Child health in a Ugandan cohort

Studies on survival, vaccination and malaria

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To my mother,
Concepta Nabayombya Semmanda

Contributors

This thesis is based on the Promise-EBF study, done in collaboration between the Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Uganda and the Center for International Health, Faculty of Medicine and Dentistry, University of Bergen, Norway.

The Promise-EBF study was a cluster-randomised trial of exclusive breast-feeding promotion by peer counsellors. It was funded by the European Union (contract no: INCO-CT 2004-003660) and the Norwegian Programme for Development, Research and Education (NUFU; grant no 43/2002, 'Essential nutrition and child health in Uganda').

The PROMISE-EBF consortium (http://www.promiseresearch.org) consisted of the following countries and institutions:

Centre Muraz, (Muraz) Burkina Faso

Dept of Paediatrics and Child Health, College of Health Sciences, Makerere University, Uganda

Dept of Paediatrics and Child Health, School of Medicine, University of Zambia

School of Public Health, University of Western Cape (UWC), Cape Town, South Africa

University of Montpellier, France

Centre for International Health (CIH), University of Bergen, Norway

International Maternal and Child Health (IMCH), Univ. of Uppsala, Sweden

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Abbreviations

ANC	Antenatal care
BCG	Bacille Calmette-Guérin
BMS	Between subject mean square
CI	Confidence interval
DHS	Demographic and health survey
DPT-HB-Hib	Diphteria-pertussis-tetanus-hepatitis B-haemophilus influenza b
EBF	Exclusive breastfeeding
EMS	Error mean square
ENM	Early neonatal mortality
ENMR	Early neonatal mortality risk
GLM	Generalised linear model
HAZ	Height for age Z scores
HIC	High income country
HIV	Human immunodeficiency virus
IM	Infant mortality
IMR	Infant mortality rate
IQR	Inter quartile range
JMS	Judge mean square
LAZ	Length for age Z scores
LMIC	Low and middle income countries
MCA	Multiple component analysis
NMR	Neonatal mortality rate
PCA	Principle component analysis
PCR	Polymerase chain reaction
PMR	Perinatal mortality rate
PNMR	Post-neonatal mortality rate
PR	Prevalence ratio
RCT	Randomised controlled trial
RR	Risk ratio (relative risk)
SBR	Stillbirth risk
SES	Socio-economic status
TBA	Traditional birth attendant
U5MR	Under 5 mortality rate
UDHS	Uganda demographic and health survey
UNEPI	Uganda national expanded program on immunization
WAZ	Weight for age Z scores
WHO	World health organization
WHZ	Weight for height Z scores
WLZ	Weight for length Z scores

Definitions

A. Types of death

Stillbirth: Death prior to complete expulsion from the mother of a fetus mature enough to have survived outside the uterus. It is the commonly used term for fetal death, and is used in this thesis to refer to late fetal deaths.

Fetal death: According to the International Classification of Diseases, revision 10 (ICD-10), an early fetal death is death of fetus weighing at least 500 g (or, if birth weight is unavailable, after 22 completed weeks gestation, or with a crown-heel length of 25 cm or more). A late fetal death is defined as a fetal death weighing at least 1,000 g (or a gestational age of 28 completed weeks or a crown-heel length of 35 cm or more). Late fetal deaths are recommended by the World Health Organization as the measure for international comparison of stillbirths.

Early neonatal death: Death of a live born infant within the first seven days.

Neonatal death: Death of a live born infant within the first 28 days.

Post-neonatal death: Death to a live birth after 28 days but within the first year of life.

Infant death: Death in the first year of life.

B. Mortality

Stillbirth risk: Number of stillbirths divided by total number of pregnancies (expressed per 1,000).

Early neonatal mortality: Probability of dying during the first seven days of life, expressed per 1,000 live births

Perinatal mortality: Number of perinatal deaths divided by total number of pregnancies (expressed per 1,000).

Neonatal mortality: Probability of dying during the first 28 completed days of life, expressed per 1,000 live births

Post-neonatal mortality: Number of post-neonatal deaths divided by the total number of live births (expressed per 1,000).

Infant mortality: Probability of dying between birth and exactly 1 year of age, expressed per 1,000 live births

Under-five-mortality: Probability of dying between birth and exactly 5 years of age, expressed per 1,000 live births.

C. Parity

Parity: Number of live births for a given woman, counting a multiple birth pregnancy as one.

Nulliparous: No previous live births for a given women.

Multiparous: A woman with one or more previous live births.

D. Births

Live birth: A baby who shows any signs of life after delivery, beyond involuntary gasps (breathing, heartbeat, pulsation of the umbilical cord, or definite movement of voluntary muscles), regardless of whether the umbilical cord has been cut or the placenta delivered.

Preterm birth: A live birth or stillbirth that takes place after 28 but before 37 completed weeks of gestation.

E. Other

Perinatal period: Whereas there is consensus that the perinatal period includes some portion of late pregnancy and some or all the first month of life, this term has been used to refer to at least 10 different periods depending on the time cut offs used and this often causes confusion. In this thesis, we use perinatal deaths to include stillbirths after 28 weeks' gestational age and early neonatal deaths in the first 7 days of life.

Traditional birth attendant: A birth attendant who acquired her skills empirically or through apprenticeship to another traditional birth attendant.

Abstract

Background: To reduce under-five mortality according to Millennium Development Goal 4, infant mortality must be reduced considerably. The aim of this thesis was to measure perinatal and infant mortality and to explore interventions (vaccination, exclusive breastfeeding (EBF) and vitamin A supplementation) that could reduce this mortality.
Methods: A cluster randomized intervention trial was conducted between 2006 and 2008 in which 12 of 24 clusters, each comprising one or two villages, in Eastern Uganda were allocated to receive peer counselling for EBF. Women in their third trimester of pregnancy were recruited in all 24 clusters. A total of 835 pregnant women were followed up for pregnancy outcomes and survival of their children until their first birthday. During pregnancy, information was collected on mother's residence, age, parity, bed net use, and whether delivery took place at home. After delivery, information was collected on vaccinations, feeding practices, growth and survival. Blood was drawn for malaria parasitaemia from 483 infants between 3 and 12 months of age.
Results: The stillbirth risk was 19 [95%CI: 11, 33] per 1,000 pregnancies and the early neonatal death risk 22 [95%CI: 13, 35] per 1,000 live births. Overall, the perinatal mortality risk was 41 [95%CI: 27, 54] per 1,000 pregnancies. Perinatal mortality was 61/1,000 pregnancies among women delivering at home who, after controlling for potential confounders, had a 3.7 (95%CI: 1.8, 7.4) times higher perinatal mortality than women who gave birth in a health facility. This association was considerably stronger among nulliparous women [Risk ration (RR) 8.0 (95%CI: 2.9, 21.6)] than among women with a previous live birth [RR 1.8 (95%CI: 0.7, 4.5)]. All perinatal deaths occurred among women who did not sleep under a mosquito net. Most of the association between bed-net use and perinatal death was driven by nulliparous women. Women living in urban slums had a higher risk of losing their babies than those in rural areas [RR: 2.7 (95%CI: 1.4, 5.3)]. The infant mortality risk was 33 [95%CI: 22, 48] per 1,000 live births, neonatal mortality risk was 23 (95% CI: 14, 36) per 1,000 live births and the post-neonatal mortality risk 10 (95% CI: 4, 19) per 1,000 live births. Infants with a history of hospitalization were more likely to die compared to those that had never been hospitalized (RR: 6.4; 95%CI: 1.0, 39.7). Women with a previous child death had a higher risk of having a post-neonatal death compared to those that had never lost a child (RR: 5.8; 95%CI: 1.1, 31.7). At 24 weeks, about 51% of the infants were fully vaccinated (i.e., had received all the scheduled vaccinations: BCG, polio 0, polio 1, DPT-HB-Hib1, polio 2, DPT-HB-Hib 2, polio 3 and DPT-HB-Hib 3). Only 46% of the infants whose mothers' had 5-7 years of primary education had been fully vaccinated compared to 65% of the infants whose mothers' had some secondary education. Infants whose mothers had some secondary education were less likely to miss the DPT-HB-Hib-2 vaccine (RR: 0.5, 95% CI: 0.3, 0.8), Polio-2 (RR: 0.4, 95%CI: 0.3, 0.7), polio-3 (RR: 0.5, 95%CI: 0.4, 0.7) and DPT-HB-Hib-3 (RR: 0.5, 95%CI: 0.4, 0.7). Other factors showing some association with a reduced risk of missed vaccinations were delivery at a health facility (RR = 0.8; 95%CI: 0.7, 1.0) and use of a mosquito net (RR: 0.8; 95%CI: 0.7, 1.0). Children in intervention areas were 1.7 times as likely as children in control areas to have malaria (PR 1.7; 95% CI: 0.9, 3.0). After controlling for potential confounders, infants not supplemented with Vitamin A had a higher prevalence of malaria compared to those who had been supplemented (PR 6.1; 95% CI: 2.1, 17.6). The association between vitamin A supplementation and malaria was greatest among stunted children.
Conclusion: The studies forming the basis for this thesis have shown that perinatal and infant mortality was high in Mbale, Eastern Uganda. They explored several risk factors for death and showed that they are multiple and include delivering at home and lack of bed nets especially among nulliparous women. They showed that less than adequate coverage of vaccination could be related to low maternal education, specifically low maternal secondary education. They examined two interventions that hitherto had limited evidence for reducing morbidity and malaria mortality. Whereas there was no association between EBF promotion and malaria, infants that had not been

supplemented with vitamin A were more likely to have malaria parasitaemia compared to those that had been supplemented.

Original papers

The thesis is based on the following papers:

I. Nankabirwa V, Tumwine JK, Tylleskär T, Nankunda J, Sommerfelt H; Promise-ebf Study Group. Perinatal mortality in Eastern Uganda: a community based prospective cohort study. PloS ONE 2011 May 6(5) e 19674.doi:10.1371/journal.pone.0019674

II. Nankabirwa V, Tumwine JK, Sommerfelt H, Mugaba PM, Tylleskär T; Promise-ebf Study Group. Infant mortality in Eastern Uganda: a community based prospective cohort study. (Submitted)

III. Nankabirwa V, Tylleskär T, Tumwine JK, Sommerfelt H; Promise-ebf Study Group. Maternal education is associated with vaccination status of infants less than 6 months in Eastern Uganda: a cohort study. BMC Pediatr. 2010 Dec 15;10:92.

IV. Nankabirwa V, Tylleskär T, Sommerfelt H, Nankunda J, Engebretsen IM, Tumwine JK; Promise-ebf Study Group. Malaria prevalence among infants and its association with breastfeeding peer counselling and vitamin A supplementation. PLoS ONE 2011 July 6(7): e21862. doi:10.1371/journal.pone.0021862

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To my mother; you have always reminded me to reflect on where I come from and where I want to go. For this, I will always be grateful.

Ayi Mukama Katonda, webale okumbikako a kasubi.

Introduction

Every minute, an estimated 17 children under the age of five years die worldwide. Approximately 16 of these are in low or middle income countries (LMICs), where vital registration systems are either incomplete or absent and where a sizable fraction of the deaths go unrecorded. Mortality estimates in many of these countries – including Uganda – are often based on hospital-based studies or demographic and health surveys (DHS) that are marked by methodological limitations. Using a cohort of mother-infant pairs in Mbale, Eastern Uganda, the studies forming the basis of this thesis aimed to address the following research questions:

1) What is the perinatal mortality risk and what are the associated risk factors?
2) What is the infant mortality risk and what are the associated risk factors?
3) Why does vaccination, an intervention which lowers under-five mortality have low coverage?
4) What factors could reduce the prevalence of malaria, one of the top five causes of mortality in Ugandan children?

To answer the questions, this thesis is presented in two main parts (figure 1): a) mortality and associated risk factors and b) interventions that could reduce mortality. In the subsequent section of the introduction, we review the literature for each of these two main parts and present a conceptual model bridging them.

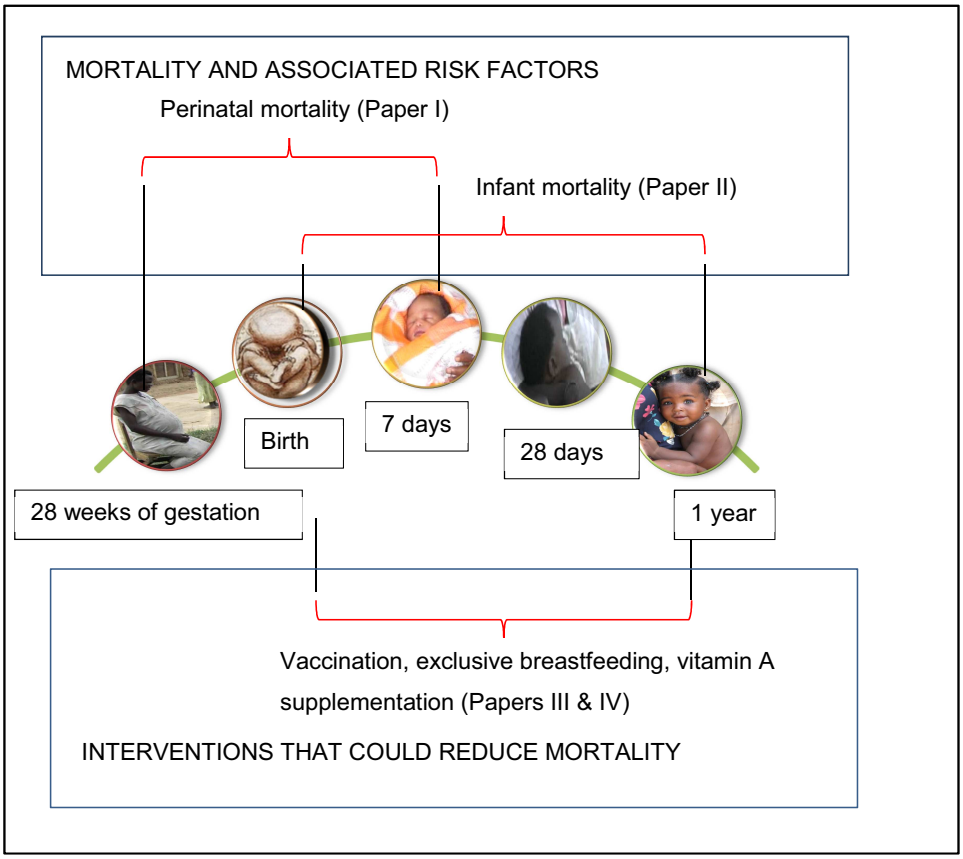


Figure 1: Topics considered in the thesis

Perinatal and infant mortality

Perinatal mortality

The term 'perinatal mortality' covers both stillbirths after 28 weeks of gestation and early neonatal deaths, i.e., deaths in the first 7 days of life (figure 2) [1-3], which often have different causes [4]. Despite this, it is still a useful term as it circumvents the potential misclassification of early neonatal deaths (ENDs) as stillbirths and vice versa. Such misclassification is common and to a large extent uncontrollable in settings where a large proportion of births takes place outside well-equipped and well-organised health facilities [1, 4, 5]. Needless to say, it carries the disadvantage of not enabling us to disentangle predictors and risk factors of stillbirths from those of ENDs.

