MORBIDITY AND MORTALITY IN HIV EXPOSED UNDER FIVE CHILDREN IN A RURAL MALAWI SETTING

By

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A dissertation submitted in partial fulfilment of the requirements for the degree of
Master of Science in Epidemiology

The University of Zambia
September, 2013

DECLARATION

I, Oscar Henry Divala hereby declare that this dissertation is my original work and has not been submitted for any other awards at the University of Zambia or any other University.

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ABSTRACT

Introduction

HIV and AIDS has significantly contributed to the rise of under-five morbidity and mortality in Africa. This threatens recent gains in infant and child survival and health. In Malawi, as in most other southern African countries, the care of HIV exposed children is mostly constrained due to the lack of area specific information on the risk to dying and morbidity of these children. Interventions to reduce childhood morbidity and mortality attributed to HIV exposure are currently available. However, there is no evidence base to support such an intervention in rural Malawian settings. This research therefore aimed at estimating and comparing morbidity and mortality events among HIV exposed and non-exposed under five children in a rural Malawian setting.

Methods

Data stem from a cohort of 7,929 under-five children born in the Continuous Registration System (CRS) based in the demographic and health site in Karonga district, Malawi from January 2009 to June 2011. Analysis was based on person years of observation, Kaplan–Meier survival analysis and Cox proportional hazard regression, which was used to calculate and compare morbidity and mortality rates among HIV exposed and unexposed children.

Results

Overall (n=7,929) cohort data of under-five children born in the CRS represented 12380.8 person years of observation (PYO) of which 3.1% were contributed by HIV exposed infants. Half were female and an overall mean age was 18.4 months (SD 13.4), with older children dominating in the HIV unexposed group. Overall all-cause morbidity rate was 337.6/1000 PYO (95% CI: 327.5/1000 PYO-348.0/1000 PYO) and HIV-exposed children morbidity rate was 1.34 times higher compared to HIV-unexposed children. IMCI pneumonia was the most frequent diagnosis among both exposed and unexposed children but was significantly higher in the HIV exposed group. Overall child mortality rate was 16.6/1000pyo (95% CI 14.5-19.1) from 206 deaths. The HIV exposed children had 4.5 times higher mortality rate as compared to the HIV unexposed children. Generally both mortality and morbidity rates were higher in the first year of life.

Conclusion

HIV exposure at birth has a greater impact on child mortality and morbidity especially in the first year of life. This burden can be reduced with effective PMTCT interventions which will reduce rates of HIV transmission to infants.

ACKNOWLEDGEMENTS

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List of Abbreviations

ART	Antiretroviral therapy
CI	Confidence Interval
CRH	Chilumba Rural Hospital
CRS	Continuous Registration System
DSS	Demographic Surveillance Site
HDSS	Health and Demographic Surveillance Site
HIV	Human Immunodeficiency Virus
KI	Key Informant
KPS	Karonga Prevention Study
MDGs	Millennium Development Goals
PMTCT	Prevention of mother to child transmission
PSU	Pneumococcal Surveillance in Under-five Children study
RR	Rate Ratio

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Chapter 1   INTRODUCTION

1.1   Background

Child mortality remains one of the biggest problems faced by countries in southern Africa. This problem has been compounded by high HIV prevalence in the region with an estimated 22.5 million people living with the virus, the majority of which are women and girls (UNAIDS, 2010). Current estimates suggest that HIV and AIDS account for the mortality of 2% of children under the age of five years worldwide of which 90% is in southern Africa. Marinda et al. (2007), in an observational study done in Zimbabwe, demonstrated that children exposed to HIV have greater mortality and morbidity rates irrespective of their HIV status. Worldwide, it is estimated that over 90% of HIV infection in children is due to mother-to-child transmission (WHO/UNAIDS/UNICEF, 2011).

If there is no intervention half of these children will die before their second birthday (Newell et al., 2004b, UNAIDS, 2011). This burden is worsened by the high prevalence of HIV which increases childhood health-care indices in southern African countries. HIV exposed children living in areas with high prevalence of HIV and infectious diseases such as malaria, pneumonia and diarrhoea are at a higher risk of dying.

Malawi has an overall adult HIV prevalence of 10.6% in the general population and of the estimated one million people living with HIV, 10% are children (National Statistical Office and ICF Macro, 2011). The prevalence of HIV is higher among the female population which in turn sustains the HIV pandemic in children. In Malawi, mother to

child transmission of HIV has been estimated to account for almost a quarter of new infections and HIV/AIDS is attributed to 20% of mortality in children under the age of five years (UN, 2010). A few studies in Malawi have described mortality and morbidity rates in children under the age of five years as a result of HIV exposure. A study of children born from HIV-positive mothers in an urban setting of Malawi showed that HIV-infected children had a higher disease frequency and mortality rates compared to those not infected (Taha et al., 2000). For a period of 20 years (1989–2009), mortality rates in an urban setting of Malawi remained high among all HIV-exposed but uninfected children and among children who themselves became infected (Taha et al., 2012)

In order to accomplish Millennium Development Goal (MDGs), especially MDG4's target of reducing child mortality by two thirds by 2015, there is a clear need for local evidence about the burden of disease in childhood. Credible estimates of what this burden entails are essential for the establishment of informed health policies in order to implement effective health interventions. Although data exist on the rate of mortality and morbidity of children under the age of five years exposed to HIV in Africa, there is still little information regarding the area-specific infectious disease morbidity and mortality rates. In Malawi most of the available data are from urban areas and this information cannot always be applied to rural settings.

