Clustering of child and adult mortality during pre and post ART rollout eras at Agincourt and Dikgale Health and Demographic Surveillance Systems in South Africa

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A Project Submitted in Partial Fulfilment of the Requirements for the Master of Science Degree in Epidemiology in the field of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences

University of the Witwatersrand, Johannesburg

October 2013

DECLARATION

I, Sikhuphukile Gillian Ndebele declare that this research report is my own work. It is being submitted for the Master of Science degree in Epidemiology in the field of Epidemiology and Biostatistics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature

…….

Full Name: Sikhuphukile Gillian Ndebele

Date: 29 October 2013

Dedicated to my sister, Nqobulwazi "Muhlekazi" Phillippa Ndebele. May your soul rest in peace…

ABSTRACT

Background: The effect of anti-retroviral therapy (ART) rollout can be measured in a number of ways including treatment coverage, behaviour change and the emergence of resistance. However, changes in population mortality are undoubtedly the most important measurable effect.

Objectives: To describe trends in child and adult all-cause mortality versus HIV/AIDS related mortality before and after ART rollout; and to identify significant clusters of child and adult all-cause mortality versus HIV/AIDS related mortality in space-time, during pre and post ART rollout eras at Agincourt and Dikgale health and demographic surveillance systems (HDSSs) in South Africa.

Design: Mortality data were extracted from both the Agincourt and Dikgale HDSSs for the period 1996–2010. Mortality rates by age group, year and village were calculated assuming a Poisson distribution and using precise person-years as the denominator. The Kulldorff spatial scan statistic was used to test for clusters of age group all-cause and HIV-related mortality both in space and time. Clusters were mapped using Quantum geographic information systems (GIS) software.

Results: Both HIV-related and all-cause mortality decreased gradually over the years after the introduction of ART in 2007 for the two HDSS sites. Several statistically significant clusters of higher all-cause and HIV-related mortality were identified both in space and time. In the Agincourt HDSS, specific areas were consistently identified as high risk areas; namely, the east/south-east corner and upper central to west regions, pre ART. In the Dikgale HDSS, no significant clusters were identified using the spatial only analysis but one significant cluster, located towards the north of the Dikgale HDSS site, was identified using the space-time scanning, post ART. In Agincourt, no significant clusters of mortality were detected after the introduction of ART whereas in Dikgale, a significant cluster for all-cause mortality in the under-five age group was detected for the years after the introduction of ART.

Conclusion: This work revealed the existence of spatio-temporal clusters of both child and adult mortality at the Agincourt and Dikgale HDSSs and that the introduction of ART had a substantial influence in reducing both HIV-related and all-cause mortality in rural South Africa. There is need though to take into account socio-demographic characteristics so as to determine fundamental risk factors influencing these spatio-temporal HIV-related and all-cause mortality patterns.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisors, Professor Benn Sartorius and Professor Osman A. Sankoh, for their tireless supervision, encouragement, patience and strive for excellence. They have been a source of inspiration to me. Profound gratitude goes to the Wits School of Public Health, headed by Professor Laetitia Rispel, for funding my studies and having the confidence that I will make it this far. I have been equally inspired by the course co-ordinator, Dr. Peter Nyasulu and the Head of Department for Epidemiology and Biostatistics, Professor Tobias Chirwa, who were so supportive of me from the onset of my studies. I also thank all members of the Department of Epidemiology and Biostatistics for providing such a pleasant environment in which to study and empowering me with such great knowledge. I wish to especially thank the Agincourt and Dikgale HDSS sites for availing their data for this research project. Gratitude is also extended to the administration staff, Mrs Angeline Zwane, for her unwavering support throughout the course of the 18 months. I also thank my fellow colleagues for their friendship and support. I am grateful to my family for always believing in me.

Lastly but not least, glory to the Almighty God for His great love and showering me with lots of blessings.

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LIST OF KEY ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CADR	Crude All-cause Death Rate
CHIVDR	Crude HIV-related Death Rate
C.I	Confidence Interval
EC	Expected Cases
GIS	Geographic Information Systems
HDSS	Health and Demographic Surveillance System
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
OC	Observed Cases
PY	Person-Years
RR	Relative Risk
TAD	Total number of All-cause Deaths
THIVD	Total number of HIV-related Deaths
VA	Verbal Autopsy

CHAPTER ONE: INTRODUCTION

1.1. Background

In 2007, the World Health Organization (WHO) estimated that as a result of the scaling up of antiretroviral combination therapy (ART) in low- and middle-income countries (LMICs), two million people living with HIV / AIDS were receiving treatment at the end of 2006, representing 28% of the estimated 7.1 million people who were in urgent need of treatment in these countries [1]. Southern Africa has approximately 34% of the world's HIV-infected people, half of whom live in South Africa [1]. In 2003, the South African government introduced ART, free at the point of use in selected public health facilities. Between 2003 and the end of 2009, approximately 1 million adults and children were enrolled onto ART. At the Agincourt and Dikgale Health and Demographic Surveillance Systems (HDSSs), ART roll out treatment began in 2007 [2].

Antiretroviral treatment considerably improves the survival of patients living with HIV / AIDS and because of its widespread introduction, there has been a substantial reduction in HIV-related adult mortality due to HIV infection [3, 4]. The effect of ART roll-out can be measured in a number of ways including; treatment coverage, behaviour change and the emergence of resistance, but eventually changes in population mortality is the most important measurable effect [5]. This study seeks to find out if there has been a change in mortality trends amongst children and adults after the ART rollout program in Agincourt and Dikgale HDSS sites in South Africa.

1.2. Statement of the problem

Lack of reliable mortality data constrains monitoring of trends in HIV/AIDS-related and other causes of death. There is need for the HIV ART program to be evaluated so as to see if it has brought any improvements to the mortality trends in South Africa particularly rural South Africa where access to health care services is a challenge. The cause of death for those who die outside of health service facilities need to be taken into consideration as it is not everyone who has access to a health service facility. Verbal autopsies (VA) then come into place to determine probable cause of death. The technique relies on clinical assessment of signs and symptoms during the terminal illness, reported retrospectively by a close caregiver of the deceased [6]. At Agincourt and Dikgale HDSSs VAs are conducted after six months (on average) following the person's death to determine probable cause.

Detailed mortality data are typically available within demographic surveillance systems and contain a wealth of detail that may be overlooked in overall analyses, and also valuable public health information. Spatial disparities may also exist within districts and sub-districts between lower administrative units such as unions or villages. Identifying spatial disparity requires population-based, up-to-date and reliable statistics on health indicators and appropriate analytical tools [7].

1.3. Justification of the study

Mortality in a population may be clustered in space and time for a variety of reasons, including socio-economics, environment and demographics. Analysing mortality clusters can therefore reveal important insights into patterns and risks of mortality in a particular setting [8]. Mortality

results are frequently collated and presented on an overall basis for relatively large populations, even for entire countries. This may conceal important small-scale variations in time and space, as well as between various population subgroups [9].

Studies have been done in both Agincourt and Dikgale, for the years 1992 – 2007 and 1996 – 2007 respectively, where they were looking at how mortality is clustered in space and time. This study seeks to update findings from these studies for the years 2009 – 2010 and then do a further assessment on the distribution of clusters of mortality before and after HIV ART rollout program in these two sites. An improved understanding of the contribution of ART to HIV/AIDS related mortality is important for scientific understanding of the dynamics of the therapy. It is also critical for policy-makers and health workers trying to respond to current and projected needs for prevention, treatment and care in local communities.

1.4. Literature review

Kolsky (1997) [10] defines clustering as a "technique of grouping records together based on their locality and connectivity within n-dimensional space." Its goal is to help understand the patterns that exist in a given data set, and reasons behind those patterns. Kolsky added that its other role is to find both heterogeneous and homogeneous groups or clusters and that these groups should be somewhat meaningful. Analysis of mortality clusters is useful as it enables to detect and monitor mortality trends in a given population and thus assist policy makers and implementers to make directed interventions targeted at a specific disease(s) and age group(s).

For instance, the study by Sartorius, et al. (2010) [11], conducted at Agincourt HDSS in South Africa, found that specific areas such as the east/southeast and upper east central regions were consistently identified as high risk areas. They also observed clusters of older adult mortality

indicating potential non-random distribution of non-communicable disease mortality. They discovered that during 1992 - 2007, the highest mortality rates were observed among children (under 5 years), 50 – 64 and 65+ (9, 19, and 46 per 1,000 person-years, respectively). A significant increase in the mortality rate over time was observed from 4.7 deaths per 1,000 person years in 1992 to 12.5 deaths per 1,000 person years in 2007. They observed that there were significant increases in trends in mortality for <5, 15 – 49, and 50 – 64 year age groups during the period 1992 – 2007. This study did not look at how the ART rollout program had influenced mortality in this area.

Again, in a study by Kanjala, et al. (2010) [9], carried out at Dikgale HDSS South Africa, they found that the overall mortality summed up to 797 deaths over 96,194 person-years observed, a crude rate of 8.2 per 1,000 person-years. They used SaTScan™ 8.0 for their space-time clustering analysis which began with a spatial-only analysis over the whole time period, allowing high and low incidence clusters with a maximum cluster size of 50% of the overall population, in which the only statistically significant cluster was one covering Ntsima and Maphoto, with a relative risk of 1.74 (p-value = 0.010). The next cluster covered Madiga and Moduane during 1996 – 1999, with a relative risk of 0.71 (p-value = 0.037). They reported on the third and final significant cluster to be the one covering Ntsima, Maphoto, Ga-Tjale and Sefateng during 2004 – 2007, with a relative risk of 1.55 (p-value = 0.040). One major limitation of this study was the relatively small size of the Dikgale site. Also, this study did not look at how the ART rollout program had influenced mortality in this area.

Besides just identifying significant clusters of mortality, this study also seeks to see if there has been any change in mortality trends before and after the ART rollout in the two sites. Several studies have been conducted to determine if there has been a change on HIV-related cause-specific mortality trends after the initiation of ART.

For instance, in a study done in rural KwaZulu-Natal (KZN) in South Africa by Herbst et al. (2009) [12], one of their interest was to compare mortality among adults before and after ART became available (2002-2003 and 2004-2006 respectively). They calculated age-standardized mortality rate ratios (SMRR) separately for males and females aged 25-49 years for all-cause mortality, HIV-related cause-mortality and non-HIV-related cause-specific mortality. They restricted their analysis to that age group as it had the highest AIDS-related burden of disease and included majority of the patients in the ART programme. They reported that in the 25-49 year age group, standardized all-cause mortality increased from 24.0 deaths per 1 000 person-years in 2000 to 33.0 deaths per 1 000 person-years in 2003 and then declined to 23.9 deaths per 1 000 person-years in 2006. Furthermore, during the same period and for the same age group, HIV-related cause-specific mortality rate increased from 19.3 deaths per 1 000 person-years in 2000 to 24.3 deaths per 1 000 person-years in 2003, and then declined to 14.6 deaths per 1 000 person-years in 2006. They concluded that there was evidence that the public-sector ART roll-out in rural South Africa had an effect on the adult population mortality with an approximate reduction of 22% and 29% in HIV-related mortality rates in women and men respectively.

Also, in a study conducted in Northern Malawi by Jahn et al. (2008) [13], they aimed to investigate mortality in a population before and after the introduction of free ART. In this study, causes of

death were established through verbal autopsies. Malawi made available free ART to more than 80 000 patients between 2004 and 2006. They found that before ART was made available in June 2005, mortality in adults (aged 15 – 59 years) was 9.8 deaths for 1,000 person-years of observation. Of which 229 of 352 (65.1%) deaths were attributed to AIDS. After the introduction of ART, they reported that overall mortality in adults had decreased by 10% from 10.2 to 8.7 deaths per 1000 person-years of observation. They further report that mortality was reduced by 35% in adults near the main road of Northern Malawi, where mortality before ART was highest (from 13.2 to 8.5 deaths per 1,000 person-years of observation before and after ART respectively). They concluded that there was a decline in population mortality shortly after the introduction of ART in their study population (rural Malawi).

Again, in study done in north-west Tanzania by Marston et al. (2012) [14], they aimed to describe the impact of ART on mortality rates among adults participating in an HIV community cohort study. They state that free ART has been made available since 2005. They used even history analysis to compare mortality rates among HIV-negative and HIV-positive adults in the 5 year period before and after the introduction of ART. Using Hazard Rate Ratios, they found that in women, the crude death rate fell for both HIV negatives and HIV positives. Furthermore, for men, the mortality among HIV negatives increased and decreased among HIV positives but was not statistically significant. They reported that the largest decrease in HIV-positive mortality over the two periods was among the 30 – 44 year age group for women and 45 – 59 year age group for men. They concluded that there has been a fairly small influence on mortality in the study population following the introduction of free ART. They suggested that in order to realise

the full potential of treatment for reducing HIV-related mortality, there has to be an improvement in the access to treatment and also to place greater focus on retaining individuals on treatment.

1.5. Study aim

The aim of the study is to investigate how the patterns of clustering of mortality vary between different age groups, pre and post the HIV ART rollout program (1996 – 2010). Also, this study seeks to examine how mortality patterns in children and adult population groups might be clustered in time and space in recent years (2009 – 2010).

1.6. Study Hypothesis

- HIV-related mortality has significantly decreased post ART rollout (that is, after 2007) at both HDSSs.
- There has been a reduction in significant clusters of HIV-related mortality versus all-cause mortality at both HDSSs, after the introduction of ART in 2007.

1.7. Study objectives

- To describe temporal trends in child and adult all-cause mortality versus HIV/AIDS related mortality at Agincourt and Dikgale HDSSs in South Africa, before and after ART rollout.
- To identify significant clusters of child and adult all-cause mortality versus HIV/AIDS related mortality in space-time at Agincourt and Dikgale HDSSs in South Africa, pre and post ART rollout.

1.8. Research questions

- Have observable mortality trends changed pre and post ART rollout?

- Are there any significant clusters of child and adult mortality in space-time after the HIV ART rollout?

CHAPTER TWO: METHODOLOGY

2.0. Introduction

This chapter presents the methods which were employed in analysing the data. It also gives a description of the study design, area, population, data collection tools and variables used.

2.1. Study design

The primary studies are prospective cohorts (longitudinal HDSS data) for the years 1996 – 2010. This secondary study will thus be a retrospective cohort study of the primary studies.

2.2. Study area

There are three Health and Demographic Surveillance System (HDSS) sites in South Africa, namely; Agincourt, Africa Centre and Dikgale of South Africa. This study only utilised data from Agincourt and Dikgale HDSS sites.

The Agincourt HDSS was established in 1992, and contains a blend of former Mozambican refugees, migrant workers and a more stable permanent population [15]. The site is situated in the northeast of South Africa, as shown in Figure 1, and covers an area in excess of 400 km^2 and consisted of 21 villages with approximately 11,700 households and a population of 70,000 people at the end of 2007 [9].

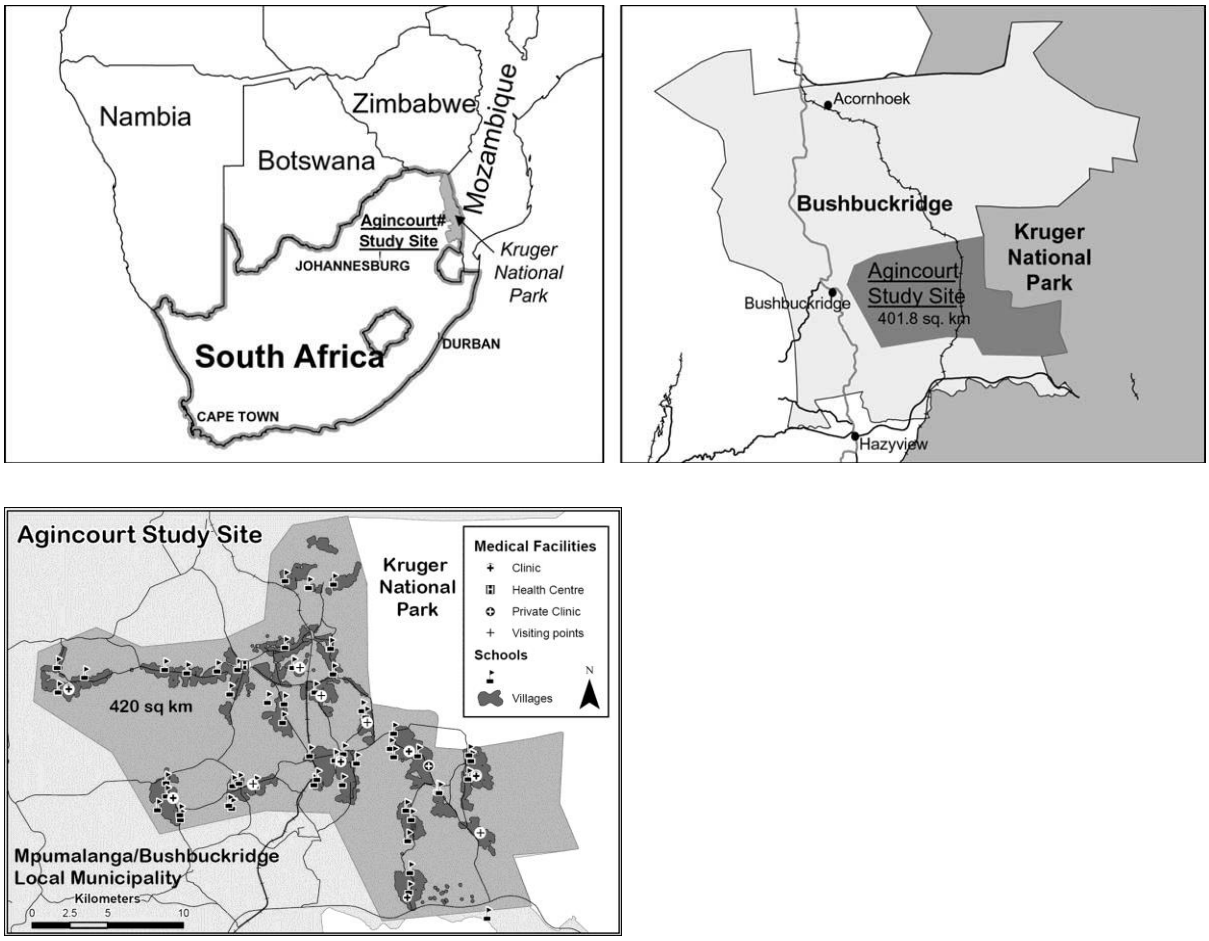

Figure 1: *The regional location of the Agincourt Health and Demographic Surveillance System site* *(Source: Kahn K et al. Research into health, population and social transitions in rural South Africa: data and methods of the Agincourt health and socio-demographic surveillance system. Scand J Public Health 2007; 35: 8_20)*

The Dikgale HDSS is located in a rural area of South Africa's northernmost province, Limpopo, and was initiated in 1996. The HDSS is 45 km to the east of the provincial city of Polokwane. Up to the end of 2007, the surveillance covered a very stable overall population of 8,000 living in a cluster of eight rural villages [9] (as shown in Figure 2).