Stillbirths

Epidemiology of stillbirths

Estimates indicate that 3.2 million stillbirths occur each year globally [2, 4, 6, 7]. Of these, 98% are estimated to occur in LMICs where vital registration systems are at best partial and at worst absent [4, 7-9]. The probability of having a stillbirth in LMIC is estimated at 20-32/1,000 births compared to 4.2-6.8/1,000 births in high income countries (HICs) [2]. The highest stillbirth estimates are found in Sub-Saharan Africa and South Asia (32/1,000 births) [2]. In the past couple of decades, there have been marked reductions in the number of stillbirths in HIC [10]. These reductions have been recorded mainly among those stillbirths that occur during labour and are attributed to improvement in intrapartum care and increased use of caesarean section [2].

Types of stillbirths

There are two broad categories of stillbirths: antepartum and intrapartum. Antepartum stillbirths occur before the onset of labour. It is estimated that about two thirds of all stillbirths are antepartum but the proportion varies with the quality of antepartum and intrapartum care [11-15]. These stillbirths may be macerated [1]. In macerated stillbirths there is often a soft skull, darkly stained amniotic fluid with peeling and/or discoloured skin.

On the other hand, intrapartum stillbirths estimated at 1 million each year, occur during labour. They are also referred to as 'fresh' stillbirths. Notably, these stillbirths have an intact skin and show no signs of maceration [2]. Distinction between these two types of stillbirths is importanat for epidemiologic research and in planning programmes. Whereas the proportion of intrapartum stillbirths indicates the quality of delivery services, proportions of antepartum stillbirths relate more to conditions during pregnancy and the quality of antenatal care; hence programs seeking to reduce either of these types of stillbirth require different interventions [2].

Causes of stillbirths

Factors directly associated with intrapartum stillbirths include complicated deliveries such as obstructed or prolonged labor (with associated asphyxia, infection and birth injury), cord prolapse, mal-presentations (e.g. breech presentation), multiple births and hypertensive diseases of pregnancy (especially pre-eclampsia and eclampsia) [2, 4, 7, 16]. Table 1 summarizes other more distal factors associated with stillbirths.

Table 1: Risk factors for stillbirths

Risk factors for antepartum stillbirths	Risk factors for intrapartum stillbirths
Maternal age > 35 years	Maternal age < 18 years
Short inter-pregnancy interval	Maternal short stature (<145 cm)
Obesity	Nulliparity
Cholestasis or other liver disease	Maternal diabetes
Thrombophilias	Grand multi-parity (> 4 pregnancies)
Tobacco/alcohol/drug abuse	Maternal obesity
Maternal exposure to smoke from cooking fires (biomass fuels)[a]	Low maternal education
Under nutrition (low body mass index or micronutrient deficiencies, e.g., folate deficiency)	Poor access to healthcare services because of distance, and/or financial barriers
Maternal infections such as syphilis, malaria	
Low maternal education	
Exposure to environmental toxins	

[a] Probable mechanism of action is via increased fetal carboxyhemoglobin and vascular resistance.
Source: Lawn et al. (2009), Yakoob et al. (2010)

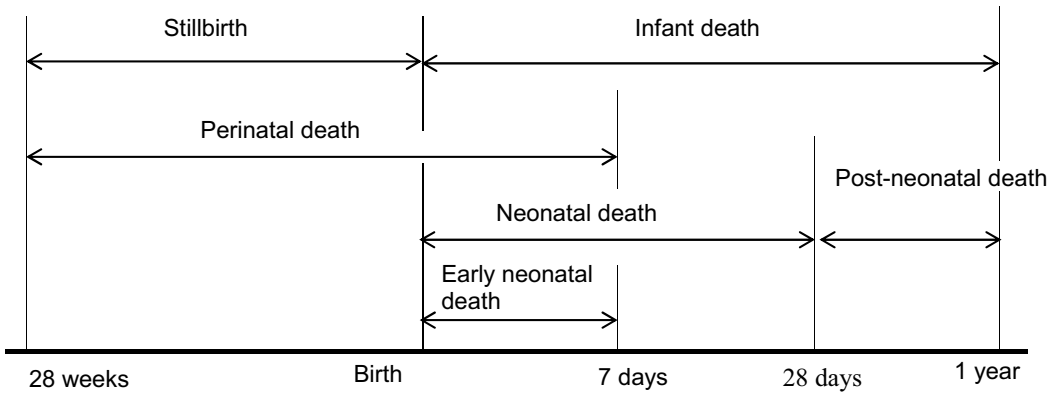


Figure 2.Stillbirth, perinatal death and categories of infant death. Adapted from Wilcox AJ*, (2010)*

Early neonatal death refers to death of a live born infant in the first week after birth (figure 2). The distinction between stillbirths and early neonatal deaths can be subjective and problematic, especially in home deliveries where faint traces of life may not be easily discernible. Still, it is estimated that nearly ¾ of all neonatal deaths occur within this period, with ¼ to ½ occurring within the first 24 hours after birth [17]. Evidently, this is the period with the highest risk of death for live born children. It is also the period that has shown the least reduction in risk over the past 30 years [17].

Epidemiology of early neonatal deaths

Globally, early neonatal mortality has hovered around 25/1,000 live births but there are huge regional, country and within country variations. The probability of an early neonatal death in LMIC is estimated at 25-31/1,000 births compared to 4/1,000 live births in HIC. The highest END estimates are found in Sub-Saharan Africa (17-37/1,000 live births) and South Asia (15-32/1,000 live births).

Causes of early neonatal deaths

Because nearly ¾ of all neonatal deaths occur in the early neonatal period, causes of early neonatal death (END) are similar to causes of neonatal deaths. The major direct causes of early neonatal deaths include prematurity, asphyxia, sepsis/pneumonia, congenital anomalies and tetanus [17, 18].

Infant mortality

Infant mortality refers to death of live born infants in the first year after birth. Infant mortality comprises of: a) neonatal mortality (including END) and b) post-neonatal mortality.

Epidemiology of infant mortality

The last century has witnessed a remarkable decline in infant mortality. Still, the probability of dying during the first year of life is 45/1,000 live births (range: 1-165/1,000 live births, median: 21/1,000) [19]. In the first half of the 20th century, the decline in infant mortality was fastest in HIC and slowest in LMICs, resulting in huge global disparities. This downward trend in IMR in high income countries began before important medical discoveries such as vaccines and antibiotics [1]. Today, rates are highest in Sub-Saharan Africa (85/1,000 live births), Eastern Mediterranean (57/1,000 live births) and South East Asia (48/1,000 live births) [19]. They are lowest in HIC at 5/1,000 live births [20].

Neonatal mortality

'Neonatal death' refers to death of live born infants within the first 28 days of life, an important component of infant mortality. Each year, an estimated 4 million newborn babies die. The highest risk of death is within the first hour after birth (figure 3). At least 95% of these deaths occur in the 68 high burden, so-called 'countdown countries'. The fourth Millennium Development Goal (MDG-4) commits all the world's countries and the entire world's leading development institutions to reducing mortality in children aged younger than 5 years by two-thirds between 1990 and 2015. Because neonatal deaths constitute 38%

of all child deaths, considerable reductions in neonatal deaths is crucial to achieve MDG-4 [17, 21].

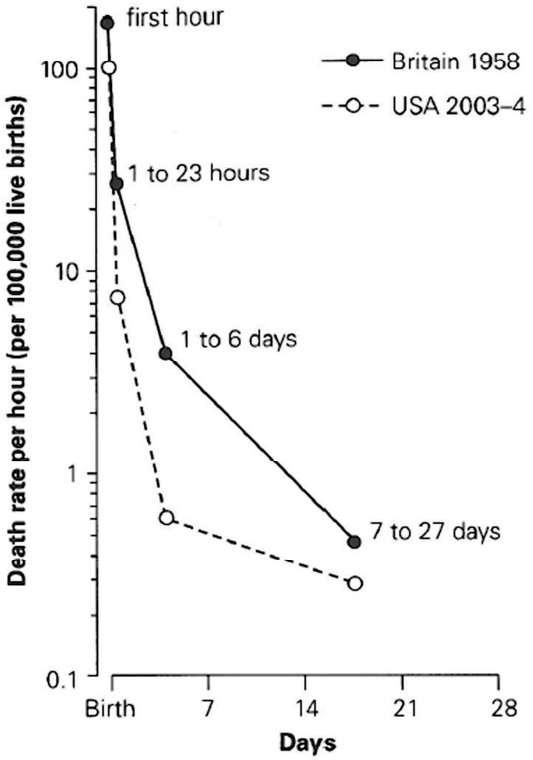


Figure 3. Neonatal mortality by time since birth, Britain 1958 and United States 2003-2004. *Source: Wilcox AJ, (2010)*

Epidemiology of neonatal deaths

Estimates of neonatal mortality vary from 44 (range 9-70)/1,000 live births in Africa to 11 (range 2-38)/1,000 live births in Europe [17]. In the past decade, there has been a decline in neonatal mortality in most regions except for Sub-Saharan Africa (figure 4). The Americas have recorded a 40% reduction in NMR mostly because of reductions in Latin America. Japan, South Korea and Malaysia have recorded the highest reductions in the western pacific region. All these three countries now have an NMR <5/1,000 live births. Asia has had mixed fortunes with considerable reductions in some countries such as Indonesia, Bangladesh and Sri Lanka with 50%, 40% and 40% reductions, respectively. More modest

reductions have been seen in other Asian countries such as India with a reduction of only 11% [17].

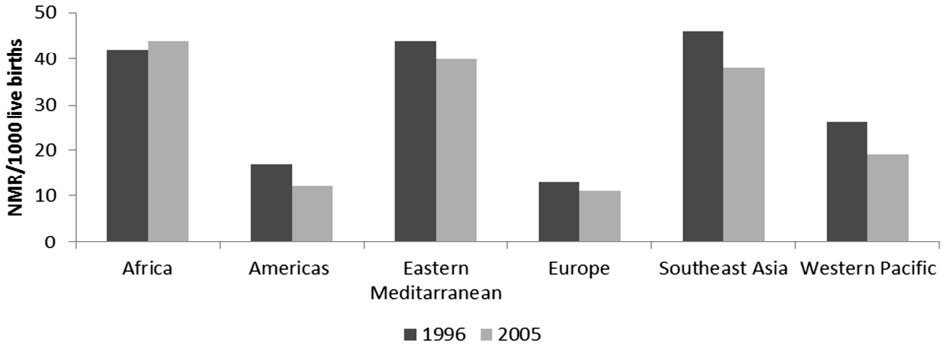


Figure 4: Trends in Neonatal mortality in different regions of the world.
Source: World health statistics (2010).

Causes of neonatal deaths

Figure 5 summarizes the estimated distribution of the major direct causes of neonatal deaths. These estimates vary from region to region and from country to country. They are based on statistical models as a consequence of the quality of available data. Countries with high estimates of NMR (NMR>45/1,000 live births) have a larger proportion of deaths (nearly 50%) that is attributable to infections such as pneumonia, diarrhea and tetanus [17]. Hence, the proportion of deaths attributable to prematurity in these countries is smaller than that in countries with lower NMR despite having larger absolute values of deaths among preterms. Other causes of neonatal deaths are summarized in Table 2 [22, 23].

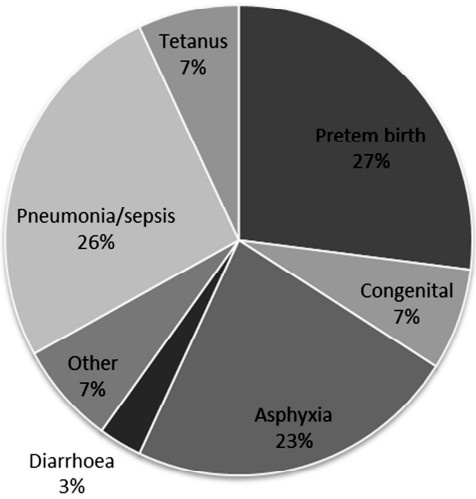


Figure 5: Distribution of the direct global causes of neonatal deaths (2000)
Source: Adapted from Lawn et al. (2005)

Table 2: Risk factors for neonatal deaths

Life cycle factors	Antepartum factors	Intrapartum factors
Low maternal age (<18 years)	Multiple pregnancy	Malpresentation
High maternal age (>35 years)	Eclampsia & pre-eclampsia	Obstructed labour
Low maternal height <150 cm	Antepartum haemorrhage	Prolonged labour
Low pre-pregnancy weight (< 47 kg)	Maternal jaundice	Maternal fever (>38 ℃)
Nulliparity	Maternal anaemia	Longstanding rupture of membranes (> 24 hrs)
High parity (>6)	Maternal malaria	
	Syphilis	
	HIV	

Source: Lawn et al. (2005), Gubhaju et al. (1999), Mturi et al. (1995)

Post-neonatal mortality

'Post-neonatal death' refers to deaths occurring after the first four weeks of birth but within the first year of life. In the past decades, most of the reduction in infant mortality is attributable to declines in post-neonatal mortality. In high income countries, the post-

neonatal mortality has gone from being greater than neonatal mortality to being half of neonatal mortality. In LMIC with high incidence of infectious diseases, post-neonatal mortality still contributes a sizable, though steadily declining, portion of infant mortality [24].

Epidemiology of post-neonatal mortality

The probability of death in the post-neonatal period was, in 2010, estimated to average 40/1,000 live births, globally. Country-specific estimates for post-neonatal mortality range from 1/1,000 live births to 104/1,000 live births with a median value of 9/1,000 live births [19] (table 3).

Causes of post-neonatal mortality

In most literature, causes of post-neonatal deaths are not distinguished from those of deaths among children younger than five years but who are older than one month. The largest killers of children after the newborn period include pneumonia, diarrhea, malaria, measles, HIV/AIDS and underlying undernutrion (figure 6) [24]. The proportion of deaths attributable to each cause of death varies considerably from region to region.

