UNIVERSITY OF THE WITWATERSRAND

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SCHOOL OF PUBLIC HEALTH

RESEARCH REPORT

ASSOCIATION BETWEEN MATERNAL FACTORS AND SURVIVAL PATTERNS OF CHILDREN, IN RURAL KWAZULU-NATAL, SOUTH AFRICA, 2004-2011.

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A research report submitted to the School of Public Health, University of Witwatersrand Johannesburg in partial fulfillment of the requirements for the degree of Masters of Science (Medicine) in Population based Field Epidemiology

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DECLARATION

I, Anne Njeri Makumi hereby declare that this research is my own work. It is being submitted for the degree of Masters of Science (Medicine) in the field of Population Based Field Epidemiology at the University of Witwatersrand, Johannesburg. It has not been submitted entirely or partially for any degree or examination at this or any other university.

Signature: 

Date: 30th October 2013

DEDICATION

I wish to dedicate this research report to my adorable parents William Makumi and Isabelle Kamau and my loving siblings Christine, Hellen and Kevin for their prayers, support and encouragement during my study period at the University of Witwatersrand in Johannesburg, South Africa.

ABSTRACT

Globally, child mortality is a great concern, especially in resource-limited settings. The Millennium Development Goal (MDG) 4 was set with an aim to reduce under-5 child mortality by two-thirds between 1990 and 2015**.** This study examines mortality trends in infants, 1-4 and above 5-year-old children in rural KwaZulu-Natal, South Africa, the causes of death as well as the association of maternal HIV status and Antiretroviral Treatment (ART) usage to child mortality.

We use a longitudinal birth cohort study design of children born between 1st January 2004 and 31st December 2010, in the Africa Centre Demographic Surveillance Area (DSA) in rural KwaZulu-Natal, South Africa. Children had to have been resident in the DSA at the time of birth.

A total of 12,413 children born in the study period were eligible for this study. The main outcome measure was mortality either in infancy, the 1-4 year period or at 5 and above years of age, while assessing its association with maternal HIV and Antiretroviral Treatment uptake (ART) status on a time-varying basis. A total of 619 children died during the study period and mortality was observed to be highest in the infant group with 67% of the children dying in infancy. Fifteen percent of mothers were HIV positive at the time of birth of the child, about 59% were HIV negative while the HIV status of the rest was unknown.

There was a three-fold increase in mortality observed for both infants and 1-4 year olds, who had mothers who were HIV infected compared to children whose mothers were HIV negative ($p<0.05$). Children whose mothers were on Antiretroviral

Treatment (ART) however had a reduced mortality compared to those whose mothers were not on treatment. Infants and 1-4year olds whose mothers HIV status was not reported had a two-fold increase in mortality. Low maternal education, single motherhood, multiple births and parity of four or more children were also associated with increased child mortality.

We concluded that although mortality varied by the age of the child, children born to mothers who were HIV positive had higher mortality rates than children born to HIV negative mothers but being on Anti Retroviral Treatment (ART) reduced children mortality. Interventions targeting HIV positive pregnant women and mothers should be carried out in the study area, with specific emphasis on reducing child mortality associated with maternal HIV status.

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DEFINITION OF TERMS

Resident participant- A member of a household residing at a physical structure within the Demographic Surveillance Area of the Africa Centre at a particular point in time **[15]**.

Asset Quintile- Wealth index as developed for use with Demographic & Health Survey data **[51].** It includes household owned items, drinking water sources, main cooking fuel, toilet type and electricity connection to the homestead. It ranges from poorest to the wealthiest **[42]**.

ACRONYMS

ART-Antiretroviral Treatment

DSA-Demographic Surveillance Area

DSS-Demographic Surveillance System

SSA-Sub-Saharan Africa

MTCT-Mother to Child Transmission

MDG-Millennium Development Goal

HIV-Human Immunodeficiency Virus

AIDS-Acquired immune deficiency syndrome

WHO-World Health Organization

PMTCT-Preventing Mother To Child Transmission

SA-South Africa

ACDIS-Africa Centre Demographic Information System

ARTemis-Antiretroviral Treatment management information System

PCV-Pneumococcal Conjugate Vaccine

RV-Rotavirus Vaccine

GBD-Global Burden of Disease

AIC-Akaike Information Criteria

PCA-Principal Component Analysis

SQL-Structured Query Language

CHAPTER 1: INTRODUCTION

In this chapter, background information on child survival is reviewed relating to the effect of maternal HIV status and antiretroviral therapy (ART) usage on child survival. The importance of maternal ART usage for child survival is explained. The published literature on maternal HIV and ART usage impact on child survival is reviewed and this chapter ends with a description of the aims and objectives of the study.

1.1 Background

Globally, child mortality is a great concern, especially in resource-limited settings. An estimated 6.9 million children died before reaching their 5th birthday globally in 2011 **[1].** The Millennium Development Goal (MDG) 4 was set with an aim to reduce under-5 child mortality by two-thirds between 1990 and 2015 **[2].** With less than three years to 2015, reaching the target still remains a challenge, as the rate of improvement worldwide is low, and in some countries progress is slow or non-existent **[2]**. Globally, under-5 mortality has been reduced by 41% between 1990 and 2011, from 87 deaths per 1000 live births to 51 deaths per 1000 live births **[1].** Sub-Saharan Africa (SSA), one of the regions with the highest levels of under-5 mortality globally and high HIV prevalence, has achieved a reduction in child mortality of 39% during this period, from 178 to 109 deaths per 1000 live births**,** between 1990 and 2011 **[1].** South Africa, a middle-income country in SSA, had under-5 mortality reduced from 62 to 47 deaths per 1000 live births over the same period **[1]**.

Child mortality varies by age. Older children experience lower mortality compared to the younger children, and health interventions needed to address causes of death in the various age groups thus differ. Globally, neonatal deaths have been shown to be declining at a slower rate of 1.8% annually compared to the under-5 mortality, which has been reducing at a rate of 2.5% annually between 1990 and 2010 **[1]**. The SSA region had the highest neonatal mortality rate at 34 deaths per 1000 live births in 2011, with the least improvement of 24% reported compared to other developing regions worldwide which saw an improvement of between 55% and 61% between 1990 and 2010/2011 **[1, 2]**. In 2011 the estimated neonatal mortality rate for South Africa was 19 deaths per 1000 live births, while infant mortality was 35 deaths per 1000 live births and the under-5 mortality rate 47 deaths per 1000 live births **[1]**. A lower mortality rate than the under-5 is expected in the over 4 year age group as was shown in Mozambique, where 5-10 years had a mortality rate of 2.8 per 1000 person years at risk, compared to the infants and 1- 5 years of 46.9 and 17.7 per 1000 person years at risk, respectively **[3]**.

A major contributor to increased child mortality is HIV **[5]**. SSA is said to be the most HIV burdened region in the world, with 69% of all HIV-infected people (adults and children) in 2011 **[5].** It is also reported to be home to 90% of all HIV-infected children (the majority of whom are infected via mother-to-child transmission) and 89% of the estimated 16.6 million children orphaned by AIDS **[5].** Mortality risk is increased for all children born to HIV-positive mothers irrespective of their own HIV status, **[21,28]** although their survival also depends on whether the child is HIV infected or not **[6, 21, 28].** In populations with high HIV prevalence, HIV is an important cause of death in young children, directly through mother-to-child

transmission **[29]**, and indirectly through orphan hood and parental illness. In a study in rural South Africa, female adolescent orphans were shown to be at significantly increased risk of HIV infection **[30]**. Most children acquire HIV through mother-to-child transmission (MTCT) before birth (in-utero), at delivery (intra-partum) or during breastfeeding (post-natal) **[31]**. In 2010, there were about 1,200 new infections in children less than 15 years of age every day, more than 90% of which occurred in the developing countries **[7]**.

Antiretroviral treatment (ART) delays HIV disease progression and substantially decreases mortality rates **[32]**. As per current WHO (and South African) guidelines, adult patients with CD4 cell counts <350/mm^3, and those with WHO clinical stage III/IV disease are eligible for ART initiation, while all infected children under-5 are eligible for ART enrollment irrespective of CD4 cell count **[8,33].** Without antiretroviral treatment, close to 50% of children who were infected in-utero or intra-partum do not survive to their second birthday **[21].** Children who acquire infection through breastfeeding after 4 weeks of age have a lower risk of death than those who are perinatally infected **[10,34].**

ART coverage has dramatically increased over the years and SSA has achieved an estimated 56% coverage of persons eligible in 2011 **[5],** although children eligible for ART treatment are accessing ART at a lower rate compared to women as shown in a study in South Africa **[35].** The ART programme was rolled out from 2004 in South Africa and about 52% of adults who became ART-eligible in 2010/2011 were accessing ART **[35]**. In rural South Africa, there is evidence of reduction in HIV-related mortality in women (22%) and men (29%) as well as a decline of 31% in

children mortality between 2000 and 2006 **[8,12]**.

Child survival patterns vary with age, and the impact of maternal HIV status and ART usage need to be examined, as well as other likely factors, in order to inform key interventions targeted at achieving MDG4 in South Africa. This study examines mortality in infants, 1-4 and above 5-year-old children in rural KwaZulu-Natal, South Africa, and the impact of maternal HIV status and ART usage on child mortality.

1.2 Problem Statement

Despite the steady progress in improving child survival in SSA, there is still need for action to address the leading causes of death: diarrhoea, malaria, and pneumonia, which account for about half of deaths in children under-5 years old. Malnutrition is also an important cause of death in children in this age group. Efforts to fight these diseases while improving nutrition for the children is required to save children lives **[2].** In 2010, worldwide, an estimated 64% of children who died before age 5 years died of infectious causes such as pneumonia, diarrhoea and malaria **[13].** Half of all deaths in infants were due to lower respiratory infections (LRI) (20.1%), diarrhoea (17.4%), and malaria (11.8%), while HIV/AIDS accounted for 1.5% of deaths. In 1-4 year olds, malaria (20.8%), LRI (12.4%), diarrhoea (11.%) and HIV/AIDS (4.9%) were the main causes of death, while in the children above 5 years of age, HIV/TB, injuries and some cancers were the main causes of death, although mortality overall was low in this age group **[36]**. An estimated 40% of the under-5 deaths were in neonates and these died mainly due to preterm birth complications, estimated at 28.6% **[13, 36]**.

The largest numbers of these deaths were in Africa, with SSA bearing the biggest burden. Globally, deaths in children under-5 years accounted for 13% of all deaths in 2010 **[40].** Research has shown that HIV dominates the causes of child mortality in addition to respiratory infections and diarrhoea in South Africa unlike other SSA countries where malaria is endemic and is reported as the leading cause of death **[14]**. Among children aged 5 years or above in South Africa, HIV has also been reported as the leading cause of mortality, in addition to injuries **[14].** In 2011**,** over 5 million persons were living with HIV and the prevalence was 10.6% in South Africa **[17]**, which may negatively impact on child survival. HIV prevalence in the study setting in KwaZulu-Natal province is estimated at 21.5% overall with 51% of women aged 25-29 years said to be HIV infected **[27]**. A considerable increase in mortality rates due to HIV had been reported in the Demographic surveillance area of Africa Centre before ART rollout **[15].**

The rapid scaling up of ART in South Africa has led to a reduction in adult HIV-related mortality and increased survival of HIV infected persons. HIV treatment and care access grew by 63% around the world between 2010 and 2011, with SSA experiencing a 59% increase in that period **[5].** South Africa had an increase of 75% during the same period **[5]**. A study in rural KwaZulu-Natal South Africa showed that maternal survival of HIV infected mothers on ART was associated with a decline of 49% in infant mortality between 2000 and 2006 **[11]**. With the rapid scaling up of HIV treatment in South Africa and the effect of treatment on child and adult mortality, there is need to continuously assess the impact of ART on child survival at a population level. ART coverage among children in low and middle-income countries has been lower than that among adults; 28 per cent of all children under-15

years in need of treatment in low- and middle- income countries have access to HIV treatment **[2]**. The effect of HIV treatment on child survival may be two fold, directly through treatment of the HIV-infected children or indirectly in both HIV-infected and uninfected children, through treating their HIV-infected parents **[11]**.