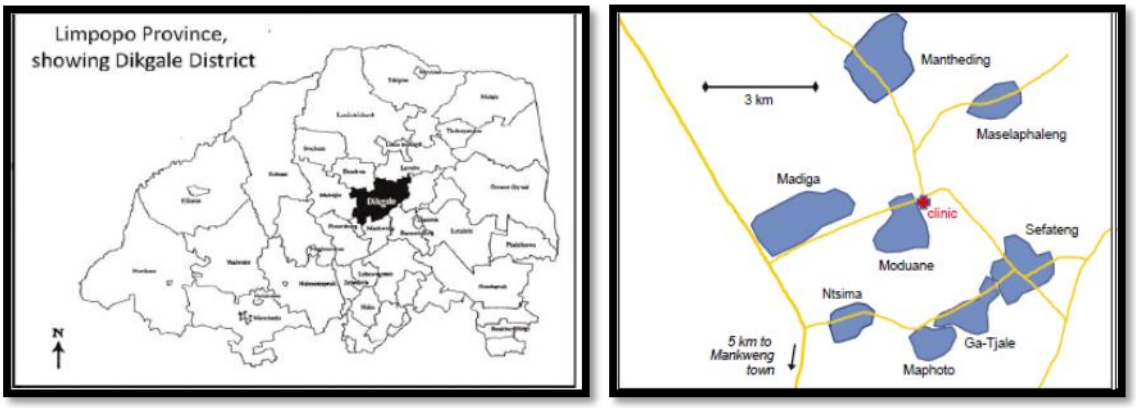

Figure 2: *Shows the Dikgale District and the Dikgale Health and Demographic Surveillance System area*

(Source: Kanjala C, Alberts M, Byass P, Burger S. Spatial and temporal clustering of mortality in Digkale HDSS in rural northern South Africa. Global Health Action Supplement 1, 2010. DOI: 10.3402/gha.v3i0.5236)

2.3. Study population

The study population comprises children under the age of 5 years and adults of the age group 15–64 years, in Agincourt and Dikgale HDSSs, for the years 1996 – 2010. These age groups were considered as they have a high mortality rate (particularly the under 5 year age group), are most affected by HIV/AIDS and comprises of a highly sexually active age group (which is the 15 – 64 age group). Furthermore, the 5–14 and 65+ age groups had very low mortality rates (insufficient data for this study) in both HDSSs.

2.4. Study sample

As these are HDSSs, entire populations at risk are captured. This study will include all eligible children and adults for the period of study. Direct inference with regards to risk can thus be made.

2.5. Data collection tools

Health and socio-demographic surveillance include registration of the entire geographically defined population at baseline, and subsequent prospective follow-up through yearly updates that are systematically recorded basic demographic events (births, deaths, and migrations) [16]. Household interviews are undertaken by experienced fieldworkers who interviewed the most knowledgeable adult available, verified existing data, and carefully recorded new events. Data are entered onsite, pass through many validity checks, and are stored and manipulated in a secure relational database. Quality assurance includes field and data checks to ensure robust numerator and denominator data for the calculation of rates. This study did not collect new data but extracted its data from the data already generated by the Agincourt and Dikgale HDSSs. Permission to use the data was sought.

2.6. Data collected

As these are HDSS data, a wide range of information is collected at individual level. This study concentrated mainly on the following variables:

Data for this study was extracted using Microsoft Structured Query Language (Microsoft SQL) and the key variables that were extracted were; individual Id, gender, date of birth, date of death, resident start and end times, observation start and end dates, village and cause-of-death.

Table 1: *Data collection sheet*

Demographic characteristics	
Individual Id	Unique Id for each individual in the dataset
Gender	Individual's gender
Date of birth	Individual's date of birth
Date of death	Individual's date of death
Village name	Indicates the village at the individual resides
Resident start date	Date on which this residency episode began
Resident end date	Date on which this residency episode ended
Observation start date	Indicates the date at which the individual was first observed
Observation end date	Indicates the date at which the individual was last observed
Cause of death data	
HIV- related deaths	Any death that is HIV-related ***(only for the Agincourt HDSS)***
Other causes of death	Death caused by any other disease besides HIV

Outcome variable: all-cause mortality and HIV-specific mortality

Explanatory variables include: age group and gender

Unit of analysis: measurements were taken at individual level to compare mortality trends across villages.

All deaths are followed up by a verbal autopsy (VA) interview which is conducted after 6 months (on average) after the person's death to determine probable cause. This is done by a trained nurse. VAs are based on the assumption that most causes of death can be singled out by their signs and symptoms, and that these can be accurately recognized, recalled and reported by lay respondents [6].

Precise person-years at risk by age, gender, year, and village were used as the denominator. Deaths and person years were aggregated annually for the period of 1 January 1996 to 31

December 2011 for all the individuals in the study population. Observation dates were used for calculating person-years, instead of Resident dates, as they are more reliable.

2.7. Data Analysis

This section shows how data was managed by which statistical package and also shows which statistical analysis was implemented for each objective.

2.7.1. Data management

The original data from the two HDSS sites was first extracted using Microsoft SQL 2005 then converted to STATA version 11 software (Stata Corp, 2008, Texas USA) format in which all data cleaning, coding, management and most of the analysis was performed. Simple descriptive statistics was carried out to gain familiarity with the data set and detect illegal, missing and inconsistent values. Spatial, temporal, and space-time scan statistics (which was used to detect and evaluate statistically significant spatial clusters) were analysed using the space-time scan statistic SaTScan™ software [17].

2.7.2. Statistical analysis

Frequencies, means, medians, ranges and standard deviations were used to describe the study population determinants (age and gender). Again, trends in mortality for all-cause mortality and HIV-related mortality for the period 1996 – 2010, were descriptively compared across villages and year using Stata 11 and MS Excel in the form of line graphs.

The following analysis was carried out for each objective:

Objective 1: Mortality trends were analysed using STATA 11, where crude death rates were generated together with their corresponding 95% C.I, and then graphed against both village and year using MS Excel. Village death rates were compared to the HDSS average. Also, temporal-trends were analysed using a Poisson model in STATA 11.

Objective 2: The study employed the Kulldorff spatial scan statistic to identify clusters or hotspots of mortality. Kulldorff spatial scan statistic was used to identify space-only clusters of high mortality only by age-group in the chosen HDSS overall for the entire aggregated period [11].The scan statistic is commonly used to test if a one dimensional point process is purely random, or if any clusters can be detected [18].

The spatial scan statistic calculates the likelihood of observing the number of deaths inside and outside each cluster, and the one with the maximum likelihood is defined as the most likely cluster, that is, least likely to have occurred by chance (tests the null hypothesis that the risk of dying is the same in all villages in the study area) [11]. SaTScan™ also allows space-time analysis and for this analysis, a discrete Poisson-based model was used in which events at particular times and places were analysed against person-years observed in the same times and places.

2.8. Ethical considerations

The study was conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of South Africa. The primary study obtained ethical approval from the Wits Human Research Ethics Committee. This study attained written consent to use the dataset from both Agincourt and Dikgale HDSS sites. Approval from the Wits Humans Research Ethics Committee, before proceeding with the study, was obtained. Data facility confidentiality was respected and adhered to. Data was aggregated

and household coordinates were not used. Also, data on individual and village identities were anonymised.

CHAPTER THREE: ANALYSIS & RESULTS

3.0. Introduction

This chapter presents the results, firstly, for the Agincourt HDSS and then for the Dikgale HDSS. Mortality data were first summarized, and then described by gender, village and year, together with Crude All-cause Death Rates (CADRs), Crude HIV-related Death Rates (CHIVDRs) and with their corresponding 95% Confidence Internals (95 C.Is). . Results for the trend analysis were recorded and finally, spatial-only and spatio-temporal analysis. The locations for all 21 villages of the Agincourt HDSS site are shown in Figure 3 below.

3.1. Agincourt HDSS

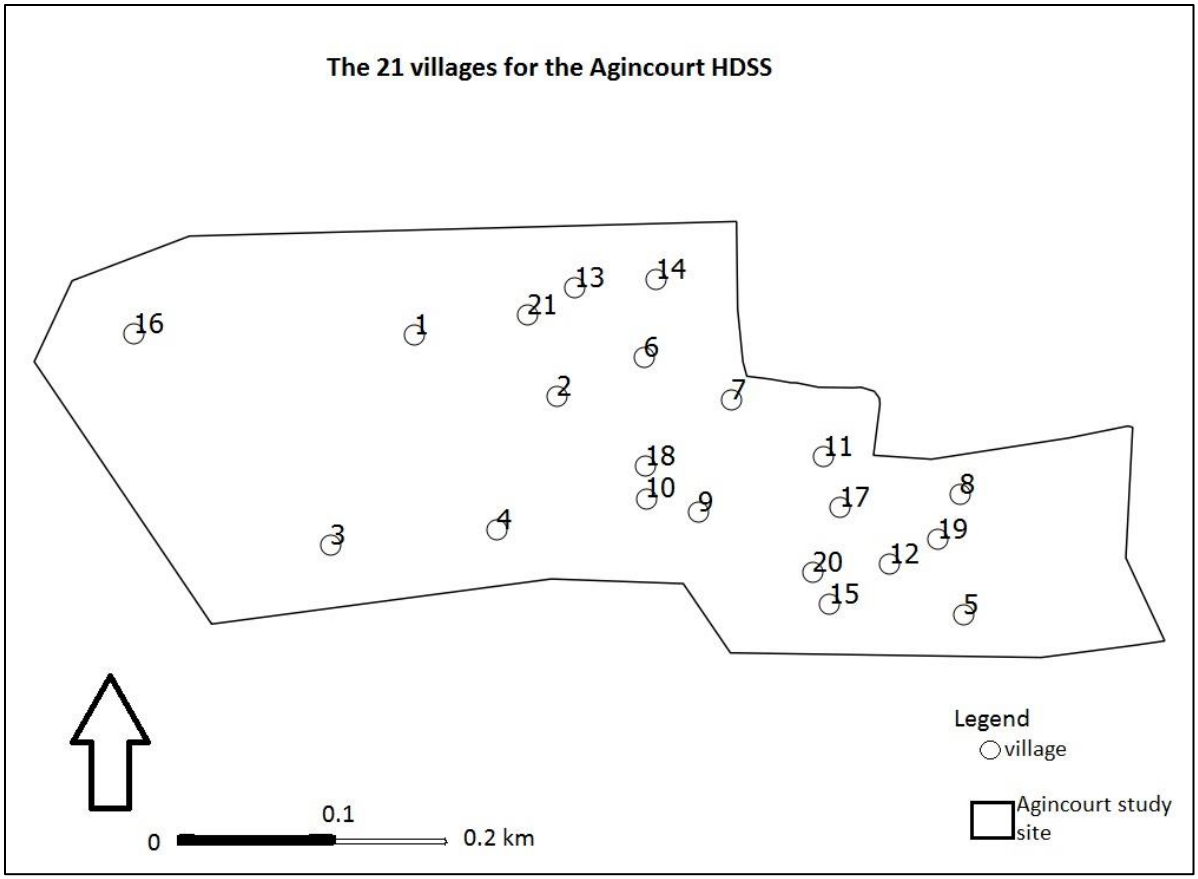

Figure 3: *Shows the location for all the 21 villages for the Agincourt HDSS using Quantum GIS*

3.1.1. Children

3.1.1a. Descriptive Statistics

Table 2: *Summary statistics for the under-five age group at the Agincourt HDSS, 1996-2010*

	Total	95% C.I
All-cause deaths	1535.00	1259.52 - 1810.48
HIV-related deaths	409.00	287.06 - 530.94
Person-years	129226.00	123264.40 - 135187.60

Table 2 above shows the total number of all-cause deaths, HIV-related deaths and person-years for the under-five age group in Agincourt for the years 1996 – 2010.

Table 3: *Crude mortality rates (per 1 000 person-years) for the under-five age group by gender at the Agincourt HDSS, 1996-2010*

Gender	All-cause deaths	Person-years	Crude all-cause mortality rates	95% C.I for CADR	HIV-related deaths	Crude HIV-related mortality rates	95% C.I for CHIVDR
Male	802	64349.62	12.46	11.61 - 13.36	188	2.92	2.52 -3.37
Female	732	64863.17	11.29	10.48 - 12.13	221	3.41	2.97 -3.89

The crude all-cause death rate for males (12 deaths per 1 000 person-years) was slightly above that of females (11 deaths per 1 000 person-years) but equivalent to the mean overall death rate of 12 deaths per 1 000 person-years. However, for the crude HIV-related mortality rates, both

genders had approximately the same death rates of 3 deaths per 1 000 person-years which also corresponded to the mean overall crude HIV-related death rate (Table 3).

Table 4: *Crude all-cause mortality rates (per 1 000 person-years) by village for the under-five age group at the Agincourt HDSS, 1996-2010*

Village	Total All-cause deaths	Person-years	Crude All-cause death rates (per 1000 person-years)	95% C.I for CADR
1	122	12335.97	9.89	8.21 - 11.81
2	84	5784.51	14.52	11.58 - 17.98
3	103	9475.69	10.87	8.87 - 13.19
4	68	5723.81	11.88	9.23 - 15.06
5	50	5172.22	9.67	7.18 - 12.74
6	91	6992.07	13.01	10.48 - 15.98
7	64	4385.99	14.59	11.24 - 18.63
8	126	9554.94	13.19	10.99 - 15.71
9	71	7457.62	9.52	7.44 - 12.01
10	80	9043.60	8.87	7.01 - 11.01
11	139	11872.46	11.71	9.84 - 13.82
12	62	4429.59	14.00	10.73 - 17.94
13	64	6106.44	10.48	8.07 - 13.38
14	48	3405.42	13.80	10.14 - 18.35
15	75	6469.56	11.60	9.12 - 14.54
16	75	6846.77	10.95	8.62 - 13.73
17	67	4650.60	14.41	11.17 - 18.30
18	23	2099.32	10.96	6.95 - 16.44
19	36	2487.49	14.47	10.14 - 20.04
20	34	2383.63	14.27	9.88 - 19.94
21	53	2548.30	**20.80**	**15.58 - 27.20**
Overall	1535	129225.97	11.88	11. 29 – 12.49

Note: Bold numbers indicate all-cause mortality rates significantly above the average for the given period ($p<0.05$).

Table 5: *Crude HIV-related mortality rates (per 1 000 person-years) by village for the under-five age group at the Agincourt HDSS, 1996-2010*

Village	Total HIV-related deaths	Person-years	Crude HIV-related death rates (per 1000 person-years)	95% C.I for CHIVDR
1	29	12335.97	2.35	1.57 - 3.38
2	23	5784.51	3.98	2.52 - 5.97
3	26	9475.69	2.74	1.79 - 4.02
4	12	5723.81	2.10	1.08 - 3.66
5	17	5172.22	3.29	1.91 - 5.26
6	18	6992.07	2.57	1.53 - 4.07
7	20	4385.99	4.56	2.79 - 7.04
8	41	9554.94	4.29	3.08 - 5.82
9	24	7457.62	3.22	2.06 - 4.79
10	24	9043.60	2.65	1.70 - 3.95
11	40	11872.46	3.37	2.41 - 4.59
12	13	4429.59	2.93	1.56 - 5.02
13	20	6106.44	3.28	2.00 - 5.06
14	9	3405.42	2.64	1.21 - 5.02
15	21	6469.56	3.25	2.01 - 4.97
16	14	6846.77	2.04	1.12 - 3.43
17	16	4650.60	3.44	1.97 - 5.59
18	7	2099.32	3.33	1.34 - 6.87
19	9	2487.49	3.62	1.65 - 6.87
20	11	2383.63	4.61	2.30 - 8.26
21	15	2548.30	**5.89**	**3.29 - 9.71**
Overall	409	129225.97	3.17	2.87 – 3.49

Note: Bold numbers indicate HIV-related mortality rates significantly above the average for the given period ($p<0.05$).

