UNIVERSITY OF THE WITWATERSRAND

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RESEARCH REPORT

TITLE

IMMUNIZATION STATUS AND CHILDHOOD MORTALITY IN AGINCOURT, SOUTH AFRICA IN 2004, IS THERE AN ASSOCIATION?

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Research report submitted in partial fulfilment of the requirements for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics at the University of the Witwatersrand, Johannesburg.

Date Submitted: 04.05.2009

Supervisor:

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Dedication

To my little daughter Aceng Tebogo,
My nephew Moses Osikol, all my brothers & sisters, Mr & Mrs Joyce Ebal,
My late sister & brother Aceng Bronia & Bua Walter, my late uncle John Akii-Bua
My late father in-law Mr Ernest Obadia Gaanakgomo Tolo
For God and my country.

Declaration

I, Dr Akii-Agetta Jimmy

Hereby declare that this research report is my own work (except where indicated in the acknowledgement) and is being submitted for the award of the degree of Master of Science (Med) in the field of Epidemiology and Biostatistics at the University of the Witwatersrand, Johannesburg. It has not been submitted for another degree at this or any other University.

Signed:.....(Signature of Candidate)

Dated: 28th day of October, 2008

ABSTRACT

Background

Immunization is important in the prevention of childhood illnesses and mortality. Understanding the relationships between immunization status and mortality will help in improving several processes or aspects of childhood disease prevention.

Objective

To determine the association between immunization status and all cause mortality in children between the ages of 1-5 years in the Agincourt Health and Demographic Surveillance Site (AHDSS) in 2002.

Methods

Secondary analysis was done on data obtained from the AHDSS to study the relation between immunization status and child mortality in 2002. This was a prospective cohort study using Cox regression analysis on 8723 children born between 01 January 1998 and 31 December 2002. Causes of death were categorized into the following groups; a) HIV, b) diarrhoea, kwashiorkor and upper respiratory tract infections, c) all other causes. Information on the types and numbers of vaccinations received and whether the child was vaccinated or not, was obtained.

Results

Male (49.38%) and female (50.6%) sex was equally distributed in the cohort. Out of a total of 230 deaths in children 1-5 years old, the mean age at death was 3.1 years. Among the children with information on immunization status (n=4823), 16 deaths were recorded in those who were never immunized (33.5%) and 19 deaths (66.5%) among those children who received vaccinations.

Vaccination was observed to be slightly associated with decreased mortality (HR 0.67, 95% CI, 0.34 - 1.32 p = 0.243) in crude analysis. Vaccination was significantly associated with decreased mortality in multivariate analysis adjusted for socio-economic variables (HR 0.28 95% CI 0.08 – 0.98 p = 0.047).

Vaccination with DTP (HR 0.02 95% CI 0.001 – 0.52 p = 0.017) was significantly inversely associated with child mortality, whereas measles vaccination was significantly associated with increased risk of child mortality (HR 15.06, 95% CI 1.80 – 126.26, p= 0.012). Children who received measles vaccine appeared to be especially at a higher risk

of dying from HIV infection (HR 35.08, 95% CI 2.38 - 516.5, p = 0.010), compared to other causes of death. Further factors associated with child mortality were; breastfeeding, child's hospital admission in previous 12 months, mothers death and socio-economic class.

Conclusion

Analysis of the current study showed an inverse association between immunization status and child mortality. However with regard to vaccine-specific associations results should be considered cautiously due to the large number of missing values in the data most likely to be attributed to the data collection and collation process. Parts of the results of this study were therefore inconclusive, and further analysis on updated data would yield useful information regarding immunization status and child mortality.

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ACRONYMS

AHDSS: Agincourt Health and Demographic Surveillance Site

HIV: Human Immuno-deficiency Virus

ICD-10: International Classifiifation of Diseases – 10

WHO: World Health Organization

BCG or Bcg: Baccille Calmete Guerine vaccine

Hib: Haemophyllus influenza vaccine

HepB: Hepatitis B vaccine

DTP or Dtp: Diptheria Tetanus Pertussis vaccine

GIS: Geographic Information System

GPS: Geographic Positioning System

Std: Standard Deviation

Kwash: Kwashiorkor

URTI: Upper Respiratory Tract Infections

SES: Socio-Economic Status

CHAPTER 1: INTRODUCTION

1.1 Background

Immunization in early childhood offers protection against childhood illnesses (Breiman, et al, 2004; Lehmann, et al, 2005; The Kasongo project team, 1981; Holt, et al, 1990). Due to limitation in health care resources in Africa, emphasis is being made on primary prevention which is more cost effective. Immunization is being offered at primary health care level in clinics and institutions such as schools. The aim of vaccinating all children in populations which are mainly rural and under resourced is to reduce morbidity and mortality from preventable illnesses.

Data collected from the Agincourt Health and Demographic Surveillance Site (AHDSS) situated in rural north eastern part of South Africa has been documented over a twelve year period and is still ongoing. For the current study, demographic and health data already collected within the frame work of the AHDSS was used prospectively to investigate by means of secondary data analysis, whether immunization status was associated with mortality in children between 1-5 years old.

1.2 Statement of the problem

The mortality rate in children during the first year of life was reported to be 16.2/1000 person years during the period, January 1992 to October 2000 and 4.4/1000 person years in children from one to under five (Hargreaves, et al, 2004). Refugee population migrations into South Africa caused by political tensions in neighbouring countries, justifies an investigation into the relationship between immunization status and child mortality. The situation has been complicated by the impact of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in Sub-Saharan Africa.