Overall, child survival depends on a set of proximate determinants **[16]** grouped into: maternal factors, environmental contamination, nutrition deficiency, injury and personal illness control. Maternal factors influence pregnancy outcome, maternal health and consequently child survival. They include maternal age, birth spacing, delivery complications, parity, maternal HIV status, maternal ART history, maternal survival, and maternal education. Nutrition factors, which relate to availability or the intake of the three major classes of nutrients by the child and the mother, including deficiency in carbohydrates, protein or vitamins and minerals, also have a bearing on the risk of dying.

Environmental contamination factors which refer to transmission of infectious agents to children and their mothers through air, food, water, fingers, soil, skin and insect vectors **[16]**. Injury factors that could be accidental or intentional, whose frequency and pattern in a population reflect risks that may be socioeconomically or environmentally different **[16]**. They include physical injury, burn and poisoning. Personal illness control factors may be preventive for healthy persons or medical treatment relating to measures taken to cure diseases. They include observing taboos, immunizations, and treatment against disease **[16]**.

The study aims to quantify the impact of maternal HIV status and ART usage on mortality in infants, 1-4 and 5 + year old children, and to investigate other factors associated with child mortality, using data from a Demographic Surveillance in rural KwaZulu-Natal.

1.3 Justification of the research

Child survival is known to have an impact on the future development of any country. Children below the age of 10 years of age comprise approximately 21% of the South African population as at 2011 **[17]**. In 2010, KwaZulu-Natal province was one of the two provinces with the highest number of children alive under-5 years in South Africa **[6].** Knowledge on the causes of mortality, mortality rates and patterns of children in South Africa will help focus efforts on areas contributing the most to the number of deaths and hence develop interventions aimed at reducing child mortality in line with MDG4.

Research has shown that HIV treatment, through ART, has direct effects on child survival, and there is increased recommendation for research efforts on the indirect effects of HIV infection of parents on their children's health and survival **[4].** Indirect effects such as maternal survival of HIV positive mothers who are on ART are expected to positively impact on child survival **[11]**. This research will therefore explore the association of child mortality with maternal survival while adjusting for maternal HIV and ART status and child ART status. The study will also investigate other factors that are related to child survival such as maternal education and maternal age at birth to determine their effect on child survival.

Most of the research on child mortality has mainly focused on under-5 mortality. It is not clear to what levels of HIV affects survival in children above the age of 5 years, and this study will therefore investigate survival experiences of children aged between 5 – 8 years in addition to the under 5 year olds.

1.4 Literature review

Globally pneumonia, preterm birth complications, diarrhoea, intrapartum-related complications, and malaria as well as under nutrition are the major causes of under-5 mortality **[1].** In SSA, causes of mortality among children above 5 years are reported to be similar to those of under-5 year olds, although the older children have much lower mortality rates than the younger ones **[14].** In South Africa, the main causes of mortality in children above 5 years of age are HIV at about 5 deaths per 1000 person years and injury estimated at 1 death per 1000 person years. Other factors include tuberculosis, diarrhoea and respiratory infections **[14].**

Worldwide, in 2011, neonatal mortality was estimated at 22 deaths per 1000 live births, while under-5 mortality was estimated as 51 deaths per 1000 live births **[1]**. The global burden of under-5 mortality is concentrated in SSA, where under-5 mortality was estimated at 109 deaths per 1000 live births, 69 deaths per 1000 live births for infant mortality and 34 deaths per 1000 live births in neonatal deaths in 2011 **[1].** In South Africa under-5 mortality was estimated at 47 deaths per 1000 live births, while infant mortality was 35 deaths per 1000 live births and neonatal mortality were 19 deaths per 1000 live births in 2011 **[1].**

HIV is a major cause of mortality in South Africa, both among adults and children

[14]. This is despite the rollout of ART in 2004, which was expected to improve child survival as has been shown in other studies **[11, 18].** There was evidence in 2006 that the public sector ART rollout in rural South Africa had an effect on reducing adult population mortality, with an approximate reduction of 22% in women**,** compared to the pre-ART period **[12]**. The risk of under-5 child mortality was four-fold if the mother was HIV infected and three-fold if the mother died, compared to a HIV uninfected mother **[11, 19]**. In South Africa, HIV prevalence among antenatal women in 2010 was estimated at 30.2%, with KwaZulu-Natal province having the highest HIV prevalence at 39.5% **[20].** Maternal ART has been shown to have a greater impact on reduction of child mortality than PMTCT (with single-dose nevirapine only) programmes in rural KwaZulu-Natal **[8]**, as the survival of the mother benefits both the infected and uninfected children. Maternal death and immunological status has also been shown to be associated with child mortality **[21]**.

Children were reported to be relatively late at presentation for HIV treatment initiation with a median age of 74 months (range 4 to 180 months) in this setting **[22].** The HIV disease in most of these children had advanced with two-thirds in WHO clinical stage III / IV and a further one-fifth were on tuberculosis treatment. Only one-tenth of the children on HIV treatment were under 18 months of age **[22].** In 2010, SA PMTCT guidelines recommended that all infants who are HIV infected should be initiated on HIV treatment immediately irrespective of CD4 cell count; this has recently been revised in April 2013 to include all children under-5 years **[33]**. There is need therefore to investigate the effect of child HIV treatment along with maternal mortality, maternal HIV status and ART history on the child's survival.

Under-5 mortality has been shown to be high in rural areas and in particular poorer households, even in regions where child mortality is low **[2].** The Africa Centre Demographic Surveillance Site (DSS) area, which is predominantly rural, has high child mortality as reported in previous studies **[14,18].** It has also been shown that children surviving infancy are still vulnerable to mortality **[18].** The 0-4 years age group have experienced reduced HIV-related mortality between the year 2000 and 2009, while the 5-14 years age group had a varying HIV-related mortality in the same period in the study area **[23]**. Given the high HIV prevalence in KwaZulu-Natal, there is therefore need to investigate further the varying patterns of HIV-related mortality in the first 8 years of life in light of maternal HIV status, maternal ART usage, child ART usage.

Maternal education has been reported as a significant determinant of child survival, with chances of survival increasing with the mother's education level **[2, 8].** Its impact is said to be greater than both income level and access to health facilities combined **[24**]. In our study area, children born to mothers with at least primary education had a 21% significantly increased risk of dying compared to children whose mothers had post-primary education, with most mothers (72%) seen to have at least primary education in the area between the periods 2000 and 2006 **[8]**.

A fully immunized child has a significantly reduced risk of child mortality and morbidity, especially from vaccine-preventable diseases **[25, 37]**. The study setting has been reported to have high coverage of childhood vaccination **[26]**. However, children born to HIV positive mothers in the area were shown to be significantly less likely to receive timely routine childhood vaccinations or to be fully immunized than

children born to HIV negative mothers, despite overall high coverage of childhood vaccination in the area [**26**]. However, no study has investigated the effect of vaccination coverage on child survival in this setting and more so following the recent roll out of pneumococcal and rotavirus vaccines. Information on child mortality in KwaZulu-Natal is thus necessary to help determine survival patterns at the various ages, especially with reference to the maternal HIV status and ART usage as well as the child's ART usage, immunization status, and other socio-demographic factors, given the big burden of the HIV epidemic in South Africa and specifically in the province.

1.5 Hypothesis

1 There is no difference in child survival between children of mothers who are HIV infected and HIV negative mothers.

2 There is no difference in child survival between children of HIV positive mothers who are on ART treatment and HIV positive mothers not on ART treatment.

1.6 Study aim and objectives

The aim of this study is to find out how maternal survival, maternal ART status and Child ART status affect child mortality in a demographic surveillance system in rural KwaZulu-Natal, South Africa.

Objectives

1 To describe the socio-demographic characteristics of infants, 1-4 and 5-8 year olds in a DSS in KwaZulu-Natal from 2004 to 2011.

2 To estimate trends in mortality and causes of death in infants, 1-4 and 5-8 year olds in a DSS in KwaZulu-Natal from 2004 to 2011.

3 To investigate maternal factors of child mortality, including ART treatment and maternal survival in infants, 1-4 and 5-8 year olds, in a DSS in Kwa-Zulu-Natal from 2004 to 2011.

CHAPTER 2: METHODOLOGY

2.0 Introduction

This Chapter gives background information on the study area, the study design, and criteria used for study population selection. The measurement methods and materials used are also described as well as the data sources and outcome of interest in this study. Data management processes and analysis have also been described in this chapter in detail.

2.1 Study setting

The Africa Centre Demographic Surveillance Area (DSA) is in uMkhanyakude district of KwaZulu-Natal province South Africa, and located near Mtubatuba town. It is 438km^2 in size and each census round includes a population of approximately 90,000 Zulu-speaking people in 11,000 households **[8, 15]**. It is a predominantly rural area, with an urban township and informal peri-urban settlements, with large variations in population densities, and homesteads are scattered rather than grouped. The principal source of income in the surveillance area is waged employment and state pensions. **[15]**

The community in this area faces a rapid and severe HIV epidemic. The KwaZulu-Natal province is known to have the highest HIV prevalence in South Africa, with a HIV prevalence of 39.5% in antenatal women in 2010. The uMkhanyakude district where the Africa Centre DSA is located also has highest HIV prevalence, 41.9%, in the country among antenatal women **[20]**.

KwaZulu-Natal province is also one of the two provinces in South Africa with the largest number (> 1 million) of children under5 years of age alive as of 2010. **[6].**

2.1.1 Study design

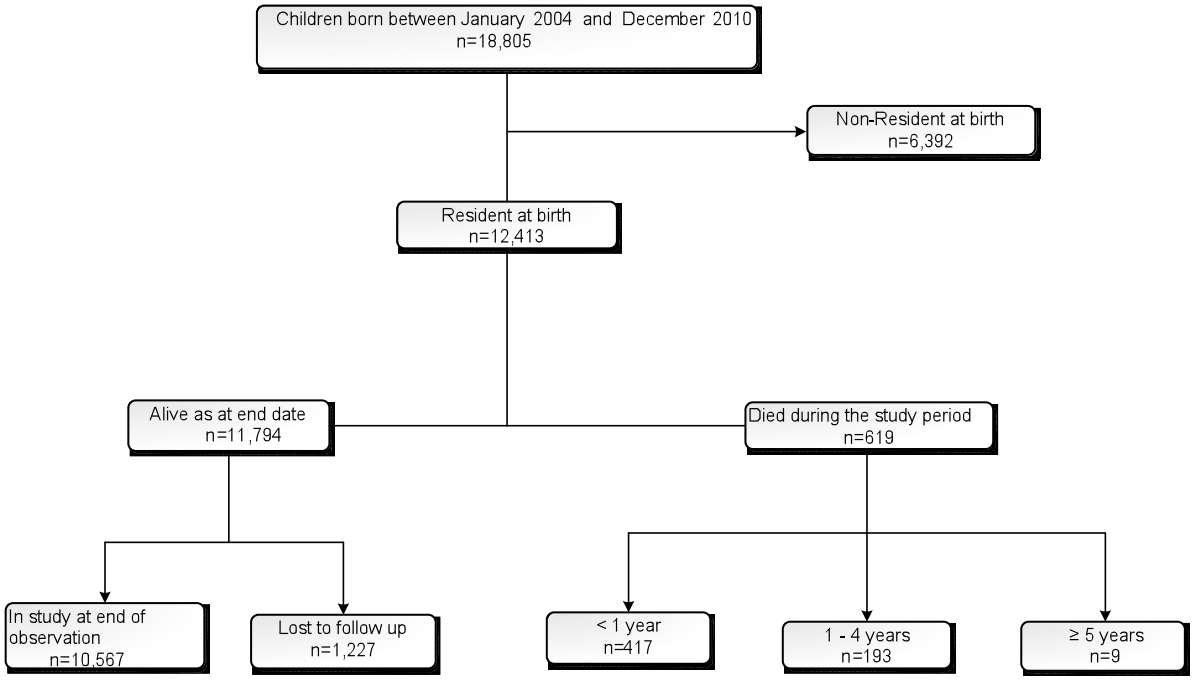
The study was a prospective Longitudinal Cohort Study of children born between 1st January 2004 and 31st December 2010, in the Africa Centre DSA in rural KwaZulu-Natal, South Africa. All children were followed up until 31st December 2011. This study period was appropriate as ART was introduced in South Africa in the year 2004, while the year 2011 was chosen so as to allow at least one year of follow-up for all children in this study while ensuring completeness of verbal autopsy data for this cohort, at the time of this study. Primary data collected twice annually in the DSA was used, as well as HIV treatment and care data collected in 17 primary health care clinics, 6 of which are in the DSA **[44]**. We used a time to event data structure in this study.