Table 3: Post-neonatal mortality rate estimates

Region/Category	**Post-neonatal mortality rate/1,000 live births**
WHO region	
African region	102
Region of the Americas	9
South-East Asia Region	29
European Region	7
Eastern Mediterranean Region	43
Western Pacific Region	10
Income group	
Low income	81
Lower middle income	34
Upper middle income	12
High income	3
Global	39

Source: WHO (2010) [19]

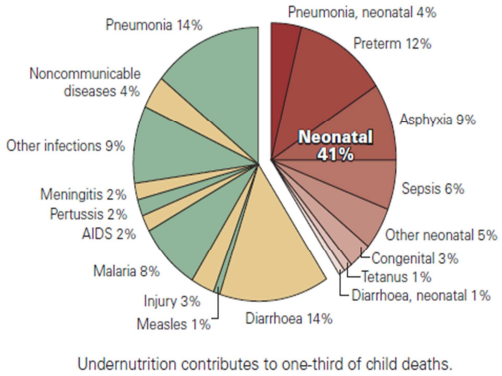


Figure 6: Global causes of death among children ages 0-59 months, 2009
Black et al. (2010)

The Ugandan context

Epidemiology of child mortality

The Uganda demographic and health survey (UDHS) is the major source of community based surveillance data in Uganda. Because Uganda does not have a vital registration system, the UDHS is also the main source of community based mortality information from a nationally representative population sample. The UDHS is a retrospective household survey that is mostly limited to prevalence estimates. The retrospective nature of the survey renders it susceptible to recall bias, especially since participants are asked to recall events and dates in the five years preceding each survey. In the past 40 years, 4 cycles of the standard UDHS have been published. Table 4 summarizes the relevant mortality indicators included in these cycles [25-28]. Two other studies that have measured mortality in infants are included. According to UDHS data, there has been a slow decline in child mortality in Uganda. Neonatal mortality has slightly decreased from 36/1,000 live births in the five year period preceding 1988 to 29/1,000 live births in period between in 2001 and 2005. Perinatal mortality was 53/1,000 in 1988 and 46/1,000 between in 2001 and 2005. A similar trend has been reported for IMR (figure 7) [29].

Table 4: Assessments of different types of child mortality in Uganda (1977-2009).

Study	Design	Community/ Hospital based study	SBR/ 1,000	ENMR/ 1,000	PMR/ 1,000	NMR/ 1,000	PNMR/ 1,000	IMR/ 1,000	U5MR/ 1,000
UDHS (1977)	Cross-sectional	Community	_	_	_	_	_	92	180
UDHS (1982)	Cross-sectional	Community	_	_	_	_	_	113	200
UDHS (1988)	Cross-sectional	Community	_	_	_	36	53	101	180
UDHS (1995)	Cross-sectional	Community	_	_	_	27	54	81	147
UDHS (2000-1)	Cross-sectional	Community	_	_	43	33	55.2	88.4	152
Gray (2001) [30]	RCT*	Community	35	25	_	_	_	_	_
UDHS (2006)	Cross sectional	Community	_	_	36	29	46	76	137
Ndibazza (2009) [31]	RCT*	Hospital	13	20	33	_	_	_	_

*RCT: randomized controlled trial

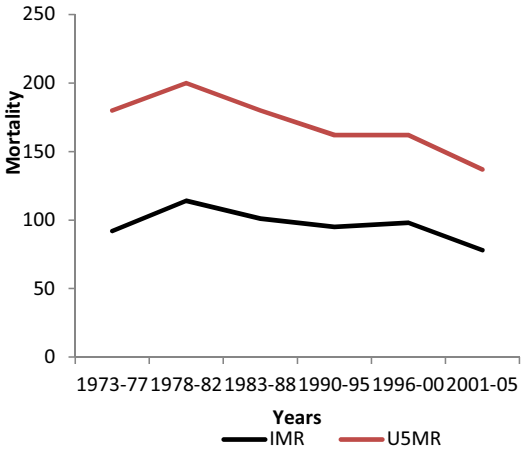
Causes of child death in Uganda

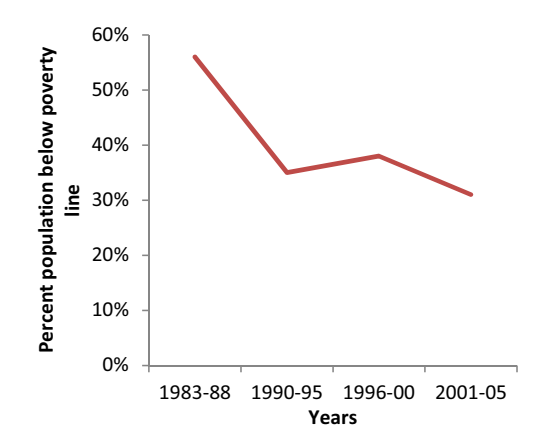
A few studies have examined the potential risk factors for child death in Uganda (table 5). In nearly all these studies, risk factors have not been disaggregated by age [18, 30-35]. The major direct causes of child death include malaria, diarrhoea, pneumonia and HIV infection [36].

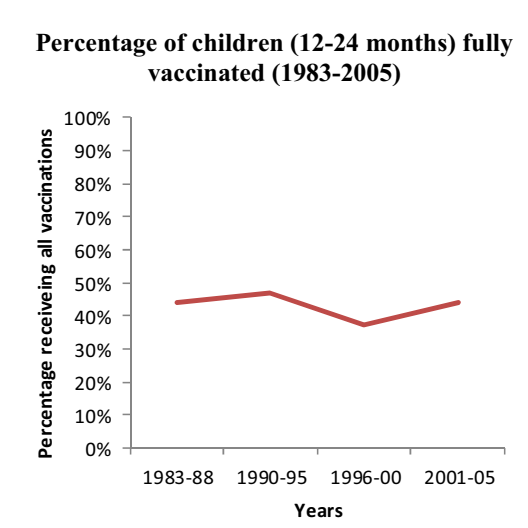
Table 5: Risk factors for child deaths in Uganda

Factors associated with child deaths
Maternal death
Maternal HIV infection
Low maternal CD4 count
Childhood HIV infection
Polygyny
Low Apgar score
Residing more than >5km from hospital
Difficulties with transport to health facilities
Lack of presumptive STI treatment during pregnancy
Low maternal education
Low paternal education

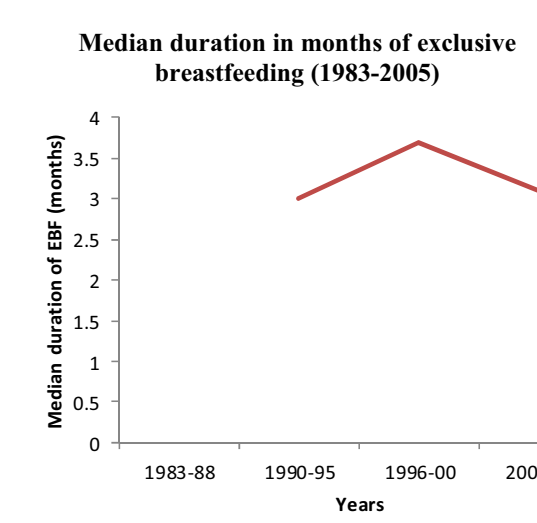
Figure 7: Trends in selected child health indicators for Uganda





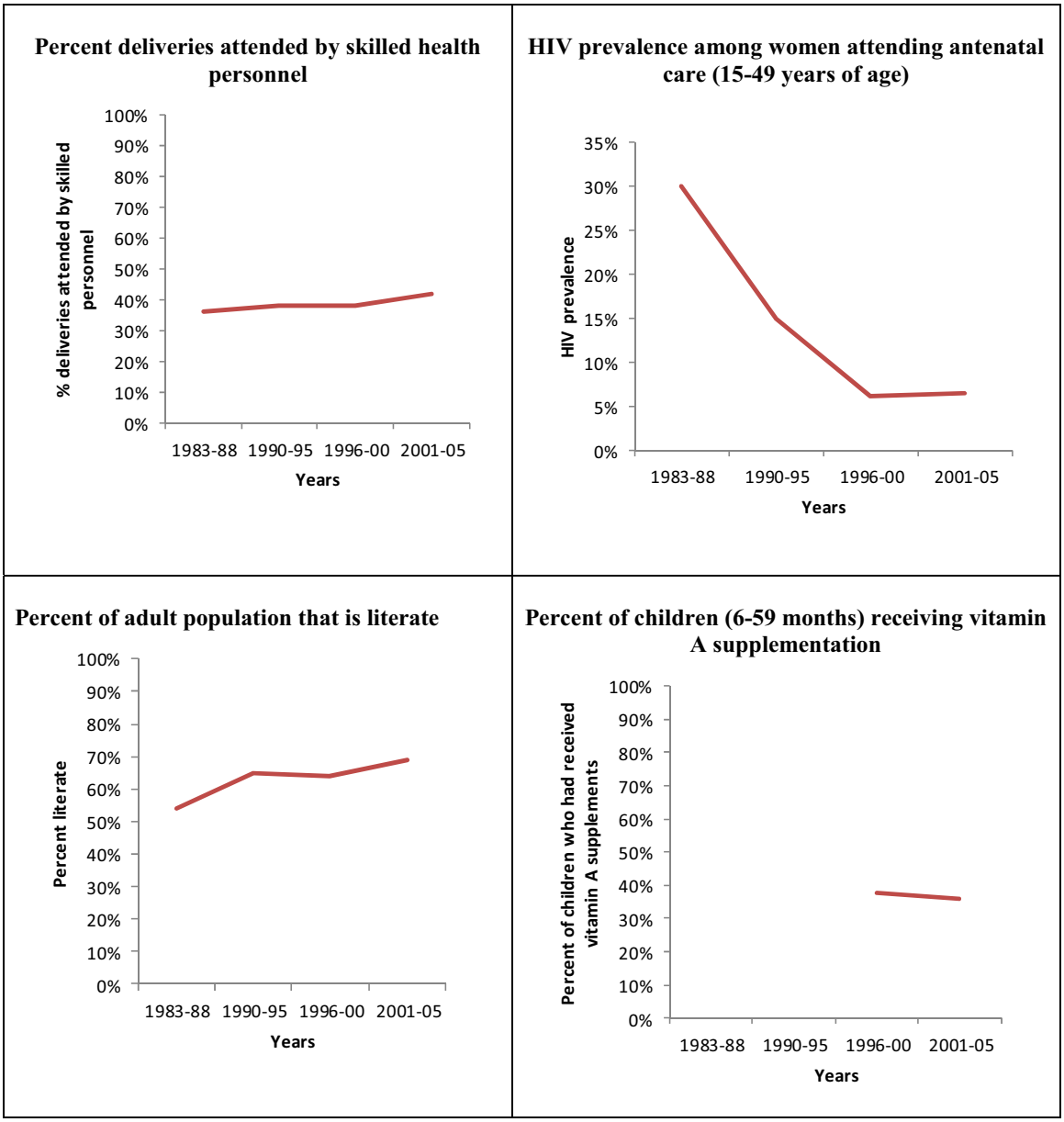


**Data for 1983-1985 applies to all children under five years*



Source: UDHS (1973-2005), UNFPA, 2008

Figure 8: Trends in selected health and socio-demographic indicators for Uganda (UDHS 1983-2005)



Source: UDHS (1973-2005), UNFPA, 2008

Interventions that could reduce mortality

The 2003 Lancet Child Survival Series listed several interventions that could reduce child mortality, such as promotion of exclusive breastfeeding, insecticide treated bednets, complementary feeding, zinc supplementation, oral rehydration therapy, antibiotics for sepsis and pneumonia, antimalarials, clean deliveries, vaccination, vitamin A supplementation, water and sanitation, tetanus toxoid and others [21, 37, 38]. This thesis focuses on three key interventions: 1) vaccination, 2) exclusive breastfeeding with regard to its association with malaria parasitaemia and 3) Vitamin A supplementation and its association with malaria parasitaemia.

1) Vaccination

Vaccination against common and dangerous childhood diseases is highly efficacious but coverage is variable and in many countries low [39, 40]. Each year, it is estimated that nearly 34 million of the world's children are not vaccinated despite ample evidence that routine childhood vaccinations are protective against tuberculosis, polio, diphtheria, pertussis, tetanus, measles, hepatitis B and Haemophilus influenza B (Hib) [39, 41-43]. In the 1980's, the child survival campaign spearheaded by UNICEF resulted in a remarkable global increase in vaccination coverage from about 25% to 75% in 10 years [44]. But there was country variation and today, about 1.4 million children die each year from vaccine preventable diseases [45]. In fact, thirty years later, only 36% of all one-year old Ugandan children are fully immunized [28] and vaccine-preventable diseases continue to be a major contributor to infant mortality [46, 47]. This is despite the fact that the Ugandan Ministry of Health provides free childhood vaccinations and has conducted several national immunization days (NIDs) [48]. Several hypotheses for this low coverage such as maternal education have been posited in Uganda and other countries with comparable coverage [49, 50]. Maternal education may increase the likelihood of vaccination through increasing knowledge on vaccination. Studies have shown a positive correlation between mother's education and knowledge of vaccination as well as between knowledge of vaccination and acceptance of vaccination [49]. In 2007, the Ugandan government launched the universal secondary education scheme. Still, less than 27% of Ugandan women in the reproductive age group have had some secondary school education [28]. Paper III of this thesis compared

women with primary school education with those having some secondary school education with regard to the BCG, polio and DPT-HB-Hib vaccination status of their infants.

2) Exclusive breastfeeding and malaria

Malaria is one of the top five causes of death in children under one year of age. Approximately 500 million episodes of malaria occur each year [51-53]. In Uganda, it has been the most important cause of child death for decades. Hence, interventions that protect children from malaria are of great importance. The possibility of a protective effect of breastfeeding against malaria has been investigated but to-date; the evidence is inconclusive limited, for two main reasons: 1) insufficient research on this topic, especially in LMIC and 2) conflicting data from the available studies. It has been hypothesized that the possible protective effect of breastfeeding is through immuno-protective mechanisms or alternatively related to lactoferrin. Lactoferrin is a protein found in breast milk and neutrophils, with antibacterial properties as well as lipoprotein remnants [54]. Its protective effect is postulated to be through inhibition of the invasion of hepatocytes by malarial sporozoites, because they compete for the same receptor in the hepatocyte plasma membrane [54]. But evidence for any effect of EBF on malaria has been conflicting [55-58]. A few studies have reported a reduced risk of malaria among exclusively breastfed infants but other studies have found no such effect (table 5).

3) Vitamin A supplementation and malaria

Vitamin A supplementation is considered as one of the major child survival interventions that could be feasible for delivery at high coverage in LMIC. This is important because it has also been hypothesized that vitamin A supplementation could protect children from malaria. Vitamin A may exert such effects by increasing phagocytosis of parasitized erythrocytes as well as reducing the pro-inflammatory response to the parasite [59]. Vitamin A may assist in the up-regulation of CD36 expression which facilitates phagocytosis. However, evidence for any association between vitamin A supplementation and malaria in children has been scanty, conflicting and inconclusive (table 6) [60-64].