For the under-five age group, Table 4 and Table 5 above show that village 21 had both the highest crude all-cause death rate (21 deaths per 1 000 person-years) and the highest crude HIV-related death rate (6 deaths per 1 000 person-years). Village 10 had the lowest crude all-cause death rate (9 deaths per 1 000 person-years) whilst village 16 and village 4 had the lowest crude HIV-related death rates of approximately 2 deaths per 1 000 person-years each.

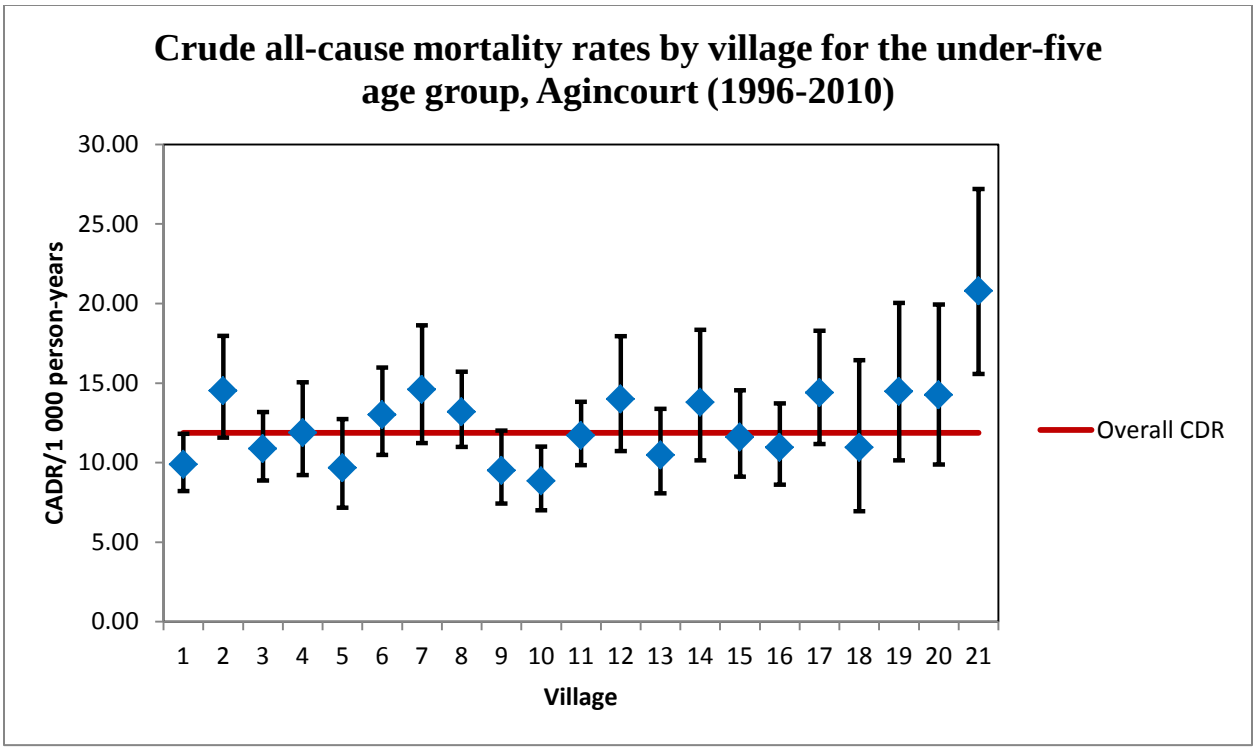

Figure 4: *Shows the crude all-cause mortality rates by village plus their corresponding 95% C.Is, for the under-five age group at the Agincourt HDSS, 1996-2010*

Most villages had crude all-cause death rates lying between 8 deaths per 1 000 person-years and 15 deaths per 1 000 person-years (Figure 4).

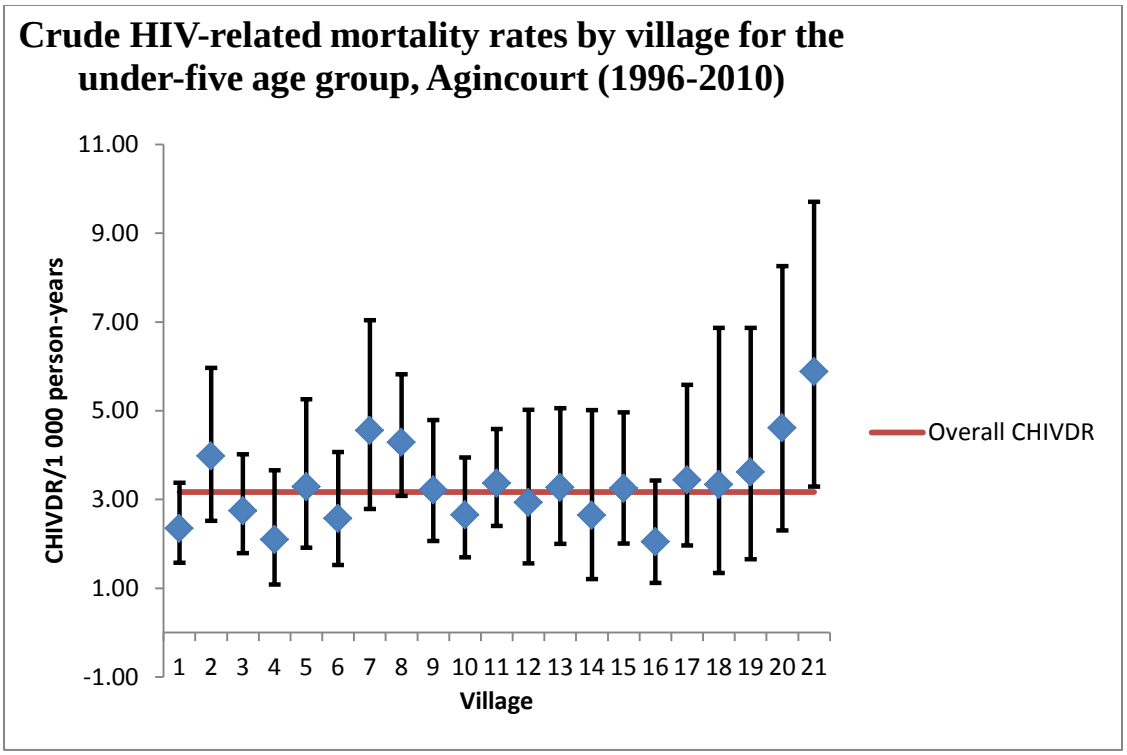

Figure 5: *Shows the crude HIV-related mortality rates by village plus their corresponding 95% C.Is, for the under-five age group at the Agincourt HDSS, 1996-2010*

Almost all villages had crude HIV-related death rates lying between 2 deaths per 1 000 person-years and 5 deaths per 1 000 person-years (Figure 5).

Table 6: *Crude all- cause mortality rates (per 1 000 person-years) by year for the under-five age group at the Agincourt HDSS, 1996-2010*

Year	Total All-cause deaths	Person-years	Crude All-cause death rates (per 1000 person-years)	95% C.I for CADR
1996	42	9673.76	4.34	3.13 - 5.87
1997	53	9430.21	5.62	4.21 - 7.35
1998	78	9130.44	8.54	6.75 - 10.66
1999	105	8945.32	11.74	9.60 - 14.21
2000	99	8901.62	11.01	8.94 - 13.42
2001	102	8807.68	11.58	9.44 - 14.06
2002	123	8542.96	**14.40**	**11.97 - 17.18**
2003	144	8282.75	17.39	14.66 - 20.47
2004	94	8064.40	11.66	9.42 - 14.26
2005	104	8141.24	12.77	10.44 - 15.48
2006	118	8331.29	14.17	11.72 - 16.96
2007	135	8490.49	15.90	13.33 - 18.82
2008	166	8777.14	**18.91**	**16.15 - 22.02**
2009	103	9079.23	11.35	9.26 - 13.77
2010	69	6627.45	10.42	8.11 - 13.19
Overall	1535	129225.97	11.88	11.29 – 12.49

Note: Bold numbers indicate all-cause mortality rates significantly above the average for a given period ($p<0.05$).

Table 7: *Crude HIV-related mortality rates (per 1 000 person-years) by year for the under-five age group at the Agincourt HDSS, 1996-2010*

Year	Total HIV-related deaths	Person-years	Crude HIV-related death rates (per 1000 person-years)	95% C.I for CHIVDR
1996	6	9673.756	0.62	0.23 - 1.35
1997	6	9430.209	0.64	0.23 - 1.38
1998	19	9130.444	2.08	1.25 - 3.25
1999	17	8945.32	1.90	1.11 - 3.04
2000	23	8901.617	2.58	1.64 - 3.88
2001	30	8807.677	3.41	2.30 - 4.86
2002	43	8542.963	**5.03**	**3.64 - 6.78**
2003	48	8282.748	**5.80**	**4.27 - 7.68**
2004	30	8064.395	3.72	2.51 - 5.31
2005	37	8141.242	**4.54**	**3.20 - 6.26**
2006	46	8331.29	**5.52**	**4.04 - 7.37**
2007	46	8490.489	**5.42**	**3.97 - 7.23**
2008	30	8777.14	3.42	2.31 - 4.88
2009	20	9079.23	2.20	1.35 - 3.40
2010	8	6627.453	1.21	0.52 - 2.38
Overall	409	129225.974	3.17	2.87 – 3.49

Note: Bold numbers indicate HIV-related mortality rates significantly above the average for a given period ($p<0.05$).

The year 2008 recorded the highest crude all-cause mortality rate of approximately 19 deaths per 1 000 person-years (Table 6) and year 2003 had the highest crude HIV-related mortality rate of approximately 6 deaths per 1 000 person-years, for the under five age group (Table 7). Moreover, the year 1996, with approximately 4 deaths per 1 000 person-years, had the lowest crude all-cause mortality rate (Table 6). The years 1996, 1997 and 2010 recorded the lowest crude HIV-related mortality rates of approximately1 death per 1 000 person-years each (Tables 6).

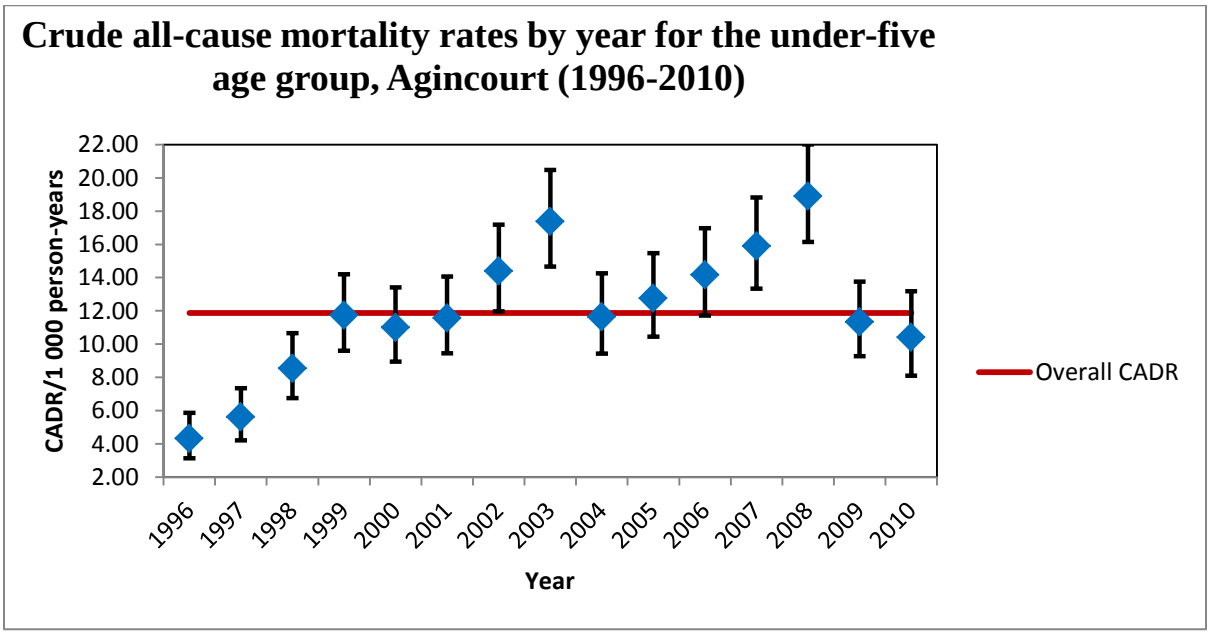

Figure 6: *Shows the crude all-cause mortality rates by year plus their corresponding 95% C.Is, for the under-five age group at the Agincourt HDSS, 1996-2010*

There was a gradual increase in the crude all-cause mortality rates from the year 2004 which recorded approximately 12 deaths per 1 000 person-years to the year 2008 which had approximately 18 deaths per 1 000 person-years. There was a drop in the crude all-cause mortality rate from the year 2008 to 2009 (from approximately 19 deaths per 1 000 person-years to 11 deaths per 1 000 person-years), as shown in Figure 6.

Notably, there was a significant linear trend, both before and after the introduction of ART (p-value=0.001 and p-value<0.001 respectively) for the under-five age group in Agincourt.

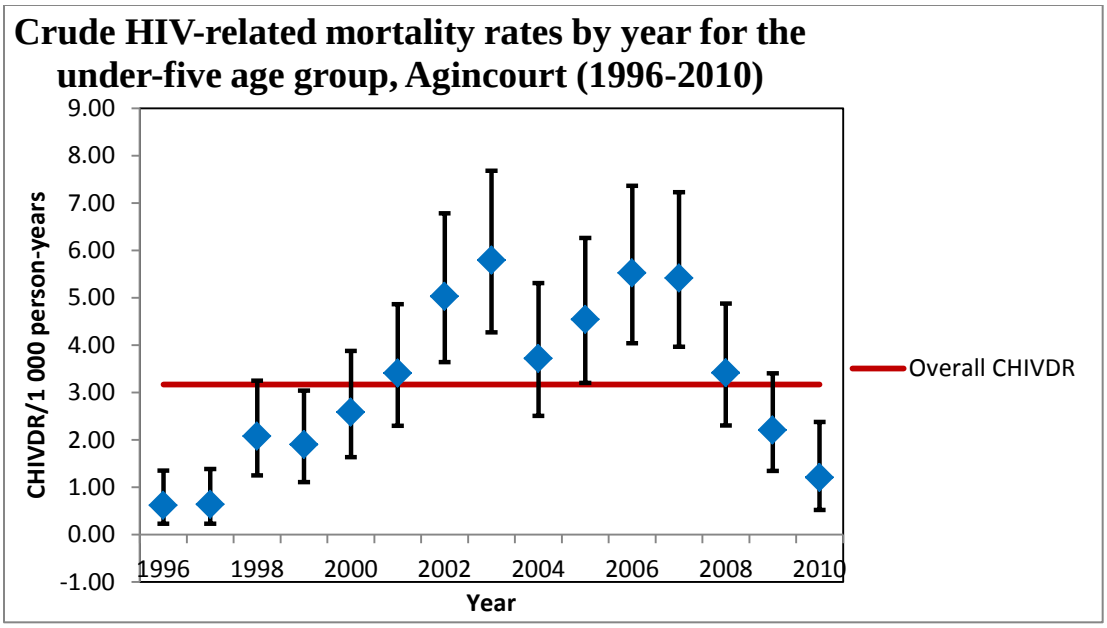

Figure 7: *Shows the crude HIV-related mortality rates by year plus their corresponding 95% C.Is, for the under-five age group at the Agincourt HDSS, 1996-2010*

Furthermore, there was a gradual decrease in the crude HIV-related mortality rates from the year 2006 (from approximately 6 deaths per 1 000 person-years) to 2010 which recorded approximately 1 death per 1,000 person-years (Figure 7). Again, there was a significant linear trend, both before (p-value<0.001) and after (p-value<0.001) the introduction of ART for the under-five age group in Agincourt.

3.1.1b. Spatial only analysis

Table 8: *Clusters of all-cause and HIV-related mortality for the under-five age group, using the purely spatial analysis scanning for high mortality rates at the Agincourt HDSS, 1996-2010*

Age group	Cluster type	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
			All-cause				
<5	Most likely	1	21	53	30	1.78	0.016
<5	Secondary	2	9,10	151	196	0.75	0.032
<5	Tertiary	4	8,19,12,17	291	251	1.20	0.302
<5	Tertiary	3	16,1,3	300	340	0.85	0.436
<5	Tertiary	2	7,6	155	135	1.16	0.936
			HIV-related				
<5	Most likely	6	3,4,1,2,16,10	128	156	0.74	0.217
<5	Secondary	10	12,19,15,20, 17,5,8,11,9,7	212	186	1.29	0.416
<5	Tertiary	1	21	15	8	1.89	0.681

Two statistically significant (at 5% level) clusters of higher all-cause mortality comprising one (village 21) and two villages (village 9 and 10) respectively, were observed for the period 1996–2010. However, using the spatial only scan analysis, there were no statistically significant clusters of higher HIV-related mortality for the under five age group (Table 8, Figure 17 and Figure 18 in Appendix 1A).