1.2 HIV and AIDS in under-five children

Ever since the first cases of human immunodeficiency virus (HIV) infection were identified, paediatric HIV has risen dramatically in developing countries. This has been a result of high HIV prevalence in women of child bearing age in these areas (UNAIDS, 2010). In 2010, about 34 million people were living with HIV worldwide, this includes

about 3.4 million children younger than 15 year (UNAIDS, 2011). Incident HIV infection in 2010 was estimated at 2.7 million, including 390 000 among children less than 15 years old(WHO/UNAIDS/UNICEF, 2011). Global mortality and morbidity of children under the age of five years is greatly attributed to the transmission of HIV from mothers to their infants.

In 2010 UNAIDS reported that approximately 1000 HIV-infected infants are born every day, mostly in southern Africa, which amounts to nearly 370,000 new paediatric infections annually (UNAIDS, 2010). In many parts of the world, women represent the population with the rapid increase in HIV infection rates. The southern African countries are the hardest hit where women, infants and young children account for more than 60% of all new HIV infections.

Children born to women living with HIV are exposed and can be infected with HIV during antepartum, intrapartum, or postpartum periods. Of the estimated 3.4 million children living with HIV worldwide, 90% reside in southern Africa and half of these children die before their second birthday if there is no any intervention (Newell et al., 2004b, UNAIDS, 2011). Latest estimates suggest that under-five deaths worldwide have dropped from more than 12 million in 1990 to 7.7 million in 2010 (Rajaratnam et al., 2010). Most of these deaths are from childhood infectious diseases which are prominent in southern Africa, where 1 in 8 children die before age 5 compared to 1 in143 in developed regions (Rajaratnam et al., 2010, You D et al., 2009).

1.3   Child morbidity and mortality by HIV and AIDS

High prevalence of HIV in southern African countries significantly increases childhood mortality rates and health care indices. HIV exposed children, especially those living in resource limited areas, where both HIV and infectious diseases are prevalent, are at a high risk of dying from common childhood illnesses. In a large cohort of HIV-exposed but uninfected infants in Latin America and the Caribbean region, approximately 60% of the children suffered from infectious diseases in the first 6 months of life (Mussi-Pinhata et al., 2007b). The 2010 estimates of HIV related mortality rates in southern Africa among under five children range from 10 % in Mozambique and Zambia to 28 % in South Africa (UNICEF, 2012).

HIV is significantly linked to high childhood morbidity and mortality in southern Africa (Obimbo et al., 2004). A pooled analysis of African trials showed higher death rates in HIV infected children compared to HIV uninfected (Newell et al., 2004a), concurring with a South African study of infants born to HIV-infected women, which, besides demonstrating the high risk of hospitalization and death in HIV infected infants, also showed high mortality in HIV uninfected infants born from HIV infected women (Venkatesh et al., 2011). Marinda et al. (2007), in a follow up study done in Zimbabwe, demonstrated that HIV exposed children have greater mortality and morbidity irrespective of their HIV status. This further highlights paediatric HIV exposure as a primary predictor of morbidity and mortality of infants in the southern Africa.

The care of HIV exposed children is mostly constrained due to the lack of area specific information on the risk to dying or hospitalization of these children. It is therefore imperative to establish population specific burden of childhood HIV.

1.4   Problem statement

The Malawi government has put in place various strategies to meet the target of reducing by two thirds the mortality of under-five children by the year 2015. However, one of the many challenges Malawi is facing in her efforts to reduce child mortality is the increased morbidity and mortality by HIV. Paediatric HIV significantly contributes to overall child mortality and morbidity especially in high-burden countries. In the recent past, extensive work has been done on documenting the impact of HIV on survival of under-five children. However, a greater proportion of this work was focused on children in urban areas with a bias to mortality only. Therefore, little information is available regarding area specific infectious disease morbidity and mortality among HIV exposed and unexposed under-five children living in rural Malawian settings.

1.5   Rationale

In order to reduce child morbidity and mortality in under-five children, there is urgent need to examine and compare area specific morbidity and mortality rates among HIV exposed and unexposed under-five children. In this study, morbidity and mortality rates in under-five children were examined and compared in a prospective manner in relation to HIV exposure status. This study will therefore help inform targeted interventions at high burden clinical conditions in order to reduce under-five morbidity and mortality by providing unique and area specific rates of clinical conditions presenting at Chilumba Rural Hospital (CRH) in relation to child's HIV exposure. Furthermore this study will help to inform population group specific interventions in combating the burden of HIV in children.

Chapter 2 AIMS AND OBJECTIVES

2.1 Research question

What are the outcome (morbidity and mortality events) differences and common clinical conditions among HIV exposed and unexposed under five children in a rural Malawi setting?