1.3 Justification for the study

I have not found any study done in South Africa on the association between immunization and child mortality in children 1-5 years old. Given the increase in reported child mortality (Kahn, et al, 2007) and also the value of immunization in reducing child mortality (Cooper, et al, 2003), it would be important to investigate whether there is an

association between immunization status and child mortality. Although a lot of studies investigating various aspects of immunization in children have been done, findings from this study, hopefully will add to the knowledge on the association between immunization and childhood mortality. It would also give more impetus in the drive to improve immunization programs specifically focusing on reducing mortality in this vulnerable age group.

1.4 Literature review

After reviewing 782 articles on vaccines and childhood mortality, only 2 were found to be methodologically sound (Cooper, et al, 2003). Most of the studies done on childhood mortality and immunization have so far yielded consistent results, that is, immunization against childhood diseases is associated with lower risk of mortality. However some studies found that specific vaccines such as BCG did not have any effect on mortality (Breiman, et al, 2004). The majority of the studies had serious methodological weaknesses such as, difficulties in determining accurately the cause of mortality, immunization status of children, issues of follow-up, control for bias and confounders between vaccinated and un-vaccinated and a lack of strong health related co-intervention. Another study done to find out whether children with BCG scars or positive tuberculin reaction survived better than those without, concluded that positive tuberculin reaction was associated with better survival, which could be attributed to non-specific protection against other infections (Garly, et al, 2003).

The two studies, one done in Zaire and the other in Bangladesh, both reporting vaccination coverage of 82% and 83%, respectively compared all cause mortality between vaccinated and un-vaccinated children (Breiman, et al, 2004; The Kasongo Project team, 1981). There was a reported 31% reduction in mortality among the vaccinated children in Zaire and a 46% reduction in mortality among those in Bangladesh. The overall decrease in all cause mortality rate among the vaccinated children was 2.1% and 1.8% respectively. Despite high vaccination coverage, a study done in Australia in Aboriginal and Torres Strait Island children, found that only 42% of the children had received all 15 scheduled vaccines in the first two years of life (Hanna, et al, 1998). In Bangladesh DTP and oral polio vaccines were observed to be

independently associated with reduced risk of mortality, while BCG was not. DTP was associated with increased survival (HR = 0.76, 95% CI 0.67 – 0.88; p = 0.001) for mortality between 6 to 9 months of age. The study was clear, well structured with confounders and limitations of the study addressed (Breiman, et al, 2004).

A follow up study in Guinea – Bissau noted no effect of polio vaccination on mortality in children 6-59 months of age whereas measles was associated with 56% reduction in mortality (Aaby, et al, 2004). The authors acknowledged that the study was interrupted by war in which all the inhabitants fled and that the national health care system including immunization broke down and no immunizations were given for 3 months. Only measles vaccination was then restarted followed by other vaccines causing underestimation of the effect of the routine vaccines and thus biasing in the results. This could probably explain why polio had no effect on mortality whereas measles had. A further study conducted among children admitted in a paediatric ward in Bissau, observed that oral polio vaccination was associated with reduced mortality compared to children who had received combined DTP and Oral polio vaccines (Aaby, et al, 2004). Subsequent studies conducted in the paediatric ward in Bissau and also in the community, showed that the protective effect of different vaccines varied with sex (Veirum, et al, 2004; Aaby, et al, 2004). As a result, re-analysis of these studies found that actually there were no differences in mortality according to sex, highlighting the difficulties in vaccination studies (Aaby, et al, 2003).

Investigation into the non specific effects of vaccination on child survival before age 2 years who had to a large part (66%) received all vaccines observed DTP vaccination to be associated with better survival. However, there were no inclusion or exclusion criteria for participants and the information given on the methodology was sparse (Vaugelade, et al, 2004). A similar well conducted study done in Papua New-Guinea, found routine vaccination to be associated with decreased overall mortality (Lehmann, et al, 2005). Studies on gender-related mortality subsequent to measles vaccination concluded that females showed a higher mortality based on re-analyses of data from three West African countries (Aaby, et al, 2003). Reports from further studies conducted in Haiti, Zaire and West Africa concluded that measles vaccination was associated with better childhood

survival (Kasongo project team, 1981; Kristensen, et al, 2000; Holt, et al, 1990; Velema, et al, 1991; Kabir, et al, 2003).

1.5 Study objectives

Main objectives

To determine the association between immunization status and all cause mortality in children between the ages of 1-5 years in Agincourt in 2002.

Specific objectives

1. To determine the immunization status of children between 1-5 years of age in Agincourt in 2002.
2. To determine all cause mortality among the immunization groups in children between 1-5 years of age in Agincourt in 2002.
3. To determine the association between immunization status and child mortality.

Research question

Is immunization status associated with childhood mortality between the ages of 1-5 years?

Hypothesis

H_O: There is no association between immunization status and childhood mortality.

H_A: There is an association

OR

Ho: The proportion of deaths is identical in all categories of immunization status.

H_A: The proportion of deaths is not the same between all categories of immunization status.

CHAPTER 2: METHODOLOGY

2.1 Introduction

Activities aimed at reducing child mortality have been undertaken in countries around the world with immunization featuring prominently. Immunization has been embraced world wide as the most efficient means of preventing childhood communicable diseases and reducing childhood mortality (Holden, 1987). Sub Saharan Africa has been hardest affected by HIV infection and further complicating efforts targeted at reducing child mortality (Newell, et al, 2004). The diversity in populations found in Agincourt and their unique social back grounds, coupled with high childhood mortality was the motivation for this study.

