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Mavabyi ya ku wa
Prevalence of and Risk Factors for Epilepsy in a rural South Africa Surveillance Site

by

Ryan Gregory Wagner

A dissertation submitted to
the School of Public Health, University of the Witwatersrand,
in fulfillment of the requirements for the degree of

Masters in Science in the branch of Medicine by research

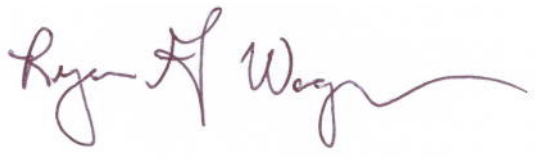
Acornhoek, 2011

To my Heavenly Father and my family-
For providing continuous strength and support.

To the South African Lowveld and her people-
From where this research was born and to whom this research belongs.

DECLARATION

I, Ryan Gregory Wagner, declare that *Mavabyi ya ku wa: Prevalence of and Risk Factors for Epilepsy in a rural South Africa Surveillance Site* is my own work. It is being submitted for the degree of Masters in Science in the branch of Medicine by research, at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted previously for any degree or examination at this or any other University.



Sixteenth day of May, 2011

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS DISSERTATION

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ABSTRACT

Mavabyi ya ku wa: Prevalence and Risk Factors of Epilepsy in a rural South Africa Surveillance Site

by Ryan G. Wagner

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Epilepsy, a chronic, often treatable condition, is one of the most common neurological conditions globally, with the prevalence of epilepsy significantly higher in developing regions of the world. In 2008, a household survey was undertaken within the Agincourt Health and Demographic Surveillance System (AHDSS) in rural, northeastern South Africa to identify the prevalence of and risk factors for active convulsive epilepsy. A single question was administered as part of the annual census to each household head. This single question sought to identify people with convulsions, while a random sample of 4,500 individuals was drawn from the Agincourt HDSS population as a way to validate the *Stage One* screening tool. During initial piloting of the *Stage One* screening question, the question was found to be adequately sensitive and significant (98.3% and 93.1%, respectively). A more specific questionnaire was administered in *Stage Two*, while a clinical exam and history was performed in *Stage Three* to conclusively diagnose epilepsy. The adjusted prevalence of active convulsive epilepsy in the three-stage study was 3.26 per 1,000, while the adjusted prevalence in the population sample was 7.72 per 1,000 individuals highlighting a significant difference due to possible methodological or cultural issues. Furthermore, a heterogeneous, random distribution of active convulsive epilepsy was found across the site, with the identification of possible familial clustering in a number of households. By utilizing univariate and

multivariate analysis, this study found sex and a family history of seizures to be significant risk factors for developing epilepsy in rural South Africa. Abnormal deliveries and problems after delivery were found to be significant in the bivariate analysis, but not the multivariate analysis. These findings highlight the need for additional research exploring epilepsy in rural South Africa.

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LIST OF ABBREVIATIONS

ACE: Active Convulsive Epilepsy

AHDSS: Agincourt Health and Demographic Surveillance System

AIDS: Acquired Immunodeficiency Syndrome

CE: Convulsive Epilepsy

CNS: Central Nervous System

CT (CAT) scan: Computed tomography or computed axial tomography scan

DALYs: Disability Adjusted Life Years

EEG: Electroencephalogram

GIS: Geospatial Information System

GPS: Global Positioning System

HIV: Human Immunodeficiency Virus

ILAE: International League Against Epilepsy

MRI: Magnetic Resonance Imaging

OR: Odds Ratio

PWE: People with Epilepsy

SEEDS: Studies of the Epidemiology of Epilepsy in Demographic Surveillance System

WHO: World Health Organization

GLOSSARY OF TERMS

Active Epilepsy is defined as having two or more unprovoked convulsions (seizures with clonic and/or tonic movement) with at least one occurring within the last 12 months.

Adjusted Prevalence (*Chapter 5*) is the crude prevalence (number affected over total number of the population) adjusted for non-response using imputation methods (see *Data Imputation*).

Collinearity (*Chapter 7*) describes a situation during multivariate analysis where two or more variables, being examined concurrently, essentially describe the same information about the observed variation. Essentially, the two or more collinear variables represent the same exposure variable in the multivariate model. One consequence of collinearity is the observance of very large standard errors.

Confounding (*Chapter 7*) is a situation that results in an inaccurate model due to a third variable being apparently associated with both the dependent (risk factor) and independent (outcome) variables, though the association is not true. This confounder variable is associated with the independent variable, but not caused by the dependent variable. The result of confounding is a distorted relationship between the risk factor and outcome. Standardization is one method used to minimize confounding.

Convulsive Epilepsy is defined as a condition characterized by recurrent (two or more) epileptic seizures with clonic and/or tonic movement, unprovoked by any immediate identified cause, according to the ILAE (ILAE 1997). Seizures will be defined by any two of the following: loss of consciousness, generalized clonic movements or rigidity (tonic), and any one of these, accompanied by incontinence of urine and/or feces, bitten tongue/injury sustained while falling, post-ictal fatigue, drowsiness, headaches or muscle ache. These definitions are based on those established by the ILAE and recently used in World Health Organization (WHO) demonstration projects (Ndoye et al. 2005; Wang et al. 2003).

Data Imputation (*Chapter 5*) is a method of analysis that is used to adjust for missing data. In the single imputation method, only one estimate of missing values is calculated and then included in the overall analysis. Multiple imputations is a method that calculates a number of possible estimates, combining these estimates to allow for calculation of uncertainty values, similar to confidence intervals. Software packages, such as STATA, have developed commands for multiple imputations.

Febrile Seizures are seizures that occur in children age three months to five with a febrile illness not caused by an intracranial infection, typically as a result of acute infection such as an upper respiratory tract infection. Young children are particularly susceptible as a result of their small surface area not allowing heat to escape the body, and have been shown to be a risk factor for developing epilepsy.

Geospatial information system (GIS) (*Chapter 6*) is a package of tools that allow researchers to collect, map, and examine data over a specific geographic area. The usefulness of geographic mapping lies in the ability of researchers to identify patterns and geographic trends as a result of the mapping- allowing researchers to identify possible underlying etiologies.

Interquartile Range (*Chapter 5*) is the expression of a range of data (distance) between the 25^{th} and 75^{th} percentile (the middle 50 percent), and is also known as statistical dispersion. It is useful in examining the distribution of data in order to determine whether the data are skewed or normally distributed.

Logistic Regression (*Chapter 7*) is a statistical tool that can be utilized in a case-control study to calculate Odds Ratios (OR), which can be thought of as the affect a specific risk factor or exposure variable has on the probability of developing the outcome, or disease. Odds ratios above one suggest exposure may result in a higher probability of the outcome, while an odds ratio below one suggests a protective effect, meaning exposure to the variable may reduce the chance of the outcome.

Multivariate Analysis (*Chapter 7*) is a biostatistical method of combining a number of unique variables into a model in an attempt to suggest the most likely 'real'

scenario in the observed population based on significance of the variables included. Numerous difficulties can arise due to collinearity and confounding of variables. P-values (indicators of significance), in conjunction with Odds Ratios, are used to indicate whether a variable should be included or excluded.

Negative Predictive Value (NPV) (*Chapter 4*) is the proportion of individuals with a negative result who are truly negative. It is an important measure to determine to what degree a negative test reflects the true underlying condition.

Point Prevalence (*Chapter 5*) describes that number of individuals affected by a certain condition within a specific population at a specific point in time, detected by cross-sectional studies. This differs from period prevalence, which describes the number of individuals affected by a certain condition over a period of time, such as a season or a year and requires a cohort or longitudinal study.

Positive Predictive Value (PPV) (*Chapter 4*) is the proportion of individuals with a positive result who are in fact truly positive and is an important measure to determine to what degree a positive test reflects the true underlying condition.

Risk Factors in this study are defined as characteristics of an individual that can contribute to the development of active convulsive epilepsy. Therefore, risk factors are attributes of an individual's life style, environment, family background, disease exposure, or peri-natal events that may result in a greater likelihood of developing epilepsy.

Sensitivity (*Chapter 4*) is often stated concurrently with the specificity and is defined as the probability of the outcome being positive when in fact the individual does have the condition. Put another way, it is the likelihood of a test to positively capture an individual who is positive for a given disease or condition.

Specificity (*Chapter 4*) is defined as the probability that the result is negative given that the individual being studied does not have the condition or disease. In other words, it is the likelihood that an individual will test negative when in fact that individual does not have the condition.

Chapter One

The Question and the Context

1.1 Introduction

In 2004, the World Health Organization (WHO) published *Epilepsy in the WHO African Region: Bridging the Gap* as part of the Global Campaign Against Epilepsy. This document aimed to shed light on the burden and subsequent impact of epilepsy on the African continent (World Health Organization 2004). What emerged from this monograph was an incomplete picture of the impact of epilepsy on this resource-lacking area, and a clear picture that further research was needed to understand the burden of disease in order to craft policy aimed at specifically addressing epilepsy in the African region of the world.

The aim of this dissertation is to do just that: provide a clear picture of the burden of *active convulsive epilepsy* in rural South Africa by examining the question:

'What is the prevalence of and risk factors for epilepsy in a rural South African population?'

By addressing this question, this dissertation seeks to expand the arguably meager body of literature focused on understanding the burden of epilepsy in rural sub-Saharan Africa.

Epilepsy

Epilepsy is one of the most common neurological disorders in the world and carries significant morbidity. Defined as a condition characterized by recurrent (two or more) epileptic seizures unprovoked by any immediate cause (ILAE 1997), epilepsy is thought to

manifest itself in 69 million people worldwide, with 80 percent of people afflicted with epilepsy living in developing countries (Ngugi et al. 2010). It contributes one percent (1.0%) to the global burden of disease and roughly 7.3 million disability adjusted life years (DALYs) in 2005 (World Health Organization 2006), epilepsy affects at least 10 million people on the African continent alone (World Health Organization 2004), comprising 20 percent of the global burden of epilepsy. Much better researched in developed parts of the world, the situation of epilepsy in Africa is unclear. In African studies, varying definitions of epilepsy make interpreting and comparing the findings of these studies difficult (Preux & Michel Druet-Cabanac 2005).

Good epidemiological studies must have an accurate numerator (number of accurately diagnosed cases) and an accurate denominator. Limited neurological specialists, poor health records, and the relative lack of computational and diagnostic medical technology make accurate diagnosis of cases difficult. There are roughly 75 EEG machines and 25 CT scanners in tropical Africa and less access to MRI machines and CT scanners in low- and lower middle- income countries (World Health Organization 2004; World Health Organization 2005).

An accurate population census, needed for an accurate denominator in prevalence studies, is not commonly found in Africa outside demographic surveillance sites. As a result of these difficulties, estimation of prevalence of epilepsy across Africa proves to be difficult and results in an insufficient body of literature examining the issue of epilepsy in Africa.

The few rigorous studies that do exist suggest that the prevalence of epilepsy is two to three times greater than that seen in resource-rich countries (Preux & Druet-Cabanac 2005). While the exact reasons for this increased prevalence are not entirely understood, adverse peri-natal

events, head trauma, and infections of the central nervous system all seem to play a role (Preux & Druet-Cabanac 2005). However, yet again, the literature is scant and warrants a community-based study that systematically investigates the risk factors that lead to the development of epilepsy.

Epilepsy in the Current South Africa

The understanding of epilepsy in South Africa is no different than that of the African continent as a whole. Few studies examine the burden (mortality, prevalence, incidence, and case fatality) of epilepsy in South Africa and no studies specifically address the incidence of epilepsy. Only one study has investigated the prevalence of epilepsy using a population-screening questionnaire for childhood disability that included a single question on seizures (Christianson et al. 2000). The remaining studies (Bird et al. 1962, Hurst et al. 1961) relied on patient records and hospital visits, both of which have the tendency to under-estimate the prevalence as numerous people with epilepsy do not seek treatment or misinterpret their physical symptoms (Shorvon & Farmer 1988), particularly common in low-resourced settings. Examining this limited data, prevalence estimates range from 2.2 per 1,000 in a select population of working-aged males (Hurst et al. 1961) to 6.7 per 1,000 in children between the ages of two and nine (Christianson et al. 2000), but again, varying methodologies and differing definitions of epilepsy make comparisons of these studies difficult.

A number of much smaller scale studies also exist from the Western Cape, but the nominal size of the sampling frame makes generalizing the results difficult. The motivation to understand the burden of epilepsy in rural South Africa is found in the lack of previous work in this field, coupled with the fact that epilepsy is a frequently treatable chronic disease that

affects all ages. This dissertation presents data from the largest population-based epidemiological study on epilepsy in rural South Africa.

In South Africa, as in much of rest of the world, epilepsy has various non-medical and non-biological facets, including stigma and cultural beliefs, that should be examined concurrently with the medical burden of epilepsy. While this research is intrinsically scientific, it is important to examine both the historical and cultural contexts as a means of developing a fuller picture of the interaction between person and disease.

Only fifteen years after the end of the brutal, nearly half-century reign of the Nationalist Party and their segregationist legislation infamously known as *apartheid*, South Africa continues to overcome the repressive legacy and social injustices left in its wake as it seeks to implement a health care system that addresses the needs of the entire population (Constitution of the Republic of South Africa, Chapter 2, Section 27 1996). Yet as physicians and lawmakers grapple with trying to create a model public health care system focused on a sound primary health care approach, the health of the country is experiencing several major health transitions and one area of the country where these transitions in disease are clearly evident is rural areas where increases in mortality are seen across most age groups (Kahn et al. 2007).

South Africa's health care system is currently faced with a quadruple and transitioning burden of disease, with trauma, emerging infectious diseases, persisting historical infectious diseases, and non-communicable diseases all contributing to the overall burden. Since the mid-1990s mortality rates across all age groups in rural South Africa have increased primarily due to the AIDS pandemic and the associated opportunistic (parasitic) and co-morbid (tuberculosis) diseases (Tollman et al. 2008). The growing burden of infectious

disease is paralleled by a growth of non-communicable disease that threatens to increase in the coming decades with an ageing and increasingly, unhealthy, South African population (Mayosi et al. 2009) in a setting of some economic improvement.

Historically, medical research funding and health care resources have focused on acute illness rather than chronic disease[*]. With the reduction in acute infections, there is a need to understand the burden of non-communicable, chronic disease within South Africa and to support the development of a health service that is able to provide effective, informed acute and chronic care at the primary level. All of this can begin to be achieved by understanding conditions such as epilepsy and then viewing that burden as part of the larger picture of non-communicable, chronic disease in South Africa.

Structure of Dissertation

The question posed in this dissertation is addressed in three parts, which are further subdivided into chapters. The first part of this thesis provides an understanding of the framework in which the research was carried out. It encompasses *Chapter Two*, which provides a review of relevant literature. *Chapter Three* describes the methodology used in the Studies of the Epidemiology of Epilepsy in the Demographic Surveillance Systems (SEEDS) and its implementation within the Agincourt Health and Socio-Demographic Surveillance System (AHDSS). *Chapter Four* explores the sensitivity of the population-based screening question used in the study to initially identify individuals with possible seizure episodes as a means to informally validate the questioning tool. The majority of this dissertation is found in

[*] Until recently, HIV was viewed as an acute disease, with funding to examine the prevention, diagnosis, and treatment. Now, researchers are beginning to view HIV as a chronic disease and research is being undertaken examining the longer-term affects of the disease (Freeman 2005).

the third part (the analysis portion) and seeks to estimate the prevalence and timing of onset of active convulsive epilepsy (*Chapter Five*), present a picture of the geographical distribution of epilepsy within the AHDSS (*Chapter Six*), as well as determine risk factors for developing epilepsy in the AHDSS through the use of univariate and multivariate biostatistical analysis (*Chapter Seven*). Finally, *Chapter Eight* of the dissertation concludes by bringing together the various pieces of this work by examining the general findings and suggesting possible avenues for further research.

Chapter Two

The Epidemiology of Epilepsy: A Review of the Literature

2.1 Introduction

Within the last fifty years, numerous population-based studies examining epilepsy and risk factors for developing epilepsy have been undertaken in both developed and developing regions of the world*, yielding widely varying results (Sander & Shorvon 1996). These studies were faced with various methodological issues including case definition, case ascertainment, and clinical diagnosis. This chapter begins by exploring the difficulties associated with defining and classifying epilepsy. It then proceeds to examine the methods used in population-based studies of epilepsy, before concluding with a review of epilepsy prevalence and risk factors from around the world.

2.1.1 Diagnosing Epilepsy

The majority of seizure disorders, among which epilepsy is included, do not present as a continuous physical manifestation and when they do present are brief and unpredictable, making diagnosis difficult. As a result, the diagnosis of epilepsy is usually made solely through good clinical history. Other tests, such as electroencephalograms (EEGs), can serve to contribute to the diagnosis (Sander & Shorvon 1987) and aid in the classification of seizure types. An abnormal EEG in isolation, however, does not constitute a diagnosis of epilepsy. The diagnosis of epilepsy relies on patient and/or caregiver recall of the seizures,

* The World Bank defines developing countries according to their annual gross national product (GNP) and results in categories of low-income, lower-middle income, and upper-middle income countries.

with one consequence of this being the possibility of under-reporting mild, absence, or complex partial seizures, which manifest themselves as subtle losses of consciousness (Zielinski 1974). One study in London found only 20 percent of patients with epilepsy suspected their condition prior to consulting their general practitioner (Hopkins & Scambler 1977).

Even after an individual has been identified as having had two or more seizures, the diagnosis of epilepsy and the classification of the syndrome depend on the physician or specialist's definition of epilepsy and their classification system. In one article discussing the methodological issues in epilepsy studies it was suggested that all epidemiological studies undertaken to examine epilepsy should have well-defined criteria on which to base the diagnosis of seizure (Sander & Shorvon 1987). Yet, even now, varying definitions of seizures and epilepsy and classifications have resulted in differing and often-incomparable studies.

In 1981 and 1989, the International League Against Epilepsy (ILAE) attempted to standardize global definitions of seizures and epileptic syndromes by classifying seizures and epileptic syndromes (ILAE 1981, ILAE 1989). These guidelines were largely ignored or used incorrectly by physicians and researchers and resulted in the re-examination and re-issuance of guidelines and definitions in the 1990s (Commission On Epidemiology & Prognosis 1993). These guidelines sought to clearly define epilepsy as a condition characterized by two or more epileptic seizures occurring more than 24 hours apart. The report goes on to define active epilepsy as at least one fit within the previous five years, irrespective of therapeutic intervention (ILAE 1997). Furthermore, classification of seizure type, risk factors, and measurement indices were also highlighted in the report in an attempt to standardize the definitions used and the results reported in the study of epilepsy. The Commission's

recommendations provide uniform definitions, yet even in the current study, the commission's definitions are modified slightly (though explicitly stated) to reflect country-specific treatment guidelines for epilepsy (Neurological Association Of South Africa 2000).

2.1.2 Classifying the Etiology of Epilepsy

The usefulness of classifying epilepsy may indicate the underlying cause of the condition, hinting at possible risk factors, suggesting possible interventions to reduce these risk factors, and allowing clinicians to employ the most effective treatment options for a person with epilepsy. The relative frequency of these risk factors varies in different parts of the world (Sander & Shorvon 1996). In developed countries, roughly one-third of case etiologies can be established (Sander & Shorvon 1987). This proportion of identifiable etiologies depends, in large part, on radiological investigations and complete histories, with the former being scarce in developing countries (Shorvon & Farmer 1988). A 2001 study from Tanzania, however, was able to identify probable underlying causes in 75 percent of the cases (Matuja et al. 2001), which is more than double that found in other African studies and may be due to the type of study employed (hospital versus population-based)(Matuja et al. 2001). Epilepsy with clear underlying etiology is termed symptomatic epilepsy. Alternatively, the term cryptogenic or idiopathic epilepsy is used if there is no identifiable underlying cause.