2.2 Broad objective

To compare morbidity and mortality events in HIV exposed and unexposed under-five children in Chilumba, a rural Malawian setting

2.3 Specific objectives

i. Determine mortality rates in HIV exposed and unexposed under-five children in Chilumba.

ii. To compare rates of clinic attendance (morbidity) between HIV exposed and unexposed under-five children in Chilumba.

iii. To examine and compare mortality rates between HIV exposed and unexposed under-five children in Chilumba.

iv. To identify common clinical conditions by HIV exposure status presenting at Chilumba rural hospital among under-five children.

Chapter 3   METHODOLOGY

3.1   Study setting

This research analysed data from studies carried out by Karonga Prevention Study (KPS) in a Health and Demographic Surveillance Site (HDSS) in Karonga district, northern part of Malawi. The HDSS is situated in the southern part of the district and is bordered by Lake Malawi in the east, Nyika National Park in the south and west and village boundaries define the demarcation in northern part(Crampin et al., 2012). The KPS is a large research institution that started its operations in 1979 as a leprosy project. However with the decline in leprosy over the years, the project has been involved in many studies related to HIV and TB. The HDSS area has two main hospitals Chilumba Rural Hospital (CRH) and St Anne's mission hospital and two health centres (Sangilo and Fulirwa). The CRH and the two health centres are government funded and offer free services while St Anne's mission hospital is funded by the Christian Health Association of Malawi and it offers paying services (see figure 1 below).
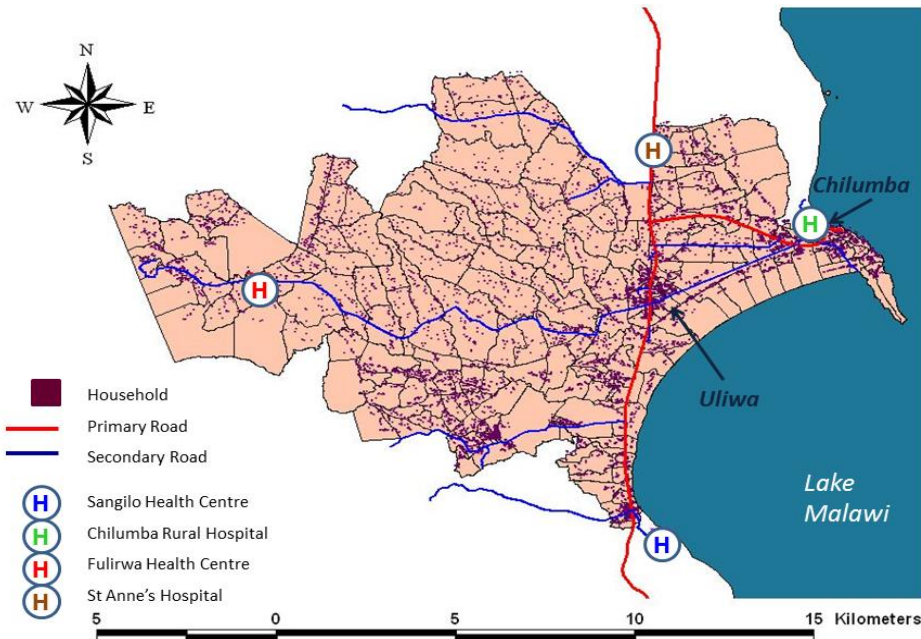
Figure 1: Map of the HDSS in Chilumba showing households and health facilities in 2011 (Crampin et al., 2012)

3.2 Study population

All children under the age of five residing and registered as permanent members of the DSS between January 2009 and June 2011 were included in the study. This includes those born in the study area and those who just migrated into the study area and were registered as permanent residents.

3.3 Sample size

This study used data from all children under the age of five residing and registered as permanent members of the DSS between January 2009 and June 2011. This gives a total of 7929 children under the age of five.

3.4 Design

3.4.1 Demographic and Health surveillance

KPS has focused on epidemiological, clinical and immunological studies of infectious diseases of public health importance. To facilitate its research activities, KPS established

the only HDSS in Chilumba area which at the end of 2011 was covering a population of 35730 from 8285 households. The HDSS has a population of more than 35 730 individuals which is predominantly rural, and the economy is centered on agriculture, fishing and petty trading (Crampin et al., 2012) Each village is divided into smaller clusters of 20–30 households. Groups of approximately 10 clusters in a defined geographical area are combined to form the 21 reporting groups, which make up the surveillance area and every individual has a unique identification number in the database. From 2002 to 2004 baseline census was conducted to register all individuals and households in the HDSS. Since then this population is closely monitored by a Continuous Registration System (CRS) which continuously captures and updates data on births, deaths and migration for individuals and households (Crampin et al., 2012). The following paragraphs discusses in detail the CRS and other surveys which captured data used in this study.

i.   Continuous Registration System (CRS)

The CRS relies on a network of village-based key informants (KIs) who are resident in each reporting group. The KIs report vital events and household movements on a monthly basis. Births and deaths reported by KIs are immediately followed up by trained interviewers. In case of a birth report, information such as date of birth, gender and parents information is recorded. Similarly, for a death report, a medically trained interviewer visits the deceased's household to fill a verbal autopsy form. Several repeat visits are arranged if no one is found at home during the first visit. The information gathered from KIs is validated and complemented by an annual census conducted to

update household composition and migration as well as changes that take place to households in the area.

ii.   HIV sero-surveys

In September 2007 HIV sero-surveys started in the DSS whereby a door-to-door HIV counselling and testing was offered to all individuals aged 15 years and older. Since then there have been four rounds of HIV sero-surveys from 2007 to 2011 with an average participation rate of between 55-60% in testing (Floyd et al., 2012). In this study besides HIV voluntary testing and counselling, individuals were also asked about their previous HIV-testing, including the timing and the results of the most recent test, and also about ART use if the participant reported that they were HIV positive (Floyd et al., 2012).