2.1.2 Sampling strategy

The data collected in the surveillance is stored in the Africa Centre Demographic Information System (ACDIS) database, and contains information from both resident and non-resident members of households in the DSA. Members of households are considered residents if they are residing at a physical structure within the surveillance area at a particular point in time **[15]**. In each round, approximately 33% of the individuals are non-resident members of households **[15]**.

A total of 18,805 children were under surveillance between 1st January 2004 and 21st December 2010 in the Africa Centre DSA. The sample used in this study was restricted to only those children who were resident in the DSA at the time of birth, totaling to 12,413 children (figure1). While the last date of censoring in the study was 31st December 2011, the last observation date for the purpose of this analysis is defined as the earlier of the following dates (i) date of death of child, (ii) date last seen incase of migration or loss to follow-up or (iii) end of study-31st December 2011.

Figure 1: Sample size flow chart of study population



2.2 Methods and data sources

2.2.1 Data collection tools

Data for this study was obtained from the Africa Centre Demographic Information System (ACDIS) and the Antiretroviral Treatment and Care program Information System (ARTemis) databases. Data collection in the Africa Centre surveillance is done twice yearly at the household level **[15]**. Data on adults at individual level as

well as socio-economic status is collected once a year during the household surveillance **[15].** In the socio-demographic surveillance, data is collected on questionnaires administered to key household informants by field workers, who record birth, deaths, migrations, pregnancies and marriage events as well as household socio-economic data **[41]**.

In the HIV surveillance, eligible individuals (adults) are visited on an annual basis by fieldworkers, who after obtaining consent collect blood by finger prick and prepare dried blood spots for HIV testing **[15]**. All data from the HIV surveillance can be linked anonymously to other data collected by the demographic information system. Consent for participation in the HIV surveillance is however never 100% in any given year **[15]**. Death notifications are done by the household informant and followed up with interviews using verbal autopsy interviews by trained nurses who interview the closest caregiver of the deceased within six months of death **[23].**

2.2.2 Data sources and measurements

Data was extracted from the Africa Centre Demographic Information System (ACDIS) for the period 2004 to 2011 for all children born in the DSA from 1st January 2004 to 31st December 2010. The ART status data was extracted from the ARTemis database. ARTemis is an operational database developed and maintained at Africa Centre, of HIV-infected people initiated on antiretroviral treatment in the Hlabisa HIV treatment and care programme. The data collected into it includes laboratory data, clinical visits data, basic details of the individuals, ART information and tuberculosis records **[44]**. This data can be linked to the HIV surveillance data using the national South African identification number, a unique identifier in both datasets, and other identifiers where needed **[11]**.

2.2.3 Study variables

2.2.3.1 Outcome variable

The outcome is defined as death (events) in any one of three periods, during infancy, young children (1-4 years) and older children (5-7 years), or censoring at the last time the child was last seen alive or at the end of the study. We used the following data in this study:

2.2.3.2 Individual factors

Age of the child at the time of death or end of observation, sex of the child, immunization status, ART usage, and whether the child was a singleton or twin, and the area of residence where the child lived were used. Immunization status, that is whether fully immunized, or received some vaccines (partially immunized) or never received any vaccines (never immunized) is calculated as at one year of age of the child, except for children followed up for less than one year; those who died or migrated or were lost to follow-up, whose vaccination status is calculated as at the time they left the study.

Immunization status is conditional on age of the child and the scheduled age for a particular vaccination dose, thus putting into consideration that a child needs to have been alive to be immunized. A fully immunized child in this study is thus defined as having received all routine vaccinations excluding Pneumococcal Conjugate Vaccine (PCV) and Rota virus (RV) vaccines (introduced in 2009 in South Africa) during the study period, predicated on the scheduled age when the vaccination doses were due and the age of the child. A partially immunized child is one who received some of the routine vaccinations excluding PCV and RV vaccines during the study period, also

predicated on the scheduled age when the vaccination doses were due and the age of the child, while a child who was never immunized is one who never received any of the routine vaccinations during the study period excluding PCV and RV vaccines.

HIV status of the child was not collected in the surveillance, hence we estimated the proportion of children on ART using number of children exposed to HIV, that is children of mothers who were HIV positive at birth as the denominator and all children reported as being on ART as the numerator.

2.2.3.4 Maternal factors

HIV status of the mother, which was obtained from the HIV surveillance data was defined as negative, positive, unknown and positive and on ART, obtained from the ARTemis database. Mother's vital status (dead or alive), date of death of the mother, mother's age, and education which we classified into three groups, less than 1year of education, Grade 1-7 and Grade 8 or higher were included. Parity of the mother was grouped into one child, two/three children or four or more children, while marital status was categorized into three categories never married, currently married and separated/divorced/widowed. Residency status of the mother in the DSA at birth of the child was also included.

2.2.3.5 Household factors

Age, sex of the household head and socio-economic variables (asset ownership) and distance to nearest health facility were used. Asset ownership used as a socio-economic index in this study has been determined using a wealth index as developed for use with Demographic and Health Survey data **[51].** The index is constructed

using a series of household assets owned and access to amenities such as water, electricity, toilet facilities and cooking energy **[42].** The wealth score ranging from 1(poorest) to 5(wealthiest) was then estimated using Principal Component Analysis (PCA) **[42]**.

2.3 Data Management and Analysis

The data at Africa Centre DSA was collected on case report forms during the household interviews. The data was then captured into the Africa Centre Data Information System (ACDIS) using SQL 2000. We undertook data checking, cleaning, coding and analysis using STATA 11 (Stata IC version 11.2; Stata Corporation, College Station, TX, USA). Data checking was done to detect incomplete, inaccurate, inconsistencies, duplicates and out of range values as per set ranges for various variables. Cleaning was then done to correct or remove these errors. Data coding was done to transform extensive data sets into smaller analyzable units by creation of categories derived from the data.

Data Analysis procedures

As this is a longitudinal study, some children moved across the age groups under 1 year, 1-4 year olds and >=5 year olds over the study period. We used age-time line as our analysis time for the time the children were in the study.

2.3.1 Describing socio-demographic characteristics of the population

To describe the socio-demographic characteristics of the infants, young children and older children, descriptive statistics such as Chi-square tests and Fischer's exact tests were used for categorical variables. For continuous variables, t-tests were used.

Graphical presentation used comprises of bar graphs for categorical variables and histogram for continuous variables.

2.3.2 Estimating trends in mortality and causes of death

The survival experience of the children in the under 1 year, 1-4 year and >=5 year age groups is estimated using Kaplan Meier curves. This was done by defining time in the study, as time to death (as the event) or censoring as the last time a child was seen alive for children who out-migrated or were lost to follow-up. Child mortality varies by age with older children experiencing lower mortality compared to the younger children, hence the analysis of mortality experience for the different age bands. Crude mortality rates are calculated in each of the three age groups, by obtaining number of deaths per child-months within each age group. Geographical variations in the mortality experience of the infants in the study area have been analyzed using thematic maps, which were constructed in MapInfo 11.5.

Period prevalence was also calculated as the proportion of children who died in infancy and at 1-4years, per child-months over the study period.

Death notifications are done by the household informant and followed up with interviews using verbal autopsy interviews by trained nurses who interview the closest caregiver of the deceased within six months of death

Underlying causes of death were obtained from the verbal autopsy database, where causes of death are recorded following physician coding and an automated method using the InterVA v3 probabilistic verbal autopsy model of the verbal autopsy interviews **[23]**. The causes of death are classified into broad categories adopted from the Global Burden Disease (GBD) tree structure **[45]**. The causes of death have been

described using proportional attributable fractions, by obtaining the number of deaths that can be attributed to a certain risk factor divided by the total deaths experienced by the children.

2.3.3 Inferential Statistics

Time dependent HIV status of the mother was assessed for association with mortality in infants, 1 – 4 year old and above 5 years olds, while controlling for other socio-demographic and health factors. The HIV status obtained from the HIV surveillance and the ART information from the treatment programme was categorized as HIV-Negative, HIV-Positive and not on ART and HIV-Positive and on ART and HIV not-reported status. The HIV status and ART use of the mother was obtained at birth of the child and thereafter during the life of the child in the study, allowing it to change from negative or not-reported to positive or positive and on ART or from positive to positive and on ART. For each child, the follow-up time was taken as time from birth until death, end of observation (31 December 2011) or date last seen, whichever came first, within the first year of life, at 1-4 years and at 5years and above. It was censored at change of HIV status of the mother, reflecting the end of the former status and the start of the new status. For each child, from birth to end of observation date, data was structured stratified by maternal HIV and ART status allowing for change from one state to another (e.g. from HIV negative to HIV positive).

Analyses were done using the Cox proportion hazards models but these did not meet the proportionality assumptions that the hazard functions be proportional over time, on testing using the log rank test. Poisson regression models, which are also appropriate for survival analysis, especially for rare events, such as in this study where we have an overall mortality rate of 5%, were then used. The use of Poisson

regression was appropriate in this analysis as it is applies to time to event data, where the rates are also not expected to vary rapidly, as is expected with this cohort **[49]**. The analysis of this data was also repeated with Weibull distribution models (parametric models) and the results obtained were similar to the results from the Poisson regression models. Only the Poisson regression results are presented in this report. Poisson regression models were used to assess association of the risk factors and rate of mortality of the child for each of the three age groups; Under1 year, 1-4 years and 5 years and above age group. The overall strength of association for each variable was assessed using the Akaike Information Criteria (AIC), comparing the model with and without the variable of interest. The model with the lowest AIC value was taken as the best model **[46]**. The factors were assessed multivariably for their association with child mortality by including in the model variables significant at the 0.25 level at the univariable level, as well as other factors shown to be associated with child mortality in literature, even if not significant univariably at the 0.25 level.

In assessing the association of maternal HIV status with infant mortality, child ART status was however not included in the model, as only 151 children were on ART by the end of the observation period, hence the child ART status was not included in the multivariate model due to the few numbers.

At fitting the models for infants, 1 – 4 year old and 5 years and above children , the immunization type variable was categorized into two categories; never and partial/fully immunized as none of the infants (under 1 year) who died were fully immunized and would therefore have been impossible to control for the immunization type in the model for this age group. The same categories were also used for the 1-

4years and 5years and above age groups. The 5 years and above age group had none of the risk factors significant at the univariable level. The multivariable analysis for this age group was therefore not computed; the results for children 5 years and above have not been presented in the tables below. The robust variance estimates were obtained to control for violation of assumptions for the relative risk. The goodness-of-fit chi-squared test was used to assess the goodness of fit of the models.

2.4 Ethical clearance

Ethics approval for the proposed study was obtained from the University of Witwatersrand Human Research ethics Committee [clearance certificate no. M120860**]**. Ethics approval for the Africa Centre surveillance was obtained from the Research Ethics Committee of the Nelson R. Mandela School of Medicine, University of Natal and updated annually **[15].** Permission to use the data, for this study, was obtained from Africa Centre using the data user agreement form. Participation in the surveillance was voluntarily for all individuals in the demographic surveillance area. Written informed consent was obtained from individuals for the HIV testing in the HIV Surveillance, and this HIV information is anonymised **[15]**. Ethical approval was also obtained for linkage of the HIV surveillance data to the ARTemis database.

CHAPTER 3: RESULTS

3.0 Introduction

General descriptive statistics for the study variables are given in this chapter. The mortality rates of the infants, 1-4 year olds, and above 5 years, as well as causes of death are also described here. This chapter also includes the results of the assessment of the association between maternal HIV status and maternal ART usage and other factors of interest independently with mortality at the univariable level, as well as the assessment of the association of all factors of interest with child mortality, using multivariable models.

3.1 Description of study participants

Overall (January 2004-December 2010) 12,413 children met the inclusion criteria. There were slightly more male children, 51% (6,276/12413), than female children and the majority of the children were singleton births, 97% (12,060/12413), while the rest were twin births. The majority of mothers in this study reported to never have been married, 71% (8,737/12,244), to have reached Grade 8 or higher in their education, 69% (8,507/12,244) (Table 1). Most mothers were between the ages of 20 and 30 years, 52% (6,370/12,244), with their ages ranging from 12 to 54 years.