There is some confusion within the literature regarding cryptogenic and idiopathic epilepsy, with some authors suggesting the two terms are synonymous, while other authors suggest that idiopathic epilepsy refers to primary generalized epilepsies that have a genetic component with rigidly defined clinical and EEG findings (Gastaut et al. 1975). Despite the varying definitions, rates of idiopathic/cryptogenic epilepsy remain between 60 and 70 percent of diagnosed cases of epilepsy, while symptomatic epilepsy makes up the remaining portion.

These rates are found consistent in both developing and developed parts of the world (Bharucha et al. 2008).

International League Against Epilepsy Classification

The ILAE initially proposed a classification system (ILAE 1989); however, this was found difficult to use in large, population-based studies and retrospective case reviews and hence was seldom employed (Manford & Hart 1992). Consequently, in 1993 the Commission of Epidemiology and Prognosis of the ILAE presented a simpler classification system (ILAE 1993). This classification system defines cryptogenic epilepsies as syndromes of unprovoked partial or generalized seizures in which no factor associated with an increased risk of seizures has been identified. Idiopathic epilepsies are partial or generalized epileptic syndromes with particularly clinical and radiological presentations and an identified genetic component, while symptomatic epilepsies are seizures associated with a known cause (ILAE 1993). The use of standardized classifications and definitions allow clinicians and researchers to compare studies from varying regions of the world. The following section details both the methodology and difficulties in studies exploring the prevalence of epilepsy.

2.2 Population-based Studies of Epilepsy

The strength of any prevalence study is determined by the methodology to accurately identify those individuals within a well-defined population who have the condition being examined. Various methods exist to determine the prevalence of a specific disorder or syndrome, with the presentation of the condition, the location of the study, the availability of local resources governing the choice of study design.

2.2.1 Framework of Prevalence Studies

Case Ascertainment

To determine the prevalence, with prevalence being defined as the proportion of a population with a specific condition or disease at a specific time, all individuals with the condition or disease (numerator) must be identified in a known, well-defined population (denominator). The ratio of the numerator over the denominator will then provide the prevalence of the condition.

In a country with well-kept, up-to-date medical records, where all patients with epilepsy present to health care centers it is possible to determine epilepsy prevalence from a review of these records. As is the case in high-income countries, the most commonly published method of case ascertainment relies on a review of medical records followed by an interview of those identified with having epilepsy (Shorvon & Farmer 1988). This hospital- or clinic-based study typically under-represents the true prevalence of epilepsy, as some patients with epilepsy do not seek medical attention as a result of denial, associated-stigma, ignorance of their condition (Miller 1960, Tsuboi 1984, Beran et al. 1985) or barriers to accessing health care[*]. In a study done in Warsaw, Poland**,** only one-third of all people with epilepsy were ever treated for the condition and only 25 percent of people with epilepsy had ever consulted a physician (Zielinski 1974) while a second study found that nearly a quarter of people diagnosed with epilepsy actually denied having it when asked by questionnaire (Beran et al. 1985). Patient and caregiver recall bias and misidentification of symptoms make the

[*] Barriers to accessing health care are especially prevalent in low-resourced regions like Agincourt (Hundt et al. 2004).

diagnosis of epilepsy difficult in the clinical setting and even more challenging as part of an epidemiological study.

Difficulties is case ascertainment is further exacerbated in developing countries where limited access to basic health care, widespread misunderstanding and ignorance of epilepsy, and enormous social stigma and cultural beliefs result in limited numbers of people accessing the health care they need (Mbuba et al. 2008). Osuntokun et al. report that as many as 80 percent of people with epilepsy seek a traditional medical practitioner and may never be seen in a clinic or hospital (Osuntokun et al. 1987). As such, population-based studies that do not rely on previous diagnosis may ultimately yield more reliable prevalence data in developing countries where inadequate medical records, limited access to treatment, and cultural beliefs may under-represent of the burden of epilepsy.

Population-based epilepsy prevalence studies

Due to underdeveloped medical reporting techniques (Stanhope et al. 1972) and people with epilepsy (PWE) not accessing health care either unknowingly or because of intentional concealment, population-based studies have been employed in efforts to determine the prevalence of epilepsy in developing parts of the world. Capture-recapture methods and door-to-door surveys are two types of population-based studies that have been utilized in developing countries to ascertain the prevalence of epilepsy.

Capture- recapture methods rely on the use of multiple techniques of case ascertainment, sampling first from a small sample and then increasing the sample, yet still including the original sample, and comparing the total number ascertained using each technique to estimate the total number of cases. This method has been used to identify a number of conditions in the developing world including two published studies examining epilepsy (Debrock et al.

2000, Pal et al. 1998). In an example from Benin (Debrock et al. 2000), three sources of information were used: a non-medical survey of key local informants, a door-to-door survey, and local medical registries. The study found that by combining the three monitoring systems, a higher prevalence was found than when calculating the prevalence from a single source of information. The study concludes that involving multiple information sources, such as key informants* (teachers, local chiefs, etc), and medical records may be an indicator of non-diagnosed, non-treated people with epilepsy; however, this requires good medical records and infrastructure, a stable population, and more resources than the door-to-door survey. As a result, the door-to-door survey remains extremely useful in examining the burden of epilepsy.

The door-to-door method of study has become indispensible for determining the prevalence of epilepsy in the developing world. The methodology relies on the administration of a questionnaire to each household or dwelling in an accurately demarcated area. A team of fieldworkers, who are specifically trained to administer the questionnaire, visits each dwelling to administer the questionnaire. Often, these fieldworkers only have a basic high school-level education with no need of medical training. As such, it is essential for the questionnaire to be sensitive and should in theory be the optimum method for the detection of all possible cases of epilepsy (Sander & Shorvon 1987). Often, the door-to-door survey forms the first stage in the two-stage prevalence study.

Epidemiologists have used this two-stage approach since the late-1970s (Placencia et al. 1992) with the first stage an inexpensive way of sampling individuals within a specific

* Solely using key informants to identify people with epilepsy has yielded lower prevalence rates when compared with door-to-door inquires (Kaamugishaa & Feksi 1988; Thorburn et a. 1991; Wig et al. 1980)

population and indentifying suspected cases, while the second stage requires a clinical diagnosis based on a medical tests, or in the case of epilepsy, a complete and accurate medical history. Thus, stage one, through a very sensitive questionnaire, provides the individuals to be examined in stage two (and the population denominator) and a medical examination in stage two results in a specific, clinical diagnosis (Placencia, Sander, et al. 1992).

This two-stage survey, discussed above, has become the standard of studies exploring the prevalence of epilepsy and has been used in various areas of the world, with a number of well-known studies taking place in Central America (Garcia-Noval 2001), South America (Cruz et al. 1986), and Africa (Birbeck & Kalichi 2004; Osuntokun et al. 1987; Rwiza 1992; Tekle-Haimanot 1990; Kaamugishaa & Feksi 1988). While population-based epilepsy studies do provide the best methodology for ascertaining prevalence, a number of factors, including the population-based nature of the study, can contribute to an under-representation of the actual burden of epilepsy. The next section highlights these factors and suggests those that might be present in the South African context.

Availability of Health Care Professionals

Studies that take place in lower and middle-income countries (LMICs) of the world provide further challenges due to the relative lack of trained medical professionals who are able to make accurate disease diagnoses. Even in South Africa which is defined as a lower-middle-income country by WHO (World Health Organization 2006), in 2004 there were only 111 neurologists for a population of well over 47 million individuals (World Health Organization 2004) and most of these are based in private practice serving only those individuals with medical insurance (M. Connor, personal communication, 12 December 2010).

Societal & Cultural Understanding & Beliefs

Besides the limited availability of Western-trained medical professionals, often, cultural understanding and social beliefs result in epilepsy not being identified or being actively hidden because of stigma in population-based studies. A study from Indonesia highlights this by suggesting that a slight variation in the description of epilepsy will result in two wholly different answers. The researchers found that individuals interpreted one definition as a disgraceful (stigmatized) hereditary condition and responded quite negatively, while the second condition was interpreted as epilepsy and individuals would respond positively if they did suffer from epilepsy (Chandra 1988). Personal experience in rural South Africa found that some people would not discuss epilepsy in the presence of children due to the fear that children would develop epilepsy as a result of the interview. Local beliefs and understanding must be included when designing and administering an epilepsy-screening tool to ensure the inclusion of all individuals suffering from epilepsy.

Sensitivity of Screening Tool

While specificity is certainly an important component in a well-designed screening tool, it is more important in the screening stage to identify all possible cases (have a high sensitivity) than it is to eliminate all possible non-cases. However, as suggested by Shorvon and Farmer, it takes much skill and epidemiological expertise in designing a study that is both adequately sensitive and very specific (Shorvon & Farmer 1988).

Certain seizure types are more discernible and easier to diagnose, such as tonic-clonic seizures that present dramatically. However, more discrete seizure types, such as absence or complex partial or myoclonic seizures may present greater difficulty, especially to someone

who is not medically trained. As a result, population-based studies likely under-report total epilepsy prevalence (Sander & Shorvon 1996).

Difficulty in quantifying the study population

It is essential to accurately define the population at risk (sample frame) and within developing countries this can prove quite difficult due to limited census data and poorly kept records (Shorvon & Farmer 1988). In the mid-1990s a number of developing world researchers realized the value of accurately demarcating populations and conducting continual longitudinal studies of these populations. These individuals came together to form the International Network for the Demographic Evaluation of Populations and Their Health, or INDEPTH*, and together formed a network of health and demographic surveillance sites (HDSS) (Tollman 2008). Utilizing a HDSS with regular demographic monitoring allows researchers to effectively identify a sample frame for a prevalence study and addresses the difficulty of poorly kept demographic records in developing countries.

2.3 The Global Prevalence of Epilepsy

2.3.1 Inter-country Heterogeneity

The prevalence of epilepsy varies greatly between developing and developed regions of the world. A recent systematic review and meta-analysis examining the prevalence of active and lifetime epilepsy systematically confirmed statistically significant variation in the reported prevalence of epilepsy (Ngugi et al. 2010). The analysis included prevalence studies in both rural and urban areas of developing and developed countries and noted that the prevalence in developing countries was double that observed in developed countries. The prevalence of

* www.indepth-network.org

active epilepsy was found to be 4.9 per 1,000 individuals (95% confidence intervals (95% CI, 2.3 to 10.3) (5.8 per 1,000 lifetime prevalence, 95% CI 2.7 to 12.4) in developed regions of the world, 5.9 per 1,000 individuals (95% CI 3.4 to 10.2) (10.3 per 1,000 lifetime prevalence, 95% CI 2.8 to 37.7) in urban developing regions, and 12.7 per 1,000 individuals (95% CI 3.5 to 45.4)(15.4 per 1,000 lifetime prevalence, 95% CI 4.8 to 49.6) in rural areas of the developing world.

Factors responsible for increased epilepsy prevalence in developing countries

Ngugi et al. found that age of subjects, methods of data collection, and types of prevalence estimates used (point versus period) were not associated with the observed heterogeneity. They did, however, find that study size and development level of the study country largely explained the heterogeneity (31.7 percent and 26.4 percent, respectively). Smaller population studies yielded higher prevalence levels and combined with a rural setting (in multivariate analysis), accounted for 42 percent of the observed heterogeneity. The study suggested that smaller population studies may exaggerate the actual burden of epilepsy as these studies are more likely to be conducted in communities in which epilepsy is suspected to be high. Ngugi et al. conclude that other factors, such as increased genetic or biological (parasitological) risk factors, may contribute substantially to the observed heterogeneity in the prevalence of active and lifetime epilepsy (Ngugi et al. 2010).

Prevalence of Epilepsy in Africa

Studies from the African continent confirm the higher prevalence levels found in developing countries, yet vary to some degree in their methodology and findings. As suggested by Ngugi et al. this increased prevalence may be a result of a greater incidence of risk factors (further discussed below) and a subsequently higher prevalence of epilepsy in the African population

(Ngugi et al. 2010). Furthermore, the study methodology used can influence prevalence estimates (Preux & Druet-Cabanac 2005). Including only studies employing standard methodology (door-to-door surveys) Preux and Druet-Cabanac found the median prevalence to be 15 per 1,000 individuals in studies from sub-Saharan Africa. Some studies from Africa found prevalence as high as 70.0 per 1,000 in Cameroon (Nkwi & Ndonko 1989) while others found prevalence as low as 5.2 per 1,000 in Ethiopia (Tekle-Haimanot et al. 1990).

Prevalence of Epilepsy in South Africa

While a number of epilepsy studies and studies on epilepsy treatment from South Africa do exist, very few studies provide information on prevalence, with only seven published studies having attempted to ascertain the prevalence of epilepsy in the Republic. Each study used different methodology and case ascertainment, resulting in widely variable prevalence-ranging from 2.1 to 13.7 per 1,000 individuals (Foyaca-Sibat & Del Rio 2007; Foyaca-Sibat et al. 2005; Del Rio et al. 2007; Foyaca-Sibat et al. 2004; Hurst et al. 1961; Bird et al. 1962; Christianson et al. 2000). The earliest study from 1961, described neuropsychiatric disorders among black South Africans at Meadowlands clinic on the outskirts of Johannesburg, located in the present-day province of Gauteng. As a part of this hospital-based research, convulsive disorders were examined using a retrospective clinic record review. Fifty individuals were identified with convulsive epilepsy, resulting in a prevalence of 2.1 per 1,000, with no reported confidence intervals. Interestingly, the authors' of this study note a very low prevalence of convulsive disorders among the Venda and Shangaan populations of the clinic catchment area (Hurst et al. 1961). The vast majority of individuals within the Agincourt HDSS identify as Shangaan.

In a study published just one year later, a cohort of 7,049 mine workers repatriated to their homes for medical reasons were studied. Seven hundred nineteen had epilepsy (10.2 percent) yielding a prevalence of 3.7 per 1,000 individuals, again with no reported confidence intervals. This study only included young males, with the authors suggesting that these individuals may have had a lower prevalence of epilepsy due to medical screening that took place prior to them being employed at the mine. One of the objectives of this screening was to identify and exclude people with epilepsy from employment due to epilepsy-associated risks, thus biasing the study population sample (Bird et al. 1962).

More recent studies from the last decade found the prevalence of epilepsy to be as high as 13.7 per 1,000 individuals in two sites near Umtata, in the province of the Eastern Cape. The results were based on a random sample of 100 households (Foyaca-Sibat et al. 2004; Foyaca-Sibat & Ra Del Rio 2007). Using the same methodology, a group of senior medical students from the University of the Transkei, found a prevalence of 9.7 per 1,000 in adults and 4.7 per 1,000 in children in the Makaula Village, again in the Eastern Cape (Del Rio et al. 2007). Confidence intervals were not reported in any of these studies. While these studies do shed light on the burden of epilepsy in South Africa, ambiguous case definitions, highly-selected study populations, and vague or limited description of the methodology make the usefulness of these studies peripheral at best. A more recent study from 2000 proves more insightful as to the burden of epilepsy amongst rural, South African children.

As part of a study examining the prevalence of childhood disability in rural South Africa, 6,692 children from eight randomly selected villages bordering the Agincourt HDSS were asked a series of ten questions pertaining to disability, with a single question asked about seizures. A clinician confirmed the diagnosis of epilepsy by examining the children who had

responded affirmative to having experienced seizures. In this study active epilepsy was defined as children who had experienced one seizure within the last two years, or were currently on anti-epileptic drugs. Diagnosis was based solely on clinical history, as no investigative facilities were available. Furthermore, due to study limitations, confirmation of seizure types according to the ILAE classification was not possible.

The prevalence of active epilepsy was 6.7 per 1,000 individuals (5.3 and 8.3 per 1,000 for children 2-5 years of age and 6-9 years of age, respectively). The prevalence of lifetime epilepsy was 7.3 per 1,000 individuals (5.6 and 9.3 per 1,000 for children 2-5 years of age and 6-9 years of age, respectively). The male-to-female ratio of the children with active epilepsy was 3:2, with a larger difference being seen in the younger age group. While this study does have a number of limitations in terms of both design and methods, it does provide a useful comparison to the current study in its geographical proximity to the Agincourt HDSS site (Christianson et al. 2000).

Age of Onset of Epilepsy

The age specific incidence of epilepsy (or reported age of onset) follows a bimodal curve in the developed world (Sander & Shorvon 1996) with the largest peak occurring in the first ten years of life, followed by a trough through the middle years of life, and a resurgence of epilepsy in the later years of life. This pattern is not observed in the studies from sub-Saharan Africa (Preux & Druet-Cabanac 2005). The lack of a second peak during the later years of life may be due to under-ascertainment, or more likely, the high mortality rates that are seen across sub-Saharan Africa result in less people reaching older age (SEEDS Protocol 2008). Studies from Africa show a single peak very early in life. Results from a study in Ethiopia show a significant peak in the first decade of life, and then gently sloping downward over the

next two decades (Tekle-Haimanot et al. 1997). This was comparable to a study from rural Tanzania finding the highest age-specific incidence during the first decade of life (Rwiza 1992). Examining the peaks in age specific incidence may suggest underlying etiologies for epilepsy and highlight specific ages where risk factors for developing epilepsy may be more pronounced.

Sex Distribution of Epilepsy

The predominance of epilepsy in one sex is inconclusive, with some studies finding a higher prevalence in males (Birbeck & Kalichi 2004; Kaamugishaa & Feksi 1988; Christianson et al. 2000) other studies finding a higher prevalence in females (Garcia-Noval et al. 2001; Nicoletti et al. 1999; Rwiza 1992) and additional studies finding no differences between the sexes (Osuntokun et al. 1987; Placencia et al. 1992; Attia-Romdhane 1993). A recent review of epilepsy studies in sub-Saharan Africa found a mean sex ratio of males to females of 1.4. Though, as noted in the article, the sex ratio was significant in only 25 percent of the studies (Preux & Druet-Cabanac 2005).

Various reasons have been suggested to explain the sex differences in people with epilepsy. Higher incidence of head trauma among males has been suggested as one possible reason (Crombie et al. 1960; Shamansky & Glasner 1979), while a study published in 1971 showed that females consult their physician for disturbed consciousness twice as often as males (Morrell 1971). Coupled with a higher incidence of syncope and psychogenic attacks in females, there is potential for greater misdiagnosis in females than in males (Sander & Shorvon 1987). Another study suggested young women in Africa may hide their condition in order to be acceptable for marriage (Preux & Druet-Cabanac 2005). No data exists to conclusively support these assertions; however, examining the age and sex distribution of

epilepsy may help to shed light on the underlying etiology of epilepsy in a population (Birbeck & Kalichi 2004).

2.3.2 Inter-village Heterogeneity

Researchers have shown a heterogeneous global distribution of epilepsy. Yet in many instances, evidence of heterogeneity on a much smaller scale (village and household level) has also been observed (Edwards et al. 2008). Studies from sub-Saharan Africa find 6 to 60 percent of patients with a family history of epilepsy. This is compared with just 5 percent of patients in the United States having a family history of epilepsy (Ottman & Lee 1995) and is one cause of heterogeneous distribution of prevalence. Areas with family clustering will appear to have a higher prevalence of epilepsy than an area with little or no family clustering.

While very limited research has been specifically directed at examining the geospatial distribution of epilepsy, studies do exist that examine patterns of morbidity and mortality in the developing world. One study from Burkina Faso found a number of statistically significant clusters of higher childhood mortality, with one village found to have definitive non-random distribution of mortality (Sankoh et al. 2001). Studies, such as these, highlight the emerging use of geospatial analysis to examine and identify disease patterns and trends with the aim of identifying geographical patterns and possibly identifying an unequal distribution of risk factors for developing epilepsy. The next section of this chapter examines the literature regarding risk factors for developing epilepsy.

2.4 Known and Suggested Risk Factors for Epilepsy

Risk factors for developing epilepsy vary according to age and geographic location. Risk factors for early incident cases of epilepsy include obstetric injury, congenital abnormalities, genetic, and developmental conditions. Head trauma, central nervous system infections, and tumors can occur at any age, with tumors more common after the age of forty (Carpio & Hauser 2009). Finally, cerebrovascular disease, including stroke, is the most common risk factor in people over the age of sixty (Carpio & Hauser 2009). Furthermore, in numerous developing countries certain endemic conditions including malaria and various parasitic conditions have been associated with epilepsy (Carter et al. 2004). What follows below is a review of available literature on potential risk factors in the African context.