In this survey, rapid antibody based HIV tests were used to determine the HIV status of the participants. In the initial phases of the survey parallel HIV testing protocol was used which involved running two different rapid tests simultaneously and use a third test as a tie breaker if the results were discordant. This HIV testing protocol was changed to serial testing following updated national guidelines. Serial HIV testing is whereby a first test is done and the result of the first test determines whether additional testing is required.

iii.   Pneumococcal Surveillance in Under-five Children study (PSU)

This was a hospital based open cohort study which started in October 2008 and ended in June 2011. The main objective of this study was to quantify the contribution of invasive pneumococcal disease (IPD) in under-five children in the Chilumba area. The study enrolled under five children who were resident in the CRS area, attending CRH with any of the following:

a) Signs meeting the WHO's definition [cough, fast breathing ($\geq$50 breaths per minute for children < 1 year old and 40 per minute for children $\geq$1 year old) and lower chest-wall in drawing] for acute lower respiratory infection (ALRI).

b) Fever of $\geq$37.5°C (axillary temperature) with or without localizing signs.

c) Signs suggestive of meningitis (neck stiffness, altered consciousness, bulging fontanel, history of convulsions).

d) Localized musculoskeletal swelling.

At enrolment parents/guardians of study participants were providing a detailed medical history of the child's condition. A KPS clinician was then performing a full clinical examination of the child. Depending on the findings from the history and clinical examination, laboratory investigations such as full blood count, malaria parasitemia, packed-cell volume and blood culture were ordered. Where indicated, a chest Xray was done.

3.4.2 HIV exposed morbidity and mortality design

This was an open cohort study of all children under the age of five years living in the DSS from January 2009 to June 2011. This was a secondary analysis of data derived from CRS, demographic surveys done annually in the DSS area and a Cohort study of Pneumococcal Surveillance in Under-five Children study. Data from these studies which have been described above were linked using unique identifiers.

i.   Definition of HIV exposure

Based on the mother's HIV status at the time of giving birth, under-five children were grouped into the following HIV exposure groups:

a) HIV exposed

A child was defined as exposed if born to a mother who had a positive HIV test result before giving birth or who tested HIV positive within one year of child's birth.

b) HIV unexposed

A child was defined as HIV unexposed if born to a mother who tested negative after the child was born and no positive test within one year after the child's birth.

c) HIV status unknown

HIV test not done on the mother or where the exposure cannot be confidently established

ii. Definition of outcome

The following were the primary outcomes of interest:

a) Mortality

This was defined as death of a child within five years after the child was born.

b) Morbidity

This was defined as any documented clinic attendance of a child under the age of five years. Visits to the clinic in a space of 14 days with the same diagnosis were considered to be related and were thus defined as a single episode.

3.4.3 Statistical analysis

Datasets from all the data sources explained above were merged using unique identifiers into one dataset. In the univariate analysis, under-five children were stratified by HIV exposure status and age group. Differences in proportions were assessed using Chi-square test and differences in means, using Student's T-test. Children with unknown HIV exposure status were included in the analysis as a separate category. Descriptive analyses of morbidity and mortality rates based on person years of observation were conducted using Kaplan–Meier survival analysis, and survival curves were compared using log-rank

tests. Univariate and multivariable Cox proportional hazard regression was used to compare rates based on person years of observation in HIV exposed and unexposed. Covariates included in the final modelling were age, gender, and HIV exposure status.

All data analyses were conducted using STATA (STATACORP, version 11.2, College Station, Texas, USA) software. A 95% confidence interval (CI) and a 5% level of significance were used to assess statistical significance. All statistical tests were two tailed.

3.5   Ethical approval

In order to maintain confidentiality, the names of the participants were removed in all datasets provided for analysis. This study received ethical approval from the College of Medicine Research Ethics Committee (protocol number P.11/12/1305) and University of Zambia biomedical Research Ethics Committee (IRB00001113 of IORG0000774). All studies which provided data for this analysis were done by the Karonga Prevention Study and were approved by Malawi National Health Sciences Research Committee.

Chapter 4   RESULTS

4.1   Baseline characteristics

Data on 7,929 under five children residing in the CRS during the study period representing 12380.8 person years of observation (PYO) were analysed. Of these 3,162 children were enrolled in the PSU study. Table 1 below shows distribution of baseline characteristics of the study population. Of the enrolled children, 5862 (73.9%) were HIV unexposed at birth, a small proportion of the children (3.1%) were HIV exposed at birth and 1821 (23.0%) had unknown HIV exposure status. There were 3,970 (50.1%) females and there were no sexual difference among HIV exposure groups. The overall mean age was 18.4 months (SD 13.4) with HIV unexposed group being significantly older than the HIV exposed (mean 18.4 vs. 13.7 months). The majority, 4,518 (57.0%) of the children lived at a distance of more than one kilometre from Chilumba rural hospital.