2.2 Study Site

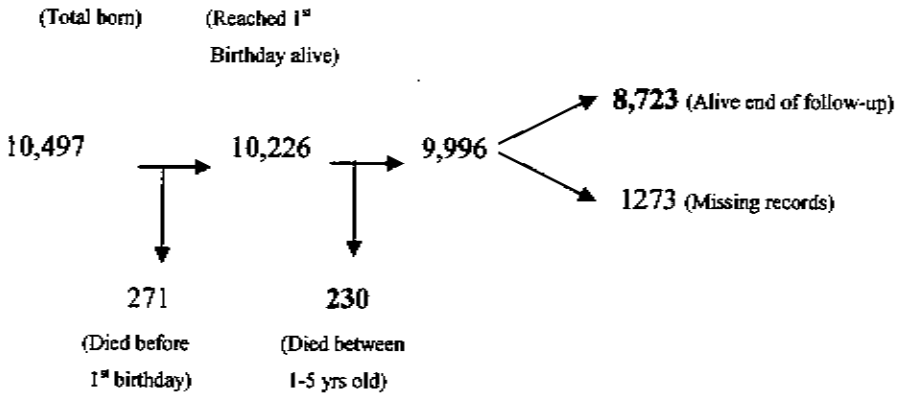
The AHDSS was initially set up in 1992 and was later established in 2002 by the University of Witwatersrand, School of Public Health. It provides population-based health and demographic information through the AHDSS system. Cross-sectional health and demographic surveillance data were collected annually by trained field workers using questionnaires in Agincourt, a study site covering an area of approximately 402 km^2. It is located in the sub district of Bushbuck ridge in Mpumalanga Province bordering Mozambique with 21 communities identified living in the area. The climatic condition is characterized as semi arid savannah, usually dry and hot with low average rainfall ranging from about 550mm to 700mm through the year, a condition suited for malaria and other tropical diseases which is common in the area.

2.3 Study Population

Mozambican immigrants predominantly living in 4 villages and the other village with immigrants of other nationalities made up the population. The population in 2001 was estimated at 68,631 persons living in 11,212 households in 21 villages. All children born between 01 January 1998 and 31 December 2002, who first made the age of one year being alive, whose immunization status and other demographic characteristics were collected in 2002 were included. These children were subsequently followed up from the time they were one year old until they were 5 years old or until 31.12.2005 (n= 10497) formed the study population. . Of these, children who died before reaching the age of one year were excluded leaving a sample of n=10226 for follow-up and analysis. Of the

10226 children, 9996 children were alive and 230 had died before their 5th birth day during the follow-up period. Of the 9996, Five (5) children died after their 5th birth day but these were censored during the follow-up period resulting in a total of 8723 children who finally formed the analytical cohort for the current analysis.

Flow Diagram



2.4 Data Collection and Management

Data collection in the original study was done by four teams each with five field workers and a supervisor. Information collected included updates of household membership, individual status variables (Relation to household head, nationality, education, etc) and vital events (Deaths, pregnancy, births, immunization, in and out migration, etc). The baseline census was started in 1992 with a detailed mapping of the villages which were hand drawn with existing dwellings represented and each given its own identification number. Continuous updating of the maps was done to include infrastructural changes. A computerized geographic information system was introduced in 1997, with hand held Geographic Positioning System (GPS). Individual households were visited annually to update membership, health and demographic information. Data, aerial photographs and household identifiers were developed into a GIS database. Digital maps were first used in 2004 to support field operations (Kahn, et al, 2007).

A full verbal autopsy was conducted by interviewing a close family member of the deceased, usually after one month of a death occurring considering traditional mourning practices. Several questions were asked about symptoms prior to death. This was followed by a review assessment independently by two medical practitioners who assigned a cause of death and classified according to the International Classification of Diseases (ICD-10). If there was disagreement, a third medical practitioner reviewed the

case and if his/her diagnosis agreed with one of the previous two, then that would be the diagnosis, and if there was overall disagreement, then the cause was coded as "ill defined". Verbal autopsy technique was validated for accuracy and reliability by comparing with hospital reference diagnosis for broad categories and individual causes of death. Data management and storage was done using Microsoft SQL server 2000. Quality control happened at five levels, from field workers daily to cross checks by team members, weekly and random checks by supervisors to programmed computer checks (Kahn, et al, 2007). This study used available data collected on immunization status, factors possibly influencing immunization and information on vital status of children residing in Agincourt study area.

2.5 Exposure and outcome measures

Immunization

Immunization was the exposure of interest in this study. Children were divided into immunization groups according to the type of vaccination received (e.g. BCG) and also those who were vaccinated or never been vaccinated. Yearly census in Agincourt is carried out to establish and update information on households on the surveillance data base. Vaccination information was recorded from the Road to Health Charts only if available. Children of recent immigrants born outside the country are not provided road to health charts except those born in South Africa. Children without Road to health charts had no vaccination records. In such cases, the parents or guardians had to confirm whether the child was vaccinated or not. Age at vaccination was not available in the data collected. Vaccination information for children under the age of 5 years was recorded in the health care utilization table which contained, ID, card colour, doses for vaccines (BCG, Polio, DTP, Hib, HepB, and Measles), immunized, hospital admission last 12 months.

Mortality

Information about child mortality was obtained by interviewing the parents or next of kin if the parent's of the child were dead or not available. A full verbal autopsy was conducted to establish cause of death in a child after a verification process by two or three medical practitioners. Cause of death was then classified according to the International classification of diseases (ICD-10).

2.6 Data processing and Analysis

Data processing, data cleaning and statistical analysis was done using the statistical software Stata, version 9.

Analysis:

Statistical analysis was performed to test the hypothesis of an association between immunization status and childhood mortality. Descriptive analysis of demographic and baseline socio-economic characteristics of children was done by, immunization status groups/categories. Baseline comparisons were done to provide initial factors to be included in the investigation of the association between mortality in children under five years and immunization status. Categorical variables were analyzed using frequency tables and Chi-square statistics to test associations. T-test was used for continuous variables.