Mothers who had the study child as the first-born were 55% (6,793/12,244) as shown in Table 1 below. At the time of birth of the study child, 56% (6,901/12,244) of all mothers were found to be HIV negative in the surveillance, while 11% (1,360/12,244) were HIV positive, and the HIV status of the rest (26%) was unknown to us, as it was not measured in the HIV surveillance. Of those mothers who were HIV positive, 3%

were on ART treatment at the time of birth of the child. At the end of study, 4% (382/9,645) of all the mothers had died while 5% (619/12,413) of the children had died (Table 2).

In this study 95% (588/619) of the children who died were singletons, while 97% (11,472/11,794) of those who survived were singleton births; all births were either singleton or twin multiple births (Table 1). Amongst all the children deaths, there were slightly more boys, 53.6% (332/619), than girls. More than half the mothers of the children who died 65%(403/619) and those who were alive 69% (8,104/11,794) had grade 8 or higher education. The majority of women in this study reported never being married at the time of birth of the child, 85%(526/619) among women whose babies died and 71%(8,318/11,794) among women whose children were alive (Table 1).

Most mothers were primiparas, especially those whose children died (61%, 375/619, versus 54%, 6,372/11,794) this difference was statistically significant (Table 1). More than half of the households where the children lived had male household heads, 59%(365/619) for children who died and 54% (6,312/11,794) for children alive**.** These proportions were also statistically significantly different (Table 1).

More than half the mothers were between 20 to 30 years both for children who died, 55% (342/619) and children who were alive 52% (6,111/11,794), and the proportions across the different age groups did not significantly differ. The heads of households for children who died were significantly older compared to household heads of children who were alive at the end of the study, with a median age of 51 years IQR (41-62) and 49 years IQR (39-59) respectively (Table 1). The median distance from a

household to the nearest clinic was almost similar for both groups of children at 2.9kms IQR (1.8-4.2) for children who died and 2.6kms IQR (1.5-4.1) for those alive (Table 1).

Table 1: Socio-Demographic Characteristics of study population by vital status

Characteristic	**Child Vital Status**			
Child Characteristics	**Alive** n (%) n=11,794 (95%)	**Dead** n (%) n=619 (5%)	**Total** N=12,413	**p-value**
Sex of child				
Female	5,850(49.6)	287(46.4)	6,137(49.4)	0.116
Male	5,944(50.4)	332(53.6)	6,276 (50.6)	
Multiple Births				
Singleton	11,472(97.3)	588(95.0)	12,060 (97.2)	0.001
Twin	322(2.7)	31(5.0)	353 (2.8)	
Maternal Characteristics				
Mother's Education at birth				
Less than 1year	283(2.4)	20(3.2)	303(2.4)	0.052
Grades 1 – 7	1,669(14.2)	111(17.9)	1,780(14.4)	
Grade 8 or Higher	8,104(68.7)	403(65.1)	8,507(68.5)	
Unknown	1,727(14.6)	84(13.6)	1,811(14.6)	
Refused	11(0.1)	1(0.2)	12(0.1)	
Marital Status at birth of child				
Currently Married	1,176(10.1)	40(6.6)	1,216(9.9)	<0.001
Never Married	8,220(70.6)	517(85.6)	8,737(70.6)	
Separated/Divorced/Widowed	152(1.3)	8(1.3)	160(1.3)	
Unknown	2,092(18.0)	39(6.5)	2,131(17.4)	
Parity at birth of child				
One child	6,372(54.7)	375(62.1)	6,747(54.7)	<0.001
Two/Three children	2,532(21.8)	134(22.2)	2,666(21.8)	
Four or more children	1,146(9.9)	69(11.4)	1,215(9.9)	
Missing	1,590(13.7)	26(4.3)	1,616(13.2)	
Age of the mother at birth				

<20 years	2,741 (23.6)	120(19.9)	2,861(23.4)	0.159
20-30 years	6,033(51.8)	337(55.8)	6,370(52.0)	
>30 years	2,754 (23.7)	142(23.5)	2,896(23.7)	
Missing	112(1.0)	5(0.8)	117(0.9)	
Sex of Household head				
Female	4,986(42.3)	238(38.5)	5,224(42.1)	0.011
Male	6,312(53.5)	365(59.0)	6,677(53.8)	
Missing	496(4.2)	16(2.6)	512(4.1)	
Asset Quintile				
Lowest	1,761(14.9)	104(16.8)	1,865(15.0)	0.047
Second	1,843(15.6)	92(14.9)	1,935(15.6)	
Middle	1,883(16.0)	109(17.6)	1,992(16.1)	
Fourth	1,843(15.6)	89(14.4)	1,93215.6)	
Highest	1,390(11.8)	50(8.1)	1,440(11.6)	
Missing	3,074(26.1)	175(28.3)	3,249(26.2)	
House hold head at birth of child Age in years: median (IQR)	49.0(39.0-59.2)	50.9(41.2-62.4)		<0.001
Mother's Age in Years: median (IQR)	23.9(20.2-29.7)	24.5(20.8-29.9)		0.231
Distance to nearest clinic (KM): median (IQR)	2.6(1.5-4.1)	2.9(1.8-4.2)		0.013

Few children born to HIV-positive mothers were on ART, 9% (16/619) of the exposed children who died and 8% (135/1,782) of the exposed children who were alive by the end of the study. The median age at commencement of ART among children who died was 10.3 months (IQR 5.7-19.0), compared to 23.7 months (IQR 13.7-47.4) for children who were alive at the end of the study.

By the end of the study, 88% (542/619) of children died before they could receive any immunizations, while 41%(4,882/11,794) of those who survived to the end of the

study had also never received any vaccinations. Among children who died, only 3% (17/619) had received all routine vaccinations and 34% (4,046/11,794) of children alive were fully immunized by the end of one year or at the time of leaving the study. The majority of the children were resident in the DSA by the end of the study, 93.1% (576/619) for children who died, and 83.5% (9,847/11,794) for children who were alive at the end of the study.

More than half of the children in this study lived in the rural areas of the DSA, 61% (375/619) of those who died and 56% (6,592/11,794) of those children who were alive. The majority of the mothers were alive by the end of the study, 97% (603/619) for children who died and 96% (11,355/11794) for children who were alive, but these proportions did not differ statistically significantly.

The mother's HIV prevalence at delivery for babies who eventually died compared to those who survived was 28% and 14% respectively. There were equal proportions of mothers who did not know their HIV status at the time of birth of the study child, among children who died, 26% (164/619) and those who survived, 26% (3,084/11794) to the end of the study. Among mothers who started ART treatment after the index child was born, the median time between a mother initiating treatment and the child dying was 10months, IQR (4-20months) as shown in Table 2. All mothers were resident at birth of the child.

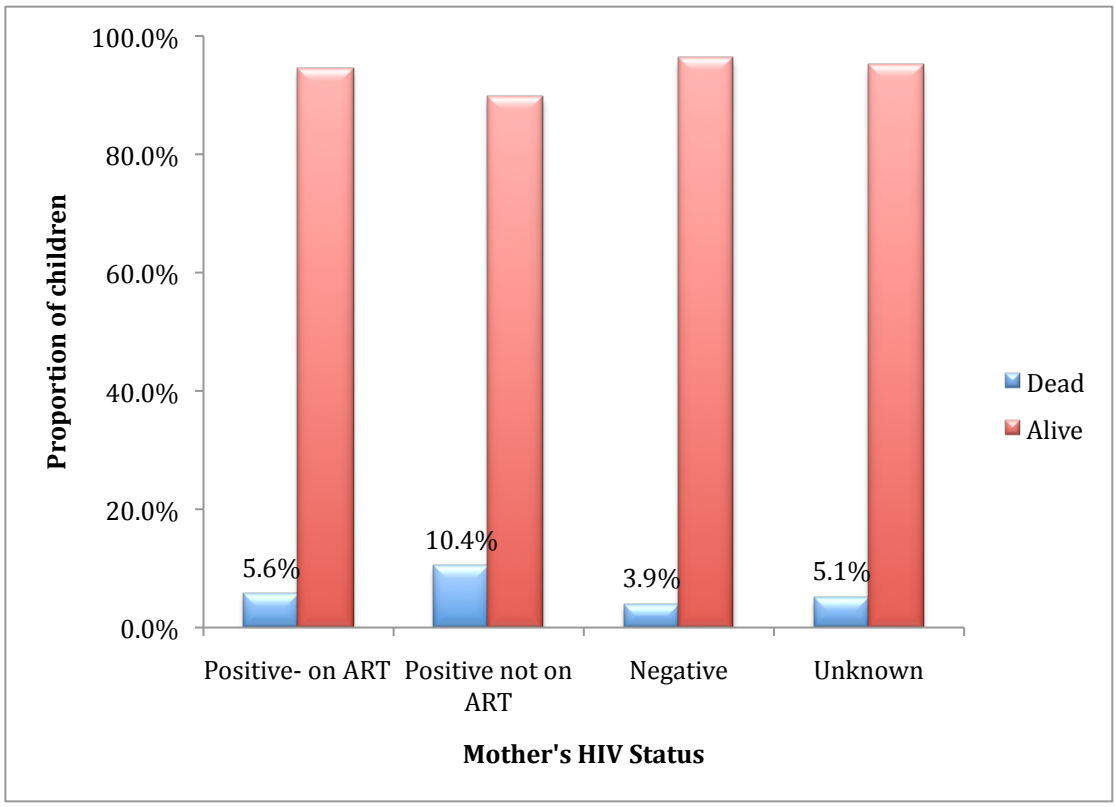
Table 2: Health Factors of study population by child vital status

Characteristic	Child Vital Status			
Child Characteristics	**Alive**	**Dead**	**Total**	**p-value**
ART Status of exposed children				
On ART	135(1.1)	16(2.6)	151(1.2)	<0.001
Not on ART	1,646(14.0)	166(26.8)	1,812(14.6)	
Un- Exposed children	10,013(84.9)	437(70.6)	10,450(84.2)	
Immunization Status of child at one year				
Fully Immunized	4,046(34.3)	17(2.8)	4,063(32.7)	<0.001
Partially Immunized	2,866(24.3)	60(9.7)	2,926(23.6)	
Never Immunized	4,882(41.4)	542(87.6)	5,424(43.7)	
Area of Residence				
Urban	781(6.6)	45(7.3)	826(6.7)	0.003
Peri-urban	3,299(28.0)	166(26.8)	3,465(27.9)	
Rural	6,592(55.9)	375(60.6)	6,967(56.1)	
Missing	1,122(9.5)	33(5.3)	1,155(9.3)	
Resident at end of observation				
Yes	9,847(83.5)	576(93.1)	10,423(84.0)	<0.001
No	1,947(16.5)	43(6.9)	1,990(16.0)	
Maternal Characteristics				
Vital Status at end of observation				
Alive	8,798(96.0)	465(97.1)	9,263(96.0)	0.232
Dead	368(4.0)	14(2.9)	382(4.0)	
HIV Status of mother at birth of the child				
Positive and on ART	328(2.8)	19(3.2)	347(2.8)	<0.001
Positive and not on ART	1,251(10.8)	109(18.1)	1,360(11.1)	
Negative	6,702(57.6)	199(33.0)	6,901(56.4)	
Unknown	3,084(26.2)	277(45.9)	3,636(29.7)	
HIV Status of mother at End date				
Positive and on ART	1,201(10.4)	39(6.5)	1,240(10.1)	<0.001
Positive and not on ART	2,157(18.5)	176(29.1)	2,333(19.1)	
Negative	5,234(45.0)	229(37.9)	5,463(44.6)	
Unknown	3,048(26.2)	160(26.5)	3,208(26.2)	

Maternal sexual Partners at birth of child				
Regular Partner	2,682(23.0)	119(19.7)	2,801(22.9)	0.114
Casual Partner	363(3.1)	22(3.6)	385(3.1)	
No Partner	2,145(18.4)	129(21.4)	2,274(18.6)	
Unknown	6,450(55.4)	334(55.3)	6,784(55.4)	
Resident at end of observation				
Yes	8,270(70.1)	528(85.3)	8,798(70.9)	<0.001
No	3,412(28.9)	86(13.9)	3,498(28.2)	
Unknown	112(1.0)	5(0.8)	117(0.9)	
Age Child Started ART (Months): median (IQR)	23.7 (13.7-47.4)	10.3 (5.7-19.0)		0.003

The majority, 59% (7,306/12413) of children in this study were born to HIV negative mothers (Table2). A higher proportion of the children who died, 10.4%, were born to HIV positive mothers not initiated on ART (figure 2), followed by those born to mothers who were HIV positive and on ART, 5.6%, which was similar to that of children whose mothers had unknown HIV status at 5.1%.