2.4.1 Brain Injuries

Injury to the central nervous system can occur anytime during one's lifespan. A number of different insults at various ages have been linked to the development of epilepsy, with the possibility of experiencing these brain insults beginning at birth and continuing throughout one's life.

2.4.2 Adverse Peri-natal Events

Quite possibly the most significant risk factor, adverse peri-natal events including birth asphyxia, obstetric injury, and boundary-zone cerebral ischemia, have been shown as a significant risk factor for early onset epilepsy. A study from Tanzania found a 4.5 times increased risk of developing epilepsy due to peri-natal complication (Matuja et al. 2001), while a study from Burundi found the risk increased 1.9 times after adverse peri-natal events (Nsengiyumva et al. 2003). A 2000 study from South Africa found that in four out of 35

children with epilepsy (8.2 percent), the cause could be traced back to events that occurred in the peri-natal period of the patient's life (Christianson et al. 2000). These three studies highlight the importance of quality pre- and post-natal medical care as a possible intervention for the reduction of adverse peri-natal events that subsequently increase a person's chance of developing epilepsy.

2.4.3 Head Trauma

Head trauma can also occur later in life. An article from the greater Cape Town area of South Africa found that head injury before epilepsy onset (post-traumatic epilepsy) was the attributable cause in 38 percent of people seen with epilepsy, with head injury due to motor vehicle accident contributing slightly less than half (42 percent) and assault contributing 30 percent, with the remainder as an unspecified accident or injury. The author points out that there was a distinct male predominance of head injury resulting from assault and motor vehicle accidents (Smith & Sacks 1985). Adeloye came to similar conclusions in patients with head injuries inflicted during the Nigerian civil war where 16.4 percent of these patients presented with seizures (Adeloye 1976).

While head injury is certain to increase the risk of developing epilepsy, little concrete data from sub-Saharan Africa exist to ascertain the magnitude of this risk. Due to inconsistent and ineffective governance of road traffic regulations and inadequate implementation of seatbelt and helmet requirements, head injuries due to vehicular accidents are likely to contribute significantly to the burden of epilepsy.

2.4.4 Cerebral Tumors

Cerebral tumors are also a significant risk factor for developing secondary epilepsy, with studies from both high-income countries and sub-Saharan Africa suggesting 1 to 10 percent of all cases of epilepsy are the result of brain tumors. One challenge facing researchers in the developing world is the relative lack of radiographic and imaging tools necessary to diagnosis tumors. As a result, use of more simplistic imagining, such as cranial radiography, is the only diagnostic tool available. A study from Nigeria that employed a CT scanner, found space-occupying lesions in roughly 11 percent of people with epilepsy (Adamolekun 1995; Ogunniyi et al. 1994) suggesting that brain tumors are a significant risk factor for epilepsy.

2.4.5 Stroke

Stroke can also be a significant risk factor for developing epilepsy due to the formation of post-stroke brain lesions. As previously mentioned, cerebrovascular disease, including stroke is the most common risk factor for epilepsy in people older than 60 years of age (Arturo Carpio & Hauser 2009), although one study does dispute stroke as a risk factor (Ogunniyi & Osuntokun 1987). Studies have shown that 1 to 42 percent of people with epilepsy have cerebrovascular disease (Preux & Druet-Cabanac 2005). A review from 2003 suggests that the age-standardized prevalence of stroke in high-income countries ranges from 461 to 733 per 100,000 (Feigin & Lawes 2003). A study completed in the Agincourt Health and Demographic Surveillance System (HDSS) found a prevalence of 3 per 1,000 individuals (SASPI 2004), and while lower than the prevalence reported in high income countries hints at a possible emerging risk factor for epilepsy as South Africa, and specifically rural South Africa, continues to experience a transitioning burden of disease.

2.4.6 Environmental Risk Factors

There are a number of environmental risk factors for developing epilepsy. Infections play an enormous role as a cause of epilepsy. In one review, infections were the cause of up to 26 percent of epilepsy cases observed (Preux & Druet-Cabanac 2005). While viruses (measles, HIV via opportunistic infection, herpes simplex encephalitis), bacteria (meningococceal meningitis, tuberculomas, and tuberculous meningitis), and fungi (aspergillosis) are all seen as risk factors for epilepsy in sub-Saharan Africa, parasites are by far a more researched infectious risk factor.

Cysticercosis

Cysticercosis is acquired by humans through the ingestion of the ova of zoonotic pork tapeworm, Taenia solium, and is thought to cause up to 50,000 deaths per annum (many more if including deaths from cysticercosis-related epilepsy). The ingestion of this helminth can occur through eating undercooked pork, which results in tapeworm infection of the gut in humans. Consuming fecal material containing ova excreted by an individual who harbors the tapeworm results in cysticercosis with cysts forming in muscle and other body tissue, including the nervous system. When the cysticercosis develops in the brain or spinal cords of either humans or pigs, the condition becomes known as neurocysticercosis, with epilepsy being the most common clinical manifestation of neurocysticercosis (Alarcon & Olivares 1975). Neurocysticercosis, a major identifiable risk factor for epilepsy in South America, has been shown to be the main cause of late onset epilepsy and of hydrocephalus in adults and may be the most common cause of new-onset seizures in childhood as well, though the data to support this claim is limited. Neurological effects of this parasite are of course only one

manifestation of infection and the actual prevalence and incidence of human cysticercosis within South Africa is not known.

Cysticercosis is not the only parasitic infection to be linked with late onset epilepsy. While certainly less documented than cysticercosis, toxoplasmosis, toxocara, oncocerciasis and malaria have been shown to cause epilepsy when these infections manifest themselves in the central nervous system. While limited studies do exist to suggest the epileptogenic properties of these parasites, further research is needed to elucidate the biological pathway leading from parasite to epilepsy.

2.4.7 Other Central Nervous System infections

Bacterial and viral infections, including meningitis and encephalitis have been linked to epilepsy. A study completed in Cameroon found 18 percent of children hospitalized with bacterial (meningococcal) meningitis experience long-term epilepsy (Mbonda 1995), while 11 percent of infants in Sudan experienced epilepsy three years after exposure to bacterial meningitis (Salih & Khaleefa 1991).

2.4.8 Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS)

There are two known biological pathways for developing epilepsy as an HIV-positive individual. Opportunistic infections, such as cryptococcosis, herpes simplex virus, toxoplasmosis, and tuberculosis, can manifest themselves as seizures in the immune-compromised individual. Furthermore, the human immunodeficiency virus can itself infect the individual's central nervous system, and present clinically as seizures (Commission On Tropical Diseases Of The International League Against Epilepsy 1994; Bartolomei &

Pellegrino 1991). In fact, 70 percent of all HIV positive individuals will present with some neurological complication during the course of their disease; 3 to 11 percent of these individuals will present with new onset seizures (Bhigjee 2005). Further attention will be given to HIV and epilepsy in *Chapter Eight* when avenues of future research are discussed.

2.4.9 Febrile Convulsions

Significant rises in body temperature have also been closely associated with seizures, especially among infants and children. Malaria, bronchopneumonia, meningitis, and septicemia have all been shown to be major causes of high body temperature (Diop et al. 2003). Malaria has been shown to be the most common cause of febrile seizures (Senga 1985), with 55 percent of cases of febrile convulsion in Togo being linked to malarial infection (Agbere et al. 1995). A study from Nigeria suggests an odds ratio of 11 for developing epilepsy after experiencing febrile convulsion (Ogunniyi & Osuntokun 1987; Commission On Tropical Diseases Of The International League Against Epilepsy 1994). While less dramatic, a study from Tanzania found an increased odds ratio of 2.9 (Matuja et al. 2001). Difficulty exists in establishing a seizure as febrile, especially when relying on caregiver recall to ascertain the seizure etiology. Nonetheless, febrile convulsions, especially in tropical regions of sub-Saharan Africa seem to be a significant risk factor for developing epilepsy later in life.

2.4.10 Demographic Risk Factors

Interestingly, studies examining socio-demographic variables as risk factors also exist, though these should be interpreted with caution. Studies suggest a higher prevalence of epilepsy in populations of lower socio-economic classes in both developed and developing countries (Shorvon & Farmer 1988), yet this association requires further investigation. A

recent article from Kenya found an association with childhood epilepsy and widowed status of the child's mother. The authors go on to suggest that this variable could be an indicator for increased poverty (Edwards et al. 2008). Whether increased poverty itself is a risk factor, or for example, inadequate pre-natal care as a result of increased poverty is the underlying risk factor is yet to be shown and caution must be taken when suggesting poverty is a social risk factor for developing epilepsy.

2.4.11 Genetic Risk Factors

While behavioral and environmental conditions can increase the susceptibility of an individual to develop epilepsy, an individual's genetic makeup may also play a role. While all humans have the potential to develop seizures, it is thought that the threshold for seizures (which varies between individuals) is most probably determined by the individual's genome (Wagner & Newton 2009). While monogenic epilepsies are relatively rare, scientists are beginning to examine the genetic susceptibility of common epilepsies including generalized and temporal lobe epilepsy (Tan et al. 2006), with studies in Tanzania and Kenya finding family history of epilepsy in first-degree relatives to be a significant risk (Matuja et al. 2001; Edwards et al. 2008). A family history of epilepsy was found in 6 to 60 percent of people with epilepsy in sub-Saharan Africa, while only five percent of patients with epilepsy present with a familial history in the United States (Ottman & Lee 1995). One suggestion for this significant difference is that the social stigma placed on people with epilepsy results in intermarriage and hence the inheritance of epileptogenic genes (Senanayake & Roman 1993). While an inheritable genetic component to epilepsy is undeniable, care must be taken to ascertain whether familial epilepsy is a result of Mendelian inheritance, the result of exposure

to a common environmental risk factor, or a combination of both. Genetic studies must be undertaken in the developing world to ascertain the true burden of gene-linked epilepsy.

This chapter has explored the available body of literature on epilepsy. Beginning with a discussion of the terms and tools used to estimate the burden of epilepsy, the chapter describes, in some detail, the reported burden and distribution of the burden of epilepsy and concluded by examining reported risk factors for developing epilepsy. The remainder of this dissertation seeks to build upon the current body of literature. *Chapter Three* examines the setting and methodology used throughout the remainder of this dissertation.

Chapter Three

The Methodological Framework

3.1 The Agincourt Health and Socio-demographic Surveillance System

The research discussed in the remainder of this dissertation took place in the Agincourt Health and Socio-Demographic Surveillance System (AHDSS) site between July 2008 and December 2009 as part of the Study of the Epidemiology of Epilepsy in the Demographic Surveillance Systems (SEEDS). This chapter provides the history and background that led to the research by providing an overview of both the AHDSS and the SEEDS project and concludes with a discussion of the methodology.

3.1.1 History and Location

The MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) was initially begun as an appendage to the former Health Services Development Unit (HSDU), and emerged in 1992 to focus on 'rural public health and health transitions research'. The Unit carries a portfolio of both observational and interventional studies including a number of multi-site collaborations. The research undertaken by the Unit is carried out in the Agincourt sub-district of the Bushbuckridge municipality with the primary aim of providing longitudinal data that seeks to elucidate transition of disease, migration patterns, and various other social variables on an individual, household, and community level (Collinson et al. 2002). A map of the Agincourt sub-district and its geographic context can be found below.

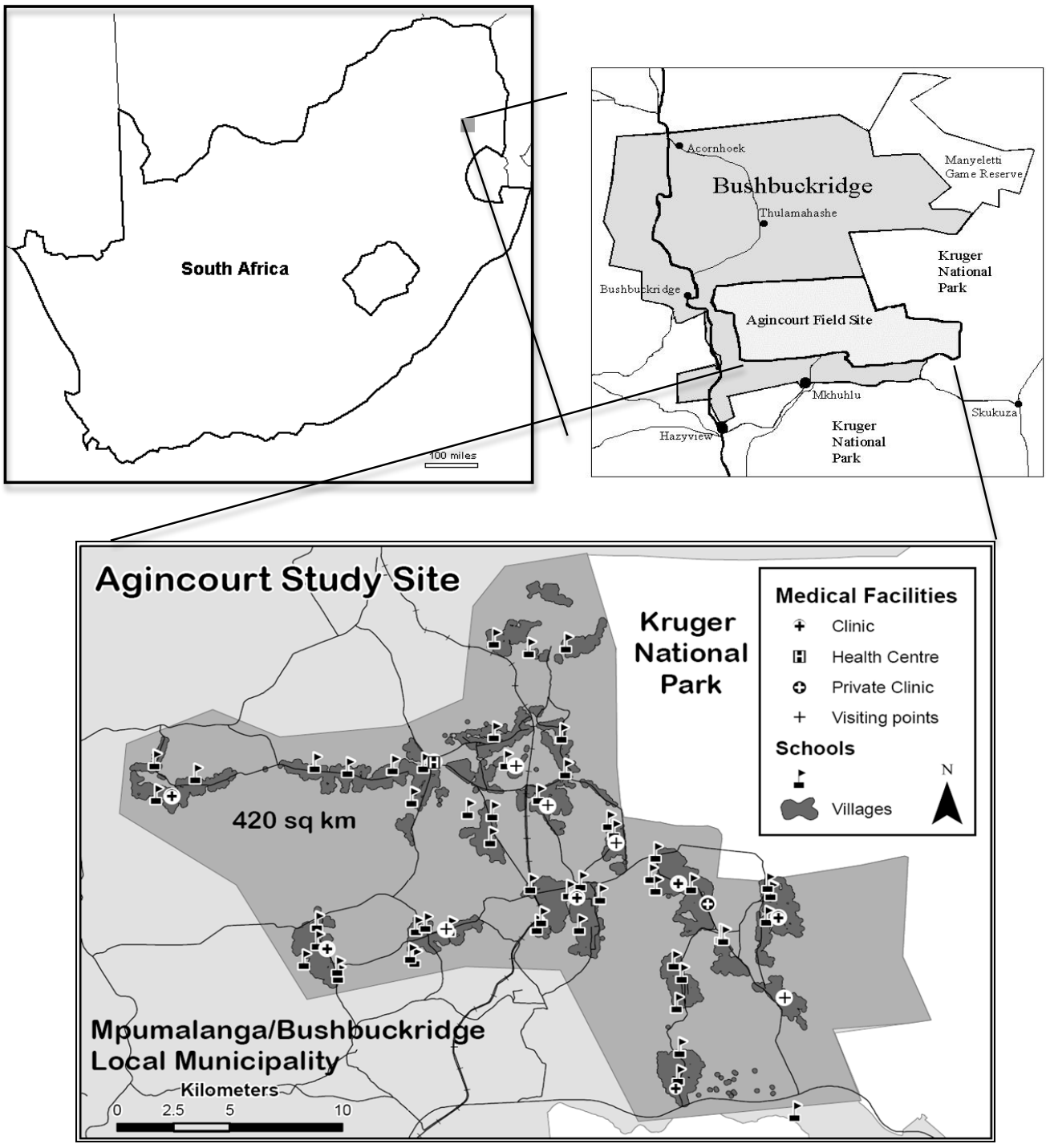


Figure 3.1: Map of South Africa, Bushbuckridge Municipality, and the Agincourt Health and Socio-demographic Surveillance Unit

The Agincourt Health and Demographic Surveillance System (AHDSS), was established as a research site aimed at informing rural health and development policy through evidence-based research (Tollman 2008). The site comprises some 420 km^2 of semi-arid scrubland and lies roughly 500 km northeast of Johannesburg in the South African province of Mpumalanga. Relatively little annual rainfall makes the area poorly suited for subsistence farming, though the area is used for game farming and low-density cattle rearing (Kahn 2006).

Annual Census

In August 1992 and every twelve months thereafter a census was, and continues to be, completed within the Agincourt HDSS. During the annual census of the Agincourt HDSS site, trained fieldworkers visit each house to ask about vital demographic information including births, deaths, marriages, in-migrations, and out-migrations at the household level. Often, one or two additional questions relating to other ongoing studies (such as stroke or coughing) are added to the census questionnaire.

3.1.2 Study Population

In 2008, the population of the Agincourt HDSS stood at 82,850 individuals found in roughly 14,000 households and twenty-five villages, yielding roughly 174 individuals per square kilometer. In 2002, the male-to-female sex ratio of the total population was 0.929 and 0.712 in the permanent population. Tsonga makes up the main ethnic group with former Mozambican refugees forming roughly 29 percent of the population. Both groups are mainly Shangaan-speaking and the former refugees, arriving during the Mozambican civil war in the 1980's, have for the most part become amalgamated into the traditional village structure, yet their access to basic resources remains lower than the general South African population (Dolan et al. 1997).

Study versus Political Villages

As a result of these former refugees village boundaries further differ when comparing study villages and political villages. Twenty-one political villages comprise 26 study, or research villages. This difference arose from the influx of Mozambican refugees as they settled on the outskirts of existing villages during their emigration in the 1980s. In essence, these settlements became their own villages, which were politically incorporated into the existing villages. However, due to the historically vast difference in their socio-economic and political demographics, the former Mozambican villages remained separate in research. Yet when information was fed back to community leaders, the Mozambican village data are amalgamated into the other villages.

Age Distribution

In 2008, the Agincourt HDSS site had an age distribution peaking at the 10-14 year age group, with 14.3 percent of the population less than 5 years old, 27.6 percent between 5 and 14 years, 55.9 percent between 15 and 64 years, and 4.5 percent older than 64 years old. Observations from 2002 to 2008 suggest children between ages 0-14 years are becoming a significantly smaller proportion of the population, due to an increase in under-5 mortality and a decreasing fertility rate (Kahn et al. 2007, Garenne et al. 2007). A population pyramid of the Agincourt HDSS can be found in *Chapter Five* (*Figure 5.1*).

3.1.3 Fertility

Total fertility rates have seen a significant decline from 6 births per woman in the late 1970s to 2.9 births per woman in 2008, with a faster decline seen in older women. Between 1992 and 2004, the birth rate has declined from 30.9 per 1,000 to 21.0 per 1,000 women of

reproductive age. As a result of declining fertility rates (and increasing mortality rates at reproductive ages), the net reproduction rate (NRR) for the Agincourt site has fallen from 1.8 in 1992 to 1.0 in 2004 (Garenne et al. 2007).

3.1.4 Migration and Employment

Both temporary (circular) and permanent migration play large roles in the population dynamics of the Agincourt HDSS site, with higher rates of temporary migration and an overall net population loss due to high levels of out-migration coupled with the previously discussed declining fertility rates (Garenne et al. 2007). Increases in both temporary and permanent migrations have been seen in both males and females over a ten-year span (Collinson et al. 2007) with nearly 60 percent of the male population participating in migration sometime during their working life, typically in order to find employment. This trend is now increasingly seen in the female population as well (Tollman, p.66). Further studies suggest that roughly 31.3 percent of the male and 17.4 percent of the *de jure*[*] population were absent for more than 6 months of the previous year and the permanent population comprises approximately 85 percent of the total population (Pronyk et al. 2001).

One reason for such high levels of labor migration is due to lack of jobs in Agincourt sub-district and the surrounding rural areas. Unemployment levels in the Agincourt HDSS site are estimated to be between 40 and 50 percent. Formal sector employment includes mining, manufacturing and service industries in more urban areas, and game and commercial farming (including work on timber plantations) in more local areas. There are widespread informal-sector activities in the form of 'tuck shops' offering various foods and produce in small

[*] The *de jure* population is defined as the permanent population (resident for six or more months each year) plus temporary migrants

quantities (Collinson et al. 2002). Public sector jobs also offer much needed employment opportunities and household reliance on government cash transfers as a source of income remains high.