Cox's Proportional Hazard Regression with age as the underlying time variable with entry and exit time defined as the child's age at recruitment and age at death or censoring (December 31, 2005), respectively was used to estimate the relative risk by calculating the hazard ratio (HR) for the association between mortality and immunization adjusting for potential confounders and other co-factors. All tests were done at 5% significance level. Results were reported with 95% confidence intervals (CI).

2.7 Ethics

Ethical approval for the main study in Agincourt was granted by the University of the Witwatersrand's Committee for Research on Human subjects (Medical) (No. M960720). Clearance from the university ethics committee was granted to proceed with the secondary data analysis (Clearance certificate No. R 14/49 Akii) and data was used for the intended purpose only. Confidentiality of the information contained in the data set was ensured as it did not contain any identifying information of the study subjects.

CHAPTER 3: RESULTS

3.1 Introduction

Out of a total of 10,497 children born between 01.01.1998 and 31.12.20002 all children alive after the first year of life (n=10,226) were followed up until 31.12.2005, date of death or their fifth birthday, whichever came first.

3.2 Description of study population

A summary of the children and their socio-demographic characteristics are shown in table 3.1. Categorical variables are summarized in percentages while continuous variables are given as averages and standard deviations. Statistics by year of birth were as follows; 1998, 2,410 (23.6%), 1999, 3,211 (22.6%), 2000, 2,115 (20.7%), 2001, 1,861 (18.2%), and 2002, 1,529 (14.9%). Male (49.4%) and female (50.6%) sex was equally distributed in the cohort. The numbers of children in certain categories were markedly lower because of the large numbers of missing information in these categories. More males (70%) were heads of house-holds than females (30%). 61% of the mothers were aged between 21 and 35 years, while 25% were below 21 years and 13% were above 35 years of age. 52% of the mothers were married compared to 48% who were un-married. More children were South African citizens (63%) than non-South Africans (37%). There were more children (42%) in the medium Socio-economic status (SES), compared to low SES (20%) and high SES (38%). Approximately 53% of the mothers had primary education and only 18% had never attended school with the other 29% having attended secondary or higher education. 98% of the children had their mothers still alive compared to 2% whose mothers were dead. Only 1.5% of the children were admitted in hospital in the previous 12 months compared to 98.5% who had not been admitted. Table 3.2 shows that among the children, who were never immunized (33.5%), there were 16 deaths and among those children who received vaccinations (66.5%), there were 19 deaths out of a total of 4823 children analyzed.

Table 3.3 shows three main causes of death which were a) HIV, b) diarrhoea, kwashiorkor and upper respiratory tract infections, c) all other causes and the fourth d) unknown cause. Since there were no children found in category d (unknown cause), no further mention of it was made in the document. Approximately 36% of the children died as a result of HIV infection or its complications, and 26% died from diarrhoea,

kwashiorkor and upper respiratory disease combined. Approximately 38% died from all other causes combined. Out of a total of 230 deaths in children 1-5 years old, the mean age at death was 3.1 years.

Table 3.1 Socio-demographic characteristics of children 1 – 5 years old born in Agincourt between 1998 and 2002

Variable	Total	Mean	Std	(%)	(n)
Child's Age (years)	8723	2.6	1.11		
Sex	8718				
Male				49.4	(4305)
Female				50.6	(4413)
Refugee status	8719				
No (SA Citizen)				63.0	(5497)
Yes (Refugee)				37.0	(3222)
Mother's Education	4988				
Never				18.0	(916)
Primary				53.0	(2642)
Secondary				24.0	(1482)
Higher				5.0	(261)
Mothers Age (years)	8383				
<20				25.0	(2086)
21-35				62.0	(5188)
>35				13.0	(1109)
Mother Marital status	3883				
Married				52.0	(2030)
Union				14.0	(530)
Not in union				34.0	(1323)
Mother's death	8723				
Mom alive				98.0	(8550)
Mom dead				2.0	(173)
Admission last 12 month	5869				
No				98.5	(5783)
Yes				1.5	(86)
Head of House-hold gender	6506				
Male				71.0	(4617)
Female				29.0	(1889)
Socio-economic status[I]	6346				
Low				20	(1269)
Medium				42.0	(2685)
High				38.0	(2392)

[I] A wealth index based on possession of household assets (e.g. TV, car, cell-phone, type of house, sanitation & water availability, Cows and goats) was estimated by use of Principal Component Analysis and used as a proxy for Socio-Economic Status. SES was categorized in low, medium and high SES status.

Table 3.2 Immunizations and deaths of children 1-5 years old in Agincourt

Variable	Total Analysed	%	(n)	Alive	deaths
Hepatitis B	**3283**				
No		11.0	(350)	347	3
Yes		89.0	(2933)	2917	16
Measles	**3277**				
No		12.0	(386)	381	5
Yes		88.0	(2891)	2877	14
Polio	**3285**				
No		0.7	(23)	23	0
Yes		99.3	(3262)	3243	19
BCG	**3279**				
No		3.0	(87)	87	0
Yes		97.0	(3192)	3173	19
Diphtheria Tetanus Pertussis	**3284**				
No		4.0	(142)	140	2
Yes		96.0	(3142)	3125	17
Haemophilias influenza	**3221**				
No		64.0	(2059)	2054	5
Yes		36.0	(1162)	1148	14
Sum of vaccinations	**4823**				
Nil (0)		33.0	(1615)	1599	16
1 – 15		67.0	(3208)	3189	19

Table 3.3 Main Cause of deaths in children 1 – 5 years old born 01.01.1998-31.12.2002, Agincourt 1999 to 2005

Cause of death	(n) Deaths	(%)
1. HIV	80	35.0
2. Diarrhoea, Kwashiorkor & URTI	59	26.0
3. All others	84	36.0
4. Unknown	7	3

HIV (Human Immune Deficiency Virus infections), **URTI** (Upper Respiratory Infections),

3.3 Association between mortality, vaccination and socio – demographic variables

Univariate and multivariate Cox regression was performed to investigate the association between vaccination and other socio-demographic variables in relation to mortality. Results are reported with 95% confidence interval and a significance level of 0.05. Out of 8,719 children who entered the study, with a total analysis time of 1.27e+08 days, there were 230 deaths. Risk reduction (Crude) for vaccinated children was about 30% (HR 0.67, 95% CI 0.39 - 1.32 p = 0.244) compared to those not vaccinated. Adjustment for socio-demographic variables, (HR = 0.28, 95% CI 0.08 – 0.98, p = 0.047) indicated a significant risk reduction in vaccinated children.