Table 1: Baseline characteristics of a cohort study of 7929 under five children, by HIV exposure status in Chilumba, Karonga.

Characteristic	Overall	HIV unexposed	HIV exposed	HIV status unknown	P value
Participants	7929 (100)	5,862 (73.9)	246 (3.1)	1,821 (23.0)	-
Sex (%)					
Male	3,959(49.9)	2,908 (49.6)	124 (50.4)	927 (50.9)	0.619[*]
Female	3,970 (50.1)	2,954 (50.4)	122 (49.6)	894 (49.1)	
Mean Age (SD) months	18.4 (13.4)	18.4 (12.4)	13.7 (10.6)	19.1 (17.0)	0.000[**]
Distance to CRH					
< 1km	3,411 (43.0)	2,351 (40.1)	130 (52.9)	930 (51.1)	0.000[*]
≥ 1km	4,518 (57.0)	3,511 (59.9)	116 (47.2)	891 (48.9)	
*Chi square test **t- test					

Missing HIV Exposure status

HIV exposure status results were unknown in 1821 children, 23.0% of the study population. Table 2 below shows a comparison of children with known HIV exposure status versus those with unknown HIV status in terms of their age and sex. There was no evidence that sex was different in the two groups (p= 0.343). However, there was evidence that most of the children without HIV exposure status results were of older age (p=0.0115).

Table 2: A comparison of age and sex distribution of children with known HIV exposure status versus with unknown HIV status.

Characteristic	Total	HIV exposure status results		P-value
		Known	**Unknown**	
Overall	7,929	6,108 (77.0)	1,821 (23.0)	-
Age months mean (SD)	18.4 (13.4)	18.2 (12.2)	19.1 (16.9)	0.0115[**]
Sex N (%)				
Male	3,959 (49.9)	3,032 (49.6)	927 (50.9)	0.343[*]
Female	3,970 (50.1)	3,076 (50.4)	894 (49.1)	
*Chi square test **t- test				

Common clinical conditions

From January 2009 to June 2011, the PSU study enrolled 3,162 children with 4180 morbid events. During this period, 84.6% of the children had one clinic visit, 12.8% had two visits and 2.7% had three or more visits. Of these children 80% were HIV unexposed, 3.8% were exposed and the remainder had unknown HIV exposure status at their first clinic attendance. The commonest diagnoses were IMCI pneumonia and uncomplicated malaria (Figure 2 below).

Figure 2: Common clinical conditions among under five children at first visit to CRH
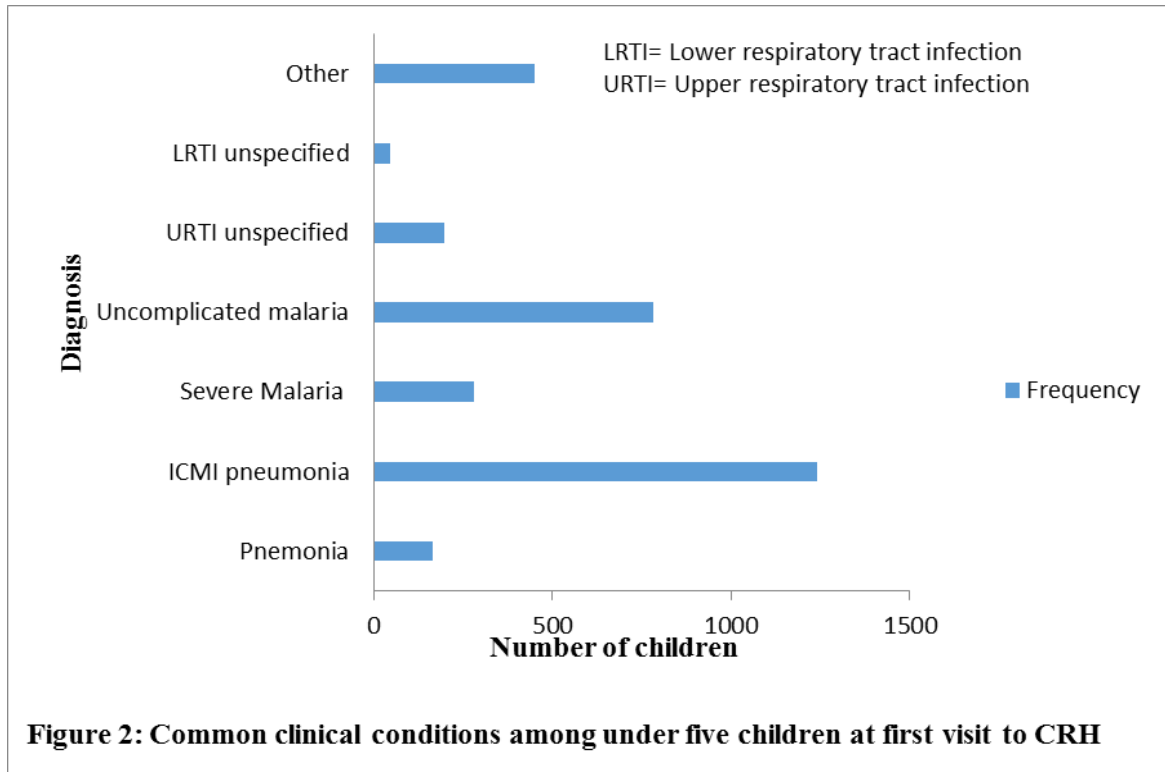
4.2 Child morbidity rates