3.1.5 Education

All villages within the Agincourt HDSS site contain at least one primary level school with the majority of villages having at least one secondary school. Only 60 percent of adults between 25-59 years old have received any formal education. Roughly 85 percent of children between the age of 10 and 14 attend primary school with less than half continuing to secondary school and only 3 percent of those individuals going on to post-secondary education (Collinson 2007). Adult male literacy stands at 62 percent with female literacy 6 points lower at 56 percent (Collinson et al. 2002).

3.1.6 Living Conditions

A variety of housing structures built with various materials are found in the Agincourt HDSS site. Materials range from mud or cement bricks for the structure to tile or corrugated metal sheets for the roofing. What little agriculture that does exist on individual stands (small plots of land) is used only to supplement the inhabitants' diet and is too little to serve as subsistence. Water from local dams and boreholes is pumped to village reservoirs, which in turn is fed (without filtration) to communal taps. There, women and children with 25-litre plastic containers collect and transport it to their households through the use of wheelbarrows[*]. Limited access and interrupted supply of water results in frequent water shortages in most villages. Household sanitation remains basic with various versions of pit

[*] Water reticulation from the recently built Njaka dam is in development, but delivery is slow.

latrines serving as the vast majority of toilet facilities. Initiatives within the last ten years have expanded electricity and telephone services and construction is currently underway to link the tar road to Thulamahashe with the tar road at Cunningmore A.

3.1.7 Burden of Disease and Mortality

Mortality rates experienced a downward trajectory until the early- to mid-1990s when the negative effects of the HIV/AIDS pandemic, and to a lesser extent non-communicable disease, began to exact their toll on the number of deaths. Increased mortality has been observed in 20-47 year olds (both sexes), 0-4 year olds (both sexes), and 50-64 year olds (in women, with men's rates continuing to decline) since 1994.

The Agincourt HDSS site utilizes a Verbal Autopsy tool to establish a cause of death through structured, field based interviews with those closest to the deceased (Kahn et al. 2000) and has found diarrhea, malnutrition, and HIV/AIDS (only since 1998) the leading causes of death for those 0 to 4 years of age. Road traffic accidents, HIV/AIDS, and assault comprise three of the leading causes of death for those between the ages of 15 and 49 years (hence the quadruple burden of disease). Chronic, vascular, and cardiac diseases were the leading causes of death for individuals older than fifty years (Tollman et al. 2008).

Changes in mortality patterns highlight the changing burden of disease in rural South Africa. In Agincourt, all age groups, except the oldest, face a staggering burden of HIV/AIDS and TB-related death. Of interest, however, is the emerging role of chronic, non-communicable disease, which, as Tollman et al. recently suggested, would contribute much more to the observed increase in mortality rate were it not for HIV and tuberculosis (Tollman et al. 2008). Work in Agincourt has shown a high prevalence of hypertension in men and women as well as high levels of obesity in women older than 35 years of age, both risk factors for

cardiac disease and stroke (SASPI 2004). Research such as this highlight the need for further studies examining chronic, non-communicable diseases that contribute to both morbidity and mortality levels in rural South Africa.

3.1.8 Health Care System

The Agincourt site contains six government run clinics (Lillydale, Cunningmore, Kildare, Belfast, Xanthia, Justicia), a private community health center mainly focused on HIV/TB treatment (Bhubezi), and one larger area public health center (Agincourt) with patients being referred to three district hospitals (Matikwane, Mapulaneng, Tintswalo), each located twenty-five to fifty-five kilometers from the site. Patients rely on mainly public transport to and from both the clinics and hospitals with incurred cost to the patients. The consultation and supply of treatment is free to the patient at the clinic and health center levels, with a small admission fee payable by all but indigent patients at the district hospital level.

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

With an initial three-stage study design performed in Kilifi, Kenya during 2003 (Edwards et al. 2008), the multi-site Studies of the Epidemiology of Epilepsy in the Demographic Surveillance Systems (SEEDS) project uses the same methodology and tools as the original Kilifi study. The overall aim of the study is to examine the prevalence, risk factors, treatment gap and outcome of epilepsy in five INDEPTH demographic surveillance sites across sub-Saharan Africa. This thesis focuses on the first two objectives of the SEEDS study in the Agincourt (South African) HDSS site.

Because of difficulty in indentifying some types of epilepsy, even in high-income populations, the SEEDS study focuses only on *active convulsive epilepsy*, which was defined in the SEEDS protocol (SEEDS Protocol 2008) and based on definitions of the ILAE (ILAE 1993; ILAE 1997) and recent World Health Organization demonstration projects (Ndoye et al. 2005; Wang et al. 2003) as:

Having any two of the following:

i. Loss of Consciousness
ii. Generalized clonic movements
iii. Rigidity (tonic)

Or one of the above and any one of the following:

i. Incontinence of urine and/or feces
ii. Bitten tongue or injury sustained while falling
iii. Post-ictal fatigue, drowsiness, headache or muscle aches

with at least two unprovoked seizures, one occurring within the previous twelve months.

The following section details the methodology used during each stage. A diagrammatic representation of the SEEDS study can be found in *Appendix 1*.

3.2.1 SEEDS *Stage One*: Census Survey

In 2008, one question regarding epilepsy was added to the Agincourt census and served as the first stage of the SEEDS study. This question needed to be very sensitive to detect all convulsions. The census respondent was asked whether anyone in the household had epilepsy or had been told that they had epilepsy. This question served as a filter question to identify those individuals in the population who may experience epilepsy. Further details regarding

the specific question as well as the methodology used in determining the question and its reliability can be found in *Chapter Four* of this thesis.

3.2.2 SEEDS *Stage Two*: SEEDS Questionnaire

Those individuals who answered 'Yes' (screened positive) to the question included in the 2008 census were then re-visited by one of a team of five trained fieldworkers who administered a two-page SEEDS *Stage Two* questionnaire to the individual, or the individual's caregiver in the case of a child or someone incapable of responding on their own behalf because of cognitive impairment. This stage added specificity to the survey, reducing the number of people that needed to be assessed by the clinician. Because the SEEDS study focuses only on *active convulsive epilepsy (ACE)*, fieldworkers were trained to ask about the date of last seizure episode and whether any abnormal movement was associated with the episode.

In order to validate the census question in *Stage One*, a random sample of 4,500 individuals was taken from the entire AHDSS. After obtaining consent, a SEEDS *Stage Two* questionnaire was administered to each individual. This questioning of the population sample was run concurrently with questioning of those who responded positively to *Stage One* questioning. As with the possible cases identified in *Stage Two*, any individuals from the population sample who responded that they had a seizure within the last year and had abnormal movement during the episode were referred to the clinic for follow-up.

Fieldworkers made three visits to individuals who were not at home or unavailable for questioning. After the third visit the individual was labeled as 'Not found' and adjusted for by using the single imputation method (to be discussed in *Chapter Five*).

3.2.3 SEEDS *Stage Three*: Clinical Diagnosis

Patients identified with seizures in *Stage Two* of the study were given a referral date to visit a SEEDS clinic where they were attended to by a trained SEEDS nurse who performed a detailed clinical history and examination in order to decide whether or not the patient had *active convulsive epilepsy*. An electroencephalogram (EEG) was performed and blood was taken for future genetic and serological testing (neither procedure has implications on this thesis).

Each patient diagnosed with *ACE* was matched with a control within the same age band (0-5 years, 6-12, 13-18, 19-28, 29-49, and greater than 50 years of age), selected from the population sample taken during *Stage Two* of the study (The SEEDS Team 2008). Each control was then interviewed and a complete medical history obtained and medical examination performed. Controls found to have *active convulsive epilepsy* where re-coded as cases and subsequently re-matched with a control. This component ran concurrently with the administration of *Stage Three* for those who responded affirmatively to *Stage Two*. The nurse in *Stage Three* was blind to whether the patient was a case or a control.

Every attempt was made to clinically examine each patient identified as having seizures in *Stage Two* of the study. Patients were visited at home at least three times for recruitment until it was determined that the patient had permanently out-migrated, refused to come, or had died. The reason for exclusion from the three-stage study was recorded into a separate database.

3.2.4 Ethical Considerations

The MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) is the umbrella governing body to the AHDSS that oversees the annual census update. The MRC/Wits-Agincourt unit operates under continual ethical clearance from the Human Research Ethic Committee at the University of the Witwatersrand (M960720).

The SEEDS study has received ethical clearance from both the Human Research Ethic Committee at the University of the Witwatersrand (M080455) and the Mpumalanga Provincial Department of Health Ethics Committee.

The Human Research Ethic Committee at the University of the Witwatersrand (Wits) granted ethical approval for the research presented in this thesis on 21 September 2009 (M090833) and the certificate is attached as *Appendix 2* of this dissertation.

Consent

All participants received an information sheet explaining the SEEDS study and were asked to sign informed consent. If the participant was unable to sign, a fingerprint was taken. If the patient was a minor or cognitively incapable of informed consent, consent was sought from the primary caregiver or immediate adult family member who were briefed on the study before agreeing to allow the patient to participate. Attempts were also made to inform the minor (or an individual with a cognitive disability) of the study. Ultimately, all participants received a copy of the informed consent. The strict confidentiality of all individuals involved in the study was maintained throughout. Beyond individual written consent and strict confidentiality, Agincourt holds a long-standing agreement with both civic and traditional leaders who are annually informed of ongoing studies and research results.

3.2.5 Data Management

Data Storage and Analysis

Data was double-entered into a mySQL database (OracleCorp, Redwood Shores, CA, U.S.A), where the data was cleaned by examining outliers and missing values and comparing the two entries before being transferred into STATA 10 (StataCorp, College Station, TX, U.S.A) where all statistical analysis was carried out. Quantum GIS Tethys (www.qgis.org), an open-source software package, was used to perform the geospatial analysis detailed in *Chapter Six*.

Records with missing data were examined in attempts to obtain the missing variables prior to computer entry. If the data could not be understood, fieldworkers were dispatched to re-visit the household where the original data collection had taken place. In the case where data could not be ascertained, it was excluded from the final analysis.

Data Security

All questionnaires collected during the SEEDS study were kept in locked filing cabinets. The project data typist and project site manager held keys to the cabinets. Data capture occurred in a secure computer room in Agincourt village, which is locked at the end of every workday. The database was protected at two levels: a password required to logon to the computer and another password required to access the database. All data typists are bound by confidentiality and were unable to access the database. Only the project site manager and primary investigators are allowed access to the database to perform routine back-ups, cleaning, and analysis.

Chapter Four

Examining Validity of the Screening Tool

4.1 Introduction

Because of the aforementioned benefits, a population-based, three-stage screening method, nested within a HDSS and utilizing the annual census to identify people with *active convulsive epilepsy* was utilized in the SEEDS study. In order to ensure that the initial screening question, embedded within the 2008 Agincourt census, was properly translated and culturally acceptable, key involvement from the community and a pilot study took place to examine the validity of the initial question. The remainder of this chapter details both the methods used and the results achieved when a single question to detect epilepsy was piloted at a district hospital in rural South Africa.

4.2 The Screening Tool

This section sets out to describe the processes and validations of the single question used in *Stage One* of the SEEDS study prior to the study entering the field. What follows is a detailed methodology of how the screening question was selected and a description of the piloting of the question at a district hospital.

4.2.1 Developing the Screening Tool

The design of the Stage One screening tool was essential in accurately identifying all people in the Agincourt population who may be suffering from epilepsy. Four questions previously used as a screening tool during a census round in the Kilfi, Kenya HDSS (personal correspondence) were identified as sensitive for detecting convulsions. These questions were derived from a World Health Organization screening questionnaire for neurological disease (Shorvon & Farmer 1988). The four questions were translated into the local vernacular, Shangaan, by three individuals: an Occupational Therapist, a Psychiatric Nurse from a local hospital, and a member of the Agincourt community outreach staff: all three conversant in Shangaan. The four questions were then back translated into English by six different people: all University of the Witwatersrand staff members and members of the local community conversant in Shangaan.

Thereafter the Shangaan translations were presented to the Community Advisory Group (CAG), a panel of 25 community members representing one of the 25 villages in the Agincourt HDSS. Each question was discussed to determine the most culturally understandable and acceptable form. Two questions were chosen due to their ease of understanding and ease of translation into culturally acceptable terms. Ultimately, these two questions were combined into one after insuring that the final question did not lose any cultural validity.

4.2.2 Piloting the Screening Tool

As suggested by Sander and Shorvon, the sensitivity and specificity of the screening method was tested by examining records of people with epilepsy at a local epilepsy clinic held at a local hospital (Sander & Shorvon 1996). The piloting of the screening tool took place at

Tintswalo Hospital, a district hospital located in Acornhoek, Mpumalanga Province, South Africa, that serves a population of roughly 300,000 individuals in a peri-urban environment.[†] Tintswalo has an active chronic disease unit that holds daily clinics, typically running between the hours of 7am and 4pm. Hypertension patients are seen on Monday; asthma on Tuesday; diabetes on Wednesday; epilepsy on Thursday; and all patients on Friday. Between 15 and 40 patients attend the clinic on any given day. Once seen, the patient with epilepsy is scheduled to return to the clinic in one months' time to update clinic staff on seizure control as well as to receive monthly 'maintenance' anti-epileptic drugs.

Two clinics, the epilepsy clinic and the hypertension clinic, were identified to participate in the piloting of the SEEDS screening question. The hypertension clinic was chosen due to the larger number of patients seen at the clinic, while the epilepsy clinic provided the pilot with people diagnosed with epilepsy.

Written approval was sought from the chief executive officer of the hospital, while verbal consent was sought from each patient in each clinic. Each patient was then asked the single screening question:

"Xana u na mavabyi ya ku wa, kumbe u'nwana u tshama a ku byela lewsaku u na mavabyi ya ku ya?"

When translated to English it reads:

"Do you have epileptic fits or has anyone ever told you that you have epileptic fits?",

[†] http://www.hoedspruit.co.za/tintswalofriends.htm

with ‘epileptic fits’ being understood in the translation as a condition that causes an individual to fall and/or loss of consciousness. This question was asked of each patient and the patient’s guardian (if present) prior to the patient seeing the nurse. The questioning was conducted in a semi-private space, simulating the semi-private space in which the census is administered. The patient’s response was then compared to their chart and their reason for visit, thus validating their response. The epilepsy clinic took place on 22 May 2008. Because of the low numbers seen during the epilepsy clinic it was determined that the pilot should be repeated at a second epilepsy (12 June 2008) clinic and a hypertension clinic (10 June 2008).

4.3 Results of the Pilot

During the first pilot at an epilepsy clinic, 26 people were screened, 19 of which had epilepsy with 18 responding ‘Yes’ to the piloted question.

In total 134 individuals were seen during the next two clinics, of which 81 (60.4%) were seen during the hypertension clinic and 53 (39.6%) individuals were seen during the epilepsy clinic. Three patients (3.7%) of the patients attending the hypertension clinic had epilepsy and 40 people in total had epilepsy, while 94 individuals (70.1%) had other chronic disease or were a guardian of a person with epilepsy. Of those with epilepsy, 100 percent (n=40) answered ‘Yes’ to the piloted question, while 94 people without epilepsy answered ‘No’ to the piloted question.

Table 4.1: Crude data from piloting of *Stage One* question, Tintswalo Hospital 2008

	Epilepsy Clinic	Hypertension Clinic
Male	37	7
Female	42	74
Total	79	81
Males with Epilepsy	30	2
Females with Epilepsy	26	1
Diagnosed with Epilepsy	56	3
Answered 'Yes' to pilot	55	3
Answered 'No' to pilot	24	78

The pilot suggested a 98 percent positive response to the question by people with epilepsy and a 100 percent negative response to the question by those people not affected by epilepsy. In other words, the question was 98 percent specific (95% CI: 0.90 to 1.00) in identifying people with epilepsy and 100 percent sensitive (95% CI: 0.95 to 1.00) in excluding those people without epilepsy.

Table 4.2: Specificity, Sensitivity, and Predictive Values from Piloting of *Stage One* question, Tintswalo Hospital 2008

		95% CI
Specificity to Screening Question	100%	0.95 to 1.00
Sensitivity to Screening Question	98%	0.90 to 1.00
Positive Predictive Value	1	0.92 to 1.00
Negative Predictive Value	0.99	0.94 to 1.00

4.4 Discussion

The data suggests that this question, when asked by an experienced fieldworker, would elicit a response that identifies whether or not a person is suffering from convulsions. However, there are a number of areas in which bias may have been introduced.

As previously discussed, often people with epilepsy do not seek medical treatment due to a number of reasons, including ignorance of condition and stigmatization by the community (Mbuba et al. 2008). The pilot study population is thus inherently biased, as they are aware of their condition (having been clinically diagnosed previously). Furthermore, if they do experience stigmatization as a result of epilepsy, it has not kept them from seeking treatment. This suggests that they understand their condition and are willing to seek treatment even with the possibility of stigma. This may differ from the general Agincourt population, as individuals who have epilepsy may not have been previously diagnosed, or they have previously been diagnosed but are hiding their condition due to stigma. The high specificity seen in the pilot highlights the fact that those who have been diagnosed with epilepsy understand the screening question. Likewise, the high sensitivity indicates that those who do not suffer from epilepsy know that they do not suffer from the condition described in the screening question.

Secondly, while it was not asked where individuals in the pilot reside, it is possible that because Tintswalo is located in a peri-urban environment and Agincourt is considered rural, patients of Tintswalo may have a better understanding the biomedical definitions of illness due to their geographic location, thus allowing them to correctly interpret the question. Utilizing the Community Advisory Group (from the Agincourt HDSS) was an attempt to

overcome this possible bias by ensuring a culturally and geographically relevant question was used.

The aim of *Stage One* in the SEEDS study was to ascertain whether or not a person has or had *convulsions,* with the following two stages determining whether the epilepsy is active and convulsive. During the piloting we tried to differentiate the type of epilepsy each patient had to ascertain whether all types of epilepsy were included, not just those with florid presentation (such as tonic-clonic seizures). This proved difficult, as the nurses did not seem to differentiate among the patients. Even the medical records failed to indicate the type of epilepsy each patient had. We resorted to asking each patient who responded affirmative to the initial screening question whether or not they had convulsions. The nurse was asked whether the patient had convulsive epilepsy, and in all cases the nurse responded in the affirmative. This highlights two important points: firstly, that while convulsive epilepsy may be a more common type of epilepsy (Cockerell et al. 1995), it is possible that people suffering from non-convulsive epilepsy may not seek treatment due to difficulty in case ascertainment and diagnosis. Secondly, the inability of the epilepsy nurse to classify the type of epilepsy experienced by each patient, with no mention of classification on the patient's medical record, highlights the difficulty in the classification of epilepsy or simply a lack of training.

To conclude this discussion, data from the pilot suggested that the single screening question succeeded in identifying people with epilepsy and excluding those without epilepsy in a district hospital. A number of possible biases were identified and addressed in various means, including the use of the Community Advisory Group and the translation and back-translation of the question as a way of insuring cultural understanding and acceptance. Using a three-

stage method, with the annual HDSS census serving as an initial screening tool, the SEEDS study sought to overcome some of the methodological issues previously discussed and provide a methodologically sound, population-based study of epilepsy in rural South Africa. The next three chapters of this dissertation explore the results of this study, with *Chapter Five* examining the prevalence of epilepsy in the Agincourt HDSS.

Chapter Five

Determining the Prevalence and Estimated-age of onset of Epilepsy

5.1 Introduction

The prevalence of epilepsy varies widely across the globe, with higher prevalence found in rural areas of developing countries. Numerous theories for this observed heterogeneity have been suggested; but there is insufficient data to prove these claims. Age of onset and age distribution of epilepsy also vary among studies and geographic locales. Limited resources and varying definitions make the study of epilepsy difficult, especially on the African continent where studies have found varying levels of epilepsy. Studies from South Africa provide some idea as to the prevalence of epilepsy in the Republic, but due to study limitations and small population sizes, these studies provide crude estimations at best. A large, population-based study aimed at establishing the prevalence of epilepsy in rural South Africa would provide a solid glimpse at the burden of epilepsy. This chapter presents the prevalence data from the SEEDS study in rural South Africa.