Children whose mothers had died were at increased risk of dying (HR = 3.96, 95% CI 2.54 - 6.19, p = 0.000), compared to children whose mothers were alive as were children with refugee status, (HR = 1.36, 95%CI 1.05 - 1.77, p = 0.021), compared to children who were citizens of South Africa. Children in the high socio-economic group had a reduced mortality risk (HR = 0.63, (95%CI 0.41 - 0.96, p = 0.031), compared to children in the low socio-economic group as had children who were breast fed (HR =0.31, 95% CI 0.14 - 0.70, p = 0.005), compared to children who were not breastfed. Children admitted to hospital in the last 12 months were at increased risk of dying (HR = 1.78, 95% CI 0.56 - 5.53, p = 0.316), than those not admitted.

No difference in mortality was observed for individual vaccines, except for measles (HR =15.06, 95% CI 1.80 – 126.26, p= 0.012). In multivariate analysis adjusting for all the vaccines, DTP vaccination was observed to be protective (HR = 0.008, 95% CI 0.00 - 0.45, p = 0.019), whereas measles vaccination remained to be a significantly positive risk factor (HR =31.1, 95% CI 2.63 – 367.6, p = 0.066). Further adjustment for socio-demographic factors did not alter risk estimates. There were some significant findings in terms of childhood mortality in relation to socio-demographic characteristics. After adjusting for socio-demographic variables, vaccinated children had a risk reduction of approximately 70% (HR 0.28 95% CI 0.08 – 0.98 p = 0.047) and children vaccinated with DTP alone had a risk reduction of nearly 99%, (HR 0.02 95% CI 0.001 – 0.52 p=0.017). All the other variables were not significantly different from the results of the univariate analysis.

Table 3.4: Univariate analysis of general characteristics of the cohort

Variable Unadjusted		(n) Deaths	Hazard ratio	95%CI	p-value
Vaccination category					
	Not vaccinated	16	1.00	-	-
	Vaccinated	19	0.67	(0.39, 1.32)	0.244
Mother	Alive	206	1.00	-	-
(Vital Status)	Dead	24	3.96	(2.54, 6.19)	*0.000
Status	SA national	124	1.00	-	-
	Refugee	106	1.36	(1.05, 1.77)	*0.021
Hospital admission Last 12 months					
	No	27	1.00	-	-
	Yes	4	1.78	(0.56, 5.53)	0.316
SES	Low	54	1.00	-	-
	Medium	95	1.15	(0.81, 1.63)	0.441
	High	41	0.63	(0.41, 0.96)	*0.031
Breastfed	No	6	1.00	-	-
	Yes	191	0.31	(0.14 – 0.70)	*0.005

*Statistically different from 1, $p<0.05$. SES (Socio-Economic Status)

Table 3.5: Univariate and multivariate Cox regression for mortality in children 1 – 5 years old and specific immunizations compared after adjusting for confounders

Variable	Vaccinated	Unvaccinated	Polio	Hib	Dtp	Hepb	Measles	Bcg
Univariate Analysis								
Unadjusted								
HR	0.67	1.00	-	0.88	0.42	0.69	15.06	-
95% CI	(0.34, 1.32)	-	-	(0.28, 2.78)	(0.09, 1.95)	(0.19, 2.48)	(1.80, 126.26)	-
P-value	0.243	-	-	0.834	0.270	0.570	*0.012	-
Multivariate Analysis								
Adjusted §								
HR	0.28	1.00	-	0.56	0.02	17.1	-	-
95% CI	(0.08, 0.98)	-	-	(0.07, 4.7)	(0.001, 0.52)	(0.7, 415.6)	-	-
P-value	*0.047	-	-	0.606	*0.017	0.08	-	-

*Statistically different from 1, $p<0.05$ § Adjusted for, mother's age, mother's death, child's sex, child's age, child's hospital admission, refugee status, child breastfed and SES (Socio-Economic Status). HR (Hazard Ratio)

CHAPTER 4: DISCUSSION

4.1 Introduction

The objective of this study was to determine the association between child mortality and immunization status. Data collected from the Agincourt Health and Demographic Surveillance Site (AHDSS) situated in rural north eastern part of South Africa has been documented over a twelve year period. For the current study, demographic and health data already collected within the framework of the Agincourt DSS site was used prospectively to investigate by means of secondary data analysis, whether immunization status is associated with mortality in children between 1-5 years old. This study used a Cox regression method to establish the relationship between immunization status and child mortality among the children living in the Agincourt area.

4.2 Immunization and childhood mortality

Immunization was significantly inversely associated with child mortality after adjustment for socio-demographic variables depicting a marked reduction in the risk of mortality. However in crude analysis, there was no significant difference in mortality between vaccinated and not vaccinated children. There was also no significant difference in mortality for all other vaccines, except for children who were vaccinated with measles. Measles vaccination appeared to be associated with increased risk of mortality. This is clearly a contradictory result given what is already known about the association of vaccinations to childhood mortality (Breiman, et al, 2004; Clemens, et al, 1988; Aaby, et al, 2002; Kristensen, et al, 2000; Lemann, et al, 2005; Cooper, et al, 2003; Mayfong, et al, 2007). Most likely this anomaly could have originated from the large number of missing information from the immunization data, i.e. only for 3,279 of the study population comprehensive information on immunization was available. 15.2 % of all deaths occurred in those for whom information on vaccinations was available, whereas 84.8 % of deaths occurred in those with inadequate information on vaccination status indicating potentially biased results. It therefore calls into question the data collection method used: Field workers used the Road to Health Cards to obtain immunization information. And if this was not available, the mother or whoever provided information was then interviewed about the immunization status of the child.