Of note, is that villages 19 and 21 had the highest risk (RR=1.80) for all-cause mortality in the under-five age group. Moreover, villages 20 and 21 had the highest risk (RR=1.90) for HIV-related deaths for the same age group.

3.1.1c. Spatio-temporal analysis

Table 9: *Clusters of all-cause and HIV-related mortality for the under-five age group, using space-time scan analysis scanning for high mortality rates at the Agincourt HDSS, 1996-2010*

Age group	Cluster type	Years	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
				All-cause				
<5	Most likely	1996 - 1998	9	4,10,2,18,3, 9,1,21,6	64	155	0.39	<0.0001
				HIV-related				
<5	Most likely	2001 – 2007	10	12,19,15,20, 17,5,8,11,9,7	148	85	2.17	<0.0001
<5	Secondary	1996 - 1997	9	16,1,3,21,4, 2,13,6,14	1	26	0.036	<0.0001

There was one statistically significant space–time cluster of higher all-cause mortality and two statistically significant space–time clusters of higher HIV-related mortality. The most likely cluster, for all-cause mortality, was situated in the central to west region of the site and comprised nine villages for the period 1996–1998 (Table 9 and Figure 19 in Appendix 1B). For HIV-related mortality, the most likely cluster was situated in the south-east and comprised of ten villages, as seen in Table 8 and Figure 12, for the period 2001–2007. A secondary cluster of 9 villages was situated in the south-east region of the site during the period 1996–1997 (Table 8 and Figure 20 in Appendix 1B).

Worth mentioning is that villages 4 and 10 had the highest risk (RR=0.65) for all-cause mortality in the under-five age group. Additionally, villages 7, 8 and 19 had the highest risk (RR=2.50) for HIV-related deaths in the under-five age group.

3.1.2. Adults

3.1.2a. Descriptive Statistics

Table 10: *Summary statistics for the 15-64 age group at the Agincourt HDSS, 1996-2010*

	Total	95% C.I
All-cause deaths	5761.00	4446.08 - 7075.92
HIV-related deaths	2680.00	1773.25 - 3586.75
Person-years	602025.70	573006.70 - 631044.70

Table 10 above shows the total number of all-cause deaths, HIV-related deaths and person-years for the 15-64 age group in Agincourt for the years 1996 – 2010.

Table 11: *Crude mortality rates (per 1 000 person-years) for the 15-64 age group by gender at the Agincourt HDSS, 1996-2010*

Gender	All-cause deaths	Crude all-cause mortality rates	95% C.I	HIV-related deaths	Crude HIV-related mortality rates	95% C.I	Person-years
Male	3122	10.80	10.42 – 11.19	1380	4.77	4.53 – 5.03	289082
Female	2639	8.43	8.12 – 8.76	1300	4.15	3.93 – 4.39	312886

The crude all-cause death rate for males (11 deaths per 1 000 person-years) was more than that of females (8 deaths per 1 000 person-years) and slightly above the mean overall death rate of 10 deaths per 1 000 person-years. Again, for the crude HIV-related mortality rates, males also had a somewhat higher death rate (5 deaths per 1 000 person-years) compared to the females whose HIV-related death rate was 4 deaths per 1 000 person-years (Table 11).

Table 12: *Crude all-cause mortality rates (per 1 000 person-years) by village for the 15-64 age group at the Agincourt HDSS, 1996-2010*

Village	Total All-cause deaths	Person-years	Crude All-cause death rates (per 1000 person-years)	95% C.I for CADR
1	552	61298.65	9.01	8.27 - 9.79
2	258	28368.28	9.09	8.02 - 10.27
3	431	48131.67	8.95	8.13 - 9.84
4	286	31150.86	9.18	8.15 - 10.31
5	216	22864.17	9.45	8.23 - 10.80
6	330	33293.88	9.91	8.87 - 11.04
7	204	20234.84	10.08	8.75 - 11.56
8	471	43621.91	10.80	9.85 - 11.82
9	374	40375.14	9.26	8.35 - 10.25
10	386	38211.34	10.10	9.12 - 11.16
11	483	56492.80	8.55	7.80 - 9.35
12	173	17359.98	9.97	8.54 - 11.57
13	274	27837.11	9.84	8.71 - 11.08
14	171	16121.61	10.61	9.08 - 12.32
15	**304**	**26713.67**	**11.38**	**10.14 - 12.74**
16	358	37110.32	9.65	8.67 - 10.70
17	147	16877.20	8.71	7.36 - 10.24
18	81	8410.29	9.63	7.65 - 11.97
19	77	9183.90	8.38	6.62 - 10.48
20	71	8051.68	8.82	6.89 - 11.13
21	114	10316.38	11.05	9.12 - 13.27
Overall	5761	602025.68	9.57	9.32 – 9.82

Note: Bold numbers indicate all-cause mortality rates significantly above the average for the given period ($p<0.05$).

Table 13: *Crude HIV-related mortality rates (per 1 000 person-years) by village for the 15-64 age group at the Agincourt HDSS, 1996-2010*

Village	Total HIV-related deaths	Person-years	Crude HIV-related death rates (per 1000 person-years)	95% C.I for CHIVDR
1	247	61298.65	4.03	3.54 - 4.56
2	97	28368.28	3.42	2.77 - 4.17
3	179	48131.67	3.72	3.19 - 4.31
4	137	31150.86	4.40	3.69 - 5.20
5	105	22864.17	4.59	3.76 - 5.56
6	164	33293.88	4.93	4.20 - 5.74
7	103	20234.84	5.09	4.15 - 6.17
8	229	43621.91	**5.25**	**4.59 - 5.98**
9	166	40375.14	4.11	3.51 - 4.79
10	178	38211.34	4.66	4.00 - 5.40
11	227	56492.80	4.02	3.51 - 4.58
12	92	17359.98	5.30	4.27 - 6.50
13	121	27837.11	4.35	3.61 - 5.19
14	74	16121.61	4.59	3.60 - 5.76
15	148	26713.67	**5.54**	**4.69 - 6.51**
16	159	37110.32	4.28	3.64 - 5.00
17	84	16877.20	4.98	3.97 - 6.16
18	41	8410.29	4.87	3.50 - 6.61
19	43	9183.90	4.68	3.39 - 6.31
20	37	8051.68	4.60	3.24 - 6.34
21	49	10316.38	4.75	3.51 - 6.28
Overall	2680	602025.68	4.45	4.28 – 4.62

Note: Bold numbers indicate HIV-related mortality rates significantly above the average for the given period ($p<0.05$).

For the 15-64 year age group, Table 12 and Table 13 above shows that village 15 had the highest crude all-cause death rates (with approximately 11 deaths per 1 000 person-years) and also the highest crude HIV-related death rate (6 deaths per 1 000 person-years). Village 19 had the lowest crude all-cause death rate (8 deaths per 1 000 person-years) whilst village 2 had the lowest crude HIV-related death rate (3 deaths per 1 000 person-years).

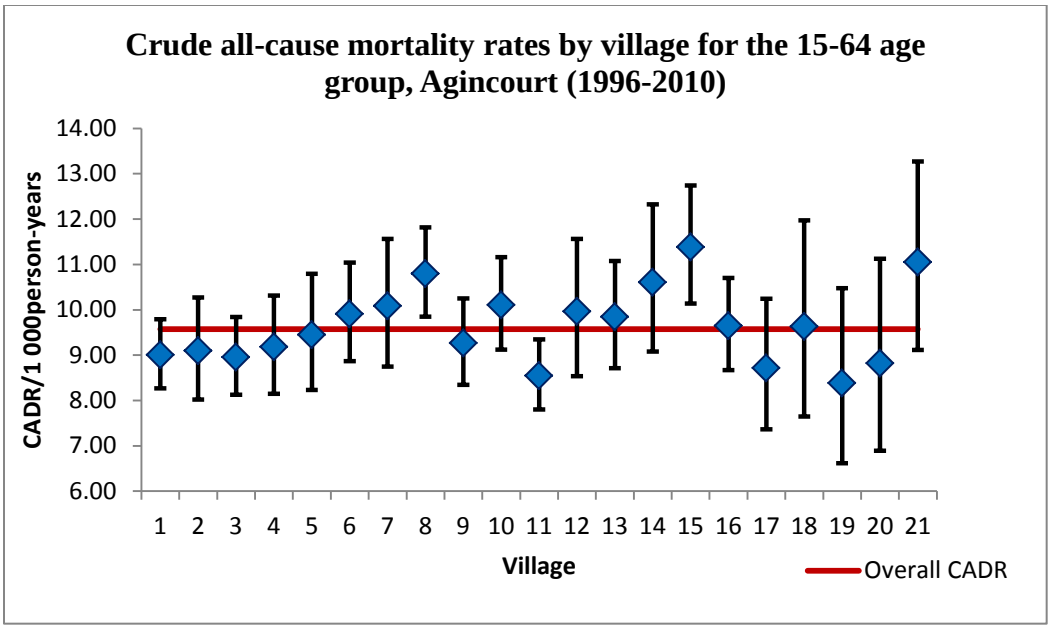

Figure 8: *Shows the crude all-cause mortality rates by village plus their corresponding 95% C.Is, for the15-64 age group at the Agincourt HDSS, 1996-2010*

In general, all villages had crude all-cause death rates lying between 8 deaths per 1 000 person-years and 12 deaths per 1 000 person-years (Figure 8).

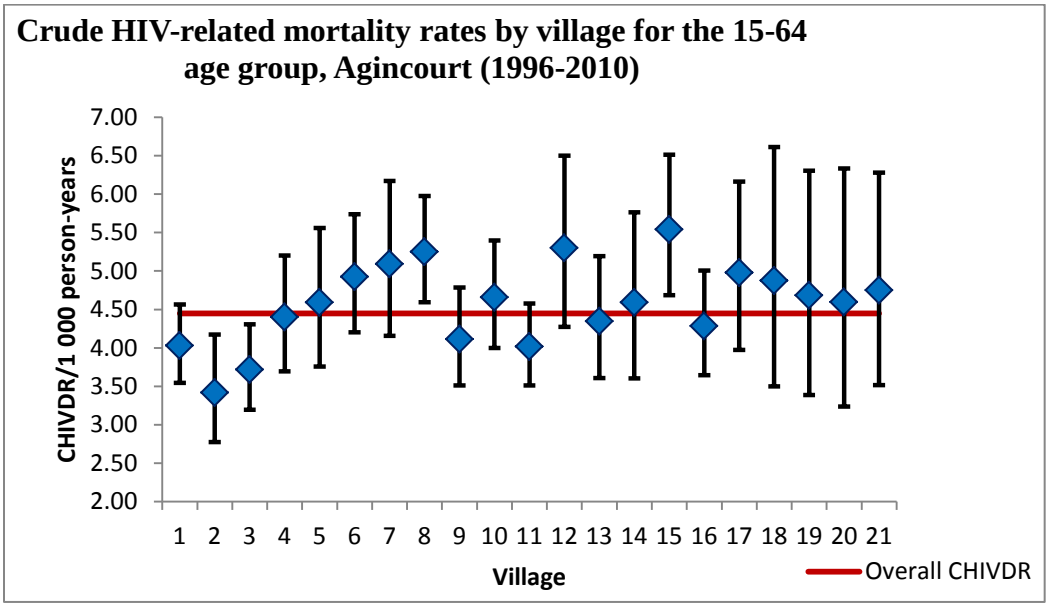

Figure 9: *Shows the crude HIV-related mortality rates by village plus their corresponding 95% C.Is, for the15-64 age group at the Agincourt, 1996-2010*

Also, all villages had crude HIV-related death rates lying between 3 deaths per 1000 person-years and 6 deaths per 1 000 person-years (Figure 9).

Table 14: *Crude all-cause mortality rates (per 1 000 person-years) by year for the 15-64 age group at the Agincourt HDSS, 1996-2010*

Year	Total All-cause deaths	Person-years	Crude All-cause death rates (per 1000 person-years)	95% C.I for CADR
1996	163	35435.91	4.60	3.92 - 5.36
1997	154	36170.22	4.26	3.61 - 4.99
1998	215	37043.59	5.80	5.05 - 6.63
1999	209	38111.17	5.48	4.77 - 6.28
2000	238	38995.30	6.10	5.35 - 6.93
2001	325	39739.85	8.18	7.31 - 9.12
2002	424	40339.38	10.51	9.53 - 11.56
2003	475	40863.65	**11.62**	**10.60 - 12.72**
2004	542	41597.15	**13.03**	**11.96 - 14.18**
2005	548	42379.00	**12.93**	**11.87 - 14.06**
2006	580	43300.45	**13.39**	**12.33 - 14.53**
2007	561	43863.27	**12.79**	**11.75 - 13.89**
2008	538	44610.87	**12.06**	**11.06 - 13.12**
2009	464	45532.85	10.19	9.29 - 11.17
2010	325	34043.02	9.55	8.54 - 10.65
Overall	5761	602025.68	9.57	9.32 – 9.82

Note: Bold numbers indicate all-cause mortality rates significantly above the average for a given period ($p<0.05$).

Table 15: *Crude HIV-related mortality rates (per 1 000 person-years) by year for the 15-64 age group at the Agincourt HDSS, 1996-2010*

Year	Total HIV-related deaths	Person-years	Crude HIV-related death rates (per 1000 person-years)	95% C.I for CHIVDR
1996	39	35435.91	1.10	0.78 - 1.50
1997	39	36170.22	1.08	0.77 - 1.47
1998	56	37043.59	1.51	1.14 - 1.96
1999	62	38111.17	1.63	1.25 - 2.09
2000	91	38995.30	2.33	1.88 - 2.87
2001	134	39739.85	3.37	2.83 - 3.99
2002	169	40339.38	4.19	3.58 - 4.87
2003	213	40863.65	**5.21**	**4.54 - 5.96**
2004	249	41597.15	**5.99**	**5.27 - 6.78**
2005	267	42379.00	**6.30**	**5.57 - 7.10**
2006	351	43300.45	**8.11**	**7.28 - 9.00**
2007	357	43863.27	**8.14**	**7.32 - 9.03**
2008	264	44610.87	**5.92**	**5.23 - 6.68**
2009	250	45532.85	**5.49**	**4.83 - 6.22**
2010	139	34043.02	4.08	3.43 - 4.82
Overall	2680	602025.68	4.45	4.28 – 4.62

Note: Bold numbers indicate HIV-related mortality rates significantly above the average for a given period ($p<0.05$).

The year 2006 recorded the highest crude all-cause mortality rate of approximately 13 deaths per 1 000 person-years and also the highest crude HIV-related mortality rate of approximately 8 deaths per 1 000 person-years, for the 15-64 year age group. Moreover, the year 1997, with approximately 4 deaths per 1 000 person-years, had the lowest crude all-cause mortality rate and also the lowest crude HIV-related mortality rate (with approximately 1 death per 1 000 person-years) (Tables 14 and 15).

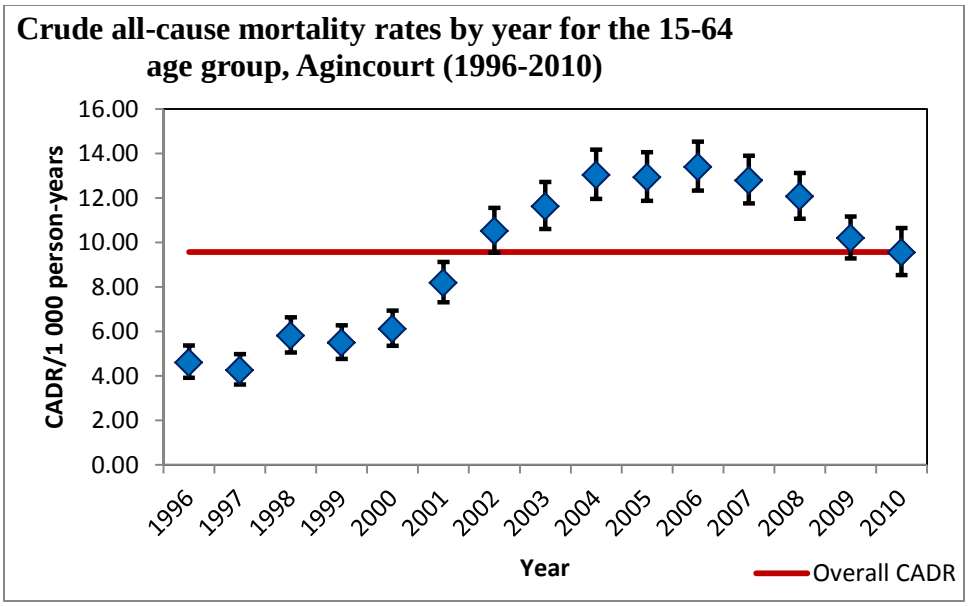

***Figure 10**: Shows the crude all-cause mortality rates by year plus their corresponding 95% C.Is, for the15-64 age group at the Agincourt HDSS, 1996-2010*

There was a gradual decrease in the crude all-cause mortality rates from the year 2006 (which had approximately 13 deaths per 1,000 person-years) to 2010 (which recorded approximately 10 deaths per 1,000 person-years) (Figure 10).