5.2 Methods used in this Chapter

5.2.1 Methodology of Calculating Prevalence

Data on both the timing and descriptions of seizures were collected in both *Stage Two* and *Stage Three* of the SEEDS study, with analysis being run on both sets of data and compared. In the case of only a year being supplied in reporting the occurrence of a seizure, the month

was set to 6 (June) and the date to the 30th, representing midway point of the year. In the event that a year and month were supplied, the date was set to the 15th, representing the mid-point of the month. In the final analysis of the prevalence, the self-reported number of seizures within the last year, the date of last seizure, and number of lifetime seizures were used to verify the definition of *active epilepsy*.

Crude prevalence is reported as the number of people with *active convulsive epilepsy* per 1,000 and expressed in six age-bands defined in the SEEDS protocol (0-5 years, 6-12, 13-18, 19-28, 29-49, 50+ years of age), by sex (SEEDS Protocol 2008).

Adjusted prevalence takes into account non-response (missing at random) in *Stages Two* and *Three* of the SEEDS study. Using a single imputation method, the number of those identified in *Stage One* and not found in *Stage Two* was multiplied by the likelihood of those being positive in *Stage Two* (likelihood was found by dividing those positive in Stage Two by those screened in *Stage Two*) and then multiplied by the likelihood of those being positive in *Stage Three* (which was found by dividing those positive in *Stage Three* by those screened in *Stage Three*). The second calculation was then repeated on those who were screened positive in *Stage Two*, but not seen in *Stage Three*. The two resulting numbers were then added to those identified positive in *Stage Three* with the summed number serving as the numerator and the total population serving as the denominator to calculate the adjusted prevalence. In summary the equation used was:

$$Prevalence_{adjusted} = N_{ACE} + (N_{St2\text{-}St1} \times P_{St2} \times P_{St3}) + (N_{St3\text{-}St2} \times P_{St3}),$$

where N_{ACE} is the number of individuals diagnosed with *active convulsive epilepsy* from the three-stage study; $N_{St2\text{-}St1}$ is the number of individuals not found between *Stage One* and *Stage Two*; P_{St2} is the probability of being positive in *Stage Two* if positive in *Stage One*; P_{St3}

is the probability of being positive in *Stage Three* if positive in *Stage Two*; and $N_{St3\text{-}St2}$ is the number of individuals not found between *Stage Two* and *Stage Three.*

Again, the adjusted prevalence is reported as the number of people with *active convulsive epilepsy* per 1,000 and expressed in six age-bands defined in the SEEDS protocol (0-5, 6-12, 13-18, 19-28, 29-49, 50+ years of age), by sex (SEEDS Protocol 2008).

5.2.2 Methodology used in estimating the Age of Onset

Data regarding the age of onset of epilepsy was ascertained during both *Stage Two* and *Three* of the SEEDS study and was self-reported. The dates reported in both *Stage Two* and *Stage Three* are analyzed and compared to one another, with the data collected in *Stage Three* being considered more accurate due to the emphasis placed on the questioning by the SEEDS' nurse. However, where *Stage Three* data is unavailable, *Stage Two* data on the onset of epilepsy is used. When only years of seizure onset are given, the month value was set to 6 (June) and the date value set to the 30th, representing the mid-point of the year. Cases in which only years were provided and the provided year corresponded with the year of birth the age of onset was set to zero. The estimated age of onset is reported by age and sex, with *interquartile ranges* given.

5.3 Results

Overall, the 2008 Agincourt population was 83,121 and of these 82,818 (99.64 percent) were screened in *Stage One* of the Agincourt SEEDS study. The remaining 303 individuals were not screened in *Stage One* due to out-migrations (n=229), deaths (n=45), individuals not found (n=17), or errors in the census reporting (n=12). *Table 5.1* shows a breakdown of those

screened in *Stage One* by age-band, while *Figure 5.1* graphically represents the age demographics of the Agincourt HDSS in 2008.

Table 5.1: Population who answered *Stage One* screening question, Agincourt 2008

Age Band	*n*	Male	Female
0 to 5 years	11518	5761	5757
6 to 12 years	13033	6418	6615
13 to 18 years	12340	6199	6141
19 to 28 years	17769	8894	8875
29 to 49 years	18505	8718	9787
50+ years	9653	3764	5889
Totals	*82818*	*39754*	*43064*

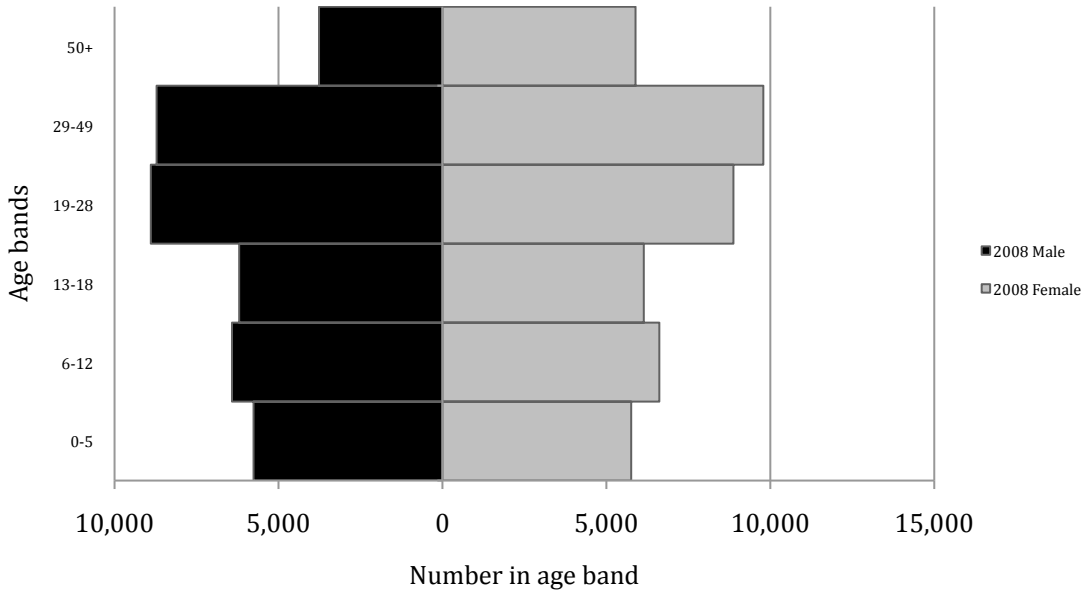


Figure 5.1: Population Pyramid of those who answered SEEDS *Stage One* screening questions, Agincourt 2008

Of these, 546 individuals (0.66 percent) answered positive to the single census question asking whether or not they had (falling/convulsive) fits or had ever been told that they had (falling/convulsive) fits.

In *Stage Two*, 515 individuals from the 546 individuals positive in *Stage One* (94.2 percent) were screened, yielding 354 individuals (68.7 percent) who had experienced seizure-like events of which one had occurred in the twelve months prior to the study. These 354 individuals were referred to *Stage Three*.

The 31 individuals screened positive in *Stage One* who were not seen in *Stage Two* were either unwilling to be interviewed (n=4) or were not found (n=27) for the administration of the *Stage Two* questionnaire.

In *Stage Three*, 328 of the 354 individuals referred to *Stage Three* (92.7 percent) were screened. Again, 26 individuals were lost to follow-up between *Stage Two and Stage Three* due out-migrations or individual not found (n=23) or the individual was unwilling to be examined (n=3). Of the 328 individuals screened in *Stage Three*, 245 individuals (74.7 percent) were diagnosed with *active convulsive epilepsy* according to the definition set forth in the SEEDS protocol and highlighted above. *Figure 5.2* provides a diagrammatic outline of the numbers at each stage of the study.

5.3.1 Population Sample

In addition to those answering positive in *Stage One*, a random sample of 4,500 individuals were selected from the Agincourt HDSS (previously discussed in *Chapter Two)*. Of these 4,500 individuals, 91.4 percent or 3,889 individuals were found and consented to answer the *Stage Two* questionnaire. *Table 5.2* below shows the age demographics of the population sample that were found.

Six hundred eleven (13.6 percent) individuals from the population sample were not found, primarily due to high levels of migration in the site. Of the 611, 40 individuals refused to be interviewed, while 571 individuals were either not found due to out-migration or had died.

Of the 3,889 individuals that were found, 67 people (1.7 percent) were found to have experienced seizures, with at least one seizure occurring in the twelve months prior to the administration of the questionnaire. Of these 67 people found positive in the population sample, 58 (86.6 percent) were assessed in *Stage Three*, with 26 people (44.83 percent) from the population sample being diagnosed with *active convulsive epilepsy*.

Comparing the three-stage study cases with the population sample cases, 38 of the 67 people identified as having seizures in the population sample were also identified in *Stage One* of the study as possibly having seizures. Of these 26 individuals diagnosed with *active convulsive epilepsy* in the population sample, 16 had also been found to have *active convulsive epilepsy* in the three-stage study.

Additionally, 56 individuals not part of the population sample or found positive in *Stage One* were diagnosed with *active convulsive epilepsy* during *Stage Three* of the study. Thirty-three of these individuals had screened negative for epilepsy during *Stage One*, while three individuals were not picked up in the census either due to an unreported in-migration or an error in census data collection. These individuals were excluded from the analysis, as they were not identified as having convulsions in *Stage One*.

Table 5.2: Demographic profile of population sample, Agincourt 2008

Age Band	*n*	Male	Female
0 to 5 years	434	217	217
6 to 12 years	760	388	372
13 to 18 years	673	363	310
19 to 28 years	757	373	384
29 to 49 years	743	283	460
50+ years	522	187	335
Totals	3889	1811	2078

5.3.2 Age of Onset of Epilepsy

Of the 245 people diagnosed as having *active convulsive epilepsy,* 240 provided information regarding the date they first experienced seizures. Out of the 240 individuals, 239 people (126 males and 113 females) provided feasible dates when comparing data collected in *Stage Two* with that collected in *Stage Three*, with one individual stating that the date of onset of seizures was before their date of birth. This datum was excluded from the analysis, with the final analysis including 239 records of self-reported age of onset of epilepsy.

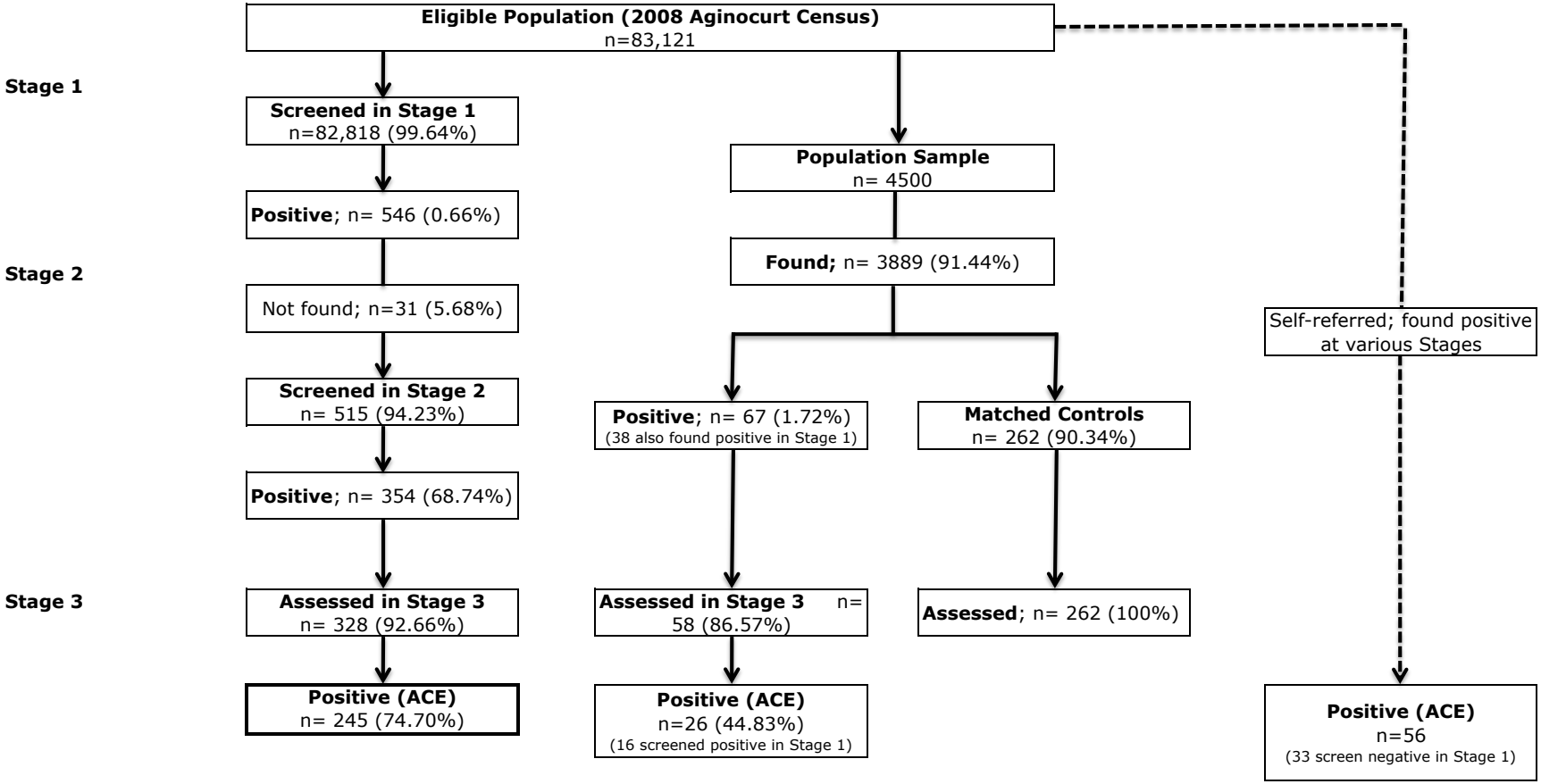


Figure 5.2: Diagram of three-stage SEEDS study by the numbers, Agincourt 2008

5.4 Analysis

5.4.1 Crude Prevalence

The overall crude prevalence of people diagnosed with *active convulsive epilepsy* within the Agincourt HDSS was found to be 2.94 per 1,000 individuals, with a 95 percent confidence interval ranging from 2.59 to 3.32.

5.4.2 Adjusted Prevalence

Using the single imputation method (discussed in the *Methods* section of this chapter) to adjust for non-response and false negatives, the adjusted prevalence of people with *active convulsive epilepsy* within the Agincourt HDSS was found to be 3.38 per 1,000 individuals.

5.4.3 Prevalence from Population Sample

Within the population sample, the 4,500 individuals randomly selected from the HDSS and screened with the *Stage Two* questionnaire, the crude prevalence of people with *active convulsive epilepsy* was found to be 6.68 per 1,000 with 95 percent confidence intervals of 4.12 to 9.25. After adjusting for non-response, the adjusted prevalence in the population sample was found to be 7.72 per 1,000 individuals. *Table 5.3* below shows the prevalence of *active convulsive epilepsy* by age-band and age among the population sample.

Table 5.3: Prevalence of *active convulsive epilepsy* in the population sample by age and sex, Agincourt 2008

Age Band	Crude Prevalence (per 1000)	95% Confidence Interval	Male Prevalence (per 1000)	95% Confidence Interval	Female Prevalence (per 1000)	95% Confidence Interval
0 to 5 years	6.91	-0.91 to 14.74	0.00	0.00	13.80	-1.83 to 29.48
6 to 12 years	2.63	-1.02 to 6.28	5.15	-2.00 to 12.31	0.00	0.00
13 to 18 years	1.49	-1.43 to 4.40	2.75	-2.66 to 8.17	0.00	0.00
19 to 28 years	9.25	2.41 to 16.10	10.72	0.23 to 21.22	7.81	-1.03 to 16.66
29 to 49 years	6.73	0.84 to 12.62	10.60	0.22 to 21.25	4.35	-1.69 to 10.38
50+ years	15.33	4.75 to 25.90	37.43	9.98 to 64.89	2.99	-2.89 to 8.86
Overall	6.68	4.12 to 9.25	9.39	4.94 to 13.83	4.33	1.51 to 7.16

5.4.4 Prevalence by Age

Prevalence was calculated for each of the six defined age-bands with the highest prevalence in the 29-49 year age-band (5.16 per 1,000; 95% CI: 3.66 to 6.67). The highest adjusted prevalence level was also in the 29-49 year age band (4.29 per 1,000). The prevalence of *active convulsive epilepsy* increased until the 29-49 year age -and and decreased in the 50+ year age-band. *Table 5.4* below shows the prevalence, both crude and adjusted, by age-band.

Table 5.4: Crude and Adjusted Prevalence of people with *active convulsive epilepsy,* Agincourt 2008

Age Band	Crude Prevalence (per 1000)	95% Confidence Interval	Adjusted Prevalence (per 1000)
0 to 5 years	0.86	0.33 to 1.41	0.98
6 to 12 years	2.23	1.42 to 3.03	2.32
13 to 18 years	2.76	1.83 to 3.68	3.00
19 to 28 years	2.64	1.89 to 3.40	3.11
29 to 49 years	4.70	3.72 to 5.69	5.46
50+ years	3.94	2.69 to 5.19	4.85
Overall	2.94	2.59 to 3.32	3.38

5.4.5 Prevalence by Sex

The male-to-female ratio of people diagnosed with *active convulsive epilepsy* was 1.11 with 129 males and 116 females diagnosed with *active convulsive epilepsy*. Examining the male-to-female ratio by age band shows that in people with epilepsy, males outnumber females 4

to 1 during the earliest years of life (0-5) with the trend reversing during the third decade of life (M:F, 19:28). During the fourth decade of life, males again outnumber females (M:F; 45:42), which is again reversed after the age of 50, where females slightly outnumber males (20 to 18, respectively). From ages 6 to 12, males outnumber females slightly less than 2 to 1, with this generally diminishing over the next three decades of life. The prevalence of *active convulsive epilepsy* is higher among males except in the 19-28 year-old and the 50+ year old age-bands. *Table 5.5* shows the number of individuals, by age-band and sex, diagnosed with *active convulsive epilepsy*, while *Table 5.6* shows the prevalence of epilepsy by age-band and sex.

Table 5.5: Age and Sex Distribution of those diagnosed with *active convulsive epilepsy*, Agincourt 2008

	Number of diagnosed cases of active convulsive epilepsy		
Age Band	*n*	Male	Female
0 to 5 years	10	8	2
6 to 12 years	29	19	10
13 to 18 years	34	20	14
19 to 28 years	47	19	28
29 to 49 years	87	45	42
50+ years	38	18	20
Totals	*245*	*129*	*116*

Table 5.6: Adjusted and unadjusted Prevalence by age-band and sex, Agincourt 2008

Age Band	**Male: Prevalence (per 1000)**	**95% Confidence Interval**	**Adjusted Male Prevalence**	**Female: Prevalence (per 1000)**	**95% Confidence Interval**	**Adjusted Female Prevalence**
0 to 5 years	1.39	0.43 to 2.35	1.52	0.35	-0.13 to 0.83	0.41
6 to 12 years	2.96	1.63 to 4.29	3.09	1.51	0.58 to 2.45	1.57
13 to 18 years	3.23	1.81 to 4.64	3.30	2.28	1.09 to 3.47	2.66
19 to 28 years	2.14	1.18 to 3.10	2.64	3.15	1.99 to 4.32	3.57
29 to 49 years	5.16	3.66 to 6.67	5.70	4.29	3.80 to 5.59	5.22
50+ years	4.78	2.58 to 6.99	5.73	3.40	1.91 to 4.88	4.27
Overall	3.25	2.69 to 3.80	3.61	2.69	2.20 to 3.18	3.16

5.4.6 Self-reported Age of Onset of Epilepsy

Fifty percent of people diagnosed with *active convulsive epilepsy* experienced onset of these seizures prior to their thirteenth birthday, with the largest number of individuals experiencing seizures during the first year of life. There is a continual downward trend with a sharp increase near the tenth year of life (n=10), and peaks at the second decade of life (n=7), the third decade of life (n=5), and two substantial peaks near the fourth decade of life (n=5). A smooth polynomial line was fitted on top of the crude data to highlight significant trends. The line shows a downward trend beginning at birth and continuing until the fourth decade of life where there is a slight rise. The graph continues its downward trend with leveling out seen just before the sixth decade of life. The remainder of the graph shows a continuing downward trend. *Table 5.7* provides the summary statistics of the reported age of onset, while *Figure 5.3* provides a graphical representation of the distribution of the age of onset. *Figure 5.4* presents the age of onset by age, highlighting the fact that males had a slightly earlier (roughly 2 years) age of onset than females.