Table 3 below shows morbidity and mortality rates among HIV-exposed and unexposed under-five children. The overall all-cause morbidity rate was 337.6/1000 PYO (95% CI: 327.5/1000 PYO-348.0/1000 PYO). HIV-exposed children were 1.34 times more likely to visit the clinic for any reason (455/1000 PYO vs. 345/1000 PYO, *p* <0.001) compared to HIV-unexposed children. The HIV exposed children were more likely to be diagnosed with IMCI pneumonia (RR 1.42, p=0.006) and confirmed (including radiological) pneumonia (RR 2.26, p=0.011) compared to HIV-unexposed children. However, there was no statistical significant difference in the remaining cause-specific rates among HIV exposed and unexposed children. After stratifying cause-specific morbidity rates by age, there was weak evidence suggesting differences across age

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groups in both HIV exposure groups as it can be appreciated by overlapping confidence intervals shown in table 4.

4.3 Child mortality rates

Overall 206 (2.9%) child deaths occurred during the study period. Of these 68.9% were HIV unexposed and 11.2% were exposed to HIV and 19.9% had unknown HIV exposure status. The Kaplan-Meier curve examining the effect of HIV exposure status on mortality is presented in Figure 3. The overall mortality rate was 4.5 times (62.3/1000 PYO vs. 13.9/1000 PYO, $p=0.001$) higher among HIV exposed children compared to HIV unexposed children (Table 3). In children under the age of one year, mortality rate was higher in the exposed group compared to the unexposed as evidenced by non-overlapping confidence intervals in table 4. However this was not the case in older children.
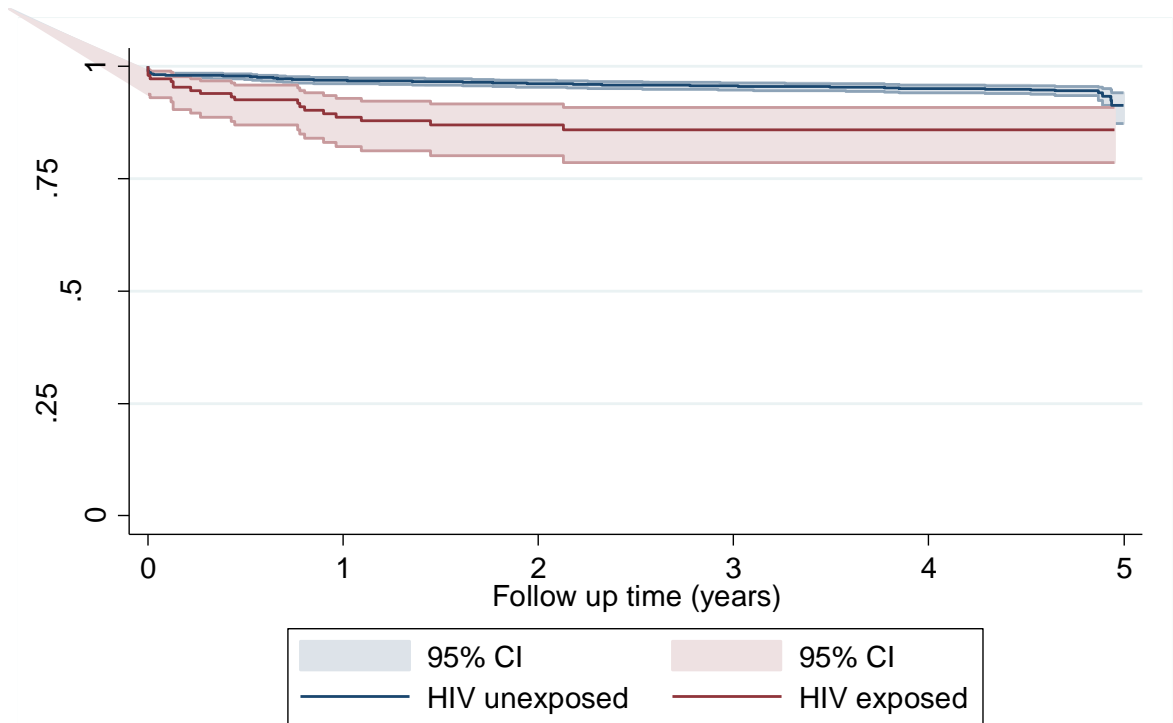

Figure 3: Child survival estimates by their HIV exposure status

Table 3: Morbidity and mortality rates among HIV-exposed and unexposed under-five children in Chilumba, Karonga

