The Burden of Epilepsy
Using population-based data to define the burden and model a cost-effective intervention for the treatment of epilepsy in rural South Africa

Ryan G Wagner
Always be on the lookout for the presence of wonder.
~ E.B. White

To my parents, Greg and Jenifer...
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Abstract

**Rationale** Epilepsy is a common, chronic, neurological condition that disproportionately affects individuals living in low- and middle-income countries, including much of sub-Saharan Africa. Epilepsy is treatable, with the majority of individuals who take anti-epileptic drugs experiencing a reduction, or elimination, of seizures. Yet the number of individuals taking and adhering to medication in Africa is low and interventions aimed at improving treatment are lacking.

**Aims** To define the epidemiology of convulsive epilepsy in rural South Africa in terms of incidence, mortality and disability-adjusted life years; to determine outpatient, out-of-pocket costs resulting from epilepsy treatment; to establish the level of adherence to anti-epileptic drugs amongst people with epilepsy; and, to determine whether the introduction of routine visits to people with epilepsy by community health workers is a cost-effective intervention for improving adherence to anti-epileptic drugs.

**Methods** Nested within the Agincourt Health and Demographic Surveillance System, this work utilized a cohort of individuals diagnosed with convulsive epilepsy in 2008 to determine health care utilization and out-of-pocket costs due to care sought for epilepsy. Additionally, using blood samples from the cohort, anti-epileptic drug adherence was measured and, following the cohort, mortality rates were determined. Using these collected epidemiological parameters, disability-adjusted life years due to convulsive epilepsy were determined. Finally, combining the epidemiological and cost parameters, a community health worker intervention was modeled to determine its incremental cost-effectiveness ratio.

**Key Findings** The burden of convulsive epilepsy is lower in rural South Africa than other parts of Africa, likely due to lower levels of known risk factors. Yet the burden, especially in terms of mortality, remains high, as does the treatment gap and health care utilization. Findings from the economic evaluation found the introduction of a community health worker to be highly cost-effective and would likely lower the burden of epilepsy in rural South Africa.

**Implications** Epilepsy contributes to the burden of disease in rural South Africa, with high levels of mortality and a substantial treatment gap. The introduction of a community-health worker is likely to be one cost-effective, community based intervention that would lower the burden of epilepsy by
improving adherence to anti-epileptic drugs. Implementing this intervention, based on these findings, is a justified and important next step.

Keywords: Africa, epilepsy, incidence, mortality, cause of death, disability-adjusted life years, out-of-pocket, costs, health care utilization, treatment cascade, adherence, intervention, economic evaluation, community health worker
Publications

This thesis is based on the following five original manuscripts. They are referred to by their roman numeral (I through V) within the text.


Abbreviations

ACE: Active convulsive epilepsy
AED: Anti-epileptic drug
AIDS: Acquire immune deficiency syndrome
ANC: African National Congress
ART: Anti-retroviral therapy
CAG: Community advisory group
CEA: Cost-effectiveness analysis
CHW: Community health worker
CI: Confidence Interval
COD: Cause of death
DALY: Disability-adjusted life year
DW: Disability weight
EEG: Electroencephalography
GBD: Global burden of disease
GDP: Gross domestic product
HDSS: Health and socio-demographic surveillance system
HIV: Human immunodeficiency virus
HREC: Human research ethics committee
ICER: Incremental cost-effectiveness ratio
ILAE: International League Against Epilepsy
INDEPTH: International Network for the Demographic Evaluation of People and their Health
IQR: Interquartile range
LMIC: Low- and middle- income country
MRC: Medical Research Council
PHC: Primary health care
PMR: Proportional mortality ratio
PRICELESS: Priority Cost-effective Lessons for Systems Strengthening
PYO: Person-years observed
QALY: Quality-adjusted life year
SEEDS: Studies of the Epidemiology of Epilepsy in Demographic Surveillance Systems
SMR: Standardized mortality ratio
SUDEP: Sudden unexplained death in people with epilepsy
UI: Uncertainty interval
YLD: Years of life lived with disability
YLL: Years of life lost
WHO: World Health Organization
ZAR: South African Rand
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Epilepsi är en kronisk neurologisk sjukdom som framförallt drabbar människor i låginkomstländer, speciellt Afrika söder om Sahara. Epilepsi är en behandlingsbar sjukdom, och de flesta som medicinerar slipper helt eller delvis anfall. Fortfarande är andelen i Afrika som får optimal läkemedelsbehandling låg, och interventioner som syftar till bättre behandlings saknas.

Avhandlingens mål är a) beskriva förekomsten av konvulsiv epilepsi i Sydafrika i termer av incidens, dödlighet och funktionsnedsatta levnadsår, b) uppskatta patientens kostnader för epilepsibehandling, c) undersöka följsamheten till behandling, och d) analysera om regelbundna hembesök från sjukvården är en kostnadseffektiv metod för att förbättra följsamheten till behandling.

Studierna har genomförts i Agincourt, Sydafrika, som sedan länge har byggt upp ett system för att följa demografi och hälsoutveckling i en avgränsad befolkning. Studierna har genomförts i en kohort av personer med konvulsiv epilepsi som startades 2008 för att undersöka deras nyttjande av hälsos- och sjukvård samt de kostnader som det medförde. Genom blodprover var det möjligt att undersöka följsamheten vid medicinering, och kohorten gjorde det också möjligt att uppskatta dödligheten. Insamlade epidemiologiska data användes för att beräkna funktionsnedsatta levnadsår. Slutligen, för att beräkna kostnadseffektiviteten kombinerades epidemiologiska data och kostnader för interventionen “hembesök från sjukvården”.

De viktigaste resultaten är att förekomsten av konvulsiv epilepsi är lägre i Sydafrika än i andra delar av Afrika, förmodligen pga. av färre riskfaktorer. Trots att förekomsten relativt andra delar av Afrika är lägre, är ändå sjukdomsbördan stor, särskilt i form av dödlighet. “Behandlingssgapet” är stort, dvs. det finns en stor grupp som idag inte får optimal medicinering. Kostnadseffektanalysen visar att “hembesök från sjukvården” är väl använda pengar, och att bördan av epilepsi förmodligen skulle minska.
Summary of work in Shangaan

Masungulo  Mavabyi ya ku wa i mavabyi ya byongo lawa ya tolovelekeke lawa ya khomaka vanhu lava tshamaka ematikweni lawa ya nga na miholo/tihakelo ta le hansi kumbe exikarhi, ku katsa ya Sub-Saharan Africa. Mayabyi ya ku wa ya huhateka, laha ku nga na vanhu vo tala lava va tekaka vutshungungi bya mavabyi ya ku wa lawa ya pfunaka ku hunguta kumbe ku herisa ku wa. Hambileswi nhlayo ya vanhu lava tekaka no tshama va tirhisa vutshungungi lebyi laha Afrika yi nga le hansi naswona tindlela to pfuna ku antswisa vutshungungi ta pfumaleka.

Swikongomelo  Ku hlamusela swivangelo na ndlela leyi mavabyi ya ku wa ematiko-xikaya ya Afrika Dzonga ya humelelaka ha kona, hi ku languta eka ku khomiwa hi mavabyi, mafu na vugono- lebyi nga vaka kona eka malembe yo karhi, ku lawula vavabyi lava nga etleriki exibedhlele, tihakelo leti vaka kona hikwalaho ka mavabyi ya ku wa, ku tumbuluxa xiyimo xa ku tshama eka vutshungungi bya mavabyi ya ku wa eka vanhu lava va nga na mavabyi ya ku wa, na, ku kambisisa leswaku ku tumbuluxiwa ka tendzo to vuyelela eka vanhu lava nga na mavabyi ya ku wa hi mutirhi wa swarihanyu emugangeni i ndlela yo hlayisa mali ku antswisa ku tshama vanhu va tirhisa vutshungungi bya mavabyi ya ku wa.

Maendlelo  Tanihilaha swi endliweke ha kona eAgincourt Health and Demographic Surveillance System, ntirho lowu wu kumile nhlayo ya vanhu lava kumekeke va ri na mavabyi ya ku wa hi lembe ra 2008 ku langutisisa matirhiselo ya mpfuno wa swarihanyu na tihakelo leti vaka kona eka mpfuno lowu lavecaka wa mavabyi ya ku wa. Ku engetela, hi ku tirhisa ngati yo ringeta ku suka eka nhlayo ya vanhu, matekelo ya vutshungungi bya mavabyi ya ku wa ya pimiwile naswona, hi ku landzelela nhlayo leyi, nhlayo ya mafu ya langutisisiwile. Hi ku tirhisa swiyimo swa tinhlamuselo hi ndlela leyi mavabyi ya humelelaka ha yona, vugono lebyi vaka kona hikwalaho ka mavabyi ya ku wa swi langutisisiwile. Eku heteleleni, hi ku hlanganisa swivangelo na ku hangalaka ka mavabyi xikan’we na swiyimo swatihakelo, mpfuno wa mutirhi wa swarihanyu emugangeni wu tumbuluxiwa ku langutisisa ku engeteleka ka xiyimo xa nhlayiso wa mali.

Leswi kumiweke  Ku tikeriwa hi mavabyi ya ku wa ku le hansi ematiko-xikaya ya Afrika Dzonga ku tlula tindzhawu tin’wana ta Africa, hikwalaho ka xiyimo xa le hansi xa vutivi bya khomo lebyi nga kona. Hambileswi ku tikeriwa, ngopfu-ngopfu loko swi ta eka mafu swi tshama swi ri le henhla, ku fana na mpfumaleko wa vutshungungi. Leswi kumekeke loko ku hleriwa xiyimo xa timali swi kumile leswaku ku tivisiwa ka mpfuno wa mutirhi wa
swarihanyu emugangeni swi vile na xiave-nkulu xo hlayisa mali naswona swi
ta yisa ehansi ku tikeriwa loko ku nga kona hikwalaho ka mavabyi ya ku wa
ematiko-xikaya ya Afrika Dzonga.

Ntshikilelo Mavabyi ya ku wa ya na xiave eka ku tikeriwa hi mavabyi
ematiko-xikaya ya Afrika Dzonga, laha ku nga na nhlayo ya le henhla ya
mafuphikan’we na nkoka wa mpfumaleko wa vutshunguri. Ku tivisiwa ka
mutirhi wa swarihanyu wa le mugangeni swi nga tshuka swi vile xin’we xa
leswi nga hlayisaka mali, mpfuno lowu nga vaka kona emugangeni lowu nga
ta yisa ehansi ku tikeriwa hi mavabyi ya ku wa hi ku antswisa ku tshama ku
tirhiswa vutshunguri bya mavabyi ya ku wa. Ku endiwa ka mpfuno lowu, ku
ya hi leswi kumiweke ku nga va xiphemu xa nkoka no va kahle lexi
landzelaka.
Prologue

So what now? This simple question began my journey as a PhD student, a journey that has spanned two universities at almost diametrically opposite poles of the globe.

As part of a multi-national research study led by Professor Charles Newton, we had established that the prevalence of active convulsive epilepsy was lower in rural northeast South Africa than it was in four other African sites. We hypothesized that this was in part due to the lower prevalence of certain, specifically parasitic, risk factors. The research had employed solid scientific methodology to answer an important question and had yielded results that aided in understanding the epidemiology of epilepsy in Africa.

Yet whilst conducting field surveys in the hot, South African lowveld, I was moved by the struggles that many people with epilepsy and their families faced daily. Furthermore, I was struck by the seemingly high treatment gap experienced by people with epilepsy in this context– albeit anecdotally at the time.

So what now? We had defined the burden of active convulsive epilepsy, at least in terms of prevalence, we had done our scientific part in publishing and presenting our results and providing our findings to the community. Yet the lives of people with epilepsy in Agincourt remained unchanged.

In October 2009, Professor Karen Hofman, the director of the newly formed Priority Cost-effective Lessons for Systems Strengthening South Africa (PRICELESS-SA) project, visited Agincourt. One of the first steps that Karen took as director of the newly formed project, which focuses on providing cost-effectiveness evidence to policy makers to assist in decision making, was to identify ongoing work that had the potential to inform policy by collecting additional costing data to allow for economic modeling. The aim was to identify 'best buys' to present to relevant stakeholders.
Karen saw potential in the ongoing epilepsy research and added resources that allowed us to collect and analyze the economic costs of epilepsy. The costs, together with an understanding of the complete epidemiological model of epilepsy, including the treatment gap, allowed us to explore the effect that an intervention would have on the burden of epilepsy, and specifically the epilepsy treatment gap. An intervention deemed cost-effective could then be presented to policy makers with the hopes that it would be implemented, or at least tested, depending on available resources.

Professor Lars Lindholm and Dr Melanie Bertram, both health economists, had experience in undertaking economic studies of this type whilst Professors Charles Newton and Lars Forsgren, both neurologists, had deep understanding of the epidemiology of epilepsy and its effects, both having worked in Africa. All four agreed to supervise this work.

So this thesis is a response to the question, So, what now? This thesis is an attempt to respond to this question by moving from observational work, where the epidemiological and economic burdens of epilepsy are defined in terms of disability-adjusted life years and out-of-pocket costs, to modeling the cost per quality-adjusted life years gained by an intervention using 'real', population-based data.

This thesis is a modest attempt to improve the lives of those who live with epilepsy in rural South Africa by informing policy through research. In doing so, this work seeks to demonstrate one way that good science has the potential to improve the lives of those in need through evidence-based interventions- by moving from observation to intervention.

\textit{Ryan G. Wagner}

April 2016

Acornhoek, South Africa
Introduction

Decision-making is what we, as humans, do. These decisions can be as minor as deciding what color socks to wear today or as major as deciding whether or not to attack a foreign country. It is estimated that during our adult lives, we make about 35,000 decisions per day. We make these many decisions by understanding the current context, evaluating all available data and modeling potential scenarios based on the different decisions that we are comparing. All of this can happen in a split second, or it can take days, months or even years for a decision to be made.

Decisions on health care priorities are, generally, no different, though often involve choices that affect large numbers of people and have the potential to directly influence—either positively or negatively—lives. Within the last several decades, priority setting in health care, using economic evaluations, including cost effectiveness analyses, has become common. Part of the reason for this is due to the recognition that national and international resources to address the health care needs of a population are limited and, in a context of constrained resources, decisions must be made on which interventions to fund and which interventions not to fund. Economic evaluations seek to improve the efficiency in health care [1]. Providing an economic evaluation on a specific health care intervention or a number of interventions is important information that can aid policy makers in making health care decisions.

In low- and middle-income countries (LMICs), where funding for health care is often constrained, the use of economic evaluations can be an especially useful way of defining an intervention, or package of interventions, that addresses the most pressing needs of the population and can assist in the setting of priorities. By comparing the expected cost versus the gained utility, in terms of quality-adjusted life years (or disability averted), of an
intervention and comparing this ratio against other interventions, or a threshold, one is able to, put simply, derive a ranking of intervention priorities.

However, in order to conduct an economic evaluation, it is necessary that both the change in burden of the condition and the cost of the intervention are known. These data are not always available in LMICs and regional modeling and imputation have attempted to address this paucity.

In the context of South Africa, which is currently undergoing rapid epidemiologic, demographic and social transitions that include increasing chronic, non-communicable diseases, an aging population and increasing disparities, a number of interventions have been introduced to bolster a dysfunctional health care system. These interventions include primary health care re-engineering and an integrated chronic disease model of care delivery, both underlining the urgent necessity for transformation. During this period of continuing transition and transformation, opportunities exist to present decision makers with scientific evidence that supports the introduction of cost-effective, community-based interventions aimed at reducing the epilepsy treatment gap.

**Objective and Aims**

The overall objective of this Ph.D. is to measure the burden of epilepsy in rural South Africa and to determine whether an intervention aimed at decreasing the treatment gap by improving adherence in people with epilepsy is cost effective. This objective can be divided into four aims, or four questions, and they are:

1.) What is the burden of epilepsy in rural South Africa in terms of incidence, mortality and disability-adjusted life years (DALYs)? (Publication 1 & 2)
2.) What are the costs to the patient associated with both epilepsy and its treatment? (Publication 3)
3.) What is the treatment gap of epilepsy in rural South Africa? (Publication 4)
4.) Given the previously defined context, is the introduction of a community health worker a cost-effective intervention to reduce the burden of epilepsy in rural South Africa? (Publication 5)

These questions are answered in a series of five papers that make up this thesis and can be found reproduced at the end of this integrating narrative. The relationship between these five papers can be found in Figure 1 below.
Figure 1 Overall schema of PhD aims, publications and relationships between projects

Structure of Integrating Narrative

What follows is an attempt to integrate and synthesize these five manuscripts into a unifying narrative. The narrative is divided into five parts and begins with a description of epilepsy: its epidemiology, associated costs, treatment gap, and interventions aimed at reducing the treatment gap. The second section of the narrative provides an overview of the context and methodologies employed in each of the five manuscripts. The third section, the Results section, synthesizes and presents the key findings from each of the manuscripts, attempting to weave together integrated findings from this PhD. The fourth section, the Discussion section, distills the results from the manuscripts, focusing on how the results speak to our current understanding of epilepsy in sub-Saharan Africa whilst also suggesting how this work may advance our knowledge and the implementation of interventions to reduce the burden of epilepsy. Finally, the fifth section presents concluding remarks and recommendations for future work. It attempts to succinctly define the next steps in the quest to reduce the treatment gap of epilepsy in sub-Saharan African and improve the lives of those with epilepsy.
People think that epilepsy is divine simply because they don’t have any idea what causes epilepsy. But I believe that someday we will understand what causes epilepsy, and at that moment, we will cease to believe that it’s divine. And so it is with everything in the universe.