Figure 2 Child vital status by HIV status of mother at childbirth



3.2 Mortality rates and causes of death

The mortality experience for the infants, 1-4 and 5 year olds and above varies by the age groups. There were a total of 619 deaths in the study period, 417 in the infant stage, 193 in the 1-4 years old stage and 9 children were 5 years and above at the time of death.

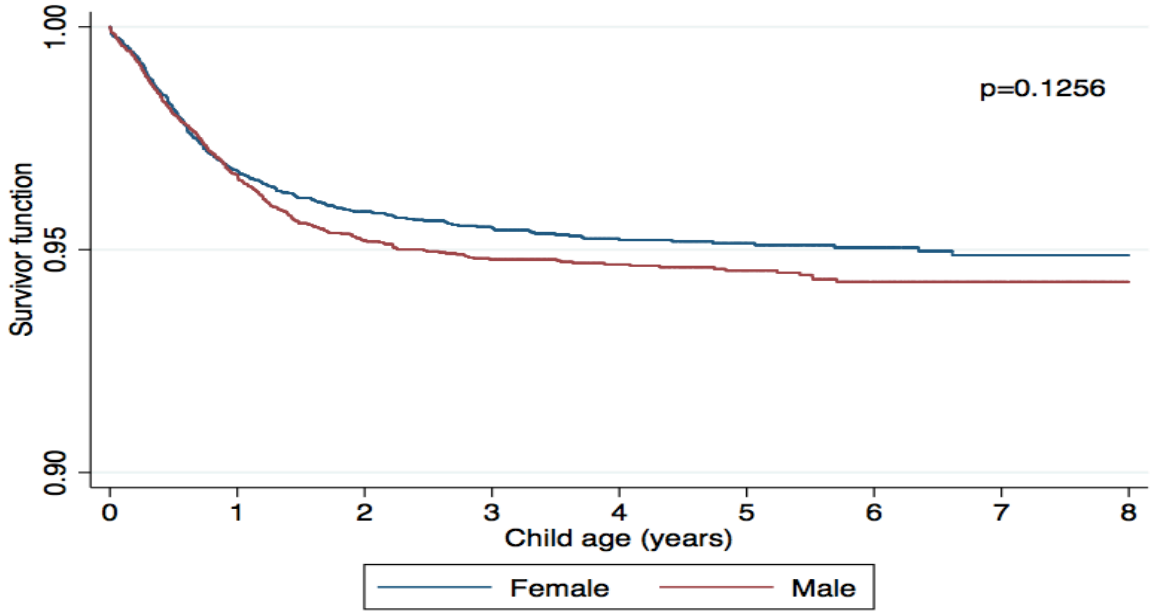
The first 28 days of life were those with the highest mortality rate, 4 deaths per 1000 child months during the study period (Table 3). At 1 year of age, the mortality rate of the children was slightly lower than the neonates at 3 deaths per 1000 child months of follow-up. The mortality rate dropped with increase in child's age to 1 death per 1000 child months of follow-up at 7 years of age.

Table 3: Period specific mortality rates

Period Incidence	Number of Deaths	Person Time (Child months)	Mortality rate/Incidence Per 1000 child months of observation
0 – 28days	39	12369	4
28 days – 1year	365	132548	3
1 - 2years	136	128846	2
2 – 3years	37	106479	1
3 - 4years	13	85116	1
4 – 5years	7	65098	1
5 – 6years	7	45302	1
6 – 7years	2	27137	1

Overall, the probability of survival dropped rapidly in the early months of childhood (Figure 3), although the cumulative survival probability varied over the period observed between males and females. Females had a higher probability of survival than males in this study, but this was not statistically significant (p=0.1256).

Figure 3: Overall survival curve by sex of the child



In the infant stage, there were 417 deaths out of the 619 deaths that occurred in the study period. Overall, infants experienced a rapid decrease in the survival function after the first few months of life compared to 1 – 4 year olds (figure 4a). It continued to decline until the end of the first year for infants and up to 4 years for 1-4 year olds, but varied by HIV status of the mother at birth. Mothers who were HIV positive and had not initiated on ART had children with the lowest cumulative probability of survival at the infant stage, compared to children whose mothers were HIV negative, HIV positive and initiated on ART or those whose HIV status was unknown. Infants whose mothers were HIV negative had the highest cumulative probability of survival. This trend was also observed for the 1 – 4year old children (Figure 4b below).

Figure 4a: Survival curves (Infants) by HIV status of mother at birth

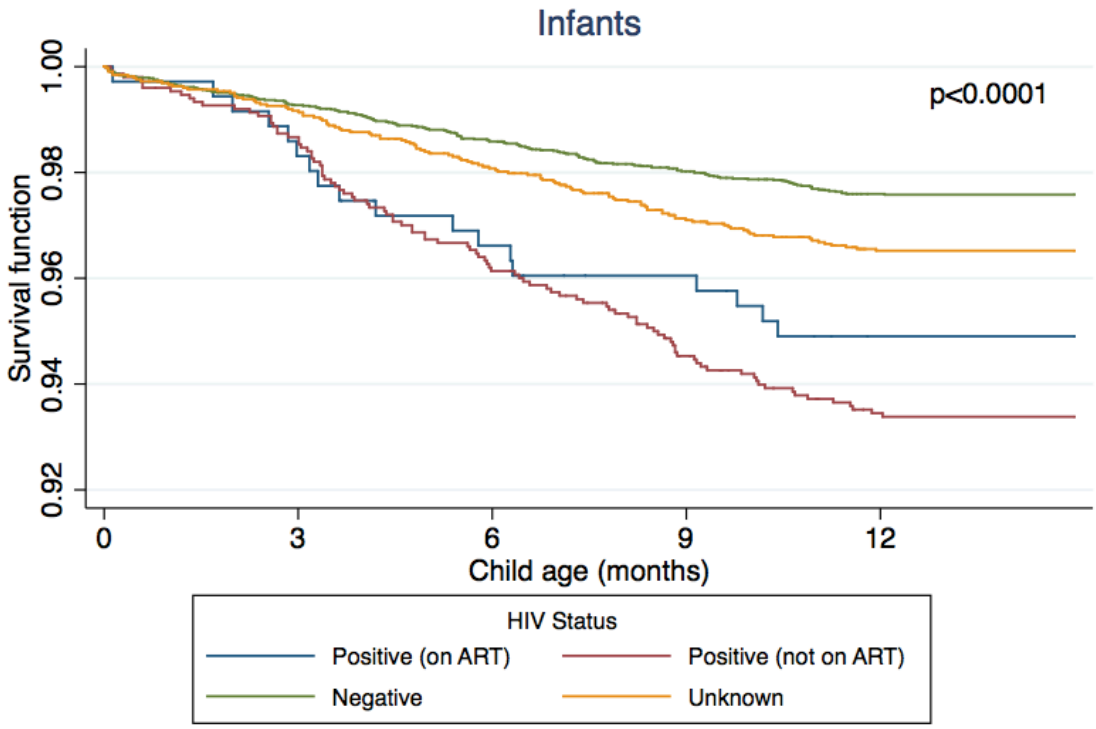
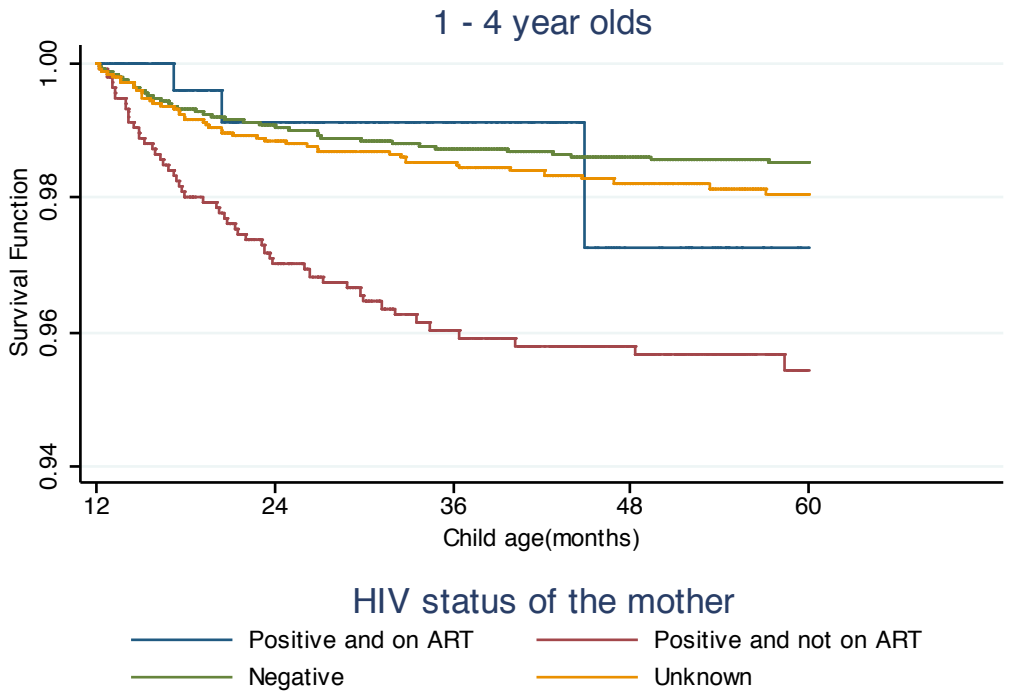
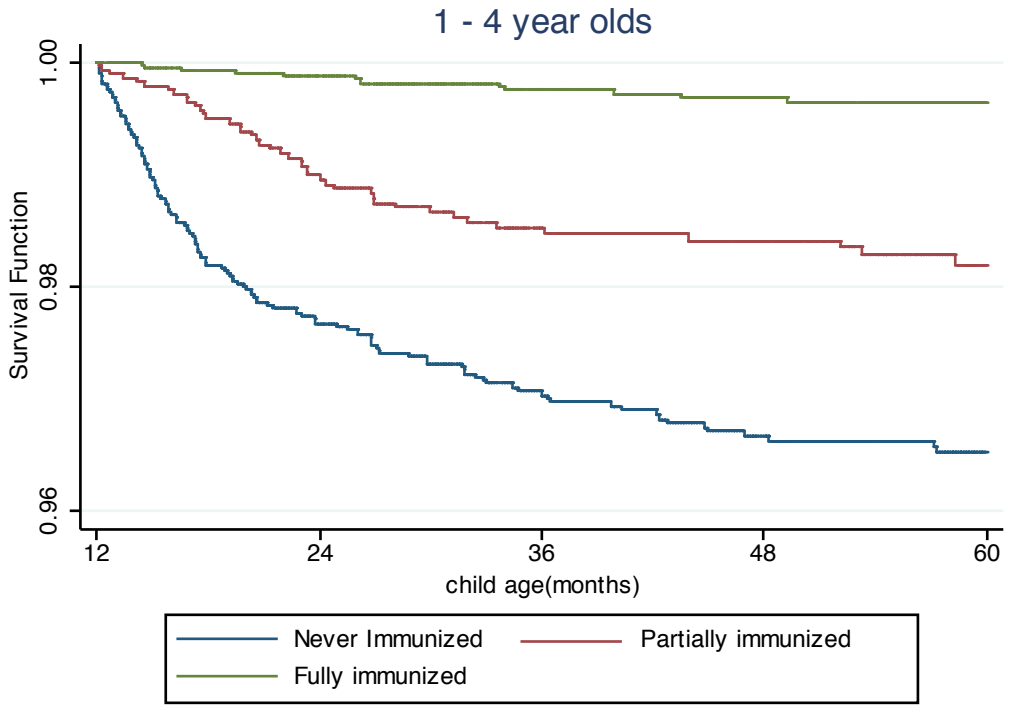


Figure 4b: Survival curves (1-4 year olds) by HIV status of mother at birth



Comparing the immunization status of the children who survived to one year of age, children who were fully immunized had the highest probability of survival followed by those who had partial immunization while children who were never immunized had the lowest probability of survival (figure 5). The mortality in the 1 – 4year olds was highest in the first year, after which the survival function had a steady decline until the 4th year.