Table 5: Summary of studies examining the association between breastfeeding and malaria

Author (Year)	Country	Study design	Sample size	Age	Exposure	Outcomes	Results
Kalanda et al. (2006) [56]	Malawi	Cohort			Early complimentary feeding	Episodes of malaria	Early complementary feeding marginally associated with increased risk of malaria episodes
Ikeh et al. (2008) [55]	Nigeria	Cross-sectional	260	0-60 months	Exclusive breastfeeding	Malaria parasitaemia	Exlusively breastfed infants were more likely to have malaria parasitaemia
Custodio et al. (2009) [58]	Equatorial Guinea	Cross-sectional	548	0-60 months	Colostrum	Malaria parasitaemia	Infants who had been fed colostrum were less likely to have malaria parasitaemia
Vora et al (2010) [57]	Uganda	Cohort	346	6 weeks-24 months	Breastfeeding	Malaria parasitaemia	HIV unexposed children 6-15 months-Insufficient data HIV unexposed children >15-24 months-no association HIV exposed children 6-15 months-breastfeeding associated with a reduced risk of malaria HIV-infected children 6-15 months-breastfeeding associated with a reduced risk of malaria HIV infected children >15-24 months-no association

Table 6: Summary of randomized controlled trials examining the association between vitamin A supplementation and malaria

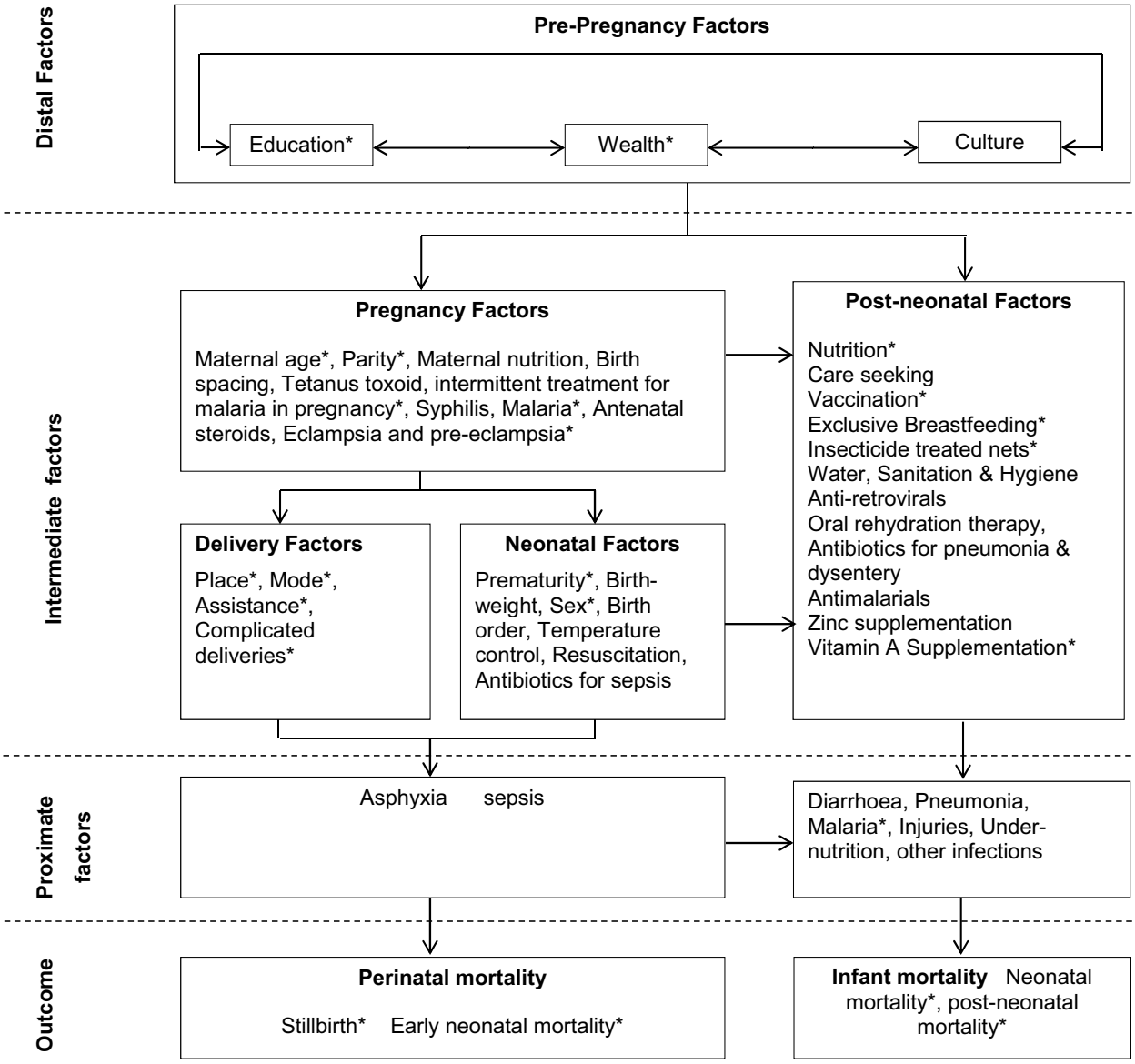
Author (Year)	Country	Sample size	Age	Intervention	Outcomes	Results
Binka et al. (1995) [63]	Ghana	21906 (mortality outcome) 1455 (morbidity outcomes)	6-60 months	Vitamin A supplementation: children aged 6-11 months received 30 mg retinol equivalent as retinyl palimitate and older children received 60 mg retinol equivalent or	Malaria mortality Fever Malaria parasitaemia Parasite density Probable malaria	No difference in malaria mortality No difference in fever incidence No difference in malaria parasitaemia No difference in parasite densities No difference in probable malaria
Shankar et al. (1999) [61]	Papua New Guinea	480	6-60 months	200,000 IU of vitamin A (or 100,000 IU for chldren < 12 months) every 3 months for 13 months	*P. falciparum* febrile episodes *P. falciparum* geometric mean density	Fewer *P. falciparum* febrile episodes in the intervention group Lower *P. falciparum* geometric mean in the intervention group
Varandas et al. (2001) [64]	Mozambique	570	6-72 months	200,000 IU of vitamin A (or 100,000 IU for chldren < 12 months)	Mortality	Overall reduction in the risk of death in the intervention group (not statistically significant)
Villamor et al. (2003) [62]	Tanzania	554	6-60 months	200 000 IU of vitamin A on the day of admission with pneumonia, a second dose on the next day, and third and fourth doses at 4 and 8 months afterdischarge, respectively. Half the dose was administered to children <12 months.	Malaria parasitaemia	No effect on malaria parasitaemia at 4-8 of follow up
Zeba et al. (2008) [60]	Burkina Faso		6-72 months	Single dose of 200 000 IU of vitamin A & 10 mg elemental zinc, six days a week	Prevalence of malaria, Malaria episodes, Time to first malaria episode	A significant decrease in malaria prevalence malaria in the intervention group Fewer malaria episodes in the intervention group Time to first malaria episode longer in the intervention group

Conceptual model

This thesis conceptualizes morbidity and mortality within an analytical framework adopted from Mosley and Chen [65] that was motivated by the work of Davis and Blake [66]. Since its inception in 1984, the proximate determinants framework by Mosley and Chen has been adapted to fit specific research areas such as maternal mortality, neonatal mortality and HIV/AIDS [67-69]. In this thesis, we extend this framework to explore factors associated with perinatal and infant mortality (figure 9). The framework, as used here and as originally posited by Mosley and Chen, emphasizes that causes of death in children are multifactorial and should be studied as such. It recognizes that there are both socioeconomic and biologic variables impacting mortality. It asserts that socioeconomic factors (distal factors) rarely cause death in children directly. Rather, these factors act through several linked intermediate and proximal factors to influence morbidity and impact mortality. It acknowledges that growth faltering and mortality in children are the cumulative consequences of several distal, intermediate and proximal factors, and only rarely, can a child's death be attributed to a single cause.

The utility of a conceptual framework in epidemiologic research cannot be emphasized enough [70]. A framework not only clarifies the multiple factors associated with deaths among children, it also provides a foundation for health policies and strategies. More importantly, it organizes apparently unrelated factors into a logical framework in which multiple factors are interlinked with child survival on one end and social-economic factors on the other. Figure 9 shows the conceptualization of variables in this thesis. It demonstrates the inter-relationships between variables and the multiple potential pathways between exposures and outcomes.

Figure 9: Conceptual framework for factors influencing perinatal and infant mortality



*Factors/outcomes in this thesis

Study aim and objectives

Overall aim

To measure perinatal and infant mortality in Eastern Uganda and to explore the possible role of interventions (vaccination, exclusive breastfeeding proportion and vitamin A supplementation) that could reduce this mortality.

Specific objectives

Paper I

1. To estimate the perinatal mortality risk in Mbale, Eastern Uganda
2. To identify the main risk factors of perinatal death in Mbale

Paper II

1. To estimate the infant mortality risk in Mbale
2. To identify the important risk factors of infant death in Mbale

Paper III

1. To describe the vaccination status of infants in Mbale
2. To compare women with some secondary school education with those having only primary school education with regard to the BCG, polio and DPT-HB-Hib vaccination status of their infants

Paper IV

1. To estimate the prevalence of malaria parasitaemia in infants in Mbale
2. To estimate the effect of peer counseling for exclusive breastfeeding on the prevalence of malaria parasitaemia
3. To estimate the association between vitamin A supplementation and the prevalence of malaria parasitaemia
4. To estimate the association between anthropometric status and the prevalence of malaria parasitaemia

Study subjects and methods

These studies were undertaken during the cluster-randomized PROMISE EBF intervention trial, where we promoted exclusive breastfeeding by individual peer counselling in the intervention areas (Clinical trials gov: NCT00397150) [71]. Data collection for this study started in January 2006 and ended in January 2010.

Study site

The studies were conducted in Mbale district which had an estimated population of 720,000 in 2002 [72] and is located 300 km North-East of Kampala.