Of note, is that there was a significant linear trend, both before (p-value<0.001) and after (p-value<0.001) the introduction of ART for the 15-64 age group in Agincourt.

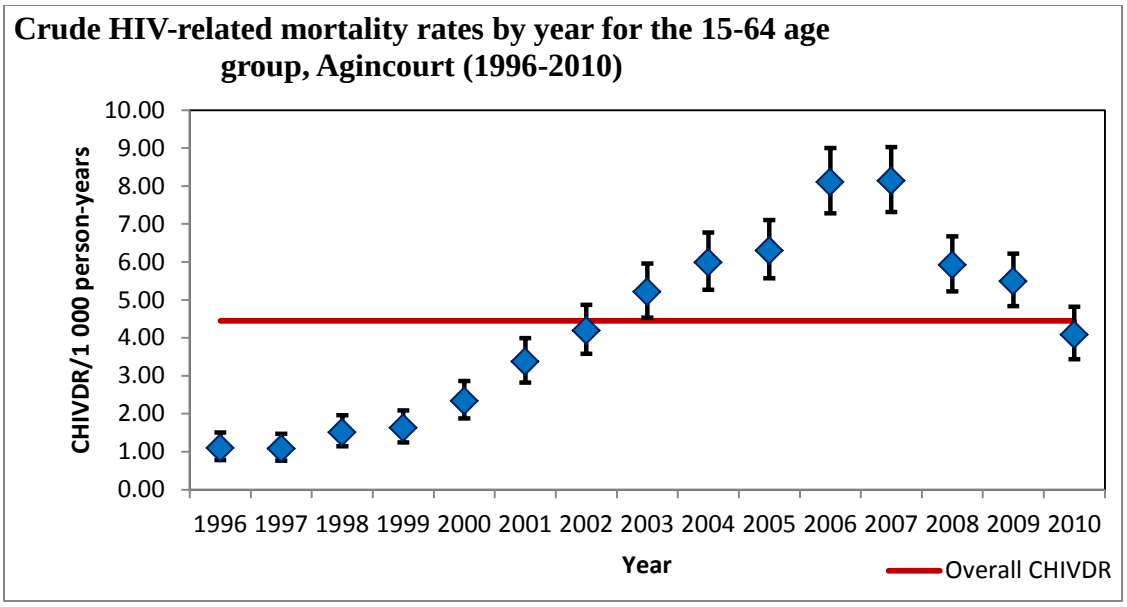

Figure 11: *Shows the crude HIV-related mortality rates by year plus the 95% C.I for the15-64 age group at the Agincourt HDSS, 1996-2010*

Also, there was a noteworthy drop in the crude HIV-related mortality rate from the years 2006 and 2007, which recorded the highest crude HIV-related mortality rates of approximately 8 deaths per 1 000 person-years each, to the year 2010 which had approximately 4 deaths per 1 000 person years (Figure 11).

Again, there was a significant linear trend, both before (p-value<0.001) and after (p-value<0.001) the introduction of ART for the 15-64 age group in Agincourt.

3.1.2b. Spatial only analysis

Table 16: *Clusters of all-cause and HIV-related mortality for the 15-64 age group, using the purely spatial analysis scanning for high mortality rates at the Agincourt HDSS, 1996-2010*

Age group	Cluster type	Number of villages	Village Number	Observed cases	Expected cases	Relative risk (RR)	p-Value
			All-cause				
15-64	Most likely	5	5,19,12, 8,15	1241	1146	1.11	0.125
15-64	Secondary	3	17,11,20	701	779	0.89	0.141
15-64	Tertiary	4	3,4,1,2	1527	1617	0.92	0.353
15-64	Tertiary	5	14,13,6, 21,7	1093	1012	1.07	0.768
			HIV-related				
15-64	Most likely	6	19,8,12,5, 17,15	701	608	1.21	0.003
15-64	Secondary	5	3,4,1,2,16	819	917	0.85	0.006
15-64	Tertiary	2	7,6	267	238	1.13	0.871

Using the purely spatial scan analysis, four clusters were created for adult all-cause mortality, but none of them were statistically significant at the 5% level. However, for HIV-related mortality, two statistically significant (at 5% level) clusters of higher mortality comprising six and five villages respectively, was observed for the period 1996–2010 (Table 16). Of note is that for all-cause and HIV-related deaths, the most likely clusters were situated in the south-east corner of the study site for the 15-64 age group (Figures 21 and 222 in Appendix 1C).

Notable is that villages 8, 15 and 21 had the highest risk (RR=1.20) for all-cause mortality in the 15-64 age group. Likewise, villages 8, 12 and 15 had the highest risk (RR=1.30) for HIV-related deaths in the same age group.

3.1.2c. Spatio-temporal analysis

Table 17: *Clusters of all-cause and HIV-related mortality for the 15-64 age group, using space-time scan analysis scanning for high mortality rates at the Agincourt HDSS, 1996-2010*

Age group	Cluster Type	Years	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
				All-cause				
15-64	Most likely	1996 - 2000	9	4,10,2,18,3, 9,1,21,6	457	871	0.48	<0.0001
				HIV-related				
15-64	Most likely	1996 – 2000	10	14,13,6,21, 7,2,18,10,1,11	117	403	0.26	<0.0001

For the adult population, there was one statistically significant space–time cluster of higher all-cause mortality and one statistically significant space–time cluster of higher HIV-related mortality. The most likely cluster, for all-cause mortality, was situated in the central to west region of the site and comprised nine villages for the period 1996–2000 (Table 17 and Figure 23 in Appendix 1D). For HIV-related mortality, the most likely cluster was situated in the central region and comprised of ten villages, as seen in Table 15 and Figure 24 (see Appendix 1D), for the period 1996–2000.

Noteworthy is that villages 3 and 4 had the highest risk (RR=0.60) for all-cause mortality in the 15-64 age group. Moreover, villages 14 and 18 had the highest risk (RR=0.50) for HIV-related deaths for the same age group.

3.2. Dikgale HDSS

For the Dikgale HDSS, the study only looked at all-cause mortality as there was no available data for HIV-related mortality. Figure 12 shows how the villages are distributed and located in the Dikgale HDSS site.

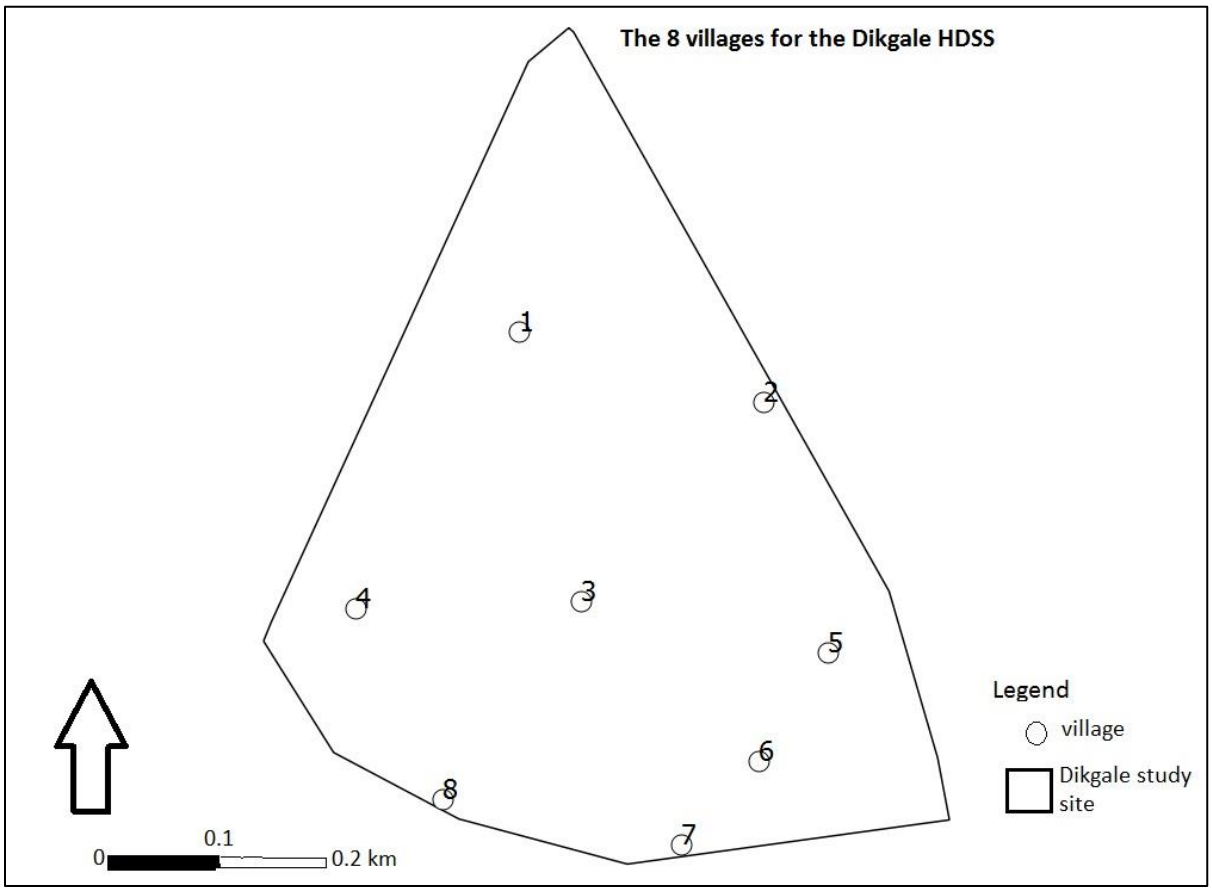

***Figure 12**: Shows the location for all eight villages at the Dikgale HDSS, using Quantum GIS*

3.2.1. Children

3.2.1a. Descriptive Statistics

Table 18: *Summary statistics for the under-five age group at the Dikgale HDSS, 1996-2010*

	Total	95% C.I
All-cause deaths	71.00	44.64 - 97.36
Person-years	13029.21	12173.44 - 13884.97

Table 18 above shows the total number of all-cause deaths and person-years for the under-five age group in Dikgale for the years 1996 – 2010.

Table 19: *Crude mortality rates (per 1 000 person-years) for the under-five age group by gender in Dikgale HDSS, 1996-2010*

Gender	All-cause deaths	Crude all-cause mortality rates	95% C.I	Person-years
Female	32	4.79	3.27 – 6.76	6687.03
Male	39	6.15	4.37 – 8.41	6342.17

Males had a slightly higher crude death rate (6 deaths per 1 000 person-years) compared to that of the females (5 deaths per 1 000 person-years) and of the mean overall crude death rate (5 deaths per 1 000 person-years) (Table 19).

Table 20: *Crude mortality rates (per 1 000 person-years) by village for the under-five age group at the Dikgale HDSS, 1996-2010*

Village	Total deaths	Person-years	Crude death rates (per 1000 person-years)	95% C.I for CADR
1	22	4401.31	4.99	3.13 - 7.57
2	0	178.88	0.00	0.00 - 20.62
3	37	5218.48	7.09	4.99 - 9.77
4	0	149.34	0.00	0.00 - 24.70
5	2	282.33	7.08	0.86 - 25.59
6	4	548.81	7.29	1.99 - 18.66
7	4	1157.64	3.46	0.94 - 8.85
8	2	1092.43	1.83	0.22 - 6.61
Overall	71	13029.21	5.45	4.26 – 6.87

Note: Bold numbers indicate all-cause mortality rates significantly above the average for the given period ($p<0.05$).

For the under-five age group, Table 20 above shows that villages 3, 5 and 6 had the highest crude all-cause mortality rates of approximately 7 deaths per 1 000 person-years each, whilst, villages 2 and 4 did not record any deaths.

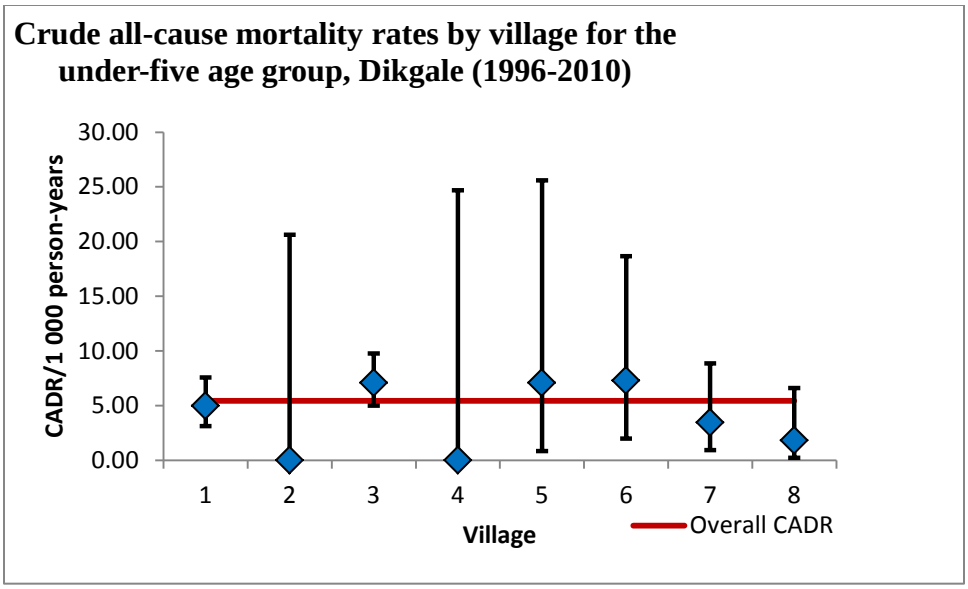

Figure 13: *Shows the crude mortality rates by village plus their corresponding 95% C.I, for the under-five age group at the Dikgale HDSS, 1996-2010*

In general, most villages had crude all-cause death rates lying between 0 deaths per 1 000 person-years and 5 deaths per 1 000 person-years (Figure 13).

Table 21: *Crude mortality rates (per 1 000 person-years) by year for the under-five age group at the Dikgale HDSS, 1996-2010*

Year	Total deaths	Person-years	Crude death rates (per 1000 person-years)	95% C.I for CADR
1996	12	1092.19	**10.99**	**5.68 - 19.19**
1997	7	1040.34	6.73	2.71 - 13.86
1998	8	988.59	8.09	3.49 - 15.95
1999	3	922.06	3.25	0.67 - 9.51
2000	2	895.47	2.23	0.27 - 8.07
2001	6	864.51	6.94	2.55 - 15.11
2002	4	807.37	4.95	1.35 - 12.69
2003	1	772.97	1.29	0.03 - 7.21
2004	3	759.46	3.95	0.81 - 11.54
2005	2	769.46	2.60	0.31 - 9.39
2006	8	771.98	10.36	4.47 - 20.42
2007	4	794.54	5.03	1.37 - 12.89
2008	6	839.19	7.15	2.62 - 15.56
2009	5	870.44	5.74	1.87 - 13.41
2010	0	840.63	0.00	0.00 - 4.39
Overall	71	13029.21	5.45	4.26 – 6.87

Note: Bold numbers indicate all-cause mortality rates significantly above the average for a given period ($p<0.05$).

The years 1996 and 2006 recorded the highest crude all-cause mortality rates of approximately 11 deaths per 1 000 person-years and 10 deaths per 1 000 person-years respectively. Of note is that the year 2010 did not record any deaths (Table 21).

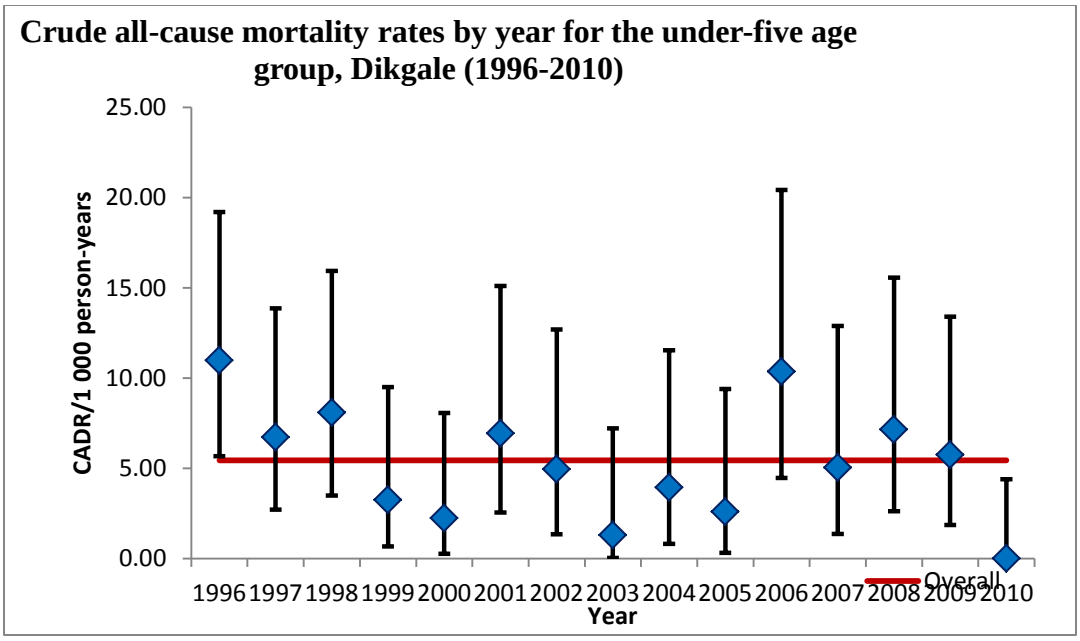

Figure 14: *Shows the crude mortality rates by year plus their corresponding 95% C.I, for the under-five age group at the Dikgale HDSS, 1996-2010*

There was a gradual decrease in the crude all-cause mortality rates from the year 2008 (which had approximately 7 deaths per 1 000 person-years) to 2010 (which recorded no deaths). Also, there was a noteworthy drop in the crude all-cause mortality rates from the years 2006 to 2007, which recorded crude all-cause mortality rates of approximately 10 deaths per 1 000 person-years to 5 deaths per 1 000 person-years respectively (Figure 14).