Figure 5: Survival curves by immunization status of the child (1 -4 year olds)



The probability of survival for the 5 years and above age group remained relatively high throughout the observation period. There was a steady drop in the survival function in the first year in this age group both for males and females, although the male's survival function dropped faster than that of females. At about 80 months of age, the cumulative probability of survival remained constant to the end of observation of the children.

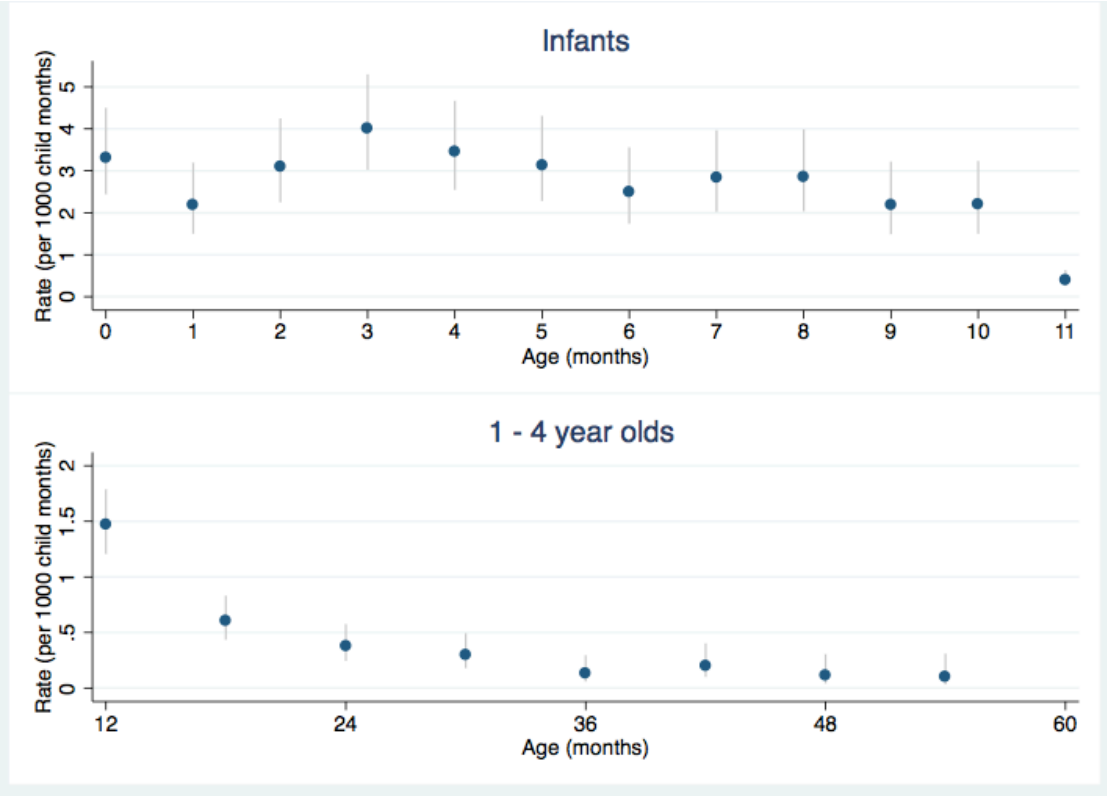
3.2.1 Mortality rates

The overall period prevalence of mortality was 119.6 per 1000 child - months of follow-up although the infant mortality rates were the highest of the three age groups (figure 6). The rate of mortality in infants was seen to begin to rise in the second month of life, reaching a peak in the third month, after which it began to drop steadily up to the twelfth month. The 1-4 year olds also had a high rate of mortality at the ages 1-2years, which then dropped steadily throughout the 4years.

Estimated mortality rates for infants were highest at the age of 3 months at 4 deaths per 1000 child-months of observation, after which it began to drop to a low of 1 death per 1000 child-months of observation as the children approached 11 months of age (figure 5).

Children who survived the first year of life, moving to the 1-4 years age group, experienced lower mortality rates than while they were infants. However mortality was high for the 1-4 years age group in the first 6months of observation, at approximately 2 deaths per 1000 child-months of observation at 12 months, before it dropped to 1 death per 1000 child-months of observation thereafter to the end of observation of the children (Figure 5).

Figure 5: Mortality rates for infants and 1 – 4 years old



3.2.2 Causes of death

The underlying causes of death of children who died in this study were categorized into the following broad categories; Maternal factors, HIV-related causes, Injuries and accidents, Communicable, Non-communicable diseases and indeterminate causes, adopted from The Global Burden Disease (GBD) tree structure [Murray & Lopez, Lancet 1997].

A total of 550 deaths (89%) out of all the 619 deaths observed were classified. Overall the leading cause of mortality was attributed to Maternal, Perinatal, Nutritional and Congenital causes; 59% of all causes were attributed to this cause (Table 4). Unspecified acute lower respiratory infections were the major constituent in this category (149/355 deaths), followed by Diarrhea and gastroenteritis (85/355)

and Pneumonia (33/355). Disorders due to low birth weight (20/355) and malnutrition (13/355) were also contributory causes of death in this category.

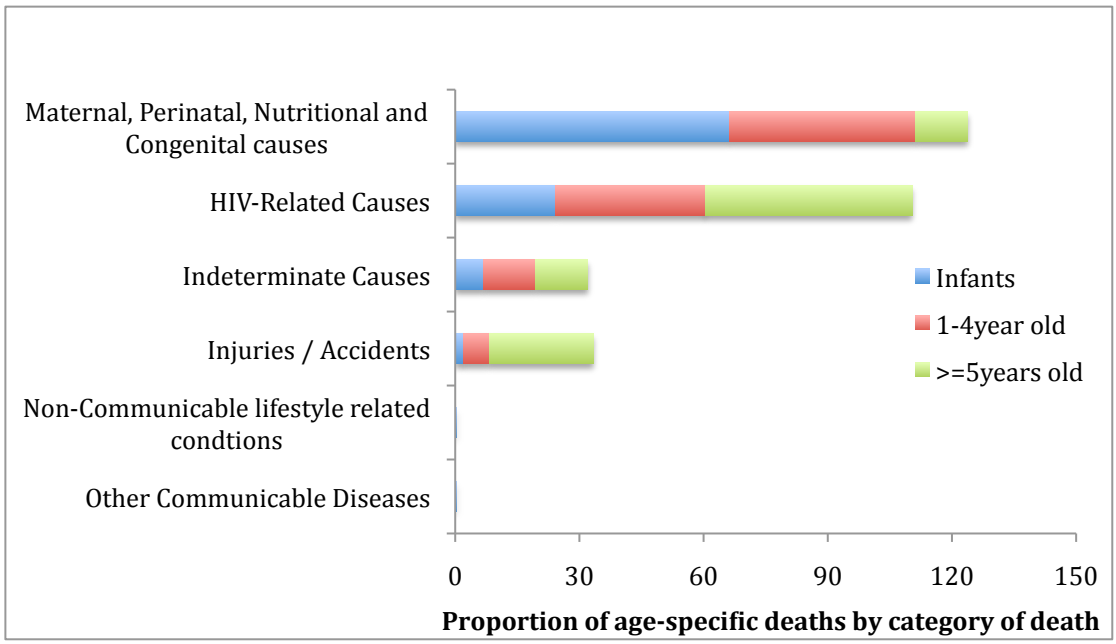
Maternal, Perinatal, Nutritional and Congenital causes were the dominant causes of death in the infants and 1-4 year old age group. HIV-Related causes accounted for more than a quarter of all deaths causes and were the second reported leading cause of death, followed by injuries and accidents. In the 5 y ears and above age group, HIV related causes (50%) were the leading cause of death unlike the other age groups, followed by Injury and accidents (25%) and Maternal, Perinatal, Nutritional and Congenital causes (13%). Overall, 11% (69/355) of the causes of death in children were indeterminate or not recorded.

Table 4: Causes of Death by age group in Africa Centre DSA, 2004 to 2011

	Infants		**1-4 years old**		**>=5years**		**Total**	
Underlying Causes of death	**Number diagnosed**	**%**	**Number diagnosed**	**%**	**Number diagnosed**	**%**	**Number diagnosed**	**%**
Maternal, Perinatal, Nutritional and Congenital causes	268	66.3	86	45.0	1	12.5	355	58.9
HIV-Related Causes	98	24.3	69	36.1	4	50.0	171	28.4
Indeterminate Causes	28	6.9	24	12.6	1	12.5	53	8.8
Injuries / Accidents	8	2.0	12	6.3	2	25.0	22	3.7
Non-Communicable & Communicable diseases	2	0.6	0	0	0	0	2	0.4

Communicable and Non-communicable diseases had the least number of deaths attributed to them, as is shown in the graph below (Figure 7).

Figure 6: Childhood causes of death, 2004-2011

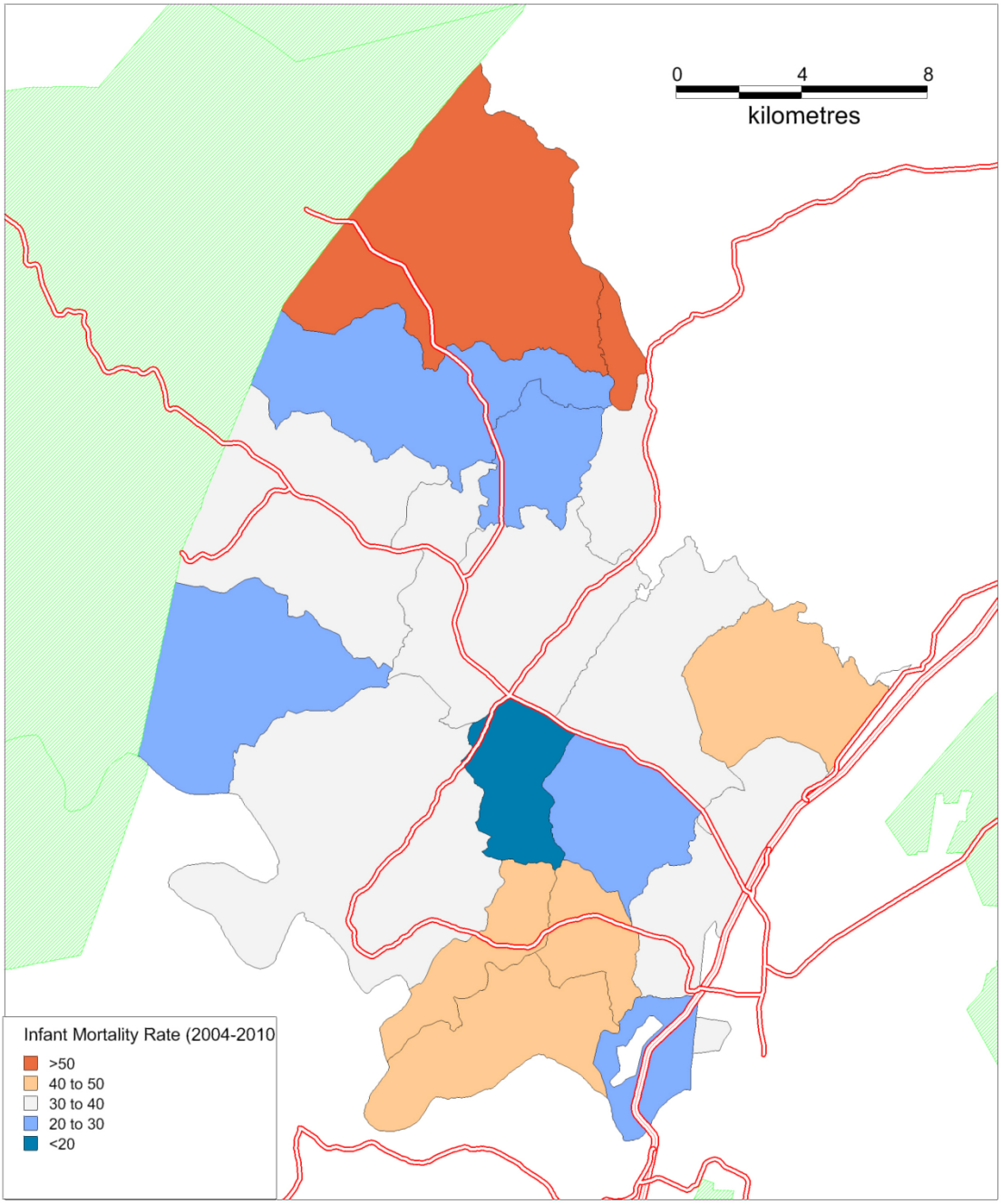


3.2.3 SUMMARY MAPS

The overall infant mortality rate of the study participants, born between 2004 and 2010 varies across the geographical region of observation as seen in figure 8 below. There was heterogeneity of mortality by traditional administrative units (Isigodi), with most areas having an infant mortality rate of 20 – 30 per 1000 child-months of observation, although this peaked to above 50 deaths in some areas.