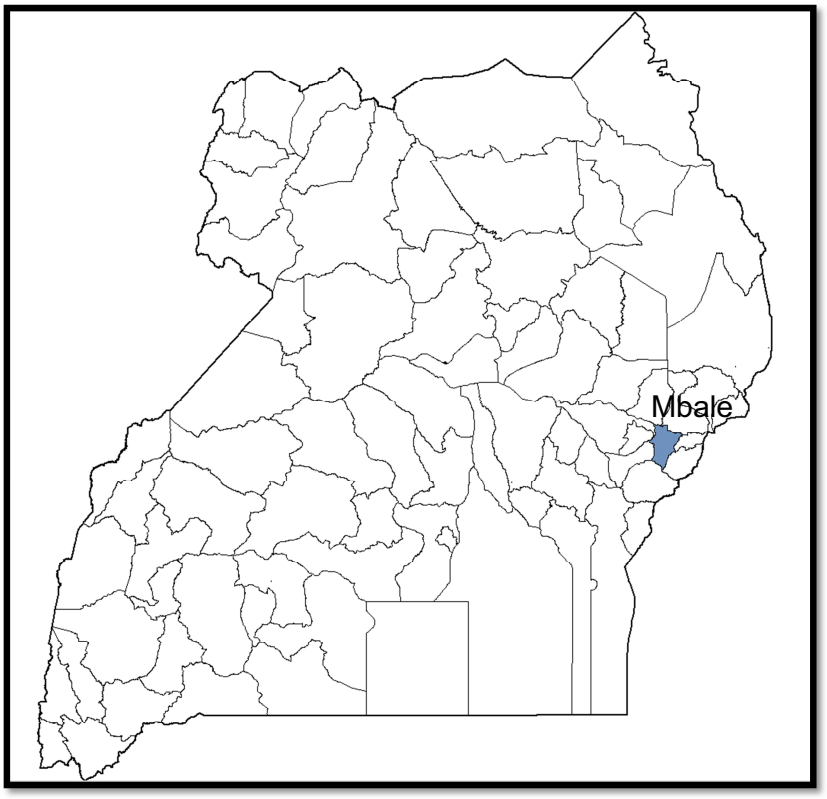


Figure 10a: Map of Uganda showing the location of Mbale

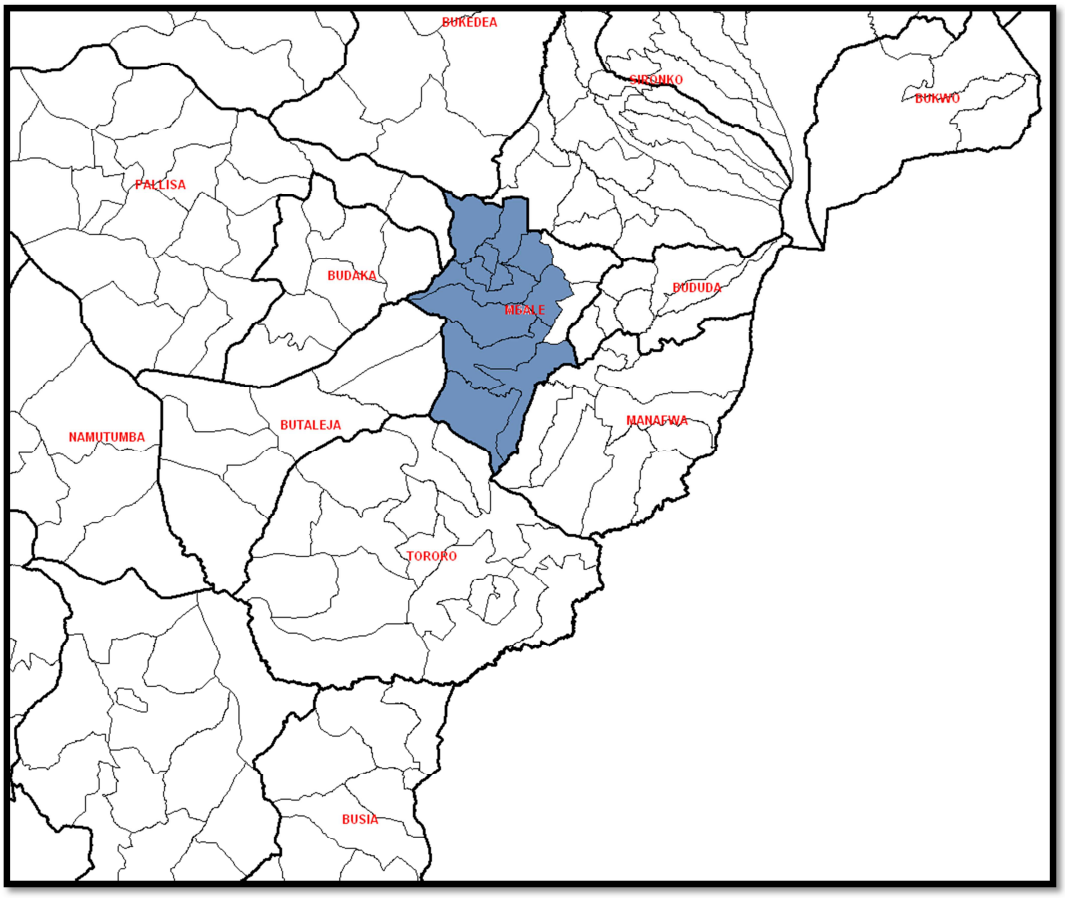


Figure 10b: Map of Mbale and surrounding areas

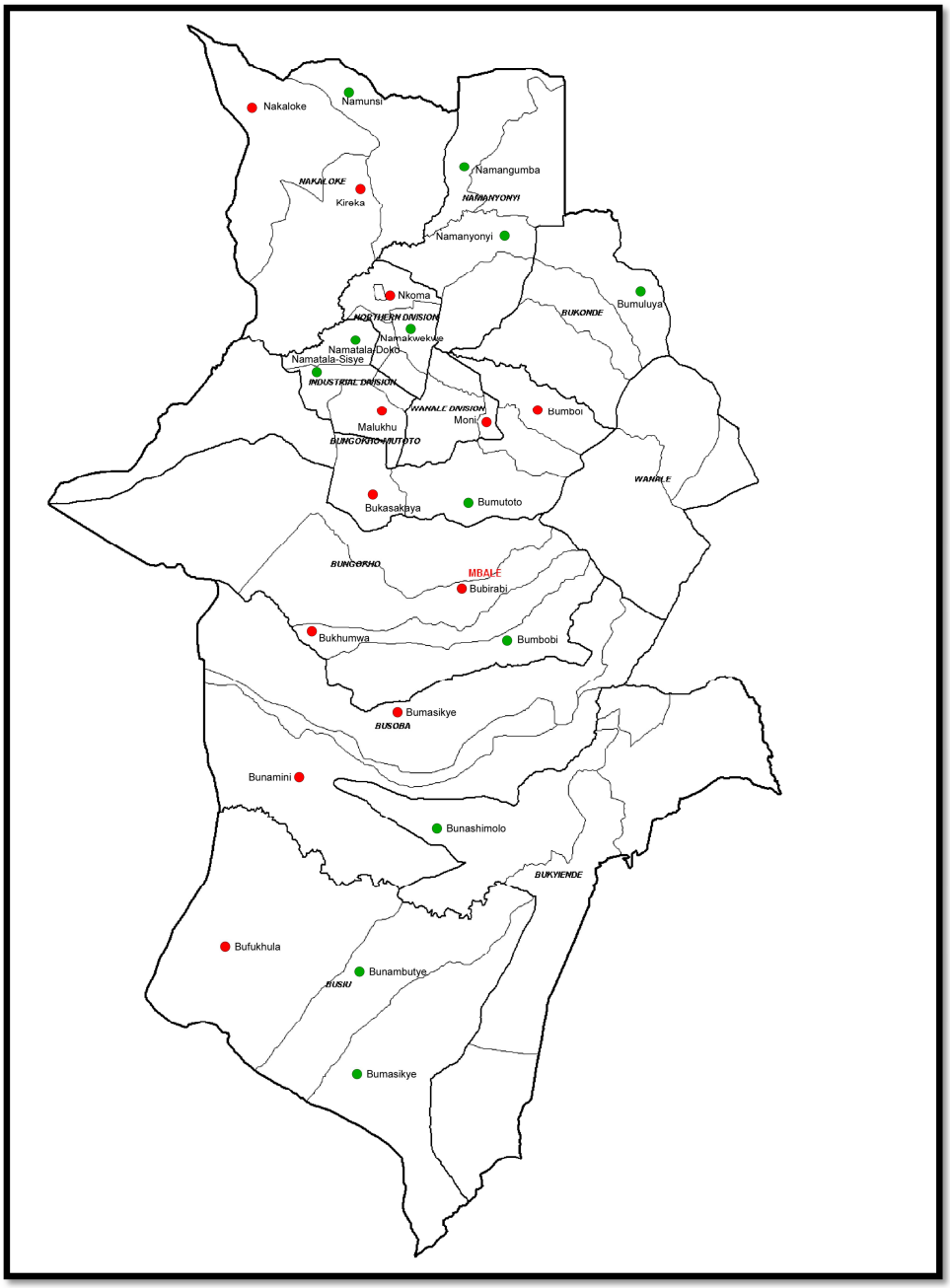


Figure 10c: Map of Mbale showing intervention ad non-intervention clusters

- Intervention cluster
- Non-intervention cluster

Mbale district, lying at the foothills of Mt. Elgon, is a high altitude area between 1200-2100 meters above sea level. Average annual rainfall is 1,500 mm. There are two rainy seasons: mid-February to end of May and August to December. Malaria is holoendemic in this area, mostly caused by *Plasmodium falciparum*. The study area was served by Mbale Hospital, which was both the district and regional referral hospital. The HIV prevalence among pregnant women in antenatal clinics in Mbale was approximately 5-6% during the study period [28]. Most of the people living in the area were subsistence farmers. Mbale district comprised of 7 counties; the study was conducted in the two biggest counties, namely Bungokho County (rural) and Mbale Municipality (urban). Twenty four clusters were included in the study, 18 rural and 6 urban. Six clusters in Mbale municipality were selected from all its three municipal divisions. Most of the urban areas were large informal settlements. Eighteen clusters in Bungokho County were chosen from eight out of its eleven sub-counties. Clusters were included if they neighboured the main road out from Mbale Municipality or were on the 1st or 2nd branch off the main road, had a population of at least 1,000 inhabitants and represented a social and administrative unit. Twelve clusters were randomly designated to receive the intervention and 12 were left as control clusters, which received routine government services.

Study designs, subjects and trial profile

Between January 2006 and May 2008, all pregnant women in the selected clusters were approached by the study team. They were eligible if they resided in the study area, were seven or more months pregnant, opted to breastfeed their infants and consented to participate in the study. In addition, women were excluded if they had an intention to leave the area during the study period, gave birth to twins (except for paper I) or to infants with serious illnesses or deformities like cleft lip/palate that could disrupt breastfeeding. In the PROMISE-EBF trial, 886 pregnant women were identified and approached. Of these, 875 women (99%) accepted to participate in the study. Out of the 875 women, 12 (1%) did not meet the eligibility criteria (two of these were excluded because they did not intend to breastfeed) and 28 (3%) relocated out of the study area after recruitment but before delivery and were lost to follow-up (figure 11). There were 835 deliveries. Paper I used this sample

of 835 women to estimate the perinatal mortality and associated risks. Out of the 835 deliveries, 16 were still births and 819 were live births.

Data collection: Papers I-IV

At recruitment, locally recruited and trained data collectors fluent in the local language, Lumasaaba, administered a pre-tested structured questionnaire. Information was collected on socio-demographic characteristics, antenatal care attendance, marital status and main source of income. Information was also collected on the current pregnancy and use of bed nets. The recruited women were followed up through the pregnancy until 18 months after delivery. Follow-up interviews were scheduled for 3, 6, 12, and 24 weeks and 18 months of age (figure 11). At each of these visits, information was collected on vaccination status, use of bed nets, anthropometric status and breastfeeding. Weight was measured using standardized scales to the nearest 0.1 kg. The scales were zeroed before each field visit. Length was measured using standard length boards to the nearest millimeter. For the perinatal and infant deaths, a standard World Health Organization (WHO) verbal autopsy questionnaire was used to collect information (for a standard algorithm) on the likely cause of death [73]. The questionnaire had both an open-ended section for reporting verbatim and a closed-ended section with filter questions. The data collectors were periodically re-trained on the questionnaires and in anthropometry.

Additional data collection: Paper IV

Data collection for paper IV was the same as for papers I-III with the addition of blood collection in a sub sample of 483 infants between 3 and 12 months of age. Children were enrolled into this sub sample consecutively, starting with the oldest until a sufficient sample size was attained. Children older than one year at the time of sample collection were excluded from the study. Because of the cluster design of the Promise-EBF study, once a cluster was visited, all eligible children were approached during the visit. All clusters were visited a couple of times until an adequate sample size was achieved.

In this sub sample, a blood specimen for malaria parasitaemia (thick and thin blood film) was collected from a finger prick by a trained laboratory technologist. Blood slides were air dried and the thin smears were fixed in 99% methanol. The slides were stained with 10% Giemsa solution for 10 minutes. The number of asexual *P. falciparum* malaria parasites per 200 white blood cells was determined on the thick film by a trained lab technologist who was blinded to the intervention allocation. Thin smears were used to identify the parasite species while thick smears were used to estimate parasite densities.

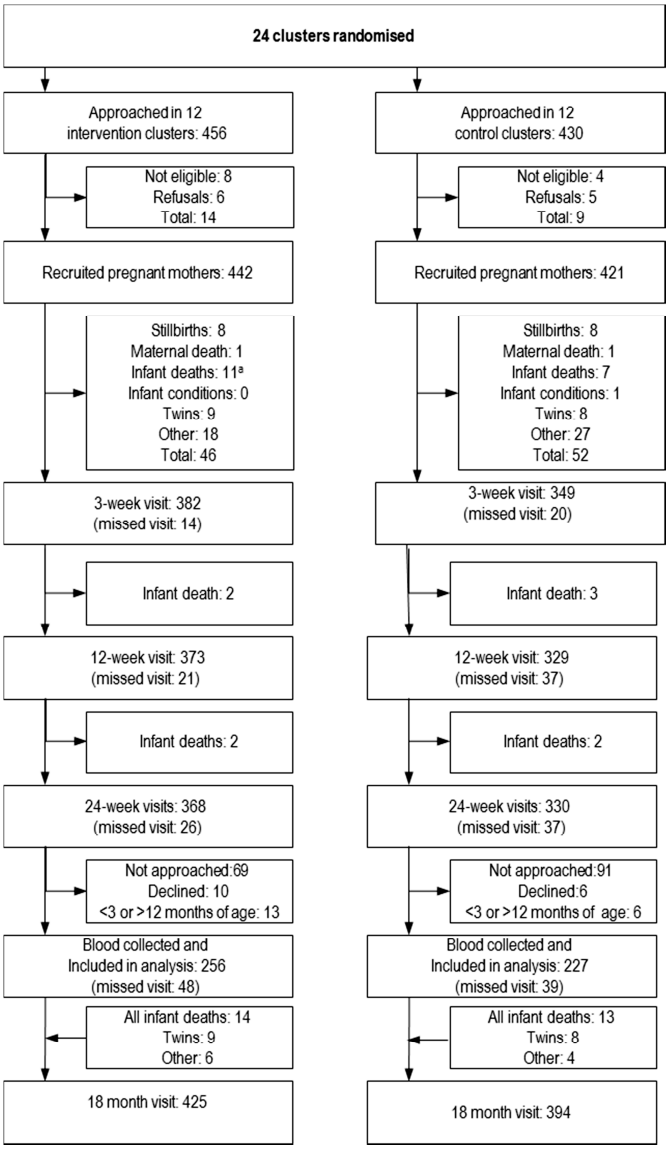


Figure 10: Trial profile

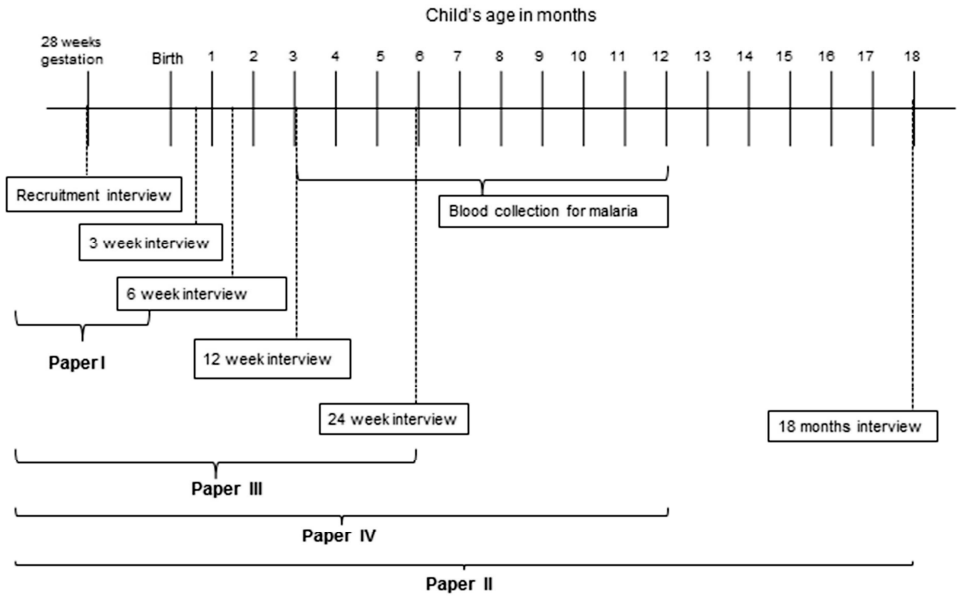


Figure 11. Timeline for data collection activities

Statistical analysis

Data were entered into hand held computers in the field using the EpiHandy software (www. openXdata.org, version 165.528-142 RC). Data analysis was undertaken using Stata version 9 (StataCorp LP, TX, U.S.). We calculated several measures of association as shown in tables 7 and 8. We used multivariable generalized linear model (GLM) regression analysis with a log link to estimate the adjusted risk ratios (RRs) and their corresponding 95% confidence intervals of the exposure variables on the outcomes. Initially, all the exposure variables (table 7) were included in the crude analyses. However, only those associated with the corresponding outcome with a P-value < 0.25 or variables that have been found to be particularly important in other studies (such as maternal education or social-economic status) were retained in the final models. Taking the design effect of the PROMISE-EBF clusters into account had no effect on the RRs or PRs and a negligible effect on precision. For Papers I and IV, we measured effect measure modification on both additive and multiplicative scales. In paper I, we examined interaction between place of

delivery and parity and in paper IV examined interaction between vitamin A supplementation and anthropometric status. We used cross product terms to test for interaction on the multiplicative scale.