A further possibility that could have been overlooked is the maintenance of the cold chain for the vaccines used to immunize children. Failure to maintain the cold chain would render the measles vaccines ineffective (MMWR 2003; Talley & Salama, 2003). In rural Bangladesh, measles vaccination was associated with a reduction in child mortality (Aaby, et al, 2003; Clemens, et al 1988; Omar, et al). Mortality due to measles complications in countries where there are still measles epidemics was also found to be highest in children under 5 years old (Grais, et al, 2007). In this study, after adjusting for all the vaccines, DTP vaccination was associated with a marked and very significant reduction in child mortality just as was, Hib (Haemophilus influenza) vaccine and hepatitis b vaccine, however BCG and measles vaccines were not. Investigation into the non-specific effects of vaccination on child survival, found that children before the age of two years vaccinated with BCG and DTP survived better than children who were not vaccinated (Vaugelade, et al, 2004). Although this was a prospective cohort study with sound methodology, the authors could not rule out the possibility of confounding from other sources. They also concluded that there was a possibility of misclassification of vaccination status especially the dead children whose vaccination cards were destroyed.

It has also been postulated that vitamin A supplementation may actually be acting by amplifying the non specific effects of vaccines (Benn, et al, 2003).

DTP and oral polio vaccine was found to have no significant effect on child mortality (Velema, et al, 1991). This is contradictory to other findings from other studies. Similarly, BCG vaccination was found to be associated with a slightly lower mortality and yet DTP was associated with a slightly higher mortality in children aged 2-8 months, although mortality was assessed over 6 months only (Aaby, et al, 2004). To assess the cell mediated immune responses in four year old children after primary vaccination with acellular pertusis vaccines it was found that cell mediated immune response at 48 months was the same as that at 7 months of age (Ausiello, et al, 1999), although the number of subjects tested were very few. The authors also thought this could have occurred as a result of asymptomatic pertussis infection sometime after vaccination later in life. A similar study also found that there was a persistence of protection up to after 6 years of age confirming the effect of immunization (Salmaso, et al, 2001). Table 3.4 also shows the risks of mortality after adjusting for socio-demographic variables. All vaccinations in

this study showed a protective effect, which is consistent with the findings from other studies, except for measles (Breiman, et al, 2004; Lehmann, et al, 2004).

As already mentioned earlier, vaccinated children had a markedly reduced mortality after adjusting for all the confounders compared to the un-adjusted as were children vaccinated with DTP. All the other variables were not significantly different from the results of the univariate analysis. After the introduction of the Haemophilus influenza type b vaccine in the child immunization program in Kenya, it was found that there was a marked reduction in the incidence of culture proven Hib invasive disease as well as mortality (Cowgil, et al, 2006). The result of this study also showed that Heamophilus influenza vaccine had a protective effect, although not statistically significant but consistent with results from other studies. The result of BCG vaccine in this study did not show that it had a protective effect on child mortality as opposed to findings from other studies. In Papua New Guinea, BCG vaccination was found to be associated with lower mortality in the 1-5 month age group, although my study looked at the 1-5 year old age group (Lehmann, et al, 2004). Velema (1991) found that BCG vaccination did not reduce mortality in children who are under 3 years of age, although it had a protective effect. Investigation into access to primary health care services found that children residing nearer to a health care facility were less likely to die compared to those staying further away (Magnani, et al, 1996). Moreover, in a cross national analysis of 43 developing countries, it was found that higher national incomes and socio-economic status was associated with lower under 5 mortality rates (Houweling, et al, 2005). In general, there has been a steady decline in under-5 child mortality from 1950 to 2000 in Sub Saharan Africa with immunization contributing to the decline (Garenne, et al, 2006). Another study done in Guinea Bissau found that BCG vaccination was associated with significantly lower child mortality and children who were vaccinated with any vaccine had a lower mortality compared to those who were not vaccinated (Kristensen, et al, 2000). A similar study which looked at BCG scar concluded that there was lower mortality for children with a BCG scar when compared to those without a scar (Roth, et al, 2005). However the authors acknowledged that there could be a possibility of a selection bias since HIV infection has been shown to cause suppression of scar formation. Although the effect of HIV/Aids on child mortality varies between different countries

(Newell, et al, 2004), it is difficult to tell its effect on overall mortality since it is difficult to determine exact cause of death using verbal autopsy.

However, a study done to compare verbal autopsy with regular cause of death registration found that the two systems compared well, and therefore verbal autopsy could be used in a rural area of a developing country without a formal cause of death registration (Garenne, et al, 1999 & 2000). It is also known that the sensitivity and specificity of verbal autopsy varies between populations and depends on the distribution of cause of death (Chandramohan, et al, 2001). It has been shown that vaccinations are not associated with the increased risk of non targeted infectious disease hospitalization (Hviid, et al, 2005), which reinforces available evidence that vaccinations have a protective effect.

Therefore, in all the studies of mortality derived from verbal autopsy, the association between cause-specific mortality and other determinants should be interpreted with caution.