Urban high-density settlements in the south east of the study area had lower mortality rates of 20 – 30 deaths than the deep rural area in the northwest of the study area which, had the highest infant mortality of above 50 deaths per 1000 child-months of observation. The rural and semi-rural area of the study area had low mortality rates ranging from less than 20 deaths to 20-30 deaths per 1000 child-months of observation.

Figure 7: Infant mortality rates in the Africa Centre DSA, 2004-2010



3.3 Inferential statistics

This section gives information on the association between maternal HIV status, maternal ART usage and mortality at the univariable and multivariable level. It also highlights details of the association between other maternal factors such as age,

education, and residency in the DSA at birth of the children as well as other household and socio-demographic factors.

3.3.1 Factors associated with infant mortality

Infants whose mothers were HIV positive and on ART had a two fold significant increase in the mortality rate compared to infants born to HIV negative mothers, while infants whose mothers were positive and not ART had a three fold increase in their mortality rate compared to those born to HIV negative mothers. Infants of mothers whose HIV status was unknown in the surveillance had a 73% increase in the mortality rate compared to those born to HIV negative mothers. ($p<0.001$) (Table 5).

Other factors associated with increased infant mortality at the 5% level of significance are marital status of the mother for those who had never married ($p=0.002$), age of the household head ($p<0.001$), twin births ($p<0.001$), and children resident in the DSA at the end of the study ($p<0.001$). Asset quintile for infants who lived in wealthy households ($p=0.013$) and infants who had received all or some vaccines that they were due to receive ($p<0.001$) were also significantly associated with reduced infant mortality (Table 5). The area of residence where the child lived, sex of the child, maternal education, sex of the household head, mother's age, and her residency at birth of the child, as well as the distance to the nearest clinic were not statistically significant at the 5% level of significance.

To test the impact of the time changing maternal HIV status and maternal ART usage in the presence of other factors, we performed multivariate regression analysis. On adjusting for other factors in the multivariable analysis, infants whose mothers were HIV positive and not on treatment had a three fold significant increase in the mortality rate, while infants whose mothers were on ART had a two fold significant

increase in the mortality rate, compared to infants born to HIV negative mothers. Infants of mothers whose HIV status was unknown in the surveillance also had a two fold significant increase in the mortality rate compared to those born to HIV negative mothers. ($p<0.05$) (Table 5).

Other factors that were significant at the 5% level of significance in multivariable analysis were marital status of the mother for those who had never married ($p=0.007$), mother's education for Grade 8 or higher ($p=0.050$), the asset quintile for infants who lived in wealthy households ($p=0.050$), age of the household head ($p=<0.001$), residency status of the infant in the DSA at the end of observation ($p<0.001$), as well as whether the infant was a singleton or twin birth ($p<0.001$) and the sex of the household ($p=0.010$). The mother's education for Grade 8 or higher became significant at the multivariable analysis.

Table 5: Factors associated with Infant Mortality

Characteristic	**Events/Total 417/12413**	**Unadjusted RR (95% C.I)**	**p-value**	**Adjusted RR (95% C.I)**	**p-value**
Child Characteristics					
Sex of child					
Female	203/5,934	1		1	
Male	214/6,062	1.02(0.84-1.24)	0. 860	1.00(0.82-1.21)	0.982
Multiple Births					
Singleton	389/11,671	1		1	
Twin	28/325	2.53(1.71-3.74)	<0.001	3.30(2.21-4.92)	<0.001
Area of Residence					
Urban	30/796	1		1	
Peri-urban	120/3,345	0.94(0.62-1.40)	0.741	0.71(0.46-1.08)	0.110
Rural	251/6,716	0.98(0.67-1.43)	0.908	0.68(0.44-1.06)	0.092
Missing	16/1,139	0.39(0.21-0.71)	0.002	0.31(0.16-0.61)	0.001

Resident-end of observation					
Yes	395/10,028	1		1	
No	22/1,968	6.89(3.79-12.54)	<0.001	7.51 (3.91-14.42)	<0.001
Sex of Household head					
Female	165/5,059	1		1	
Male	239/6,438	1.13(0.93-1.38)	0.223	1.30(1.07-1.59)	0.010
Maternal Characteristics at birth of child					
Mother's age					
<20 years	81/2,793	1		1	
20-30 years	230/6,223	1.28(0.99-1.65)	0.061	0.93(0.71-1.22)	0.604
>30 years	103/2,866	1.23(0.91-1.65)	0.177	0.84(0.58-1.21)	0.356
Mother's Education					
Less than 1year	14/289	1		1	
Grades 1 – 7	80/1,700	0.96(0.54-1.68)	0.880	0.91(0.52-1.59)	0.729
Grade 8 or Higher	264/8,243	0.65(0.38-1.11)	0.115	0.58(0.33-1.01)	0.050
Unknown/Refused	59/1,764	0.68(0.38-1.22)	0.197	0.68(0.37-1.24)	0.205
Marital Status					
Currently Married	28/1,219	1		1	
Never Married	352/8,492	1.88(1.26-2.80)	0.002	1.80(1.18-2.76)	0.007
Separated/Divorced/Widowed	4/159	1.20(0.42-3.43)	0.733	1.35 (0.47-3.84)	0.579
Unknown	33/2,126	0.73(0.44-1.22)	0.230	0.66(0.39-1.11)	0.118
Parity					
Two/Three children	43/1200	1		1	
Four or more children	101/2,623	0.93(0.65-1.33)	0.683	0.94(0.64-1.38)	0.757
One child	254/6,539	1.02(0.81-1.28)	0.892	1.12(0.86-1.46)	0.406
Unknown/Missing	19/1,634	0.26(0.15-0.44)	<0.001	0.25(0.14-0.47)	<0.001
HIV Status-mother -Time changing					
Negative	106/5,561	1		1	
Positive and on ART	26/500	2.54(1.65-3.93)	<0.001	2.23(1.42-3.52)	0.001
Positive and not on ART	33/1,185	3.40(2.67-4.33)	<0.001	3.21 (2.50-4.13)	<0.001
Not-Reported	252/4,750	1.73(1.37-2.22)	<0.001	2.11(1.64-2.73)	<0.001
Maternal Characteristics at End of observation					

Resident as at birth of child					
Yes	374/10,673	1		1	
No	40/1,209	1.06(0.76-1.48)	0.718	1.02(0.73-1.43)	0.894
Unknown	3/114	0.81(0.25-2.64)	0.724	-	-
Asset Quintile					
Lowest	72/1,793	1		1	
Second	61/1,874	0.82(0.58-1.15)	0.240	0.86(0.61-1.22)	0.403
Middle	68/1,924	0.89(0.64-1.24)	0.481	0.94(0.67-1.33)	0.729
Fourth	65/1,867	0.88(0.63-1.22)	0.438	1.00(0.70-1.44)	0.990
Highest	33/1,407	0.59(0.39-0.90)	0.013	0.64(0.40-1.01)	0.050
Missing	118/3,131	0.88(0.65-1.18)	0.391	1.00(0.73-1.38)	0.999
Household Head Age in years	404/11,901	1.01(1.01-1.02)	<0.001	1.02(1.01-1.02)	<0.001
Distance to nearest clinic (KM)	417/12,413	1.04(0.99-1.09)	0.156	1.02(0.96-1.08)	0.499

3.3.2 Factors associated with 1-4 year olds mortality

Mortality in the 1-4 year olds born to HIV-positive mothers not on treatment was four fold compared to those born to HIV-negative mothers ($p<0.001$). Further, children in this age group born to mothers, whose HIV status was unknown in the surveillance ($p<0.001$) as well as those born to HIV positive mothers and on treatment ($p=0.045$), had approximately twice as high the mortality rate of those born to HIV negative mothers. The sex of the child ($p=0.03$) and whether the child received some vaccines immunized ($p<0.001$) were associated with child mortality in this age group. The residency status of the child in the DSA at the end of the study ($p=0.02$) was also associated with the 1-4 year olds mortality.

On adjusting for other factors, the impact of the time changing HIV status and ART usage of the mother remained the same as in the univariable analysis.

Children born to HIV positive mothers on ART treatment (p<0.001) and HIV status unknown had a two-fold increase in mortality compared to children born to HIV negative mothers, while children of HIV positive mothers not on ART treatment had a mortality rate three times as much as those born to HIV negative mothers.

Other factors associated with 1-4year olds mortality were whether the children received any vaccinations (p <0.001), whether the child was resident in the DSA at the end of the study (p=0.04), as well as parity of four or more children (p=0.02). Parity of four or more children became significant in the multivariable analysis (Table 6).

Table 6: Risk Factors for 1-4 year olds Mortality

Characteristic	Events/Total 193/11,996	Unadjusted RR (95% C.I)	p-value	Adjusted RR (95% C.I)	p-value
Child Characteristics					
Sex of child					
Female	80/5,934	1		1	
Male	113/6,062	1.39(1.04-1.84)	0.025	1.27(0.96-1.69)	0.095
Multiple Births					
Singleton	191/11,671	1		1	
Twin	2/325	0.37(0.09-1.50)	0.165	0.48(0.12-1.96)	0.308
Immunization Status; 1-year					
Never Immunized	138/5,026	1		1	
Partially/Fully Immunized	55/6,970	0.27(0.20-0.37)	<0.001	0.27(0.19-0.37)	<0.001
Area of Residence					
Urban	15/796	1		1	
Peri-Urban	44/3,345	0.67(0.38-1.20)	0.182	0.57(0.31-1.04)	0.067
Rural	120/6,716	0.89(0.52-1.52)	0.682	0.69(0.38-1.25)	0.217
Missing	14/1,139	0.62(0.30-1.27)	0.189	0.49(0.22-1.08)	0.075

Resident-End of observation					
Yes	173/10,028	1		1	
No	20/1,968	1.70(1.07-2.70)	0.024	2.23(1.37-3.65)	0.001
Sex of Household head					
Female	72/5,059	1		1	
Male	118/6,438	1.29(0.96-1.72)	0.091	1.34(1.00-1.80)	0.053
Maternal Characteristics at birth of child					
Mother's age					
<20years	39/2,793	1		1	
20-30years	107/6,223	1.22(0.85-1.76)	0.282	1.00(0.69-1.46)	0.996
>30years	46/2,866	1.12(0.73-1.71)	0.601	0.85(0.51-1.43)	0.541
Missing	1/113	0.60(0.08-4.35)	0.610	-	-
Mother's Education					
Less than 1year	6/289	1		1	
Grades 1 – 7	29/1,700	0.82(0.34-1.98)	0.660	0.81(0.34-1.94)	0.633
Grade 8 or Higher	133/8,243	0.79(0.35-1.80)	0.582	0.74(0.32-1.73)	0.493
Unknown/Refused	25/1,764	0.77(0.31-1.87)	0.560	0.68(0.27-1.71)	0.415
Marital Status					
Currently Married	17/1,219	1		1	
Never Married	167/8,492	1.48(0.90-2.44)	0.122	1.38(0.83-2.30)	0.216
Separated/Divorced/Widowed	4/159	1.84(0.63-5.39)	0.265	1.29(0.40-4.20)	0.674
Unknown	5/2,126	0.18(0.07-0.48)	0.001	0.14(0.05-0.40)	<0.001
Parity					
Two/Three children	28/1,200	1		1	
Four or more children	38/2,623	1.57(0.97-2.55)	0.069	1.91(1.11-3.27)	0.019
One child	121/6,539	1.32(0.92-1.90)	0.131	1.24(0.85-1.83)	0.269
Unknown/Missing	6/1,634	0.23(0.10-0.55)	0.001	0.25(0.10-0.63)	0.003
HIV Status of mother (Time changing)					
Negative	43/5,240	1		1	
Positive and on ART	36/1,140	1.88(1.01-3.47)	0.045	1.89(1.02-3.51)	0.043
Positive and not on ART	17/860	3.67(2.55-5.28)	<0.001	3.12(2.18-4.46)	<0.001
Not reported	97/4,756	2.18(1.48-3.21)	<0.001	2.04(1.36-3.04)	<0.001