Table 5.7: Interquartile Range and Mean of Onset of *active convulsive epilepsy*, Agincourt 2008

	Male (n=114)	Female (n=104)	Total (n=218)
1 percentile	0	0	0
25th percentile	3	6	4
50th percentile	10	15	12
75 percentile	25	29	27
99th percentile	71	64	65
Mean	16.06	19.48	17.67

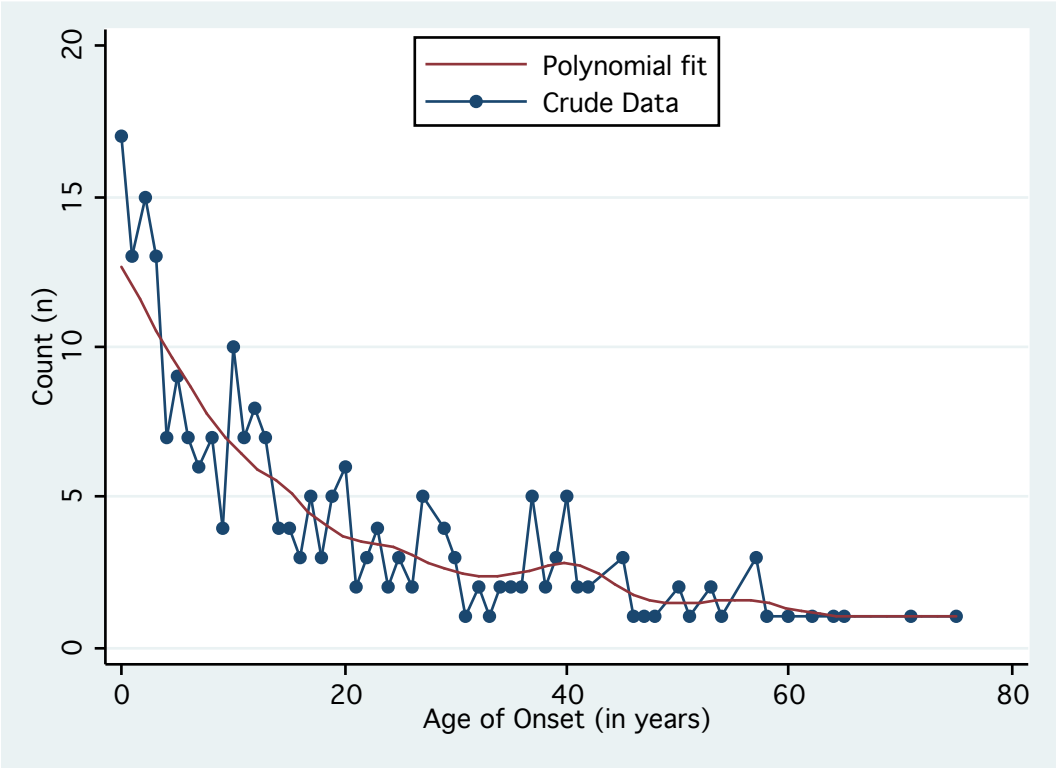


Figure 5.3: Crude and fitted trends of age of onset (in years) of *active convulsive epilepsy*, Agincourt 2008

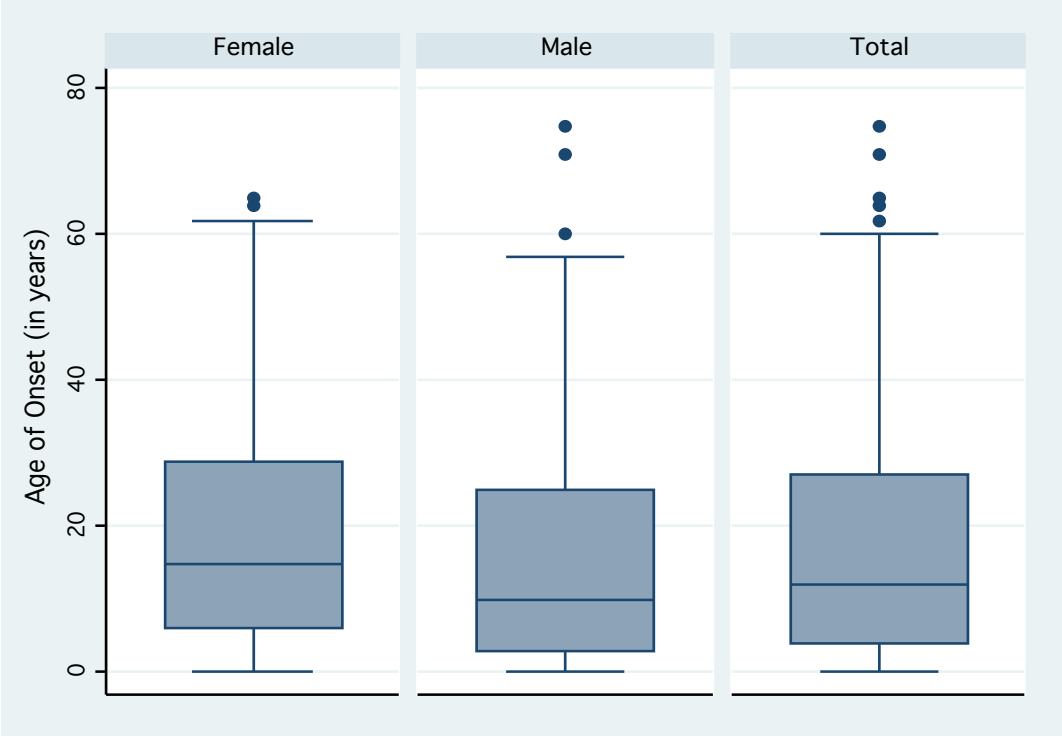


Figure 5.4: Box plot by age of the age of onset (in years) of active convulsive epilepsy, Agincourt 2008

5.5 Discussion

The aim of this chapter was to provide the crude and adjusted prevalence of *active convulsive epilepsy* in rural South Africa. By utilizing the annual Agincourt census in *Stage One* of the three-stage population screening method, we found the prevalence of *active convulsive epilepsy* to be significantly lower (2.94 per 1,000) than any study thus far reported in sub-Saharan Africa. Even adjusting for non-response, our findings are also much lower than the 12.7 per 1,000 that Ngugi et al. found in his meta-analysis of studies in rural, developing countries (Ngugi et al. 2010). We suspect that the prevalence figure from the population sample may more accurately reflect the prevalence of *active convulsive epilepsy* within the Agincourt HDSS. There are a number of possible reasons for this low prevalence.

Stigma & Cultural Beliefs

One possible factor for the low prevalence rate is the social stigma and cultural beliefs associated with epilepsy. Epilepsy is one of the most stigmatized neurological conditions and can result in individuals not disclosing their condition due to social stigma and fear of community rejection. During the second stage of the current study, at least one respondent refused to be interviewed in front of small children for fear that the children would develop epilepsy; believing that just spoken words can result in the manifestation of this condition.

It is also possible that family members with epilepsy are thought to bring shame or hardship upon the family by experiencing the condition. As such, family members would be wary of divulging the fact that a member of their family did suffer from the syndrome to an outsider. While no direct evidence for this situation came to light during the study, an anecdotal situation did arise. In one household, a fieldworker was offered a small boy suffering from

epilepsy. The mother asked if the fieldworker could take the small boy because the family could no longer provide care for the boy. The situation suggests that this household may have been faced with an enormous burden as a result of the family member suffering from epilepsy.

Methodological Issues

A second possible factor that may account for an under-estimation of the prevalence is the possibility that the methodology was either inherently flawed or improperly implemented. The three-stage method of screening a population has been used previously (Isaac & Kapur 1980; Edwards et al. 2008) with the Stage One question "Does this person have fits?" having a 90.4 percent specificity for detecting *active convulsive epilepsy* in Kilifi, Kenya and, as discussed in *Chapter 3*, a 100 percent specificity for detecting active epilepsy in a pilot study carried out in a local hospital in the local language prior to the current study entering the field (SEEDS Protocol 2008). Furthermore, the *Stage Two* questionnaire has been used extensively in Kilifi, Kenya (SEEDS Protocol 2008) and is originally based on questionnaires used in other international studies. It is important to note that the study only sought to establish the prevalence of *active convulsive epilepsy*, where other studies have examined all epilepsies. This may contribute to a slightly lower prevalence finding; however, it seems unlikely that the methodology or definition on which this study was based is flawed or could explain the significantly lower prevalence rates.

It is possible that the implementation of the study, or one of the stages of the study, was done incorrectly. Early on in the study, it was noted that the positive response rates in *Stage One* were low compared to rates seen during *Stage One* in the Kilifi study that employed the same methodology. As such, each team of census fieldworkers were re-trained on the

administration of the *Stage One* question. There was no noticeable change in the positive response rates of *Stage One* after the re-training.

An internal check was built into the study to ascertain the specificity of the *Stage One* questioning, which could be used to further adjust the prevalence to reflect not attending any of the stages. Using a randomly selected sample of individuals from the *Stage One* population, the population sample yielded a much higher crude prevalence level (6.68 versus 2.7 per 1,000 individuals). The difference is even larger after adjusting for non-response. These results suggest that the prevalence in the whole population may be higher than that found in the three-stage study and that the difference can be accounted for by the lack of sensitivity in *Stage One* of the study. One avenue of further research would be to interview the thirty-three individuals who screened negative in *Stage One* and were later diagnosed to have *active convulsive epilepsy* in *Stage Three* to determine why they had responded negative in *Stage One*.

Increased Mortality Levels

South Africa is currently faced with an enormous burden of disease, especially Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS). One consequence of this disease is a decreased life expectancy and an increased mortality level in the population, especially in the rural population where individuals are thought to return home to die (Clark et al. 2007). As a result, it is possible that people affected by epilepsy and infected with HIV are dying as well, causing more people with epilepsy to die and a subsequently lower prevalence level. By examining incidence it would be possible for researchers to determine how many people are developing epilepsy, which when compared to the prevalence level, could determine how many people with epilepsy are dying.

Risk Factors

It is plausible that the prevalence figures reported in this study may in fact reflect a true lower prevalence of *active convulsive epilepsy* in rural South Africa than elsewhere in Africa. This result could be due to less pervasive risk factors or better public health care. For example, it is known the cerebral malaria can result in the emergence of epilepsy later in life (Carter et al. 2004) and the Agincourt area is hypo-endemic for malaria, suggesting that while malaria remains a risk factor for developing epilepsy, the low prevalence of malaria within the Agincourt HDSS may in fact result in a lower prevalence of epilepsy. Further attention will be directed in *Chapter Six* to discussing and examining risk factors for epilepsy.

Over-reporting of Prevalence

While under-reporting of the prevalence of *active convulsive epilepsy* is possible, it is also possible that acute symptomatic seizures (such as abstinence seizures in individuals with alcohol dependency) were incorrectly diagnosed as epilepsy resulting in an over-reporting of the prevalence. While this is a possibility, it is unlikely to significantly contribute to the overall prevalence.

5.5.1 Prevalence Trends by Age

One interesting finding, when comparing the results of this study with those found by Christianson et al. is the similarity in prevalence levels when using the population sample data and the parameters set out in the 2000 study described previously (Christianson et al. 2000). Within the population sample of the current study, a prevalence of 6.6 per 1,000 in children aged 6-12 years was observed, while Christianson et al. found a prevalence of 6.7 per 1,000. Yet, when calculating the prevalence in the 3-stage study, the prevalence in

children 6 to 12 years of age was found to be 2.3 per 1,000 individuals, significantly lower than that found be Christianson et al. The similar findings suggest that the actual prevalence rate in rural South Africa may be closer to that found in the population sample.

Overall, we would expect to see an increasing prevalence of *active convulsive epilepsy* as epilepsy is a chronic condition. Decreases in the prevalence after the first 18 years of life and again after 50-plus years of life can be explained by spontaneous remission or death. Further research is needed to fully ascertain the cause of the decreased prevalence seen during the time periods; however, a significant level of mortality is observed during the first five years of life as well as between 15 and 49 years of age in the Agincourt HDSS (Tollman 2007).

5.5.2 Prevalence by Sex

Studies from elsewhere in Africa have shown varying results in the prevalence of epilepsy by sex (Birbeck & Kalichi 2004). Our results show a significant outnumbering of females by males in the early years of life, with an overall lifetime ratio close to one. This is supported by a number of studies from elsewhere in Africa, which found a slightly higher prevalence in males than females. This may be explained by males' more violent behavior resulting in increased traumatic brain injury related seizures. Road traffic accidents and assault, two major causes of traumatic brain injury, have been found to be leading causes of death in individuals aged 15 to 40 years within the Agincourt HDSS (Tollman et al. 2008). However, further causal evidence is needed before a conclusion can be drawn.

5.5.3 Age of Onset

The findings in the current study loosely concur with those found in Tanzania and Ethiopia, which suggest the highest incidence of epilepsy occurs in the first decade of life (Rwiza et al.

2005; Tekle-Haimanot et al. 1997). Interestingly, we found the highest onset of epilepsy occurred during the first year of life, which might reflect adverse peri-natal events or underlying genetic or congenital disorders as possible risk factors. The peak seen during the adolescent (10-15) years of life may be indicative of environmental, including infectious, risk factors as well as trauma as has been suggested elsewhere. Finally, the spike near the fourth decade of life may be interpreted as an emergence of the bimodal distribution of epilepsy seen in the developed world (World Health Organization 2005). It has been documented elsewhere that South Africa is in the midst of the disease transition, with increasing levels of cerebrovascular disease, diabetes, and obesity (Mayosi et al. 2009). With these increased levels of cerebrovascular disease, an increased incidence of epilepsy later in life is subsequently expected, though if the peak near the fourth decade of life is a result of cereberovascular disease, it is slightly earlier than has been reported in the developed world, though it is in line with evidence from sub-Saharan Africa suggesting an earlier age of onset of stroke (SASPI 2004). Nonetheless, further research into the incidence and ultimately underlying causes of symptomatic epilepsy in rural South Africa are required to truly understand the reported age of onset.

The study discussed in this chapter is seminal at examining the prevalence of epilepsy in the largest epilepsy prevalence study undertaken in rural South Africa to-date. Two broad findings emerge: (1) the use of a health and demographic surveillance system as the initial screening tool may result in the under-reporting of positive events, and (2) the prevalence of epilepsy is lower (both crude and adjusted) in rural South Africa than that found elsewhere in Africa, while both the age and sex distribution of prevalence and age of onset are similar to those findings reported elsewhere on the African continent.

Chapter 6 will build on this chapter by examining and mapping the geographic distribution of epilepsy within the Agincourt HDSS with the aim of further understanding the burden of *active convulsive epilepsy*.

Chapter Six

Analyzing the Distribution of Epilepsy within the Agincourt Health and Demographic Surveillance System

6.1 Introduction

Physicians and scientists have employed geospatial mapping numerous times over the last 250 years. By examining a disease's spatial distribution researchers attempt to ascertain the underlying etiologies of a specific disease (Cameron et al. 1985; Jensen et al. 1988). One of the more famous, historical anecdotes is the mapping of London's Soho district by Dr John Snow, whose map enabled him to track the source of a cholera epidemic to single water pump on Broad Street (Johnson 2006).

Since Snow's seminal work in the 1850s, mapping has become much more advanced and technical, with numerous computer packages and statistical methods available that allow for the input of crude data and the output of complex maps. Scientists have attempted to map numerous diseases including cancer and malaria with varying results (Hjalmars 1996; Schellenberg et al. 1998). Recently, emphasis has been placed on mapping mortality, its causes and trends in an attempt to examine a population's health and to suggest where key interventions should be aimed (Sartorius & Kahn 2010). While mapping is certainly not a new tool, it does provide useful information that allows researchers to examine the distribution of an illness or condition in attempts to elucidate the underlying etiology of the disease.

Chapter Six seeks to map the prevalence of epilepsy across the 25 villages in the Agincourt HDSS using mapping software and the prevalence data from the SEEDS study. In doing so, this chapter aims to expose any geographical patterns that exist and concludes with a discussion of possible reasons these patterns exist in the Agincourt HDSS in an attempt to develop specific strategies aimed at alleviating the burden of these high prevalence areas.

6.2 Methods

Village demarcation and HDSS boundary information was provided by the Agincourt HDSS and is updated annually as part of the annual census. Individual households are visited with the exact geographic (X,Y-) coordinates being recorded by handheld global positioning satellite (GPS) devices. Village area demarcation was achieved through creating polygons surrounding all dwellings within the political village and only represents the areas containing dwellings. It is difficult to accurately demarcate non-residential areas within the HDSS due to somewhat indiscriminate boundaries. As such, some areas within the map will not form part of any particular village, but still comprise part of the Agincourt HDSS.

With the differences previously discussed in *Chapter Three*, the prevalence levels in this chapter are calculated for both research and political villages, while the mapping looks at only political villages, which have been demarcated by the village leaders.

6.3 Results

The prevalence of epilepsy by research village ranged from 0.89 to 5.04 per 1,000 individuals, with Dumphries C, Somerset B, Lillydale B, and Croquet Lawn all experiencing epilepsy prevalence under 1.50 per 1,000. Cunningmore B, Rholane, and Newington C all experience prevalence levels above 5.00 per 1,000 individuals. *Table 6.1* presents the prevalence, 95 percent, and 90 percent confidence intervals by village as well as the differences between study and political villages. In the case where the 95 percent confidence intervals observed in each village do not overlap the overall prevalence (2.94 per 1,000), the result is noted as low or high. Villages where the 90 percent confidence intervals for the prevalence are either entirely above or below the overall prevalence, the village prevalence is noted as marginally low, or marginally high. Croquetlawn, Lillydale B, and Dumphries C had low prevalence levels compared to the overall prevalence[*], while Ireagh A and Somerset B had marginally lower prevalence[**]. Cunningmore B is the only village with a marginally higher prevalence[**]. *Table 6.2* provides the prevalence in each of the 21 political villages, while *Figure 6.1* presents a mapping of the prevalence of epilepsy in the political villages

Villages with Clinics or Health Care Centers

By observing the maps, no noticeable gradient is found in or around village containing clinics or health care centers. *Table 6.2* presents villages with clinics or health care centers and their prevalence.

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[*] Significant differences of prevalence levels are considered when the 95 percent confidence intervals fall entirely above or below the overall prevalence.

[**] Prevalence levels are considered marginally significant if their 90 percent confidence interval fall completely above or below the over prevalence.