4.3 Demographic Characteristics

In the univariate analysis, children whose mothers died were more likely to die, compared to those whose mothers were alive. Since one third of deaths were associated with HIV infections as the main cause of death, it is therefore plausible that the mothers also died of the same cause (Kahn, et al, 1999). Also children who were categorized as refugees had a higher risk of dying in this analysis. However, when adjusted, there was no difference in mortality between refugees and the South African citizens. This result is consistent with previous findings in a study done in Agincourt which found that there was no difference in mortality between refugees and locals (Adjusted), but the mortality levels were higher among refugees (Hargreaves, et al, 2004). Refugees are generally disadvantaged compared to citizens regarding access to social services. The possible reason for this lack of difference could be the fact that the parents of these children had lived in the area for a long time and actually there was no difference in the standard of living compared to South African citizens. South African citizens living in the area do not necessarily have preferential treatment compared to immigrants, although one could argue that access to social services may be easier for South African citizens. Some of the

refugees were also in the higher socio economic groups so the level of poverty could have been equally distributed between South African citizens and refugees.

Living in a poverty stricken area, be it urban or rural, impacts negatively on access to services like immunization (Fotso, et al, 2007). A univariate analysis in this study found that children in the high socio economic group had a reduced risk of mortality when compared to the lower socio-economic group. When adjusted, there was no difference between the three socio economic groups. Higher socio economic status is thought to be protective and therefore children in this category are less likely to die ompared to those in the low socio economic class (Houweling, et al, 2005; Bakajika Kapuku, 2008). In the current study, children who were breastfed were significantly less likely to die compared to those who were never breast fed. When adjusted, there was no difference between children who were breastfed and those not breastfed. Results may have been affected by high proportion of missing data in the current study. Previous studies found that breast feeding was associated with reduced deaths from respiratory and diarrhoea diseases (Arifeen, et al, 2001; Yoon, et al, 1996) and decreased risk of mortality (Bahl, et al, 2005).

4.4 Immunizations and Cause Specific Mortality

Analysis of the immunizations and cause specific mortality yielded inconclusive and conflicting results. The main causes of mortality was categorized into three; a) HIV, b) Diarrhoea, kwashiorkor and upper respiratory tract infections, c) all others. Although the results generally showed that most children were at a higher risk of dying from other causes, compared to HIV and Diarrhoea, it was nevertheless not conclusive because of the small number of deaths as well as the large number of missing records of vaccinations. For example, Measles vaccination was found to be a risk factor for mortality due to HIV infection as well as for Diarrhoea, Kwashiorkor and Upper respiratory tract infections. This result is spurious because from what is already known measles vaccination is protective and is associated with a reduction in child mortality. Because of this discrepancy, the result table was not presented in this report. A study done in South Africa to determine the impact of supplementary measles vaccination found that there were fewer infections and deaths after the campaign (Uzicanin, et al,

2002). A similar study conducted in Uganda focussing on the incidence of measles, found a significant reduction in incidence after a mass campaign (Nanyunja, et al, 2003). In the Matlab DSS site, Bangladesh measles vaccination was associated with a 36% reduction in childhood mortality directly ascribed to deaths from diarrhoea, malnutrition and upper respiratory diseases (Clemens, et al, 1988). Data from a case control study conducted in India found measles vaccination to be associated with reduced child mortality in an area with high vaccination coverage (Kabir, et al, 2003). Vaccination with standard Edmonton Zagreb measles vaccine at an early age of 4.5 months in measles endemic area confirmed the protective effect of measles vaccine (Cesario, et al, 2008; Aaby, et al, 1993). A possible explanation for the spurious results in the current analysis could be in the data collection method used. Although the study design was good, there were large numbers of missing information on children's immunization implying that for these children the Road to Health Cards were never available to confirm their vaccination status. Children with missing information could have had peculiar characteristics thereby creating a possibility of a biased result. Specific dates when the different vaccinations were given were also missing from the data. These dates when the different vaccinations were given would have added detail to the results of analysis.

DTP on the other hand was found to be protective for HIV infections. It was also found to be protective for Diarrhoea, Kwashiorkor and Upper respiratory tract infections although this was not statistically significant. Children infected with HIV have been found to be at an increased risk for incomplete vaccination, thereby exposing them to infections and subsequently the likelihood of dying (Setse, et al, 2006). BCG was found to be protective for Diarrhoea, Kwashiorkor and Upper respiratory tract infections otherwise was statistically not significant. A study done in the Matlab DSS site in Bangladesh noted that BCG, Measles and DTP vaccinations were associated with increased survival in children between 6 weeks to 9 months of age (Breiman, et al, 2004). Overall, there was inconsistency in the results of this study which may be most likely attributed to the process of data collection and collation.

4.5 Limitations of the study

This study utilized secondary data obtained from the AHDSS. Despite a good study design, missing information on children's immunization posed a considerable problem

with over 50% missing from each vaccine category. For example, 62.4% of the children had missing information on measles vaccination. The effect of this can be seen in the results obtained after analysis of the data and may have introduced bias because we do not know for sure what happened to the other children with missing information. The sample size for analysis was therefore very small especially the number of deaths in the vaccination categories. The use of verbal autopsy could have also introduced a misclassification bias in this study although efforts were made to verify the final cause of death.

The field workers encountered difficulties during the data collection process because for many children their Road to Health Cards was not available and therefore, no information on vaccination could be recorded. Under such circumstances, the field workers then had to rely on the mothers or guardians to confirm whether the child was vaccinated or not. The other problem was that some of the people found at the homes did not have any such information which then complicated matters further. The immunization processes like maintenance of the cold chain could not be verified therefore it was assumed to have been satisfactory. It is possible that data management did not pay much attention to the immunization information since it was not the primary subject of investigation. Therefore, these results are subject to interpretation with caution taking into consideration methodological difficulties.