Maternal Characteristics at End of observation					
Resident as at birth of child					
Yes	173/10,673	1		1	
No	19/1,209	1.07(0.67-1.72)	0.774	1.09(0.67-1.78)	0.727
Asset Quintile					
Lowest	30/1,793	1		1	
Second	28/1,874	0.88(0.53-1.47)	0.623	0.83(0.50-1.40)	0.494
Middle	40/1,924	1.22(0.76-1.96)	0.400	1.30(0.80-2.10)	0.289
Fourth	22/1,867	0.70(0.41-1.22)	0.209	0.87(0.49-1.54)	0.630
Highest	17/1,407	0.72(0.40-1.30)	0.271	0.75(0.40-1.43)	0.388
Missing	56/3,131	1.13(0.72-1.75)	0.594	1.09(0.69-1.72)	0.717
House hold Age in years	190/11,497	1.01(1.00-1.02)	0.223	1.01(1.00-1.02)	0.303
Distance to nearest clinic (KM)	193/11,996	1.07(1.00-1.14)	0.065	1.06(0.98-1.15)	0.172

CHAPTER 4. DISCUSSION

The reduction in child mortality is one of the millennium development goals **[2**]. This study focused on investigating the association between maternal HIV status and ART usage in HIV infected women on child mortality in a rural setting in KwaZulu-Natal, for children born between 1st January 2004 and 31st December 2010.

In this study, we show that the factors associated with an increased infant mortality were maternal HIV infection at birth of the child especially for mothers not on ART treatment, twin births, low maternal education, single motherhood, low socio-economic status and an advanced age of the household head. In addition, high parity of the mother and lack of immunization, were also found to be associated with increased mortality for the 1-4 years old children.

Mortality was highest in infants, steadily decreasing during the 1-4 year ages and was substantially lower after 5 years of age. Infant mortality was heterogeneous and varied in the study area although it was not statistically significant. The main causes of death in the study population were Maternal, Perinatal, Nutritional and Congenital factors comprising acute lower respiratory infections, diarrhea, pneumonia and disorders due to low birth weight and malnutrition.

4.1 Maternal HIV status and ART usage

Children born to HIV positive mothers experienced high mortality rates in our study. We however observed that ART treatment usage among HIV positive mothers reduced the child mortality rates as has been shown previously by a similar study in

this setting. The study reported that children of mothers who were started on ART had reduced mortality levels equivalent to the mortality in children of HIV-negative mothers **[11].** Mothers whose HIV status was unknown in the surveillance had increased child mortality rates compared to those who were HIV negative, suggesting that a proportion of mothers whose HIV status was unknown might have been HIV positive. A study conducted in this setting to investigate geographical variation in HIV prevalence observed that there was considerable geographical variation in HIV prevalence. Areas along the national road that are also high-density urban areas had a high HIV prevalence compared to other areas within the DSA **[39]**. Our study shows that child mortality in these areas was also relatively high at between 30-50 deaths per 1000 child-months of observation, which suggest the association between HIV and child mortality.

Children in rural areas have also been shown to have higher mortality rates than children from urban areas **[2],** as was observed in one deep rural area of our study area, which had the highest infant mortality rate of more than 50 deaths per 1000 child months of observation. This could be partly explained by limited access to health facilities in such areas due to longer distances to a clinic; more than half (53%) children in this study were residing in households located at least 3kms away from the nearest health clinics.

One study reported that management of paediatric HIV in SSA faces many challenges, some of which relate to access to HIV programs for HIV infected pregnant mothers, with majority of them travelling long distances to receive care and treatment **[38].** The concerns of raising HIV-free children by HIV infected mothers

are also not likely to be addressed in a timely manner. Further this poses a challenge of HIV infected children presenting late at health facilities for testing and commencement of treatment, loss to follow-up and consequently poor adherence.

4.2 Other factors associated with child mortality

Some proximate determinants of child survival by Mosley and Chen were also among the significant factors of child mortality in our study **[16],** in addition to maternal HIV and ART usage.

We showed that infants whose mothers had education levels of grade 8 or higher had a reduced mortality than those whose mothers had less than one year's education. The MDG report 2012, reported that maternal education impacts under5 child mortality; children of educated mothers are more likely to survive than children of mothers with no education **[2]**. Ndirangu et al. also showed that children of mothers with high education status had reduced mortality compared to children whose mothers had little or no education in this study setting **[8]**.

There was also significantly lower mortality for children who had received any vaccines during the study period**.** In a study in rural Ghana, Nyarko et al. reported that immunization enhances child survival by a two-thirds reduction in mortality among children who had been fully immunized [**37**].

At the 1-4 years of age, children whose mothers had four or more children at birth of the study child had increased mortality compared to those who had two or three children. This could mean that mothers with more than three children are likely to be

burdened with care for the children and may not adequately provide all necessary attention to their younger children given that they are also likely to be older in age, than those having fewer children. However, we also observed that first-born children had increased mortality rates than those who were born second or third. This is in line with the findings of a study based on the 2011 Demographic Health Survey in Ethiopia, which showed that children at a higher birth order number of two or three had a low risk of child mortality, than first born children **[43]**.

Maternal survival was not associated with child mortality in this study, although a similar study in this setting showed that children of mothers who had died had a 3-fold increased risk of dying than children of mothers who were alive **[11]**. This inconsistency with our findings could be a sample size issue in our study; few mothers died during the study period at the three age groups of the children and we therefore excluded this variable in the final analysis.

We also show that child mortality reduced with increased household assets with the relatively wealthier households being associated with reduced infant mortality by almost half. Our findings are in line with the MDG report 2012 findings, that children born into poor households are twice as likely to die compared to those born into wealthier households **[2]**.

Children resident in the DSA at the end of the study are seen to have a higher rate of mortality than those who were not. This could be explained by the fact that the majority (84%) of children were still resident in the DSA by the end of the study, and

case ascertainment of deaths is higher within the DSA, as a result of the Africa Centre activities within the DSA.

Twin births also had a significantly higher mortality rate than singleton births. However, it was also observed in this study that there were very few twin births as over 97% were singleton births. Although, twin births are few in this setting a similar study showed that twin births had an 85% increase in child mortality compared to the singleton births **[8]**. These findings have also been shown in a study in rural Agincourt South Africa, which showed that multiple births had a two-fold increase in child mortality compared to the singleton births [**47].**

Marital status was also associated with infant mortality; for children who had mothers who never married, their mortality rate was higher than children whose mothers were married at the time the child was born. These findings agree with those of a study in Ethiopia, which showed that children whose mothers were never married, had separated or divorced had a higher mortality than those whose mothers were in a union **[43].** Further, most of the single mothers in this study were also having children for the first time, and firstborn children have also been shown to have an increased risk of mortality compared to other children.

The age and sex of the household head was also associated with infant mortality. Households headed by men and the older the household head, the higher the risk of mortality. A plausible explanation would be that since more than half the households in this study were headed by men, the mothers in these households were less likely to have autonomy in their choice and use of health services. They are also not likely to

have autonomy in decision-making with regard to child health seeking behavior, as the male household heads were likely to make decisions for their households.

4.3 Mortality rates and Causes of death

Mortality in this study was highest in the first few months of the child, reaching a peak in the 3rd month of life, after which it begins to decrease to a near constant rate after the 4th year of life of the child. The report on the levels and trends in child mortality (2012), observed that although most of the under-five mortality had decreased in the last few years, neonatal deaths were reducing at a slow rate and more than half of the under-five deaths occur during the neonatal period **[1]**. The report also observed that the leading causes of death in the under-five children are pneumonia, preterm birth complications, diarrhoea and intrapartum-related complications **[1]**.

In this study, acute lower respiratory infections (LRTI) and pneumonia are the leading cause as has been shown in a study in this setting, where LRTIs caused 43% in all infant deaths. The study done between the years 2000 and 2002 also showed that diarrheal diseases were the second leading causes of under-5 mortality, after HIV/AIDS **[48]**. In our study, diarrhoea caused 24% of all deaths while disorders due to low birth weight and malnutrition caused 6% and 4% respectively. Malnutrition and low birth weight in this setting could be as a result of HIV/AIDs causes **[50]**, as the study setting as previously discussed is a high HIV prevalence area. A study on paediatric HIV in SSA **[38]** also highlighted malnutrition as one of the main challenges of HIV in children. Overall our results on causes of death in the children are similar to those also found in a study to establish cause-specific mortality rates in

SSA and Bangladesh **[14]**. Respiratory infections were found to be the leading causes of death in under5 children in all the twelve sites in that study. Deaths attributed to diarrhoeal diseases were also varied widely in the sites, but mainly occurring in the West African sites. South Africa sites were leading in HIV/AIDs related causes **[14]**.

4.4 Limitations of the study

Given the findings of this study, it is also important to note the following limitations in our study.

The HIV status of some mothers was not known. The association with child mortality and mother's HIV status is therefore only conclusive for mother's for whom HIV status was known. It was however observed that children of mothers whose HIV status was not known had mortality rates lower than children of mothers who were HIV Negative suggesting that a portion of the mothers with unknown HIV status were likely to be HIV positive.

We also did not have information on the HIV status of the children, as this is not collected in the surveillance. However, we know that children born to HIV infected mothers may have higher mortality rates than those born to HIV negative mothers **[21].**

Access to PMTCT care for HIV positive mothers has been shown to benefit child survival in our study setting **[8].** Information on access to PMTCT care services for HIV positive mothers in the study was however not available in our study population.

There was the limitation of possible out migrations and loss to follow-up of the children, leading to possible selection bias, as we may not have captured all cases of mortality.

Missing information in the verbal autopsy data on causes of death was also a limitation, for which we considered it as unknown or indeterminate cause in this study.

The cox regression models did not meet the proportionality assumptions of constant hazards; as such only the Poisson model results are presented in this report.

Further, it was not possible to collapse groups or cells with small numbers, as this would have altered the meaning of some groups & variables. These cells/groups with small numbers were retained in the entire analysis of this study.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

We can conclude that although mortality varied by the age of the child, children born to mothers who were found to be HIV positive in the HIV surveillance had higher mortality rates than children born to HIV free mothers and being on ART treatment reduced children mortality. Immunization of the children regardless of the mother's HIV status reduced the child mortality rates. Children of mothers who had given birth to other children before had lower mortality rates than those who were first born while more education acquisition of the mother reduced mortality rates of the children. Children of mothers who were currently married had lower mortality rates than children whose mothers were never married, divorced, separated or widowed. Children who were resident within the DSA at the end of the study had a reduced mortality rate than those who weren't.

5.2 Recommendations

Interventions targeting HIV positive pregnant women and mothers should be carried out in the study area, with specific emphasis on reducing child mortality associated with maternal HIV status. This includes ensuring access to reliable HIV testing facilities, access to ART treatment and HIV programs and reduction of incidences of pediatric HIV by adoption of the health promotion approach five model by Naidoo & Willis **[38]**. This would ensure testing is done early and mothers are aware of their HIV status, ensure HIV infected children commence treatment early and other drug-related challenges such as drug resistance, poor adherence are addressed.

The importance of child immunization at scheduled times should also be emphasized to mothers.

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Appendices

Ethics clearance certificate for this study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Anne N Makumi

CLEARANCE CERTIFICATE	**M120860**
PROJECT	Impact of Maternal Factors on Survival Patterns of Children under 15 Years of Age in Rural Kwa-Zulu-Natal, South Africa 2003-2012
INVESTIGATORS	Miss Anne N Makumi.
DEPARTMENT	School of Public Health
DATE CONSIDERED	31/08/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 31/08/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Edmore Marinda

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...