	Overall PYO =12380.8		HIV unexposed PYO=10249.1		HIV exposed PYO=369.1		Rate Ratio	P-value
	Events	Rate/1000 PYO (95% CI)	Events	Rate/1000 PYO (95% CI)	Events	Rate/1000 PYO (95% CI)		
Morbidity								
All-cause	4180	337.6 (327.5-348.0)	3536	345.0 (333.8-356.5)	168	455.2 (390.1-528.0)	1.34	<0.001
Cause specific								
IMCI pneumonia	1478	119.4 (113.5 125.6)	1272	124.1 (117.5-131.1)	65	176.1 (138.1-224.5)	1.42	0.006
Uncomplicated Malaria	1105	89.3 (84.1-94.6)	956	93.3 (87.5-99.4)	43	116.5 (86.4-157.1)	1.25	0.153
Severe Malaria	335	27.1 (24.3-30.1)	295	28.8 (25.7-32.2)	5	13.5 (5.6-32.5)	0.47	0.087
Pneumonia	148	12.0 (10.2-14.0)	123	12.0 (10.1-14.3)	10	27.1 (14.6-50.3)	2.26	0.011
Unspecified URTI	241	19.5 (17.2-22.1)	204	19.9 (17.4-22.8)	10	27.1 (14.6-50.3)	1.36	0.339
Unspecified LRTI	62	5.0 (3.9-6.4)	54	5.3 (4.0-6.9)	3	8.1 (2.6-25.1)	1.54	0.462
Mortality								
Total deaths	206	16.6 (14.5-19.1)	142	13.9 (11.8-16.3)	23	62.3 (41.4-93.7)	4.50	0.000

Table 4: Morbidity and mortality rates by age group and HIV exposure in children under the age of five in Chilumba

Age group (months)	N	HIV unexposed Rate/1000 PY (95% CI)	n	HIV exposed Rate/1000 PY (95% CI)
IMCI pneumonia				
≤11	464	176.9 (161.5-193.7)	32	229.6 (162.4-324.7)
12-23	471	177.5 (162.2-194.3)	16	148.3 (90.9-242.1)
24-35	211	83.4 (72.9-95.4)	11	154.0 (85.3-278.1)
36-59	126	51.6 (43.3-61.4)	6	118.8 (53.4-264.4)
Uncomplicated Malaria				
≤11	214	81.6 (71.4-93.3)	10	71.8 (38.6-133.3)
12-23	310	116.8 (104.5-130.5)	15	139.1(83.8-230.7)
24-35	258	102.0 (90.3-115.2)	13	182.0 (105.7-313.5)
36-59	174	71.2 (61.4-82.7)	5	99.0 (41.2-237.9)
Severe Malaria				
≤11	214	81.6 (71.4-93.3)	10	71.8 (38.6-133.4)
12-23	310	116.8 (104.5-130.6)	15	139.1 (83.8-230.7)
24-35	258	102.0 (90.3-115.2)	13	182.0 (105.7-313.5)
36-59	174	71.2 (61.4-82.6)	5	99.0 (41.2-237.9)
Pneumonia				
≤11	77	29.4 (23.5-36.7)	8	57.4 (28.7-114.8)
12-23	24	9.0 (6.1-13.5)	1	9.3 (1.3-65.8)
24-35	13	5.1 (3.0-8.8)	1	14.0 (2.0-99.4)
36-59	9	3.7 (1.9-7.1)	0	-
Mortality				
≤11	80	30.5 (24.5-38.0)	18	129.2 (81.4-205.0)
12-23	22	8.3 (5.5-12.6)	3	27.8 (9.0-86.2)
24-35	18	7.1 (4.5-11.2)	2	28.0 (7.0-112.0
36-59	22	9.0 (5.9-13.6)	-	-

4.4 Multivariable analysis of under-five children morbidity and mortality rates

In adjusted analysis (Table 5), children who were exposed to HIV were at 1.2 times risk of visiting a clinic for any reason (adjusted Hazard Ratio; HR: 1.21 95% CI: 1.03-1.43). The risk of all-cause morbidity was 41% lower among children residing within a distance of one kilometre to CRH. Sex of a child was not associated with all-cause morbidity. Being diagnosed with IMCI pneumonia was not associated with sex and HIV exposure

status while living close to CRH was 51% protective. The risk of death among HIV exposed children was 2.4 times higher compared to HIV unexposed children (HR: 2.4, 95% CI: 1.67-3.59). Sex and distance to CRH were not significantly associated with mortality among HIV exposed and unexposed under five children.