Table 6.1: Prevalence and Confidence Intervals of *active convulsive epilepsy* by village, Agincourt 2008

	Study Village	*n*	Political Village	Prevalence in Study Villages (per 1000)	95 % CI	90% CI	CI compared to Overall Prevalence*
1	**Agincourt**	7,248	Agincourt	2.90	1.66 to 4.14	1.86 to 3.94	-
2	**Croquetlawn**	3,247	Croquetlawn	1.23	0.002 to 2.43	0.22 to 2.24	low
3	**Cunningmore A**	5,475	Cunningmore A	2.92	1.49 to 4.35	1.72 to 4.12	-
4	**Cunningmore B**	3,571	Cunningmore B	5.04	2.72 to 7.36	3.09 to 6.99	marginally high
5	**Huntington**	2,852	Huntington	2.45	0.64 to 4.27	0.93 to 3.98	-
6	**Ireagh A**	3,661	Ireagh A	1.64	0.33 to 2.95	0.54 to 2.74	marginally low
7	**Ireagh B**	2,347	Ireagh B	2.56	0.51 to 4.60	0.84 to 4.27	-
8	**Justicia A**	5,141	Justicia	2.14	0.88 to 3.40	1.08 to 3.20	-
9	**Kildare A**	4,677	Kamalamule	2.78	1.27 to 4.29	1.51 to 4.05	-
10	**Kildare B**	4,703	Kamalamule	2.34	0.96 to 3.72	1.18 to 3.50	-
11	**Lillydale A**	6,764	Lillydale A	3.25	1.89 to 4.61	2.11 to 4.39	-
12	**Lillydale B**	2,317	Lillydale B	1.29	-0.17 to 2.76	0.01 to 2.52	low
13	**Newington B**	3,396	Newington B	2.94	1.12 to 4.77	1.41 to 4.47	-
14	**Newington C**	1,841	Newington C	5.43	2.07 to 8.79	2.61 to 8.25	-
15	**Somerset A**	3,078	Somerset	3.25	1.24 to 5.26	1.56 to 4.93	-
16	**Xanthia**	4,183	Xanthia	4.06	2.13 to 5.99	2.45 to 5.68	-
17	**Rholane**	1,935	Rholane	5.68	2.33 to 9.04	2.87 to 8.50	-
18	**Kildare C**	1,112	Kalamamle	1.8	-0.69 to 4.29	-0.34 to 3.89	-
19	**Justicia B**	1,055	Justicia	2.84	-0.37 to 6.06	0.14 to 5.54	-
20	**Somerset B**	990	Somerset	1.01	-0.97 to 2.99	-0.65 to 2.67	marginally low
21	**Khaya Lami**	1,615	Khaya Lami	4.33	1.13 to 7.54	1.64 to 7.03	-
23	**Belfast**	6,109	Belfast	3.27	1.84 to 4.71	2.07 to 4.48	-
24	**Dumphries A**	2,263	Dumphries A	2.65	0.53 to 4.77	0.87 to 4.43	-
25	**Dumphries B**	2,109	Dumphries B	4.27	1.48 to 7.05	1.93 to 6.60	-
26	**Dumphries C**	1,129	Dumphries C	0.89	-0.85 to 2.62	-0.57 to 2.34	low
	Overall			2.94			

* Confidence intervals were compared to the overall prevalence, with low representing CI range below the overall prevalence, marginally low with the 90% CI entirely below the overall prevalence, and marginally high with the 90% CI range entirely above the overall prevalence

Table 6.2: Prevalence of *active convulsive epilepsy* by political village, Agincourt 2008

Political Village	Study Village	Prevalence in Politcal Villages (per 1000)
Agincourt	**Agincourt**	2.90
Belfast	**Belfast**	3.27
Croquetlawn	**Croquetlawn**	1.23
Cunningmore A	**Cunningmore A**	2.92
Cunningmore B	**Cunningmore B**	5.04
Dumphries A	**Dumphries A**	2.65
Dumphries B	**Dumphries B**	4.27
Dumphries C	**Dumphries C**	0.89
Huntington	**Huntington**	2.45
Ireagh A	**Ireagh A**	1.64
Ireagh B	**Ireagh B**	2.56
Justicia	**Justicia A** **Justicia B**	2.26
Kamalamule	**Kildare A** **Kildare B** **Kildare C**	2.48
Khaya Lami	**Khaya Lami**	4.33
Lillydale A	**Lillydale A**	3.25
Lillydale B	**Lillydale B**	1.29
Newington B	**Newington B**	2.94
Newington C	**Newington C**	5.43
Rholane	**Rholane**	5.68
Somerset	**Somerset A** **Somerset B**	2.70
Xanthia	**Xanthia**	4.06

Table 6.3: Prevalence of *active convulsive epilepsy* in study village with Health Care Facilities, Agincourt 2008

Study Village		Health Care Facility	Prevalence (per 1000)
Agincourt	**1**	Agincourt Health Centre	2.90
Lillydale A	**11**	Lillydale Clinic Bhubezi Clinic	3.25
Cunningmore B	**3**	Cunningmore Clinic	2.92
Kildare A	**9**	Kildare Clinic	2.78
Belfast	**23**	Belfast Clinic	3.27
Xanthia	**16**	Xanthia Clinic	4.06
Justicia A	**8**	Justicia Clinic	2.14

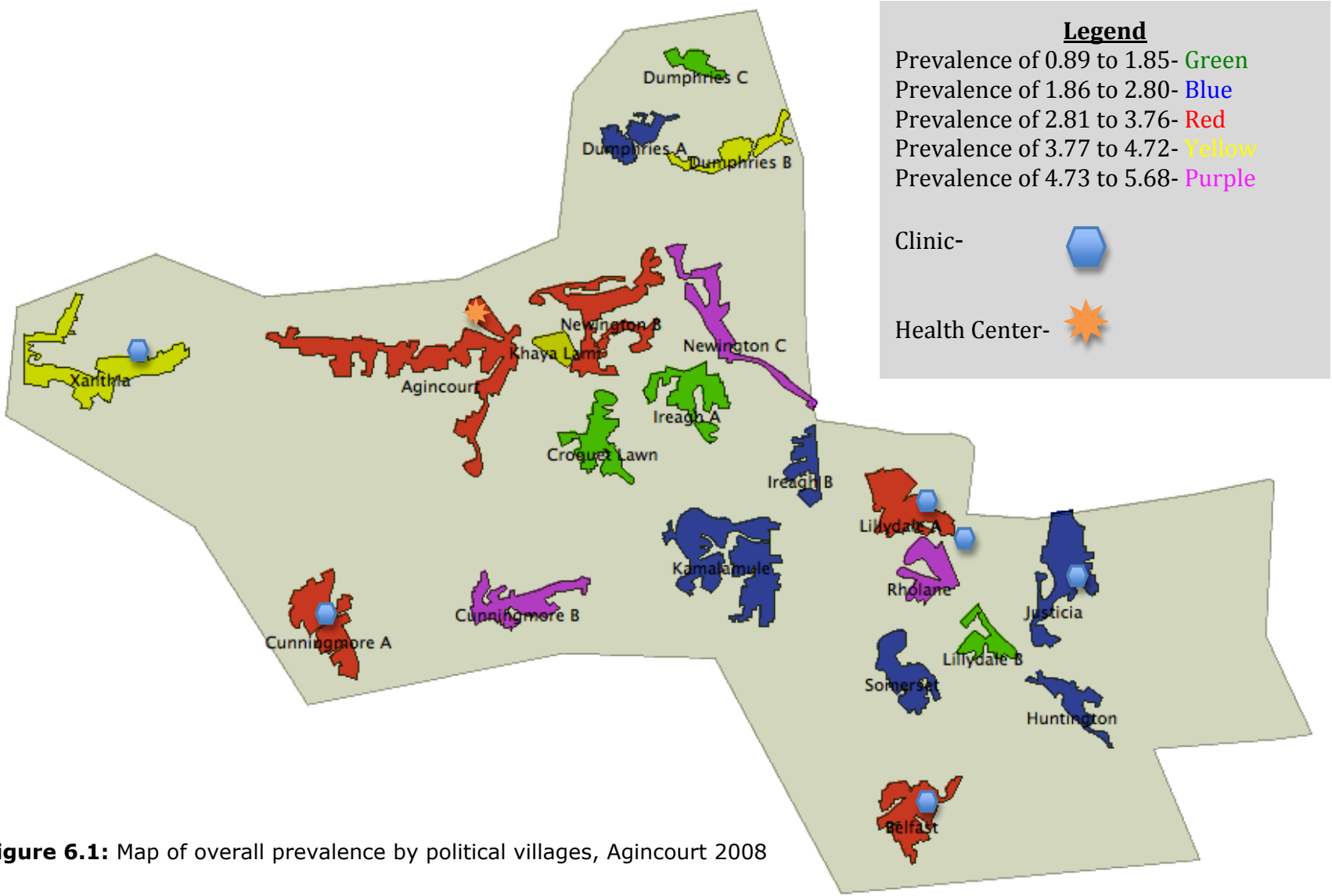


Figure 6.1: Map of overall prevalence by political villages, Agincourt 2008

Household Heterogeneity

Examining prevalence at a household level highlights some clustering. *Table 6.4* presents the number of households experiencing more than one case of *active convulsive epilepsy*. Six households reported having two occupants with *active convulsive epilepsy*, while one household reported have three occupants with *active convulsive epilepsy*.

Table 6.4: Number of individuals diagnosed with *active convulsive epilepsy* by household, Agincourt 2008

Number of ACE in household	n
One	230
Two	6
Three	1

6.4 Discussion

The results presented in this chapter suggest a heterogeneous distribution of the prevalence of epilepsy across the villages that make up Agincourt Health and Socio-demographic Surveillance Site. While this heterogeneity is observed, the underlying reason for these differences is unknown, though several hypotheses emerge.

Under-reporting of Cases

As previously discussed in *Chapter Five*, we suspect an under-reporting of cases of *active convulsive epilepsy* possibly due to methodological issues or social stigma. Under-reporting may have occurred at household levels or village levels resulting in the observed heterogeneous distribution of epilepsy. Differences in response rates and awareness of epilepsy have been highlighted as possible causes for heterogeneity in another sub-Saharan African study (Edwards et al. 2008). One future avenue of research would be to examine

response rates for *Stage One* and *Stage Two* for each village. Underestimation of prevalence because of non-ascertainment of all the cases in large population-based studies has been shown to be a possible issue in a recent review article (Preux & Druet-Cabanac 2005).

Familial Clustering

The heterogeneity observed within the Agincourt HDSS may in fact represent the true distribution of epilepsy within the study site and may arise from either familial clustering or exposure to a common risk factor. With seven of households experiencing two or more individuals suffering from *active convulsive epilepsy*, it is probable that familial clustering does contribute to the heterogeneity of the distribution of epilepsy; however, the exact contribution is unknown. Further studies exploring the heritability of epilepsy and a genetic mapping of families with people suffering from epilepsy would allow for researchers to understand the true burden of epilepsy caused by consanguinity, though as suggested elsewhere, it is probable that genetic interactions with environmental factors is a significant probability (Goudsmit et al. 1983). *Chapter Seven* will build upon this analysis by examining consanguinity as a possible risk factor for developing *active convulsive epilepsy*.

Exposure to Similar Environmental Risk Factors

A further explanation for the observed heterogeneous distribution of epilepsy would be exposure to similar environmental risk factors at the village level, causing some villages to have a greater burden of epilepsy than other villages, which would result in case clustering as suggested elsewhere (Edwards et al. 2008). A further study mapping environmental risk factors over the prevalence of epilepsy may shed light on whether environmental risk factors are responsible for the observed heterogeneity.

Access to Resources

A final possible reason for the observed distribution could be a result of the location of resources, such as a clinic or health center. Though, as reported in the analysis, villages with a clinic or health center were not found to have significant prevalence levels- either high or low. Our results concur with those of a study done in Kilifi, Kenya, which found no prevalence gradient surrounding the district hospital, even though it had been shown that people living closer to the hospital were treated more frequently when compared with those living further away (Edwards et al. 2008; Schellenberg et al. 1998). A future study comparing whether an individual suffers from epilepsy and the distance, by road, to the nearest clinic, health center, or hospital may shed light on whether health care location impacts an individuals choice of household location. Other studies mapping socioeconomic status or natural resources may shed further light on the underlying issues resulting in the observed heterogeneity.

6.4.1 Conclusion

While this chapter was not a highly technical geo-spatial analysis of the burden of epilepsy in rural South Africa, it does provide a strong foundation for further studies geared at exploring the exact cause of the observed heterogeneity- whether it represents the true distribution of epilepsy or whether, due to methodological or social constraints, the observed heterogeneity is in fact caused by bias. Mapping of risk factors (discussed in *Chapter Seven*) would enable researchers to determine the geographic distribution of risk factors and suggest possible etiology by comparing risk factor distribution with prevalence distribution. Further studies on the heritability would help researchers to elucidate the true impact of genetics on the prevalence of epilepsy in the Agincourt study site.

Chapter Seven

Identifying the Risk Factors for Epilepsy in the Agincourt Health and Demographic Surveillance System

7.1 Introduction

Epilepsy is not a single disease, but rather conditions with different causes and outcomes that may express themselves solely by the recurrence of epileptic seizures (Sander & Shorvon 1996). While there are numerous potential causes of epilepsy, often it is difficult to establish the temporality of events. As such, in attempting to ascertain the etiology of *the epilepsies,* physicians and scientists are faced with the enormous task of unraveling the, oftentimes, intricate interactions that together result in the outward manifestation of seizures, with two or more seizures defining epilepsy. It is essential to maintain a broad perspective- realizing that multiple, often intersecting and diverse factors, can summarily result in the complex syndrome known as epilepsy. This chapter identifies possible risk factors in the Agincourt cohort of people with epilepsy by performing bivariate and multivariate analysis on data collected as part of the SEEDS epilepsy study in Agincourt. The chapter concludes by discussing ways of reducing these risk factors with targeted interventions.

7.2 Methods used in the Modeling

7.2.1 Variables selected for analysis

Variables selected for analysis were based on a thorough literature review during the writing of the protocol. Events or conditions previously shown to be risk factors for epilepsy or seizures were included in the analysis. The variable include sex, location of birth, family history of non-febrile seizures, history of febrile seizures, head trauma, history of consuming cassava, pork, soil, dog or cats within the dwelling, history and length of alcohol consumption, and skull shape. Additionally, within the under-18 years analysis, mother's marital status and mother's education level were also examined.

7.2.2 Univariate Analysis

Each variable is examined individually, excluding missing values, with logistic regression then being performed to calculate Odds Ratio (OR). Binary variables were coded 0 and 1 with 0 representing the event of less risk. For example, in the case of head injury, having a previous head injury would be coded as 1 while not experiencing a previous head injury would be coded as 0 as head injury has been documented as a risk factor for epilepsy (Adeloye 1976).

Categorical variables were coded beginning with 0 (again representing the least risk) and continuing with positive integers (1,2,3…). When the univariate analysis was performed the Odds Ratio of the least risk event was set as 1.

The single continuous variable (length of alcohol consumption) was recoded as a categorical variable in four discrete categories (1-5 years, 6-10 years, 11-20 years, and 20+ years). This re-categorization was performed due to the small number of observations as a continuous

variable. The temporal demarcations were chosen primarily due to distribution of the observations.

7.2.3 Multivariate Analysis

A stepwise, multivariate regression was performed beginning by examining the effects of age and sex and adding and subtracting additional socio-demographic and clinical variables (inclusion $p<0.20$ and exclusion $p>0.20$). As controls were age-matched with cases, the reported Odds Ratios were adjusted by age and thus the age variable was dropped due to the age-adjustment. P-values between 0.000 and 0.050 are considered significant.

Variables ascertained in individuals under the age of 18 were examined in a separate multivariate model, since the information was obtained from the parents.

7.2.4 Tests for fit

A goodness of fit test was performed on the multivariate models in order examine the Pearson's chi-squared value and examined the theoretical versus the actual distribution of the data. This was achieved by using the *estat gof* command found in STATA 10.

7.3 Results

7.3.1 Univariate Analysis

Univariate analysis was performed on a number of variables, with 15 variables found to have a p-value less than or equal to 0.20. All of the variables examined are shown in Tables 7.1, 7.2 and 7.3, with variables having a p-value less than or equal to 0.20 being highlighted in

bold text. The Odds Ratios seen in the age category cannot be interpreted due to the fact that controls were age-matched (by age-band) to cases, which consequently influenced the Odds Ratios when age is examined.

In the univariate analysis, the Odds Ratio of five variables could not be calculated due to zero exposure of the variable in the control arm of the population. Instead of equally inflating each cell of the 2 x 2 table, three asterisks in *Table 7.1* represent variables that are significant, but Odds Ratios cannot be calculated. These variables are someone in the family with a past history of seizures, mother with seizures, history of febrile seizures, and skull shape. While the Odds Ratios could not be calculated, each variable is considered significant. The inability to calculate the Odds Ratio highlights the relatively small case number in the case-control study, which is further discussion in *Limitations* Section (*Section 7.4.1*) of this chapter.

Alcohol consumption, while not typically considered a risk factor, was evaluated with the results shown in *Table 7.2*.[‡] A history of alcohol consumption was not significant, while consuming alcohol for between 6 and 10 years could be included in the multivariate analysis (OR= 0.39, p-value 0.175) based on the methodology set out previously.

Table 7.3 examines the p-values of variables only asked of cases and controls under the age of 18 and primarily examines the affects of mother's marital status and education, finding that a separated mother and a mother who attended formal education (and more specifically

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‡ Withdrawal from alcohol causes seizures, but is not considered to be epilepsy in the definition presently being used. However, the current analysis may shed light on alcohol and whether, because of possible withdrawal seizures, there is a higher risk for developing epilepsy- based on the assumption that the longer you drink alcohol, the greater the likelihood of experiencing withdrawal seizures.

received a high-school education) are possible risk factors that should be included in the multivariate model.

Table 7.1: Age-adjusted Odds Ratios for Socio-demographic and historical possible associated factors, Agincourt 2008

Variable of Interest	*Controls (n=265)*	Cases (n=292)	Odds Ratio (95% CI)*	p-value
Age**				
0-5	13	18	1	.
6-12	48	34	0.51 (0.22 to 1.18)	0.117
13-18	30	38	0.91(0.39 to 2.16)	0.839
19-28	52	58	0.81 (0.36 to 1.80)	0.599
29-49	81	99	0.88 (0.41 to 191)	0.751
50+	41	45	0.79 (0.35 to 1.82)	0.583
Sex				
Female	178	142	1	.
Male	87	150	**2.31(1.62 to 3.29)**	**>0.001**
Location of Birth				
Hospital	10	17	1	
Clinic	144	110	0.64 (0.28 to 1.50)	0.311
Home	97	58	0.67 (0.27 to 1.68)	0.399
Unknown	8	3	1.17 (0.24 to 5.67)	0.844
Birth Events				
Normal Delivery	165	246	1	.
Abnormal Delivery	8	19	**2.28 (0.94 to 5.54)**	**0.068**
No problems after delivery	178	249	1	**.**
Problems after delivery	2	14	**6.08 (1.35- to 7.48)**	**0.019**
Family History of Non-febrile Seizures				
Someone in family with seizure	11	41	**3.69 (1.85 to 7.34)**	**>0.001**
Someone in family with past history of seizure	0	12	***	0.001
Mother with Seizures	0	3	***	0.143
Father with Seizures	1	2	1.68 (0.15 to 18.69)	0.670
Sibling with Seizure	2	14	**6.60 (1.48 to 29.38)**	**0.013**
History of Febrile Seizure	0	3	***	0.099
Head Trauma				
History of Head Injury	18	31	**1.62 (0.87 to 2.98)**	**0.124**
Loss of conciousness with head injury	5	25	**2.54 (0.82 to 7.92)**	**0.107**
Sociodemographic and Clinical				
Skull Shape	0	23	***	>0.001
History of Eating Cassava	157	190	**1.27 (0.89 to 1.80)**	**0.181**
History of Eating Pork	69	59	**0.75 (0.51 to 1.11)**	**0.149**
History of Eating Soil	19	18	0.82 (0.42 to 1.61)	0.563
History of Dogs in dwelling	54	68	1.16 (0.77 to 1.74)	0.475
History of Cats in dwelling	22	16	**0.63 (0.32 to 1.23)**	**0.175**

*/** Odd Ratios calculatedby age are non-intpretable because cases and controls were age-matched. Numbers are presented to show matching.
*** indicates an Odds Ratio could not be calculated due to zero exposure in the control population
Bold highlights variables that are considered significant (p<0.200)

Table 7.2: Age-adjusted alcohol consumption and length of alcohol consumption as possible associated factors for *active convulsive epilepsy*, Agincourt 2008

Variable of Interest	*Controls*	Cases	Odds Ratio (95% CI)	p-value
History of Alcohol Consumption	29	34	1.03 (0.60 to 1.78)	0.913
Length of Alcohol Consumption				
1-5 years	9	12	1	.
6-10 years	11	7	0.39 (0.10 to 1.52)	**0.175**
11-20 years	9	10	0.45 (0.11 to 1.78)	0.255
21+ years	0	4	*	0.993

* indicates an Odds Ratio could not be calculated due to zero exposure in the control population

Table 7.3: Age-adjusted Odds Ratios for mother's education and marital status in individuals ages 18 years or younger, Agincourt 2008

Categorical Variable of Interest	*Controls*	Cases	Odds Ratio (95% CI)*	p-value
Mother's Marital Status				
Married	35	31	1	.
Never Married	25	32	1.29 (0.63 to 2.67)	0.486
Divorced	3	4	1.37 (0.28 to 6.67)	0.693
Separated	7	1	**0.16(0.02 to 1.39)**	**0.097**
Widowed	6	6	1.04 (0.30 to 3.65)	0.948
Did mother attend formal education	16	6	**0.34 (0.12 to 0.96)**	**0.041**
Mother's Education Level				
Primary Education incomplete	8	5	0.58 (0.09 to 3.85)	0.575
Primary Education	18	22	1.09 (0.21 to 5.68)	0.91
Secondary Education	16	32	1.51 (0.29 to 7.79)	0.621
High-School/A-level	13	3	**0.17 (0.02 to 1.22)**	**0.079**
Post-secondary Education	3	4	1	.