Table 7. Study designs, sample sizes, exposures and outcomes used for Papers I-IV

Paper	Study design	Sample size	Exposures	Outcomes
I	Prospective cohort study	835	Maternal age, parity, education, residence, marital status, wealth index, Antenatal care attendance, use of bed nets, place of delivery and complications of delivery	Still-birth, early neonatal death, perinatal death
II	Prospective cohort study	819	Maternal age, parity, education, residence, marital status, wealth index, antenatal care attendance, place of delivery, complications of delivery, previous child deaths, hospitalizations, self-reported maternal HIV status	Neonatal death, post-neonatal death, infant death
III	Prospective cohort study	696	Maternal education	BCG, polio 0-3 and DPT-HB-Hib 1-3 vaccination status of infants at 24 weeks
IV	Cluster randomized trial and retrospective cohort study	483	Peer counselling for breastfeeding, Vitamin A supplementation, Anthropometric status	Malaria parasitaemia

Table 8: Measures of occurrence and association computed in studies forming the basis for papers I-IV

Paper	Measures of occurrence	Measures of association
I	Still birth risk/1,000 pregnancies Early neonatal mortality rate/1,000 live births Perinatal mortality risk/1,000 pregnancies Perinatal mortality risks for various socio-demographic categories	Risk ratios, Risk differences
II	Neonatal mortality risk/1,000 live births Post-neonatal mortality risk/1,000 live births Infant mortality risk/1,000 live births Infant mortality risks for various socio-demographic categories	Risk ratios
III	Proportion vaccinated	Risk ratios
IV	Prevalence of malaria parasitaemia	Prevalence ratios, Prevalence differences

Definitions

Marital status: In Uganda, it is now common to find couples living together without being formally married and we classified these as 'co-habiting'. We categorized marital status into three categories: 'married', 'cohabiting' and other (single, widowed, divorced or separated) for papers I and II. For papers I and II, we categorized marital status into two categories: 'married' and 'un-married' to increase power because the outcome (death) for these studies was rare. The unmarried category comprised cohabiting, single, divorced, widowed and separated.

Place of delivery: We categorised place of delivery also into two groups: 'home', and 'hospital/clinic/local maternity/traditional birth attendant's place or on the way to hospital'. Home deliveries were defined as those deliveries that took place at home without a skilled birth attendant.

Education: For papers I and II, education was grouped into two categories: 'less than or equal to 7 years of education' and 'more than 7 years of education'. For paper III and IV, education was grouped into five categories: 'none' '1-4 years', '5-7 years', '8-11 years' and '12 or more years'. Primary education was defined as 5-7 years and secondary education as 8-11 years of schooling.

Socio-economic status: We created a composite index of wealth (socio-economic status) using multiple correspondence analysis (MCA). Because the MCA technique allows combination and ranking of a large number of variables into smaller and fewer variables without prejudgment, it is considered a more accurate indicator of socioeconomic status (SES) than single items such as occupation or possession of particular items. Also, in comparison to principal component analysis (PCA), the MCA technique is more appropriate for discrete variables. This was important in this study because several relevant variables could only be categorical. Furthermore, unlike PCA, which clusters variables together, MCA clusters the categories within these variables together. We used MCA on possession of a TV, radio, mobile phone, chair, cupboard, refrigerator, type of toilet, type of house walls as well as presence of electricity and water in the home. Scores were categorized into quintiles.

Anthropometric indicators: Weight-for-length (WLZ), length-for-age (LAZ) and weight-for-age (WAZ) Z scores were calculated in relation to the WHO growth standard with the software WHO Anthro for personal computers, version 2 [74]. A child was classified as wasted if it had a WLZ score below -2 standard deviations (SDs) (i.e. WLZ < -2); stunted if LAZ < -2 and underweight if it had WAZ < -2.

Ethical considerations

Ethical approval was obtained from the Makerere University Research and Ethics Committee, the Uganda National Council for Science and Technology, and from the

Regional Committee for Medical and Research Ethics for Western Norway (REK VEST, approval number 05/8197).

We obtained informed consent from each study participating mother before enrolment into the study. At the first contact with the study team, a trained data collector explained to the respondent the purpose of the study, issues pertaining to confidentiality, risks and benefits, and expectations associated with the study. The respondents were assured that participation was voluntary and that they could withdraw from the study at any time or decline to participate in any part of the study without prejudice to further care. A written copy of the consent form with all the above information was left with the respondent. Upon consenting for the study, the respondent gave either a thumbprint or a signature. All signature/thumbprint forms were kept secure cupboard in the study office.

Malaria results from the collected blood specimens were returned to the participants. Infants with positive malaria slides received free malaria treatment from the study and from Mbale regional referral hospital. The study also de-wormed over two hundred children in the community, including some children not participating in our study.

Summary of results

Paper I

In a cohort of 835 women, there were 34 perinatal deaths (table 9). The perinatal mortality risk was 41 [95%CI: 27, 54] per 1,000 pregnancies, with a stillbirth risk of 19 per 1,000 pregnancies and an early neonatal mortality risk of 22 per 1,000 live births (figure 8).

Nearly half of the deaths were associated with a complicated delivery: 6 had a prolapsed cord, 4 obstructed labour, 2 two antepartum haemorrhage, 2 breech-presentations and 1 mal-presentation. Other likely associated conditions, identified via verbal autopsies, were preterm birth (8), fever/malaria in pregnancy (8), neonatal tetanus (1), and preeclampsia (1), while no cause or likely associated condition of those listed in table 9 could be identified for two deaths. None of the perinatal deaths that occurred at home were registered anywhere and there was no death certificate available for any of the deaths, including those that occurred in hospital.

Stillbirths

Nulliparous women were in the adjusted analysis substantially more likely to have a stillbirth than women with a prior live birth [RR: 7.2 (95% CI: 2.0, 25.5)]. Other factors associated with stillbirths included delivering at home [RR 4.2 (95% CI: 1.5, 12.1)] and living in an urban area [RR 2.9 (95% CI: 1.1, 7.7)].

Early neonatal deaths

Women who delivered at home were 3.1 (95% CI: 1.2, 8.5) times more likely to have an early neonatal death compared to women who delivered in a health facility in the adjusted analysis. The risk of early neonatal death was 2.5 (95% CI: 1.0, 6.6) times higher for women in urban areas compared to those in rural areas.

Perinatal deaths

None of the women who used mosquito bed nets experienced a perinatal death. The excess unadjusted perinatal mortality attributable to not using a bed net was 70 (95% CI: 47, 93)

per 1,000. After adjusting for place of delivery (a proxy for health seeking behaviour), the excess risk was 71 (95% CI: 48, 93) per 1,000. This excess risk was substantially higher in nulliparous women [risk difference 134 (95% CI: 73, 196) per 1,000] than in women with a previous live birth [risk difference 49 (95% CI: 27, 72) per 1,000] (P-value for homogeneity of risk differences = 0.010). In the adjusted analysis, women who delivered at home were 3.7 times more likely to experience a perinatal death than those who delivered in a health facility or under the guidance of a traditional birth attendant. This association was substantially stronger among nulliparous women [RR: 8.0 (95% CI: 2.9, 21.6)] than among those with a previous live birth [RR: 1.8(95% CI: 0.7, 4.5)], p-value for RR homogeneity = 0.029. The adjusted difference in the perinatal death risk between home and an alternative place of delivery was also substantially stronger among nulliparous women [adjusted risk difference 159 (95% CI: 53, 264) per 1,000] than among women with a previous live birth [adjusted risk difference 7 (95% CI: -11, 25) per 1,000], P-value for homogeneity of risk differences = 0.006. Delivering at home was also associated with experiencing a stillbirth [RR: 4.2 (95% CI: 1.5, 12.1)] as well as with early neonatal death [RR: 3.1 (95% CI: 1.2, 8.5)].

The adjusted perinatal mortality risk among nulliparous women was 3.3 (95% CI: 1.5, 7.0) times higher than in woman who had given birth to a live baby in a prior pregnancy, most of this difference being attributed to the association between parity and stillbirth risk.
Women in the urban areas had a 2.7 (95% CI: 1.4, 5.3) times higher adjusted risk of losing their babies perinatally compared to those in the rural areas. Taking the design effect of the PROMISE-EBF clusters into account had no effect on the RR and a negligible effect on its precision.

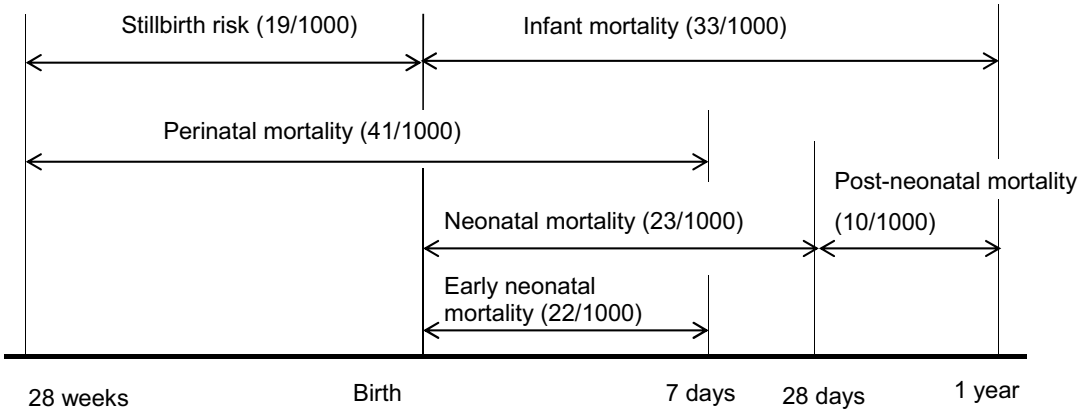


Figure 8. Perinatal and infant mortality risks

Table 9: Summary characteristics of the 34 perinatal deaths from a cohort of 835 women in Mbale, Eastern Uganda

Number	Place of delivery	Age of child (days)	Type of perinatal death	Maternal/fetal likely cause of death	Location/ Residence	Age of mother	Parity
1	Home	0	Still birth	Preterm birth	Rural	21	0
2	Home	0	Still birth	Preterm birth	Rural	17	0
3	Home	0	Still birth	Preterm birth	Urban informal settlement	28	3
4	Home	0	Still birth	Preterm birth	Rural	23	0
5	Home	0	Still birth	Malaria/Preterm birth	Rural	14	0
6	Home	0	Still birth	Fever/Malaria	Rural	16	0
7	Home	0	Still birth	Fever/Malaria	Urban informal settlement	19	1
8	Home	0	Still birth	Fever/Malaria	Urban informal settlement	19	0
9	Home	0	Still birth	Breech Presentation	Rural	42	7
10	Home	0	Still birth	Prolapsed cord	Urban informal settlement	18	0
11	Home	0	Early neonatal death	Ante-partum haemorrhage	Rural	26	6
12	Home	0	Early neonatal death	Ante-partum haemorrhage	Rural	21	0
13	Home	0	Early neonatal death	Obstructed labour	Urban informal settlement	24	3
14	Home	0	Early neonatal death	Obstructed labour	Urban informal settlement	20	1
15	Home	0	Early neonatal death	Breech presentation	Rural	33	7
16	Home	0	Early neonatal death	Prolapsed cord	Urban informal settlement	17	0
17	Home	0	Early neonatal death	Prolapsed cord	Rural	30	0
18	Home	0	Early neonatal death	Prolapsed cord	Rural	16	0
19	Home	0	Early neonatal death	Prolapsed cord	Rural	39	2
20	Home	0	Early neonatal death	Prolapsed cord	Rural	26	4
21	Home	4	Early neonatal death	Tetanus	Urban informal settlement	26	2
22	Hospital	0	Still birth	Preeclampsia	Rural	18	0
23	Hospital	0	Still birth	Preterm birth	Urban informal settlement	34	7
24	Hospital	0	Still birth	Obstructed labour	Rural	18	0
25	Hospital	0	Still birth	Malaria/Preterm birth	Urban informal settlement	31	1
26	Hospital	0	Still birth	Malaria /Preterm birth	Urban informal settlement	18	0
27	Hospital	0	Still birth	Not determined	Rural	22	0
28	Hospital	0	Early neonatal death	Fever/Malaria	Urban informal settlement	25	1
29	Hospital	0	Early neonatal death	Fever/Malaria	Urban informal settlement	38	3
30	Hospital	0	Early neonatal death	Prolonged labour	Rural	23	3
31	Hospital	0	Early neonatal death	Prolonged labour	Rural	39	8
32	Hospital	0	Early neonatal death	Mal presentation	Rural	37	10
33	Hospital	3	Early neonatal death	Obstructed labour	Urban informal settlement	17	0
34	Hospital	0	Early neonatal death	Not determined	Rural	26	1

Paper II

In our cohort with 819 live births, there were 27 infant deaths resulting in an infant mortality of 33 (95% CI: 22, 48) per 1,000 live births (figure 8). Of these deaths, 19 were neonatal [neonatal mortality: 23 (95% CI: 14 to 36) per 1,000 live births] and 8 post-neonatal [post-neonatal mortality: 10 (95% CI: 4 to 20) per 1,000 children alive after 28 days]. More than half of the neonatal deaths were in babies of mothers with a complicated delivery. Risk factors for neonatal deaths were similar to those for perinatal deaths in paper I. Immediate causes of post-neonatal deaths, identified via verbal autopsy included malaria (3), respiratory tract infections (3) and diarrhoea (1). The cause of death remained undetermined for one of the deaths.

Women who delivered at home had a tendency towards an increased experience of a neonatal death compared to women that delivered in a health facility, RR of 2.1 (95%CI: 0.8, 5.2). The risk of a neonatal death was higher for women in urban areas compared to those in rural areas [RR of 2.5 (95%CI: 1.0, 6.2)]. Infants whose mothers' had previously lost a child were more likely to die in the post-neonatal period compared to those whose mothers' had never lost a child [RR of 5.8; 95%CI: 1.1, 31.7)]. Hospitalization was also a significant predictor of post-neonatal mortality [RR: 11.2 (1.9 to 64.3)]. Women who said that they were infected with HIV had a 4.9 (95%CI: 0.7, 35.9) times higher risk of their infants dying compared to HIV-negative women (table 10). There was no significant association between infant mortality and previous child deaths, wealth, education or place of delivery.

Table 10: Sensitivity analysis for the association between self-reported HIV status and Infant mortality

Assumption	RR (95% CI)
Making no assumptions about self-reported HIV status	
HIV Positive	4.9 (0.7, 35.9)
Don't know	2.0 (0.4, 8.6)
Negative	1
Assuming that all those who did not know their status were HIV positive	
HIV Positive	2.0 (0.5, 8.9)
Negative	1
Assuming that all those who did not know their status were HIV Negative	
HIV Positive	2.7 (0.6, 12.0)
Negative	1

Paper III

In this paper, we compared vaccination coverage among infants whose mothers had secondary education to those whose mothers had only primary education. Data was collected from 696 women. Table 11 compares baseline characteristics of the 696 women from whom data was collected and the 167 that were not seen at 24 weeks, otherwise lost to follow up. Out of the 696 women, 176 (25%) had some secondary education while 305 (44%) had only primary education. For all vaccinations (BCG, polio 0-3 and DPT-HB-Hib1-3) women with some secondary education achieved higher vaccination coverage for their infants than women with a primary education. Vaccination coverage dropped steadily from BCG (the first vaccination) to DPT-HB-Hib 3, more so for those with only primary education. At 24 weeks, 177 (58%) of those with primary education had their infants vaccinated with DPT-HB-Hib 3 while 135 (77%) of those with a secondary education had their children vaccinated with DPT-HB-Hib 3.