Noteworthy, is that there was no significant linear trend, both before (p-value=0.136) and after (p-value=0.106) the introduction of ART for the under-five age group in Dikgale.

3.2.1b. Spatial only analysis

Table 22: *Clusters of all-cause mortality for the under-five age group, using the purely spatial analysis scanning for high mortality rates in Dikgale HDSS, 1996-2010*

Age group	Cluster type	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
			All-cause				
<5	Most likely	1	3	37	28	1.63	0.166
<5	Secondary	2	5,6	6	5	1.35	0.956

Using the purely spatial scan analysis, two clusters were created but both were not statistically significant (at the 5% level) for higher all-cause mortality, in the under five age group (Table 22 and Figure 25 in Appendix 2A). Of note, is that village 3 had the highest risk (RR=1.63) of all-cause mortality and is situated in the central part of the Dikgale sub-district.

3.2.1c. Spatio-temporal analysis

Table 23: *Clusters of all-cause mortality for the under-five age group, using space-time scan analysis scanning for high mortality rates in Dikgale HDSS, 1996-2010*

Age group	Cluster Type	Years	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
				All-cause				
<5	Most likely	2006 - 2009	1	3	16	8	2.43	0.404
<5	Secondary	1997 – 1998	1	6	3	1	7.49	0.646
<5	Tertiary	1996	1	1	5	2	2.92	0.980

Three clusters were created but none was a statistically significant space–time cluster of higher all-cause mortality in the under five age group (Table 23 and Figure 25 in Appendix 2A). It is

important to mention that, village 6 had the highest risk (RR=7.49) for all-cause mortality and is located in the south-east part of the study site.

3.2.2. Adults

3.2.2a. Descriptive Statistics

Table 24: *Summary statistics for the 15-64 age group at the Dikgale HDSS, 1996-2010*

	Total	**95% C.I**
All-cause deaths	526	426.79 - 625.21
Person-years	71878.11	69997.75 - 73758.46

Table 24 above shows the total number of all-cause deaths and person-years for the 15-64 age group in Dikgale for the years 1996 – 2010.

Table 25: *Crude mortality rates (per 1 000 person-years) for the 15-64 age group by gender at the Dikgale HDSS, 1996-2010*

Gender	**All-cause deaths**	**Crude all-cause mortality rates**	**95% C.I**	**Person-years**
Female	227	6.19	5.41 – 7.05	36660.97
Male	299	8.50	7.56 – 9.51	35217.14

Males had a higher crude death rate (9 deaths per 1 000 person-years) compared to that of the females (6 deaths per 1 000 person-years) and of the mean overall crude death rate (7 deaths per 1,000 person-years) (Table 25).

Table 26: *Crude mortality rates (per 1 000 person-years) by village for the 15-64 age group at the Dikgale HDSS, 1996-2010*

Village	Total deaths	Person-years	Crude death rates (per 1000 person-years)	95% C.I for CADR
1	187	22572.59	8.28	7.14 - 9.56
2	6	1461.26	4.11	1.51 - 8.94
3	179	26921.69	6.65	5.71 - 7.70
4	9	868.52	10.36	4.74 - 19.67
5	22	1847.72	**11.91**	**7.46 - 18.03**
6	28	3761.38	7.44	4.95 - 10.76
7	46	6962.65	6.61	4.84 - 8.81
8	49	7482.31	6.55	4.84 - 8.66
Overall	526	71878.11	7.32	6.71 – 7.97

Note: Bold numbers indicate all-cause mortality rates significantly above the average for the given period ($p<0.05$).

For the 15-64 year age group, Table 26 above shows that village 5 had the highest crude all-cause mortality rate, closely followed by village 4 (with approximately 12 deaths per 1 000 person-years and 10 deaths per 1 000 person-years respectively) whilst village 2 had the lowest crude all-cause death rate of approximately 4 deaths per 1 000 person-years.

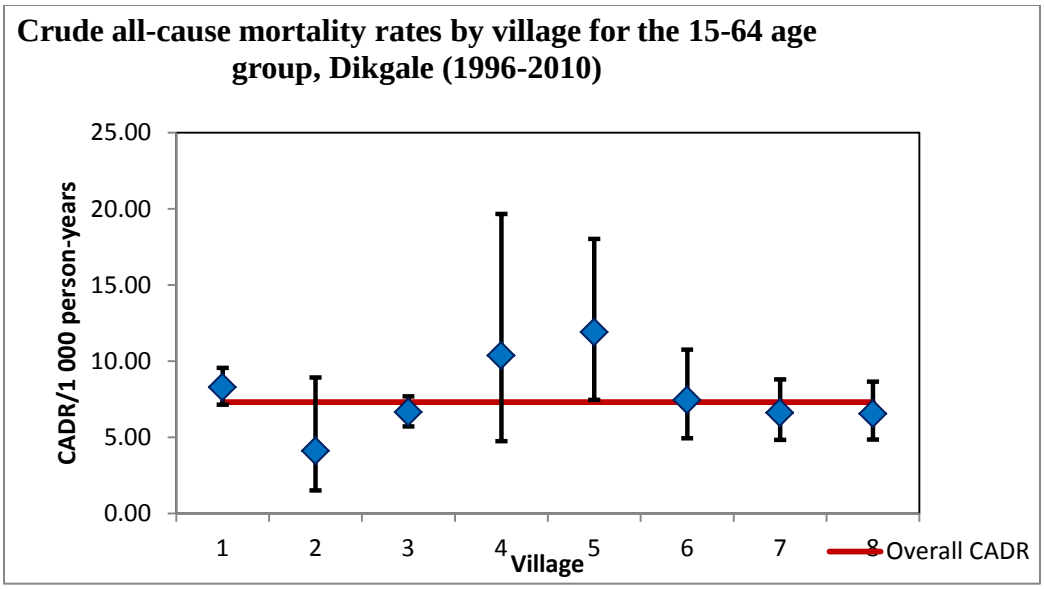

Figure 15: *Shows the crude mortality rates by village plus their corresponding 95% C.Is, for the 15-64 age group at the Dikgale HDSS, 1996-2010*

In general, most villages had crude all-cause death rates lying between 4 deaths per 1 000 person-years and 9 deaths per 1 000 person-years (Figure 15).

Table 27: *Crude mortality rates (per 1 000 person-years) by year for the 15-64 age group at the Dikgale HDSS, 1996-2010*

Year	Total deaths	Person-years	Crude death rates (per 1000 person-years)	95% C.I for CADR
1996	34	4428.27	7.68	5.32 - 10.73
1997	24	4510.86	5.32	3.41 - 7.92
1998	19	4579.58	4.15	2.50 - 6.48
1999	23	4629.71	4.97	3.15 - 7.45
2000	36	4675.12	7.70	5.39 - 10.66
2001	28	4707.90	5.95	3.95 - 8.60
2002	24	4697.64	5.11	3.27 - 7.60
2003	43	4721.76	9.11	6.59 - 12.27
2004	56	4763.43	**11.76**	**8.88 - 15.27**
2005	42	4871.38	8.62	6.21 - 11.65
2006	57	4953.87	**11.51**	**8.71 - 14.91**
2007	35	4977.85	7.03	4.90 - 9.78
2008	44	5049.74	8.71	6.33 - 11.70
2009	39	5128.50	7.60	5.41 - 10.40
2010	22	5182.50	4.25	2.66 - 6.43
Overall	526	71878.11	7.32	6.71 – 7.97

Note: Bold numbers indicate all-cause mortality rates significantly above the average for a given period ($p<0.05$).

The years 2004 and 2006 recorded the highest crude all-cause mortality rates of approximately 12 deaths per 1 000 person-years each. Moreover, the years 1998 and 2010, with approximately 4 deaths per 1 000 person-years, had the lowest crude all-cause mortality rates (Table 27).

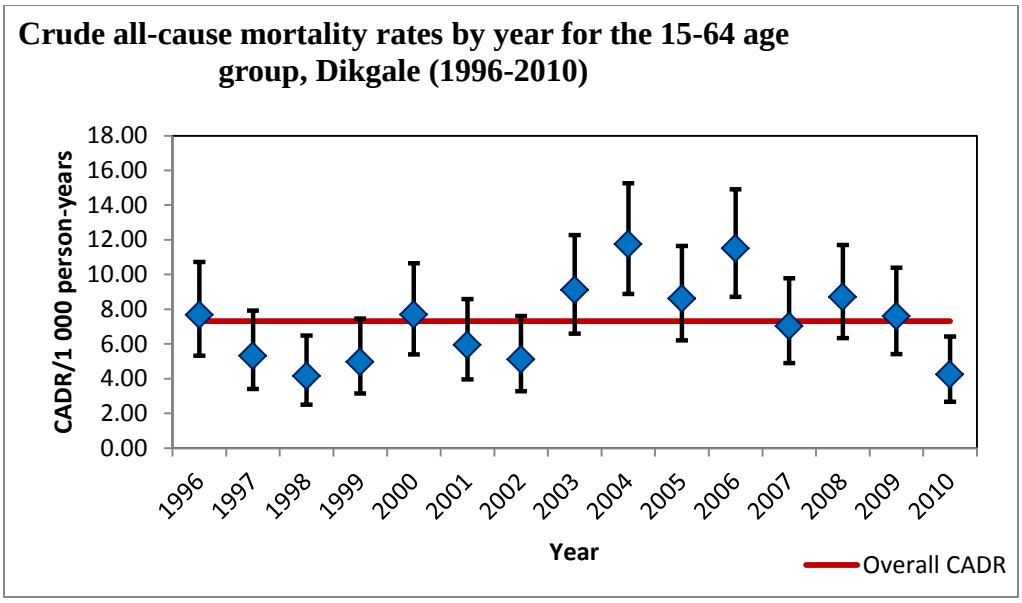

Figure 16: *Shows the crude mortality rates by year plus their corresponding 95% C.Is, for the 15-64 age group at the Dikgale HDSS, 1996-2010*

There was a gradual decrease in the crude all-cause mortality rates from the year 2008 (which had approximately 9 deaths per 1 000 person-years) to 2010 (which recorded approximately 4 deaths per 1 000 person-years). Also, there was a noteworthy drop in the crude all-cause mortality rates from the years 2006 to 2007, which recorded crude all-cause mortality rates of approximately 12 deaths per 1 000 person-years to 7 deaths per 1 000 person-years respectively (Figure 16).

Notably, there was a significant linear trend before (p-value<0.001) the introduction of ART but no significant linear trend after (p-value=0.065) the introduction of ART for the 15-64 age group in Dikgale.

3.2.2b. Spatial only analysis

Table 28: *Clusters of all-cause mortality for the 15-64 age group, using the purely spatial analysis scanning for high mortality rates in Dikgale HDSS, 1996-2010*

Age group	Cluster type	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
			All-cause				
15-64	Most likely	1	5	22	14	1.65	0.160
15-64	Secondary	1	1	187	165	1.20	0.210
15-64	Tertiary	1	4	9	6	1.42	0.863

Using the purely spatial scan analysis, three clusters were created but all were not statistically significant (at the 5% level) for higher all-cause mortality, in the 15-64 age group (Table 28 and Figure 26 in Appendix 2B). Noteworthy is that village 5 had the highest risk (RR=1.65) for all-cause mortality and is located in the south-east corner of the study site.

3.2.2c. Spatio-temporal analysis

Table 29: *Clusters of all-cause mortality for the 15-64 age group, using space-time scan analysis scanning for high mortality rates in Dikgale HDSS, 1996-2010*

Age group	Cluster Type	Years	Number of villages	Village number	Observed cases	Expected cases	Relative risk (RR)	p-Value
				All-cause				
15-64	Most likely	2003 - 2008	1	1	104	69	1.63	0.007
15-64	Secondary	2004 – 2006	3	5,6,7	34	18	1.93	0.147
15-64	Tertiary	2006	1	3	23	14	1.70	0.941
15-64	Tertiary	2001 - 2006	1	4	6	2	2.71	0.986

For the adult population, there was one statistically significant space–time cluster of higher all-cause mortality out of the four created clusters. The most likely cluster comprised one village (village 1) for the period 2003–2008 (Table 29 and Figure 27 in Appendix 2B). Worth mentioning is that village 5, again, had the highest risk (RR=3.70) for all-cause mortality and is located in the south-east corner Dikgale HDSS.

CHAPTER FOUR: DISCUSSION AND CONCLUSION

Different from cross-sectional studies (which are one-off studies) and clinical trials (which use an individual as the unit of study), HDSSs use the village (with individuals and residential units as primary subjects) as the unit of study which is followed up prospectively. This provides a wealth of detailed and valuable public health data and the ability to track changes in population and the effect of interventions over time.

4.1. Mortality trends

The results of this study have shown that after the introduction of ART in 2007 at the Agincourt and Dikgale HDSSs, both HIV-related and all-cause mortality gradually decreased over the years. This was particularly evident with the 15-64 age group were it was observed that both all-cause and HIV-related deaths were notably increasing from 1996-2007 but began to steadily decline after the initiation of ART in 2007. Although this study did not directly examine the survival of HIV-infected individuals after the initiation of ART, the findings presented do however suggest that ART does have a considerable influence on HIV-related mortality. Additionally, these results concur with the findings from the studies by Herbst et al. (2009) [12] and Jahn et al. (2005) [13]. They found evidence of a reduction in HIV-related mortality shortly after the introduction of ART in rural South Africa and rural Malawi respectively. Worth mentioning, is the peak in the crude all-cause mortality rate during the year 2006, for both HDSS sites, amongst both children and adults.

In this study, at both HDSS sites, males had slightly higher crude death rates (both all-cause and HIV-related) compared to their female counterparts, for both children and adults. The gender gap in mortality will remain unstable for quite some time because of the continued changes in the

underlying factors which are either, social, economic and behaviour change. In the long run, these factors determine health and longevity for both females and males [19].

At the Agincourt HDSS, in the under five age group, village 21 recorded both the highest crude all-cause mortality rate and crude HIV-related mortality rates. This village is situated in the upper central to west part of the Agincourt sub-district. However, in the adult population, village 15 had the highest crude all-cause and HIV-related mortality rates and this village is situated at the lower south-east corner of the Agincourt study site. This might be as a result of a highly mobile and migrant population in this village which has risk associated with it [11].

For the Dikgale HDSS, village 5, which is situated in the south-east corner of the Dikgale study site and is closer to the urban centre of Mankweng, had the highest crude all-cause mortality rates for both children and adults. While, village 2 recorded the lowest crude all-cause death rate. This village is located in the north-east part of Dikgale HDSS and is located further away from the Mankweng urban centre. These variations may or may not reflect patterns of HIV transmissions between urban and rural, as Kanjala et al. (2010) [9] speculated.

4.2. Clustering

By employing the Kulldorf's scan-statistic, this study managed to highlight high risk areas within the Agincourt and Dikgale HDSS sites. This will aid in targeting health interventions within the HDSS sites plus placing more emphasis in research regarding fundamental risk factors influencing these spatial-temporal HIV-related and all-cause mortality patterns.

4.2.1. Spatial only analysis

4.2.1a. Agincourt HDSS

Two statistically significant clusters (for the period 1996–2010) of higher all-cause mortality appeared for the under-five age group. One comprised of village 21 (upper central to west) and the other was covering villages 9 and 10 (lower central). However, there were no statistically significant clusters of higher HIV-related mortality. Of note, is that villages 19 (south-east) and 21 had the highest risk for all-cause mortality in the under-five age group. Moreover, villages 20 (south-east) and 21 had the highest risk for HIV-related deaths for the same age group.

Four clusters were created for adult all-cause mortality, but none of them were statistically significant. However, for HIV-related mortality, there were two statistically significant clusters of higher mortality comprising six and five villages respectively, for the period 1996–2010. Noteworthy, is that for all-cause and HIV-related deaths in the adult population, the most likely clusters were situated in the south-east corner of the Agincourt study site. Furthermore, villages 8, 15 (south-east) and 21 had the highest risk for all-cause mortality while, villages 8, 12 and 15 (south-east) had the highest risk for HIV-related deaths in the same population group.