Table 5: Risk factors for mortality and all cause morbidity using cox regression in under five children in Chilumba

	Crude HR (95% CI)	Adjusted HR (95% CI)
Mortality		
HIV exposure status		
HIV exposed	3.55 (2.28-5.52)	2.44 (1.67-3.59)
HIV unexposed	1	1
Sex		
Female	0.93 (0.71-1.22)	0.95 (0.71-1.29)
Male	1	1
Distance to CRH		
<1km	0.93 (0.70-1.22)	1.03 (0.75-1.41)
≥1km	1	1
Morbidity		
All cause		
HIV exposure status		
HIV exposed	1.25 (1.07-1.47)	1.21 (1.03-1.43)
HIV unexposed	1	1
Sex		
Female	0.99 (0.91-1.07)	1.0 (0.91-1.08)
Male	1	1
Distance to CRH		
<1km	0.61 (0.56-0.65)	0 .59 (0.54-0.64)
≥1km	1	1
IMCI pneumonia		
HIV exposure status		
HIV exposed	1.23 (1.01-1.5)	1.14 (0.93-1.40)
HIV unexposed	1	1
Sex		
Female	1.00 (0.90-1.1)	1.00 (0.89-1.11)
Male	1	1
Age (months)	0.98 (0.98-0.99)	0.98 (0.98-0.98)
Distance to CRH		
<1km	0.50 (0.46-0.56)	0.49 (0.44-0.54)
≥1km	1	1

Chapter 5   DISCUSSION

This study among HIV exposed and unexposed children under the age of five years in a rural Malawi setting has revealed a potent detrimental effect of mother's HIV infection on morbidity and mortality of children under the age of five years. HIV exposure remains the key predictor of morbidity and mortality in children under the age of five years. Overall, HIV exposed under-five children were 1.2 times more likely to visit the clinic for any reason and at more than twice the risk of death compared to HIV unexposed children. In addition, these findings also convincingly highlight a high burden of morbidity and mortality borne by children in their first year of life irrespective of their sex. Infections were the major reason for visiting a clinic, and IMCI pneumonia was the leading infection diagnosed seconded by uncomplicated malaria. The high burden in children under one year might also suggest that past preventive interventions were less focussed to impact those most affected.

There have been few studies from similar rural settings which have described morbidity in HIV exposed children (Taha et al., 2000, Venkatesh et al., 2011, Mussi-Pinhata et al., 2007a). In this study, HIV exposed children had higher incidence rate of all-cause morbidity. Despite this high all-cause morbidity rate in HIV exposed children, cause specific morbidity rate was observed to be similar in both groups except for pneumonia which had higher incidence rate in HIV exposed children compared to unexposed children which concurs with a cohort study in South Africa which reported high rates of respiratory infections among HIV infected children (Venkatesh et al., 2011). Morbidity rates of the common conditions stratified by age in months were observed not to be

different in between HIV exposed and unexposed children. This finding concurs with other African studies which observed that infections not specifically related to HIV were common in all children (Taha et al., 2000, Spira et al., 1999).

In this study, child's HIV exposure status was associated with an increased risk of death (2.4 times) among children under the age of five years. This finding is consistent with results from a study which followed up Malawian children from 12 months to the age of three years in an urban area which showed that risk of mortality was three times higher in children born to HIV positive mothers versus children of HIV uninfected mothers (Taha et al., 2000). Similar results have also been observed by several other studies within the southern African region with the risk of mortality in HIV exposed children ranging from two to eight times (Zaba et al., 2005, Marinda et al., 2007, Newell et al., 2004a, Naniche et al., 2009).

In addition, children under the age of one year and HIV exposed were observed to have higher morbidity and mortality rates compared to the older ones irrespective of sex. The risk of high mortality among HIV-exposed children under the age of one year reported in this cohort is consistent with a PMTCT based Malawian cohort in a similar rural area which reported a cumulative mortality of more than four times greater among HIV exposed than among HIV-unexposed children (Landes et al., 2012). It is difficult to certainly determine that the observed morbidity and mortality risk is secondary to HIV infection or only HIV exposure. This is because there was no confirmatory HIV test done on children and HIV exposure status was solely based on their mother's HIV status. However some studies have documented that HIV infection increase the risk of mortality (Newell et al., 2004b, Newell et al., 2004c) which may suggest that there was a large

proportion of HIV infected children in the HIV-exposed group leading to the higher risk of morbidity and mortality observed in this study.

The distribution of baseline characteristics was similar between those with unknown HIV exposure status and those with known HIV status. In addition to that, the study was based in a HDSS which has a real-time system of capturing events using KIs which makes the estimates more reliable.

As discussed above, this study lacked confirmation of child HIV status which is crucial in assessing the effect of maternal HIV status on child morbidity and mortality. Thus it was difficult to determine whether HIV exposure alone (without infection) could be associated with risk of child morbidity and mortality. Additionally, PSU study which was capturing morbidity data failed to capture data on some patients treated as outpatients in other health centers in the CRS area since it was based at CRH which is surrounded by three other health centres. Another reason could be because data collection of PSU study was only done during working hour and weekdays which made it fail to capture data on children treated during weekends and after working hours. Thus morbidity rates calculated in this study are underestimates.

Chapter 6   CONCLUSION

This study reveals high morbidity and mortality rates in HIV exposed children compared to the unexposed children. It is of particular concern that morbidity and mortality rates are higher in the first year of life. This might be due to the fact that most of the exposed children were probably infected which may suggest that past preventive interventions were less focussed to impact those most affected. Therefore close monitoring of HIV exposed infants, especially in their first year of life, remains essential. This in turn supports public health efforts in prevention of mother to child transmission of HIV during pregnancy and in breastfeeding. Therefore, interventions that improve PMTCT services and facilitate early identification and follow up of HIV exposed children are urgently needed to reduce the high burden of childhood morbidity and mortality.

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