Infants whose mothers had a secondary education were less likely to miss polio-0, polio-2, DPT-HB-Hib 2, polio-3, and DPT-HB-Hib 3 vaccines compared to infants whose mothers had received only primary education. After adjusting for potential confounders, infants of mothers having some secondary schooling were protected from missing the polio-2 vaccine compared to those whose mothers only had been to primary school (RR: 0.4, CI: 0.3-0.7). In addition infants whose mothers had received some secondary education were 50% less likely to miss DPT-HB-Hib 2 (RR: 0.5, CI: 0.3 – 0.8), Polio-3 (RR: 0.5, CI: 0.4 – 0.7), and DPT-HB-Hib 3(RR: 0.5, CI: 0.4 – 0.7).

At 24 weeks, 355 (51%) of the infants had received all the scheduled vaccinations (BCG, Polio 0-3, and DPT-HB-Hib 1-3). Out of the 176 infants whose mothers' had some secondary education, 115 (65%) were fully vaccinated at 24 weeks while 140 (46%) of those whose mothers only had a primary education were fully vaccinated. Other factors associated with a reduced risk of missing their vaccinations were delivery at a health facility (RR=0.8; 95%CI: 0.7, 1.0) and use of a mosquito net (RR=0.8; 95%CI: 0.7, 1.0). There was no association between vaccination status and wealth index.

Table 11: Characteristics of those contributing information for paper III and those lost to follow up at 24 weeks

Characteristic	Participants in study at 24 weeks N=696 Number (%)	Participants not seen at 24 weeks Number (%) N=167 Number (%)
Mother's age		
≤ 19	153 (22%)	42 (25%)
20-24	227 (33%)	60 (36%)
25-29	165 (24%)	39 (23%)
≥30	152 (22%)	26 (16%)
Marital Status		
Married	433 (62%)	94 (56%)
Cohabiting	206 (30%)	49 (29%)
Other (single, widowed, divorced, separated)	57 (8%)	24 (14%)
Religion		
Catholic	130 (19%)	28 (17%)
Protestant	314 (45%)	72 (43%)
Islam	228 (33%)	62 (37%)
Other	24 (4%)	5 (3%)
Wealth quintiles		
Poorest 20%	146 (21%)	28 (17%)
Middle 40%	280 (40%)	65 (39%)
Richest 40%	270 (39%)	74 (44%)
Residence		
Rural	554 (80%)	108 (65%)
Urban	142 (20%)	69 (35%)
Mothers education		
None	64 (9%)	17 (10%)
1- 4 years	124 (18%)	28 (17%)
5 - 7 years	305 (44%)	73 (44%)
8 - 11 years	176 (25%)	38 (23%)
12 or more years	27 (4%)	11 (7%)
Parity		
0	160 (23%)	59 (35%)
1—2	210 (30%)	51 (31%)
3—4	163 (23%)	36 (22%)
5 or more	163 (23%)	21 (13%)
Gender of infant*		
Girl	350 (50%)	36 (56%)
Boy	346 (50%)	28 (44%)
Place of delivery		
Home	302 (43%)	125 (75%)
Health facility	394 (57%)	42 (25%)
Use of mosquito net		
Yes	320 (46%)	31 (19%)
No	376 (54%)	136 (81%)

Paper IV

In this paper, we compared malaria prevalence for a subsample of 483 children in the cohort. The prevalence of *P. falciparum* malaria was 11% in the intervention area and 10% in the control areas. Infants in the intervention areas were 1.7 times as likely as those in the control areas to have malaria parasitaemia (RR 1.7; 95% CI: 0.9, 3.0). There was no association between exclusive breastfeeding in the first six months of life and malaria (prevalence ratio 1.3; 95% CI: 0.7, 2.2).

Out of 205 children that had received vitamin A supplementation according to the vaccination cards, 11 (5%) had positive blood slides for *P. falciparum* compared to 14% (40 out of 278) of the children that had not received Vitamin A supplementation. In a crude analysis, children who had not received vitamin A were more likely to have malaria parasitaemia than those who had received it (RR 2.7; 95% CI: 1.4, 5.1). The association between having received vitamin A and having malaria parasitaemia became stronger after controlling for use of bed nets, age of the infant and residence (RR 6.1; 95% CI: 2.1, 17.7).

The WLZ was 0.12, inter-quartile range (IQR): -0.81, 1.0 and standard deviation (SD) 1.3. Mean LAZ was -0.7 (IQR: -1.5 to 0.1, SD: 1.1) and the mean WAZ was -0.5 (IQR: -1.2 to 0.2, SD: 1.2) at 12 weeks. Further, 7% of the children were wasted, 11% were stunted and 9% were underweight. There was no association between LAZ and malaria parasitaemia. However, there was effect measure modification on both the additive and multiplicative scales between LAZ and vitamin A supplementation as indicated by a significant cross product term (P-value for cross product term was < 0.001). Among children who had been supplemented with vitamin A, every unit increase in LAZ score was associated a 50% reduced risk of malaria parasitaemia (RR 0.5; 95% CI: 0.4, 0.6). Increments in LAZ scores were not associated with a reduced risk of malaria parasitaemia among children who had not been supplemented with vitamin A (RR 1.0; 95% CI: 0.7, 1.4). These findings were independent of socio-economic status.

The excess risk of malaria attributable to stunting was substantially greater among those who had not been supplemented with Vitamin A; risk difference 38/1,000 (95%CI: 8/1,000, 68/1,000) than among those children who had received Vitamin A supplementation; risk difference -6/1,000 (95%CI -158/1,000, 146/1,000), P-value for homogeneity of risk differences = 0.013.

Differences between the children that were included and not included in the study

A lower proportion of mothers of the infants not included in this study were above 29 years of age, and on an average had fewer children compared to the mothers of those infants who were included the study. Mothers of the infants not included also had a somewhat higher level of education, higher socioeconomic status and more of them lived in urban areas (table 12). A lower proportion of the infants not included in this study had received vitamin A and relatively fewer slept under bed nets compared to those included in the study (table 13).

Table 12: Maternal characteristics of infants contributing information to paper IV and those not included in the study[a]

Characteristic	Sample included in study		Mothers of infants not included in study	
	Intervention group (n=256)	Control group (n = 227)	Intervention group (n=158)	Control group (n = 160)
Mother's age				
≤ 19	58 (23%)	44 (19%)	31 (20%)	45 (28%)
20-24	79 (31%)	67 (30%)	51 (32%)	62 (39%)
25-29	60 (23%)	54 (24%)	51 (32%)	27 (17%)
≥30	59 (23%)	62 (27%)	25 (16%)	26 (16%)
Mother's Education				
None	20 (8%)	30 (13%)	11 (7%)	10 (6%)
1- 4 years	48 (19%)	45 (20%)	38 (24%)	14 (9%)
5 - 7 years	121 (47%)	83 (37%)	71 (45%)	77 (48%)
8 - 11 years	60 (23%)	57 (25%)	30 (19%)	49 (31%)
12 or more years	7 (3%)	12 (5%)	8 (5%)	10 (6%)
Residence				
Urban	57 (22%)	34 (15%)	55 (35%)	31 (19%)
Rural	199 (78%)	193 (85%)	103 (65%)	129 (81%)
Marital Status				
Married	167 (65%)	152 (67%)	85 (54%)	90 (56%)
Cohabiting	72 (28%)	58 (26%)	51 (32%)	53 (33%)
Other*	17 (7%)	17 (7%)	22 (14%)	17 (11%)
Religion				
Catholic	49 (19%)	41 (18%)	29 (18%)	26 (16%)
Protestant	112 (44%)	98 (43%)	78 (49%)	75 (47%)
Islam	87 (34%)	79 (35%)	47 (29%)	55 (34%)
Other	8 (3%)	9 (4%)	4 (3)	4 (3%)
Household wealth index				
Poorest 20%	68 (27%)	39 (17%)	24 (15%)	26 (16%)
Middle 40%	113 (44%)	88 (39%)	64 (41%)	56 (35%)
Richest 40%	75 (29%)	100 (44%)	70 (44%)	78 (49%)
Antenatal care attendance				
No	80 (31%)	49 (22%)	43 (27%)	52 (32%)
Yes	176 (69%)	178 (78%)	115 (73%)	109 (68%)

a Mothers experiencing a perinatal death are excluded from this table

Table 13: Characteristics of infants contributing information to paper IV and those not included in the study[a]

Characteristic	Sample included in study		Sample not included in study	
	Intervention group (n=256)	Control group (n = 227)	Intervention group (n=158)	Control group (n = 160)
Number of siblings				
0	54 (21%)	53 (23%)	38 (24%)	50 (31%)
1	36 (14%)	29 (13%)	25 (16%)	34 (21%)
2	34 (13%)	33 (15%)	21 (13%)	31 (19%)
3	33 (13%)	26 (11%)	25 (16%)	16 (10%)
>= 4	99 (39%)	86 (38%)	48 (30%)	29 (18%)
Gender of infant				
Girl	133 (52%)	109 (48%)	67 (49%)	76 (55%)
Boy	123 (48%)	118 (52%)	71 (51%)	62 (45%)
Place of delivery				
Home	126 (49%)	84 (37%)	67 (42%)	47 (29%)
Hospital/Local maternity/clinic/TBA/other	130 (51%)	143 (63%)	91 (58%)	113 (71%)
Vitamin A supplementation				
No	151 (59%)	127 (56%)	122 (77%)	115 (72%)
Yes	105 (41%)	100 (44%)	36 (23%)	45 (28%)
Age of infant				
3-6 months	142 (55%)	135 (58%)		
7-12 months	114 (45%)	95 (42%)		
Slept under mosquito net				
Yes	108 (42%)	113 (50%)	69 (44%)	61 (38%)
No	148 (58%)	114 (50%)	89 (56%)	99 (62%)

a Perinatal deaths are excluded from this table

Discussion

This thesis presents the risks of stillbirths, early neonatal death, perinatal death, neonatal death and infant death in a cohort of mother-infant pairs in Mbale, Eastern Uganda. It explores several risk factors for these deaths. Also, it identifies potential interventions that could reduce infant morbidity and consequently mortality in Mbale. Specifically it has examined vaccination coverage and its association with maternal education, the association between vitamin A supplementation and malaria, and the association between exclusive breastfeeding promotion and malaria parasitaemia at 24 weeks after birth. But are these findings internally valid? Can they be generalized to other populations? This section will consider relevant methodological aspects of the study and discuss their major findings.

Methodological considerations

Reliability / precision

In this discussion, reliability is used synonymously with precision and it refers to the consistency of measurements across persons [75-77]. Through nondifferential misclassification, unreliable measures can hide true associations between exposures and outcomes [78]. Because mortality is a relatively rare outcome, the confidence intervals for our mortality risks are relatively wide. In the search for factors associated with mortality, we report no association between several variables and their corresponding outcomes. It is probable that some of variables could have had significant effects with a larger study. Papers III and IV had 80% power to detect a risk ratio of 0.5.

Of all variables measured in this study, anthropometric variables – especially length – have been singled out in literature as unreliable measures [79-81]. While standardized techniques of measuring anthropometry have been available for nearly three decades, length continues to be difficult to measure [82, 83]. Errors in length measurement may arise from ‘instrument error’ or ‘observer error’ [79]. The latter type is the most difficult to deal with as it involves

positioning the child while adjusting the instrument at the same time. Reliability of length measurements becomes even more questionable if the child is agitated. We assessed the reliability of both weight and length measurements in this study. Overall, the reliability coefficients for the anthropometric measurements in this thesis were all above the 90% threshold that is recommended in literature [80, 84-86]. The effect of nondifferential misclassification in anthropometric variables in this study is therefore likely to be small.

Internal validity

Three major threats to the internal validity of the findings reported here will be considered: 1) information bias, 2) selection bias and 3) confounding.

Information bias (misclassification bias)

During the design and conduct of this study, several steps were taken to reduce the likelihood of common forms of both differential and non-differential misclassification of exposures and outcomes. Measures taken to reduce misclassification include:

1) Training of data collectors on interviewing skills. Interviewers were encouraged to present themselves in a non-judgmental manner, ask the questions exactly as they were written in the questionnaire, maintain neutrality and to avoid leading the respondents towards particular answers.
2) All questionnaires were translated into Lumasaaba, the local language.
3) Questionnaires were pre-tested and then improved to minimize ambiguity and increase clarity of the questions.
4) Direct data entry into an electronic system (epihandy) in the field circumvented data entry errors. However, this system also delayed the correction of other types of data entry errors occurring in the field.

Recall bias is a common form of differential misclassification. For all the studies forming the basis of this thesis, recall bias is unlikely to have explained the reported findings because these were prospective studies; most exposures were measured before the outcomes. Therefore, the outcomes were unlikely to have influenced measurement of the exposures. To further reduce information bias in study behind paper III, measurement of the

outcome (vaccination status) was based on information recorded in the road to health child health cards as opposed to relying on mother's recall.

Great effort was taken to mask the data collectors to the intervention allocation. For instance data collection and peer counselling for exclusive breastfeeding were conducted on different days by different teams. However, this being a community behavioural intervention in which the participants could not be masked, the data collectors could not be fully masked. We can therefore not rule out that the data to some extent was collected differentially based on intervention allocation.

To reduce the number of data collection errors during measurement of the outcomes in papers I and II, a standard World Health Organization (WHO) verbal autopsy questionnaire that had been validated in Uganda was used to collect information and a standard algorithm used to determine the likely cause of death [73]. The verbal autopsy questionnaire had an open-ended section for reporting verbatim as well as a closed-ended section with filter questions. While verbal autopsies have been shown to have higher sensitivity than hospital records in some settings [87], less than perfect specificity scores may result in misclassification of deaths and causes of deaths [88]. Nearly half of the births in our cohort occurred at home and most of the deaths also occurred at home. Even in hospital settings, the distinction between early neonatal deaths and stillbirths is difficult. The fine line between stillbirths and early neonatal deaths is amplified in deliveries that occur at home where there are no skilled health workers who can identify faint signs of life. It is probable that some early neonatal deaths could have been misclassified as stillbirths and vice versa. But, given that the proportion of stillbirths and early neonatal deaths in our study is in line with WHO estimates for East Africa, the extent of this misclassification is likely to have been moderate.

Paper IV required collection of blood specimens to examinemj for malaria parasites. A trained laboratory technician and microscopist blinded to exposure status, collected and examined the specimens to reduce ascertainment bias. A key question in this paper was the effect of peer counseling for exclusive breastfeeding on malaria prevalence among infants. This exposure was randomly allocated with half the clusters receiving the exposure and the other half receiving the standard of care provided by the government. Diagnosis of malaria

in this study was based on microscopy, which has been shown to have a sensitivity of 30.5% and a specificity of 100% in comparison to PCR [89]. Despite the fact that the microscopist in this study was well trained, the low sensitivity of microscopy may have reduced the apparent prevalence and thereby the precision of the associations.