* Odds Ratios are adjusted by age due to age-matched controls.
Bold highlights variables that are considered significant (p<0.200)

7.3.2 Multivariate Modeling

Variables that exhibited a p-value less than 0.20 and have documented causal pathways were included in the multivariate analysis. In the final multivariate model, sex and familial history of seizures were found to be independent significant risk factors (p-values <0.05) with Odds Ratios ranging from 2.09 and 3.31, respectively. Previous seizures in the family had an Odds

Ratio of 3.31, while male sex contributed with an Odds Ratio of 2.09. *Table 7.4* provides the Odds Ratio, Confidence Intervals, and p-values expressed in the final multivariate model. Abnormal delivery and problems after delivery, though not statistically significant, were kept in the model as it has been shown to be a significant factor within the literature (with problems after delivery found significant in individuals under the age of eighteen).

In examining the effect of the mother's marital status and educational status in individuals under 18 (cases: n=66, controls: n=58), problems after delivery and a history of head injury were found to be significant risk factors, while a mother's education appeared to be protective if the mother had not completed primary education or she had completed secondary education.

Table 7.4: Possible Risk Factors of *active convulsive epilepsy* in age-adjusted multivariate modeling for adults and children, Agincourt 2008

Variable of Interest	Odds Ratio (95% CI)*	p-value
Sex	2.09 (1.38 to 3.18)	0.001
Abnormal Delivery	2.17 (1.11 to 23.49)	0.097
Problems after delivery	5.10 (1.11 to 23.49)	0.051
Someone in family with seizure	3.31 (1.48 to 7.41)	0.002

* Odds Ratios are adjusted by age due to age-matched controls.

Table 7.5: Possible Risk Factors of *active convulsive epilepsy* in age-adjusted multivariate modeling for children, Agincourt 2008

Variable of Interest	Odds Ratio (95% CI)*	p-value
Problems after delivery	20.53 (1.49 to 282)	0.024
History of Head Injury	11.72 (1.27 to 108.46)	0.030
Mother's Education Level		
Primary Education incomplete	**0.11 (0.01 to 0.90)**	**0.040**
Primary Education	1.25 (0.24 to 6.54)	0.785
Secondary Education	**0.10 (0.01 to 0.61)**	**0.013**
High-School/A-level	1.78 (0.71 to 4.46)	0.214
Post-secondary Education	1	.

* Odds Ratios are adjusted by age due to age-matched controls.

7.4 Discussion

The results from this multivariate analysis of risk factors further add to the literature in suggesting a number of possible risk factors for the development of epilepsy in sub-Saharan Africa.

7.4.1 Sex

One variable identified as a possible risk factor, though not stated in the literature is sex. The current study suggests that males in rural South Africa are at greater risk for developing epilepsy than females. While studies from sub-Saharan Africa have shown a higher prevalence of epilepsy in males than females (Preux & Druet-Cabanac 2005), no study has suggested sex as a possible risk factor.

We hypothesize the sex is not the underlying risk factor, but that being male puts the individual at a higher risk for other risk factors, such as head trauma. It might also be possible that certain X-linked epilepsy disorders may manifest themselves more frequently in males. Furthermore, it is possible that females may be more hidden than males.

7.4.2 Peri-natal events

Problems after delivery have been shown to be a significant risk factor in this study (OR=4.69) while problems with delivery have been shown to be statistically insignificant (OR=2.24, p-value=0.097). This is supported by studies from Tanzania and Burundi, where researchers found an increased risk of developing epilepsy to be 4.5 and 1.9 times, respectively, after experiencing peri-natal complications. (Matuja et al. 2001; Nsengiyumva et al. 2003). While where the child was born was not a significant variable in the univariate analysis, South Africa may be an anomaly when compared to the rest of sub-Saharan Africa

where most children are born at home without professional medical help (Diop et al. 2003). Furthermore, adverse peri-natal events as a risk factor for epilepsy highlight the importance of quality mother and child health care in South Africa.

7.4.3 Family history of epilepsy

A family history of epilepsy appears to be a more significant risk factor for developing epilepsy in the developing world then in the developed world. Family history of epilepsy has been shown to be a significant risk factor for developing epilepsy in at least three studies from sub-Saharan Africa (Edwards et al. 2008; Matuja et al. 2001; Nsengiyumva et al. 2003) and results from this study show that family history of fits are a significant risk factor (OR=3.31) in rural South Africa as well.

While some studies were able to further specify the relationship between family members experiencing fits, the numbers from the current study proved too small to explore such a relationship. From the univariate analysis it is apparent that having a sibling with epilepsy is a significant risk factor; however, this significance is not found in the multivariate model.

One interesting line of future research would be to understand the etiology of the familial risk, whether it is because of genetics or because of common exposure to an environmental risk factor. As in much of rural Africa, families often reside in close proximity to one another, thereby possibly exposing themselves to a common environmental risk factor. Whether it is this general exposure that causes epilepsy or a truly genetic factor, or a combination of the two, sub-Saharan Africa can make enormous contributions to the genetic research of epilepsy due to the large, proximal family samples (Farnarier & Genton 1996).

7.4.4 History of Head Injury

Head injury has been shown to be a significant risk factor for epilepsy (OR=13.0) in a study from Nigeria (Ogunniyi & Osuntokun 1987) and it is likely that head injury accompanied by loss of consciousness is a risk factor in rural South Africa as well. However, due to the small number of cases with past head injury with loss of consciousness the multivariate analysis in the adult (older than 18 years) model was unable to show head injury with accompanied loss of consciousness as a significant risk factor. However, the under-18 year old model (*Table 7.5*) head injury was shown to be a significant risk factor (OR=11.7).

7.4.5 Mother's level of education

The person with epilepsy's mother's education level was protective when the mother had either not completed formal primary school (OR=0.11) or when she had completed secondary school (OR=0.10). The latter may be a marker for the socio-economic status of the mother: a higher level of schooling would allow the mother to seek a better job, which in turn would allow her better medical care. A mother with an incomplete primary education, in turn, may have more time for her children, due to lack of work, and may prevent exposure to various risk factors.

While this study shows both a higher level of education and little to no education as significant protective factors, this is not supported by previous literature and appears at least in part contradictory and may simply be a chance finding.

7.4.6 Additional Risk Factors and Future Studies

While blood samples were taken as part of the SEEDS study, the analysis has not been completed. As a result, one further facet to the risk factor analysis presented in this

dissertation would be to include the findings of the blood analysis of exposure to certain parasites, including toxocara, toxoplasmosis, and cysticercosis and infections such as HIV, all of which have been shown to be significant risk factors for developing epilepsy. However, the lack of exposure to cats, dogs, and pigs suggest that these may not be risk factors in this community.

7.5 Limitations

As with any epidemiological study, limitations are inherent and while every attempt was made during the planning and implementation of the case control study, limitations did appear. One obvious limitation is the lower number of controls than of cases. This could result in possible methodological bias and low power to detect significant variations in exposure variables among cases and controls. As originally calculated in the study protocol, at a prevalence of 4 per 1,000, 240 cases with a one-to-one case-control ratio would allow 80 percent power to detect an Odds Ratio at the 5 percent significance level for any risk factor with a frequency of at least 5 percent in the controls (SEEDS Protocol 2008). Practically, this limitation manifested itself during the univariate analysis when the calculation of Odds Ratios for a number of variables was impossible due to zero observations of exposed controls. At least one-to-one matching of cases to controls could have addressed the limitation.

A second inherent limitation was the difficulty in ascertaining the temporality of events in certain supposed risk factors and the depth to which these possible risk factors were explored due to resources available. These limitations have been discussed previously in literature

examining epilepsy in the developing world (Sander & Shorvon 1996; Shorvon & Farmer 1988). Due to poor medical record keeping and individual recall bias, it is at times difficult to ascertain whether a traumatic cerebral event or seizures began first. In exposure to certain variables, such as helminths and other infections, it is impossible to establish a timeline, unless the time of infection was marked with outwardly manifested symptoms and diagnosed at that time. Most studies, including the present study, are designed as retrospective rather than prospective case-control studies with the exposure variable being measured at the time of the study, with no suggestion of whether the exposure occurred before the onset of epilepsy.

One interesting finding to highlight in the current research is the extremely low number of individuals with a history of febrile convulsions. One possible limitation that this low prevalence may highlight is the difficulty in translating the term 'febrile convulsion' into the local vernacular. A common term that is used within the Agincourt HDSS, and quite possibly throughout Africa, is the term 'hot body'. Whether this indicates a fever due to acute infection or hot body due to the arid climate is difficult to distinguish, and hence could result in an under-reporting of febrile convulsions.

While limitations exist in the current study, this study is the first community-based epilepsy study that has investigated possible risk factors for developing *active convulsive epilepsy* in rural South Africa. It adds to the meager, yet growing, body of work from sub-Saharan Africa exploring epilepsy an often debilitating chronic condition that can be treated effectively through regular doses of anti-epileptic drugs. Future studies will build upon this work by focusing on whether well-placed interventions can reduce the burden of certain risk factors as well as addressing how the current health care system deals with this chronic condition. The

next chapter (*Chapter Eight*) summarizes the overall findings of this dissertation and concludes by examining a number of research avenues that build upon this current work.

Chapter Eight

Discussion of Overall Findings

8.1 General Discussion

In concluding this dissertation it is fitting to ask, 'Where does the current study fit within the global body of epilepsy research and literature- what has been learned from this study and what still needs to be understood about epilepsy in rural South Africa?' This dissertation, which uses data from the Agincourt HDSS SEEDS study, has shown a relatively large, possibly underreported burden of epilepsy in rural South Africa. While an adjusted prevalence of 3.25 per 1,000 individuals was found in the three-stage study, a built-in validation tool found an adjusted prevalence of more than twice that (7.72 per 1,000), which is likely to be the more accurate estimate. This finding suggests that methodological or social issues may play a factor in population-based studies aimed at determining the prevalence of *active convulsive epilepsy*. Furthermore, it confirms previous research, which suggests that studies aimed at examining epilepsy need to take into consideration underreporting (Preux & Druet-Cabanac 2005), even with sensitive and piloted screening tools.

This work went further in examining the distribution of epilepsy, finding a significant heterogeneity across a number of villages. A number of households within the Agincourt HDSS field site experienced more than one individual suffering from similar epileptic fits. These findings suggest a possible genetic component, though genetic studies would be necessary to confirm this hypothesis. It is also possible that an environmental risk factor or factors may be responsible for the uneven distribution of the burden of epilepsy. Our findings

concur with a similar study completed in Kenya and further add to the body of evidence suggesting that the burden of epilepsy is not homogeneously distributed across small areas (Edwards et al. 2008). Research aimed at understanding the interplay between environmental and genetic risk factors in rural South Africa remains to be undertaken.

The role of several socio-demographic and clinical risk factors for epilepsy was examined. Our findings support research from other areas of the developing world. A family history of seizure, head injury, and birth related injury were all found to be risk factors in a multivariate model. Interestingly, mother's education level had previously not been found to be a risk factor thus supporting the importance of the mother in the development and well-being of the child. A mother with more education may indicate access to better health facilities, resulting in less perinatal trauma, a risk factor for developing epilepsy. Further markers for a mother's socio-economic status could be added in future studies to establish the mother's affect on her child's risk of developing epilepsy. Also, examining whether a mother's education status is an indicator for better employment would help to confirm the current hypothesis.

This dissertation has expanded the current body of epilepsy research. Though, as with all research, more questions have arisen than have been answered. What follows below is a brief discussion on additional avenues of epilepsy research that might allow researchers to advance the understanding of epilepsy in rural South Africa and the African continent as a whole.

8.2 Future Directions

8.2.1 Treatment Gap

The treatment gap of epilepsy is the number of people with *active epilepsy* not on treatment (including both diagnostic and therapeutic deficit) or on inadequate treatment as a percentage of the total number of people with *active epilepsy* (Meinardi et al. 2001; Kale 2002). A recent systematic review of epilepsy treatment gap in developing countries found an overall treatment gap of 56 percent (95% CI 31-100) (Mbuba, Ngugi, Newton, & Carter 2008). Future studies can begin to understand the treatment gap of epilepsy in rural South Africa, where anti-epileptic drugs are free in public health settings. Studies aimed at determining where obstacles in seeking health care are may bring to light areas in which interventions can dramatically improve the number of individuals diagnosed with epilepsy and on adequate treatment, but first, the treatment gap must be assessed.

8.2.2 Co-morbidities with Epilepsy

One observation to arise from this current study, and supported by literature from elsewhere (Torta & Keller 1999), is the fact that people with epilepsy also suffer from a large range of co-morbidities. Numerous individuals diagnosed with *active convulsive epilepsy* in the current study also suffered from cerebral palsy. Alcohol dependency also seemed prevalent in those identified with epilepsy. Psychosocial co-morbidities have also been shown to be significantly higher in those suffering from epilepsy.

In order to begin to understand the health care needs of individuals with epilepsy, it is essential that the health care service provide support for co-morbidities too; as often these co-morbidities can be more severe than the epilepsy itself (Torta & Keller 1999). Specifically,

psychosocial disorders may coexist with epilepsy (Boro & Haut 2003). A subsequent study might seek to identify further medical and psychological needs of those suffering from epilepsy in order to ascertain a clearer picture of the burden (both direct and indirect) of epilepsy.

8.2.3 Economic Impact of Epilepsy

The World Bank estimates that 90 percent of the financial burden of epilepsy is carried by developing countries (World Bank Report 1993). Epilepsy has a financial impact on the individual patient, the patient's family, the health care system, and society as a whole. Economic studies examining the costs associated with epilepsy have been undertaken in a number of developed countries (Cockerell et al. 1994; Begley et al. 2000), but only one published study from a developing country (Thomas et al. 2001). Using the data regarding the burden of epilepsy from the current study, efforts are currently underway to assess the economic consequences of living with epilepsy in the Agincourt HDSS. Findings from this study would significantly contribute to the body of literature exploring the economic impact of epilepsy in developing countries.

8.2.4 Human Immunodeficiency Virus (HIV) and Epilepsy

In examining any disease or syndrome it is important to evaluate the context in which the study is taking place. The African continent and sub-Saharan Africa in particular is currently being ravaged by an HIV/AIDS pandemic. Recent indicators from South African suggest that 29.4 percent of pregnant women between the ages of 15 and 49 are HIV-positive, with an estimated prevalence of 17.8 percent in the general population (Department Of Health 2010). These figures highlight the fact that HIV is, and will continue to be, a serious health issue for years to come.

With as many as 70 percent of HIV-positive individuals experiencing some sort of clinically relevant neurological co-morbidity during the duration of their illness and 20 percent of these individuals presenting with epilepsy, it is essential that research examining HIV and epilepsy be undertaken now to explore the interaction of these two diseases (Bhigjee 2005).

8.2.5 Intra-African Comparison

One significant strength of the SEEDS study is the fact that it is being concurrently carried out, using the same methodology and definitions, at five sites throughout sub-Saharan Africa. As a result, inter-country studies can be easily undertaken to compare such variables as prevalence and risk factors. Furthermore, combining the data from the five sites will provide far greater numbers, resulting in smaller confidence intervals and more accurate estimates of prevalence and risk factors for epilepsy in sub-Saharan Africa. Any further research can build upon these strengths by embarking on comparative studies across sites. For example, a study aimed at identifying cost-effective interventions could examine the effect of different health care systems on the various interventions.

Furthermore, the SEEDS study has created five sub-Saharan African cohorts of people with *active convulsive epilepsy* as well as a network of researchers and physicians keen on exploring the impact of epilepsy across sub-Saharan Africa. The SEEDS study has taken the first steps in 'combating stigma, restoring dignity, and reducing the treatment gap' by identifying the burden and possible risk factors. Yet SEEDS has only laid the foundation for future work that will continue to examine the syndrome of epilepsy.

8.3 Conclusion

This dissertation has attempted to 'bring epilepsy out of the shadows', by identifying epilepsy as a significant burden of disease in rural South Africa. Beyond identifying epilepsy as a significant burden, this dissertation has explored the methodology used in epilepsy prevalence studies, examined the heterogeneous geographic distribution of the prevalence of epilepsy within the Agincourt HDSS, and also identified family history of seizures and birth-related injury as possible risk factors for developing epilepsy in the rural South African context. This work is however a prelude to future research that will seek to further understand this debilitating, yet often controllable condition. In conclusion, this dissertation serves as a foundation for future work in the hopes of one day implementing cost-effective, population-based interventions aimed at reducing the burden of epilepsy in rural South Africa and ultimately, the developing world.

APPENDIX 1: Diagram of SEEDS Study

Stage One

Screening of Agincourt Health & Socio-demographic Surveillance System

Entire population of Agincourt Health and Socio-Demographic Surveillance Site (AHDSS) screened during 2008 census using single question (*Stage One* question discussed in *Chapter Four*)

Stage Two

Screening of *Stage One* positives

Individuals screened positive during *Stage One* are interviewed at their homes by SEEDS fieldworkers to ascertain *active convulsive epilepsy*[1].

Population Sample surveyed

From the entire AHDSS population, a population sample of 4500 individuals is selected with these individuals being visited at their homes by SEEDS fieldworkers. Those having convulsions are referred to *Stage Three.*

Stage Three

***Active Convulsive Epilepsy* confirmed**

Individuals who may have *active convulsive epilepsy* (ACE) are referred to the clinic for a clinical history and examination. If a medical diagnosis of ACE is made, an EEG is performed and blood is drawn.

Selection of age-matched controls

Each ACE case is age-matched with a control selected from the *Stage Two* population sample. A clinical history and examination is performed on each control and blood is drawn.

Bloods collected for analysis of exposure to environmental and infections risk factors

Blood drawn from both cases and controls will be tested for a number of infectious diseases including: cysticercosis, toxocara, toxoplasmosis, onchocerciasis malaria and HIV. (Results from these tests do not form any part of this dissertation.)

[1]*Active convulsive epilepsy* is defined as condition characterized by two or more epileptic seizures, one occurring within the last 12 months, with clonic movement, unprovoked by any immediate cause.

APPENDIX 2: HREC/Wits Ethical Approval for MSc (Med) by research

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mr Ryan G Wagner

CLEARANCE CERTIFICATE	**M090833**
PROJECT	Mavabyi ya ku wa: The Prevalence of an Risk Factors for Epilepsy in a Rural South African Surveillance Site
INVESTIGATORS	Mr Ryan G Wagner.
DEPARTMENT	School of Public Health
DATE CONSIDERED	09.08.28
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 2009/09/21 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

UNIVERSITY OF THE WITWATERSRAND
PROF AJ WOODIWISS
Co - Chair
2009 -09- 21
HREC (Medical)
JOHANNESBURG

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : M Connor/R Twine

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

.....

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