The upper central to west and south-east regions of the Agincourt HDSS were consistently identified as high risk clusters, that is, there was a non-random distribution of mortality. These regions, as suggested by Kahn (2006) [20], comprise of a vulnerable subgroup (former Mozambican refugees) with poorer, less infrastructure and in general, live further away from health facilities. Moreover, in a study done in Agincourt (for the years 1992-2007) by Sartorius, et al. (2010) [11], they found that the most likely clusters were located mainly in the south-east corner and upper central parts of the Agincourt sub-district, using the purely spatial analysis scanning.

4.2.1b. Dikgale HDSS

In the under-five age group, two clusters were created but both were not statistically significant. Also, for the adult population, three clusters were created but all were not statistically significant for higher all-cause mortality. Likewise, a study done in Dikgale (for the years 1996-2007) by Kanjala, et al. (2010) [9] did not yield significant clusters of mortality after using the purely spatial analysis. Noteworthy is that villages 3 and 5 had the highest risks of all-cause mortality in the under-five and 15-64 age groups respectively.

4.2.2. Spatio-temporal analysis

4.2.2a. Agincourt HDSS

There was one statistically significant space–time cluster of higher all-cause mortality and two statistically significant space–time clusters of higher HIV-related mortality. The most likely cluster, for all-cause mortality, was situated in the central to west region of the site and comprised nine villages for the period 1996–2000. For HIV-related mortality, the most likely cluster was situated in the south-east and comprised of ten villages, for the period 2001–2007. A secondary cluster of 9 villages was situated in the south-east region of the site during the period 1996–1997.Villages 4 and 10 (lower central) had the highest risk for all-cause mortality in the under five age group. Furthermore, villages 7, 8 and 19 (south-east) had the highest risk for HIV-related deaths in the under-five age group.

One statistically significant space–time cluster of higher all-cause mortality and one statistically significant space–time cluster of higher HIV-related mortality was created for the 15-64 age group. The most likely cluster, for all-cause mortality, was situated in the central to west region

of the site and comprised nine villages for the period 1996–2000. For HIV-related mortality, the most likely cluster was situated in the central region of the site and comprised of ten villages, for the period 1996–2000. Villages 3 and 4 (central/west) had the highest risk for all-cause mortality in the 15-64 age group .Furthermore, villages 14 and 18 (central) had the highest risk for HIV-related deaths for the same age group.

Hargreaves, et al. (2004), as cited by Sartorius, et al. (2010) [11], stated that Mozambican households (which are mainly to the east of the site) generally have a lower standard of living compared to South African households, which are more to the west of the Agincourt HDSS. This may explain the high risk in HIV-related mortality in the south-east region and as suggested by Sartorius, et al. (2010) [11], the western parts of the Agincourt site may be contributing to a relatively higher spatial risk of non-communicable diseases.

4.2.2b. Dikgale HDSS

Three clusters were created but none was a statistically significant space–time cluster of higher all-cause mortality in the under five age group. Although, for the adult population, there was one statistically significant space–time cluster of higher all-cause mortality out of the four created clusters. This most likely cluster comprised one village (village 1) for the period 2003–2008. Of note is that villages 6 and 5 had the highest risks of all-cause mortality in the under-five and 15-64 age groups respectively.

These results coincide with the findings by Kanjala et al. (2010) [9], who reported that, by using the space-time analysis, village 1 emerged as the only significant high-risk cluster. They went on to comment that, the central part of the Dikgale HDSS, which appears to have been less affected by increasing adult mortality, has the availability of HIV counselling, testing and treatment

services. This may explain why none of the villages in the central part of the site had significant high-risk clusters of all-cause mortality.

4.3. Conclusion

The hypothesis for this study was to observe if there was any significant change in clusters before and after the introduction of ART. The space-time analysis results for Agincourt, for both age groups, showed that significant clusters of HIV-related mortality were only detected before the introduction of ART (1996-2000). As for the Dikgale HDSS, significant clusters of all-cause mortality were observed before and just after the introduction of ART (1996-2008). Therefore, with that in mind, one can perceive that ART rollout did significantly change patterns and reduce the number of clusters of mortality.

Finally, this work revealed the existence of spatial-temporal clusters of both child and adult mortality at Agincourt and Dikgale HDSSs and that HIV-related mortality decreased with the introduction of ART in rural South Africa. There is therefore need to continue targeting prevention of HIV-related infections through increasing ART treatment, free at point of use, in rural South Africa and other regions.

4.4. Recommendations

In as much as the findings of this study will certainly aid in targeting health interventions within the two HDSS sites, it is important, for future studies, to take into account socio-demographic characteristics so as to determine fundamental risk factors influencing these spatial-temporal HIV-related and all-cause mortality patterns.

Also, other methods of analysis, such as the Bayesian smoothing techniques, which take into account the heterogeneity of the population at risk, can be employed, as suggested by Sankoh et al. (2002) [21].

Again, instead of analyzing all-cause mortality as a whole, cause-specific mortality can be used to help determine specific diseases affecting certain villages/areas and thus, assist in the appropriate allocation of public health resources for better health outcomes. Resources should not be uniformly distributed across villages, as this study has shown that there exist geographical variations in mortality. Villages that are constantly identified as high risk areas can be targeted for HIV/AIDS prevention programs based on health education by promoting best practices in HIV/AIDS prevention and sexual health education.

To conclude, the application of GIS and spatial scan statistics can help policy makers and public health workers to better understand mortality patterns both in space and time, thus, aiding them with their investigations for potential disease clusters and to firmly ascertain that a problem truly exists.

Appendix

Appendix 1: Maps for Agincourt HDSS

Appendix 1A

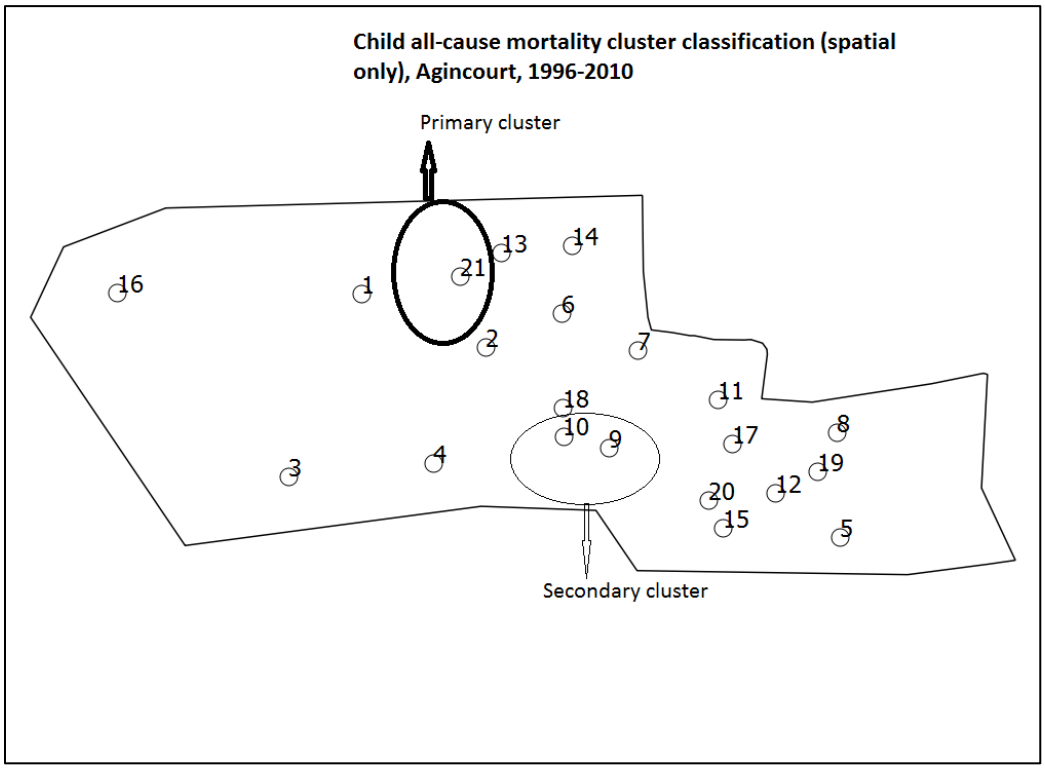

Figure 17: *Shows clusters of spatial all-cause child mortality at the Agincourt HDSS, 1996-2010*

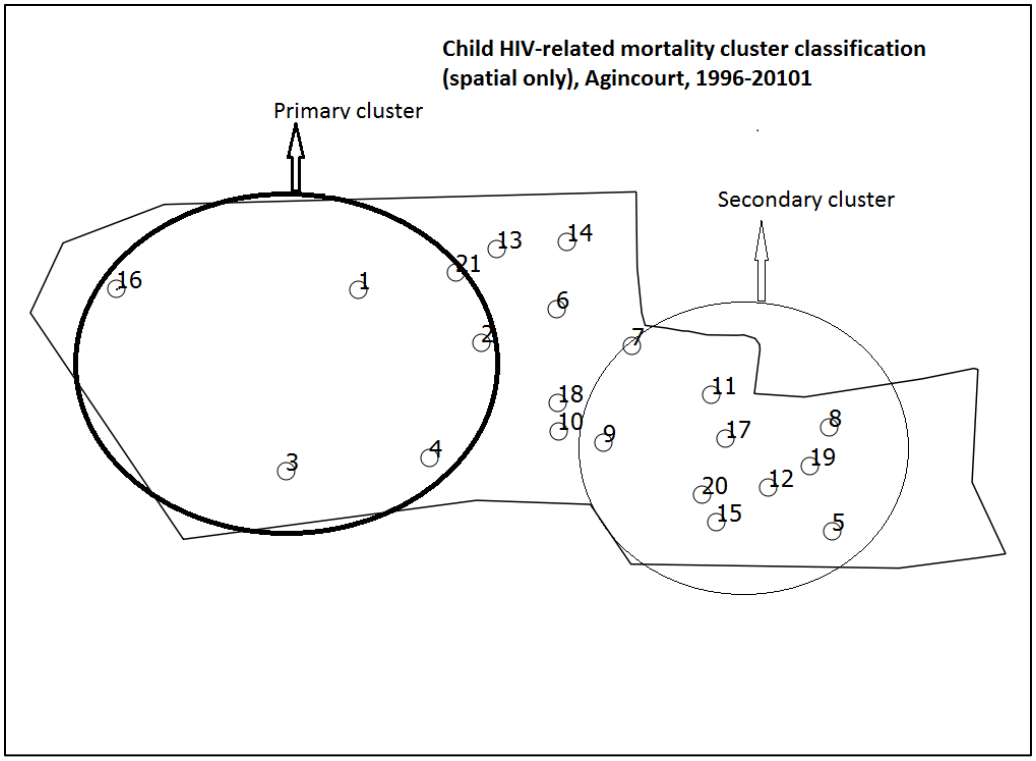

Figure 18: *Shows clusters of spatial HIV-related child mortality at the Agincourt HDSS, 1996-2010*

Appendix 1B

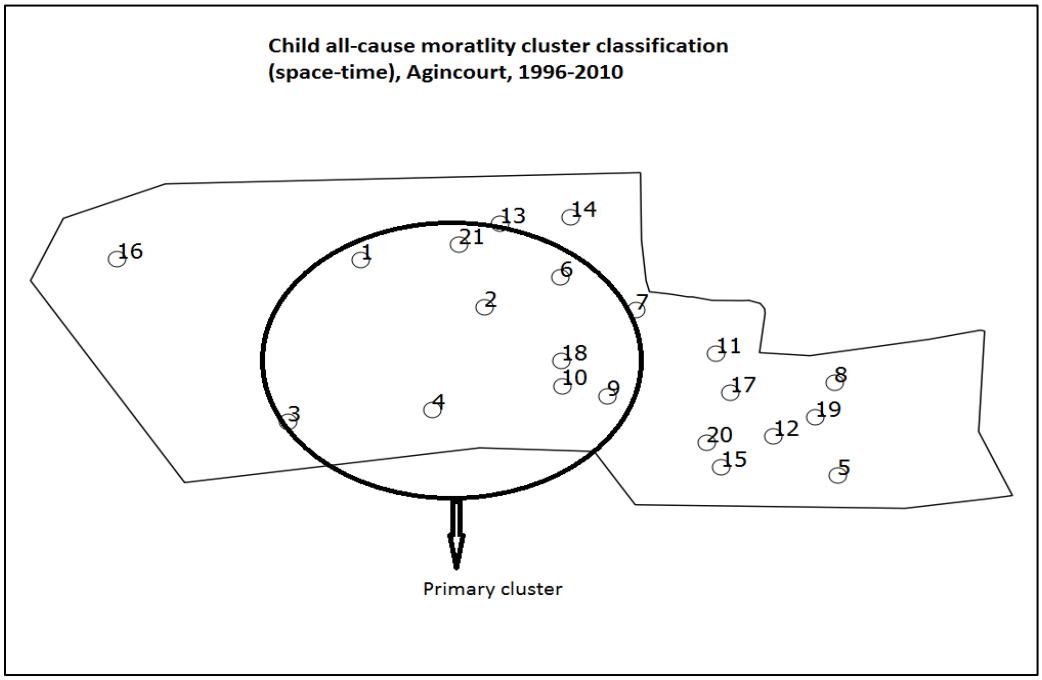

Figure 19: *Shows clusters of temporal all-cause child mortality at the Agincourt HDSS, 1996-2010*

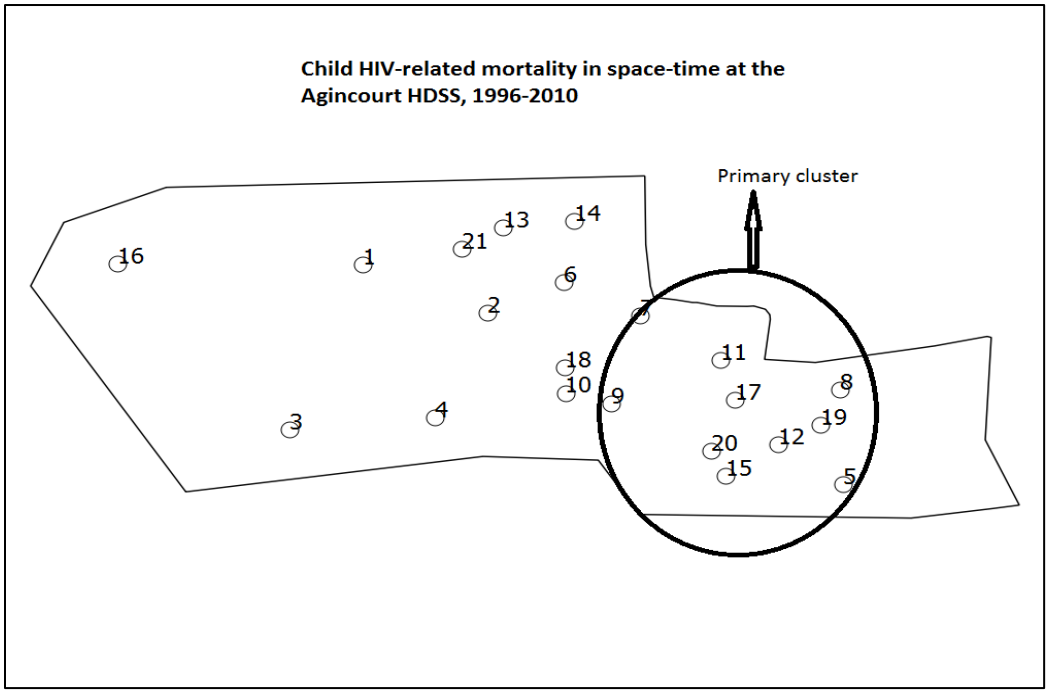

Figure 20: *Shows clusters of temporal HIV-related child mortality at the Agincourt HDSS, 1996-2010*

