis identified risk factors that were significantly associated with increased mortality in PWE but not observed in the overall analysis. In Agincourt, high mortality rates were observed in males (RR=2.12, 95% CI: 1.15-3.92), those with previous history of head injuries (RR=4.03, 95%CI: 2.09-7.79), adults who were married (RR=3.35, 95%CI: 1.50-7.52), and adults who consumed alcohol (RR=3.15, 95% CI: 1.57-6.31). In Ifakara, high mortality rates were observed in babies who had difficulties in breathing or crying soon after delivery (RR=3.34, 95% CI: 1.09-10.25), and in those who had more than 12 seizures per year (RR=2.42, 95% CI: 1.12-5.21) and those with motor impairment (RR=4.07, 95% CI: 1.57-0.54). In Kilifi, high mortality rates were seen those with sickle cell disease (RR=7.51, 95% CI: 1.86-30.44) and motor impairment (RR=2.75, 95% CI: 1.87-4.07) Table 4-2.

Overall estimates of excess mortality across the three sites as measured by SMR was 4.8 (95% CI: 4.2-5.6) times higher in PWE than general population. Mortality estimates in PWE were higher than the general population in each HDSS sites. SMRs were 3.20 (95%CI: 2.41-4.27) in Agincourt, 4.66 (95%CI: 3.46-6.29) in Ifakara and 6.22 (95%CI: 5.15-7.50) in Kilifi. Analysis of excess mortality in PWE by site identified several sub-populations with SMR greater than country specific estimates. Supplement Table S2 provides estimates for SMR by sub-population and site.

Discussion

Excess mortality

Understanding the magnitude of excess mortality in PWE as well as risk factors are important for developing epilepsy management programs aimed at reducing epilepsy related causes of deaths and morbidities. Our previous systematic review identified only 7 good quality population-based studies of excess mortality in PWE from LMIC in

the study period of approximately 25 years (1990-2014). (Levira et al., 2017) The median mortality rate in PWE was estimated to be 19.8 (95% CI: 16.7–23.5) deaths per 1000 person-years; 2.6 times higher than mortality rate of the general population (Levira et al., 2017). The review also indicated substantial uncertainties in estimates of excess mortality in PWE in sub-Saharan Africa and other LMICs. Using standard definitions and methodology, this study provides evidence of excess mortality of a magnitude of 5 times greater in people diagnosed with active convulsive epilepsy, compared to the general population in large community/population-based surveys in sub-Saharan Africa. The estimates are approximately twice of what has been previously reported in the literature. This study also identified sub-populations of PWE with greater excess mortality than the overall mortality in PWE and identified potentially modifiable risk factors for mortality in PWE.

In high income countries (HICs), mortality in PWE is higher than general population; however the magnitude is lower than estimates observed in this study (Forsgren et al., 2005b). In studies conducted in HICs, excess mortality as estimated through Standardized Mortality Ratio (SMR) was 1.3-3 times higher in population-based studies.(Thurman et al., 2016b) In clinical settings, mortality in PWE was much higher, especially in children where mortality was 7 times higher than general population (Thurman et al., 2016b). Other studies in developed countries have observed no change over time in both epilepsy mortality rate and excess mortality in PWE compared to general population (Neligan et al., 2010).

The estimates of excess mortality in PWE were comparable across the three sub-Saharan African countries. These results were expected given the observed similarity in high epilepsy treatment gaps, population attributable risk factors and clinical features in the studied population (Hunter et al., 2016, Kariuki et al., 2014, Ba-Diop et

al., 2014a, Newton et al., 2012a). Extended follow-up duration in Agincourt (from 4 to 7.4 years) and Kilifi (from 2.7 to 8 years) did not significantly change previous mortality in epilepsy and excess mortality (Ngugi et al., 2014a, Wagner et al., 2015). These findings indicate there are stable, but increased, mortality rates in PWE compared to the population without epilepsy in Agincourt and Kilifi cohorts.

Risks factors analysis

Risk factors for excess mortality in PWE include behaviors, health conditions and characteristics or exposures that increase than usual the probability of death. Convulsive seizures are the most important risk factor for excess mortality associated with traffic accidents, burns, falls, or drowns (Strauss et al., 2003). Poor access to anti-epileptic drug (AED), seizures frequency, age onset of epilepsy, adverse perinatal events, and pre-existing health conditions such as cognitive and motor impairment are some of the risk factors for excess mortality in PWE (Ngugi et al., 2014a). Certain risk factors can be modifiable, meaning; health interventions can significantly reduce excess mortality in PWE such as reducing seizures frequency through increased access to AED. Some risk factors are associated with both occurrence of epilepsy and excess mortality, including but not limited to, specific epilepsy etiology such as parasitic infections, adverse perinatal events, cerebrovascular diseases, and road traffic injuries. Identifying and preventing these risk factors is expected not only reduce excess mortality in PWE but prevent the development of epilepsy.

This study identified overall and site-specific risk factors for excess mortality in PWE. We identified social and demographic factors, clinical, clinical historical conditions, as well as cerebral activities related to excess mortality in PWE. It is worth noting that a substantial number of factors were found to be associated with having epilepsy and risk factors for excess mortality. These factors include; adverse perinatal events,

history of head injuries, illiterate, poor hygienic practices (eating soil), and cerebrovascular diseases. Mitigating these factors has the potential to reduce epileptogenic and excess mortality concurrently.

Social and demographic factors

Males were observed to experience higher mortality than females in this study; however, the reasons behind these differences have not well researched. Some studies have linked the differences to the different etiologies of epilepsy (Engberg Aa et al., 2001). Epilepsy in females are more idiopathic and generalized while in symptomatic and localized epilepsies are more common in males. Individuals with regular alcohol consumption were observed to experience high mortality, possibly due to high exposure to accident-related injuries. The increased mortality in adults or mothers of children with epilepsy who were illiterate is possibly a consequence of epilepsy on social demographic indicators. PWE who are educated are more likely to be well informed about their condition hence avoid misconceptions that may increase their risks of premature mortality. Educating PWE may also lead to participation in less risky jobs activities such as teaching and customer care compared to high risky jobs such as driving and physical labor. Higher mortality rates were observed among individuals who were divorced/separated/widowed than married. These findings demonstrate the negative social and psychological consequence of epileptic seizures. These individual are more likely to be suffering from psychosocial disabilities as a result of difficulties in social interaction (Sperling, 2004). High mortality in those in households with cats may be linked to severe brain complications caused by households contamination of pork (*Taenia solium, T. multiceps*) and cat (*Toxoplasma gondii*) tapeworms (Wagner et al., 2009). Eating soil or geophagia is an ancient practice in Africa and other parts of the world believed to be associated with psychiatric

disorders, culture, poverty, famine, and mineral deficiency in pregnant women (Woywodt et al., 2002). Regardless of the reasons for the practice, eating soil has been linked with soil-transmitted parasites some of which are responsible for epilepsy (Wagner et al., 2009, Kind et al., 2017). Limited to access to comprehensive health care during delivery, such as resuscitation and caesarean, may result in epilepsy cases with severe brain damage and increased risk of mortality compared to normal deliveries. Antenatal and perinatal events such as obstructed labor, difficulties breathing and crying have been well described in the literature as risk factors of severe form of childhood epilepsies in LMIC (Burton et al., 2012a) and have been found to be risk factors for death in this study.

Clinical history

High mortality in people with onset of epilepsy at older ages indicates that the etiology of epilepsy may be linked to cerebrovascular diseases, parasitic infections and accidents/cerebra trauma (Diop et al., 2005a, Brodie et al., 2005, Shorvon, 2011). In study areas where the epilepsy treatment gap is high, a positive association between seizure frequency and mortality was expected especially in those with daily seizure, seizure occurring both day and night, and in PWE having more than 12 seizures per year. Reducing seizure frequency and severity by expanding treatment with AED may be an effective approach in reducing both epilepsy and accident related causes of death in PWE (Strauss et al., 2003, Sperling, 2004).

Clinical examination

Co-morbidities with neurological disorders such as cardiovascular and cerebrovascular diseases have been observed to increase mortality in PWE in many developed countries as observed in this study (Forsgren et al., 2005b). Co-morbidities with motor and cognitive impairment were also found to be associated with an

increased mortality in PWE in this study as well as sickle cell disease. Addressing these co-morbidities could be effective in reducing premature mortality in epilepsy (Keezer et al., 2016). Premature mortality in PWE could be prevented by streamlining interventions targeting management of severe cases of neurological disorders and infections as well as severe cases of status epilepticus (Munyoki et al., 2010, Malek et al., 2016, Gilmore et al., 2015). Preventive measures against accidents (head injuries) which were also associated with higher mortality in PWE could reduce the incidence of epilepsy associated with cerebrovascular accidents. Excessive snoring is one factor found to be more common in people with epilepsy than healthy individuals (Im et al., 2016). Snoring is thought to be strongly associated with sleep apnea, a dangerous condition that, when untreated, can lead to death. We observed high mortality in PWE who were snoring more than 3 nights per week. Several studies suggest that up to 70% of SUDEP occurred during sleep (Ali et al., 2017). There is limited information on causes of sleep disorders in PWE but contribution of certain AED, seizures, and various epilepsy syndromes are likely (Bazil, 2017).

EEG

Generalized slowing of brain functions is often observed in PWE and is indicative of diffuse brain dysfunction. Severe abnormal EEG has been liked to increased seizures frequency. In this study, PWE with severe abnormal EEG features were observed to experience a higher mortality compared to those with normal EEG features. These results are consistent with other studies that linked abnormal EEG features in PWE with higher seizure recurrence (Moran et al., 2004). These findings demonstrate the need for health system's investment in targeted EEG that will be essential in early identification of individual at risk of premature mortality not only in PWE but also in people with other neurological disorders (Phabphal et al., 2013) Other forms of

diagnosis such as prolonged implantable electrocardiography monitoring may be potential in reducing a high rate of misdiagnosis of epilepsy (Petkar et al., 2012).

Limitations

Based on our current knowledge, the SEEDS project is the largest, standardized population-based study of prevalence and mortality in PWE in sub-Saharan Africa. This study accounted for common and major methodological limitations such as epilepsy definition, cases identification, and mortality ascertainment previously identified in the epidemiological literature on epilepsy in sub-Saharan Africa (Ba-Diop et al., 2014a, Preux et al., 2005a, Logroscino et al., 2005). The focus on ACE in this study limits the ability to fully determine the excess mortality in PWE in sub-Saharan Africa. However, the choice to focus on ACE was due to the difficulty in ascertaining non-convulsive, non-active cases of epilepsy.

Conclusions

This study provides evidence of excess mortality, with a pooled magnitude of mortality 5 times greater in PWE compared to those without epilepsy in sub-Saharan Africa. These findings indicate that PWE in sub-Saharan Africa are at substantially greater risk of death than people without epilepsy. In this study, we identified sub-populations and risk factors of excess mortality in PWE that could potentially mitigate the development of epilepsy and the increased mortality. These findings suggest that the mortality in PWE may be reduced by implementing interventions that strengthen clinical management of epilepsy, including better access to AED, reducing adverse perinatal events with improved care at birth, implementing community preventive measures against accidents, introducing behavior changes such as that of eating soil, properly managing parasitic infections in both human and domestic animals,

increasing access to education to PWE, empowering PWE with employment and adequately managing co-morbidities such as cerebrovascular, cardiovascular, and motor and cognitive impairment.

Supporting information

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate* (95%Confidence Interval)		
Females	22.52 (13.58-37.36)	21.38 (13.80-33.14)	24.96 (18.97-32.84)
Males	47.82 (33.82-67.63)	26.12 (17.36-39.31)	27.11 (20.96-35.07)
Facility deliveries	20.65 (8.60-49.62)	22.33 (12.68-39.33)	15.73 (6.55-37.79)
Home deliveries	13.58 (1.91-96.42)	16.13 (7.25-35.91)	16.57 (11.84-23.19)
Seizure history in family	39.19 (5.52-278.21)	46.92 (6.61-333.07)	28.24 (17.02-46.84)
Seizure in family	22.76 (8.54-60.65)	20.10 (10.05-40.18)	33.43 (22.21-50.30)
Head injury	111.82 (63.51-196.90)	55.05 (20.66-146.68)	29.65 (18.16-48.39)
Recent hospital admission	41.06 (24.32-69.33)	30.27 (20.61-44.46)	27.24 (21.62-34.32)
Eat cassava	35.89 (25.38-50.75)	23.22 (15.81-34.10)	24.29 (19.59-30.13)
Eat soil	38.55 (26.95-55.13)	32.08 (20.92-49.20)	35.22 (27.82-44.59)
Dog in the household	52.80 (32.82-84.93)	25.02 (18.13-34.53)	25.86 (18.47-36.19)
Cat in the household	86.52 (32.47-230.53)	23.80 (17.39-32.58)	27.56 (21.44-35.42)

*Mortality rate per 1000 person years

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate* (95%Confidence Interval)		
Eat pork	53.52 (31.70-90.37)	18.98 (12.61-28.56)	30.12 (20.79-43.62)
Snore > 3 nights a week	33.18 (22.75-48.38)	28.20 (18.90-42.07)	29.49 (23.45-37.10)
BMI <18	17.16 (2.42-121.80)	16.17 (6.07-43.09)	13.60 (8.05-22.96)
BMI 18-24	24.90 (6.23-99.57)	11.97 (4.49-31.89)	21.72 (12.87-36.68)
BMI 25-30	55.38 (28.82-106.44)	28.39 (15.72-51.26)	29.05 (20.06-42.08)
BMI 30+	37.81 (25.93-55.14)	21.90 (13.62-35.24)	27.38 (19.92-37.62)
Adult specific risk factors			
Adult marital status			
Single	17.74 (9.23-34.09)	36.34 (21.91-60.28)	33.92 (24.36-47.25)
Married	59.48 (36.98-95.68)	15.17 (6.82-33.77)	35.41 (23.31-53.77)
Divorced/separated/widow	63.43 (37.56-107.09)	46.34 (17.39-123.46)	73.14 (42.47-125.96)
Illiterate adult	77.97 (49.12-123.75)	44.94 (25.52-79.13)	42.05 (30.72-57.55)
Alcohol consumption	101.39 (56.15-183.08)	20.62 (7.74-54.93)	41.72 (21.71-80.18)

BMI: Body mass index (Kg/m^2), *Mortality rate per 1000 person years

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95%Confidence Interval)		
Child specific risk factors			
Maternal marital status			
Married	7.58 (1.07-53.83)	19.28 (11.63-31.99)	14.28 (9.86-20.69)
Single	30.01 (11.27-79.97)	12.48 (1.76-88.57)	45.79 (11.45-183.10)
Divorced/separated/widow	18.13 (2.55-128.72)	31.58 (7.90-126.28)	27.35 (13.68-54.69)
Unemployed mother	21.62 (9.00-51.94)		16.61 (10.32-26.72)
Illiterate mother	58.37 (8.22-414.34)	16.52 (5.33-51.24)	17.73 (11.78-26.69)
Mother's history of seizure			56.34 (14.09-225.27)
Delivery problem-Mothers	68.06 (17.02-272.14)	23.64 (5.91-94.51)	18.11 (8.14-40.32)
Difficulties crying after birth	33.87 (4.77-240.47)	51.55 (19.35-137.34)	18.98 (6.12-58.86)
Difficulties breathing after birth		49.41 (15.94-153.20)	23.01 (5.75-92.00)
Incomplete immunization	38.11 (5.37-270.55)		20.26 (5.07-80.99)

*Mortality rate per 1000 person years

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95%Confidence Interval)		
Clinical history			
Age onset 0-5	24.52 (13.19-45.57)	26.32 (16.98-40.79)	20.03 (15.30-26.22)
Age onset 6-12	18.15 (7.55-43.60)	15.72 (7.06-34.98)	26.68 (16.35-43.56)
Age onset 13-18	19.26 (6.21-59.70)	14.74 (5.53-39.28)	25.40 (13.22-48.82)
Age onset 19-28	52.04 (26.03-104.07)	23.37 (8.77-62.27)	33.29 (16.65-66.57)
Age onset 29+	68.33 (42.48-109.91)	48.08 (22.92-100.86)	65.78 (42.89-100.88)
Sickle cell disease			191.68 (47.94-766.43)
< 12 seizure per year	38.18 (27.00-53.98)	13.79 (7.64-24.91)	20.35 (15.38-26.92)
> 12 seizure per year	27.98 (15.05-52.00)	33.38 (20.45-54.48)	22.02 (14.21-34.14)
Seizure type-Generalized	37.99 (25.87-55.79)	21.55 (13.74-33.78)	25.80 (17.69-37.62)
Seizure type-Focal	36.11 (23.30-55.97)	26.55 (15.72-44.82)	27.14 (21.68-33.98)
Seizure type-Others			31.61 (14.20-70.36)

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95%Confidence Interval)		
Untreated with AED	26.17 (14.86-46.08)	20.09 (12.82-31.50)	23.63 (18.23-30.63)
Number of different type of seizure-1	36.80 (26.78-50.58)	24.05 (17.27-33.50)	25.82 (20.95-31.82)
Number of different type of seizure-2	21.75 (9.05-52.25)	26.29 (13.15-52.58)	26.90 (17.35-41.70)
Number of different type of seizure-3			101.46 (14.29-720.26)
Seizure frequency-Daily	31.06 (10.02-96.31)	41.48 (22.97-74.90)	44.37 (29.49-66.78)
Seizure frequency-Monthly	43.45 (29.80-63.36)	26.76 (18.48-38.76)	23.77 (16.99-33.27)
Seizure frequency-Weekly	31.02 (7.76-124.04)	7.19 (1.01-51.05)	40.36 (25.75-63.28)
Seizure time-Day & Night	41.22 (28.64-59.31)	26.71 (19.18-37.20)	31.48 (25.36-39.09)
Seizure time-Day	30.33 (17.22-53.41)	6.52 (0.92-46.26)	18.24 (12.12-27.45)
Seizure time-Night	24.61 (10.24-59.13)	18.95 (8.51-42.18)	12.75 (4.78-33.97)

AED: Antiepileptic drug

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95% Confidence Interval)		
Imaging			
EEG general background			
Mild	43.62 (24.16-78.77)	28.50 (12.81-63.44)	22.03 (13.49-35.95)
Moderate	30.54 (4.30-216.78)	24.20 (7.81-75.05)	11.00 (2.75-43.97)
Normal	30.90 (19.94-47.90)	19.64 (10.88-35.46)	20.81 (15.01-28.85)
Severe	96.44 (40.14-231.71)	28.55 (4.02-202.67)	44.16 (25.08-77.76)
EEG Asymmetry	35.20 (11.35-109.14)	31.83 (4.48-225.96)	21.59 (3.04-153.29)
EEG Focal feature	39.79 (26.44-59.87)	16.92 (7.60-37.65)	27.81 (17.74-43.60)
EEG epileptiform activity	53.28 (30.94-91.76)	10.88 (4.08-28.99)	18.21 (11.62-28.55)
EEG Focal temporal	50.14 (27.77-90.55)	13.73 (5.15-36.58)	25.55 (16.30-40.06)
EEG Focal extra temporal	49.24 (25.62-94.64)	10.54 (3.40-32.68)	16.38 (9.30-28.85)
EEG involve Temporal lobe	62.95 (26.20-151.25)	12.23 (3.06-48.90)	30.03 (16.63-54.23)

EEG: Electroencephalogram

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95%Confidence Interval)		
EEG Generalized	114.68 (16.15-814.11)		20.73 (8.63-49.81)
EEG photosensitivity: abnormal	29.90 (4.21-212.26)	59.64 (22.38-158.91)	17.20 (4.30-68.76)
EEG hyperventilation: abnormal	26.77 (8.63-83.00)	10.16 (1.43-72.16)	
EEG Summary-Abnormal	43.05 (28.07-66.03)	21.95 (12.47-38.65)	23.95 (17.63-32.53)
EEG Summary-Normal	26.94 (13.47-53.87)	21.11 (10.56-42.21)	22.00 (14.98-32.32)
EEG Summary-Undetermined	34.60 (16.49-72.57)		
Clinical features and examination			
Falls to the ground during seizure	42.58 (31.36-57.83)	23.88 (17.07-33.43)	25.85 (21.05-31.74)
Seizure duration-10 min+	24.16 (6.04-96.62)	25.33 (12.67-50.66)	32.50 (24.42-43.26)
Seizure duration-5-9 minutes	29.84 (11.20-79.50)	23.81 (15.00-37.79)	20.83 (14.28-30.37)
Seizure duration-< 5 minutes	41.98 (30.79-57.23)	24.04 (13.65-42.33)	22.98 (16.06-32.86)

EEG: Electroencephalogram

Table S1: Estimates of mortality rate in PWE per 1000 person years by site and risk factors continue

Risk factors	Agincourt	Ifakara	Kilifi
	Mortality rate (95%Confidence Interval)		
No BCG vaccine scar	30.67 (15.96-58.94)	16.67 (5.38-51.68)	38.01 (27.16-53.20)
Burn marks	60.32 (34.26-106.21)	28.45 (13.56-59.67)	33.36 (23.18-48.00)
Systolic blood pressure: > 140	73.59 (44.37-122.07)	75.72 (31.52-181.92)	63.92 (42.48-96.19)
Diastolic blood pressure: > 90	71.62 (42.42-120.93)	61.83 (23.21-164.74)	76.83 (47.76-123.58)
Pre-existing neurological	41.49 (25.79-66.74)	48.95 (27.11-88.38)	45.26 (31.83-64.36)
Cognitive impairment	49.31 (30.65-79.31)	41.88 (21.79-80.50)	49.16 (36.58-66.06)
Motor impairment	28.35 (12.74-63.10)	81.17 (33.79-195.01)	56.67 (41.57-77.25)
Previous status epilepticus		47.03 (15.17-145.81)	23.63 (16.88-33.07)
Febrile seizure			21.08 (14.13-31.44)
History of encephalopathy		58.66 (8.26-416.40)	22.25 (14.65-33.79)
History of febrile seizure	47.58 (17.86-126.78)	16.95 (8.47-33.88)	19.13 (13.03-28.10)