- Hippocrates

Background

Epilepsy: Definitions, Causes, Burden & Treatment

Epilepsy is one of the most serious, common neurological conditions globally and a major public health problem due to the burden it places on the patient, the family and society. A condition, resulting from abnormal electrical discharges of the brain, epilepsy directly affects at least 65 million people worldwide [2] and indirectly affects at least 500 million people [3,4]. In 2013, epilepsy was estimated to account for 116,000 deaths globally [5]. The 2010 global burden of disease study suggested that only one other condition (acquired immune deficiency syndrome- AIDS) had a greater disability weight than severe, uncontrolled epilepsy [6].

The term “epilepsy” encompasses a family of disorders characterized by recurrent, unprovoked seizures. In 2005, the International League Against Epilepsy proposed the following definition for epilepsy:

A disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure [7].

An epileptic seizure is defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuroactivity in the brain” [7]. Practically, clinicians diagnose epilepsy in patients who have two or more unprovoked epileptic seizures occurring more than 24 hours apart [8]. In 2014, the definition was amended to include patients experienced one
epileptic seizure with greater than a 60 percent chance of having a second seizure within the subsequent 10 years [9]. 

There are a number of conditions that present as recurrent seizures, though are not considered to be epilepsy. These include provoked seizures (seizures resulting from acute head trauma, drug or alcohol toxicity or withdrawal or metabolic insult) [10], neonatal seizures, febrile seizures or single seizure events [11]. To differentiate between epilepsy and non-epilepsy in the presence of seizures can be difficult without clear patient history or documentation of a previous diagnosis; especially when conducting epidemiological studies in contexts where records are lacking [8]. A clear patient history or witness report of repeated seizures, devoid of an acute condition, is essential for a diagnosis of epilepsy.

Active epilepsy is generally defined as having one seizure within the last 2 to 5 years or currently taking anti-epileptic drug (AED) treatment [10]. In some contexts, for clinical purposes and because of potential recall bias or lack of medical records, active epilepsy is considered as having a seizure within the last year, or currently taking AED treatment [12–15].

Epileptic seizures can present in different ways and often include an alteration of consciousness or involuntary motor, sensory autonomic or psychic events [10]. Seizure classification takes into account a number of factors, relying on accurate witness accounts of the physical manifestation of the seizure. Electroencephalography (EEG), where available, can also be useful in assisting in the determination of seizure type and highlighting underlying focal abnormalities [16].

**Seizure Classification**

Seizure classification relies on an accurate witness description of the time immediately preceding the seizure (pre-ictal phase), the events during the seizure (ictus), including sensory or motor symptoms, such as convulsive movements, incontinence, and any alterations in consciousness [8]. Seizure types can be divided into generalized seizures, which almost always present with loss of consciousness and motor or nonmotor activities and involve both hemispheres of the brain; focal seizures, which generally present with motor or nonmotor activity, with or without loss of consciousness, and only involve one hemisphere of the brain, but may progress to involve both hemispheres (secondary generalization); and finally, unknown, which include epileptic spasms [17]. Using a simplified matrix, highlighted by Thurman and colleagues in a recent article attempting to standardize definitions used in epidemiological studies on epilepsy [8], one is able to
generally make a diagnosis of the type of seizure by the onset (generalized or focal) and the involved systems (motor or nonmotor). This can indicate a seizure’s etiology, which in turn can inform the treatment for the epilepsy.

**The Etiology of Epilepsies**

The International League Against Epilepsy [17] highlights three main underlying causes, or etiologies of epilepsy. These three etiologies are: **genetic etiologies**, **structural or metabolic etiologies**, and **unknown (or idiopathic) etiologies**. Genetic epilepsy is specified in cases of identified genetic modifications resulting in the manifestation of epilepsy. Examples of genetic epilepsy include Dravet syndrome or the SCN1A mutation. Often this type of epilepsy is identified through genetic testing or clear family history of seizures [17].

*Structural or metabolic epilepsies* include epilepsies arising from a condition or disease that results in an increased risk of seizures. Such conditions include stroke, head trauma, and infections, such as neurocysticercosis or tuberous sclerosis.

Finally, epilepsies with no known, identifiable cause are categorized as epilepsy of unknown etiology. Roughly two-thirds of all cases of epilepsy have no known etiology and similar levels are found in both high-income- and LMICs [18]. The determination of underlying etiologies can be made by characterizing the patient’s “the age of onset, cognitive and developmental antecedents and consequence, motor and sensory examinations, EEG features, provoking or triggering factors and patterns of seizure occurrence with respect to sleep” [17]. Whilst the determination of the underlying etiology of an epilepsy is useful for treatment, it is not always possible to derive, especially in LMICs, where the burden of epilepsy is highest [2,8].

**Epidemiologic Burden of epilepsy**

Over the last half century, numerous studies have been carried out in different parts of the world in an attempt to determine the prevalence of epilepsy and to compare the burden across different regions. However, comparisons across studies have been difficult to make due to differing study methodologies, including case ascertainment and diagnosis [8,19]. Findings are often derived from small studies that lack the representivity to make generalized claims. Studies that do exist suggest a higher burden of epilepsy in LMICs when compared to high income countries. This higher burden is thought to be a result of higher levels of known risk factors, including infections and poor antenatal and perinatal care in these contexts [20].
Until recently, very few, large, population-based studies had been conducted on the African continent to ascertain the epidemiology of epilepsy. However, within the last eight years, several large, population-based studies and robust systematic reviews and meta-analyses have been undertaken and confirm a higher burden of epilepsy in LMICs, whilst also highlighting the variation of burden by country.

Prevalence
The prevalence of epilepsy is highest in LMICs—two to three times higher [2]—and also higher in rural areas, with especially high prevalence figures reported in sub-Saharan Africa [21,22]. A 2014 meta-analysis by Ba-Diop and colleagues found the mean prevalence of epilepsy to be 9.39 per 1000 individuals and a median of 14.2 (interquartile range (IQR): 8.0-33.2) per 1000 individuals living in sub-Saharan Africa [21]. These prevalence figures are nearly three times higher than the prevalence found in high-income countries (5.8 per 1000; IQR: 2.7-12.4) [2]. The prevalence in the 2014 meta-analysis was found to vary by African region, with highest levels in east and west Africa. Furthermore, prevalence was found to vary significantly by methodology of case ascertainment with door-to-door surveys reporting higher prevalence figures than cross-sectional surveys [21].

Large population-based studies in five African sites, employing the same methodology, and forming the genesis of this PhD, found varying prevalence figures of active convulsive epilepsy across the African continent, again, with highest levels found in east and west Africa, and the lowest found in South Africa (Figure 2). It is likely that the endemicity and distribution of known risk factors for epilepsy are responsible for the varying prevalence [12].

Risk Factors
There are a number of known risk factors for epilepsy. Risk factors reported in studies from sub-Saharan Africa include genetic factors (family history of seizures) [13,23–25], adverse perinatal and antenatal events [12,21,26], previous febrile seizures [21], head trauma [13] and parasitic infections, including malaria [27], cysticercosis [28–31], onchocerciasis [32,33], toxocariasis [29,34] and toxoplasmosis [35]. Kamuyu and colleagues found that exposure to both toxocara and onchocerca had a combined effect on the prevalence of active convulsive epilepsy that was greater than exposure to either single parasite [36]. Hypertension was also found to be associated with adult-onset epilepsy in the multi-site study from sub-Saharan Africa [12], a concerning finding given the noted rise of hypertension levels in sub-Saharan Africa [37].
Incidence

There are few studies from Africa that examine the incidence of epilepsy. A recent systematic review identified only eight studies [21], with incidence rates ranging from 64.0 (95%CI: 44-84) per 100,000 person-years of follow-up in Ethiopia [39] to 187.0 (95%CI: 133-256) per 100,000 person-years of follow-up in Kenya [40]. However, due to the differing methodologies employed in the different studies, it is difficult to compare the reported incidence rates.

A meta-analysis by Ngugi and colleagues found median incidence rates to be nearly two times greater in LMICs than those in high-income countries (45.0 (IQR: 30.3-66.7) versus 81.7 (IQR: 28.0-239.5) per 100,000 individuals) [41]. The authors suggest that the reason for the heterogeneity is multifactorial and include differences in the prevalence of known risk factors, such as malaria, neurocysticercosis, head trauma and genetic factors, as well as health service provision [41]. The authors conclude by calling for
large, population-based incidence studies of epilepsy; a gap that this PhD begins to fill.

Interestingly, the incidence rates found in a number of studies performed in Africa are higher than the prevalence figures from the same area would suggest [20]. Newton and Garcia propose that this is likely due to higher levels of mortality experienced by people with epilepsy in LMICs, or, potentially, higher rates of spontaneous remission [20].

**Mortality**

Studies have shown an increased age-standardized mortality rate of 2 to 3 times the general population in people with epilepsy [42]. Studies from LMICs suggest that mortality rates are 6 to 9 times greater than mortality in the general population [43,44]. Ba-Diop and colleagues in their recent systematic review of the epidemiology of epilepsy in sub-Saharan Africa identified 6 studies exploring the mortality of epilepsy in this region, which, in every study, observed higher mortality rates in people with epilepsy compared to people without epilepsy [21]. Standardized mortality ratios (SMR) ranged from 7.2 (95%CI: 4.4-11.6) in west Uganda [45] to 6.5 (95%CI: 5.0-8.3) in rural Kenya, with the highest mortality seen in those aged 18-24 years [43].

A number of risk factors have been identified for mortality in people with epilepsy in high-income countries, including having epilepsy and neurological deficits from birth, duration of epilepsy (higher mortality experienced in first 2 years after onset), seizure type (higher in convulsive seizures), remote symptomatic epilepsies and seizure frequency [42]. Few studies have explored these factors in LMICs. A study from rural China found early age of epilepsy onset, duration of epilepsy and residing in close proximity to a body of water to be risk factors [46] whilst a more recent study from rural Kenya found non-adherence to AEDs, cognitive impairment and older ages (50 years and older) to be risk factors for premature mortality [43].

This increase in mortality can be due directly to epilepsy (such as status epilepticus or sudden unexplained death in people with epilepsy- SUDEP) or indirectly related to epilepsy (an accident, such as drowning, due to seizures, or suicide). A recent study from rural Kenya found 56 percent of deaths in people with epilepsy to be directly related to epilepsy, with 38 percent attributed to status epilepticus, and another 7 percent attributed to SUDEP [43]. Yet, generally, studies exploring cause of death in people with epilepsy are lacking in LMICs and further studies would be useful to tailor context-specific interventions aimed at reducing the observed excess mortality [43].
Aggregate Burden Metric: The Disability-adjusted Life Year (DALY)

Epilepsy, like many conditions, is responsible for both excess morbidity and excess mortality, which have been shown to be higher in LMICs than in high-income countries. Combining morbidity and mortality into a single metric allows one to compare the burden of one disease against the burden of another disease and presents a more accurate burden of a disease (especially for non-communicable diseases, which have substantial morbidity) than if just mortality was used to determine the burden [48]. The combination of morbidity and mortality can be useful when comparing disease burden within or across different geographic regions as well as when determining resource allocation. However, for such comparisons, a common metric, such as the disability-adjusted life year, or DALY, must be used.

The DALY is an aggregate measure that combines both morbidity and mortality of a specific disease or condition. Put another way, the DALY is the sum of the years of life lost (YLL) due to a condition plus the years of life lived with a disability (YLD) due to a condition [49,50]. Developed by Chris Murray in 1990, with support from the World Bank, the development of the DALY has resulted in the Global Burden of Disease (GBD) study, which seeks to quantify the total global burden of disease by world region, country and disease type. Due to the paucity of epidemiological data from LMICs for many diseases and conditions, the GBD study employs a number of modeling techniques, including meta-regression and cause of death ensemble modeling [51], to estimate disease prevalence, incidence and duration and cause of death, respectively [52], when data is lacking. This, along with other practical and theoretical challenges persist in the calculation and interpretation of DALYs [53–55]. Figure 3 above presents the interplay between the various disease parameters, as they relate to epilepsy.

**Figure 3** The epidemiological states of epilepsy, adopted from Ibinda and colleagues, 2015 [47]
The most recent update of the GBD study, published in 2015, included 301 acute and chronic diseases and injuries in 188 countries [56]. Prior to this, the 2010 GBD study employed a number of updated definitions and methods that were used again in the most recent update [52,57]. Included in the 2010 GBD definitions was a revised standard life expectancy table, with a life expectancy for both males and females of 86.02 years at birth, a figure representing the highest years of healthy life currently attainable globally. Furthermore, disability weights, or the measure of disability associated with a specific disease state, were revised to reflect the results of a global survey of more than 40,000 individuals, including face-to-face interviews in Bangladesh, Indonesia, Peru and Tanzania; telephonic interviews in the United States and an open, web-based survey [6]. This approach differed from earlier GBD studies that had relied on expert opinion to determine disability weights [6] and aimed to provide greater representivity.

Methodologically speaking, perhaps the most obvious change presented in the 2010 GBD study was the approach used to calculate years of life lived with disability (YLD). Previous GBD studies calculated YLDs by multiplying the incidence of a condition by its disability weight and expected duration. The 2010 GBD study determined YLDs by multiplying the prevalence of the condition by its disability weight. The revised methodology allowed for the calculation of co-morbidities and took advantage of the greater global availability of prevalence data. The resulting YLD figures are likely to vary depending on which method is employed to calculate YLDs [58]. The prevalence of a condition is equal to the product of the average incidence multiplied by the average duration only when the age distribution of the population is stable and the incidence and duration of the condition are not age-varying [59]. As such, the change in methodology used to calculate YLDs is likely to cause a change in resulting DALYs, something that Paper II of this PhD will explore.

Epilepsy in terms of DALYs
The 2010 GBD study found epilepsy to rank 36th in its contribution to the global burden of disease, contributing 17.4 million DALYs or roughly 0.75 percent of all DALYs, globally [60]. It is important to note that the 2010 GBD study’s definition of epilepsy is epilepsy of idiopathic etiology. Idiopathic epilepsy is likely to account for 60 to 70 percent of all epilepsies [18] and accounted for 58 percent in the 2010 GBD study [61]. Half of the burden attributed to epilepsy in the 2010 GBD study was due to morbidity (YLDs) whilst the other half was due to premature mortality (YLL) [61].

Within Africa, specifically eastern and southern sub-Saharan Africa, epilepsy ranked 19th in its contribution to the total disease burden and 14th in western
Africa—higher than anywhere else in the world [61]. A study from rural China, using 2000 GBD methodology found epilepsy to contribute 2.08 DALYs per 1,000 individuals [62]. A more recent study from rural Kenya found epilepsy to be responsible for 4.3 DALYs per 1,000 individuals (95% uncertainty interval (95%UI): 3.4-5.2), with 74 percent of the burden due to morbidity and 26 percent due to premature mortality [47]. The highest burden was found in those age 13-28 years old. The few studies exploring the burden of epilepsy, in terms of DALYs, that do exist, differ from estimates derived from the GBD study [47,62]. This highlights the need to conduct national or sub-national studies, using contextually derived data, to determine the disease burden, if such information is to be used for setting local health care priorities.

**Stigma and the Social Burden**

Epilepsy, whilst certainly a condition of biological origin and manifestation, also has social implications on the individual with epilepsy and, often, his or her family. This burden is not captured within the DALY, and, in Africa, has been shown to be substantial [63], often due to traditional beliefs that epilepsy is the result of a curse or is a contagious condition [20]. A number of studies from Africa have found epilepsy to be associated with high levels of stigma, especially in poorer, often rural areas [20]. A study by Birbeck and colleagues from Zambia found that people with epilepsy had higher perceived stigma scores, poorer employment status and less education, with less access to water, lower levels of household electrification and greater food insecurity than people with other chronic conditions, excluding HIV/AIDS [64]. Lower marriage prospects and increased physical and sexual abuse were also experienced by some women with epilepsy [64,65]. Stigma has also been found to result lower quality of life in people with epilepsy [66–69]. In many LMICs, lack of medical facilities and social stigma contribute to people with epilepsy being hidden away, unable to contribute to the household’s welfare and unable to contribute to the economic burden of epilepsy.