Selection bias

There are two potential sources of selection bias: selection of respondents into the study and loss of respondents to follow up.

Selection of participants into the study

Pregnant women included in the study were identified by study recruiters before being before approached by data collectors. Recruiters were local women from the study areas, often leaders in their communities with good knowledge of the local geography and families within the study clusters. Recruiters made several rounds in their villages to identify pregnant women. These recruitment rounds coupled with other community visits in their role as community leaders created an excellent opportunity to identifying pregnant women in the clusters. In addition, the communities were very close knit and pregnancies as well as births are major community events. It is unlikely that a visible pregnancy or a birth would go unnoticed.

Out of the 886 women who were approached to participate in the study by the recruiters, 875 consented to participate resulting an extremely high response proportion of 99%. Of these, 12 (1%) women did not meet the eligibility criteria of the PROMISE-EBF trial and were excluded. Reasons for exclusion were unrelated to exposures and outcomes in this thesis except for two women ineligible because they did not intend to breastfeed their infants. They were accordingly not included in this cohort study. It may be argued that some of these were HIV positive mothers who had chosen replacement feeding and that there is an association between HIV and infant mortality. If valid, these two arguments would constitute a selection bias, which is that, participants who were not going to receive the exposure but who were more likely to get the outcome where excluded from the study. In

sensitivity analyses assuming the worst case but highly unlikely scenarios in which both mothers who did not participate because they had no intention of breastfeeding their babies experienced a perinatal or an infant death, perinatal mortality, infant mortality and RR estimates would be only marginally affected by their inclusion in the study cohort.

Four-hundred-and-eighty-three infants out of 801 alive after day 7 were included in the study forming the basis for paper IV. Though there were some differences between those included in the study and those not, these differences were unlikely to have substantially affected the reported prevalence ratios and the conclusions of the study. This is because most of the differences were among those variables that were not strongly associated with malaria parasitaemia (with the exception of vitamin A supplementation, residence and use of a bed net). Sensitivity analyses in which PRs were calculated for the association between vitamin A supplementation, residence and use of a bed net in reconstructed cohorts that included children non included in the study, showed that each of these variables still had an association with malaria parasitaemia for a fairly wide range of malaria prevalence estimates (6% to 16%) in the children that were not included in the study.

Loss to follow up

For papers I and II, loss to follow up was minimal. It is unlikely that selection bias resulting from this loss could explain our findings. In paper III, 19% of the mother-infant pairs eligible after delivery were not seen. However, there was no significant difference between those lost to follow-up and those that remained in the study with regard to education level (table 11).

Confounding

The main method used to control for confounding was multivariable analysis. Multiple sets of confounders were considered and the findings were largely robust to the different sets. We did, however, not have data enabling us to adjust for distance to the health centres. Although this is a weakness of the study, it is unlikely to have caused substantial

confounding of the results as all the study areas were within 30 minutes by car to a local health centre.

Discussion of the main findings

Using a cohort study design, the studies forming the basis for this thesis sought to answer the following key questions: What are the perinatal and infant mortality risks in Mbale, Eastern Uganda? What are the associated risk factors? Why does vaccination, which lowers infant mortality, have low coverage? Is there an association between exclusive breastfeeding and malaria prevalence? Is there an association between vitamin A supplementation and malaria? This section reconsiders each of these questions in light of the findings in this thesis and findings from studies elsewhere.

What is the perinatal and infant mortality risk in Mbale Eastern Uganda?

The perinatal mortality risk was 41 per 1,000 pregnancies, with a stillbirth risk of 19 per 1,000 pregnancies and an early neonatal death risk 22 per 1,000 live births. Consistent with other literature, mortality risks were highest around the time of birth and gradually tapered off after the first day of life [1]. Hence the infant mortality risk (33/1,000 live births), neonatal mortality risk (23/1,000 live births) and post-neonatal mortality risk (10/1,000 live births) were lower than the perinatal mortality risk.

Our estimates of perinatal mortality risk are comparable to the 2001-2005 DHS estimate of 36/1,000 pregnancies in Uganda [5, 24]. The infant mortality estimate in this study is, on the other hand, considerably lower than the 2001-2005 DHS estimate for Uganda and for the Eastern Region (75/1,000 live births and 70/1,000 live births respectively) [28]. It is possible that mortality was reduced by study activities such as transporting ill children to hospitals and ensuring that they received the prescribed treatment. For example, in the malaria study, children were tested for malaria and those with positive blood slides received

a full course of treatment from the study team. In addition, several ill children were transported from their homes to Mbale Regional Referral Hospital throughout the course of the study. Hospitalized infants received free drugs from the study. These study activities could have contributed to a reduction in mortality after the perinatal period.

What factors are associated with mortality?

There was a particularly strong association between the use of bed nets and perinatal mortality. Thus, all stillbirths and early neonatal deaths were recorded among women who did not sleep under mosquito bed nets. The risk of perinatal death associated with not sleeping under a bed net was particularly high among nulliparous women. It is generally accepted that insecticide treated bed nets reduce malaria transmission and decrease mortality [90] but to-date, evidence on the impact of bed nets on perinatal mortality has been mixed [12]. Malaria in pregnancy damages the foetal placental unit and it has been shown to lower the mean birth weight by an average of approximately 150 g in primigravidae [91, 92]. Low birth weight in turn, predisposes to perinatal mortality [93]. Similar to our findings, a systematic review of five randomized trials, four of which were from Sub-Saharan Africa, concluded that mosquito bed nets reduced foetal loss in the first to fourth pregnancy [92, 94-97]. On the other hand, a Kenyan trial in which a rural population was randomized to receive or not to receive insecticide-treated bed-nets found no difference in perinatal death risk between the intervention and control arms.

In a review of 40 DHSs with complete data, almost half of all the perinatal deaths occurred after a home delivery [17]. This proportion is likely to be higher if considering the number of deliveries that started at home but ended up as a perinatal death in a clinic. In the current study, home delivery was an important risk factor for stillbirths, early neonatal deaths and accordingly perinatal deaths. Women who delivered at home were 4 times more likely to have a stillbirth and 3 times more likely to have an early neonatal death. This finding could be an underestimate because some of the women who lost their babies in hospital initially tried to deliver at home and only went to the hospital when it was too late to save the child. The finding of an increased likelihood of death associated with home deliveries is consistent with findings elsewhere [4, 98]. Nulliparity increased the risk of perinatal deaths 3-fold, most of this being explained by the increase in the stillbirth risk.

There was a substantially higher risk of stillbirth, early neonatal and neonatal death in urban slums than in rural areas. A study in the urban slums of Nairobi found very high mortality, particularly in the perinatal period [99]. It is interesting to note that antenatal care attendance did not seem to significantly influence perinatal mortality, while facility delivery was associated with a substantially lower perinatal death risk. Antenatal care is considered to be one of the four main pillars of safe motherhood [100]. But evidence supporting a specific impact of antenatal care on perinatal mortality is weak. A systematic review of randomized trials that compared standard to alternative models of antenatal care found no effect on perinatal mortality risks (OR 1.06; 95% CI: 0.82, 1.36) [101]. Our findings add to the growing body of evidence that the strategy of screening high risk pregnancies during antenatal care is of limited benefit in preventing perinatal deaths. HIV-positive women tended to be more likely to lose their infants compared to HIV-negative women. Also, infant deaths were higher among children that had had at least one hospitalization. These findings are consistent with findings elsewhere [32, 33, 36] and lend credibility to our findings.

In conclusion, factors associated with perinatal infant death included home delivery, absence of bed nets, nulliparity, residence in rural areas or urban slums and hospitalization.

Why does vaccination, an intervention with good evidence for lowering mortality have low coverage?

Paper III reports that most of the women (71%) had either no education or had been educated up to the primary level only. There was a strong association between mothers having had secondary as compared to only primary education and their children' vaccination status. Thus, at 24 weeks, only 46% of the mothers with only a primary school education had their children fully vaccinated compared to 65% of those with secondary school education. Infants whose mothers' had some secondary education were on an average 50% less likely to miss Polio-2, DPT-HB-Hib 2, Polio-3 and DPT-HB-Hib 3 vaccinations. This relationship between vaccination and education grew stronger with time

from BCG to DPT-HB-Hib 3. Vaccination coverage was highest with BCG, the first vaccination, and declined steadily with subsequent vaccinations and child age. A similar drop is seen in national estimates [28, 102]. In the studies behind this thesis, the decline was greatest for those with the least education (0-4 years of education).

Overall, 63% of the children in this study received DPT-HB-Hib 3. This is consistent with the national estimates (63% - 68%) in 2007 [103]. Several studies have shown that maternal education is associated with better utilization of health care services [20, 49, 104-107]. Findings presented in this thesis are consistent with this notion. They show that mothers with some secondary schooling made better use of the otherwise free vaccination programme. Studies elsewhere have found that levels of knowledge and use of vaccination services are greater for women with at least some secondary schooling [107-110].

In addition to secondary education of the mother, other factors that were associated with reduced risks of missed vaccinations were delivery at a hospital or health centre and use of mosquito bed nets. A study in Papua New Guinea reported that 70% of study participants learnt about when to take their children for vaccination from the local maternal and child health (MCH) staff [104]. This could be an important reason for why women who delivered at health facilities were more likely to have their children fully vaccinated.

Wealth was not associated with childhood vaccination in this cohort. Though this finding is similar to findings in the Philippines [109] and Guinea-Conakry [111] it contrasts findings in Ghana [112]. Moreover, a systematic review of recent DHS data from 54 countries found that in comparison to other health care services, vaccination services had the smallest coverage gap between the poorest and richest quintiles of the population [40]. The rather precise estimate of family wealth not being associated with the risk of missing childhood vaccination represents a strong support for The Ugandan Government's policy of providing childhood vaccination services at no direct cost.

In summary, our findings and those from other studies indicate that low maternal education and delivering at home may contribute to low vaccination coverage, despite the fact that vaccination is an intervention with good evidence for lowering mortality.

Is there an association between promotion of exclusive breastfeeding and malaria prevalence?

In our study, peer counseling for exclusive breastfeeding did not reduce the prevalence of malaria parasitaemia among infants. Similarly, exclusive breastfeeding for the first three months did not have a significant effect on malaria parasitaemia. This is consistent with findings from another Ugandan cohort that found no association between breastfeeding and malaria parasitaemina among HIV-unexposed infants [57]. However, a cross-sectional study among Nigerian children found a significantly higher prevalence of malaria parasitaemia among exclusively breastfed children [113]. Conversely, a study among Malawian children found that children who were not exclusively breastfed had a marginally increased risk of malaria episodes [56]. Based on the findings presented above, we conclude that it is unlikely that exclusive breastfeeding reduces the prevalence of malaria parasitaemia among healthy infants.

Is there an association between vitamin A supplementation and malaria, one of the top five causes of mortality among children?

There was a strong association between vitamin A supplementation and malaria parasitaemia. Children aged 3-12 months who had not received Vitamin A supplements were about six times more likely to have *P. falciparum* malaria than those who had received them. In Uganda, the national expanded programme on immunization recommends that children between six and twelve months of age receive 100,000 IU of vitamin A while children less than six months whose mothers' did not receive postpartum vitamin A supplementation or who are not breastfeeding receive 50,000 IU. Vitamin A is necessary for normal immune function and although earlier animal studies showed vitamin A deficiency to be protective, it is now hypothesized that vitamin A could protect against malaria. Cross-sectional studies in humans have shown vitamin A to be associated with malaria, but causality has been uncertain [114]. To date, there are only two prospective studies that have studied the relationship between vitamin A and malaria. A double blind placebo-controlled trial in Papua New Guinea reported that vitamin A supplementation reduced the frequency

of *P. falciparum* malaria by 30% among preschool children [61]. A second clinical trial in Ghana found no association between vitamin A supplementation and morbidity due to malaria [63]. However, the Ghanian study did not have sufficient power to detect a difference of less than 70% between the two groups [115]. The effect of vitamin A supplementation in this study is in line with findings from the Papua New Guinea study. It is hypothesized that vitamin A acts by increasing phagocytosis of parasitized erythrocytes as well as reducing the proinflammatory response to the malaria infection [59]. Though the evidence seems to be leaning towards an association between Vitamin A supplementation and protection against malaria, it is still too early to tell with reasonable certainty whether in fact, such an association exists. More research is necessary to explore the role of vitamin A supplementation in malaria endemic areas as an adjunct malaria prevention strategy.

External validity (generalizability)

The findings in this thesis can be extrapolated to regions with similar socio-demographic characteristics because nearly all children in the study villages were recruited into the study. Generalizability in this study could be limited by the fact that clusters included in this study were close to main roads and therefore had better access to health facilities compared to some of the excluded clusters.

Conclusions

The studies behind this thesis show that perinatal and infant mortality is high in Mbale, Eastern Uganda. They explored and identified several risk factors for mortality and show that they are multiple and complex. Whereas some factors such as exposure to HIV appeared to have an effect throughout infancy, the effect of others, such as delivery at home was limited to the perinatal period. The multifaceted nature of the risk factors for infant death no doubt calls for multipronged, carefully developed and planned interventions and mindfully constructed intervention strategies. This is particularly important when even those interventions with good evidence for lowering mortality such as childhood vaccination have less than universal coverage. Our studies have shown that the suboptimal vaccination coverage is associated with low maternal education, and that children of mothers with secondary education were more likely to be vaccinated than babies of mothers with only primary education. The studies examined two interventions that hitherto had limited evidence for reducing the occurrence of malaria. Whereas there was no association between exclusive breastfeeding promotion and malaria, infants that had been supplemented with Vitamin A were less likely to have malaria parasitaemia.

Recommendations

In this study, several factors acted to predict or reduce perinatal mortality and infant morbidity or mortality. Whereas some of these factors were active at specific points in time, others appeared to envelope the entire infancy period. It is clear that reductions in perinatal and infant mortality will require multiple interventions, perhaps covering the entire lifespan (a continuum of care) [7] but being delivered at strategic points in time. The findings presented in the thesis have the following research and policy implications:

A. Policy implications

In order to reduce perinatal, infant and thereby child mortality, there is a need to:

1. target efforts to substantially increase the number of deliveries taking place in health facilities, in order to reduce the unacceptably high perinatal mortality
2. continue advocacy to ensure that pregnant women, especially young and nulliparous women, have access to and use adequate delivery facilities and bed nets
3. recognize that perinatal mortality is a problem in urban slums and that there is a need to increase access to maternal and child health services in these areas
4. target resources for routine childhood vaccination at women with low formal education
5. establish a national vital registration system so that improvements can be recorded and, where possible ascribed to specific or composite interventions

B. Further research

From these studies, there are some interesting associations that merit further investigations:

1. to measure the degree to which increasing bed net usage and health facility delivery will reduce perinatal mortality, especially among nulliparous women
2. to evaluate the role of vitamin A supplementation as a low cost protective intervention against malaria

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