BCG: Bacillus Calmette–Guérin

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Overall	3.21 (2.41-4.27)	4.66 (3.46-6.29)	6.22 (5.15-7.50)
Females	1.80 (1.09-2.99)	4.22 (2.72-6.54)	5.96 (4.53-7.84)
Males	5.07 (3.59-7.17)†	5.14 (3.41-7.73)	6.49 (5.02-8.40)
Facility deliveries	13.10 (5.45-31.48) †	11.56 (6.57-20.36) †	15.86 (6.60-38.11) †
Home deliveries	10.59 (1.49-75.16)	7.76 (3.48-17.26) †	17.39 (12.43-24.3)†
Seizure history in family	4.24 (0.60-30.12)	19.36 (2.73-137.46)	4.81 (2.90-7.97)
Seizure in family	1.86 (0.70-4.97)	3.60 (1.80-7.20)	8.27 (5.49-12.44) †
Head injury	8.63 (4.90-15.20) †	5.10 (1.92-13.60)	4.68 (2.87-7.64) †
Recent hospital admission	3.35 (1.99-5.66)	5.58 (3.80-8.20) †	7.50 (5.95-9.45) †
Eat cassava	2.85 (2.02-4.03)	4.50 (3.06-6.61)	5.96 (4.81-7.39)
Eat soil	2.72 (1.90-3.89)	4.31 (2.81-6.61)	5.49 (4.34-6.95)
Dog in the household	4.08 (2.53-6.56) †	4.89 (3.54-6.74) †	6.05 (4.32-8.46)
Cat in the household	7.30 (2.74-19.46) †	4.77 (3.49-6.53) †	6.23 (4.85-8.00)

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Eat pork	4.44 (2.63-7.50) †	3.62 (2.41-5.45)	4.53 (3.13-6.56)
Snore > 3 nights a week	2.70 (1.85-3.94)	5.33 (3.57-7.95) †	6.74 (5.36-8.48) †
BMI <18	10.53 (1.48-74.74)	5.53 (2.07-14.73)	14.25 (8.44-24.06) †
BMI 18-24	13.48 (3.37-53.91) †	3.86 (1.45-10.29)	13.99 (8.28-23.62) †
BMI 25-30	5.18 (2.69-9.95) †	5.68 (3.14-10.25)	4.94 (3.41-7.15)
BMI 30+	3.13 (2.15-4.57)	3.52 (2.19-5.66) †	4.25 (3.09-5.84)
Adult specific risk factors			
Adult marital status			
Single	1.91 (0.99-3.67)	7.22 (4.35-11.98) †	12.44 (8.93-17.32) †
Married	3.86 (2.40-6.21)	1.72 (0.77-3.84)	2.43 (1.60-3.70)
Divorced/separated/widow	2.77 (1.64-4.68)	2.20 (0.83-5.86)	3.82 (2.22-6.57)
Illiterate adult	4.20 (2.65-6.67) †	4.21 (2.39-7.41)	3.76 (2.75-5.14)
Adult consuming alcohol	4.86 (2.69-8.77) †	2.07 (0.78-5.51)	2.46 (1.28-4.73)

BMI: Body mass index (Kg/m^2),

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Child specific risk factors			
Maternal marital status			
Married	5.34 (0.75-37.89)	9.69 (5.84-16.07) †	14.89 (10.28-21.5) †
Single	18.51 (6.95-49.31) †	7.91 (1.11-56.13)	45.87 (11.4-183.4) †
Divorced/separated/widow	12.69 (1.79-90.08)	11.97 (2.99-47.88)	29.11 (14.56-58.2) †
Unemployed mother	15.74 (6.55-37.82) †		17.20 (10.69-27.6) †
Illiterate mother	39.45 (5.56-280) †	9.62 (3.10-29.82)	18.87 (12.54-28.3) †
Mother's history of seizure			61.25 (15.3-244.9) †
Delivery problem-Mothers	28.61 (7.15-114.3) †	9.94 (2.49-39.74)	18.60 (8.36-41.41) †
Difficulties crying after birth	12.99 (1.83-92.24)	20.10 (7.54-53.56) †	20.14 (6.49-62.43) †
Difficulties breathing after birth		17.55 (5.66-54.42) †	25.02 (6.26-100.0) †
Incomplete immunization	21.25 (2.99-150.8) †		21.59 (5.40-86.32) †

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Clinical history			
Age onset 0-5	4.46 (2.40-8.28)	9.45 (6.10-14.65) †	12.65 (9.66-16.55) †
Age onset 6-12	2.36 (0.98-5.67)	6.37 (2.86-14.18)	10.25 (6.28-16.73) †
Age onset 13-18	2.00 (0.64-6.19)	3.19 (1.20-8.49)	6.51 (3.39-12.52) †
Age onset 19-28	3.51 (1.75-7.01)	3.59 (1.35-9.57)	5.16 (2.58-10.31) †
Age onset 29+	3.10 (1.93-4.99)	2.25 (1.07-4.71)	2.47 (1.61-3.78)
Sickle cell disease			200.0 (50.0-799.9) †
< 12 seizure per year	3.85 (2.72-5.45) †	2.45 (1.36-4.43)	4.06 (3.07-5.37)
> 12 seizure per year	2.06 (1.11-3.84)	5.45 (3.34-8.89)	5.99 (3.87-9.29)
Seizure type-Generalized	3.43 (2.34-5.04)	4.11 (2.62-6.44)	4.35 (2.98-6.34)
Seizure type-Focal	3.14 (2.02-4.86)	5.78 (3.42-9.75)	7.24 (5.78-9.06) †
Seizure type-Others			10.63 (4.78-23.66)

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Untreated with AED	2.81 (1.59-4.94)	3.36 (2.15-5.27)	6.29 (4.85-8.15)
No of different type of seizure-1	3.23 (2.35-4.44)	4.37 (3.14-6.09)	5.87 (4.76-7.23)
No of different type of seizure-2			19.53 (2.75-138.65)
No of different type of seizure-3	2.31 (0.96-5.56)	8.58 (4.29-17.15) †	8.38 (5.41-12.99) †
Seizure frequency-Daily	2.84 (0.92-8.81)	12.61 (6.98-22.77) †	21.05 (13.9-31.67) †
Seizure frequency-Monthly	3.63 (2.49-5.29) †	4.49 (3.10-6.51)	5.54 (3.96-7.75)
Seizure frequency-Weekly	2.31 (0.58-9.23)	2.08 (0.29-14.73)	15.69 (10.0-24.5) †
Seizure time-Day & Night	3.46 (2.41-4.98)	5.25 (3.77-7.32)	7.81 (6.29-9.70) †
Seizure time-Day	3.26 (1.85-5.74)	2.09 (0.29-14.82)	4.46 (2.96-6.71)
Seizure time-Night	2.36 (0.98-5.66)	3.09 (1.39-6.87)	2.20 (0.82-5.85)

AED: Antiepileptic drug

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Imaging			
EEG general background			
Mild	2.66 (1.47-4.81)	6.06 (2.72-13.49)	8.82 (5.40-14.40) †
Moderate	4.33 (0.61-30.70)	8.26 (2.66-25.62)	3.77 (0.94-15.09)
Normal	2.73 (1.76-4.23)	3.33 (1.84-6.01)	3.78 (2.73-5.24)
Severe	16.76 (6.97-40.26) †	14.37 (2.02-102.04)	21.21 (12.0-37.3) †
EEG Asymmetry	3.94 (1.27-12.21)	19.37 (2.73-137.53)	13.80 (1.94-97.98)
EEG Focal feature	3.35 (2.22-5.03)	3.44 (1.55-7.66)	7.04 (4.49-11.04)
EEG epileptiform activity	5.41 (3.14-9.32) †	3.26 (1.22-8.68)	6.55 (4.18-10.26)
EEG Focal temporal	5.00 (2.77-9.03) †	4.31 (1.62-11.47)	8.03 (5.12-12.58) †
EEG Focal extra temporal	5.26 (2.74-10.11) †	3.21 (1.03-9.94)	5.63 (3.20-9.91)
EEG involve Temporal lobe	8.39 (3.49-20.15) †	4.17 (1.04-16.66)	10.79 (5.98-19.49) †

EEG: Electroencephalogram

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
EEG Generalized	38.84 (5.47-275.7) †		9.89 (4.11-23.75)
EEG photosensitivity: abnormal	2.10 (0.30-14.93)	31.67 (11.88-84.37)	13.08 (3.27-52.28)
EEG hyperventilation: abnormal	2.74 (0.88-8.50)	3.48 (0.49-24.68)	
EEG Summary-Abnormal	4.10 (2.67-6.28) †	4.45 (2.52-7.83)	6.93 (5.10-9.40)
EEG Summary-Normal	2.14 (1.07-4.28)	4.00 (2.00-7.99)	4.01 (2.73-5.89)
EEG Summary-Undetermined	2.21 (1.05-4.63)		
Clinical features and examination			
Falls to ground during seizure	3.55 (2.61-4.82) †	4.57 (3.26-6.39)	5.92 (4.82-7.27)
Seizure duration-10 min+	2.74 (0.69-10.98)	6.68 (3.34-13.36)	7.45 (5.60-9.91) †
Seizure duration-5-9 minutes	2.97 (1.11-7.91)	4.03 (2.54-6.39)	4.17 (2.86-6.08)
Seizure duration-< 5 minutes	3.57 (2.62-4.87) †	6.87 (3.90-12.09) †	7.13 (4.99-10.20)
No BCG vaccine scar	4.10 (2.13-7.87)	2.63 (0.85-8.15)	3.28 (2.34-4.59)

EEG: Electroencephalogram, BCG: Bacillus Calmette–Guérin

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Table S2: Standardized mortality ratio of death in PWE by risk factors and site

Risk factors	Agincourt	Ifakara	Kilifi
	Standardized Mortality Ratio (95%Confidence Interval)		
Burn marks	3.93 (2.23-6.91)	5.25 (2.50-11.01)	8.21 (5.71-11.82) †
Systolic blood pressure: > 140	3.60 (2.17-5.97)	3.86 (1.61-9.28)	4.16 (2.76-6.26)
Diastolic blood pressure: > 90	3.25 (1.92-5.48)	3.15 (1.18-8.39)	8.29 (5.16-13.34) †
Pre-existing neurological	3.54 (2.20-5.70)	10.94 (6.06-19.75) †	15.35 (10.80-21.8) †
Cognitive impairment	4.32 (2.69-6.96) †	9.80 (5.10-18.84) †	24.38 (18.14-32.7) †
Motor impairment	2.61 (1.17-5.81)	24.76 (10.31-59.4) †	18.77 (13.77-25.5) †
Previous status epilepticus		14.48 (4.67-44.90) †	11.44 (8.17-16.0) †
Febrile seizure			12.78 (8.56-19.0) †
History of encephalopathy		20.02 (2.82-142.09)	13.05 (8.59-19.8) †
History of febrile seizure	14.95 (5.61-39.83) †	6.00 (3.00-11.99)	11.73 (7.99-17.23) †

† Statistically significant different from the overall site estimate (Based on non-overlapping confidence intervals)

Causes of death in epilepsy: Estimates and implication in using physicians and automated diagnosis of verbal autopsies in sub-Saharan Africa

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Abstract

Background

Despite being the most affordable alternative, most countries in SSA opt not to use VA due to financial and human resources constrains. Probabilistic and mathematical-based models have recently emerged as convenient and affordable alternative to physician in assigning causes of death in developing countries.

Objective

This study assess the design, process and output of InterVA-4 in ascertaining possible causes of death in people diagnosed with epilepsy in Studies of Epidemiology of Epilepsy in sub-Saharan Africa (SEEDS).

Methods

We reviewed the InterVA-4 model assessing key issues relevant to accuracy in predict causes of death in epilepsy specifically on signs, symptoms, and conditions, unconditional probabilities for causes of death, conditional probabilities for indicators and pre-defined list of causes of death.

Results

The assessment indicated that, InterVA-4 produces valuable data on causes of death statistics in PWE. Four area of improvements include; i) revising probabilities of signs and symptoms related to injuries, accidents, children, and depression, ii) creating separate categories for SE and SUDEP, iii) incorporating text mining technique techniques in capturing signs and symptoms that may be narrated on circumstances occurred prior to death as described by caretakers, and iv) proper training to interviewer on filling VA forms.

Conclusion

Regular updates of the model is critical when more knowledge on risk factors for epilepsy are premature mortality are generated.

Keywords: Epilepsy, text mining, verbal autopsy, InterVA-4, SUDEP, SE

Background

With nearly 75% of deaths happen at home and never get to the hospital for post-mortem investigation, causes of death statistics is nearly impossible to produce in most SSA countries (Jha, 2014). Verbal autopsy (VA) provides convenient and affordable alternative to post-mortem in producing causes of death statistics in most limited resources countries. Cause of death assignment for every death is normally certified with two independent trained physicians and in some cases a third physician is called in case of disagreement.

With considerable limited resources, most SSA countries do not opt for death certification with VA as it require field VA interviewer and the use of multiple physicians to certify every death through time demanding review of VA questionnaires. Probabilistic and mathematical-based models have recently emerged as convenient and affordable alternative to physician in assigning causes of death in developing countries (Garenne, 2014). The most popular models that have rigorously reviewed and validated are Inter-VA, Random Forest, Tariff, Simplified Symptom Pattern (SSP) and King-Lu (Desai et al., 2014, Murray et al., 2014). The methods take use of signs, symptoms, and circumstances occurred prior to death and automatically determine probable causes of death at population level.

Due to the growing use of these automatic models especially in Health and Demographic Surveillance System (HDSS) and other research settings, it is essential to understand their reliability and performance in accurately producing causes of death in the population. Murray's publication compared automated models with 12,535 death cases from diverse populations for which the true cause of death had been clinically established and concluded that Tariff, SSP, and RF outperformed physician coding in

different sub-population and for the majority of causes of death investigated (Murray et al., 2014).

Causes of death statistics are valuable public health tools needed in developing effective preventative measures aimed at reducing premature mortality in people with epilepsy PWE (Mu et al., 2011a). Critical to epilepsy is estimating epilepsy-related mortality rate as it is closely linked to access to care and treatment in PWE. The most relevant epilepsy-related causes of death accounting for majority deaths are in PWE are status epilepticus (SE), sudden unexplained death in epilepsy (SUDEP) and injuries (Walker, 1972, Gilmore et al., 2015). Epilepsy-related cause's accounts for majority of death in PWE epilepsy in SSA compared to developed country possibly due to low coverage of interventions such as antiepileptic drugs (AED) aimed at managing epileptic seizures (Ngugi, 2012).

Several studies have VA process in estimating neurological-related causes of deaths in LMIC focusing among others on epilepsy, stroke and cerebrovascular diseases (Mateen et al., 2012). To our best knowledge, there has been no study that has critically accessed the applicability of automated tools in accurately predicting causes of death in PWE.

This article assess the design, process and output of InterVA-4 in ascertaining possible causes of death in people diagnosed with epilepsy in Studies of Epidemiology of Epilepsy in sub-Saharan Africa (SEEDS). The decision to assess InterVA-4 model is based on the fact that SEEDS sites and most HDSS sites are currently using the software for research purpose with substantial number of staff being trained on its application (Murray et al., 2014).

Methods

Study settings and populations

SEEDS studies were designed to systematically collect comparable data on the prevalence and mortality of active convulsive epilepsy (ACE) in population-based house-to-house surveys (Ngugi et al., 2013a). The study populations were living in poor rural districts of Ifakara in Tanzania (Geubbels et al., 2015), Agincourt in South Africa (Kahn et al., 2012), and Kilifi in Kenya (Scott et al., 2012). Cohort of 1,308 people identified with ACE are reported in this study; 366 in Ifakara, 245 in Agincourt, and 697 in Kilifi (Scott et al., 2012). The cohorts have been under HDSS's continuous surveillance since diagnosis with the median follow-up durations of 7, 6 and 8 years in Agincourt, Ifakara and Kilifi, respectively.

Mortality assessment and verbal autopsy

Mortality assessment is conducted during continuous surveillance of updates of demographic events routinely implemented 1-3 times annually. Cause of death is ascertained using verbal autopsy (VA) because post-mortem examinations are not conducted in most LMIC (Sankoh et al., 2014a, Mikkelsen et al., 2015). VA involves in-depth structured interviews of the care taker of the diseased on signs, symptoms, conditions and health-seeking choices prior to death using structured questionnaires. Standard VA questionnaires adopted from World Health Organization (WHO) used in all study sites (World Health Organization, 2004). Questionnaires are further reviewed by trained physicians who at the end of process assign the cause of death using International Disease Classification version 10 (ICD10) (World Health Organization, 2004).

InterVA-4 model

InterVA-4 model is designed to produce causes of death using probability theorem conceived by Bayes (Bayes, 1991). Bayes' theorem provides the probability of death from a particular cause (an event), based on symptom preceding death (prior knowledge) that might be associated to that cause. We describe the description of the theorem as detailed in the original article on the recent InterVA-4 model(Byass et al., 2012). If C_i represent a causes of death and I_j symptoms, then, probability of death from cause i condition of observing j symptom is defined as;

$$P(C_i|I_j)=\frac{P(I_j|C_i)\times P(C_i)}{P(I_j|C_i)\times P(C_i)+P(I_j|!C_i)\times P(!C_i)}$$

where $P(!C_i)=1-P(C_i)$.

Using a normalizing assumption, probabilities for each cause can be calculated such that conditional probability over all causes totals to 1:

$$P(C_i|I_j)=\frac{P(I_j|C_i)\times P(C_i)}{\sum_{i=1}^{m} P(C_i)}$$

Using an initial set of unconditional probabilities for causes of death $P(C_i)$ (also can be denoted as $P(C_i/I_0)$ and a matrix of conditional probabilities for indicators $P(I_j/C_i)$, it is possible to repeatedly apply the same calculation process for each indicator ($I_1 \ldots I_n$) that applies to a particular death:

$$P(C_i|I_{1\ldots n})=\frac{P(I_j|C_i)\times P(C_i|I_{0\ldots n-1})}{\sum_{i=1}^{m} P(C_i|I_{0\ldots n-1})}$$

Model assessment

We reviewed the InterVA-4 model assessing key issues relevant to accurately predict causes of death in epilepsy specifically on symptoms $I_1 \ldots I_n$, unconditional probabilities for causes of death $P(C_i/I_0)$, conditional probabilities for indicators $P(I_j/C_i)$ and pre-defined causes of death list $C_i \ldots C_m$.

Results

Recent mortality status of PWE in SEEDS cohort is summarized in Table 5-1. During mortality surveillance, overall 188 (14%) died; 43 (12%) in Ifakara, 39 (16%) in Agincourt and 109 (17%) in Kilifi. Causes of death from InterVA-4 were available in 167 (89%) deaths (Table 5-5).

Table 5-1: SEEDS residency and mortality status

	Agincourt	Ifakara	Kilifi	Total
Initial cohort size	**245**	**366**	**697**	**1,308**
Lost to follow-up	2	4	27	33
Final cohort				
Sex				
Males	128	171	340	639
Females	115	191	327	633
Age				
0-5	9	20	22	51
6-18	43	113	233	389
19-49	138	190	344	672
50+	53	39	71	163
Total	**243**	**362**	**670**	**1,275**
Residency status				
Alive	166	222	369	757
Out-migration	41	97	192	330
Deaths	**36**	**43**	**109**	**188**
Median follow-up (years)	7.4	6.3	8.6	

InterVA-4 accept 245 signs, symptoms, conditions, demographic status, and health care seeking practices from standard VA tools, preferably WHO VA instruments of the

year 2012. Signs, symptoms and conditions relevant to epilepsy were age, sex, history of epilepsy, sudden death, convulsions, convulsions that lasting for 10 or more minutes, mental confusion, depression and injuries.

Probabilities for sign and symptoms leading to death conditioning on disease status ($P(I_j/C_i)$) are estimated from a diversity of incomplete sources and moderated by expert opinion as there are no reliable source of data quantifying these probabilities. In case of expert opinion, meetings constituting expert of different discipline were convened to quantify relationships between indicators and causes. The latest scale of perceived probability is presented in Table 5-2.

Table 5-2: Qualitative probability scale used by expert

Label	Value	Interpretation
I	1	Always
A+	0.8	Almost always
A	0.5	Common
A-	0.2	
B+	0.1	Often
B	0.05	
B-	0.02	
C+	0.01	Unusual
C	0.005	
C-	0.002	
D+	0.001	Rare
D	0.0005	
D-	0.0001	
E	0.00001	Hardly ever
N	0	Never

Source: Glob Health Action 2012, 5

The highest probabilities (1-0.1) for sign and symptoms leading to death for people with epilepsy are described in Table 5-3. In the table, probabilities for convulsions and history of epilepsy were 1 in PWE. Probabilities for sudden death and convulsions lasted 10 minutes or more were considered high in PWE (0.8).

Table 5-3: Top probabilities of signs and symptoms in people with epilepsy

Signs, symptoms, conditions, demographic status	Probability	Label
History of epilepsy	1.00	Always
Convulsions	1.00	Always
Died suddenly	0.80	Almost always
Convulsions lasted 10 minutes or more	0.80	Almost always
Male	0.50	Common
Female	0.50	Common
Duration of final illness < 3 weeks	0.50	Common
Duration of final illness 3 weeks or more	0.50	Common
Dry season	0.50	Common
Headache	0.50	Common
Unconsciousness started suddenly	0.50	Common
Convulsions lasted less than 10 minutes	0.50	Common
Became unconscious immediately after convulsions	0.50	Common
Received vaccines as appropriate for age at death	0.50	Common
Age 65+ years	0.20	Common
Age 50-64 years	0.20	Common
Age 15-49 years	0.20	Common
Age 5-14 years	0.20	Common
Wet season	0.20	Common
Unconscious for at least 24 hours before death	0.20	Common
Cough lasting < 3 weeks	0.10	Often
Diarrhoea lasting < 2 weeks	0.10	Often
Discharged from hospital very ill	0.10	Often

Children under five, history of depression and mental confusion and accidents were assigned the least probabilities (Table 5-4).

Table 5-4: Least probabilities of signs and symptoms in people with epilepsy

Sign, symptom, condition, demographic status	Probability	Label
Age 1-4 years	0.02	Often
Age 1-11 months	0.02	Often
History of depression	0.005	Unusual
Mental confusion for more than 3 months	0.005	Unusual
History of mental confusion	0.002	Unusual
Suffered any injury or accident that lead to death	0.00001	Hardly ever
Road traffic accident	0.00001	Hardly ever
Injured in non-road transport accident	0.00001	Hardly ever
Accidental fall	0.00001	Hardly ever
Drowning	0.00001	Hardly ever
Burns	0.00001	Hardly ever
Violence/assault	0.00001	Hardly ever

The model is designed to produce 62 causes of deaths that are aligned with the International Classification of Diseases version 10 (ICD-10). Special category is assigned to deaths of unknown cause. SUDEP and SE are not separately included in the list of causes of death. One category is assigned to all epilepsy deaths which was equivalent to ICD10 codes for epilepsy (G40) and status epilepticus (G41). Analysis of deaths in PWE resulted in 19 causes of deaths of death, where 46 were directly or indirectly related to epilepsy and 121 were unrelated to epilepsy (Table 5-5).

Proportion of death attributable to epilepsy (proportionate mortality ratio) (PMR) was estimated at 14.4%. There were more epilepsy-unrelated deaths (PMR=72.5%) compared to epilepsy-related death (PMR=27.5%). Epilepsy and accidents accounted for 14.4% and 13.1% of all epilepsy-related deaths. The leading causes of epilepsy-unrelated death were HIV/AIDS related death (13.8%), neoplasm (11.4%), stroke (6.6%), and acute cardiac diseases (5.4%).

Table 5-5: Causes of deaths in people with epilepsy in SEEDS cohort

Epilepsy-related			**Unrelated**		
	Deaths	**PMR**		**Deaths**	**PMR**
Direct			Acute resp. infect incl. pneumonia	10	6.0
Epilepsy	24	14.4	HIV/AIDS related death	23	13.8
Indirect			Malaria	5	3.0
Falls	4	2.4	Meningitis and encephalitis	6	3.6
Downing	4	2.4	Pulmonary tuberculosis	8	4.8
Burns	5	3.0	Neoplasm	19	11.4
Intentional self-harm	3	1.8	Diabetes mellitus	5	3.0
Traffic accidents	5	3.0	Acute cardiac diseases	9	5.4
Poisoning from plant/animal	1	0.6	Stroke	11	6.6
			COPD including Asthma	8	4.8
			Maternal death	5	3.0
			Others	12	7.2
Total	**46**	**27.5**		**121**	**72.5**

Discussion

Data collection

Signs, symptoms and conditions relating to a disease of interest play an important role in accurately determining InterVA-4 the causes of death. Therefore, proper filling of the structured VA questionnaires with sufficient amount information plays an important role in the use of automated tools in general. With respect to epilepsy, history of epilepsy, convulsions, sudden death and convulsions lasted 10 minutes or more were the most important conditions highly likely to identify epilepsy deaths.

Case 1 represents a scenario where the four key conditions were not captured; thus InterVA-4 classified the death as undetermined (Table 5-6). A review of circumstances occurred prior to death indicates the cause was possible epilepsy based on narratives from caretaker who reported;

"*The deceased was not sick even though he was epileptic. On the event day after lunch he went for a walk. He came back without notice. The next day he was found dead when family members tried to wake him up for farm activities*"

This probable epilepsy case was not picked by InterVA-4 mainly because the interviewer did not capture sudden death and history of epilepsy in the questionnaire despite being reported in narrative. Sudden deaths may be the most difficult cases for InterVA-4 to capture when the four key condition are not properly collected.

Probabilities of signs, symptoms and conditions

The probability for accidents and injuries in PWE was perceived to be extremely low by expects therefore the software was not primarily programmed to link epilepsy deaths with accidents. Most accidents-related deaths in PWE are attributed to epileptic seizures (Bifftu et al., 2017); however, InterVA4 software categorized most of these

deaths as accidents. Here is an example (Case 2) with InterVA-4 reporting “Falls” as the cause of death but physician coded this as epilepsy death;

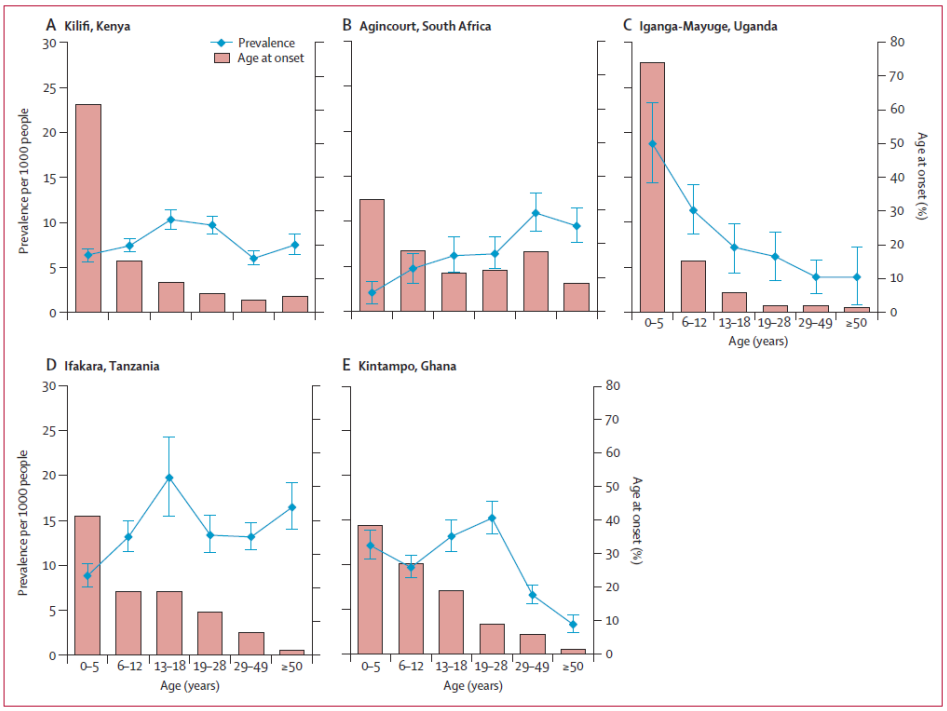
“*The deceased had epileptic fit. He fell down and died instantaneously*”

Here is another narrative (Case 3) of a death of a person with history of epilepsy where InterVA-4 coded the death as “Accident exposure to smoke fire & flame” that should have otherwise be reported as epilepsy death.

“*The deceased had a fire accident. He was burnt all over the body. He was sent to Mngeta healthcare centre and later he was referred to St. Francis hospital in Ifakara where he continued with treatment. However, his condition worsened and eventually he died*”

An additional input indicator linking accidents to epilepsy may be necessary. The question could for example be phrased “did accident occurs during seizures?”. The main challenge here is the configuration choice on whether underlying or immediate cause of death information is preferred (Benn et al., 2009). Underlying cause of death if often preferred in public health due to its relevance in producing vital statistics related to cause of disease rather than its effect. Future configuration of automated cause of death should re-consider this issue so as to enable reliable burden of epilepsy mortality be estimated.

Apart from accidents and injuries, higher perceived probabilities of conditions related to young age (younger than 5), history of depression, and history of mental confusion should be considered as these conditions are common in PWE than general population. In SEEDS study’s population, age onset of epilepsy is highest in at age 0 through 5 and lowest in older ages (50 + year) (Figure 5-1) (Ngugi et al., 2013b).



Source: Lancet Neurol 2013; 12: 253–63

Figure 5-1: Age-specific prevalence and age at onset of convulsive epilepsy

Experts on the other hand perceived a constant probability of 0.2 in age categories 5-14, 15-49, 50-64, and 65+. On the other hand, a lowest perceived probability of 0.02 was deliberated for children younger than 5 years. The current perceived age-related conditional probability do not reflect the epidemiological profile of SSA countries, therefore needs to be adjusted. Depression and/or anxiety in PWE is not routinely diagnosed in most LMIC (Mbewe et al., 2013), however, it is estimated that 15 to 60% of PWE are likely to suffer from these conditions (Gilliam et al., 2005, Jacoby et al., 1996, Heersink et al., 2015).

Pre-defined list of causes of death

InterVA4 highly associated sudden death and seizures lasting for at least 10 minutes with likelihood of epilepsy deaths, however, specific death's categories for SUDEP and SE were not created respectively. Status epilepticus (SE) (persistent convulsive seizures lasting for over 5 minutes) is common in PWE, reported to be associated with premature mortality in PWE. Verbal autopsy information collected from caregiver of

the diseased can provide valuable information in identified SUDEP (Lathers et al., 2009). SUDEP is not only excluded in the list of cause of death in InterVA4, but also with ICD10 in which “Epilepsy, unspecified” code is often used. On the other hand, SE is widely recognized and specific category has been assigned (i.e. G41.-).

The distinction between SUDEP and SE is essential in understanding and determining the risk factors and monitoring deaths in PWE. Mortality rate generally increased in PWE; however SE is associated with 61% increase in mortality. On the other hand, PWE without SE have been reported to experience 16% increase in mortality. In a lifetime of PWE, it is estimated that nearly 10% of adults and 20% of children will status epilepticus (Chin et al., 2004, Hauser, 1990). Creating a separate coding for SE could be improve with further probing for seizures lasted at least 10 minutes with an additional question such as “did seizure ended with death”.

Circumstances prior to death

VA interviews collects substantial amount of text information that are relevant in establishing causes of death in PWE. The WHO 2008 version of VA questionnaires requires the interviewer to collect and document the following information when available; 1) Short narrative of circumstances occurred prior to death from caretaker of the diseased, 2) Cause of death according to their best understanding of the patient, 3) Cause of death as reported on death certificate if death certificate was provided, 4) Cause of death reported on burial permit, 5) Post-mortem report, 6) Antenatal care card, 7) Prescription information, 8) Medical records, 9) Discharge cards, and 10) Laboratory results.

These free text narratives provides valuable clue in differentiating epilepsy and unrelated causes of death and improves the reliability and precision of death

certification among physicians (Table 5-6). Case 1 and 4 below provides a typical example of free text that may provide additional clue in additional to signs and symptoms entered in the model.

"*The deceased had epilepsy problem. When he had this problem, he encountered high fever, body inflammation, cough and tighten ribs. He was sent to St Francis hospital for further treatment. His condition worsened and he died*"

In majority of cases InterVA-4 perfectly captured what might be the real cause of death. For example in Case 4, neoplasm (02.03 Respiratory neoplasms) was assigned in a case with the narrative below;

"*The deceased had epilepsy problem. When he had this problem, he encountered high fever, body inflammation, cough and tighten ribs. He was sent to St Francis hospital for further treatment. His condition worsened and he died*"

In some cases physicians seems to have capture the possible cause of death right compared to InterVA-4 based on narratives as illustrated in the Case 8 where physician decided the cause of death was Malaria while InterVA-4 model capture this as meningitis (01.07 Meningitis and encephalitis)

"*The deceased suffered from a high fever as well as epileptic fit. The doctor prescribed ALU (for malaria treatment) however his condition worsened and he eventually died*"

Unfortunately, these text narratives are not utilized by automated models. Text mining technique can be used to analyse these text and improve predicted causes of death in epilepsy. Text mining involves computational extraction of selected information from unstructured text data. (Singh, 2005) The methods has shown promising results in medical research including in identify rate diseases and adverse drug events in clinical

trials (Harpaz et al., 2014). Future development of automated causes of death software's needs to invest in integrating text mining in order to improve accuracy of causes of death statistics.

Cause specific mortality fraction

Epilepsy-related death in selected studies from SSA is reported to contribute to 30 up to 60% of deaths in PWE (Ngugi et al., 2014c, Carpio et al., 2005, Kamgno et al., 2003b, Kaiser et al., 2007). In developed countries where epileptic seizures are properly managed, contribution of epilepsy-related causes of deaths are lower than causes unrelated to epilepsy such as neoplasms, cerebrovascular diseases, and cardiac diseases (Forsgren et al., 2005b, Cockerell et al., 1994, Nilsson et al., 1997, Lhatoo et al., 2005, Benn et al., 2009).

Indirect causes are those associated with events such as falls, burns, drowning and road traffic accidents. Injuries in PWE are implicated to epilepsy due to presence of unprovoked seizures and in some countries are the leading causes of death in PWE (Si et al., 2016). The risks are much higher in active convulsive epilepsy (ACE) were death is likely to be the ultimate outcome of injuries.

There were more epilepsy-unrelated deaths (72.5%) compared to epilepsy-related death (27.5%) when InterVA-4 model was applied. This may be possibly explained by the fact that, most epilepsy-related accidents were coded as accidents. In previous analysis of Kilifi and Agincourt cohort with fewer deaths and use of physicians; proportion of epilepsy related death were approximately 50% of all death, with accidents and injuries accounting for about 10% (Wagner et al., 2015, Ngugi et al., 2014a). Stroke and acute cardiac diseases were coded in majority of deaths (12%)

possibly due to increased rate of cerebrovascular diseases in most SSA countries (Feigin et al., 2015).

High number of HIV/AIDS related death may be associated with the variations in unconditional probability of death from HIV/AIDS ($P(C_i/I_0)$) between South Africa (Agincourt) and East Africa (Tanzania and Kenya). The model allows location specific configuration on these diseases to either be “high” (1 death per 100), “low” (1 death per 1000) or “very low” (1 death per 10000). Agincourt used “high” prevalence setting while Tanzania and Kenya applied “low” settings for HIV/AIDS death.

Conclusions

Verbal autopsy procedure provide an opportunity for physicians to determine cause of death by reviewing detailed structured questionnaires of signs, symptoms, health conditions, and circumstances occurred to the diseased provided by caretakers. Causes of death certification are done using ICD10 intended to promote accuracy, consistency and comparability of causes of death across time and places. Despite being the most affordable alternative, most countries in SSA opt not to use VA due to financial and human resources constrains.

InterVA-4 provides a unique opportunity to LMIC aiming at improving causes of death statistics. The assessment indicated that, InterVA-4 produces valuable data on causes of death statistics in PWE. The model could be further improved with continuous improvement specifically in; i) revising probabilities of signs and symptoms related to injuries, accidents, children, and depression/anxiety, ii) creating separate categories for SE and SUDEP, iii) incorporating text mining technique techniques in capturing signs and symptoms that may be narrated on circumstances occurred prior to death as described by caretakers, and iv) proper training to interviewer on filling VA forms.

Table 5-6: Narrative of reported on circumstances occurred prior to death

Case	Epilepsy	Accident	InterVA-4	ICD10	Narrative of circumstances prior to death
1	No	No	Undetermined		The deceased was not sick even though he was epileptic. On the event day after lunch he went for a walk. He came back without notice. The next day he was found dead when family members tried to wake him up for farm activities.
2	Yes	Fall	Other transport accident	G40.9	The deceased had epilepsy. He fell down, had epileptic fits, and then died instantaneously.
3	Yes	Burn	Accident expos to smoke fire & flame	G40.9	The deceased had a fire accident. He was burnt all over the body. He was sent to Mngeta healthcare centre and later he was referred to St. Francis hospital in Ifakara where he continued with treatment. However, his condition worsened and eventually he died
4	Yes	No	Respiratory neoplasms		The deceased had epilepsy problem. When he had this problem, he encountered high fever, body inflammation, cough and tighten ribs. He was sent to St Francis hospital for further treatment. His condition worsened and he died
5	Yes	Fall	Other transport accident	G40.9	The deceased had epilepsy. On the event day, he fell in a watery place and died instantly.
6	Yes	Drown	Other transport accident		The deceased went for a bath. He fell in a pit and died.
7	Yes	Fall	Acute respiratory infect including pneumonia		The deceased suffered from epileptic fit. He encountered hemoptysis and abdominal pain. He was sent to Mbingu dispensary however his condition worsened until he died.
8	Yes	No	Meningitis and encephalitis	B54	The deceased suffered from a high fever as well as epileptic fit. The doctor prescribed ALU (for malaria treatment) however his condition worsened and he eventually died

Mortality of neurological disorders in Tanzania: Analysis of baseline data from Sample Vital Registration with Verbal Autopsy (SAVVY)

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Abstract

Background: Neurological disorders (ND) have a profound consequence on human productivity, quality of life and survival. There are limited data on the burden of ND in Tanzania due to insufficient coverage of civil and vital registration systems.

Objectives: This study was conducted to estimate mortality of ND in all ages in Tanzania using data from the Sample Vital Registration with Verbal Autopsy (SAVVY) study.

Methods: Multistage random sampling was employed to select 23 districts, 1397 census enumeration areas and 154,603 households. During the baseline survey conducted between 2011 and 2014, deaths which occurred 12 months prior to the baseline survey were documented followed by verbal autopsy interviews. Causes of death were certified using International Classification of Diseases.

Results: The baseline survey enrolled a total of 650,864 residents. A total of 6645 deaths were reported to have occurred 12 months before the date of survey. Death certification was available for 5225 (79%) deaths. The leading causes of death were cerebrovascular diseases with a cause-specific mortality fraction (CSMF) of 1.64% (95% CI: 1.30–1.99) and 3.82% (95% CI: 2.92–4.72) in all ages and adults older than 50 years, respectively. Stroke accounted for 92% of all cerebrovascular deaths. Mortality of epilepsy was estimated with a CSMF of 0.94% (95% CI: 0.68–1.20); meningitis with a CSMF of 0.80% (95% CI: 0.56–1.04); cerebral palsy and other paralytic syndromes with a CSMF of 0.46% (95% CI: 0.27–0.65); and intrauterine hypoxia in neonates with a CSMF of 2.06% (95% CI: 1.12–3.01). Overall, mortality of ND was estimated with a CSMF of 4.99% (95% CI: 4.40–5.58).

Conclusions: The SAVVY survey provides estimates of mortality burden of ND in Tanzania. The study provides a basis for monitoring trends of ND and contributes to advancing knowledge of the burden of diseases. Integrating morbidities measures into the SAVVY design will provide comprehensive measures of burden of ND taking into account lifetime disabilities created by ND.

Keywords: Cerebrovascular, epilepsy, meningitis, cerebral palsy, intrauterine hypoxia.

Background

Neurological disorders (ND) have a profound consequence on human productivity, quality of life and survival in developed and developing countries. The most prevalent ND globally include dementia (progressive memory loss); Parkinson's (impaired motor system); multiple sclerosis (problem with vision, movement, sensation or balance); epilepsy (sudden recurrence of unprovoked seizures); and stroke (two or one sides paralysis or numbness).

Dementia and Parkinson's disease are the most common ND in most developed countries with a reported increasing trend (Mackenbach et al., 2014). The increases in ND's mortality in developed countries are higher than increases in other chronic diseases such as cancer and diseases of circulation (Pritchard et al., 2017). Substantial proportions of neurological disorders in developed countries are thought to be attributed to increased life expectancy (aging) and unhealthy lifestyle (Chin et al., 2014).

In most developing countries, on the other hand, etiological studies reported that most ND originate from infections of the central nervous system (CNS)and brain trauma (Birbeck, 2001, Winkler et al., 2008c, Winkler et al., 2008b, Winkler et al., 2009a). The most common reported ND in sub-Saharan Africa (SSA) include stroke, epilepsy, meningitis, paraparesis, neuropathies, and traumatic brain injuries (Howlett, 2014, Winkler et al., 2009c, Smart et al., 2017).

In 2010, Global Burden of Disease (GBD) report indicated that non-communicable diseases (NCD) accounted for 54% of global burden of disease

(morbidities and premature mortality); an increase from 43% in 1990 (Murray et al., 2012). With the rapid epidemiological transition in developing countries, mortalities associated with age-related and lifestyle ND are expected to increase in the presence of infection-related ND; therefore, deliberate efforts in understanding the epidemiology of ND is necessary.

The morbidity and mortality burden of stroke as an example is reported to increase in developing countries, accounting for 75% of global deaths and 81% stroke-related Disability Adjusted Life Years (DALYs) (Feigin et al., 2015).

In SSA, there is a paucity of national data on the epidemiology of ND. Most references of national estimates of the burden of NDs are cited from the modelled estimates of GBD study. However, for most developing countries, input parameters used in modelling are obtained from inadequate vital registrations records or small local studies. Coverage of mortality and morbidity for China and India as an illustration was only 15% and 1%, respectively, for mental, neurological and substance abuse at the time GBD for the year 2013 was estimated (Baxter et al., 2016). Model-based estimates from GBD not only are free from coverage limitations but also considerable reliance on geospatial data and experts' opinions (Feigin et al., 2015). Global estimates in some countries and cases deviate from the true epidemiological profile and thus are deemed unreliable for local planning by policy makers (AbouZahr et al., 2017).

Tanzania lacks national mortality data on ND due to the insufficient coverage of civil and vital registration systems as in many SSA countries (Dalal et al., 2011,

Dewhurst et al., 2012). Poor cover-age of civil and vital registration systems at a national level and over-reliance on global estimation have concealed crucial statistics necessary in understanding population health, improving health outcomes and monitoring disease trends (Pakpoor et al., 2017, Phillips et al., 2015). Several studies have linked higher coverage of civil and vital statistics with improved health outcomes in several countries (Phillips et al., 2015).

Several studies have linked higher coverage of civil and vital statistics with improved health outcomes in several countries (MEASURE Evaluation, 2018). SAVVY stands of SAmple Vital registration with Verbal autopsY, which is a community-based system implemented in a nationally representative cluster sample (MEASURE Evaluation, 2018). Since nearly 75% of deaths occur at home in most developing countries and cause of death determination is nearly absent in Tanzania as in many Low and middle-income countries (LMIC), VA remained the only tool reliable for providing vital statistics information (Mikkelsen et al., 2015, Sankoh et al., 2014a, Setel et al., 2006). VA remained the only tool reliable for providing vital statistics information.

We examined the SAVVY data to estimate mortality rates of the neurological disorders by sex, age, residence, and zones in Tanzania.

Material and Methods

Design and sampling

SAVVY is a community-based system implemented in a nationally representative cluster sample (MEASURE Evaluation, 2018). Multistage random sampling was employed to select 23 districts, 1397 enumeration areas, and

154,603 households from mainland Tanzania, stratified by residency and zones to meet the proposed overall sample. The sampling frame for this study was based on the 2002 Population and Housing Census for Tanzania Mainland. A full description of design and methods has been published elsewhere (Kabadi et al., 2015). Figure 6-1 shows the map of Tanzania with shaded sampled districts.

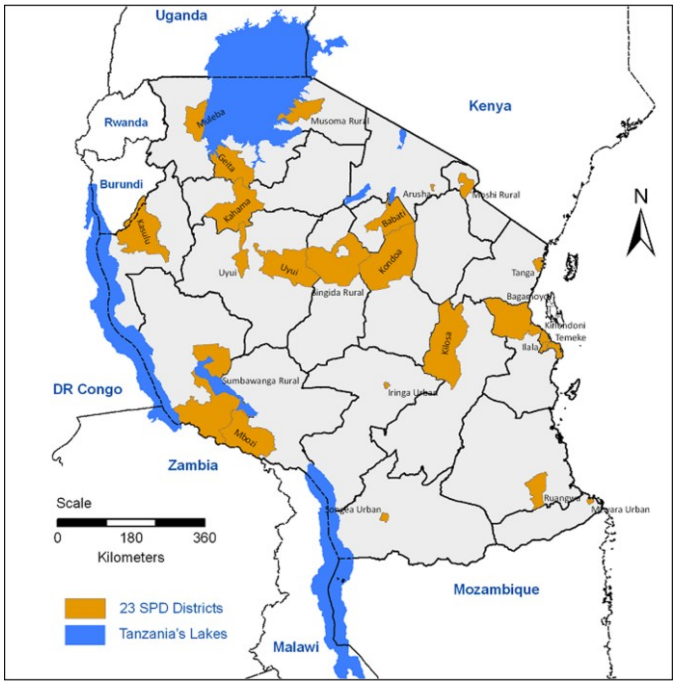

Figure 6-1: Geographic locations of 23 SAVVY districts on Tanzania map

Baseline census

Baseline censuses were sequentially conducted in 23districtsbetween 2011 and 2014 in order to establish denominators for estimating different demographic indicators. During the baseline census, the socio-demographic information of the household members was collected which included: age, sex, education, and relationship to head of household. Deaths that had occurred during the 12 months prior to the census date were retrospectively documented in all households.

Verbal autopsy

Verbal autopsy (VA) interviews were conducted for all documented deaths by trained SAVVY VA coordinators with the most appropriate person in the household after setting up an appointment. Standard verbal autopsy questionnaires (2007 version) that have been developed by the World Health Organization (WHO) in collaboration with other stakeholders were used (World Health Organization, 2007). Completed VA questionnaires were sent to physicians for a cause of death certification.

Physician's assignment of causes of deaths

The cause of death for each interviewed death was determined using the International Classification of Diseases, tenth revision (ICD-10), as published by the WHO (World Health Organization, 2004). Each VA questionnaire of the deceased was reviewed independently by two physicians to ascertain causes of deaths and produce death certificates. In case of discrepancies, two independent physicians met to resolve the discrepancies. If disagreed, the cause of death was declared undetermined (meaning there was no sufficient information to determine the cause of death). Physicians reviewing VA questionnaires were medical doctors (not neurologists) independent of the research institution trained on death certification using ICD-10 classification.

Death certificates were requested and documented during VA interviews. However, these certificates were rarely available and coded in ICD-10; therefore, for consistency reasons, we did not consider these certificates. Neurological causes of deaths were classified using code ranges of G00–G99

for diseases of nervous system, I60–69 for cerebrovascular diseases,P20 for intrauterine hypoxia, C71 for malignant neoplasm of brain, D33 for benign neoplasm of brain and other parts of the CNS, Q00–Q07 for congenital malformations of the nervous system, S06 for traumatic brain injuries/intracranial injury, and R25–R29 for symptoms and signs involving the nervous and musculoskeletal systems Neurological causes of deaths were classified using code ranges of G00-G99 for diseases of nervous system, I60-69 for cerebrovascular diseases and S06 for traumatic brain injuries/ intracranial injury for deaths (Jette et al., 2015, Roth et al., 2015).

Statistical analysis

National Population and Housing Census data were used to provide a basis for data weighting. The gross weight was estimated as the product of reciprocal of the probability of selection of districts within zones, enumeration area (EA) within districts and households within EA. Mortality rate was estimated as a weighted ratio of the number of deaths and population. Cause-specific mortality fraction (CSMF) was calculated as a ratio of deathsduetoaspecificcauseoverthetotalnumberofdeathsforwhichcauseofdeathinformationwasavailable.CSMFwere compared across the subpopulation by calculating the mortality rate fraction (MRF), which is the ratio of two CSMF. Females, urban, and age 50 and above and lake zone were set as the reference category for CSMF comparisons. Lake zone is known to have poor intervention coverage for a substantial number of health systems performance indicators; therefore, we set it as a reference category (Kumalija et al., 2015).

Results

A total of 650,864 residents in 154,603 households were enrolled during the baseline census survey. There were 91, 329 (51%) households in rural areas and 63,274 (41%) in urban areas. The majority of households were headed by males (72%). The average household size was 4.5 in rural areas and 3.7 in urban areas. A total of 6645 deaths were documented to have occurred 12 months prior to the baseline survey corresponding to an annual weighted crude death rate of 10.8 (95% CI: 10.8–10.9) deaths per1000 population. The age distribution of the reported deaths is shown in death pyramid in Figure 6-2.

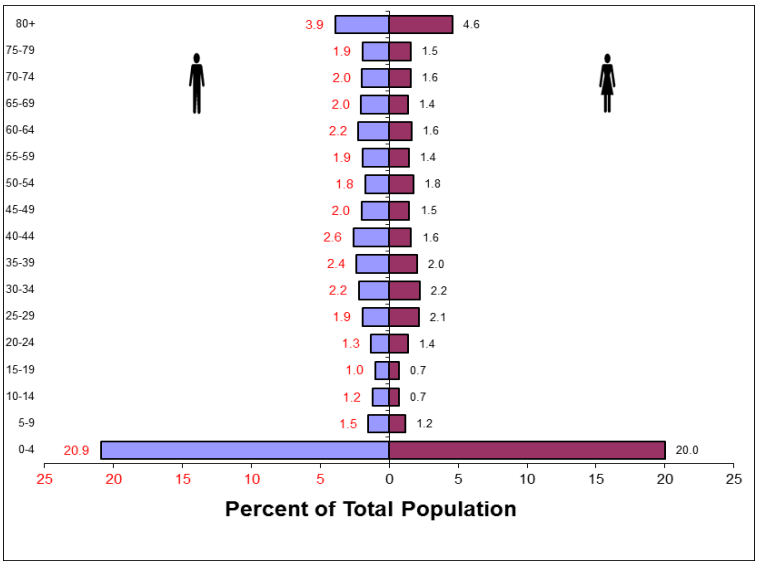

Figure 6-2: Age distribution of reported 6,645 deaths (3,509 males and 3,136 females) from SAVVY districts

VA interviews were conducted for 6608 (99%) of the documented 6645 deaths. Causes of death certification were completed for 5225 (79%) of 6608 VA interviewed deaths. Of 5225 deaths with complete cause of death, 872 (17%) were newborn aged 0–29 days (VA form 1), 1096 (21%) were children aged 29 days–14 years (VA form 2) and 3257 (62%) were adults older than 15 years

(VA form 3). Causes of death could not be ascertained for 1383 deaths due to absence of a reliable caregiver to respond to the VA interview, incomplete VA inter-views, and incomplete cause of death determination by physicians, among other things.

Causes of neurological deaths

A total of 261 neurological deaths were determined; 72(27.6%) were children younger than 5 years, 22 (8.4%) were children aged 5–19 years, 65 (24.9%) were adults aged 20–49 years, and 102 (39.1%) were adults older than 50 years. All neurological deaths were coded into30 three- or four-digit ICD-10 causes and later grouped into nine major categories of cerebrovascular diseases, meningitis, epilepsy, cerebral palsy and other paralytic syndromes, intrauterine hypoxia, malignant and benign neoplasms of brain and CNS, congenital malformations of the nervous system, other neurological disorders, and symptoms and signs involving the nervous and musculoskeletal systems Table 6-1.

Table 6-1: Distribution of causes of neurological death by age group

	Age group				
	<5	5-19	20-49	50+	All ages
Cerebrovascular diseases	1.4		27.7	65.7	33.0
Stroke, not specified as haemorrhage or infarction	1.4		24.6	60.8	30.3
Hypertensive encephalopathy				1.0	0.4
Sequelae of stroke, not specified as haemorrhage or infarction			3.1	2.9	1.9
Sequelae of other and unspecified cerebrovascular diseases				1.0	0.4
Epilepsy	4.2	40.9	36.9	11.8	18.4
Other generalized epilepsy and epileptic syndromes				1.0	0.4
Epilepsy, unspecified	4.2	40.9	36.9	11.8	18.4
Meningitis	34.7	22.7	10.8	4.9	16.1

Bacterial meningitis, not elsewhere classified	4.2				1.2
Meningitis due to other and unspecified causes	1.4				0.4
Meningitis, unspecified	29.2	22.7	10.8	4.9	14.6
Cerebral palsy and other paralytic syndromes	11.1	18.2	3.1	9.8	9.2
Cerebral palsy	1.4				0.4
Cerebral palsy, unspecified	8.3	13.6			3.5
Hemiplegia, unspecified				4.9	1.9
Paraplegia, unspecified		4.6	1.5	2.9	1.9
Paralytic syndrome, unspecified	1.4		1.5	2.0	1.5
Intrauterine hypoxia	25.0				6.9
Malignant and benign neoplasms of brain and CNS		9.1	7.7	1.0	3.1
Malignant neoplasm of brain			3.1		0.8
Malignant neoplasm of spinal cord, cranial nerves and other parts of CNS		9.1	3.1	1.0	1.9
Benign neoplasm of brain and other parts of central nervous system			1.5		0.4
Congenital malformations of the nervous system	12.5		1.5		3.8
Congenital hydrocephalus	1.4				0.4
Congenital hydrocephalus, unspecified	4.2		1.5		1.5
Spina bifida	1.4				0.4
Spina bifida, unspecified	4.2				1.2
Congenital malformation of nervous system, unspecified	1.4				0.4
Other neurological disorders	4.2		6.2	2.9	3.8
Migraine				1.0	0.4
Migraine, unspecified			3.1	1.0	1.2
Polyneuropathy, unspecified (Neuropathy NOS)			1.5	1.0	0.8
Hydrocephalus	4.2		1.5		1.5
Symptoms and signs involving the nervous and musculoskeletal systems	6.9	9.1	6.2	2.9	5.4
Other and unspecified symptoms and signs involving the nervous and musculoskeletal systems				1.0	0.4
Headache			6.2	2.0	2.3
Other and unspecified convulsions	6.9	9.1			2.7
Number of deaths	72	22	65	102	261

Neurological disorders mortality

Of the reported ND-related deaths, the leading causes were cerebrovascular diseases (33.0%), epilepsy (18.4%), meningitis (16.1%), cerebral palsy and other paralytic syndromes (CP) (9.2%), and intrauterine hypoxia (IH) (6.9%). All

causes mortality of ND was estimated with a CSMF of 4.99% (95% CI: 4.40–5.59) (Table 6-2). There were no differences in CSMF among males (4.76%) and females (5.27%) (MRF = 0.90, 95%CI: 0.70–1.16). Compared to adults aged 50 years and above, mortality of ND was estimated to be lower among children aged 0–4 (MRF = 0.71, 95% CI: 0.52–0.97), and comparable in children aged 5–19 (MRF = 1.07, 95% CI: 0.64–1.72) and adults aged20–49 (MRF = 1.07, 95% CI: 0.64–1.72). Mortality was lower by 23.0% in urban (4.35%) than rural (5.63%) areas (MRF = 0.77, 95% CI: 0.40–0.99). Mortality of ND was comparable across zones. Using census population and crude death rate of 2012 and CSMF observed in this study, we estimated the number of neurological deaths to range from 18,000 to 22,000 in Tanzania in 2012.

Table 6-2: Cause-specific mortality fraction (%) estimates of neurological disorders and epilepsy by sex, age, residency, and zone

	Neurological disorders			Epilepsy		
	D	**CSMF (95%CI)**	**MFR (95%CI)**	**D**	**CSMF (95%CI)**	**MFR (95%CI)**
Sex						
Males	134	4.76 (4-5.55)	0.90 (0.70-1.16)	36	1.28 (0.86-1.69)	2.37 (1.23-4.88)
Females	127	5.27 (4.38-6.16)		13	0.54 (0.25-0.83)	
Age						
<5	72	4.13 (3.19-5.06)	0.71 (0.52-0.97)	3	0.17 (0-0.37)	0.23 (0.04-0.84)
5-19	22	6.25 (3.72-8.78)	1.07 (0.64-1.71)	9	2.56 (0.91-4.20)	3.45 (1.30-8.72)
20-49	65	4.72 (3.6-5.84)	0.81 (0.58-1.12)	24	1.74 (1.05-2.43)	2.35 (1.15-5.03)
50+	102	5.82 (4.72-6.91)		13	0.74 (0.34-1.14)	
Residency						
Rural	149	5.63 (4.75-6.50)		30	1.13 (0.73-1.54)	0.65 (0.35-1.19)
Urban	112	4.35 (3.56-5.13)	0.77 (0.60-0.99)	19	0.74 (0.41-1.07)	
Zone						
Western	31	4.74 (3.11-6.37)	0.75 (0.46-1.21)	7	1.07 (0.28-1.86)	1.00 (0.31-3.16)
Northern	25	3.53 (2.17-4.88)	0.56 (0.33-0.93)	3	0.42 (0-0.90)	0.40 (0.07-1.65)
Central	43	4.68 (3.31-6.04)	0.74 (0.48-1.15)	12	1.30 (0.57-2.04)	1.22 (0.46-3.45)
Southern Highlands	39	6.61 (4.60-8.61)	1.05 (0.67-1.64)	4	0.68 (0.01-1.34)	0.63 (0.14-2.37)
Eastern	43	4.8 (3.41-6.21)	0.77 (0.49-1.18)	8	0.89 (0.28-1.51)	0.84 (0.27-2.56)
Southern	33	4.65 (3.10-6.20)	0.74 (0.46-1.18)	7	0.99 (0.26-1.71)	0.92 (0.28-2.91)
Lake	47	6.27 (4.54-8.01)		8	1.07 (0.33-1.80)	

Overall	**261**	4.99 (4.40-5.58)		**49**	0.94 (0.68-1.20)	

Ref: Reference category, CSMF: Cause-specific mortality Fraction, MFR: Mortality Fraction Ratio, CI: Confidence interval

Cerebrovascular mortality

Cerebrovascular diseases are a category of a broader group of diseases of the circulatory system. Cerebrovascular diseases accounted for 19.0% of all deaths from diseases of circulation, after hypertension which accounted for 66.0% of deaths from diseases of circulation. A total of 86 cerebrovascular deaths were reported out of 5225 certified deaths. Among those who died of cerebrovascular diseases, stroke was the leading cause of death, constituting 92.0% of all reported cerebrovascular deaths. The remaining 8.0% constituted hypertensive encephalopathy, sequelae of stroke not specified as hemorrhage or infarction, and sequelae of other unspecified cerebrovascular diseases. The mortality of cerebrovascular-related deaths was estimated with a CSMF of 1.64% (95% CI: 1.30–1.99); with a higher estimate in adults older than 50 years (3.82%) than adults aged 20–49(1.31%) (MRF = 3.4, 95% CI: 1.19–5.58) (Table 6-3).There was a comparable estimate in urban (1.98%) and rural (1.32%) populations (MRF = 1.5, 95% CI: 0.95–2.37). No significant differences were observed between lake zone and other zones. In adults older than 50 years, the mortality of cerebrovascular-related deaths was estimated with a CSMF of 3.82% (95% CI: 2.92–4.72). CSMF was lower in males (2.87%) than females (4.93%) (MRF = 0.58, 95% CI: 0.34–0.97), comparable in urban (4.19%) and rural (3.42%) (MRF = 1.23, 95% CI: 0.73–2.06), and lower in central zone (1.68%) compared to lake zone (6.22%) (MRF = 0.27, 95% CI: 0.08–0.76).

Epilepsy mortality

Of all ND-related deaths, epilepsy accounted for 18.4%; 4.2% among children < 5 years, 40.9% among children aged 5–19, 36.9% among adults aged 20–49, and 11.8%among adults older than 50 years (Table 6-1). Unspecified convulsive epilepsy (98.0%) and other generalized epilepsy and unspecified epileptic syndromes (2.0%) were the category reported for all deaths.

Of 5225 certified deaths, 49 were epilepsy-related with a CSMF of epilepsy of 0.94% (95% CI: 0.68–1.20) with significantly higher estimates in males (1.28%) than females (0.54%) (MRF = 2.37, 95% CI: 1.23–4.88) (Table 6-2). Epilepsy mortality was higher in children aged 5–19 (MRF = 3.45, 95% CI: 1.30–8.72) and adults aged 20–49 (MRF = 2.35, 95%CI: 1.15–5.03) than adults aged 50 years and above. Epilepsy mortality was observed to be comparable in urban (0.74%) and rural (1.13%) areas (MRF = 0.65, 95% CI: 0.35–1.19). Epilepsy mortality was also com-parable across zones.

Table 6-3: Cause-specific mortality fraction (%) estimates of cerebrovascular disorders (95%CI) by sex, age, residency, and zone

	Cerebrovascular diseases			Cerebrovascular diseases (50+ years)		
	D*	**CSMF (95%CI)**	**MFR (95%CI)**	**D***	**CSMF (95%CI)**	**MFR (95%CI)**
Sex						
Males	38	1.99 (1.43-2.55)		27	2.87 (1.80-3.93)	0.58 (0.34-0.97)
Females	48	1.35 (0.92-1.78)	0.68 (0.43-1.06)	40	4.93 (3.44-6.42)	
Age						
<5	1	0.06 (0.00-0.17)	0.02 (0.00-0.09)			
5-19	0					
20-49	18	1.31 (0.71-1.91)	0.34 (0.19-0.58)			
50+	67	3.82 (2.92-4.72)				
Residency						
Rural	35	1.32 (0.89-1.76)		29	3.42 (2.20-4.65)	
Urban	51	1.98 (1.44-2.52)	1.50 (0.95-2.37)	38	4.19 (2.89-5.50)	1.23 (0.73-2.06)
Zone						
Western	11	2.14 (1.10-3.17)	0.79 (0.33-1.81)	9	6.08 (2.23-9.93)	0.99 (0.37-2.47)

Northern	9	1.27 (0.44-2.09)	0.59 (0.23-1.43)	7	2.30 (0.62-3.99)	0.37 (0.12-1.00)
Central	8	0.87 (0.27-1.47)	0.41 (0.15-1.01)	6	1.68 (0.35-3.01)	0.27 (0.08-0.76)
Southern Highlands	12	2.03 (0.89-3.17)	0.95 (0.41-2.14)	10	6.54 (2.62-10.45)	1.05 (0.41-2.59)
Eastern	18	2.01 (1.09-2.93)	0.94 (0.45-1.98)	12	3.87 (1.72-6.02)	0.62 (0.26-1.48)
Southern	12	1.69 (0.74-2.64)	0.79 (0.34-1.78)	10	3.68 (1.44-5.91)	0.59 (0.23-1.46)
Lake	16	1.68 (0.70-2.67)		13	6.22 (2.94-9.49)	
Overall	**86**	**1.64 (1.30-1.99)**		**67**	**3.82 (2.92-4.72)**	

Meningitis mortality

Bacterial meningitis accounted for 16.1% of all ND deaths; 34.7% among children < 5 years, 22.7%among children aged 5–19, 10.8% among adults aged 20–49, and 4.9% among adults older than 50years (Table 6-1). No viral-related meningitis deaths were identified by physicians. Of certified deaths, meningitis-related mortality was estimated with a CSMF of 0.80% (95% CI: 0.56–1.04) (Table 6-4). Compared to adults older than 50 years (CSMF = 0.28%), meningitis mortality was high in children 0–4 (1.43%) (MRF = 5.02, 95% CI: 1.89–16.81) and those aged 5–19 years (1.42%) (CSMF= 4.98, 95% CI: 1.15–21.64). Meningitis mortality was comparable in urban (0.66%) and rural (0.94%) (MRF =0.70, 95% CI: 0.35–1.35) areas and among males (1.04%) and females (0.79%) (MRF = 1.04, 95% CI: 0.54–2.04). Subanalysis of meningitis mortality in children similar to the above indicated no differences in CSMF related to sex, age, residency, and zone.

Table 6-4: Cause-specific mortality fraction (%) estimates of meningitis disorders by sex, age, residency, and zone

		Meningitis			**Meningitis (age 0-19)**	
	D*	**CSMF(95%CI)**	**MFR (95%CI)**	**D**	**CSMF (95%CI)**	**MFR (95%CI)**
Sex						
Males	23	0.82 (0.48-1.15)	1.04 (0.54-2.04)	18	1.57 (0.85-2.29)	1.25 (0.57-2.84)
Females	19	0.79 (0.43-1.14)		12	1.26 (0.55-1.97)	

Age						
<5	25	1.43 (0.88-1.99)	5.02 (1.89-16.81)		1.43 (0.88-1.99)	1.01 (0.38-3.37)
5-19	5	1.42 (0.18-2.66)	4.98 (1.15-21.64)	25	1.42 (0.18-2.66)	
20-49	7	0.51 (0.13-0.88)	1.78 (0.49-7.13)	5		
50+	5	0.28 (0.03-0.53)				
Residency						
Rural	25	0.94 (0.57-1.31)		19	1.57 (0.87-2.27)	
Urban	17	0.66 (0.35-0.97)	0.70 (0.35-1.35)	11	1.24 (0.51-1.97)	0.79 (0.34-1.75)
Zone						
Western	5	0.76 (0.10-1.43)	0.67 (0.17-2.11)	5	1.26 (0.16-2.37)	0.58 (0.15-2.01)
Northern	4	0.56 (0.01-1.11)	0.47 (0.10-1.68)	1	0.56 (0.00-1.65)	0.25 (0.01-1.91)
Central	1	0.11 (0.00-0.32)	0.09 (0.00-0.65)	0		
Southern Highlands	14	2.37 (1.14-3.60)	1.97 (0.80-5.17)	12	4.33 (1.93-6.73)	0.04 (0.02-0.03)
Eastern	5	0.56 (0.07-1.05)	0.46 (0.12-1.55)	1	0.31 (0.00-0.91)	0.14 (0.00-1.05)
Southern	4	0.56 (0.01-1.11)	0.47 (0.10-1.68)	3	1.39 (0.00-2.95)	0.64 (0.11-2.65)
Lake	9	1.20 (0.42-1.98)		8	2.18 (0.69-3.68)	
Overall	**42**	**0.80 (0.56-1.04)**		**30**	**1.43 (0.92-1.94)**	

Ref: Reference category, CSMF: Cause-specific mortality Fraction, MFR: Mortality Fraction Ratio, CI: Confidence interval

Cerebral palsy and other paralytic syndromes

CP accounted for 9.2% of all ND deaths; 11.1% among children< 5 years, 18.2% among children aged 5–19, 3.1% among adults aged 20–49, and 9.8% among adults older than 50 years (Table 6-1). Cerebral palsy deaths were reported in children younger than 20 years while paralytic syndromes (hemiplegia, paraplegia, and paralysis) were common in adults older than 20 years. A total of 24 deaths from CP and other paralytic syndromes were identified with a CSMF of0.46% (95% CI: 0.27–0.65). Mortality of cerebral palsy in children younger than 5 years was estimated with a CSMF of 0.40% (95% CI: 0.10–0.70).

Intrauterine hypoxia

A total of 18 deaths from IH were coded. IH accounted for 6.9% of all ND deaths and 25.0%among children younger than 5 years died of ND. Given the fact that

IH is diagnosed at birth or the early days of neonatal life, mortality associated with IH in neonates was estimated with a CSMF of 2.06%(95% CI: 1.12–3.01). The remaining ND-related deaths were broadly grouped as malignant and benign neoplasms of the brain and CNS, congenital malformations of the nervous system, other neurological disorders, and symptoms and signs involving the nervous and musculoskeletal systems. The mortality of these ND combined were estimated with a CSMF of 0.80% (95% CI: 0.56–1.04). Malignant and benign neoplasms of the brain and CNS were reported and estimated in individuals aged < 5 years with a CSMF of 0.23% (95% CI: 0.07–0.39). Congenital malformations of the nervous system were reported and estimated in children < 5 years with a CSMF of 0.52% (95% CI: 0.18–0.85).

Discussion

This study provides the first detailed analysis of national data on neurological disorders in Tanzania. The study utilized a SAVVY approach developed to provide a standardized methodology in generating mortality estimates, causes of death and disease classification needed for local, regional and international comparability of mortality statistics. The adopted approach, which included national random samples of enumeration areas provided by the National Bureau of Statistics (NBS), multistage sampling methodology, use of two independent causes-of-death certifiers and ICD-10guarantee credibility of the study's findings.

The main neurological disorders identified were cerebrovascular diseases, epilepsy, meningitis, cerebral palsy and other paralytic syndromes, and intrauterine hypoxia. Cerebrovascular disorders were the leading cause of death, most of which were attributed to stroke. We estimated that the number of neurological deaths in Tanzania ranged from 18,000 to 22,000 in 2012.

Cerebrovascular diseases

Hypertensive diseases are the major risk factor for ND, specifically stroke and dementia (Iadecola et al., 2008). The STEPwise approach to Surveillance (STEPS) survey designed by WHO estimated high blood pressure (>140/90 mmHg)in 25.9% of adults aged 25–64 years in Tanzania in 2012 (Mayige et al., 2013). High mortality estimates attributed to hypertension and cerebrovascular disorder observed in SAVVY are incoherent with the prevalence of hypertension reported in STEPS survey. A recent hospital mortality study for Tanzania mainland reported an increase of stroke-related mortality to 27% between 2006–2010 and 2011–2015. In the study period from 2006 to 2015,deaths attributable to stroke were 3.1% while cardiorespiratory and cardio-circulatory diseases accounted for 6.6% and 5.6%, respectively (Mboera et al., 2007). Comparable estimates of cerebrovascular mortality by residency in this study indicate lifestyle-related diseases equally affect rural and urban residents. These observations deviate from the common knowledge that urban residents are at higher risk for NCD in general compared to rural residents. Insufficient coverage of human resources and medicine supply for cardiovascular diseases may also explain why Tanzania lags behind in slowing down the increasing trends in the majority of NCD. In 2014, the Tanzania Service Provision Assessment Survey (TSPA) indicated a lack of guidelines for healthcare providers for NCD service (Ministry of Health and Social Welfare (MoHSW) [Tanzania Mainland], 2015).

The TSPA indicated that less than 10% of facilities have providers who have recently received training in providing services for cardiovascular and other chronic diseases (Ministry of Health and Social Welfare (MoHSW) [Tanzania Mainland], 2015).

Despite the fact that majority of Tanzanians access their health services through dispensaries and health facilities, the TSPA indicated the availability of essential medicines for cardio-vascular and other chronic diseases is lower in most dispensaries and health facilities than in hospitals.

Epilepsy

The population estimate of 7.3 (95% CI: 6.9–7.6) deaths per 100,000 was comparable to estimates in the three large demographic surveillance sites: 5.4 (95% CI: 4–6.7) in Rufiji, 7.9 (95% CI: 6.1–9.7) in Ifakara Rural and 3.9 (95% CI: 1.3–6.4) deaths per 100,000 population in Ifakara Urban (Levira et al., 2018). Epilepsy mortality rate and CSMF were comparable to estimates reported elsewhere in most developing countries. The majority of interventions targeting epilepsy are those aimed at eliminating the *Taenia solium* tapeworm, which is responsible for the development of taeniosis, a major cause of preventable epilepsy (Blocher et al., 2007, Blocher et al., 2011). Tanzania, the National Schistosomiasis Control Program (NSCP) routinely implemented school-based mass drug administration targeting both schistosomiasis and systicercosis (Braae et al., 2017)

Several interventions have been devised to reduce parasite infections in Tanzania; however, most of these interventions have proved to yield modest efficacy, and therefore need to be re-evaluated (Mwidunda et al., 2015).

Despite these efforts, mortality of epilepsy has remained stable over the years in Tanzania with reference to the previous national demographic surveillance system's study conducted in 1992–1995, which estimated an epilepsy mortality rate of 15 and 5 deaths per 100,000 population in males and females, respectively (Aspray, 2005).

Probable contributors to stagnation in reduction of epilepsy mortality include the rise of cerebrovascular diseases attributed to epilepsy such as stroke, the increase in emerging infectious diseases such as HIV, and an increase in traumatic brain injuries as a result of wide use of bikes/motor bikes without a helmet and vehicles without a seatbelt. These factors probably explain why in this study we have more mortality due to epilepsy in adults than in children, who normally have more epilepsy in general in SSA, especially those originating from febrile seizures.

Meningitis

The mortality of meningitis was low, accounting for less than<0.8% of all deaths and 1.5% in children aged younger than 5 years. Analysis of WHO-reported cases of meningitis in Africa identified 11 regions (the 'meningitis belt') that account for 90% of all meningitis in SSA(Tanzania not included) (Zhao et al., 2018). High meningitis mortality in children may be explained by the fact that the

meningitis pathogen that accounts for most cases of acute bacterial meningitis affects neonates and children. Observed meningitis deaths in adults may mostly constitute AIDS or TB-related deaths based on the fact that meningitis (cryptococcal) is a leading cause of death among HIV-infected individuals in SSA and in the studied population, where the latest HIV prevalence was estimated in adults aged 15–49. However, the unexpected low mortality of meningitis in adults may be explained by the fact that meningitis may be reported as immediate but not the underlying cause of death. The analysis in this study focused on underlying causes of death.

Cerebral palsy and other paralytic syndromes

Cerebral palsy is a lifelong disability in children of non-progressive brain damage which most likely occurred during the antenatal, perinatal, or early postnatal period. Clinical presentations include challenges in coordination, stiff and/or weak muscles, tremors, and in some cases problems in sense organs and reasoning. The burden of CP in Africa is estimated at 2–2.5 cases per 1000 live births and globally affects 0.2% of neonates (Donald et al., 2014, Graham et al., 2016). Improving care at birth may have potential in reducing perinatal adverse events that are likely to result in the development of this disorder. There are scarce data on mortality in cerebral palsy in Africa, hence this study provides valuable statistics for future studies of the disorder. Mortality from paralytic syndromes (including hemiplegia and paraplegia) was more common in individuals older than 50 years. These disorders maybe sequelae of stroke,

degenerative diseases, or infection of the nervous system; therefore, further investigation of its epidemiology is needed.

In general, IH is the form of birth asphyxia that affects the brain as a result of oxygen deprivation of the fetus (Hutter et al., 2010). Birth asphyxia is a more general term, and we anticipate that most clinicians would classify IH as birth asphyxia. Despite the possibility for misclassification, physicians were able to capture IH deaths, which were the second leading cause of neurological death in children under 5 years. Poor maternal health condition, fetus development, and adverse perinatal events are the major culprits for the development of these disorders (Hutter et al., 2010). Improving antenatal and care at birth by scaling-up facility delivery and improving basic and comprehensive emergency obstetric and newborn care may significantly reduce pregnancy- or birth-related neurological morbidities such as cerebral palsy and mortality.

Comparison with modeled estimates

Our estimates were lower or higher than those reported by GBD reports Table 6-5 (IHME, 2016). The estimated CSMFs of cerebrovascular diseases were comparable to estimates from the GBD for adults aged 15–49 years and close to estimates for all ages. SAVVY estimates of deaths attributable to epilepsy and road traffic injuries were higher in all age categories and overall than those reported in the GBD. On the other hand, the GBD reported higher estimates for deaths attributable to meningitis. The observed differences may be linked to methodological limitations in both approaches; however, SAVVY estimates are more likely to be closer to true population estimates. A substantial proportion of

data used in generating the GBD for Tanzania are those derived from health and demographic surveillance systems, most of which are located in poor rural areas (Mrema et al., 2015, Geubbels et al., 2015). Recently, the 2017 GBD report in Tanzania compiled cerebrovascular diseases data dated from 2010 to 1993 due to the limited number of studies and poor coverage of civil and vital registration systems (Institute for Health Metrics and Evaluation, 2018).

Missing and misclassifying neurological disorders was the main possible limitation of this study attributed to lack of clinical training in neurology among physicians conducting death certification. A substantial proportion of deaths were coded as malaria in this study; however, some of the clinical manifestations of cerebral malaria such as fever, vomiting, and convulsions are also clinical manifestations of neurological disorders such as meningitis and epilepsy. Other possible misclassifications include those related to misclassifying cerebrovascular disorder as hypertensive disease, or vice versa. We did not observe traumatic brain injuries or intracranial deaths in this study despite the high mortality of road injuries estimated at 2.4% in all ages and 5.8% (95% CI: 4.7–7.1) in adults aged 15–49 years (results not reported but provided for contextual reasoning). Road injuries are one of the main causes of brain injuries; therefore, lack of information from VA or medical records may have resulted in missing some traumatic brain injury deaths in this study (Smart et al., 2017, Winkler et al., 2009c, Okeng'o et al., 2017).

Table 6-5: Cause-specific mortality comparison to GBD

	Age 0-4 years		Age 15-49 years		All ages	
	SAVVY	**GBD**	**SAVVY**	**GBD**	**SAVVY**	**GBD**
Cerebrovascular	0.05 (0.01-0.36)	0.07 (0.04-0.09)	1.21 (0.77-1.92)	1.23 (0.96-1.52)	1.65 (1.34-2.03)	3.16 (2.66-3.63)
Epilepsy	0.35 (0.17-0.74)	0.11 (0.08-0.14)	1.95 (1.36-2.80)	0.55 (0.43-0.69)	0.94 (0.71-1.24)	0.25 (0.22-0.30)
Meningitis	1.47 (1.02-2.10)	3.53 (2.30-6.07)	0.47 (0.22-0.99)	1.53 (1.06-2.23)	0.78 (0.58-1.06)	2.10 (1.61-2.94)
Road injuries	0.91 (0.57-1.44)	0.54 (0.36-0.84)	5.8 (4.71-7.11)	2.41 (1.89-2.99)	2.43 (2.05-2.88)	1.48 (1.29-1.67)

Legend:
Data sources
SAVVY: Analysis of Sample vital registration with verbal autopsy
GBD: Extracted from Global Burden of Disease report

With regards to comparability of this study across countries, regions, and internationally, adoptions of newer versions of ICD-10 and the tabulation list of neurological disorders are likely to result in different mortality estimates elsewhere (Mathers et al., 2005). The recent version of ICD-10 recommends grouping some hypertensive disorders as cerebrovascular deaths; such changes are likely to result in estimates that are incomparable to what was observed in this study (ICD10 Data, 2018).

Conclusions

The SAVVY survey provided estimates mortality burden of neurological disorders in Tanzania to the level of zones. Cerebrovascular diseases, epilepsy, meningitis, cerebral palsy and other paralytic syndromes, and intrauterine hypoxia are the leading causes of neurological mortality in Tanzania. The SAVVY sampling design strengthens the study in terms of representativeness for the nation and reliability of cause-of-death determination, and provides national baseline data on epidemiological information on neurological disorders needed for prevention and intervention programs. These estimates are rare in most SSA; therefore, we believe our archived data sets will contribute to advancing knowledge of neurological disorders. On the other hand, the burden associated with morbidities of neurological disorders might be far higher than that of mortality. In the case of stroke, mortality rates and deaths have substantially declined in most countries; however, the number of people living with stroke-related disabilities has been increasing. Reliable morbidity data can only be obtained when there is routine healthcare services data of good quality

and community-based surveys. Integrating measures of morbidities such as DALYs in SAVVY design may pro-vide a complete picture of disease, social and economic burden not only of neurological disorders but also of other prevalent diseases.

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Author contributions

FL analyzed data and drafted the initial manuscript. HM designed the study. HM, CN, and PO interpreted results, revised the manuscript, and supervised the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics and consent

The study protocol was approved by Ifakara Health Institution Internal Review Board, National Institute of Health Research and Commission of Science and Technology, Tanzania (Clearance reference letter No.NIMR/HQ/R.8a/Vol. IX/1256). All participants were enrolled through verbal consent.

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Paper context

In the context of low- and middle-income countries, it has been established that the majority of neurological disorders are linked to infections and brain injuries. However, in the context of epidemiological transition, we hypothesize that there is high emerging incidence of age-related neurological disorders such as dementia, cerebrovascular and heart diseases. We utilize a SAVVY study; a national representative sample and explore mortality of neurological disorders in Tanzania by sex, residence, and special geographic areas (zone).

Secular trends in neurological disorders mortality in Tanzania: analysis of data from Health and Demographic surveillance sites in Tanzania

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Abstract

Background

Neurological disorders are associated with higher mortality than the general population. We determined the magnitude and changes in the mortality associated with neurological disorders from Health and Demographic Surveillance System (HDSS) sites in Tanzania from 1999 to 2014.

Methods

Study population constituted of all residents of Rufiji, Ifakara rural and Ifakara urban HDSS sites in Tanzania. Causes of death were obtained through verbal autopsy and classified using International Classification of Disease and Injuries version 10 (ICD10). Mortality rates and secular trends were estimated using survival models.

Results

We analysed a total of 25 060 deaths in a population surveillance of 275 331 residents. Causes of deaths were complete in 80% of deaths. Age-standardized mortality rates were 34.3 (95%CI 31.5-37.1), 30.1(95%CI 26.8-33.4) and 22.9(95%CI 17.3-28.6) deaths per 100 000 person-years in Rufiji, Ifakara rural and Ifakara urban respectively. Leading cause of neurological mortality were cerebrovascular diseases with mortality rate estimates of 24.5(22.3-26.7) in Rufiji, 15.1(12.8-17.5) in Ifakara rural and 12.9(9.1-16.8) deaths per 100 000 in Ifakara urban. Annual mortality reduction of neurological disorders was observed in Rufiji (Hazard Ratio (HR) =0.96, 95%CI: 0.94-0.97) and Ifakara rural (HR=0.94, 95%CI: 0.90-0.97) HDSS but not in Ifakara urban (HR=1.02, 95%CI: 0.86-1.22).

Conclusions

This study provides evidence of no progress in the reduction of non-cerebrovascular neurological and all-cause neurological mortality in rural and urban HDSS sites respectively. This study calls for renewed efforts in addressing preventable causes of neurological disorders in LMIC were parasitic and viral infections are key aetiological factors for neurological dysfunction.

Keywords: Cerebrovascular, epilepsy, meningitis, convulsions, seizure, verbal autopsy, ICD10, survival analysis, Kaplan Meier.

Background

Neurological disorders are associated higher disability and mortality than the general population. The most prevalent neurological disorders in LMIC are stroke, Alzheimer diseases, epilepsy, Parkinson diseases, multiple sclerosis, and motor neuron diseases (Whiteford et al., 2013, IHME, 2016). Global Burden of Disease report (GBD) estimated neurological disorders (including stroke) account for 15% of global deaths (IHME, 2016, Global Burden of Disease, 2016). Some studies of mortality from neurological disorders, projected an increase for both high and low-income countries (Pritchard et al., 2013).

The aetiology of some neurological disorder in LMIC is not well understood, but the contribution of viral and parasitic infections (Mallewa et al., 2013, Newton, 2013, Howlett, 2014, Belman et al., 1988). In addition to vital and parasitical infection, increases incidence of the neurological disorder has been linked to treatment's side effects such as those for malaria and HIV/AIDS. Antimalarial drugs have been associated with increased incidence of headache and dizziness (Bitta et al., 2017). Antiretroviral drugs prescriptions have emerged with several neurological complications in people living with HIV (Robertson et al., 2008, Hall, 2006, Newton, 2006). AIDS-related neurological disorders include AIDS dementia complex; retinal abnormalities; areflexia; pyramidal tract signs and tremor and incoordination (Belman et al., 1988, De Cock, 1989).

Limited expertise in neurology and insufficient diagnostic infrastructure are among the major challenges in understanding mortality associated with neurological disorders and in averting preventable deaths in LMIC (Smart et al., 2017, Winkler et al., 2009c, Okeng'o et al., 2017). Furthermore, people with neurological disorders are stigmatized

and marginalized in most communities in LMIC, hence not represented in health and mortality statistics (Whiteford et al., 2013). The most reliable source of mortality of neurological disorder globally and in LMIC is the GBD study. The mortality rate of neurological disorders in low-income countries was estimated at 33 (95% Confidence interval (CI): 27-39) deaths per 100 000 in 2015. The leading causes of neurological deaths in LMIC are cerebrovascular diseases with a mortality rate from ischemic stroke estimated at 68 (95%CI: 55-80) and hemorrhagic stroke at 81 (95%CI: 70-93) deaths per 100 000. Other disorders with high mortality rate include Alzheimer disease 6 (95%CI: 5-7) and epilepsy 4 (95%CI: 3.5-4.79) deaths per 100,000 population.

Tanzania, like many other LMIC, lack comprehensive vital registration system necessary for generating population estimates of deaths, their causes, and following trends (Chang et al., 2011, Ferreira Ide et al., 2009, O'Callaghan et al., 2004, Gomes, 2011, O'Callaghan et al., 2000, Aspray, 2005, Tsai, 2005, Mikkelsen et al., 2015). This has resulted in absence of reliable data on magnitude, distribution, and trends of mortality of neurological disorder in the country. There are limited studies that provide the estimate of mortality of neurological diseases in Tanzania.

In response to this lack of data on these vital statistics, Ifakara Health Institute established three HDSS sites, aimed at monitoring demographic and health statistics in large population cohorts in place of a civil and vital registration system. In addition to monitoring key health and demographic events in the selected area, causes of death are determined for every reported death using International Classification of Diseases and Injuries (ICD) (Mrema et al., 2015, Geubbels et al., 2015, Sankoh et al., 2014b). Epidemiology of mortality from neurological disorders has not been described before in these large population cohorts.

The objective of this study is to determine the magnitude and if there has been a reduction in mortality of neurological disorder in three HDSS sites from 1999 to 2014.

Methods

Study populations were all residents of the large three HDSS sites in Tanzania; Rufiji HDSS (R-HDSS), Ifakara Rural (IR-HDSS) and Ifakara Urban HDSS (IU-HDSS) (Figure 7-1). The three demographic surveillances had a total of about 275,331 active residents in 60,882 households at the time of data extraction. HDSS sites were designed as an open dynamic cohort, which enrolls individuals through baseline enumeration, birth, and in-migration and exits individuals throughout migration and deaths.

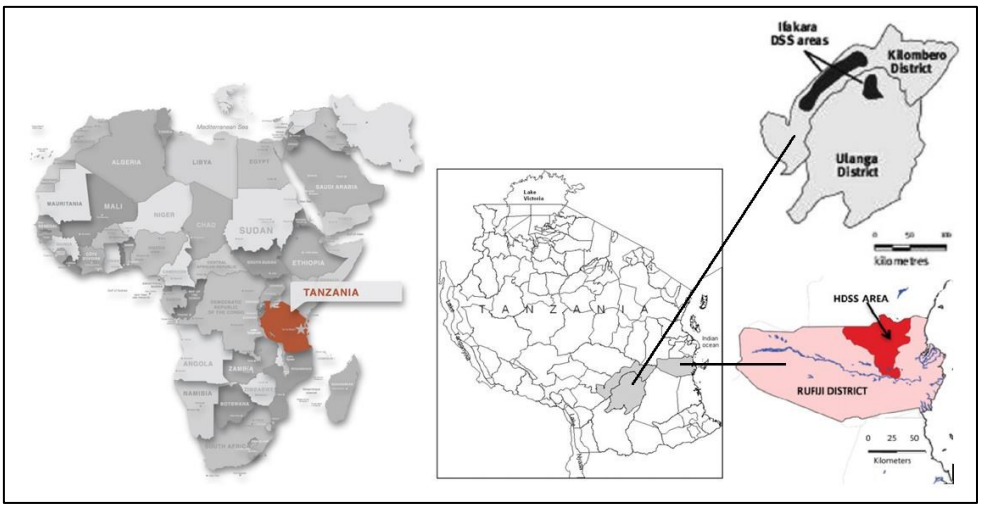

Figure 7-1: Location map of HDSS areas within Tanzania and Africa

To ascertain the cause of death, verbal autopsy (VA) was employed because post-mortem examinations are not conducted routinely in Tanzania, similar to many LMIC (Sankoh et al., 2014a, Setel et al., 2006, Mikkelsen et al., 2015). The process involves in-depth structured interviews of the care taker of the diseased on signs, symptoms, pre-existing conditions and health-seeking choices prior to death using VA questionnaires. Questionnaires are further critically reviewed by trained physicians

who at the end of process assign the cause of death. Over the study period, two versions of VA tools have been employed in the study area. The first version was adopted from World Health Organization (WHO) and employed in the study area from 1999 to 2007. The tools in the first version comprised of autopsy questionnaires with fewer questions and condensed list of causes of death based local disease burden. The second version was a fully-designed WHO verbal autopsy questionnaires and disease classification (ICD10) tool which was used from 2008 to 2014.

Neurological causes of deaths were classified using ICD10 code ranges of G00-G99 for diseases of nervous system, I60-69 for cerebrovascular diseases and S06 for traumatic brain injuries/ intracranial injury for deaths (Jette et al., 2015).

Mortalities from neurological disorder were estimated using survival analysis models. HDSS residency episodes were organized in long format and merged with basic demographic variables including sex and causes of death variables from causes of death file from VA. Exposure time was estimated from individual's residence episodes started at enrolment, birth or in-migration and ended at out-migration or death or at the end of the analysis period. Mortality rates estimates were grouped in time intervals (years) and mortality rate ratio compared by sex, age and time. Mortality rate ratios were estimated using Mantel-Haenszel method. International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) standard life table was used as standard population in comparing mortality between the three sites (Sankoh et al., 2014b).

We used the Kaplan-Meier method to estimate the probability of neurological deaths in the population of adults aged 15 years and above. Kaplan-Meier estimates were stratified by site to ascertain trends in the probability of neurological deaths as

individual's ages. Cox regression model was employed to estimate of the effect of potential covariates and secular trends of neurological mortality. Stata software version 13 (StataCorp LP, College Station, Texas) was used for descriptive statistics and statistical analysis (Boston et al., 2003).

The study protocol was approved by Ifakara Health Institution Internal Review Board, National Institute of Health Research and Commission of Science and Technology, Tanzania. All participants were enrolled through verbal consent. Before enrolled in the population-based cohort, participants were introduced to the rationale of the demographic surveillance system and were informed about publication of their information without individual identification.

Results

There was total of 539,886 residents observed aggregated to 2,393,199 person-years of observations. Across three sites, there were 25,060 deaths over the analysis period; 13,739 (55%) in R-HDSS, 9,345 (37%) in IR-HDSS and 1,985 (8%) in IU-HDSS. Causes of death were available for 20,046 (80%) of deaths, 1,480 (6%) had complete verbal autopsy interviews but the cause could not be determined and 3,534 (14%) had the missing cause of death. The reasons for the missing cause of death include migration, missing of the household during routine household surveillance, refusal of an interview and on-going causes of death assignment by physicians.

Total of 907 deaths from neurological diseases in the three HDSS sites were observed over the study periods. An additional file describe in tabular form the number of deaths and by sex, age, year, cause of death and site (Supporting information Table S1). Cerebrovascular diseases (mainly stroke) contributed 618 (68.1%) deaths followed by 146 (16.1%) epilepsy, 87(9.6%) meningitis and 56 (6.2%) other neurological deaths.

Neurological mortality

The total follow-up periods were 16, 11, and 4 years in R-HDSS, IR-HDSS, and IU-HDSS sites respectively. Standardized mortality rates were 34 (95%CI: 31-37), 30 (95%CI: 27-33) and 23 (95%CI: 17-29) deaths per 100 000 person-years in R-HDSS, IR-HDSS, and IU-HDSS respectively (Table 7-1).

Within sites, the mortality rate was comparable for males and females in R-HDSS and IU-HDSS but higher in males than females in IR-HDSS (Rate Ratio (RR)= 1.29, 95%CI: 1.02-1.64). Adults aged 50 years and above had the highest mortality rate (RR=14, 95% CI:10.5-18.8) than children under five years, children 5-14 years (RR=25.5, 95% CI:19-34), and middle-aged 15-49 years (RR=9.2, 95% CI:7.8-10.9).

Estimates of mortality of disease of disease of neurological disorder and cerebrovascular diseases across sites were observed to fluctuate annually with the overall declining trend over the study period (Figure 7-2).

The proportions of individuals died with a neurological disorder in the hypothetical population of 1000 increased by age reaching 16, 14 and 10 by age 60 (Table 7-3) in R-HDSS, IR-HDSS, and IU-HDSS respectively. No site differences were observed in the probability of dying per 1000 population age (Figure 7-3). Results of Cox regression analysis showed the decline in mortality rate in R-HDSS (Hazard rate ratio (HR)=0.96, 95% CI: 0.94-0.97), IR-HDSS (HR=0.94, 95% CI: 0.9-0.97), and no change in IU-HDSS (Table 7-4). No sex differences were also observed all sites.

Table 7-1: Mortality rates of neurological diseases by type, sex, age and site

Variable	Rufiji HDSS		Ifakara Rural		Ifakara Urban	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted
Cerebrovascular diseases						
Males	72.3(63.4-82.5)		24(18.8-30.6)		19.2(10.9-33.9)	
Females	67.5(59.3-76.8)		23.8(18.7-30.2)		24(15.1-38)	
15-49	10.4(7.8-13.8)		4(2.5-6.4)		2.7(.9-8.5)	
50+	218.4(198-240.7)		105.8(88.1-127.1)		98.2(67.4-143.3)	
15+	69.8(63.6-76.5)	24.3(22.1-26.5)	23.9(20.1-28.3)	14.8(12.6-17.1)	21.8(15.3-31.2)	12.9(9.1-16.8)
Overall	**38.2(34.9-41.9)**	**24.5(22.3-26.7)**	**13.7(11.5-16.2)**	**15.1(12.8-17.5)**	**13.7(9.6-19.6)**	**12.9(9.1-16.8)**
Epilepsy						
Males	6.2(4.4-8.9)		10.3(7.6-14)		4.5(1.7-11.9)	
Females	6.3(4.5-8.9)		6.2(4.2-9.1)		4.9(2-11.7)	
5-14	4.4(2.6-7.3)		4(2.2-7.3)			
15-49	8(5.8-11.1)		11(8.3-14.6)		8.2(4.3-15.7)	
50+	5.4(2.9-10.1)		7.4(3.7-14.9)			
5+	6.3(4.9-8)	5.4(4-6.7)	8.2(6.5-10.5)	7.2(5.5-8.9)	4.7(2.4-9)	3.9(1.3-6.4)
Overall	**5.2(4.1-6.7)**	**5.4(4-6.7)**	**7.6(6.1-9.5)**	**7.9(6.1-9.7)**	**4.1(2.1-7.9)**	**3.9(1.3-6.4)**
Meningitis						
Males	6.1(3.5-10.8)		12.9(8.4-19.7)		3.7(.5-26.3)	
Females	2.6(1.6-4.3)		6.3(4.5-9)		1(.1-6.9)	
0-4	2.8(1.7-4.5)		3.4(2.1-5.5)		5.2(2.3-11.5)	
5-14	2(1-4.3)		2.6(1.2-5.4)		1.8(.3-13)	
15-49	1.3(.6-2.9)		3.4(2-5.6)		3.6(1.4-9.7)	
50+	3.8(1.8-8)		4.6(1.9-11.1)		3.6(.5-25.8)	
Overall	**2.7(1.9-3.8)**	**2.4(1.5-3.3)**	**4.9(3.7-6.4)**	**4.7(3.4-6.1)**	**3.2(1.5-6.7)**	**3(.7-5.2)**

- Adjusted for age using INDEPTH standard population [Sankoh O, Sharrow D, Herbst K, et al. The INDEPTH standard population for low- and middle-income countries, 2013. *Glob Health Action* 2014; **7**: 2328

Table 7-2: Mortality rates of neurological diseases continue

	Rufiji HDSS		Ifakara Rural		Ifakara Urban	
Variable	**Crude**	**Adjusted***	**Crude**	**Adjusted***	**Crude**	**Adjusted**
Neurological (excluding cerebrovascular deaths)						
Males	10.7(8.3-13.7)		18.2(14.8-22.4)		9.7(5.2-18)	
Females	10.1(7.8-13)		11.2(8.6-14.6)		9.5(5.2-17.1)	
0-4	7.1(4.2-12)		19(13.4-27)		18.5(7.7-44.5)	
5-14	7.6(5.2-11.2)		7.7(5-11.8)		1.8(.3-13)	
15-49	10.8(8.2-14.3)		15.5(12.3-19.6)		11.8(6.9-20.4)	
50+	17.9(12.7-25.2)		22.3(14.9-33.2)		7.3(1.8-29.1)	
Overall	**10.4(8.7-12.4)**	**9.8(8.0-11.6)**	**14.7(12.5-17.3)**	**15.0(12.5-17.4)**	**9.6(6.2-14.7)**	**10.0(5.7-14.2)**
All neurological conditions						
Males	49.2(43.8-55.3)		31.9(27.3-37.4)		21.4(14.1-32.4)	
Females	48.1(42.9-53.9)		24.8(20.8-29.6)		25(17.3-35.9)	
0-4	7.6(4.6-12.7)		20.8(14.9-29.2)		18.5(7.7-44.5)	
5-14	7.9(5.4-11.5)		7.7(5-11.8)		1.8(.3-13)	
15-49	21.2(17.4-25.9)		19.6(15.9-24.1)		14.5(8.9-23.7)	
50+	236.2(215.1-259.5)		128.1(108.4-151.4)		105.5(73.3-151.9)	
Overall	**48.6(44.8-52.8)**	**34.3(31.5-37.1)**	**28.3(25.2-31.9)**	**30.1(26.8-33.4)**	**23.3(17.7-30.6)**	**22.9(17.3-28.6)**

*Adjusted for age using INDEPTH standard population [Sankoh O, Sharrow D, Herbst K, et al. The INDEPTH standard population for low- and middle-income countries, 2013. *Glob Health Action* 2014; **7**: 23286

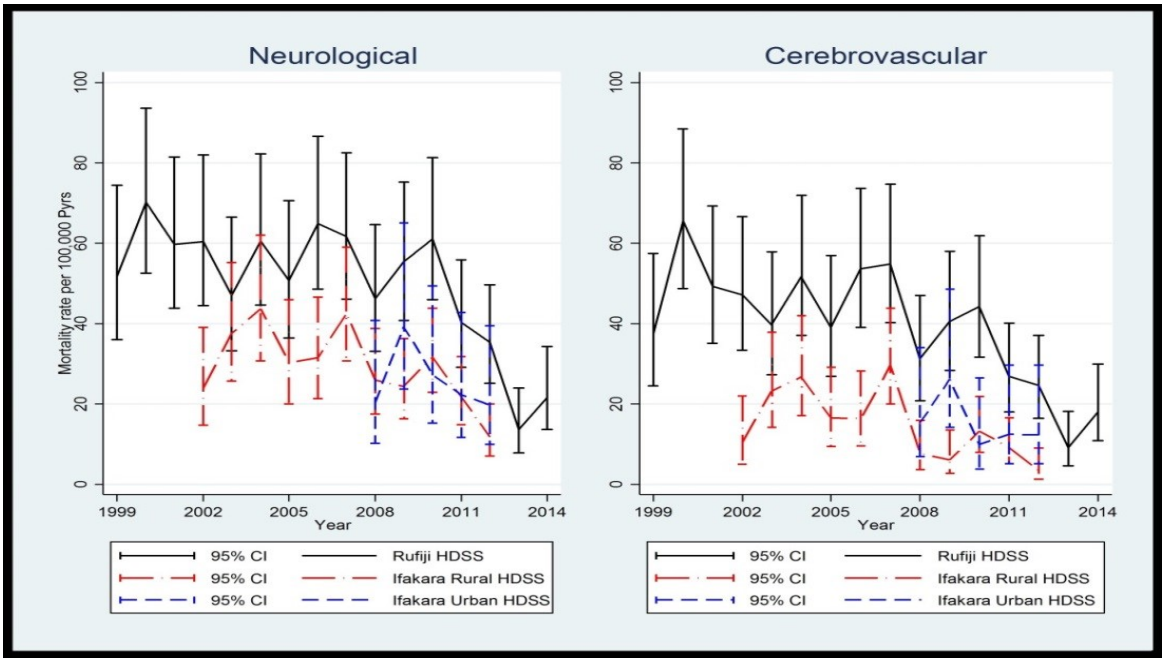

Figure 7-2: Trends in neurological and cerebrovascular disorder 1999-2014.

Cerebrovascular mortality

Stroke was the dominant (89%) cause of death in cerebrovascular diseases and mainly occurred in adults older than 50 years (Supporting information Table S1). Standardized mortality rates for adults above 15 years of age were 24.3 (95%CI: 22.1-26.5), 14 (95%CI: 12.6-17.1) and 12.9 (95%CI: 9.1-16.8) deaths per 100,000 person years in R-HDSS, IR-HDSS and IU-HDSS respectively (Table 7-1).

Within sites, mortality rate was comparable for males and females (Overall RR=1.13, 95%CI: 0.97-1.33). Adults aged 50 years and above had the highest mortality rate than adults aged 15-49 (Overall RR=22.5, 95% CI: 17.5-29). Cerebrovascular mortality rate were observed to fluctuate annually with overall declining trend (Figure 7-2).

Table 7-3: Kaplan Meier probability* of dying from neurological disorders

	Neurological			Cerebrovascular			Epilepsy			Meningitis		
Age	Rufiji	IR	IU	Rufiji	IR	IU	Rufiji	IR	IU	Rufiji	IR	IU
15	1.2	1.8	1.1	0.1	0.1	0.0	0.4	0.6	0.0	0.5	0.9	0.4
20	1.5	2.8	2.0	0.1	0.1	0.2	0.7	1.5	0.7	0.5	0.9	0.4
25	2.7	3.5	2.5	0.2	0.2	0.2	1.6	2.1	1.2	0.6	1.0	0.4
30	3.7	4.0	2.8	0.5	0.3	0.2	2.1	2.4	1.5	0.7	1.0	0.4
35	4.9	5.4	3.7	1.3	0.6	0.5	2.3	3.0	1.8	0.8	1.4	0.6
40	6.3	6.9	4.8	2.1	1.0	0.5	2.7	3.9	1.8	0.9	1.6	1.8
45	7.3	7.9	5.8	2.8	1.4	1	2.9	4.1	2.4	0.9	2.0	1.8
50	9.8	9.0	6.5	5.1	1.8	1	3.1	4.1	3.0	0.9	2.3	1.8
55	11.8	10.4	8.0	7.0	3.1	2.4	3.1	4.3	3.0	0.9	2.3	1.8
60	16.4	13.6	9.7	11.6	4.9	3.4	3.1	4.8	3.0	0.9	2.8	2.5

IR:Ifakara Rural, IU: Ifakara Urban, *Deaths per 1000 population

The proportions of individuals died with cerebrovascular diseases in the population increased by age reaching 12, 5 and 3 deaths per 1000 by age 60 (Figure 7-3) in R-HDSS, IR-HDSS and IU-HDSS respectively. No site differences were observed except in R-HDSS were high mortality were at old ages was observed (Figure 7-2). Results of cox regression analysis indicated decline in mortality rate in R-HDSS (HR=0.95, 95% CI: 0.93-0.97), IR-HDSS (HR=0.89, 95% CI: 0.85-0.94), and no change in IU-HDSS (Table 7-4). No sex differences were also observed all sites.

Epilepsy mortality

Total of 146 (16%) epilepsy deaths were observed in the three HDSS sites. Age standardized mortality rates were 5.4, 7.9 and 3.9 deaths per 100,000 person years in R-HDSS, IR-HDSS and IU-HDSS respectively (Table 7-1). Mortality was comparable within sites for males and females, but overall mortality rate was higher for males than females (Overall RR=1.19, 9 5%CI: 1.05-1.36). Adults aged 50 years and above had the highest mortality rate than adults aged 15-49 (Overall RR=9.2, 95% CI: 7.8-10.9). Estimates of secular trend of mortality of epilepsy across sites were observed to fluctuate annually especially for IU-HDSS and IR-HDSS (Table 7-4). Results of Cox regression analysis indicated no change in epilepsy mortality rate in R-

HDSS (HR=0.99, 95% CI: 0.94-1.04), IR-HDSS (HR=0.94, 95% CI: 0.87-1.01), and IU-HDSS (HR=1.19, 95% CI: 0.77-1.85) (Table 7-4). No sex differences were observed all sites (Table 7-4).

Table 7-4: Hazard ratio estimates by site and cause of neurological death

	Female(Male in reference category)	95% CI	Year	95% CI
Rufiji HDSS				
Neurological	0.87	0.73-1.02	0.96	0.94-0.97
Cerebrovascular diseases	0.85	0.71-1.02	0.95	0.93-0.97
Epilepsy	1.01	0.61-1.67	0.99	0.94-1.04
Meningitis	1.08	0.54-2.17	1.07	0.99-1.16
Ifakara rural HDSS				
Neurological	0.78	0.61-0.98	0.94	0.9-0.97
Cerebrovascular diseases	0.98	0.7-1.37	0.89	0.85-0.94
Epilepsy	0.63	0.39-1.00	0.94	0.87-1.01
Meningitis	0.55	0.3-0.99	1.13	1.02-1.24
Ifakara Urban HDSS				
Neurological	0.96	0.55-1.68	1.02	0.86-1.22
Cerebrovascular diseases	0.94	0.45-1.97	0.96	0.76-1.22
Epilepsy	1.09	0.29-4.08	1.19	0.77-1.85
Meningitis	5.49	0.66-45.66	0.96	0.62-1.5

Meningitis mortality

Most meningitis deaths occurred in children and elderly in all HDSS sites. IR-HDSS and IU-HDSS had exceptionally high mortality rate in individuals aged 15-49 years of age (Supporting information Table S1). Standardized mortality rates were 2.4 (95%CI: 1.5-3.3), 4.7 (95%CI: 3.4-6.1) and 3.2 (95%CI: (0.7-5.2) deaths per 100,000 person years in R-HDSS, IR-HDSS and IU-HDSS respectively (Table 7-1). Within sites, mortality rate was comparable for males and females (Overall age adjusted RR=1.21, 95%CI: 0.79-1.84) in R-HDSS and IU-HDSS but higher in males than females in IR-HDSS (Age adjusted RR=1.84, 95% CI: 1.02-3.33). There were no age differences in mortality rate (Overall sex adjusted RR=1.78, 95% CI: 0.9-3.5). Meningitis mortality rate were observed to remain constant over the study period (Figure 7-4).

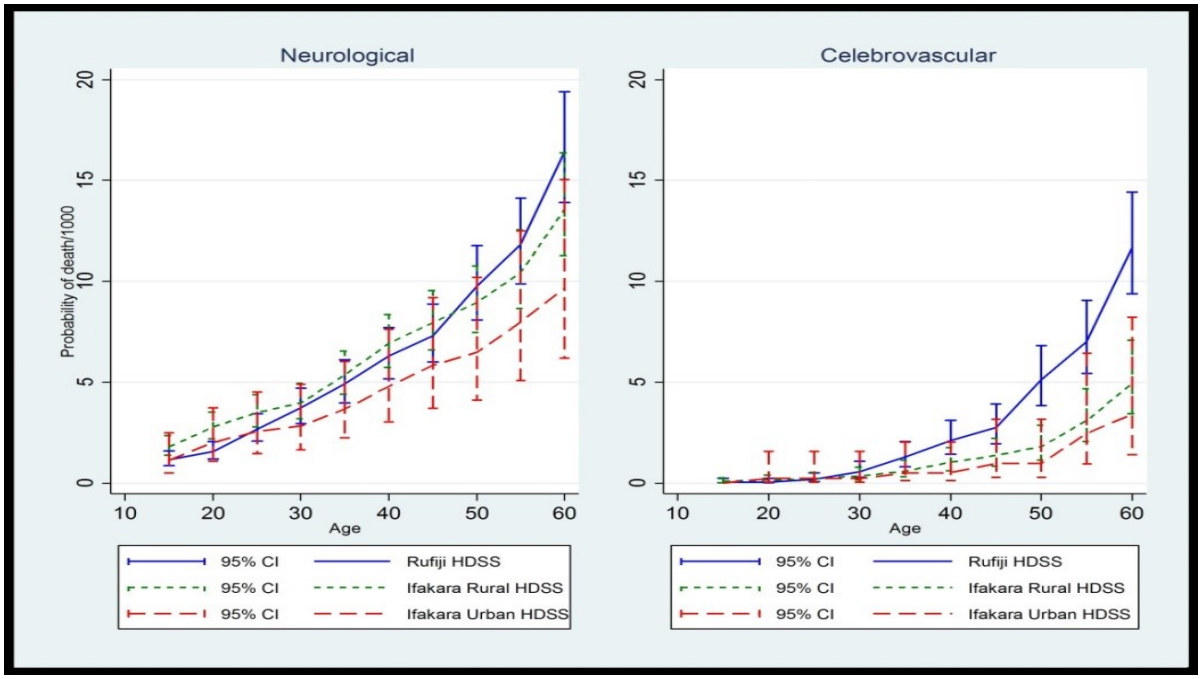

Figure 7-3: Probability of death from neurological cerebrovascular diseases

The proportions of individuals died with epilepsy in the population cohort increased by age reaching 3.1, 4.8 and 3 deaths per 1000 by age 60 in R-HDSS, IR-HDSS and IU-HDSS (Table 7-3). No site differences were observed (Figure 7-5).

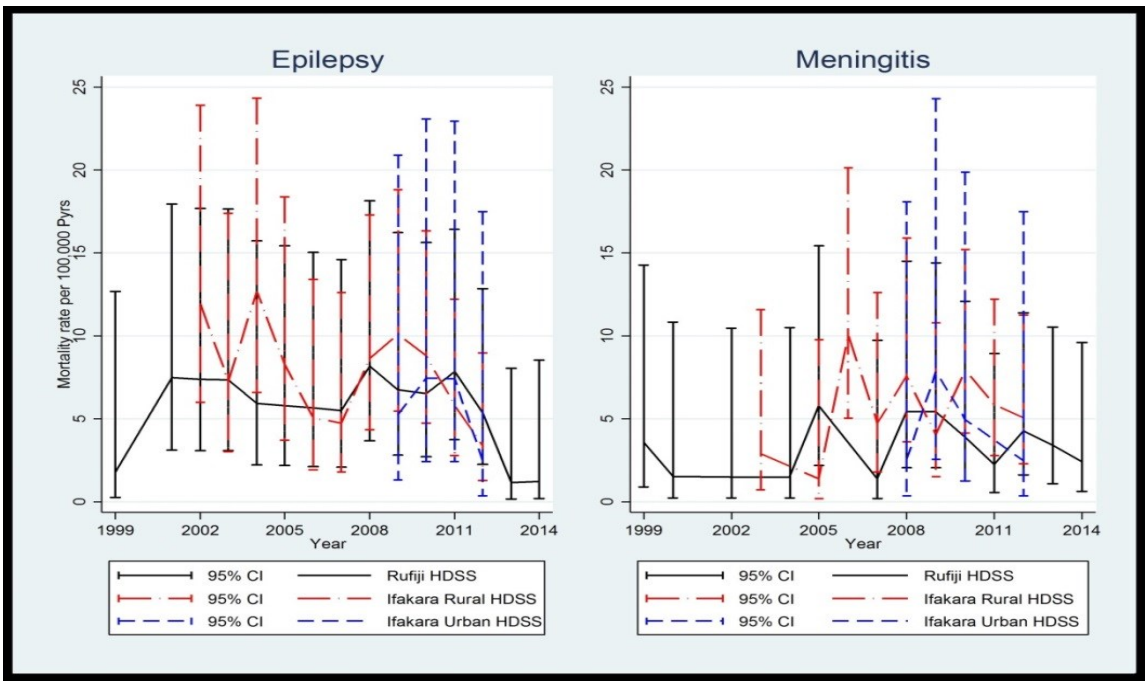

Figure 7-4: Trends in epilepsy and meningitis mortality 1999-2014.

The proportions of individuals died with meningitis in the population increased by age reaching 0.9, 2.8 and 2.5 deaths per 1,000 by age 60 R-HDSS, IR-HDSS and IU-HDSS respectively (Table 7-3). Results of Cox regression analysis indicated no change in trends in meningitis mortality in R-HDSS (HR=1.07, 95% CI: 0.99-1.16) and IU-HDSS (HR=0.96, 95% CI: 0.62-1.5) and increasing trend in IR-HDSS (HR=1.13, 95% CI: 1.02-1.24) (Table 7-4). No sex differences were also observed RHDSS and IU-HDSS while lower risks were observed in females than males (Age adjusted HR=0.55, 95% CI: 0.3-0.99).

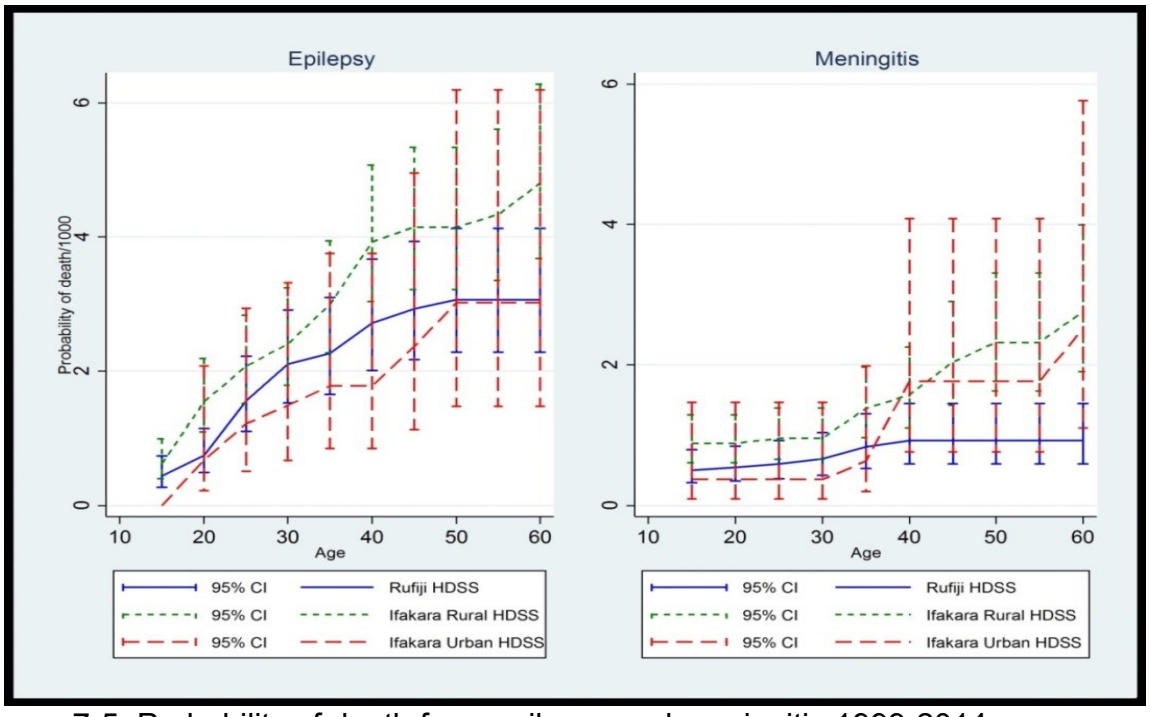

Figure 7-5: Probability of death from epilepsy and meningitis 1999-2014.

Discussions

This study provided evidence of site specific variations in the magnitude, distribution and trends of mortality from neurological disorders from HDSS sites in Tanzania. The total population followed from HDSS sites was approximately 275,000, which is sufficiently large to provide reliable estimates of magnitude, distributions and trends mortality of neurological disorders. Cause specific neurologic mortality distributions

were comparable across sites with highest mortality attributed to cerebrovascular disorder, followed by epilepsy and least by meningitis. The overall high mortality rates across sides were highly driven by high mortality rate from cerebrovascular disorders in older ages. Reduction in neurological mortality was observed in Rufiji HDSS only, due to substantial reduction in cerebrovascular deaths.

This study categorized cerebrovascular deaths as neurological death. This classification however differs from GBD reporting which do not include cerebrovascular deaths as neurological deaths. Excluding cerebrovascular deaths to match GBD reporting produced mortality estimates of neurological disorder to 50% lower than estimates when cerebrovascular disorders were included. The estimated mortality rates across sites were within the range of estimates reported in GBD report (27-39 deaths per 100 000) for 2015 in low income countries. There was no reductions non-cerebrovascular mortality of neurological disorders across sites over the study period.

As expected cerebrovascular mortality were highest among older individuals above fifty years old compared to young adults as observed from crude site specific mortality estimates. Most cerebrovascular deaths were stroke. GBD reported mortality from ischemic stroke at 68 (95%CI: 55-80) and haemorrhagic stroke at 81 (95%CI: 70-93) deaths per 100 000, comparable to estimates for individual aged 50 and above. Reductions in cerebrovascular mortality were observed in rural sites only (R-HDSS and IR-HDSS).

Estimates of mortality from epilepsy were comparable across HDSS sites and remained within the range of estimates from GBD for low income countries (4-6 deaths per 100,000 annually) in R-HDSS and IU-HDSS but high in IR-HDSS (6.1-9.5 deaths

per 100,000). Epilepsy mortality were also within the estimates from recent GBD (6.9 range 4.2-11.8 deaths per 100,000) report for Tanzania. All estimates of mortality from epilepsy were higher than global estimate as reported GBD report for 2015 with epilepsy mortality annual rate of 1.19 ranges from 1.14-1.23 deaths per 100 000 population. Population based HDSS estimates from Adult Morbidity and Mortality Project (AMMP) implemented between 1992 and 1995 in Tanzania estimated epilepsy mortality annual rate of 15 male and 5 female deaths per 100,000 population (Aspray, 2005, Ministry of Health, 1997).

High mortality rate from neurological disorders in LMIC may be greatly associated with insufficient health care, poor access and adherence to medication such as antiepileptic drugs. Detailed analysis of epilepsy deaths revealed poor health seeking practices where almost a quarter of diseased had consulted witchdoctors or were treated at home and less than forty per cent attended government hospital. Poor access to health care for management of seizures may explain high frequency of convulsions (64%), lost conscious (42%), injuries (24%) and sudden fatal events (48%) that lasted within 24hours.

Limitations

The study reported mortality rates of neurological deaths from large population-based cohort where causes of death were available 80% all deaths. Reasons for incomplete causes of death were mostly associated with on-going causes of death assignment by physicians and migrations therefore missing at random assumption were applied. Under this assumption, the actual mortality of neurological disorder may be higher than reported in this study. Most VA studies reported lower completeness than

reported in this study, typical example include Vietnam national mortality survey where completeness of 69% in males and 54% in females was reported (Ngo et al., 2010).

High mortality decline of neurological disorders post 2008 may be influenced by the change in VA questionnaires in 2008. However this is only observed in cerebrovascular diseases but not in epilepsy, meningitis or the other neurological disorders.

There were insufficient data across sites that may have assisted on analysis of risk factors for observed variations in the number of cases and mortality rates of neurological disorders across sites over time. Reduced mortality in some sites may not necessarily mean decline in the number of cases in the population (Okeng'o et al., 2017). Only one epilepsy prevalence study was available for IR-HDSS were prevalence of active convulsive epilepsy was estimated at 14.8 (95% CI: 13.8–15.4) per 1000 population screened and established an association between Active convulsive Epilepsy (ACE) with *Onchocerca volvulus*, *Toxocara canis*, *Toxoplasma gondii*, *O. volvulus* and adult onset of ACE with *T. canis*, *Taenia solium* and *O. volvulus* (Ngugi et al., 2013a).

Conclusion

The magnitude of mortality of neurological disorders from HDSS sites in Tanzania are within the estimates provided by GBD for low income countries. The estimates are higher than global estimates. Cerebrovascular diseases were the leading neurological mortality in the population, followed by epilepsy and meningitis. Reductions in neurological mortality were observed in HDSS sites in rural settings where reductions in cerebrovascular diseases were also observed. No change in neither neurological nor cerebrovascular mortality was observed in urban HDSS site. The combined

estimates of mortality of neurological disorder excluding cerebrovascular disorder did not change over the study period across all HDSS sites.

This study provides evidence of no progress in the reduction of non-cerebrovascular neurological disorders in Rural HDSS site (R-HDSS and IR-HDSS) and any neurological disorder in IU-HDSS site. This study calls for renewed efforts in addressing neurological disorders in low income countries were parasitic and viral infections are key aetiological factors of neurological disorders.

Supporting information

Table S1: Number and per cent of neurological deaths by sex, age, year in Rufiji HDSS

	Cerebrovascular	Epilepsy	Meningitis	Others	Total
Male	223 (49)	30 (48)	15 (47)	17(59)	285 (49)
Female	230 (51)	32 (52)	17 (53)	12(41)	291 (51)
Age					
0-4	1 (0)		12 (38)	2(7)	15 (3)
5-14	1 (0)	15 (24)	7 (22)	4 (14)	27 (5)
15-49	48 (11)	37 (60)	6 (19)	7 (24)	98 (17)
50+	403 (89)	10 (16)	7 (22)	16 (55)	436 (76)
Year					
1999	21(5)	1 (2)	2 (6)	5 (17)	29 (5)
2000	43 (9)		1 (3)	2 (7)	46 (8)
2001	33 (7)	5 (8)		2 (7)	40 (7)
2002	32 (7)	5 (8)	1 (3)	3 (10)	41 (7)
2003	27 (6)	5 (8)			32 (6)
2004	35 (8)	4 (6)	1 (3)	1 (3)	41 (7)
2005	27 (6)	4 (6)	4 (13)		35 (6)
2006	38 (8)	4 (6)		4 (14)	46 (8)
2007	40 (9)	4 (6)	1 (3)		45 (8)
2008	23 (5)	6 (10)	4 (13)	1 (3)	34 (6)
2009	30 (7)	5 (8)	4 (13)	2 (7)	41 (7)
2010	34 (8)	5 (8)	3 (9)	5 (17)	47 (8)
2011	24 (5)	7 (11)	2 (6)	3 (10)	36 (6)
2012	23 (5)	5 (8)	4 (13)	1 (3)	33 (6)
2013	8 (2)	1 (2)	3 (9)		12 (2)
2014	15 (3)	1 (2)	2 (6)		18 (3)
Total	**453 (100)**	**62 (100)**	**32 (100)**	**29 (100)**	**576 (100)**

Table S1: Number and per cent of neurological deaths by sex, age, year in Ifakara Rural

	Cerebrovascular diseases*	Epilepsy	Meningitis	Others	Total
Male	67 (50)	46 (61)	31 (65)	12 (55)	156 (56)
Female	68 (50)	29 (39)	17 (35)	10 (45)	124 (44)
Age					
0-4	3 (2)	7 (9)	21 (44)	3 (14)	34 (12)
5-14		11 (15)	7 (15)	3 (14)	21 (8)
15-49	18 (13)	49 (65)	15 (31)	5 (23)	87 (31)
50+	114 (84)	8 (11)	5 (10)	11 (50)	138 (49)
Year					
2002	7 (5)	8 (11)		1 (5)	16 (6)
2003	16 (12)	5 (7)	2 (4)	3 (14)	26 (9)
2004	19 (14)	9 (12)		3 (14)	31 (11)
2005	12 (9)	6 (8)	1 (2)	3 (14)	22 (8)
2006	13 (10)	4 (5)	8 (17)		25 (9)
2007	25 (19)	4 (5)	4 (8)	3 (14)	36 (13)
2008	7 (5)	8 (11)	7 (15)	2 (9)	24 (9)
2009	6 (4)	10 (13)	4 (8)	4 (18)	24 (9)
2010	15 (11)	10 (13)	9 (19)	2 (9)	36 (13)
2011	11 (8)	7 (9)	7 (15)	1 (5)	26 (9)
2012	4 (3)	4 (5)	6 (13)		14 (5)
Total	**135 (100)**	**75 (100)**	**48 (100)**	**22 (100)**	**280 (100)**

Table S1: Number and per cent of neurological deaths by sex, age, year in Ifakara Urban

	Cerebrovascular diseases	Epilepsy	Meningitis	Others	Total
Male	12 (40)	4 (44)	1 (14)	5 (100)	22 (43)
Female	18 (60)	5 (56)	6 (86)		29 (57)
Age					
0-4			1 (14)	4 (80)	5 (10)
5-14			1 (14)		1 (2)
15-49	3 (10)	9 (100)	4 (57)		16 (31)
50+	27 (90)		1 (14)	1 (20)	29 (57)
Year					
2008	6 (20)		1 (14)	1 (20)	8 (16)
2009	10 (33)	2 (22)	3 (43)		15 (29)
2010	4 (13)	3 (33)	2 (29)	2 (40)	11 (22)
2011	5 (17)	3 (33)		1 (20)	9 (18)
2012	5 (17)	1 (11)	1 (14)	1 (20)	8 (16)
Total	**30 (100)**	**9 (100)**	**7 (100)**	**5 (100)**	**51 (100)**

Discussion and conclusions

Summary findings

This thesis provides knowledge on uncertainties of epilepsy in SSA in relation to mortality, risk factors, and causes of death in PWE. The knowledge and evidence were generated from five studies using empirical data from community-based studies.

Systematic review

The first thesis objective was aimed at reviewing and summarizing available evidence on excess mortality in PWE compared to general population in LMIC. Systematic review in Chapter 3 identified only 7 studies in LMIC over the period of 25 years. Estimated excess mortality of ranged from 1.3-7.2 times higher in PWE compared to general population (median=2.6).

Meta-analysis of this systematic review indicated that up to 80% of total variability's in the estimate of excess mortality (SMR) was only due to differences between studies. These differences may be due to methodological variations between studies or other unknown factors. The estimated excess mortality of 2.6 was median value and not pooled estimate as large variability's between studies could not allow combined estimate of 7 studies.

In conclusion, until this systematic review was done, there were no sufficient data to provide empirical evidence of excess mortality in PWE in LMIC.

SEEDS study: Excess mortality

At the time the systematic review was completed, new data on mortality of PWE were emerging from SEEDS studies. SEEDS studies had already followed PWE for over 8 years and documented deaths in people with and without epilepsy. Chapter 4 of this thesis was dedicated at pooling and generating new evidence of excess mortality in PWE from SEEDS studies.

The pooled excess mortality was 4.8 times higher in PWE than general population (95% CI: 4.2-5.6). SEEDS estimate is higher than summary findings from systematic review in reported in the literature in Chapter 3. SEEDS studies were conducted to account for methodological limitations encountered in most epilepsy studies related to screening, diagnosis, mortality and causes of death assessment, and population representativeness.

SEEDS study: Risk factors

The studies also identified modifiable risk factors potential for intervention programs and mitigating the negative impact of epilepsy.

Causes of death automation

In addition to summarizing excess mortality in PWE, systematic review in Chapter 3 summarized causes of deaths in PWE from different studies. Summary estimates from different studies in LMIC indicated most PWE died of direct (SE and SUDEP) and indirect (injuries) causes of epilepsy death. These studies compiled causes of death information from variety of sources including physicians, verbal autopsies and death certificates.

In Chapter 5, this thesis assessed the application of automated tools in ascertaining causes of death in PWE. The assessment indicated that, the use of automated tools is potentials, convenient and affordable alternative to post-mortem and physician death certification. Unlike the use of other sources of cause of death information, automated tool estimated lower number of epilepsy-related deaths (27.5%) compared to around 50% when physician make diagnosis of cause of death. Chapter 5 also provides valuable information and recommendation needed for further development

and refinement of these tools especially with regards to coding SUDEP, SE, and injuries.

National estimates

Chapter 6 and 7 provides national and community-based estimates of mortality of epilepsy and other neurological disorders from national (SAVVY) and community-based studies (HDSS). The findings indicate epilepsy the second leading cause of death after cerebrovascular disorders. The estimates of mortality rate in the population ranged from 7-8 and 4-8 deaths per 100,000 populations in SAVVY and HDSS respectively.

HDSS data

HDSS sites have become platform for monitoring demographic indicators in most SSA. Analysis of HDSS data was aimed at ascertaining whether there has been declining trends in epilepsy and other neurological disorders over time. In Chapter 7 of this thesis, results of the analysis indicated epilepsy mortality did not change over the past 15 years.

Synthesis

This thesis generated new insights into the epidemiology of epilepsy in SSA. Limited data of studies of burden of epilepsy mortality in SSA point to either lack of interest in the subject, resources limitations from governments and funding bodies, and lack of knowledge of the negative impact of epilepsy. This study provides rigorous evidence of excess mortality needed for advocacy to health care providers, governments, and funding bodies for increased investment in care, preventions and reduction of the negative impact of epilepsy in SSA. The community and health care providers will

benefit from evidence on modifiable risk factors for incidence and excess mortality from SEEDS study.

Discussion

Excess mortality in epilepsy: Systematic review in LMIC

The median mortality rate in PWE is estimated at 20 deaths per 1,000 people with epilepsy (range 10-45) in population-based studies. The estimated excess mortality in LMIC is 2.6 times higher in PWE (range 1.3-7.2) than the general population. Epilepsy-related deaths accounted for 50% of all reported deaths in PWE; with 27% being due to SUDEP and SE and the remaining injuries.

Previous review of excess mortality reported much lower number of studies from SSA compared to this study (Nevalainen et al., 2014, Carpio et al., 2005). This reviews provided comprehensive summary of mortality estimates in epilepsy from high quality studies. Qualities of studies were judged according to criteria suggested by the ILAE for epidemiological studies based on methodological limitations identified in different studies (Preux et al., 2005a, Ba-Diop et al., 2014b, Logroscino et al., 2005). The methodological limitations were related to five key areas which are; epilepsy case ascertainment, diagnosis, mortality assessment, diagnosis of causes of death, and population representativeness.

Case ascertainment refers to how PWE are identified. Door-to-door surveys are the best while identification in clinical settings is the least preferred option in studies conducted in SSA. Diagnosis by neurologist or through criteria issued by ILAE is likely to yield to optimal number of PWE. Mortality assessment relates to how PWE are followed over time and mortality in then captured with minimum lost to follow-up. Patient's lost to follow-up in cohort studies is the major challenge in most SSA

countries where medical records and civil and vital registration is almost absent. Post-mortem examination is the gold standard method for death certification, unfortunately, rarely implemented in SSA. Verbal autopsy and death certificates offered in clinical settings frequently used as alternative to post-mortem. Lastly, study population must representative of the general population. Deliberate efforts must be made to ensure population at high risk for epilepsy are not included.

Qualities of studies were reviewed and those prone to yield biased estimates were excluded. In a review period of 25 years, 12 and 8 population-based and clinical cohort studies met the inclusion criteria. All clinical cohorts had quality < 80%. Majority of these studies were done in patients with refractory epilepsy, children, and in onchocerciasis-endemic areas. There were 7 good qualities (quality > 80%) population-based studies merit further review and meta-analysis. This indicates that there has been a significant less effort and funding dedicated to epilepsy given the wide geographic coverage of the review in sub-Saharan Africa, Asia, and South America.

Scarcity in human and financial resources for epilepsy care, management, and research are among the key factors liked to low knowledge of epilepsy in most SSA countries (Newton et al., 2012a, Ba-Diop et al., 2014a). In HIC, PWE substantially benefits from high quality care, however funding for epilepsy research remains a major challenge. Adjusted for relative prevalence, US National Institute for Health's funding for epilepsy was 1.8 times higher in stoke, 2.9 in Alzheimer disease, 6.9 times in Parkinson disease, 7.8 times multiple sclerosis, and 58.5 times amyotrophic lateral sclerosis (Meador et al., 2011). The funding gap could not be explained by differences in the overall impact of these diseases relative to epilepsy especially Parkinson disease, multiple sclerosis, and amyotrophic lateral sclerosis. Possible explanations

for disproportionate funding among others were a poorer quality funding proposals and lack of expertise on grant review panels.

The study estimated either weighed mean or median of mortality indicators rather than pooled estimate due to high heterogeneity across studies. The high heterogeneity observed illustrates high degree of uncertainty possibly due to differences in studied population and methods applied in screening, diagnosis, and mortality assessment. Despite the observed limitations, this review generated best available evidence of excess mortality of nearly three times higher than the general population. The review generated and contributed to a limited body of literature of the epidemiology of epilepsy in PWE and setup a platform for more focused investigation in light of data and methodological challenges observed.

Excess mortality in epilepsy: SEEDS study

SEEDS estimate of excess mortality is five times higher in PWE than the general population in SSA countries. SEEDS study provide more compelling evidence of mortality burden in PWE in SSA than previously thought as reviled in Chapter 3. SEEDS project is the largest, standardized population-based study of prevalence and mortality in PWE in sub-Saharan Africa. This study accounted for common and major methodological limitations identified in literature in Chapter 3.

SEEDS studies were nested in HDSS, a reliable platform that guarantee homogeneous population, mortality assessment, and reliable causes of death estimation with standardized verbal autopsy tools and disease classification using ICD 10. Door-to-door survey was employed in the entire HDSS site covering individuals of all ages with three stages screening tools recommended by ILAE strengthened SEEDS studies relative to others.

Risk factors for excess mortality

Risk factors analysis identifies behaviours, health conditions, characteristics or exposures that increase than usual the probability of adverse outcomes. The analysis is necessary in designing appropriate interventions needed to mitigate negative impact of epilepsy. Systematic review in Chapter 3 provided substantial information on risk factors for mortality in epilepsy compiled from several studies. Estimates of risk factors were not uniformly estimated across studies making it difficult to generate pooled estimates. Taking the case of treatment with AED, the following classification were used; adherence vs. non adherence, good vs. poor adherence, AED vs. AED and traditional, and dosage levels of phenobarbital; 30–60, 90–180, and 210–240 mg. Regardless of the classification adopted by a study, high mortality were observed in PWE with suboptimal access treatment, recent diagnosis, younger, males, high seizures frequency, long duration in epilepsy, focal seizures, and symptomatic (acquired) epilepsy aetiology.

SEEDS study provides site-specific and pooled estimates of impact of risk factors on excess mortality in epilepsy. Uncontrolled seizures were significantly increased the risk of death in PWE with high frequency of seizures (daily, seizure occurring during the day and night), and in those having more than 12 seizures per year. This study also observed higher mortality in PWE who experienced injuries in the past. High seizures frequency and injuries may possibly be linked with poor access to AED, however this study did not find lower mortality in those on treatment. This may be due the fact that majority of PWE are not receiving appropriate treatment and those who access AED, may not be receiving constant supply.

Perinatal adverse events attributed to substantial increase in excess mortality in epilepsy in SEEDS study. Adverse events are difficulties occurred during birth and in

certain circumstances may lead to neurological complications in newborn. These events include obstructed labour, prolonged rapture of membranes, difficulty breathing and crying right after birth. These events are not predictable; however they are more likely to result in neurological complication if deliveries happen to occur at home or in facilities with poor delivery care. Children born in home or in poor resources settings are also less likely to be fully immunized. This study indicated increased mortality in children without “BCG vaccine scar”, an indication they were not protected against tuberculosis. Although there has been improvement in improving care at birth in SSA, majority of deliveries still occurs in at home or in facilities with limited resources. Perinatal events may also explain why majority of epilepsies in developing countries more prevalent in children younger than 20 years compared to older ages in developed countries.

Co-morbidities with cardiovascular diseases in this study were linked to increased mortality in epilepsy. This study did not investigate causal pathways; however, other studies have observed significant cardiac changes in PWE (Jansen et al., 2010). Cognitive and motor impairments were associated with increased mortality in epilepsy therefore proper management of these co-morbidities is likely to decrease the burden of epilepsy mortality (Keezer et al., 2016). Co-morbidities with neurological deficit and severe deficit of cerebral function observed on EEG were linked to increased mortality in epilepsy. Evaluation of these risk factors in PWE could be potential in developing strategies targeting these individuals.

Parasites infections are known risk factor for epilepsy in most SSA countries. This study found PWE living in household with cat are associated with increased mortality. Cats are carrier of the parasite *Toxoplasma gondii,* known to cause epilepsy in LMIC. Eating soil is another hygienic risk factor associated with soil transmitted parasitic

infection (Wagner et al., 2009, Kind et al., 2017). This study could not explain the mechanism for the increased risk of mortality in PWE with antibodies for *Toxoplasma gondii* relative to other parasites, and those eating soil. It is worth noting these factors are also responsible for epilepsy incidence therefore mitigating these factors may result in decreased incidence and mortality in PWE.

Availability and use of information risk factors is essential in designing epilepsy intervention programs are likely to result in substantial improvement in health status of PWE.

Automated causes of death in epilepsy deaths

With nearly 75% of deaths happen at home and never get to the hospital for post-mortem investigation, causes of death statistics is nearly impossible to produce in most SSA countries. Verbal autopsy procedure provide an opportunity for physicians to determine cause of death by reviewing detailed structured questionnaires of signs, symptoms, health conditions, and circumstances occurred to the diseased provided by caretakers. Causes of death certification are done using ICD10 intended to promote accuracy, consistency and comparability of causes of death across time and places. Several studies have applied VA on neurological diseases in LMIC focusing among others epilepsy, stroke and cerebrovascular diseases (Mateen et al., 2012).

With considerable limited resources, most SSA countries do not opt for death certification with VA as it require field VA interviewer and the use of multiple physicians to classify every death through time demanding review of VA questionnaires. Mathematical and statistical model has been proposed as an alternative to physicians coding, however, their use has not been thoroughly evaluated in epilepsy deaths.

Several studies have been published comparing software and provide strength and limitation of each. The use of InteVA4 model has recently gained momentum due to funding limitations in most demographic surveillance system (Murray et al., 2014). Four key issues were observed on InterVA-4 output: i) the system was not design to produce SUDEP and SE as causes of death; ii) possible epilepsy deaths were frequently coded as injuries (accidents); and iii) circumstances occurred prior to death as described by caretakers may play an important role is precisely determine the cause of death; and vi) at population level, proportion of direct and indirect were lower than unrelated causes of epilepsy.

Sudden death and seizures lasting for at least 10 minutes are the least parameters needed for certifying SUDEP and SE as cause of death in epilepsy respectively. Verbal autopsy information collected from caregiver of the diseased can provide valuable information in identified SUDEP (Lathers et al., 2009). InterVA4 highly associated sudden death and longer seizures with likelihood of epilepsy deaths, however, specific death's categories for SUDEP and SE were not created respectively. The distinction between SUDEP and SE is essential in understanding and determining the risk factors for death in PWE. SUDEP is not only excluded in the list of cause of death in InterVA4, but also with ICD10 in which "Epilepsy, unspecified" code is often used. On the other hand, SE is widely recognized and specific category has been assigned to it (i.e. G41.-). Automatic coding for SE could improve with further probing for seizures lasted at least 10 minutes with an additional question "did seizure ended with death".

Most accidents-related deaths in PWE were attributed to epileptic seizures; however, InterVA4 software categorized these deaths as accidents. The software was not programmed to link accidents, epilepsy deaths and epilepsy status. An additional

question linking accidents to epilepsy may be phrased “did accident occurs during seizures?” On the other hand, these deaths were coded as epilepsy deaths by physicians. The main challenge here is the configuration choice on whether underlying or immediate cause of death information is preferred. Underlying cause of death if often preferred in public health due to its relevance in producing vital statistics related to cause of disease rather than its effect. Future configuration of automated cause of death should re-consider this issue so as to enable reliable burden of epilepsy mortality be estimated.

VA interviews collects substantial amount of text information that are relevant in establishing causes of death in PWE. The WHO 2008 version of VA questionnaires requires the interviewer to collect and document the following information when available: i) Short narrative of circumstances occurred prior to death from caretaker of the diseased, ii) Cause of death according to their best understanding of the patient, iii) cause of death as reported on death certificate if death certificate was provided, iv) cause of death reported on burial permit, v) post-mortem report, vi) antenatal care card, vii) prescription information, viii) medical records ix) discharge cards; and x) laboratory results.

These text narratives provides valuable clue in differentiating epilepsy and unrelated causes of death and improves the reliability and precision of death certification among physicians. Unfortunately, these text narratives are not utilized by automated models. Text mining technique can be used to analyse these text and improve predicted causes of death in epilepsy. Text mining involves computational extraction of selected information unstructured text data (Singh, 2005). The methods has shown promising results in medical research including in identify rate diseases and adverse drug events in unstructured text data (Harpaz et al., 2014). Future development of automated

causes of death software's needs to invest in integrating text mining in order to improve accuracy of causes of death statistics.

Epilepsy mortality in Tanzania

This study provided comprehensive review of excess mortality in PWE in LMIC and in SSA. Chapter 6 and 7 were devoted to Tanzania as an illustrative country of SSA with comprehensive community-based to evaluate levels and trends of epilepsy mortality. SAVVY (Chapter 6) and HDSS (Chapter 7) focused empirical evidence of national level and secular trends in estimate of epilepsy and other neurological mortality. National levels and population trends data are rare in most SSA due to poor coverage of vital registration systems. This study utilized data from well-designed national representative mortality and causes of death survey. The survey adopted a design intended to generate mortality estimates and causes of death from the community using verbal autopsy rather than post-mortem examination.

The results indicate epilepsy the second leading cause of death in Epilepsy after epilepsy with estimated mortality rate of 7.0 deaths per 100,000 population. There were no best national estimates to compare and contrast these estimates in SSA countries. Compared to GBD report, SAVVY estimates of epilepsy mortality were comparable to estimates from GBD report for Tanzania. SAVVY study provides first detailed analysis of national data on neurological disorders in Tanzania.

Secular trend in epilepsy

Ifakara Health Institute (IHI) established three HDSS sites in different settings in Tanzania to be used as a platform for assessing demographic events and trends, and evaluating impact of health intervention (Geubbels et al., 2015, Mrema et al., 2015).

This study utilized the platform and determined the magnitude and changes in the mortality associated with epilepsy from 1999 to 2014.

This study provides evidence of no progress in the reduction of epilepsy in rural (Ifakara Rural and Rufiji HDSS) as well as semi-urban (Ifakara urban HDSS) settings over the past 15 years. These results shows epilepsy is the second leading cause of death that has persisted over years and demand renewed efforts.

Limitations

Verbal autopsy

Deviations from true estimates may be associated to individual certification and coding practices among physicians who were involved in the study. High estimates malaria mortality far more than previous estimates from several epidemiological studies mainly due to the fact that malaria is common illness encountered by most physicians in their routine practice. However some of clinical manifestation of cerebral malaria such as fever, vomiting, and convulsions are also clinical manifestations of neurological disorders such as meningitis and epilepsy. With lack of clinical training in neurology among death certifiers, substantial number of neurological deaths may have been missed in this study.

The study utilized population-based studies that never consider sample size needed to estimate mortality of neurological disorders. Diseases relatively smaller number of deaths such as epilepsy and meningitis may require larger sample size compared to diseases such as cerebrovascular diseases (Mateen et al., 2012). This may be the case with this study especially on studies conducted on HDSS sites. On the other hand, SAVVY sample size was large enough to account for sample size needed to estimate mortality rate of most common neurological disorders.

In SSA SAVVY approach has only been successfully in Zambia and Mozambique (Statistics; et al., 2012, Mudenda et al., 2011). SAVVY approach was developed to provide a standardized methodology in generating mortality estimates, causes of death and disease classification needed for local, regional and international comparability of mortality statistics. The limiting factor in the use of VA is cost (AbouZahr et al., 2010), due to the fact that, it the approach most often require trained interviewers and physicians during VA interview and death certification. The use of improved automated tools will greatly reduce SAVVY cost when combined with data collection using mobile devices and volunteer or community health workers.

Non-convulsive epilepsy

SEEDS study focused on convulsive epilepsies which accounts for 50-60% of all epilepsies in SSA. (Adamolekun, 1995) Verbal autopsies could in similar way missed non-convulsive epilepsies which may limit the ability to fully determine the excess mortality in PWE by excluding this subpopulation. However, the choice to focus on ACE is justifiable specifically with regards to human and technological resources.

Morbidities of neurological disorders

This study focused on mortality burden of neurological disorders. However, it is generally known that the burden associated with morbidities might be substantially higher than estimated in this study. Taking an example of stroke, stroke, mortality rates and deaths have substantially declined in most countries however the number of people living with stroke related disabilities has been increasing (Feigin et al., 2015). Reliable morbidity data can only be obtained when there is routine health care services data of good quality and community-based surveys.

Implications of public health

Investment in epilepsy research in SSA

The systematic review identified limited number of good quality studies of on epilepsy mortality in LMIC over the past 25 years. There may be multiple factors associated with this including lack of funders' interest in financing epilepsy research, lack of expertise in neurology, and poorer quality funding proposals. This study provided important information on status of epilepsy research and call for renewed efforts to funding agencies and researchers to reconsider prioritizing SSA due to its high burden.

Local and international organizations including ILAE, International Bureau for Epilepsy (IBE), Epilepsy Alliance Europe has been established to advocate and mobilize funding and research for care in PWE. These organizations have been substantially contributed in improving care, treatment and increased funding for epilepsy, however major activities has been less directed to developing countries where 90% of epilepsy burden reside.

This study recommends and support for a more equitable approach earlier proposed by Chin to through establishing a global fund for epilepsy (Chin, 2013). The proposal includes include among others integrating epilepsy into primary health care, establishing geographically representative collaboration of major neurology and epilepsy societies and foundations, public health organizations, thought leaders, and industry. Activities of the funds may include "support expert and peer training of primary health workers, procurement of antiepileptic drugs, diagnostic testing, information and telecommunication technologies, and social services" (Chin, 2013).

Epilepsy care and management

This study provided evidence of high excess mortality in PWE in SSA than reported elsewhere in the world. The excess mortality was associated with high frequency of seizures which is largely attributed to high treatment gap. This study recommends improving delivery of epilepsy treatment targeting major barriers to access to AED with a package of care proposed by Mbuba (Mbuba et al., 2009). Mbuba et al proposed, first; increasing capacity of identifying PWE through regular epidemiological surveys and training of teachers, and community health workers, second; train health care providers (nurses and clinical officers) in diagnosing epilepsy, third; providing education and psycho-educational interventions, fourth; ensure continuous supply of AEDs (when possible generic formulation), and fifth; increasing participation of NGO's and other community-based organization who are actively involved with advocacy for mental health. Mbuba also detail on how, who and setting by which the proposed package can be practically implemented.

Mitigating risk factors

High prevalence and mortality of epilepsy in SSA can be prevented with cost-effective intervention. Most observed risk factors were modifiable; meaning the burden can significantly reduce with promotion of actions, behaviors and priorities. Mitigating risk factors for epilepsy requires participation of different sectors. New programs may not be needed; however strengthening the existing programs may provide spilling over effect to epilepsy. Table 8-1 provides summary of identified risk factors, action to be taken and responsible sector. Some of the actions proposed are adopted from Mbuba et al. (Mbuba et al., 2009).

Strengthen monitoring and evaluation platforms

Scarcity of data on the burden of epilepsy in SSA if largely attributed to lack of civil and vital registration systems. Using SAVVY and HDSS platform, this study estimated levels and secular trend in epilepsy mortality in Tanzania. Managing SAVVY and HDSS is expensive thus many SSA fail to invest in these platform. Sustainable availability of burden of epilepsy will require strengthening of vital registration systems and community disease surveillance.

With regards causes of death, the use of community health workers in conducting VA and the use of automated tools will timely provide epidemiologic data needed for planning of health care services in PWE. Establishing long term cohort of epilepsy patient will provide valuable platform needed to monitor and estimate the burden of epilepsy, related risk factors, causes of death and effectiveness of intervention.

Conclusions

This thesis provided evidence of higher excess mortality in PWE than estimated elsewhere in SSA using empirical data from large community based studies. Risk factors analysis indicates majority of premature deaths in PWE in SSA are preventable. Secular trend analysis shows epilepsy mortality has no declined in the past 15 years. With rapid demographic transition in SSA, the burden of epilepsy mortality is expected to substantially increase in future if no action is taken.

Table 8-1 Proposed action for modifiable risk factors for excess mortality in PWE

Risk factor	Sector	Action

Perinatal adverse events (obstructed labor, difficulties breathing and or crying)	Health	1. Improve care at birth, 2. Provide training to midwifes, 3. Improve emergency obstetric care, 4. Promote safe facility delivery.
1. Parasite infection 2. Poor hygiene (eating soil)	Health and agriculture	1. Educate the public on animal human disease transition, 2. Assist community on deworming domesticated animal, 3. Educate the community on soil transmitted infections.
Illiterate	Education and health	1. Improve access to education, 2. Health in primary education curriculum 3. Develop advocacy strategies that target illiterate individuals such as radio programs, 4. Educate the public on causes of epilepsy and associated misconception such as those linking epilepsy with curse and demonic possession
Marital status (divorced, separated, widowed).	Health	1. Provide education and psychoeducational interventions to PWE 2. Health care workers trained in psychological support and counselling
High seizures frequency	Health	1. Increase government support in procurement and supply of AED 2. Improve access to AED especially in remote area
Co-morbidities (sickle cell, hypertension, and motor, cognitive, and sleep disorders)	Health Researchers	1. Incorporate screening of co-morbidities on treatment guidelines 2. Train health care providers in managing co-morbidities. 3. Conduct research on incidence of co-morbidities and associated risk factors in PWE.
Head injuries	Health	1. Develop community interventions on road safety 2. Improve access imaging diagnosis (CT scan, MRI)
Neurologic deficits	Health	1. Train workers on diagnosing neurologic deficits 2. Improve access imaging diagnosis (EEG)

PWE: People with epilepsy, EEG: Electroencephalography, AED: Antiepileptic drugs, MRI: Magnetic resonance imaging, CT: computed tomography

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Curriculum Vitae

Professional profile

Francis Levira is research scientist trained at master's level in epidemiology and biostatistics. His major interest is to contribute to design and evaluation of high impact multi-disciplinary and collaborative research aimed at improving maternal, newborn and population health. He has participated in several evaluations including Mid-term evaluation of Health Sector Strategic Plans (HSSP III) and Tanzania Countdown Case Study for Maternal and Newborn Health.

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4. Publications

Levira F, Todd G. Urban Health in Tanzania: Questioning the Urban Advantage. *J Urban Health* 2017; **94**: 437-49.

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I certify that the information given to the best of my knowledge is correct and reflects my true curriculum vitae.

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