**The Economic Burden of Epilepsy**

In addition to the epidemiologic and social burden of epilepsy, epilepsy also carries a substantial financial burden. Epilepsy results in significant economic costs in terms of treatment, lost productivity and increased health care utilization [70]. Estimates suggest that some countries spend as much as one percent of their total national health care expenditure on epilepsy care and treatment [71].
Costs are often divided into direct and indirect, with direct costs including both “medical and nonmedical resources devoted to the prevention, treatment or rehabilitation of individuals” with epilepsy and indirect costs defined as the “value of time lost from work...due to sickness and premature mortality” (Figure 4) [72].

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(NM)- nonmedical, direct cost  
(M)- medical, direct cost

**Figure 4** The various costs of epilepsy from a societal perspective; patient, direct costs are often termed ‘out-of-pocket’ costs

The costs due to epilepsy have been found to vary by stage of the disorder, type and frequency of seizures, drug resistance, disability of the individual and frequency and type of health care services utilized, including diagnostic and treatment tools available [72–77]. In the United States, incident cases of epilepsy have been found to be costlier than prevalent cases [78]. In a 2006 review, mean annual direct costs due to epilepsy were found to range from 2006 international dollar (I$) 40 to I$4768, with costs from LMICs ranging from I$40 to I$384. Indirect costs contributed between 12 and 85 percent of the total cost and were higher in high-income countries [79]. The international dollar was used in this review to allow for comparison across studies.

A recent systematic review of 22 studies on the economic impact of epilepsy by Allers and colleagues identified out-of-pocket costs and lost productivity as substantial burdens to households with people with epilepsy [80]. The few African studies that have been carried out exploring costs due to epilepsy found that the majority of costs result from anti-epileptic drugs [79]. A population-based Burundian study found people with epilepsy who were taking AEDs had a 440 percent increase in their annual health care costs compared to individuals without any neurological condition [81]. A study
from Cote d’Ivoire found out-of-pocket costs to be a significant determinant of non-adherence to AEDs [82]. In the absence of social health insurance, people in many LMICs are forced to pay for care out-of-pocket, often resulting in financial catastrophe, poor treatment adherence or complete cessation of treatment [80]. Often out-of-pocket costs are found to be regressive [83], with the poorest paying the most.

Overall, there is a paucity of population-based studies exploring the economic cost of epilepsy in LMICs, especially Africa. Further research is needed to determine the economic burden of epilepsy in these countries. This information can assist with policy planning aimed at reducing the economic burden of epilepsy [80].

**Health care Utilization**

Health care utilization by people with epilepsy is an important factor of both costs and adherence, with the relationship between these three factors—health care utilization, cost and adherence—multi-directional and complex [72,84].

Studies from high-income countries find greater health care utilization amongst people with epilepsy compared to both people with other chronic conditions [85,86] and the general population [87]. A recent study from rural Kenya found epilepsy to be associated with a significant number of hospital admissions as well as substantial duration of stay at the hospital [88]. These higher rates of utilization can be a result of filling of chronic AED prescriptions [89] and emergency room usage [90]. The cost of care correlates to utilization and, in contexts of high out-of-pocket costs and no insurance, it is not surprising that health care utilization is low resulting in a substantial treatment gap.

**The Epilepsy Treatment Gap**

Epilepsy is a treatable condition with up to 70 percent of individuals experiencing seizure freedom with optimal AED therapy [91]. The primary aims of anti-epileptic drug treatment are the achievement of seizure freedom without adverse outcomes [92], reduction in morbidity and mortality and improved quality of life in people with epilepsy [93]. The majority of people with epilepsy respond well to monotherapy [91,94], with polytherapy initiated if the first drug is poorly tolerated or ineffective [91]. In the roughly 30 percent of people with epilepsy who do not respond to AEDs (often known as refractory epilepsy), achieving seizure freedom is difficult [92,94]. New interventions including epilepsy surgery, the ketogenic diet,
neurostimulation (e.g. vagus nerve stimulation) [95] and new antiepileptic
drugs in development may assist in reducing or eliminating seizures in
patients with refractory epilepsy. Yet in many LMICs, these interventions are
not available and reliance on anti-epileptic drugs is necessary. However, in
order for AEDs to be effective, people with epilepsy must be correctly
diagnosed with epilepsy, have access to quality AEDs, must be prescribed the
correct dose of the drug, and must properly take the drug, per the
recommended dose.

In many LMICs, lack of access to quality AEDs, limited or no interaction
with health care workers and other factors result in an estimated epilepsy
gap greater than 50 percent [96,97]. The epilepsy treatment gap, defined as
the difference between the number of people with active epilepsy and the
number of people whose seizures are adequately suppressed, expressed as a
percentage [4,98], has been found to be higher both in LMICs (compared to
high-income countries) and in rural areas (compared to urban areas) [97].
Several studies from countries in Africa, including Ethiopia, The Gambia,
Nigeria, Togo, Uganda, Tanzania and Zambia, all reported treatment gaps in
excess of 95 percent [97]. A recent study from rural Kenya found an epilepsy
treatment gap of 62.4 percent (95%CI: 58.1-66.6), similar to findings from a
small study in rural South African children [99].

A recent review by Ba-Diop and colleagues highlights the fact that 59 percent
of people with epilepsy in sub-Saharan Africa are estimated to not be taking
any form of medication, whilst 33 percent of individuals with epilepsy who
receive AEDs are poorly managed [21]. Much needs to be done to reduce the
epilepsy treatment gap and understanding the determinants of the treatment
gap is an important first step.

**Determinants of the Treatment Gap**

A number of factors and causes have been suggested to account for the large
treatment gap seen in many LMICs. These factors include characteristics of
the health care system (lack of skilled health care providers, unavailability of
AEDs at health facilities), inability to access health facilities, high cost of
anti-epileptic drugs and misconceptions of the cause of epilepsy and fears of
stigmatization [96]. A study from rural Kenya found that failure to seek
biomedical treatment for epilepsy was associated with traditional animistic
beliefs (adjusted odd ratio (aOR) 0.86; 95%CI: 0.78-0.95); living more than
30 km from health faculties (aOR 3.89; 95%CI: 1.77-8.51); paying for AEDS
(aOR 2.99; 95%CI: 1.82-4.92), having learning difficulties (aOR 2.30;
95%CI: 1.29-4.11); having had epilepsy for longer than 10 years (aOR 4.60;
95%CI: 2.07-10.23); and, having focal seizures (aOR 2.28; 95%CI: 1.50-
Limited adherence was associated with negative attitudes regarding epilepsy (aOR 1.10; 95%CI: 1.03-1.18) and taking AEDs for longer than 5 years (aOR 3.78; 95%CI: 1.79-7.98) [100]. It was also found that the sensitivity and specificity of self-reported adherence was low [100].

When examining determinants, or risk factors, for the observed epilepsy treatment gap, it is important to examine both characteristics of the health care system as well as characteristics of the user. Andersen, in his behavior model, suggested that health-seeking behavior is a function of four domains: health care system factors; an individual’s predisposing factors (e.g. demographics, social structure, health beliefs), enabling factors (e.g. availability of transportation or money) and perceived need of care (e.g. number of seizures and necessity of consultation) [84]. Employing such a framework can help to explore the often complex interplay between health-care seeking behavior and adherence, an area of research lacking in sub-Saharan Africa.

**Interventions to reduce the epilepsy Treatment Gap**

A number of interventions to reduce the epilepsy treatment gap in LMICs and specifically, sub-Saharan Africa have been proposed [96,101], with some interventions evaluated [102–107]. Generally, these studies have focused on educating people with epilepsy and health care workers. In some studies, this has led to an increased understanding of epilepsy [103,105,107] and an increased patient recruitment [103,104]; however, only in studies from Zimbabwe where education and AEDs were provided, was an increase in adherence seen [102,103]. These findings suggest that education, whilst important at improving the understanding of epilepsy, cannot alone improve adherence to AEDs (at least in contexts lacking the free availability of AEDs to patients).

Studies have highlighted the need to develop effective, affordable community-based interventions that are sustainable [108]. Combining education campaigns and improving access to AEDs would reduce stigma and break down barriers to effective care [109]. A publication by Chisholm and colleagues found that up to 40 percent of the burden of epilepsy could be reduced by increasing AED coverage and, furthermore, first line AEDs were found to be highly cost-effective [110].

LMICs, including much of Africa, are faced with a shortage of medical professionals, especially in rural areas. Introducing community health workers, individuals who lack formal professional tertiary education, but are provided with job-related training, have been introduced to address this void and could be further capacitated to assist in epilepsy management.
Community health workers have been found to increase the uptake of immunization and breast feeding, improve tuberculosis treatment outcomes and reduce child morbidity and mortality [111]. Studies have also shown community health workers to be a cost-effective intervention for the treatment and follow-up of other chronic conditions, including HIV [112]. Training community health workers in rural South Africa to educate community members and traditional healers about epilepsy and epilepsy treatment options and regularly visit people with epilepsy to improve adherence and initiate referral when needed, is one possible way of improving adherence at the primary health care level [20] and is in line with the South African government’s envisaged role of CHWs [113].

The integration of epilepsy treatment into the existing primary health care system through the introduction of community health workers is one potential one way to reduce the burden of epilepsy [21] and the use of economic evaluation can be used to justify the cost-effectiveness of such an intervention.

**Use of Economic Evaluation**

Health care for people with epilepsy, like health care in general, is dependent on economic factors, including the amount of investment the payer, whether it is a country, an insurance company or an individual, is willing to make. This then translates into the number of staff employed, the facilities built and maintained and the type AEDs and other therapies available [114].

The use of economic evaluations, often in the form of cost-effectiveness analysis (which can include cost-utility analysis), have been used both to guide decision makers as well as clinical practice [1,115]. Economic evaluations can provide important information that can be used to inform decisions.

In undertaking an economic evaluation, the cost of the intervention is compared to the expected gains, often expressed as utility gains. The utility weight, or quality-adjusted life year (QALY), is commonly found in such analyses to reflect the change in utility. The QALY is inherently different than the DALY (discussed earlier). The QALY reflects the utility weight, or preference of an individual for a specific health state, whilst the disability weight (used to calculate DALYS) reflects the reduction in health due to a disease or condition [116]. The utility value calculations rely on paired comparison questions, which require individuals to rank the health state of two hypothetical individuals with differing health states [6]. Both DALYs and
QALYs can be used in cost-effectiveness analysis, with QALYs often preferred due to the relative ease in deriving utility estimates.

A number of economic evaluations exploring the treatment of epilepsy have been undertaken with the majority of these focusing on therapeutic options. Specifically, a number of studies have been undertaken to determine the cost-effectiveness of new AEDs and AEDs as add-on-therapy [117]. In some countries, an economic evaluation is a pre-requisite for drug licensing. Few of these studies are from LMICs. A cost-effectiveness study by Chisholm and colleagues in 2005 found that first line AEDs were cost-effective and by increasing drug coverage by 50 percent, 13 to 40 percent of the global burden of epilepsy could be eliminated at an annual cost per capita of I$ 0.20 to I$ 1.33 [110]. This is further supported by the World Health Organization, which identified epilepsy as one of the most cost-effective conditions to treat [118]. But again, few cost-effectiveness studies have been conducted in LMICs, where arguably, resources are most scarce and yet, most needed. Furthermore, no cost-effectiveness study on a community-based intervention to reduce the treatment gap of epilepsy in rural sub-Saharan Africa has been undertaken.

Just as Pachlatko writes in his 1999 essay on ‘The Relevance of Health Economics to Epilepsy Care’, “The study of the economic consequences of the disease is clearly in the interest of the patient”, with the majority of people with epilepsy found in LMICs. Furthermore, “to justify and promote epilepsy care, cost-effectiveness studies should be carried out for certain interventions” (p.6) [114]. All health care settings have finite resources and combining robust estimates on the burden of a specific condition, such as epilepsy, with cost-effectiveness analysis of a proposed intervention can provide decision makers with useful information to assist in deciding which package of care should be implemented. South Africa is one country where priority-setting, supported by evidence-based economic evaluations of proposed health care interventions, would likely yield better health gains for less money [119].

The Republic of South Africa

South Africa, the southernmost country on the African continent and home to roughly 54 million individuals, is one of four African countries demarcated as an upper-middle-income country, in terms of economy, by the World Bank [120]. Yet, South Africa remains one of the most unequal societies in the world; an inequality that often exists along racial lines [121].
The present situation emerges from a history of struggle, oppression and violence that was known to the world as *apartheid*. *Apartheid*, literally translated from Afrikaans as ‘the state of being apart’, fractured the country along racial lines into a series of ethnic homelands, or *Bantustans*, to which the various ethnic tribes that comprised the South African population were allocated and forcibly resettled. Rights and movements of non-whites were greatly restricted, whilst the ruling white minority enjoyed residence in urban, economic hubs and fertile land. The governmental functions were decentralized, with each homeland responsible for carrying out the necessary legislative and judicial functions.

After years of intense and bloody domestic struggles, including such infamous events as the 1960 Sharpeville Massacre and the 1976 Soweto uprising, and increasing international pressure and condemnation, the Apartheid regime began to crumble in the mid-1980s, with the repudiation of a number of *Apartheid* era laws. Finally, with the release of Nelson Mandela, a prominent leader of the banned African National Congress in early 1990, the winds of political change swept the country and culminated in the first democratic elections being held in 1994. With these elections, the modern South Africa emerged as a rich and vibrant ‘rainbow nation’, though still beset with challenges and inequalities; a legacy of the nearly 45-year rule of the Nationalist Party and their policies of *Apartheid*.

**The Health care System of South Africa**

During the era of *Apartheid*, the health care system was fragmented and decentralized, with each *Bantustan* responsible for the health of its population. With the abolishment of *Apartheid*, a national Department of Health was formed from the 14 racially divided health departments, health care fees were abolished at the primary health level and for pregnant women and children less than 6 years old [122]. Furthermore, the 1997 position piece entitled ‘Transformation of the Health System in South Africa’, emphasized the idea of strong primary health care (PHC) delivered through the development of a district health care system [123].

The idea of primary health care, adopted internationally during the 1978 Alma Ata conference, can actually trace part of its origins to early work by Doctors Sydney and Emily Kark and their work on the community-oriented primary care model at the Pholela Health Centre in rural KwaZulu-Natal, South Africa, in the 1940s [124]. The Pholela Centre, staffed by local community members, focused on both preventative and curative health care based on population-based investigations of the community’s needs. This model placed emphasis on the health of families and the community [25]. The Gluckman Report, published in 1944, intended for a South African
national health service built on the success of the Pholela project [126]. Yet, even with a rich, albeit early, history of PHC work and a re-centralized national Department of Health after the end of Apartheid, South Africa and its investment in health, exceeding 200 billion South African Rand (ZAR), or 8.6 percent Gross Domestic Product in 2009-10 [127], have failed to deliver, in part due to the colliding epidemics facing the population [122].

The South African Burden of Disease and Lessons Learned
The South African population is currently undergoing rapid demographic and health transitions marked by an ageing population faced with increasing non-communicable diseases and persisting communicable diseases [121,128,129]. Perhaps, most notably, South Africa has the greatest proportion of people living with HIV globally, a staggering 6.3 million individuals, or 11.9 percent of the total population in 2013 [130]. The number of new cases in 2013 was 341,000 individuals and 146,000 individuals died as a result of HIV/AIDS [130]. However, the dramatic change in the South African government HIV policies, from a view of skepticism and anti-retroviral therapy (ART) bans [131], to an active rollout of ART in 2003, coupled with massive foreign investment through such programs as the United States’ President’s Emergency Plan for AIDS Relief (PEPFAR), has resulted in a reduction of the number of deaths due to HIV [132]. By 2012, 2.6 million people living with HIV in South Africa were on treatment and the numbers enrolled on treatment continue to increase. However, the number of new cases of HIV remains unabated.

In response to the shifting burden of disease and the current state of the South African health care system, the South African Department of Health has focused on re-engineering the primary health care (PHC) system, looking to create primary health care teams, including a professional nurse, environmental health and health promotion practitioners and six community health workers. Additionally, district-based clinical specialist teams and school health services are also being developed [133].

At the same time that PHC re-engineering is underway, an integrated chronic disease model of care is being rolled out across health facilities as a way to address the emerging burden of chronic disease. Learning from the effective rollout of HIV treatment, an integrated chronic disease management model, derived from Wagner’s Chronic Care Model and the World Health Organization’s Improved Care for Chronic Conditions Framework, is being implemented to provide affordable and effective care to patients with other chronic conditions [134].
Underpinning all of these efforts is the intention of delivering universal health coverage in South Africa over the next 20 years, through the introduction of a national health insurance [135]. Yet, even with health care system innovations and interventions, substantial disparities remain. In the private sector, which caters to 16 percent of the South African population, annual per capita expenditure amounts to $1,400. This compares to only $140 in the public sector. Only 30 percent of the Republic’s clinicians staff the public health sector, which is responsible for the health care needs of 40 million uninsured individuals, or roughly 84 percent of the Republic’s population. One quarter of these uninsured individuals pay out-of-pocket for access to private sector care due to the crisis facing the public health care infrastructure [132] and its perceived (and, perhaps, actual) lack of quality care.

Nowhere are these shortcomings and disparities more felt, and conversely opportunities for improvement more evident, than in rural areas of South Africa. However, just as Sidney Kark believed more than 70 years ago, the priorities of the health care system must be determined by the needs of the population [125]; and the regular and longitudinal surveillance of a rural population, such as the site in which the current work is nested, provides one source of such information.

**The Rationale**

The rationale for this work lies in the fact that epilepsy is a common, chronic neurological disorder that results in substantial epidemiological, social and economic burdens and a lower quality of life for people with epilepsy. People living in sub-Saharan Africa are disproportionately affected by epilepsy. Seizures can be reduced or eliminated in 70 percent of people with epilepsy [91] and yet the treatment gap in sub-Saharan Africa remains substantial. Contextually relevant, community-based interventions have been suggested as one way to reduce the treatment gap and undertaking a cost-effectiveness analysis of such an intervention, using locally derived disease parameters, can provide decision makers with important information on the value of such an intervention.
Materials and methods

The Context

The Agincourt Health and Demographic Surveillance System

The Agincourt Health and Socio-demographic Surveillance System (HDSS), located 500 km northeast of Johannesburg, South Africa, within the Bushbuckridge district, is a rural research site affiliated with the South African Medical Research Council and the University of the Witwatersrand’s School of Public Health within the Faculty of Health Sciences. The Agincourt HDSS (http://www.agincourt.co.za) has conducted longitudinal population-based research since its inception as a research site in 1992. The purpose of the longitudinal research is to document the complex and, often unpredictable social, epidemiological and demographic transitions occurring within this rural South African population [136]. These data have assisted researchers and policymakers in determining how, when and where to most effectively intervene to enhance the quality of life and productivity of rural South Africans.

Spread over 450 km² of semi-arid scrubland and comprising nearly 21,000 households (a household defined as those who eat together) in 31 villages (Figure 5), the Agincourt HDSS comprises a dynamic open cohort of 114,765 individuals (2015 mid-year population figure) who reside within the geographically well-defined site. During the annual census, each household within the HDSS is visited and a household roster is updated, capturing changes in residency status and vital events, including births, deaths and migrations. In the case of a new household, a household roster is completed when first identified and then updated on subsequent rounds.

Additional information is also often regularly collected during census rounds and can include information on individuals’ education and labor status,
migration patterns, government grant uptake and socio-economic status. These additional data allow researchers to more deeply explore the socio-demographic determinants of this rapidly transitioning, rural population.

**Figure 5** Map of South Africa and the Agincourt Health and Demographic Surveillance Site (HDSS), 2015
On a number of occasions, a question, or set of questions, has been added to the annual census to screen for individuals with a specific condition of interest to researchers. Examples of such conditions include tuberculosis, stroke and seizures. Positive responses to these questions can then followed up with more detailed questioning by a team of specially trained fieldworkers.

**The Agincourt sub-district**

The land that comprises the Agincourt sub-district was formerly part of the Gazankulu Bantustan and is home to the Shangaan people, a xi-Tsonga-speaking people. During the Mozambican civil war, which began in 1977 and continued through the 1980s and early '90s, refugees fled Mozambique and many settled in northeastern South Africa, including villages within the Agincourt sub-district. Roughly one-third of the Agincourt HDSS population are Mozambican immigrants.

Within the site, a network of roads connects the villages to one another–about 50 percent of the main roads are now tarred, with dirt roads serving to connect the remainder. Within villages, smaller roads and footpaths link households. During periods of heavy rain, certain roads can become impassable due to erosion and flooding, making transportation difficult.

Most houses within the study site have electricity, though the use of electricity for cooking and running appliances varies from household to household. Earlier work has found that the death of the primary breadwinner within a household results in that household’s greater reliance on natural resources, including collection of firewood from the open land surrounding the village [137]. Water is piped into the site from a number of dams surrounding the area and most households have access to a communal water tap or, though currently less common, have running water within their dwelling. The availability of water is irregular with some households having to travel to adjoining villages to collect water.

Unemployment within the population remains high due to lack of job opportunities in the area, with 33 percent of the population unemployed in 2012 (personal correspondence, Mark Collinson). As a result of the lack of job opportunities, a large proportion–29 percent of the total population in 2015-participates in circular migration [138]. Circular, or temporary migration, involves traveling out of the study site for more than 6 months in a 12-month period, with many individuals traveling to larger urban areas for work or in hopes of finding work.
Whilst unemployment remains high, the socio-economic status of the population has improved over the last 20 years, driven largely by the government’s social grant system, especially the child care grant [139] and old age pension [140], and remittances from migrant household members [141].

All villages within the Agincourt study site have a primary school and the majority also have a high school, yet the quality of the education remains poor with consistently low levels of matriculation.

Over the past 20 years, life expectancy has dropped to its lowest levels—57.4 years for females (in 2006) and 50.0 for males (in 2008)—before recovering. In 2012, life expectancy for males was 60.9 years, whilst life expectancy for females was 67.7 years [142].

The main driver of this reduced life expectancy through the mid-2000s was the HIV pandemic. Chances of dying in 2005-06 for those aged 25-34 were 6.5 times greater for females and 4.5 times greater for males compared to 1992-93 (unpublished data). With the introduction of ARTs in the mid-2000s, life expectancy began to increase.

South Africa is undergoing a major epidemiological transition and the Agincourt sub-district is no different. Within the last 20 years, mortality within the sub-district has been marked by increasingly high and recently receding levels of infectious causes of death, driven primarily by the HIV pandemic. Underlying levels of non-communicable disease, trauma and accidental and maternal causes of death (Figure 6), the so-called quadruple burden of disease [129,143]- all contribute to overall mortality [144].

**Agincourt sub-district health care system**

The Agincourt sub-district contains six government primary health care (PHC) clinics that are staffed by nurses and provide free PHC services during regular business hours. Services offered at these facilities include immunizations, family planning, testing and treatment for sexually transmitted infections (now including HIV and initiation to anti-retroviral therapy) minor trauma and routine chronic medications for chronic conditions, including epilepsy [145].

In addition to the six PHC clinics within the site, a larger government community health center provides PHC services as well as to 24-hour acute maternity care. The health center also has a limited number of beds for 48-hours patient observation [145]. Professional nurses are responsible for...
managing the day-to-day responsibilities of the health centers and clinicians do make visits.

**Figure 6** Causes of death in Agincourt between 1992 and 2011, reproduced from Kabudula and colleagues [144]

A public-private partnership community health center was set up in the sub-district in the mid-2000s to provide HIV and TB treatment. This center was privately funded and, over time, has extended its coverage to also include care for other chronic diseases.

Referrals from the sub-district’s PHC facilities are made to three government hospitals that are located 25-55 kilometers from the site [146]. These hospitals are staffed by clinicians and supported by professional nurses. Patients generally travel to hospitals via public transport. Generally, clinicians diagnose patients with epilepsy at the hospital. Patients are then referred to the clinic or health center of their choosing for monthly AED collection [147]. Patients with epilepsy are expected to return to the hospital every 6 months for review of seizure frequency and treatment.

Traditional healers and faith healers are also popular, alternative forms of health care used by individuals within the site. Often it is perceptions
regarding cause of illness that is the primary driver of health seeking behavior [148].

**The Studies of the Epidemiology of Epilepsy in Demographic Surveillance Systems (SEEDS)**

As mentioned earlier, a question, or set of questions, can be added to the annual HDSS census to provide screening for a study interested in identifying a certain condition. In 2008, two questions were added to the annual Agincourt census to ascertain potential cases of convulsive epilepsy. These questions, “Do you have epilepsy?” and “Have you ever been told by someone else that you have epilepsy?”, translated, piloted and asked by trained fieldworkers in the local xi-Tsonga language, served as the first stage of a three stage study that was designed to determine the prevalence and risk factors for **active convulsive epilepsy (ACE)**. This study, known by its acronym, SEEDS, or the Studies of the Epidemiology of Epilepsy in Demographic Surveillance Systems, sought to identify all individuals with ACE in 5 sub-Saharan African HDSS sites, sites part of the INDEPTH network. These sites, Kilifi (Kenya), Iganga (Uganda), Kintampo (Ghana), Ifakara (Tanzania) and Agincourt (South Africa) were specifically chosen due to the heterogeneity of endemic, potential risk factors [12].

After identifying those who responded affirmatively to one or both of the ‘screening questions’, a specially trained team of fieldworkers re-visited these individuals to ask more detailed questions regarding the presentation of the seizures as well as the periodicity and frequency of the seizures. In essence, these questions were aimed at crudely defining cases as **active convulsive epilepsy**: active, meaning having had at least two unprovoked seizures more than 24 hours apart with at least one occurring within the last 12 months— or currently taking AEDs; and, convulsive, meaning the presentation of clonic, and/or tonic movements. This comprised Stage 2 of the study.

If individuals screened positive in Stage 2, they were referred to the study’s epilepsy clinic to be examined by a trained professional nurse to diagnose the patient as having ACE (these diagnoses were later confirmed by the study neurologist). All individuals diagnosed with ACE at this stage (Stage 3), were also asked to provide blood samples for analysis— to assess both anti-epileptic drug (AEDs) levels to determine adherence as well as exposure to potential parasitic risk factors.
Figure 7 2008 study design schema and number of participants at each stage [23]
From this three-stage study, 245 individuals were diagnosed with ACE- an adjusted prevalence of 7.0 per 1,000 individuals (95% confidence interval (95%CI) 6.4-7.6) [23]. An additional 66 individuals were identified as having ACE- 56 after being referred to the study team by the community and 10 (26 minus the 16) who screened positive in the population sample (Figure 7). In total, this resulted in 311 individuals initially being diagnosed as having ACE in 2008.

Active convulsive epilepsy was defined as two or more unprovoked convulsive seizures occurring more than 24 hours apart with no known underlying cause, with at least one seizure occurring in the 12 months preceding the study or currently taking anti-epileptic drugs (AEDs) [13,23].

Figure 8 Cohorts derived from 2008 cross-sectional SEEDS survey

**Incidence**

An incident case of convulsive epilepsy was defined as an individual who had two or more seizures or a second unprovoked seizure between the date of the first cross-sectional survey (1 August 2008) and the date of the second cross-sectional survey (1 August 2012) without any known, acute underlying cause. This definition of incidence used in this study represents the incidence of newly diagnosed epilepsy [8].

Incidence rates were derived by dividing the number of incident cases by the total number of person-years observed (pyo) in the cohort without epilepsy in 2008. Individuals lost to follow-up, either due to death or out-migration from the study site, were excluded from the denominator.
Mortality

Mortality rates were derived by following two cohorts of individuals: those diagnosed with epilepsy, and those without epilepsy, between 2008 and 2012. The mortality rate was determined by dividing the number of deaths in the cohort of people with convulsive epilepsy by the total number of years in this cohort. The results were expressed as both age- and sex-specific rates, with the 95% confidence interval (95% CI). The standardized mortality ratio (SMR) was derived by comparing the rates between those with and without epilepsy.

Risk Factors

In Paper I, 11 variables were examined for associations with mortality, using Poisson regression. These data were collected from either the 2008 cross-sectional survey or during the 3-month follow-up visits. Variables collected during the follow-up visits were expressed as time-dependent covariates in the regression models. Reported rate ratios were adjusted for current age.

Causes of Death

We were interested in understanding not only the difference in mortality rates between those with and without epilepsy, but also in the causes of death (COD) that people with epilepsy experienced. As all individuals in both cohorts were residing within the Agincourt HDSS, each death was captured and a verbal autopsy (VA) was performed as part of regular HDSS operations.

Globally, nearly two-thirds of all deaths go unregistered [151]. The VA is routinely used in many LMICs, including at HDSS sites [152], to ascertain causes of death in the absence of standardized civil registries of vital statistics [153,154]. Within Agincourt, lay fieldworkers are rigorously trained to collect information on the symptoms and events leading up to the time of death using a standardized interview tool. This information is collected from the person closest to the deceased. This information is then entered into a database where it is analyzed by two independent, locally practicing clinicians to determine the cause of death. A third, independent clinician arbitrates in cases of non-consensus. A cause of death is considered “unclassifiable” when deliberations between all three clinicians fail to reach consensus. In this study, an independent neurologist reviewed and confirmed all cause of death results in people with epilepsy who had died.
Table 1 Causes and categories of death in people with epilepsy, derived from Lhatoo & Sander, 2005 [155]

<table>
<thead>
<tr>
<th>Deaths related to epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.) Directly-related</strong></td>
</tr>
<tr>
<td>Sudden unexplained death in epilepsy</td>
</tr>
<tr>
<td>Status epilepticus</td>
</tr>
<tr>
<td><strong>2.) Indirectly related</strong></td>
</tr>
<tr>
<td>Accidents resulting from seizure</td>
</tr>
<tr>
<td>Aspiration pneumonia from seizure</td>
</tr>
<tr>
<td>Iatrogenic; drug toxicity and idiosyncratic reactions</td>
</tr>
<tr>
<td>Suicides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Underlying disease-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary or secondary CNS neoplasia</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>CNS infections</td>
</tr>
<tr>
<td>Inherited neurodegenerative disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deaths unrelated to epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicable</td>
</tr>
<tr>
<td>Non-communicable</td>
</tr>
</tbody>
</table>

Cause of death diagnoses were classified as epilepsy-related deaths, either directly related (e.g. status epilepticus), indirectly related (e.g. burns or drowning during a seizure), not related to epilepsy or unclassifiable [155] (Table 1). Sudden unexplained death in people with epilepsy (SUDEP) was defined as sudden death in a person with epilepsy with or without evidence of a seizure, except documented status epilepticus, where any clinical autopsy did not reveal a toxicological or anatomical COD [155]. The subdivision of CODs, directly- or indirectly-related to epilepsy, follows a similar reporting structure to a recent article from rural Kenya [43].

Deaths unrelated to epilepsy were further subdivided into communicable or non-communicable CODs. Proportional mortality ratios (PMRs) were calculated by dividing the total number of deaths attributed to each COD category by the total number of deaths in the epilepsy cohort.
Remission & Duration

In order to determine the remission rate of convulsive epilepsy, the age-specific prevalence, incidence and mortality figures were input into the DisMod II software program, freely available from the World Health Organization (http://www.who.int/healthinfo/global_burden_disease/tools_software/en). The DisMod program models the remission and duration of epilepsy based on input parameters and using a set of differential equations [156]. The DisMod II program is useful for both supplementing incomplete epidemiological parameters as well as checking for internal consistency of existing estimates [156]. However, it is modeling software that uses best available data to model missing parameters. It does not replace the value of primary data, which can often be more accurate as well as costlier, both in terms of time and resources.

Paper II: Disability adjusted life years (DALYs)

Using epidemiological parameters defined in Paper I, including DisMod II estimates for duration, and previous work on prevalence [23], Paper II estimated the disability-adjusted life years (DALYs) due to convulsive epilepsy in the Agincourt sub-district of rural South Africa. To allow for internal consistency and to ensure comparability, the prevalence, incidence and duration figures used to calculate DALYs were output figures generated by DisMod II. The DisMod II results were smoothed using in-built functions—piecewise linear interpolation, moving average and cubic spline and reported in 6 age bands for both males and females with the 95% uncertainty interval (95%UI; with the uncertainty interval presented, as opposed to the confidence interval, as a result Bayesian methods used to determine the parameters’ values). The 95%UI were derived using Monte Carlo simulations with 1000 iterations and the input parameters were assumed to be normally distributed.

Disability Weight

The disability weights used in this study were derived from the 2010 Global Burden of Disease study, which corresponded to specific epilepsy disease states, depending both on whether or not an individual was on treatment as well as current seizure frequency [6] (Table 2). The disability weight used for the YLD calculations in Paper II was 0.346, a disability weight that represents the estimated proportion of various epilepsy disease states in the sub-Saharan African region (personal correspondence, T. Vos).
**Years of Life Lost (YLL)**

Years of life lost were calculated as the sum the number of deaths (directly attributable to epilepsy) per year multiplied by the GBD standard life expectancy at the age of death. Using the GBD standard life expectancy allows for burden comparisons across different settings; however, in settings where life expectancy is lower than the standard life expectancy of 86.02 years (for example, in rural South Africa) [157], the use of the global life expectancy values is likely to result in higher YLL estimates due to the higher standard life expectancy value.

**Years of Life lived with Disability (YLDs)**

The 2010 GBD study, have revised a number of methods, including the calculation of years of life lived with disability [52]. Previous GBD studies relied on incidence and duration figures to determine YLDs, with YLDs calculated by multiplying the incidence by the duration and the disability weight (DW) (Equation 1).

\[
YLD_i = \text{incidence \times duration \times DW} \quad \text{(Equation 1)}
\]

In the 2010 GBD study, the formula to calculate YLDs changed to be the multiple of prevalence and disability weight (Equation 2).

\[
YLD_p = \text{prevalence \times DW} \quad \text{(Equation 2)}
\]

*Paper II* compares the YLD values when using the two different approaches to calculating YLDs. Results are reported by age and sex without age weighting or discount rates, comparable to the 2010 GBD study [157].

**Sensitivity Analyses**

All results, including reported YLL, YLD and DALY estimates are presented with 95%UI, which were calculated using the R boot package with 1000 iterations. This operation was implemented in R, an open-source statistical software package [158–160]. The uncertainty interval reported takes into account the uncertainty in the epidemiological parameters used to estimate the reported YLL, YLD and DALY figures.

Furthermore, the disability weights used to calculate the YLDs in *Paper II* were varied to explore the effect of the disability weight on DALY estimates. The four disability weights presented in the 2010 GBD study (and presented here in Table 2), represented various disease states and disease severity.
Treated, seizure free was included as a possible disease state as the definition of convulsive epilepsy used in the 2008 and 2012 cross-sectional surveys included individuals diagnosed with epilepsy who were seizure free and currently on treatment [23].

Table 2 Disability weights associated with various states of epilepsy, GBD 2010 [6]

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Disability Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure freedom</td>
<td>0.072</td>
</tr>
<tr>
<td>Treated epilepsy, with recent seizures</td>
<td>0.319</td>
</tr>
<tr>
<td>Untreated epilepsy</td>
<td>0.42</td>
</tr>
<tr>
<td>Severe Epilepsy</td>
<td>0.657</td>
</tr>
<tr>
<td>Epilepsy in sub-Saharan African region*</td>
<td>0.346</td>
</tr>
</tbody>
</table>

*used in 2010 GBD study (personal correspondence, T. Vos)

**Paper III: Patient Costs & Health Care Utilization**

In order to ascertain the out-of-pocket, outpatient costs and self-reported health care utilization by people with convulsive epilepsy, a survey was conducted in 2010. A specially trained fieldworker visited all individuals identified as having active convulsive epilepsy in the 2008 survey and asked questions regarding both epilepsy and non-epilepsy health care utilization over the preceding 12 months. Questions on out-of-pocket, outpatient costs were asked regarding the last visit to the health care facility.

Due to the non-normal distribution of health care and traditional healer visits and out-of-pocket costs, results in Paper III were reported as median and interquartile range (IQR), with the average number of annual visits also presented. As indicated in Paper III, the time traveling to consult with a traditional healer was not collected in this survey, with only traditional healer fees being reported in Paper III.

**Paper IV: Treatment Gap**

The treatment gap was determined in Paper IV by analyzing the blood collected from individuals during the 2008 cross-sectional survey. Individuals enrolled in the study were asked whether they were currently
taking AEDs and, if so, which one(s), with individuals shown a poster presenting AED tablets and their packaging to aid in recognition.

Blood samples were analyzed for the presence of four AEDs: phenobarbitone, phenytoin, carbamazepine and sodium valproate in those who reported taking these AEDs, using a TDx FLx analyzer (Abott Laboratories, Abott Park, IL, USA). The levels of AEDs in the blood were also determined. Individuals were considered adherent if AEDs were detected in their blood sample. Detectable limits were 1.1 μg/mL (4.74 μmol/L) for phenobarbitone, 1.0 μg/mL (4.0 μmol/L) for phenytoin, 0.5 μg/mL (2.1 μmol/L) for carbamazepine and 1.0 μg/mL (6.9 μmol/L) for sodium valproate.

The therapeutic ranges were defined as 10-40 μg/mL (43.1-172.4 μmol/L) for phenobarbitone, 10-20 μg/mL (40-80 μmol/L) for phenytoin, 4-12 μg/mL (17.2-51.6 μmol/L) for carbamazepine [161] and 50-120 μg/mL (346.5-831.6 μmol/L) for sodium valproate [162].

Sensitivity and specificity of the self-reported treatment gap were also reported in Paper IV. The specificity was calculated by dividing the true negatives (those without detectable levels of AEDs who had reported not taking AEDs) by the sum of the true negatives and false positives (those who had not reported taking AEDs and had detectable AED levels in their blood samples). The sensitivity was derived by dividing the true positives (those who had reported taking AEDs and had detectable AED levels in their blood) by the sum of the true positives and false negatives (those who had reported not taking reported taking AEDs and had detectable AED levels in their blood).

**Treatment Gap Determinants**

Twenty-two variables (21 in children) that had been associated with non-adherence in a previous study [100] or hypothesized to be associated with the treatment gap were initially analyzed in Paper IV for an association with the observed treatment gap. Adopting the Andersen behavioral model as a framework, the variables were either derived from the 2008 cross-sectional survey (age, sex, employment, religion, union status, history of traditional medicine use, seizure type and frequency, neurological deficit, learning difficulties, self-reported AED use, duration of time with epilepsy, presence of burns and previous hospitalization) or from the annual Agincourt census data from 2008 (ethnicity, currently employed, labor status, residency status socio-economic quintile, Euclidian distance to nearest health facility and kin availability, including mother’s availability).
The socio-economic status was a household level variable derived by using an asset index, comprised of responses to questions on building material of the residence, access to water, owned possessions and livestock. Kin availability was defined as the number of co-residents within the dwelling recorded during the 2008 census.

**Univariate and Multivariate Models**

Initially, each variable was interrogated in a univariate model with the outcome being either self-reported or measured adherence. Variables found to have a p-value of 0.25 were included in the multivariate model, with odds ratios and 95%CI reported in *Paper IV*. A recent study found adherence to differ between children (those less than 18 years of age) and adults (those older than 18 years) [88]. As such, a separate multivariate model was constructed and analyzed for each age group. Variables having a p-value of less than 0.05 in the multivariate model were considered significant.

**Paper V: Cost-effectiveness modeling**

**Intervention**

*Paper V* calculated the cost-effectiveness of introducing a community health worker (CHW)-led intervention aimed at educating local community leaders and traditional healers about epilepsy and visiting people with epilepsy quarterly to assess adherence to their AEDs. During these quarterly visits, CHWs would review patient-held seizure diaries, inquire about seizure frequency, provide basic psychological support and refer patients to primary health care facilities if seizures are not controlled. Assuming a 1.5 percent prevalence of active epilepsy (based on earlier work in the Agincourt subdistrict [23]), four CHWs will be needed for the sub-district.

**Intervention Effectiveness**

The intervention presented in *Paper V* was modeled to result in 90 percent adherence levels within two years of implementation, leading to seizure freedom in 60 percent and a reduction in seizure in an additional 40 percent of people with epilepsy. These assumptions are based on studies showing that 70 percent of people with epilepsy can be adequately controlled with pharmacotherapy [91] as well as loosely based on results from earlier studies from Zimbabwe and Ethiopia that employed PHC nurses to lead epilepsy care clinics [103,163]. Interventions that have used CHWs to improve adherence for tuberculosis and HIV drugs have found levels of effectiveness similar to those modeled in *Paper V*[164,165].
**Intervention Costs**
In addition, the intervention will require a project coordinator, training costs for one week per year and consumables (airtime, stationary, pamphlets and local transport costs (Table 3)). Figures used to estimate the costs of personnel, training and consumables were derived from estimates presented in a recent study exploring the costs and effects of CHWs on hypertension control, modeled in the same context [166].

**Table 3** Costs associated with intervention of CHWs for the improvement of AED adherence in rural South Africa

<table>
<thead>
<tr>
<th>Intervention Costs</th>
<th>in ZAR (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salaries</strong></td>
<td></td>
</tr>
<tr>
<td>4 Community Health Workers</td>
<td>240000</td>
</tr>
<tr>
<td>1 Program Coordinator</td>
<td>400000</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td></td>
</tr>
<tr>
<td>Trainer salary</td>
<td>5000</td>
</tr>
<tr>
<td>Room &amp; equipment rental</td>
<td>500</td>
</tr>
<tr>
<td><strong>Consumables</strong></td>
<td></td>
</tr>
<tr>
<td>Cell phone &amp; airtime</td>
<td>5000</td>
</tr>
<tr>
<td>Stationary</td>
<td>3000</td>
</tr>
<tr>
<td>Pamphlets</td>
<td>2500</td>
</tr>
<tr>
<td>Local transport (40 ZAR/day)</td>
<td>8320</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>664320</td>
</tr>
</tbody>
</table>

A Markov model with four health states, representing the chronicity and potential transitions of a person with epilepsy over time was developed and presented in Paper V and re-produced below (Figure 9). The four health states were: (1) being diagnosed with epilepsy and not adherent to treatment; (2) being adherent to treatment; (3) remission; and, (4) death. Each health state had a utility and cost associated with it.
Health State Utility Values

Utility values (1= full utility; 0= dead) for each of the 4 health states in the Markov model were determined by subtracting 1 from the disability weight presented in the 2010 GBD study [6] and presented earlier in Table 2. The resulting QALYs can be found below (Table 4).

Figure 9 Markov model representing four distinct states and potential transitions likely experienced by people already diagnosed with epilepsy

Health State Costs

Health care utilization costs for each state were derived from the Mpumalanga Province Department of Health’s uniform patient fees schedule [167]. Lost productivity in each state was estimated using the 2014 South African gross domestic product (GDP) per capita of purchasing power parity international dollar ($) 13,215 and an exchange rate of 1 South African Rand (ZAR) to $5.39 [168]. This resulted in a GDP per capita of 71,229 ZAR and a GDP per capita per day of 195 ZAR. It was assumed that people with epilepsy who were non-adherent lost 4 days per month and one hospitalization lasting 7.5 days per year; people who were adherent lost 20 days per year and those who were in remission (or dead) did not have any lost productivity.

Table 4 Health state utility values derived from disability weights reported in the 2010 GBD study

<table>
<thead>
<tr>
<th>Health State Utility Values</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed; non-adherent</td>
<td>0.58</td>
</tr>
<tr>
<td>Diagnosed; adherent</td>
<td>0.8292</td>
</tr>
<tr>
<td>Remission</td>
<td>0.928</td>
</tr>
</tbody>
</table>
Anti-epileptic drug costs were estimated by calculating the proportion of drugs and drug combinations found in Paper IV by the cost per unit of drug as reported in the South African Database of Medicine Prices [169]. It was assumed that people who were non-adherent or in remission (or dead) were not taking AEDs and there were no associated costs.

**Transition Probabilities**

Transition probabilities, or the probability of moving from one health state to another (or remaining in the same health state) and represented by arrows in the Markov model (Figure 9), were determined from contextually specific data (remission and mortality rates were taken from Paper I) and when local data was not available, assumptions were made using published studies and best available data.

Remission rates from adherent and non-adherent states to the state of remission were assumed to be the same. Both mortality and remission rates however, varied by age and sex in the model (in line with results from Paper I). The probability of transitioning from non-adherence to death was modeled as five times greater than the probability of transitioning from a state of adherence to death. This is a figure comparable to unadjusted figures published from the United States [170].

Transition probabilities from remission to death, both age- and sex-varying, were estimated as the background mortality rate in the Agincourt sub-district. Age-varying relapse figures were derived from an article by Annegers and colleagues [171], with the model assuming that 50 percent of relapsing individuals would transition from remission to a state of adherence and 50 percent would transition from remission to a state of non-adherence.
Cost-effectiveness Analysis

In Paper V, an incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs between the intervention and non-intervention scenarios divided by the difference in QALYs due to the intervention. The effectiveness of the intervention was reduced by 50 percent and costs increased by 50% to explore the sensitivity of both change in the efficacy and the cost of the modelled intervention on the ICER. Due to differences in mortality and remission between males and females, results were presented by sex in Paper V. Analysis was conducted in Microsoft Excel (Microsoft Corporation, Redwood, WA, USA).

Ethical Considerations

The MRC/Wits Agincourt Research Unit has had, and actively maintains, a strong relationship with the communities in which it works. Prior to entering the field, projects are presented to the Community Advisory Group (CAG), which is comprised of one member from each of the villages in which the Unit works. Additionally, each study that conducts work within the Unit must adhere to the highest international ethical standards, which is confirmed through ethical approval from the relevant collaborating partner’s institution, as well as the University of the Witwatersrand’s Human Research Ethics Committee (Wits HREC) and the Mpumalanga Province Department of Health’s Research and Ethics Committee. The annual Agincourt census has been approved by the Wits HREC (M960720, M081145).

The specific studies that comprise this PhD have also received specific ethical clearance from the Wits HREC and the Mpumalanga Province Department of Health’s Research and Ethics Committee: the baseline epilepsy study, used to derive the cohorts and measure the treatment gap (M080455), the 2012 follow-up study used to derive incidence and mortality figures (M120660) as well as the 2010 cost study (M100566).

In addition to ethical approval, all individuals invited to participate in each of the studies provided written informed consent. In instances of participants less than 18 years of age as well as those incapable of providing their own consent due to cognitive impairment, written informed consent was sought from the parent or guardian, with assent being sought from the individual, if older than 4 years.
Results

The results from the five papers that comprise this PhD build on one another and present a detailed analysis of the epidemiology and outpatient, out-of-pocket costs of epilepsy in rural South Africa. Furthermore, Paper IV defines the determinants and level of the epilepsy treatment gap. Using the information from the first four papers, an economic evaluation of a CHW-led intervention is conducted in Paper V. What follows below is a summary of the key results from each of the five papers.

Underlying Epidemiology: Incidence, Remission & Mortality

By following up the two cohorts of individuals established during the 2008 cross sectional survey and presented in Paper I, we identified 48 incident cases of epilepsy in 2012 (median age: 24; IQR: 13-34; male-to-female sex ratio: 1.0) and 33 deaths in people with epilepsy between 2008 and 2012.

We determined the crude incidence of convulsive epilepsy in rural South Africa to be 17.4 per 100,000 per year (95%CI: 13.1-23.0). The sensitivity of the 3-stage screening survey was found to be 48.6% in Kenya [172]. Assuming a similar sensitivity in South Africa, the adjusted incidence was 35.7 per 100,000 per year (95%CI: 27.0-47.3). The crude incidence was similar in both males and females (17.7 (95%CI: 11.8-26.4) per 100,000 individuals per year versus 17.1 (95%CI: 11.4-25.5) per 100,000 individuals per year, respectively). Incidence was highest in those less than 5 years of age and peaked again in those aged 50+ (Table 5).
Table 5: Incidence, remission and mortality of convulsive epilepsy by age band (in years), Agincourt 2008-2012

<table>
<thead>
<tr>
<th>Age band</th>
<th>Crude Incidence* (95%CI)</th>
<th>Remission % per year (95%CI)</th>
<th>Crude Mortality Rate** (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>0-5</td>
<td>23.5 (7.6-72.8)</td>
<td>16.0 (14.8-17.1)</td>
<td>30.5 (28.5-32.6)</td>
</tr>
<tr>
<td>6-12</td>
<td>20.5 (10.7-39.5)</td>
<td>3.3 (3.1-3.6)</td>
<td>6.6 (5.8-7.3)</td>
</tr>
<tr>
<td>13-18</td>
<td>15.2 (6.3-36.6)</td>
<td>4.5 (4.2-4.8)</td>
<td>0.4 (0.2-0.6)</td>
</tr>
<tr>
<td>19-28</td>
<td>13.6 (7.3-25.2)</td>
<td>9.3 (8.8-9.8)</td>
<td>1.3 (0.9-1.7)</td>
</tr>
<tr>
<td>29-49</td>
<td>16.3 (9.2-28.6)</td>
<td>0 (0- 0.1)</td>
<td>3.1 (2.8-3.4)</td>
</tr>
<tr>
<td>50+</td>
<td>22.8 (11.9-43.8)</td>
<td>2.0 (1.6-2.4)</td>
<td>6.5 ( 6.0-7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>17.4 (13.1-23.0)</td>
<td>4.6 (4.1-5.0)</td>
<td>3.9 (3.4-4.5)</td>
</tr>
</tbody>
</table>

* per 100,000 individuals/year
** per 1,000 individuals/year

Remission
Using the DisMod II software and incidence, prevalence and mortality figures from Agincourt, remission was estimated to be 4.6 percent (95%CI: 4.1-5.0) per year for males and 3.9 percent (95%CI: 3.4-4.5) for females. Remission rates were highest in those less than 5 years of age for both males and females.

Mortality
People with convulsive epilepsy in Agincourt experienced a crude mortality ratio of 3.1 (95%CI: 2.1-4.2) compared to the general population, whilst the standardized mortality ratio was found to be 2.6 (95%CI: 1.7-3.5). Mortality rates in people with epilepsy were significantly higher in those aged 6-12, 19-28 and 50+ years of age, with those aged 50+ and having epilepsy experiencing the greatest difference compared to those aged 50+ without convulsive epilepsy (96.7 compared to 34.7 per 1000 individuals).

The verbal autopsy confirmed that epilepsy was directly or indirectly related to 39.4 percent of the 33 deaths recorded in people with convulsive epilepsy. Communicable conditions accounted for 36.4 percent of deaths in people with epilepsy, whilst non-communicable conditions, excluding epilepsy, accounted for 18.2 percent of deaths (Table 6).

Risk Factors for Mortality in People with Convulsive Epilepsy
After adjusting for age, only being male (compared to females) was associated with a higher risk of mortality (adjusted rate ratio: 2.6; 95%CI 1.2-5.4; p-value = 0.013).
Table 6 Causes of death in people with convulsive epilepsy, Agincourt 2008-2012

<table>
<thead>
<tr>
<th>ICD-10 Code and Cause of Death</th>
<th>n</th>
<th>PMR %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Directly related to epilepsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08.01 Epilepsy related</td>
<td>11</td>
<td>33.3%</td>
</tr>
<tr>
<td><strong>Indirectly related to epilepsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowning</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>12.08 Intentional Self-harm</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Unrelated to epilepsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01.02 Acute Respiratory Infection/Pneumonia</td>
<td>3</td>
<td>9.1%</td>
</tr>
<tr>
<td>01.03 HIV/AIDS-related death</td>
<td>3</td>
<td>9.1%</td>
</tr>
<tr>
<td>01.04 Diarrheal diseases</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>01.09 Pulmonary tuberculosis</td>
<td>6</td>
<td>18.2%</td>
</tr>
<tr>
<td>02.02 Digestive Neoplasms</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>03.03 Diabetes Mellitus</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>04.99 Other/unspecified cardiac disease</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>05.01 COPD</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>05.02 Asthma</td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Unclassifiable</strong></td>
<td>2</td>
<td>6.1%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>33</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Epidemiological Burden: in terms of DALYs**

Incidence and mortality rates were utilized, along with previously calculated prevalence figures, to derive the remission and duration of convulsive epilepsy. Duration figures were in turn used to calculate years of life lived with disability (YLDs), presented in Paper II along with years of life lost due to convulsive epilepsy (YLL) as well as overall disability-adjusted life years (DALYs).

Convulsive epilepsy was found to account for 332 DALYs (95%UI: 216-455) in the Agincourt sub-district using the prevalence-based approach for calculating YLDs, the 2010 GBD life table and the mean disability weight (0.346) for epilepsy in sub-Saharan Africa. This equated to 4.1 (95%UI: 2.7-5.7) DALYs per 1000 individuals per year. The majority of DALYs (74%) were due to premature mortality (YLLs), with males contributing 59 percent to the total number of DALYs (Table 7).
### Table 7 Relative and absolute YLL, YLD and DALY estimates by age band (in years), Agincourt 2010

<table>
<thead>
<tr>
<th>Age band</th>
<th>YLL (95%UI)</th>
<th>YLD (95%UI)</th>
<th>DALYs (95%UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Figures (per 1000 individuals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>0 (0-0)</td>
<td>0.3 (0.2-0.5)</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>6-12</td>
<td>4.5 (0-9.2)</td>
<td>0.8 (0.6-1.0)</td>
<td>5.3 (0.7-11.9)</td>
</tr>
<tr>
<td>13-18</td>
<td>0 (0-0)</td>
<td>1.0 (0.7-1.2)</td>
<td>1.0 (0.7-1.2)</td>
</tr>
<tr>
<td>19-28</td>
<td>2.7 (0-6.8)</td>
<td>0.9 (0.7-1.2)</td>
<td>3.7 (0.9-6.8)</td>
</tr>
<tr>
<td>29-49</td>
<td>3.3 (1.0-6.8)</td>
<td>1.6 (1.4-1.9)</td>
<td>4.9 (1.9-8.4)</td>
</tr>
<tr>
<td>50+</td>
<td>8.5 (3.0-15.1)</td>
<td>1.4 (1.1-1.8)</td>
<td>9.9 (4.1-16.0)</td>
</tr>
<tr>
<td>All ages</td>
<td>3.0 (1.6-4.5)</td>
<td>1.0 (0.9-1.1)</td>
<td>4.1 (2.7-5.7)</td>
</tr>
<tr>
<td>Absolute Figures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>0 (0-0)</td>
<td>3.5 (1.7-5.2)</td>
<td>3.5 (1.7-5.2)</td>
</tr>
<tr>
<td>6-12</td>
<td>58.4 (0-145.7)</td>
<td>10.0 (7.3-13.2)</td>
<td>68.4 (8.6-155.4)</td>
</tr>
<tr>
<td>13-18</td>
<td>0 (0-0)</td>
<td>11.8 (8.6-15.2)</td>
<td>11.8 (8.6-15.6)</td>
</tr>
<tr>
<td>19-28</td>
<td>47.8 (0-118.2)</td>
<td>16.3 (12.5-20.1)</td>
<td>64.0 (14.5-130.5)</td>
</tr>
<tr>
<td>29-49</td>
<td>59.9 (18.42-118.4)</td>
<td>30.1 (24.9-35.3)</td>
<td>90.0 (33.5-151.7)</td>
</tr>
<tr>
<td>50+</td>
<td>81.4 (26.88-137.2)</td>
<td>13.2 (10.0-16.6)</td>
<td>94.5 (40.0-155.1)</td>
</tr>
<tr>
<td>All ages</td>
<td>247.4 (129.4-373.2)</td>
<td>84.8 (76.5-93.8)</td>
<td>332.1 (215.9-454.8)</td>
</tr>
</tbody>
</table>

Changing the disability weight from 0.346 to 0.657 (disability weight for severe epilepsy), resulted in a near doubling of YLDs (Figure 10) and an increase of DALYs by 23 percent. Overall DALYs increased by 10 percent for both males and females when the incidence-based approach was used, rather than the prevalence-based approach to calculate years of life lived with disability (Table 8).
Figure 10 YLDs calculated by using prevalence-based method and varying disability weights, presented with 95% uncertainty interval

Table 8 Comparison of prevalence- versus incidence-based approach for calculating YLDs and subsequent DALY figures

<table>
<thead>
<tr>
<th>Method</th>
<th>YLD</th>
<th>Δ% of YLDs</th>
<th>Δ% of DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>56.7</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>35.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>For Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>49.8</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>35.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Economic Burden: Out-patient costs**

From those identified with active convulsive epilepsy in 2008, 250 individuals were alive, present and able to answer questions on the cost of outpatient, out-of-pocket care and their health care use during the 12 months preceding the study. The majority of respondents (59%) were found to be receiving an epilepsy-related government disability grant, whilst 4 individuals reported receiving smaller non-epilepsy related grants.
The median cost per clinic visits was found to be $1.74 (IQR: 0-4.80) (mean: $2.74; standard deviation (SD): 3.74) whilst the median cost per outpatient hospital visit was found to be $9.08 (IQR: 6.11-12.91) (mean 9.74; SD: 5.34), significantly (p<0.001) higher. Transportation represented the largest contribution to hospital visit costs, whilst opening a file and food and drink purchased as a result of the visit were tied in their contribution to the cost of a clinic visit (Table 9).

The median cost of a visit to the traditional healer was $52.36 (IQR: 34.90-87.26), with 87 percent of respondents having to pay cash for services (as opposed to poultry or in-kind payments).

**Health Care Utilization**

Health care utilization by people with convulsive epilepsy, for both non-epilepsy and epilepsy-related visits, can be found below in Table 10. The vast majority (96%) of people received non-epilepsy related care when they last needed it, which for 154 (62%) was in the previous 30 days. For 91 percent of individuals, it was in the last year.

Slightly more than half (53%) of people with convulsive epilepsy reported consulting for epilepsy care at a clinic, 162 (65%) at a hospital and 34 (14%) with a traditional healer. More than half (67%) had previously sought care from both a biomedical facility and a traditional healer, whilst 24 percent had only ever sought care from biomedical facilities (compared to 11 individuals– or 4 percent- who reported only seeking care for epilepsy from a traditional healer). Ten individuals reported never seeking care for epilepsy. The median number of visits to the clinic for epilepsy care within the last year was 10 (IQR 0-12), whilst the median number of visits to the hospital for epilepsy care was 2 (0-12) (Table 11). The average number of visits to the hospital in the previous year was 4.1 (SD 4.75), whilst the average number of visits to the clinic for epilepsy care was 6.5 (SD:5.75).

The majority of time spent utilizing care was time spent waiting to be seen by the health care worker (people reported waiting for 120 minutes in the clinic (IQR: 10-420) and 240 minutes in the hospital (IQR 30-600)), representing roughly 63 and 65 percent of time utilizing care, respectively, (Figure 11).
Table 9 Out-of-pocket, outpatient costs associated with seeking care for epilepsy, Agincourt 2010

<table>
<thead>
<tr>
<th></th>
<th>Clinic*</th>
<th>Hospital*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct Medical Costs (per visit)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy Medication</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Opening file</td>
<td>3.49 (3.49-5.24)</td>
<td>3.49 (3.49-3.49)</td>
</tr>
<tr>
<td><strong>Direct Non-Medical Costs (per visit)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transportation</td>
<td>2.79 (2.09-4.89)</td>
<td>5.41 (4.19-7.33)</td>
</tr>
<tr>
<td>Food/drink purchased due to visit</td>
<td>3.49 (2.62-5.24)</td>
<td>4.36 (3.49-6.98)</td>
</tr>
<tr>
<td>*Median international dollars I$ (IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10 Health care utilization patterns for people with convulsive epilepsy, Agincourt 2010

<table>
<thead>
<tr>
<th></th>
<th>Sought attention for General care (%)</th>
<th>Median visits in previous year (IQR)</th>
<th>Sought attention for epilepsy-related care (%)</th>
<th>Median visits in previous year (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government Clinic</td>
<td>235 (94)</td>
<td>1 (0-15)</td>
<td>189 (76)</td>
<td>10 (0-12)</td>
</tr>
<tr>
<td>Government Hospital</td>
<td>228 (91)</td>
<td>0 (0-12)</td>
<td>216 (86)</td>
<td>2 (0-12)</td>
</tr>
<tr>
<td>Traditional Healer</td>
<td>185 (74)</td>
<td>0 (0-11)</td>
<td>179 (73)</td>
<td>0 (0-10)</td>
</tr>
</tbody>
</table>
Figure 11 Proportion of time spent seeking care at a government clinic or government hospital, Agincourt 2012
Treatment Gap: Presenting a cascade

*Paper IV* presented the results of the epilepsy treatment gap in rural Agincourt South Africa, with findings based on responses from 292 individuals with epilepsy, 186 (64%) who report currently taking AEDs (98 taking monotherapy, 61 taking polytherapy, and 27 unsure), and blood results from 182 (59%) individuals.

**Sensitivity of Self Report**

Eighty-one (71%) of individuals who self-reported AED use had any level of AEDs in their blood, whilst 50 (83%) individuals with convulsive epilepsy who reported not being on AEDs had some level of AEDS in their blood, corresponding to a self-reported adherence sensitivity of 62% and a specificity of 23%.

Adults were significantly more likely to report taking AEDS than children and were significantly more adherent. There was no significant difference in either self-reporting or adherence by sex, whilst self-reported AED use increased by age, with adherence highest in those aged 29 to 49 years (Table 11).

**Table 11** Self-reported adherence versus AEDs in blood by age band (in years), Agincourt 2008

<table>
<thead>
<tr>
<th>Age band</th>
<th>Self-reported AED use (95%CI)</th>
<th>Adherent (measured as AED detected in blood) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>24% (9%-49%)</td>
<td>25% (6%-63%)</td>
</tr>
<tr>
<td>6-12</td>
<td>26% (14%-43%)</td>
<td>11% (3%-34%)</td>
</tr>
<tr>
<td>13-18</td>
<td>66% (50%-79%)</td>
<td>32% (18%-51%)</td>
</tr>
<tr>
<td>19-28</td>
<td>68% (56%-79%)</td>
<td>43% (28%-60%)</td>
</tr>
<tr>
<td>29-49</td>
<td>75% (66%-83%)</td>
<td>45% (34%-58%)</td>
</tr>
<tr>
<td>50+</td>
<td>77% (62%-88%)</td>
<td>36% (20%-55%)</td>
</tr>
<tr>
<td>All ages</td>
<td>64% (58%-69%)</td>
<td>37% (30%-44%)</td>
</tr>
</tbody>
</table>

Of the blood samples collected, 138 (76%) were found to have detectable amounts AEDs and 67 individuals (37%) were found to have therapeutic levels, corresponding to the AED treatment cascade for convulsive epilepsy presented below (Figure 12).
Determinants of adherence

In the analysis of determinants for the epilepsy treatment gap, presented in Paper IV, a number of variables were shown to be significant in the univariate model for both children and adult models and included in the multivariate model, with self-reported adherence as the outcome. However, in the multivariate adult model, only seizure frequency (adjusted Odds Ratio (aOR): 3.31; 95%CI: 1.50-7.36; p=0.003) was found to be significant. Number of years with seizures was found to be borderline significant (aOR: 1.49; 95%CI: 1.00-2.22; p=0.052). In the model where the outcome was adherence measured by AED(s) detected in the blood, a high number of household co-residents was found to be associated with lower adherence (aOR: 0.56; 95%CI: 0.32-0.97; p=0.04).

In the child’s multivariate model, with self-reported adherence as the outcome, being greater than 15km from the nearest hospital was significantly associated with a lower self-report of AED usage (aOR: 0.15; 95%CI: 0.04-0.80; p=0.0026) whilst greater seizure frequency (aOR: 8.62; 95%CI: 1.57-47.30; p=0.013) and learning difficulties (aOR: 6.64; 95%CI: 1.07-41.01;
p=0.041) were significantly associated with self-reported AED usage. No determinants were found to be associated with adherence.

The Cost-effectiveness of the CHW for improving AED adherence

*Paper V* found that a community health worker intervention to improve the adherence to AEDs in people with epilepsy costed 664,320 ZAR per year per sub-district with an estimated population of 100,000 individuals, with a 1.5 percent prevalence of epilepsy. This translated to a cost of roughly 443 ZAR per individual with epilepsy.

The effect of the intervention, taking into account the additional cost of AEDs (due to higher levels of adherence) resulted in 5.90 QALYs gained at a cost of 47,480 ZAR, or roughly 8,053 ZAR per QALY gained for males and 10,009 ZAR per QALY gained for females.

Increasing the cost of the intervention by 50 percent resulted in a cost per QALY of 11,809 ZAR and 15,419 ZAR for males and females, respectively. Reducing the effect of the intervention by 50 percent resulted in an incremental cost effectiveness ratio of 25,437 ZAR per QALY gained for males and 35,246 ZAR per QALY gained for females; an increase of 3 and 3.5 times cost per QALY, respectively.
Many people make the mistake of confusing information with knowledge. They are not the same thing. Knowledge involves the interpretation of information. Knowledge involves listening.
- Henning Mankell

Discussion

Utilizing one of the most epidemiologically and economically well-defined cohorts of people with convulsive epilepsy on the African continent, this PhD set out to answer four questions shared in the introduction and highlighted again below. The four questions are:

1.) What is the burden of epilepsy in rural South Africa in terms of incidence and mortality as well as DALYs?
2.) What are the costs to the patient associated with health care treatment for epilepsy?
3.) What is the treatment gap in the population with epilepsy and what are the determinants for non-adherence?
4.) Is a community health worker a cost-effective intervention that would reduce the burden of epilepsy in rural South Africa?

These four questions are an attempt to move from observational epilepsy research in rural South Africa to intervention work by modeling an intervention and determining its cost-effectiveness by using locally derived data. It is an attempt to acknowledge the burden of epilepsy, both epidemiologically and economically, and also to ask what can be done to address this burden. Over the next several pages, I distill the key findings from this thesis that answer these questions, noting areas that require additional research or posing potential limitations on the interpretation of the results. After answering these questions, I reflect on the methodology employed and the innovations achieved in this work as well as posit potential next steps in carrying this work forward.
Key Findings

Question One: What is the burden of epilepsy in rural South Africa in terms of incidence and mortality as well as DALYs?

Incidence

*Paper I* presents the incidence and mortality rates of convulsive epilepsy as well as the modeled remission rate [44]. *Paper I*, together with my previous published work on the prevalence of epilepsy [23], allows one to see a complete picture of the epidemiology of convulsive epilepsy in rural South Africa.

Compared to a number of other studies from Africa [39,173–175], we found the incidence rate to be lower in rural South Africa. However, these other African studies identified all cases of epilepsy and did not just focus on convulsive epilepsies, which is likely to account for some of the difference of reported incidence rates. A recent study from rural Kenya that looked only at convulsive epilepsy and employed the same case identification methodology as the work presented in this PhD found a crude incidence rate of 37.6 per 100,000 persons per year (95% CI: 32.7-43.3) [149], which is significantly higher than the crude incidence found in rural South Africa (17.4 per 100,000 per year (95% CI: 13.1-23.0)). We know from previous work that individuals in rural Kenya have higher exposure to a number of parasites that have been linked with the development of epilepsy [36] as well as a greater frequency of adverse perinatal events [12], which are likely to contribute to the higher incidence rates.

The highest incidence rates found in Agincourt were in the first decade of life, likely cases of genetic etiology as well as potentially perinatal trauma, with the latter previously found to be associated with *convulsive epilepsy* in Agincourt [23]. However, the incidence rate again peaks in those aged 50 years and older, a trend also found in high-income countries [176] likely linked to cardiometabolic disease and its outcomes (i.e. stroke) as well as brain tumors [21]. Given both the demographic and epidemiologic transitions currently underway in South Africa, marked both by an increase in fertility and a reduction in under-5 mortality, an aging population (Figure 13) and an increase in non-communicable diseases, including cardiometabolic disease, one key finding from this thesis is, given the incidence rates found in *Paper I*, the number of individuals with epilepsy is likely to rise in the coming years in rural South Africa and much of sub-Saharan Africa as these countries continue to undergo both demographic and epidemiologic transitions.
**Key Finding #1:** The number of individuals with epilepsy is likely to rise in rural South Africa due to the demographic and epidemiologic transitions currently underway.

**Figure 13** 1994 and 2015 population pyramids from the Agincourt HDSS, with a 2.5 percent increase in those aged 50+ in 2015 compared to 1994.
Mortality

The crude mortality rate of 29.4 per 1000 individuals (95% CI: 20.9-41.4) reported in Paper I is similar to a study from rural Kenya, which found a crude mortality rate of 33.3 per 1000 individuals (95%CI: 25.9-42.8) [43]. It is important to note that both studies specifically looked at convulsive epilepsy, which is known to be associated with a higher mortality rate than non-convulsive epilepsy [42]. Studies have also shown mortality to be associated with AED adherence [43,45,170], yet this was not examined in the current study.

Whilst the crude mortality rate for people with convulsive epilepsy was similar to findings from other studies, the standardized mortality ratio (SMR) of 2.6 (95%CI: 1.7-3.5) found in Agincourt was lower than that previously reported in rural Kenya (SMR: 6.5; 95%CI; 5.0-8.3) Uganda (SMR: 7.2; 95% CI: 4.4-11.6), and Cameroon (SMR: 6.2; 95%CI: 2.7-14.1), but similar to that reported from Ethiopia (SMR: 2.9) [177]. It is likely that the lower SMR in rural South Africa is due to the higher mortality rates observed, a consequence of the HIV pandemic (population HIV prevalence of 19.4% in 2010) and resulting HIV mortality in the Agincourt sub-district [144,178]. Even with HIV (and a non-statistically significant difference of HIV prevalence amongst those with and without epilepsy in Agincourt [23]), people with convulsive epilepsy in Agincourt have a nearly 3 times greater chance of dying when compared to people without epilepsy.

### Key Finding #2: People with epilepsy in rural South Africa have a significantly greater chance of dying, even within a context of high HIV infection and emerging non-communicable diseases.

Males with convulsive epilepsy in Agincourt have a significantly greater chance of dying than females (aRR: 2.6 (95% CI: 1.2-5.4)). It is not clear why this trend is observed, though other studies have found that older women in Agincourt tend to seek medical care earlier and more often [179], Men in Agincourt have been found to be less likely tested for HIV and receiving treatment [180]. Interestingly, we did not find any association between being HIV-positive and mortality in people with epilepsy. In fact, the majority of deaths in the cohort of people with active convulsive epilepsy were in older, HIV-negative individuals.

Prolonged seizures, or potential status epilepticus, were determined to be the cause of death in one-third of all individuals with epilepsy who died. This is similar to the 37.7% reported in a study from rural Kenya [43]. We recently found convulsive status epilepticus to be common in people with convulsive
epilepsy in Africa [150], which reaffirms the burden of prolonged seizures in this population. Public campaigns explaining what to do when witnessing someone experiencing a seizure (or a prolonged seizure) may be one way to attempt to address these findings. Additionally, improved adherence in the rural South African context, which experiences a substantial treatment gap (see Question Three below), could potentially reduce mortality due to prolonged seizures.

Overall Paper I found a lower proportion of deaths directly and indirectly related to epilepsy when compared to rural Kenya (39.4% versus 55.7%, respectively), again, a likely result of the higher prevalence of HIV and increasing mortality due to non-communicable diseases in rural South Africa [43].

The proportion of deaths due to non-epilepsy related causes, including both non-communicable and communicable causes, suggest a high prevalence of co-morbidity in people living with epilepsy in Agincourt. Earlier studies from Agincourt have already demonstrated a high co-morbidity with HIV (18 percent HIV prevalence found in the 2008 cross-sectional survey [23]); however, in a rapidly transitioning context, with demonstrably high levels of both communicable and non-communicable diseases, understanding multi-morbidity patterns in people with epilepsy is warranted for the development of interventions that address both the burden of epilepsy as well as co-morbid conditions.

Limitations
It is important to note that the mortality rates reported in Paper I were derived from a prevalent cohort of people with epilepsy, which may have resulted in a lower mortality estimate due to the fact that mortality rates in people with epilepsy are significantly higher in the first 1 to 2 years after seizure onset [42,181]. Because of the HDSS’ routine surveillance, we will be able to follow-up the 48 incident cases of convulsive epilepsy, identified in 2012, and examine this trend in Agincourt.

Disability-adjusted Life Years
What is presented below is a brief discussion of the epidemiological findings of Paper II. Methodological considerations regarding the use of DALYs can be found towards the end of this chapter in the section entitled, Methodological Considerations.

Using rates and duration figures, derived in Paper I, the results presented in Paper II confirm that convulsive epilepsy results in 4.1 DALYs per 1000 individuals (95% CI: 2.7-5.7) in rural South Africa. This relative DALY figure
is lower than figures reported both in the 2010 Global Burden of Disease estimates for South Africa [60] and a recent study published from rural Kenya [47] (Table 12). However, it is higher than a 2006 study from rural China, which found epilepsy caused 2.08 DALYs per 1000 individuals [62]. The Chinese study used a less severe disability weight and earlier GBD methodology to calculate its DALY figures making comparison with the current study difficult.

The current study and both the 2010 GBD national estimates for South Africa and the study from rural Kenya used different definitions of epilepsy, which is likely to result in some of the observed difference (Table 12). In both the 2010 GBD study and the study from rural Kenya, only epilepsy cases due to idiopathic or unknown origin were included in the calculations. Epilepsy cases of idiopathic origin represent only a portion of the total cases used to calculate the figures in Agincourt and, as such, when compared with both other estimates, would actually be lower, suggesting a greater difference between rural South Africa and that reported nationally for South Africa by the 2010 GBD study and the rural Kenyan study. A number of epidemiological studies from rural Kenya have found the prevalence [12] and incidence [149] of convulsive epilepsy to be higher, confirming the finding that the DALYs attributable to convulsive epilepsy are also higher in rural Kenya.

**Table 12** Comparison of relative DALY figures for epilepsy from 2010 Global Burden of Disease estimates for South Africa [60], rural Kenya [47] and Agincourt, South Africa [182].

<table>
<thead>
<tr>
<th></th>
<th>YLL (95%UI)</th>
<th>YLD (95%UI)</th>
<th>DALYs (95%UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agincourt HDSS</td>
<td>3.0 (1.6-4.5)*</td>
<td>1.0 (0.9-1.1)**</td>
<td>4.1 (2.7-5.7)</td>
</tr>
<tr>
<td>GBD 2010 for SA</td>
<td>2.0 (1.6-2.5)*</td>
<td>3.3 (2.2-5.4)**</td>
<td>5.3 (4.2-7.6)</td>
</tr>
<tr>
<td>rural Kenya</td>
<td>3.2 (2.3-4.1)</td>
<td>1.1 (1.1-1.2)</td>
<td>4.33 (3.4-5.2)</td>
</tr>
</tbody>
</table>

*/**Significantly different

Of, perhaps, more interest, is the comparison of the results from Paper II with the results from the 2010 GBD study for South Africa, which not only shows higher DALYs attributed to epilepsy, but also a reversal in the proportion of DALYs due to morbidity (YLDs) versus mortality (YLLs). One key finding from Paper II, and discussed in more depth within the Methodological Considerations section below, is the necessary use of locally derived data for the production of contextually relevant disease burden
estimates. This is nicely showcased when comparing the results from Paper II with the 2010 GBD results for South Africa: the findings of the 2010 GBD study for South Africa cannot be extrapolated to the Agincourt sub-district of rural South Africa.

Even taking into account the differing definition of epilepsy used in Paper II compared to the 2010 GBD work, the burden of epilepsy, in terms of DALYs was found to be lower than that reported in the 2010 GBD study. Furthermore, based on robust longitudinal data, mortality due to epilepsy contributes more to the overall burden than disability associated with the condition— a result different from the 2010 GBD estimates for South Africa. It may be that the Agincourt sub-district does not represent the rest of South Africa and hence the discrepant findings; however, understanding what data source or sources were used to derive the 2010 GBD study’s finding would be an important first step. Nonetheless, these differences highlight the importance of using contextually relevant data to derive contextually specific disease burden.

**Key Finding #3: When calculating the burden of disease, in DALYs, for a specific context it is important to use contextually derived data to inform those calculations.**

>>> In response to Question One, the number of incident cases of epilepsy in rural South Africa is lower than other sub-Saharan African countries, whilst mortality rates are high and significantly higher amongst males (in terms of increased mortality). Even though the burden is lower, the number of new cases is expected to rise in the coming years, especially amongst older individuals, due to the demographic and epidemiologic transitions currently underway throughout sub-Saharan Africa. DALYs are one way to estimate the burden of epilepsy, but the use of context specific data is important to derive contextually relevant results.

**Question Two: What are the costs to the patient associated with treatment for epilepsy?**

*Paper III* presented both the outpatient health care utilization by people with convulsive epilepsy in rural South African and the associated out-of-pocket costs and partially answers the question, 'What are the costs to the patient associated with treatment for epilepsy?'. It only partially answers the question as *Paper III* only looked at one aspect of costs due to epilepsy (see
Figure 4, which highlights the various costs associated with epilepsy and epilepsy care. *Paper III* did not present inpatient costs for epilepsy care, which have been shown to be significant [79], nor were health care system costs (facility overhead costs, etc.) or indirect patient costs (except for time seeking care) included. Future work exploring these costs is warranted. Whilst *Paper III* focused on a specific type of cost, out-patient, out-of-pocket cost due to epilepsy, it made valuable contributions in understanding both health care utilization and out-of-pocket, outpatient costs for people with convulsive epilepsy, with the key findings discussed below.

**Health care utilization**

Studies from high-income countries have found that people with epilepsy utilize health care more often than individuals with asthma, diabetes or migraines [89,90,183]. In Agincourt, people with convulsive epilepsy utilize high levels of health care, with a greater use of clinics than hospitals, according to self-reported number of visits in the previous 12-months. The median numbers of visits to the government clinic for epilepsy care was found to be 10 (IQR: 0-11) and hospitals 2 (IQR: 0-10), which correlates to the expected number of annual clinic and hospital visits, according to national guidelines [184]. People with convulsive epilepsy in Agincourt were found to utilize health care more often than those older than 50 years, living in Agincourt and having a chronic condition [179], suggesting that epilepsy contributes substantially to the clinics’ patient load.

Interestingly, when asked, patients were more likely to seek non-epilepsy care from clinics and epilepsy care from hospitals even though *Paper III* found that a visit to the hospital took longer and cost significantly more than a visit to the clinic. Understanding whether this is due to a perceived inadequacy of skilled manpower at the clinics (a cited cause for people not to seek care in other studies [185–187]) or the non-availability of AEDs (reported by 10 percent of respondents) is an important step to inform how best to strengthen epilepsy care delivery within the clinic.

**Costs and Time resulting from seeking care**

Costs of AEDs have been cited as one reason for the substantial epilepsy treatment gap in LMICs. In this regard, South Africa is unique as AEDs are provided to the patient without charge (the charge is fully incurred by the government). Even with this, *Paper IV* has highlighted a substantial treatment gap in rural South Africa, which supports previous work suggesting that access to AEDs is only one of a number of risk factors to affect the treatment gap [100]. Access to a continuous supply of AEDs is important [188], with *Paper III* highlighting the fact that 10 percent of patients reported that AEDs were not always available and, for nearly a
quarter of respondents (22 percent), a lack of AEDs would discourage them from utilizing care.

For those who utilized care, out-of-pocket costs varied significantly by health facility, with hospital visits costing significantly more than clinics. Transportation to and food and drink purchased during visits were found to be higher for hospital visits than clinic visits, with this likely linked to the increased distance and time associated with utilizing a hospital for care. Previous work in the area has also found transportation costs to be substantial [189].

People with epilepsy spent a substantial amount of time seeking care for epilepsy, with time spent seeking care from the hospital significantly more than from the clinic. Costs, including lost time, associated with seeking epilepsy care have been found to be associated with the epilepsy treatment gap [96]. As such, reducing costs and lost time by increasing epilepsy care utilization at clinics (thereby also reducing transportation costs) by strengthening care delivery will likely improve the epilepsy treatment gap. Further understanding of the availability of AEDs and mapping the frequency of AED stock-outs in Agincourt is also needed.

**Traditional healer usage**

People in rural South Africa seek care from both biomedical and traditional healers, with nearly three-quarters of all respondents in Paper III disclosing use of traditional healers for both epilepsy and non-epilepsy related care. Nearly 15 percent of respondents reported using a traditional healer in the last 12-months, though this is much lower than reported biomedical facility usage during the same period. However, traditional healer fees were found to be significantly higher (even without transportation costs included) than cost for both clinic and hospital visits. This finding concurs with other work in South Africa, which has found a similar pattern [190].

Traditional healers maintain an important role within rural South Africa and may provide to a more culturally nuanced explanation of epilepsy, with more traditional beliefs found to be a deterrent for seeking biomedical epilepsy care [100]. Traditional healers have the potential to play a role in South African health care delivery [191] and identifying ways of working with traditional healers and strengthening the link between biomedical and traditional caregivers may be one way to improve health care and outcomes for people with epilepsy [192], including adherence to AEDs. Current work in Agincourt aims to strengthen that link by further exploring the role of traditional healers in care delivery.
Limitations
Out-of-pocket costs for the last visit to the health care facility or traditional healer were self-reported, which could potentially result in recall bias, either intentional or unintentional and should be acknowledged when interpreting the results. Additionally, health care utilization was also self-reported. Further work linking patients with health care records (discussed below under Methodological Considerations: Working within an HDSS) would reduce the potential bias resulting for self-reported utilization. More generally, building upon the findings of Paper III and repeating the questionnaire may also strengthen the validity of the reported costs and utilization of health care for people with convulsive epilepsy in rural South Africa.

Key Finding #4: Health care utilization seems congruent with national treatment guidelines; however, strengthening and improving utilization of care from clinics will likely reduce out-of-pocket, out-patient costs.

This work found that people with epilepsy seek care both from biomedical facilities as well as traditional healers, with utilization levels of government facilities correlating to government treatment guidelines. Costs and time associated with seeking care at hospitals were significantly higher and took significantly longer, primarily due to travel time and waiting to be seen by a health care worker. Efforts to strengthen epilepsy care at the PHC level are warranted, with greater use of clinics likely to result in a reduction in outpatient, out-of-pocket costs to people with convulsive epilepsy in rural South Africa. Due to the high levels of traditional healer usage, exploring ways of strengthening the interaction between biomedical and traditional care is warranted in the rural Agincourt context.

Question Three: What is the treatment gap in the population with epilepsy and what are the determinants for non-adherence?

The Epilepsy Treatment Cascade
Borrowing from HIV literature [193], Paper IV presents the epilepsy treatment cascade. The presentation of the treatment cascade attempts to elucidate key barriers to seizure control in the rural Agincourt population of people with convulsive epilepsy. It attempts to explore the care continuum-from diagnosis, to treatment, to adherence and ultimately (though not presented in this work) to seizure freedom- and, in doing so, highlights potential bottlenecks in reaching the ultimate objective of epilepsy treatment: seizure freedom and terminal remission.
Interestingly, when presenting the epilepsy treatment cascade, one observes a substantially reduced proportion of those who have been told they have epilepsy compared to those who reported taking treatment (a difference of 29 percent) and between those who report taking AEDs and those who have measurable levels of AEDs in their blood (22 percent). In many ways, these observations suggest the need for additional education, as suggested elsewhere [100,194,195]. People with epilepsy should be educated on the importance and value of taking AEDs (to reduce the gap between those who know they have epilepsy and those who self-reported as taking AEDs). Furthermore, health care workers must educate patients on how to properly take AEDs (to reduce the gap between self-reported use and measurable AEDs in the blood). Additional work is needed to explore the correlation between seizure frequency and reported and measured AED use in this context.

*Paper IV* found the epilepsy treatment gap, defined as the percentage of people diagnosed with active epilepsy not on treatment or on inadequate treatment at a specific time over the total number of individuals with active epilepsy [4,15], to be 63 percent (95%CI: 56-70) similar to studies from rural Kenya [100] and a smaller study in children from South Africa [99]. Comparing the blood analysis results to self-reported AED use, *Paper IV* reports a low specificity– the number who reported not taking AEDs, but had measurable levels of AEDs in their blood (23 percent), suggesting that, again, additional education and support for people with convulsive epilepsy is needed.

A particularly worrying finding from *Paper IV* is the significantly lower levels of adherence found amongst children (those age younger than 18 years). This finding replicates earlier findings from rural Kenya [100,107]. Whilst it is possible that differing AED pharmacokinetics result in this observed difference, self-reported AED usage is also lower amongst children with convulsive epilepsy in rural Agincourt. Non-adherence has been shown to be linked with increased mortality and morbidity, including more seizures and higher levels of status epilepticus, and negative outcomes such as lower educational attainment, greater cognitive impairment and poorer quality of life [64,85,86,170,196]. Additional research is urgently needed to understand why this trend is observed as well as to determine how best to intervene.

*Measuring adherence & Minding the Gap*
In some ways, *Paper IV* presents a comparison of a direct (AED level in the blood) versus an indirect (self-reported AED use) method for measuring AED adherence. Measuring AED levels in the blood is the most common way
for measuring adherence [197]; however, as intimated above, understanding the correlation between adherence levels and seizure frequency is also needed and, from a clinical standpoint, is useful for informing decisions (increasing dosage, adding an additional AED, etc.). Health care providers in rural Agincourt should be able to understand this interplay between AED usage, adherence, seizure frequency and outcome. Additional training, with the introduction of the epilepsy treatment cascade, may be warranted to highlight this interplay.

**Key Finding #5:** *The proportion of people with convulsive epilepsy in rural South Africa on adequate anti-epileptic drugs, measured by blood serum levels, remain low, especially amongst children.*

This work answers Question 3 by providing evidence of a high epilepsy treatment gap in rural South Africa, even in a context where patients are not charged for AEDs. By presenting the treatment cascade, rather than the treatment gap, this work attempts to highlight the key gaps in achieving a reduced treatment gap and ultimate seizure freedom. Further work is urgently needed to understand why children in Agincourt have a significantly higher level of non-adherence, both reported and measured, when compared with adults.

**Question Four: Is a community health worker a cost-effective intervention that would reduce the burden of epilepsy in rural South Africa?**

*The Cost-effectiveness Analysis*

A number of cost-effectiveness analyses for various aspects of treating epilepsy, including behavior modification, changing diets, epilepsy surgery, and vagus nerve stimulation [198–202], have been previously carried out, yet to the best of my knowledge, no study has explored the cost-effectiveness of a community health worker for the treatment of epilepsy in rural sub-Saharan Africa, or more specifically, a CHW to improve adherence to AEDs.

This PhD has shown that undertaking a program of community health workers tasked with regular visits to people with epilepsy, educating people with epilepsy and the community and assisting with referrals, when necessary, is a cost-effective intervention that will result in increased quality-adjusted life years (QALYs).
A Community Health Worker in the South African context

Paper V builds upon previous literature that shows community health workers to be a cost-effective intervention for improving adherence to other chronic medication regimens [164,203,204] as well as for measuring blood pressure and delivering information on hypertension [166].

South Africa, as highlighted earlier in this work, is undergoing a primary health care reengineering and revitalization that seeks to address the ongoing transitioning burden of disease [129]. These national efforts speak to the ability of the health care system to address chronic disease treatment and prevention. Within the primary health care team, envisaged and articulated by the South African National Department of Health, community health workers play a central role [133] and fill an important void in the understaffed South African health care system.

Any successful intervention must be culturally relevant, locally integrated, sustainable and guided by scientific evidence. The introduction of a community health worker, an already accepted cadre of health care providers in South Africa, for improving the adherence and treatment of people with epilepsy, seems like a promising, cost-effective option in this rural context.

Limitations

The cost-effectiveness analysis and results presented in Paper V are derived from an economic evaluation that relies on best available data to inform the model. Like any model, the reliability of the results is limited by the reliability of the input parameters. However, the results of the sensitivity analysis support the findings that this proposed intervention is cost-effective. Attempting to implement the intervention in the Agincourt sub-district and measuring the cost and effect could also support the usefulness of undertaking economic evaluations prior to implementation (see further discussion below, Using cost-effectiveness analysis to determine an intervention).

Two other limitations discussed further in Paper V, include the quantification of the impact of the intervention and the use of disability weights to derive the utility values used in this study. Both limitations have important implications on the study and further work is needed to examine how best to model the full benefit of community health workers [205] and to understand whether utility values (as well as disability weights) vary by context and/or culture.
Introducing a community health worker to reduce the burden of epilepsy by improving adherence to AEDs in rural South Africa was found to be cost-effective. Question 4 was clearly answered by conducting a cost-effectiveness analysis using locally derived data, supported at times by expert opinion, to establish the incremental cost effectiveness ratio, which was found to be lower than one times South Africa GDP, the often agreed upon threshold for an intervention to be considered cost-effective. Sensitivity analyses performed in Paper V supports the robustness of these findings.

**Methodological Considerations**

**Working within an HDSS**

The work of this PhD was conducted within the Agincourt sub-district of rural South Africa and completely nested within the robust Agincourt Health and Demographic Surveillance System (HDSS). This work serves as an example of how an HDSS platform can be used beyond routine surveillance of vital events and monitoring of demographic trends. Nesting the current work within the HDSS infrastructure was not only cost-effective, as both community relationships and necessary infrastructure already existed, but design efficient, with the population of the sub-district already enumerated and regularly visited. The regularity of HDSS updates results in lower rates of attrition and greater ease of follow-up in cohort studies.

**Methodological Finding #1**: The robust HDSS platform allows for unique nesting of population-based ‘disease-specific cohorts’, which can allow for the derivation of incidence, mortality and remission rates.

The broader and, perhaps more innovative use of HDSS platforms—extending beyond routine surveillance and linking individuals to the health care system and collecting biological specimens—has recently gained traction [206]. In many ways these opportunities will achieve, on a larger scale, what this PhD has achieved on a smaller scale: routine surveillance of a cohort, collection of blood specimens to explore risk factors and documented
morbidity and mortality, all to determine the burden of convulsive epilepsy in rural South Africa, and highlight an opportunity to address this burden.

As recently suggested in an editorial discussing the value of the HDSS system and the INDEPTH network, “Health system improvement has to be motivated by local need” captured at “the level where data can best be used for improvement of the health of individuals” [207]. This PhD serves as an example of the promise of an expanded HDSS platform, whilst also suggesting a future possibility for this current work: linking individuals with convulsive epilepsy in Agincourt with data from the health care system to complement the self-reported data on health care utilization and AED use presented in Papers III and IV.

**Using DALYs to define the Burden**

*Paper II* not only provided an estimate of the burden of epilepsy in terms of DALYs, but went further to explore the various parameters that comprise the DALY calculation. In doing so, *Paper II* highlighted the substantial differences that arise, both when different methods to calculate YLDs (prevalence versus incidence) are used, and also the substantial effect that varying disability weights have on YLDs. What emerges from this work are two important messages: 1.) clear and consistent methodologies are needed when attempting to compare DALY estimates and 2.) use of contextually relevant data are essential when deriving DALY estimates.

*Paper II* used the 201 GBD disability-weights to derive DALY estimates. Yet at least one study has found that health state preferences can differ amongst different cultures [208]. Others have also suggested that disability weights do not, in fact, represent disability, but rather the perceived desirability of one health state versus another [209]. Further research, carried out in LMICs, is needed to further unpack the disability weight, its meaning and determine whether disability weights vary by culture. If found to vary by culture, this would, as shown in *Paper II*, likely influence overall burden estimates.

Furthermore, *Paper II* uses the global life expectancies (86.02) for both males and females. This value is nearly 30 years greater than the life expectancies experienced by males and females living in Agincourt (56.52). It is necessary, when comparing disease burdens across different contexts or countries to use the same definitions (including life expectancies) as the life of person living in rural South Africa has the same value as a person living in the United States. However, when attempting to conduct national or sub-national burden studies to inform analyses for decision-making, using
national or sub-national values, such as life expectancies, is preferred. However, in such cases, these analyses could not then be compared to other analyses using different life expectancies.

**Methodological Finding #2:** The DALY is an effective metric for combining disease morbidity and mortality, though methodologies and parameters employed must be carefully interrogated.

**Using cost-effectiveness analysis to determine an intervention**

*Paper V* undertakes an economic evaluation of a hypothetical, well-defined intervention, using contextually relevant disease parameters and estimates of intervention cost and effect derived from expert opinion and previously published studies. Economic evaluations, specifically those exploring epilepsy care, have previously been suggested as a resource to support decision making both at the policy level, by providing decision makers evidence on the cost-effectiveness of an intervention or set of interventions, and also at the clinical level to assist clinicians in deciding appropriate epilepsy treatment [115]. *Paper V* highlights a potential third area where economic evaluations could be useful: in intervention research funding.

Much like how certain countries or contexts require economic evaluations before licensing a new drug or medical technology, it is possible that medical research funding bodies (such as the National Institutes of Health or Wellcome Trust) could require an economic evaluation prior to funding an intervention study. Whilst it is the case that intervention studies are often aimed at defining the effectiveness of a specific intervention— a figure needed to undertake an economic evaluation- studies are generally powered to be able to explore the effect of the intervention. Using the hypothesized efficacy and cost, it would be possible to determine the likely cost-effectiveness of the study. Studies below a certain threshold (or ICER) would then be funded, as they show greater promise. As such, economic evaluation could potentially play a role in intervention research resource allocation; however, the availability of ‘good’ data is necessary.

The availability of data to conduct economic evaluations, especially in LMICs, if often lacking. The quality of any economic evaluation is based on the quality of the data used in the analysis. There is an urgent need to generate such data, especially cost data, in LMICs to support the use of economic evaluations. As discussed above, health and demographic
surveillance systems, such as Agincourt, are in a unique position to generate such data.

An initial step, which has begun in countries like South Africa, is educating both researchers and policymakers on the relevance and usefulness of economic evaluations in health care resource allocation and decision making. By generating the requisite data and educating both the potential producers of such data (researchers) and the users (policy makers), economic evaluations will likely grow in their use and relevance in LMICs, including much of sub-Saharan Africa, where resources are limited and difficult decisions need to be made.

**Methodological Finding #3:** Cost-effectiveness analysis prior to implementation of a study or policy can be useful when relevant, accurate data is available.

**Policy Recommendations and next steps**

This work has confirmed that the epidemiological burden of epilepsy in rural South Africa is substantial, both in terms of incident cases and mortality. Mortality is higher amongst older males and roughly 40 percent of all mortality in people with epilepsy is epilepsy related. This PhD has explored methodologies used to aggregate the morbidity and mortality of a condition or disease into a single metric, the DALY, which can be used to compare the burden of different conditions, hence providing a way for researchers and policy makers to ‘rank’ the burden of diseases and suggest priorities in disease interventions. The work of this PhD had further to highlighted the fact that context-specific data, such as disability weights, are necessary in order to derive context-specific results. This work has shown that the out-of-pocket, outpatient costs amongst people with epilepsy are high, but are likely to represent only a portion of the total economic burden to the patient, his or her family and society. This PhD has shown that the treatment gap for epilepsy is substantial, even with the ‘free’ availability of AEDs. Finally, this PhD concludes by suggesting that the introduction of a community health worker that improves AED adherence is cost-effective in the rural South African context.

Whilst this work fills a number of important gaps in the understanding of convulsive epilepsy in rural South Africa, a number of important questions remain (or have arisen as a result of this work). These questions will form the basis of future work on epilepsy in Agincourt and contribute to a greater
understanding, which, in turn, can hopefully be used to develop a more robust and targeted multi-sectoral response to the burden of epilepsy. These questions include:

- The introduction of community health workers in rural South Africa was found to be cost-effective when modeled; how does this compare to the implementation of this intervention in rural South Africa?
- What is the complete societal cost of epilepsy within this context and what is the most appropriate way to measure lost productivity in a context of high unemployment?
- In recognition that PWE experience higher rates of co-morbidities than people without epilepsy [210], what is the prevalence of co-morbidities and impact of this multimorbidity on health care utilization?

Each of these questions could form the basis of a PhD (or a postdoc!) and each question is important to fully understand epilepsy in this context. However, whilst observational work is important and contributes to our understanding of epilepsy and the burden that epilepsy places on the individual and society, it is important that this work moves us towards improving epilepsy care, eliminating the epilepsy treatment gap and reducing the global burden of epilepsy. Now is the time to move from observation to intervention; now is the time to act!
Concluding Remarks

So what now? The work of this PhD has answered four questions and in doing so has confirmed and refined existing knowledge of convulsive epilepsy and its treatment in a rural sub-Saharan African context. By employing strong methodological principles and conducting rigorous studies, this PhD has evaluated the cost-effectiveness of community health workers tasked with reducing the burden of epilepsy in rural South Africa. This work has found such an intervention to be cost-effective.

However, in many LMICs, epilepsy remains a neglected disease. This may be due to the lack of political attention paid to epilepsy or possibly the misguided belief that nothing can be done for those who have epilepsy. With the recent World Health Organization resolution, during the 68th World Health Assembly, calling for integration of “epilepsy management, including health and social care, particularly community-based services within the context of universal health coverage”, to support “the establishment and implementation of strategies for the management of epilepsy”, and to “ensure public awareness of and education about epilepsy” [211], the opportunity to intervene to reduce the burden of epilepsy seems upon us. Yet it is up to researchers, advocates and national policy makers to realize this opportunity.

Nowhere is opportunity more present than in South Africa, where change and revitalization of the primary health care system is underway and the implementation and role of the community health worker is already embraced.
It is my hope that this PhD can serve as a reminder of the irreplaceability of good epidemiological studies, the importance of contextual understanding and the unique insight that economic evaluation can provide. It is my hope that this work in some small way, will contribute, to the discussion on how best (and urgently!) to deliver care to those who need it most and, ultimately, improve the lives of people with epilepsy living in Africa.
The more that you read, the more things you will know. The more you learn, the more places you’ll go!

Don’t cry because it’s over. Smile because it happened.

-Theodor Seuss Geisel

Acknowledgements

The journey of this PhD has been amazing. Nelson Mandela summarizes it well: “After climbing one great hill, one only finds that there are many more mountains to climb”. Taking this analogy further, the opportunity to undertake this PhD has provided me with the skills and tools necessary to climb the mountain and a team of individuals who have climbed the mountain with me—catching me as I lost my footing and re-energizing me with a cup of coffee during fika on many a cold winter’s day in northern Sweden. It is this group of individuals who allowed me to complete the climb and reach the summit.

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