Appendix 1C

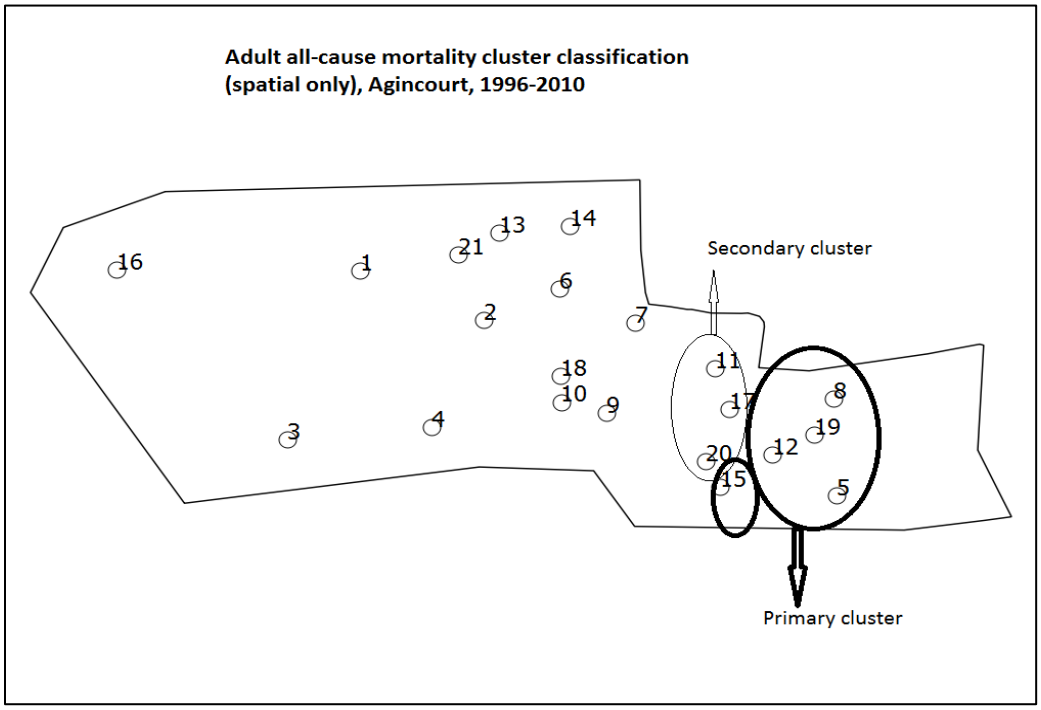

Figure 21: *Shows clusters of spatial all-cause adult mortality at the Agincourt HDSS, 1996-2010*

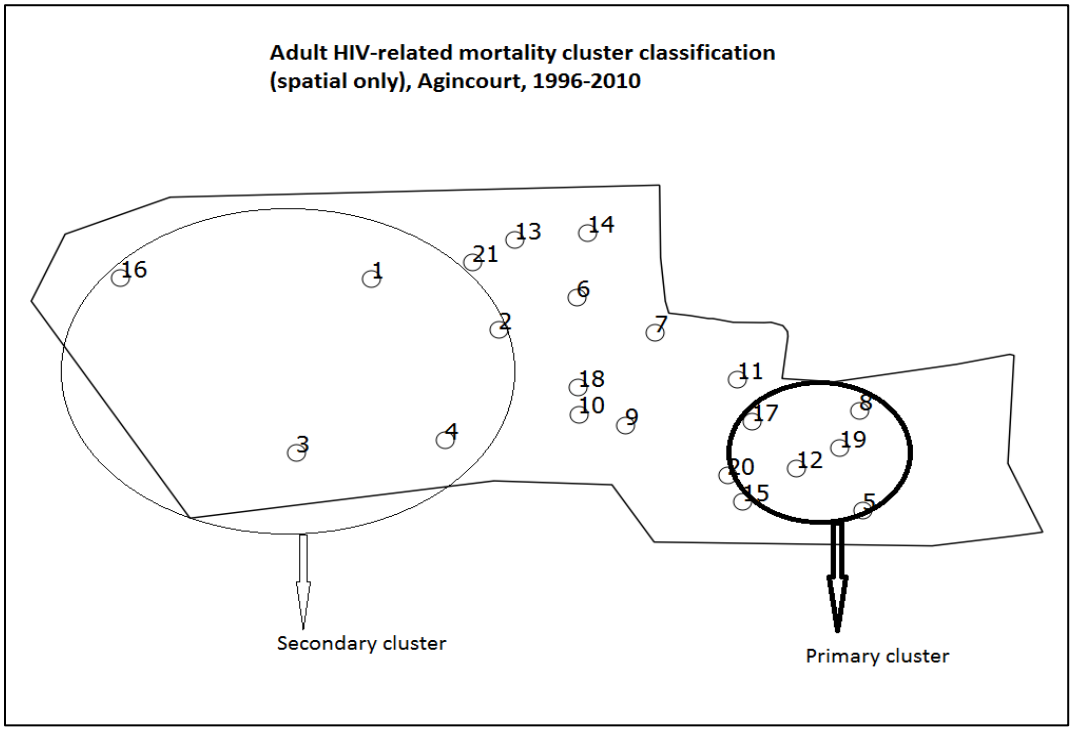

Figure 22: *Shows clusters of spatial HIV-related adult mortality at the Agincourt HDSS, 1996-2010*

Appendix 1D

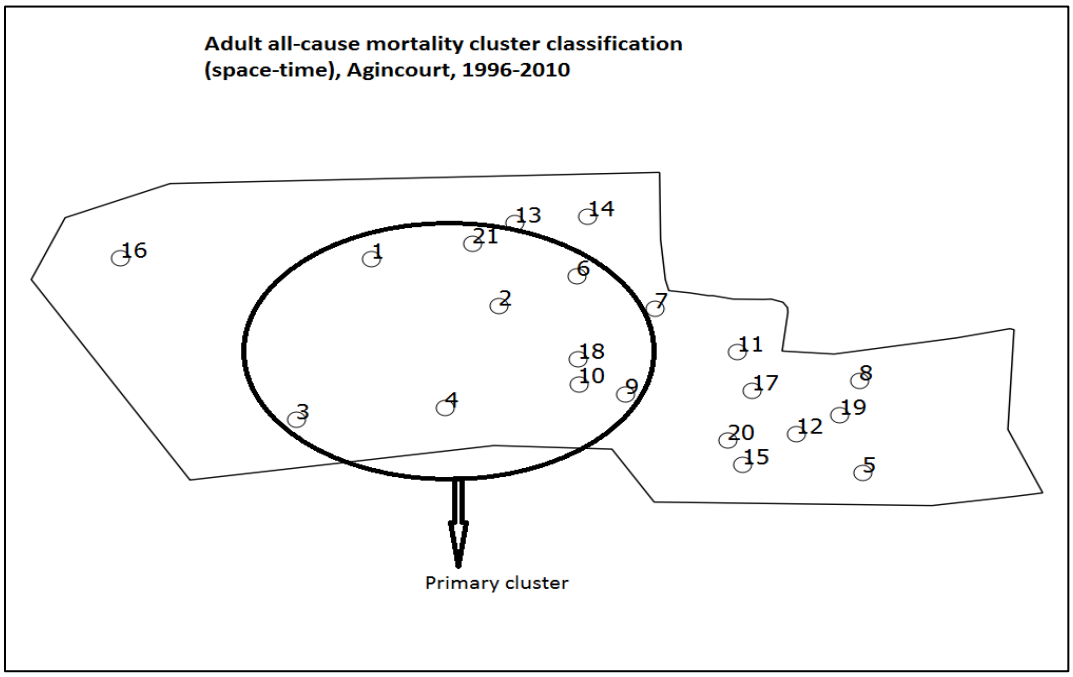

Figure 23: *Shows clusters of temporal all-cause adult mortality at the Agincourt HDSS, 1996-2010*

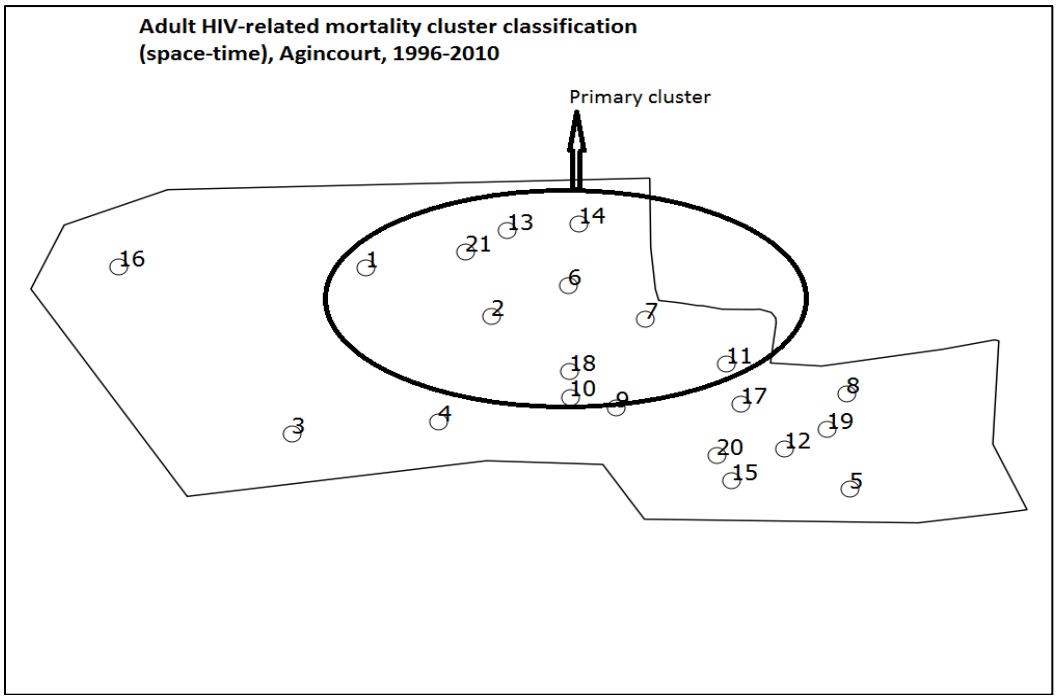

Figure 24: *Shows clusters of temporal HIV-related adult mortality at the Agincourt HDSS, 1996-2010*

Appendix 2: Maps for Dikgale HDSS

Appendix 2A

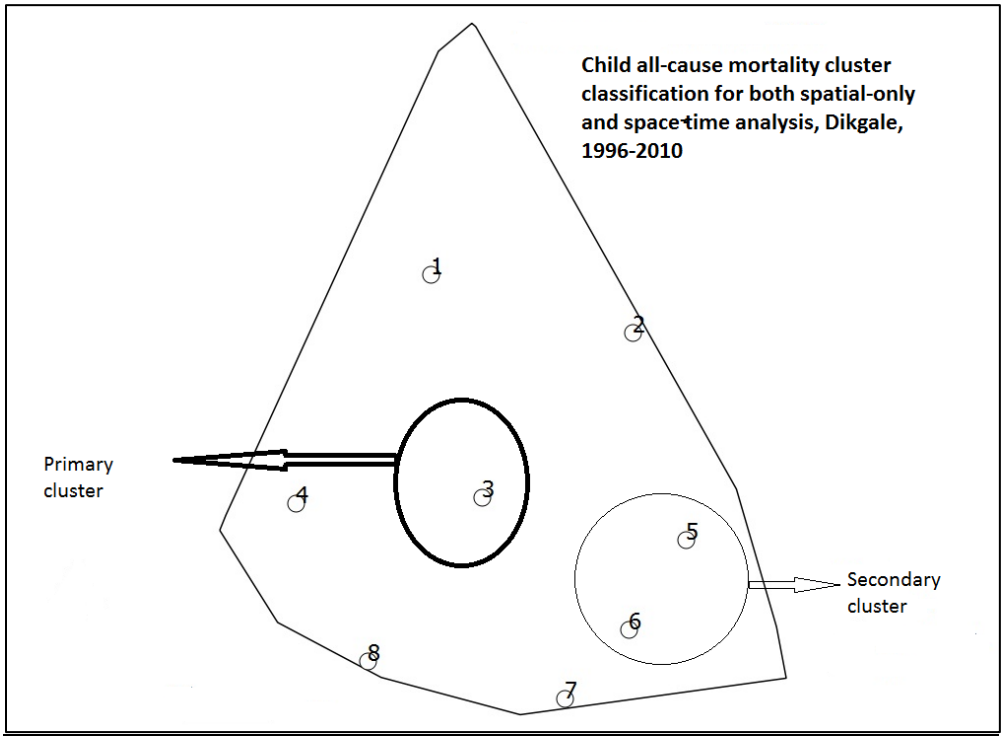

Figure 25: *Shows clusters of both spatial and temporal all-cause child mortality at the Dikgale HDSS, 1996-2010*

Appendix 2B

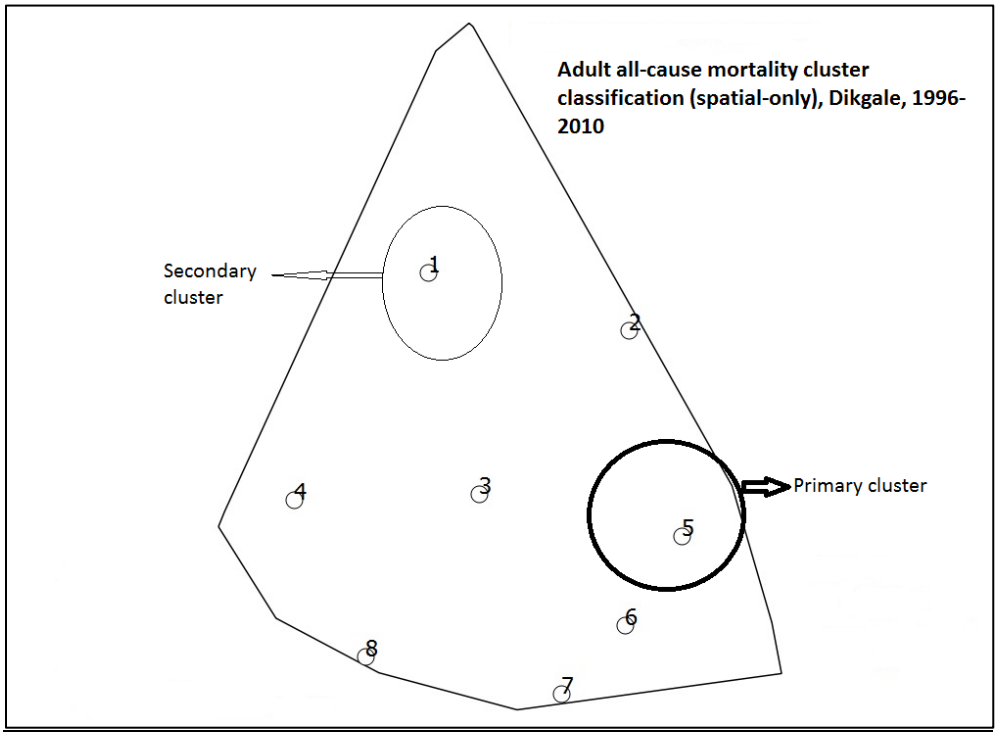

Figure 26: *Shows clusters of spatial all-cause adult mortality at the Dikgale HDSS, 1996-2010*

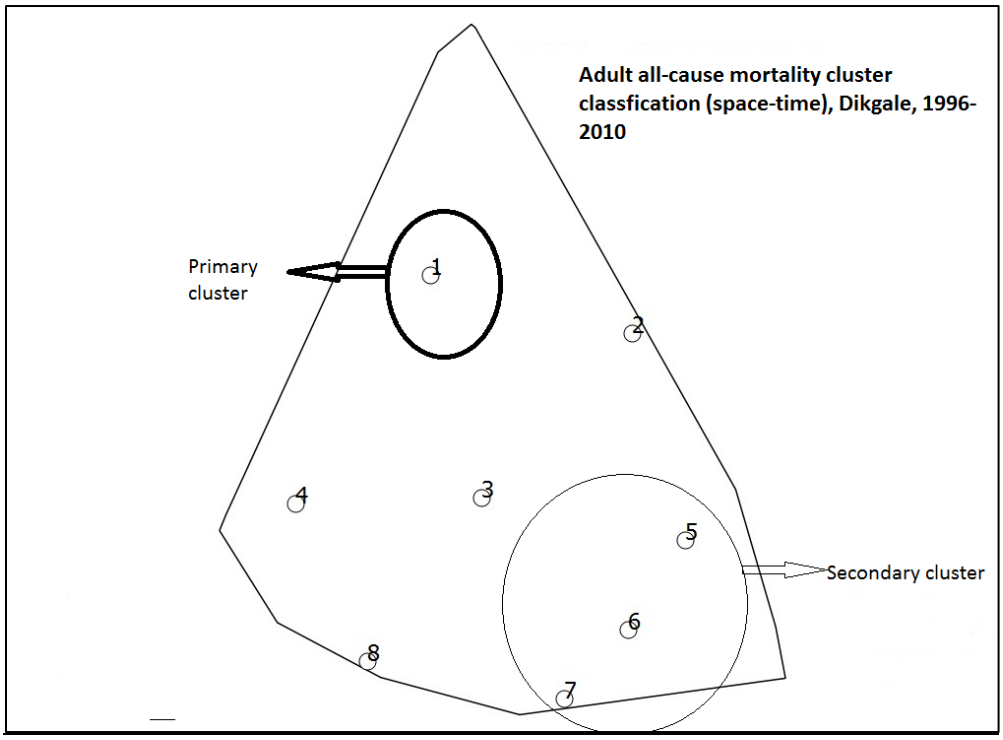

Figure 27: *Shows clusters of temporal all-cause adult mortality at the Dikgale HDSS, 1996-2010*

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Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Sikhuphukile G Ndebele

CLEARANCE CERTIFICATE **M120942**

PROJECT Clustering of Child and Adult Mortality at Agincourt and Dikgale Health and Demographics Surveillance Systems in South Africa: Pre and Post Human Immunodefiency Virus Anti-Retroviral Treatment Roll-Out

INVESTIGATORS Ms Sikhuphukile G Ndebele.

DEPARTMENT School of Public Health

DATE CONSIDERED 29/08/2012

DECISION OF THE COMMITTEE* Approved unconditionally

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

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Ben Sartorius

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...