4.6 Strengths of the study

Despite the large number of missing information about the vaccinations, still a fairly large number of children with information were analysed. This was a follow up study with data from a reputable demographic surveillance information system in Agincourt. Although mortality information was ascertained through verbal autopsy, the information collected went through a stringent verification system to ensure that there was agreement on the cause of death.

CHAPTER 5: CONCLUSION AND RECOMMENDATION

5.1 Conclusion

Several studies assessing the relation between immunization and childhood mortality concluded that vaccinations offer protection and are associated with reduced childhood mortality (Cooper, et al, 2003; The Kasongo Team project, 1981; Whittle, et al, 2002; Lehmann, et al, 2005; Velema, et al, 1991; Aaby, et al, 2004). These studies have so far come up with consistent reports about the benefits of immunization in different settings, both in the developing and the developed world. In preventable disease endemic regions of the world, such studies have found very strong associations between immunizations and their effect on lowering child mortality. Similarly in this study, immunization was found to be associated with a significant reduction in mortality in children 1-5 years old. However there were some methodological difficulties encountered during data collection with over 50% of data on immunization missing. Of note, analysis of measles vaccination showed that children vaccinated against measles were at a higher risk of dying compared to those who were not vaccinated.

Analysis of child mortality and socio demographic characteristics such as breast feeding, socio economic status and mothers death after adjusting for confounders, found that there was no association as well contrary to findings from other studies. Measles vaccination was also found to be a risk factor for deaths in children who had died from HIV infection as the main cause of death. Again this is contradictory to the findings of several studies conducted in areas with high prevalence of HIV infection in Sub Saharan Africa where HIV infection alone was the main cause of death. This result is contradicted by other studies that confirm the protective effects of measles vaccination (Newell, et al, 2004; Kabir, et al, 2003; Cooper, et al, 2003; Holt, et al, 1990). In this analysis, having found that children who were immunized had a significantly lower risk of dying compared to those who were never immunized, disparities in the results of the association between specific vaccinations and mortality would have yielded different results from the one found if immunization data were complete.

5.2 Recommendations

Immunization is a very important tool in the prevention of childhood mortality and morbidity. Immunization has been used in many countries with great success and has become one of the main tools in the prevention of childhood diseases in primary health care. It has been used to eradicate certain communicable diseases and also stem epidemics in some countries. As a result of support from the World Health Organization and non governmental organizations, most childhood vaccines have become cheap and poor countries with endemic communicable diseases are able to conduct immunizations. There is still room for improvement in the data collection methods especially in the demographic surveillance site, with emphasis on the road to health cards. Also of utmost importance, there is a need to re-evaluate the maintenance of the cold chain in rural areas to ensure the effectiveness of vaccines being administered to children. Another issue to be considered would be the access of social services to refugees and its impact on child mortality in these areas with large numbers of refugees from neighbouring countries. Thus more studies will be needed to assess the association between immunization and childhood mortality especially in the 1-5 year old age group.

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❖ APPENDICES

1: Copy of immunization questionnaire

HEALTH CARE UTILIZATION TABLE
Health Care Utilization Table Description
The highest level an individual has attained at the time of the observation. This was captured in the baseline study(1992), updated in 1997 and 2002, it is also captured for all new members entering the study area for the first time.

Column	Data type	Description	Codes (if other than numeric, or numeric has additional meaning)	
ID	Number	ID number of individual whose health utilization is documented		
CardColor	Text	For all children under five years of age, the colour of the Road To Health Card is recorded		
BCG	Number	Vaccines and doses as indicated in the RTHC for under-fives		
Polio	Number	Vaccines and doses as indicated in the RTHC for under-fives		
DTP	Number	Vaccines and doses as indicated in the RTHC for under-fives		
Hib	Number	Vaccines and doses as indicated in the RTHC for under-fives		
HepB	Number	Vaccines and doses as indicated in the RTHC for under-fives		
Measles	Number	Vaccines and doses as indicated in the RTHC for under-fives		
Immunized	Text	If there is no card, this field indicates whether the child has been immunized or not		
AdmittedLast12Months	Text	Ever been admitted to hospital in past year		
Admissions	Number	Number of such admissions		
Hospitals	Text	Names of hospital in order of admissions or referrals if more than once or one hospital	-	Not applicable, because the delivery/death was not in a hospital
			MP	Mapulanang
			MT	Matikwane
			O	Other hospital not listed above
			PM	Peterstburg-Mankweng
			Q	DeliveryHospital unassigned
			RF	Rob Ferreira
			T	Tintswalo
			X	DeliveryHospital unknown

INMIGRATIONS TABLE
Inmigrations Table Description
The table records all migration details into all households within the study area.

2: Copy of the Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Akil

CLEARANCE CERTIFICATE	PROTOCOL NUMBER M070627
PROJECT	Immunisation Status and Childhood Mortality in Agincourt, South Africa, Is there an Association?
INVESTIGATORS	Dr AJ Akil
DEPARTMENT	School of Public Health
DATE CONSIDERED	07.06.29
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

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

DATE 07.07.02 CHAIRPERSON .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof KK Grobusch

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10005, 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

3: Copy of the AHDSS original Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Tollman

CLEARANCE CERTIFICATE — PROTOCOL NUMBER M 960720

PROJECT	Investigating and responding to changes in the health and population dynamics of rural South Africans
INVESTIGATORS	Dr S Tollman
DEPARTMENT	HSDU/Community Health, Acornhoek
DATE CONSIDERED	970725

DECISION OF THE COMMITTEE *

Approved unconditionally
Generic Protocol - "Blanket approval"

DATE 970731

CHAIRMAN ..... (Professor P E Cleaton-Jones)

c c Supervisor: Dr S Tollman
Dept of Community Health, Medical School

==========

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 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.

DATE 7/5/96 ..... SIGNATURE .....

The University's United States Federal Wide Assurance Number is: SF,IORG0000862,IRB00001223.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES