The Contribution of the Matlab Safe Motherhood Programme to Perinatal Mortality in Bangladesh

Suchismita Roy

Thesis submitted in accordance with the requirements
for the degree of Doctor of Philosophy
University of London
2015

Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Funding by: Aga Khan Foundation International Scholarship Programme
Research group affiliation: Department of Infectious Disease Epidemiology,
Faculty of Epidemiology and Population Health

Declaration by Candidate

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I have read and understood the School's definition and policy on the use of third parties (either paid or unpaid) who have contributed to the preparation of this thesis by providing copy editing and, or, proof reading services. I declare that no changes to the intellectual content or substance of this thesis were made as a result of this advice, and, that I have fully acknowledged all such contributions.

Signed: ..... Date: .....

Name: SUCHISMITA ROY

Student Identification Number: lsh 240715

For

my parents

Abstract

Current knowledge on mortality rates for stillbirths, early and late neonatal deaths and perinatal deaths in South Asia is dependent on statistically modelled estimates. There is very little information on the contribution of intrapartum complications and preterm births to stillbirths and mortality in the first month of life in rural Bangladesh.

First, I systematically reviewed studies and performed a meta-analysis to obtain reliable estimates for the above mentioned mortality rates in South Asia. Second, I examined the association between the presence of a programme increasing professional birth attendance, facility delivery and emergency care access and reductions in mortality levels in a retrospective cohort in Matlab, Bangladesh. Third, I examined the determinants of preterm birth and whether this programme was associated with preterm prevalence reduction. Fourth, I explored the contributions of intrapartum complications and preterm births to perinatal deaths in this cohort.

The systematic review found that perinatal mortality levels were high in Afghanistan, Bangladesh, India, Nepal and Pakistan and low in Sri Lanka and Maldives. Stillbirths were underreported. The cohort study found that the presence of the Matlab Safe Motherhood Programme was strongly associated with greatly reduced stillbirths and very early (Day 0-2) neonatal deaths. This programme did not contribute to the neonatal mortality decline after Day 3 or to preterm birth trends. Preterm birth accounted for a third of stillbirths and deaths in the neonatal period. Against expectations, only two intrapartum complications (haemorrhage and multiple pregnancy) was associated with increased odds of perinatal mortality. Dystocia and hypertensive diseases of pregnancy showed no effect.

Stillbirth and very early neonatal death reduction in Bangladesh can be achieved by improving access to facilities and emergency care. Focused antenatal care for women might possibly reduce preterm births but further research is needed to understand how the prevalence of preterm birth can be reduced.

(300 words)

Acknowledgements

I would like to thank my supervisor, Professor Carine Ronsmans, for her active guidance, support, constructive comments and patience during the course of my PhD.

I am very grateful to staff at the school who helped me throughout the long and demanding PhD process: Lisa Hurt, on my advisory committee, for her help and support; Ruth Farmer and Cono Ariti, my current and previous statistical supervisors for their support; Prof. Oona Campbell and Dr. Veronique Filippi for their encouragement through the demanding process of the PhD and special thanks to Jenny Fleming, my research degree administrator for always being available for me.

Very big thanks to my PhD field supervisor, Dr. Anisur Rahman for his unending patience and mentorship during and after the fieldwork in Matlab, Bangladesh. The PhD would not have been possible without the toil and energy of the community health workers, nurse-midwives and doctors of ICDDR,B. Special thanks to my ICDDR, B colleagues and friends Dr. Huda and Dr. Pervin for their unflagging support. Thanks also to Dr. Riechenbach, Dr. Koblinsky, Dr. Chowdhury and Dr. Moran for their support in facilitating data access and to Mr Dasgupta for his help in obtaining and managing the Matlab data files. Thanks to Dr. Alam and Mr. Saha for their help with the Health and Demographic Surveillance System data.

My grateful thanks to the Aga Khan Foundation International Scholarship Programme for providing the funding for my PhD. I would also like to thank the Allan and Nesta Ferguson Foundation and the Charles Wallace Trust Bangladesh for their bursaries that helped with miscellaneous costs. I thank Dr. Julia Mortimer for her professional proof reading. I acknowledge that consent was taken from all the people who are pictured in the images in the thesis. The copyrights of any images not taken by me belong to the accredited sources.

I would also like to thank Mr. Tim Satchwell and Mr. Michael Massey (LSHTM IT department), my physiotherapist Dr. Mark Rainford and student counsellor Dr. Emma Nabavian for their help in helping me manage the repetitive strain injury (RSI) that I developed.

Thank you to my LSHTM friends for their company and active support throughout the tough times. Linda, Lori, Pippa, Nick and Susie were my PhD cheerleaders. Yemi, Ronnie and Jenny

provided the physical and virtual high-fives. I specially thank Chris, Clara and Francesca for reading and commenting on various chapters, warts and all, and cheering me on throughout the journey.

Thank you to Mani, my life partner who weathered all the difficult times with me in this journey and gave me fresh hope and energy to battle another day. Lastly, thank you to my parents for their love and support during my PhD. Without their encouragement and belief in me, this PhD would not have been undertaken.

Table of contents

Table of Contents

Table of Contents

List of tables

List of Tables

List of Tables

List of Tables

List of figures

List of Abbreviations and Acronyms

ANC- Antenatal care

AIDS- Acquired Immune Deficiency Syndrome

BDHS- Bangladesh Demographic and Health Survey

BEmOC- Basic Emergency Obstetric Care

BMI- Basal Metabolic Rate

BMMS- Bangladesh Maternal Mortality Survey

BRAC- Bangladesh Rural Advancement Committee

CEmOC- Comprehensive Emergency Obstetric Care

CHRW- Community Health Research Worker

CHW- Community Health Worker

CID- Current Identification Number

CPD- Cephalo Pelvic Disproportion

C-section or C/S- Caesarean Section

DCP- Disease Control Priorities

DHS-Demographic and Health Survey

EmOC- Emergency Obstetric Care

END- Early neonatal death

ENDR- Early Neonatal Death Rate

ENMR- Early Neonatal Mortality Rate

FWV- Female Welfare Visitor

FTP- Full Term Pregnancy

GA- gestational age

GHWA- Global Health Workforce Alliance

HDSS- Health and Demographic Surveillance System

HIC- High Income Country

HIV- Human Immunodeficiency Virus

H/O- History of

ICD-10-International Classification of Diseases-Tenth Revision

ICDDR,B- International Centre for Diarrhoeal Disease Research, Bangladesh

ID- Identification

IUD- Intrauterine Death

IUGR- Intrauterine Growth Retardation

KMC- Kangaroo Mother Care

LBW-Low Birth Weight

LFPV-Lady family Planning Visitor

LIC- Low Income Country

List of Main Abbreviations and Acronyms

LMIC-Low and Middle Income Country

LMP- Last Menstrual Period

LND-Late Neonatal Death

LNDR- Late Neonatal Death Rate

LNMR- Late Neonatal Mortality Rate

MHRC-Matlab Health Research Centre

MNCH-Maternal and Neonatal Child Health

MOHP- Ministry of Health and Population

NFHS- National Family Health Survey

NGO- Non Government Organization

NIPS- National Institute of Population Studies

NOS-Not otherwise specified

NR- Not Reported

OR-Odds Ratio

PAR- Population Attributable Risk

PI-Pregnancy Identification

PiH- Pregnancy Induced Hypertension

PPH- Post Partum Haemorrhage

PND-Perinatal Death

PNDR- Perinatal Death Rate

PNMR- Perinatal Mortality Rate

pPROM- preterm Pre-labour Rupture of Membranes

PRISMA- Preferred Reporting Items for Systematic reviews and Meta-analyses

RCOG- Royal College of Obstetricians and Gynaecologists

RCT- Randomized Control Trial

RID- Research Identification Number

RR- Relative Risk

SB-Stillbirth

SBA-Skilled Birth Attendance

SBR- Stillbirth Rate

SES-Socioeconomic Status

SL NO- Serial No

STI-Sexually Transmitted Diseases

TBA- Traditional Birth Attendant

THC- Thana Health Complex

UNFPA- United Nations Population Fund Agency

UTI-Urinary Tract Infection

VVF- Vesico Vaginal Fistula

List of Main Abbreviations and Acronyms

WHO- World Health Organization

Chapter 1. Preface

The knowledge on mortality rates for stillbirths, early and late neonatal deaths and perinatal deaths in South Asia is currently based on statistically modelled estimates. Information is scarce on the contribution of intrapartum complications and preterm births to stillbirths and to mortality during the first month of life in rural Bangladesh. In this thesis, a systematic review of published studies provides information on the levels of above-mentioned mortality rates in eight South Asian countries (Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka and Maldives). This thesis explores the contribution, if any, of a maternal, neonatal and child health programme (the Matlab Safe Motherhood Programme) to reductions in the levels of stillbirths, early neonatal deaths, late neonatal deaths and preterm births in rural Matlab in Bangladesh.

Matlab is divided into two areas, the Government service area and the ICDDR,B[1] service area which are roughly similar in area, population and socio-demographic characteristics. The Government service area is serviced by government birthing facilities while the ICDDR,B service area has a Matlab Safe Motherhood Programme which has established four delivery sub-centres and a hospital in addition to the government birthing facilities. Details of the Matlab and its Safe Motherhood Programme are elaborated in Chapter 3.

1.1 Structure of the thesis

The thesis begins with general background (Chapter 2) providing pertinent information on the research topic. The background chapter describes definitions encountered in the thesis and what is currently known about the global burden of stillbirths, early and late neonatal deaths and preterm deaths with special reference to South Asia. This is followed by a description of the issues involved in defining and measuring these types of mortalities and the risk factors that predispose towards these deaths. A conceptual framework is presented which postulates the links of these deaths to proximal and distal determinants. Complications during labour and delivery are presented and this is followed by their relationship with stillbirth, early neonatal and late neonatal mortality and the timing and relative burden of these mortality outcomes.

[1] ICDDR,B- International Centre for Diarrhoeal Disease Research, Bangladesh. It is an international health research organisation located in Bangladesh conducting public health and clinical research into maternal, neonatal and child health, diarrhoeal diseases, vaccines and translating research to policy and advocacy.

The chapter concludes with the rationale for this study which explores the contribution of this work to the body of current knowledge.

Chapter 3 describes a systematic review of published studies conducted to calculate empirical rates for stillbirths, early neonatal deaths, late neonatal deaths and perinatal death rates for South Asia and its constituent countries.

Chapter 4 describes a cohort study of the contribution of the Matlab Safe Motherhood Programme to changes in the levels and trends of mortality rates for stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths. The chapter begins with background information on the programme, study area, its health facilities and its surveillance system. It then describes the background characteristics of two populations in Matlab, one with and one without the Matlab Safe Motherhood Programme. The trends in mortality rates over the study period are presented first followed by findings from the logistic regression analysis exploring the association between socio-demographic characteristics and each of the mortality outcomes. Any differences in mortality rates over time in the two areas are examined.

Chapter 5 explores the determinants of preterm births in the Matlab study area. It also investigates the strength of association between gestational age and stillbirths, early and late neonatal deaths and the contribution of preterm births to these mortality outcomes in the study area.

Chapter 6 explores the strength of association of effect of intrapartum (labour/delivery) complications on perinatal mortality in women in Matlab.

The thesis ends with Chapter 7, which provides an overall discussion and conclusion to the body of work.

1.2 Summary of the thesis objectives

The overall aim of this study is to investigate the contribution of the Matlab Safe Motherhood Programme to reductions in stillbirths, early and late neonatal mortality and preterm births in a rural area of Bangladesh. A summary of the thesis objectives is shown in Table 1.1.

Table 1.1: List of thesis objectives and their location in the thesis where these are presented and discussed.

Overall Objective	**Specific Objectives**	**Where presented**
1. To systematically review studies in order to obtain reliable estimates for the rates of stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths in South Asia	1.1 To obtain summary estimates for the afore-mentioned mortality rates by calculating rates directly from data in published population-based studies for the South Asia region and at national levels for the 8 constituent countries (Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka and Maldives)	Chapter 3. Systematic review mortality rates by mortality outcome type (section 3.4.4)
	1.2 To compare the summary estimates obtained in the review with estimates available in the current literature.	Chapter 3. Summary estimates in review compared to estimates in the literature (section 3.4.7)
	1.3 To obtain the ratio of rates of stillbirths to early neonatal deaths at the regional and national level for each of the eight countries of South Asia and for the whole of South Asia.	Chapter 3. Ratios of stillbirth rate to early neonatal mortality rate (section 3.4.8)
2. To examine the contribution of the Matlab Safe Motherhood Programme to the levels and trends in mortality for stillbirths, early neonatal deaths, early neonatal deaths disaggregated by day since birth and late neonatal deaths in two areas, one with and one without the Programme, in a rural cohort in Matlab, Bangladesh.	2.1 To examine the levels and trends in the rates of stillbirths, early neonatal deaths, early neonatal deaths disaggregated by day since birth and late neonatal deaths in two areas of Matlab, Bangladesh during 1987-2009.	Chapter 4. Trends in mortality outcomes (section 4.4.8).
	2.2 To examine the levels and trends in uptake of delivery care in the two areas of Matlab by: i. Type of birth attendant ii. Place of delivery iii. Mode of delivery.	Chapter 4. Uptake in Professional Delivery Care (section 4.4.5)
	2.3 To examine the socio-demographic determinants of stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths.	Chapter 4. Trends in mortality outcomes (section 4.4.8)
	2.4 To examine if there are any differences in mortality rates over time in the two areas and if so, whether the differences are explained by the socio-demographic changes taking place in Matlab over the study period .	Chapter 4. Time Trends by Area (section 4.4.9)

Table 1.1(continued).

Overall Objective	Specific Objectives	Where presented
3. The overall objective is to examine the contribution of preterm births to stillbirths and neonatal deaths in a rural cohort in Matlab, Bangladesh during 2005-2009.	3.1 To examine the distribution of gestational age at birth and the distribution of preterm births in a rural cohort in Matlab, Bangladesh.	Chapter 5. Description of study sample and Prevalence of preterm births (Sections 5.4.1 and 5.4.2)
	3.2 To examine the socio-demographic determinants of preterm births in Matlab.	Chapter 5. Association between socio-demographic characteristics and preterm births (Section 5.4.4)
	3.3 To examine the association between gestational age and stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths.	Chapter 5. Association between gestational age and mortality (Section 5.4.6)
	3.4 To examine if there are any differences in preterm birth rates in the two areas over time and if so, whether the differences are explained by the socio-demographic changes taking place in Matlab over the study period.	Chapter 5. Association between socio-demographic characteristics and preterm births (Section 5.4.4)
	3.5 To measure the contribution of preterm births to stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths by calculating the population attributable risk percentage of preterm births for these mortality outcomes.	Chapter 5. Percentage of mortality outcomes attributable to preterm births in Matlab (Section 5.4.6)
4. To examine the contribution of intrapartum complications to perinatal deaths in a rural cohort in Matlab, Bangladesh.	4.1 To examine perinatal mortality, socio-demographic characteristics and length of gestation by highest level of care accessed in a cohort of women in Matlab, Bangladesh	Chapter 6. Description of sample (Section 6.4.1)
	4.2 To examine perinatal mortality, delivery location and socio-demographic characteristics by whether or not data on intrapartum complications are available in women who deliver at health facilities.	Chapter 6. Results related to intrapartum complications (Section 6.4.2)
	4.3 To examine the prevalence of intrapartum complications in women delivering at health facilities.	Chapter 6. Results related to intrapartum complications (Section 6.4.2)
	4.4 To examine the prevalence of intrapartum complications by delivery location, socio-demographic characteristics and preterm gestation in births for which any intrapartum complication was present or absent.	Chapter 6. Results related to intrapartum complications (Section 6.4.2)
	4.5 To examine the strength of association between intrapartum complications and perinatal deaths in women delivering at health facilities.	Chapter 6. Results related to intrapartum complications (Section 6.4.2)

1.3 Study type

This thesis employs a multi-methods approach. Secondary analysis of data was used to obtain results for the majority of the thesis chapters. Chapter 3 involves the use of a systematic review and meta-analysis. Chapter 4, 5 and 6 are the secondary analyses of socio-demographic data, newborn mortality data from a retrospective cohort (1987-2009) collected by ICDDR,B's Matlab Health and Demographic Surveillance System (HDSS)and intrapartum complication data from a previous Matlab study (Matlab Maternal Morbidity Study) of a retrospective cohort (2007-2008) Details on the data used are given separately in these chapters.

1.4 Student's role in the study and background

Student's role-

I formulated the research questions for the study under guidance of my supervisor. I also liased with ICDDR,B colleagues in Dhaka and Matlab to ensure data availability and permission for field visits and performed all analyses and interpretation under guidance of my supervisor and statistical advisor when necessary. A large proportion of the time of the PhD was spent in liaising with Bangladesh colleagues as information was sourced from different sources (Matlab socio-demographic records, Matlab birth records, Matlab Morbidity Study) with which were in some cases partially complete for the time periods under study. Hence it was necessary to limit study periods to years in which data were available. I visited Dhaka and Matlab two times in the course of the PhD, and met and worked with data management officers, research investigators, heads of departments and hospital personnel to collect, amend and harmonize data and understand the background context of the data. Preparation of the data for analyses was complicated and time-consuming. For example, data coding for variables (e.g. birth attendant, place of delivery) changed when data was available over long periods of time (1987-2009) and required harmonisation and frequent communication. Extraction of information was often convoluted (e.g. gravidity and parity data were obtained from combinations of: number of sons dead/alive, number of daughters dead/alive, number of miscarriages and number of stillbirths). Identification numbers of women on admission data from Matlab hospital and sub-centre admission registers did not link with demographic records and so I used statistical methods of linking based on probability of a true match by STATA 'reclink' function. For my chapter on intrapartum complications, I required diagnoses from the hospital admission registers. However the available information on intrapartum complications in admission records datasets had not been updated using the more complete diagnoses in the

treatment records and so I abandoned this exercise. Intrapartum complication data was finally obtained from another study (Matlab Morbidity Study) and also required extensive communication to prepare for analysis.

Background-

I am Bengali and a Bangladeshi citizen fluent in the local language and I closely understand the culture, cultural barriers, issues of stigma and health seeking behaviour of the Matlab villagers as well as those of community health workers in Matlab. I obtained my medical degree from a tertiary level teaching hospital in Dhaka, Bangladesh. Following this, I worked in public health research for two years in projects taking place in Matlab and other rural areas conducted by ICDDR,B in Bangladesh. I have a thorough understanding of the workings of public and private rural hospitals and delivery centres, the Matlab research hospital and subcentres, as well as of the overall health governance and policy in Bangladesh.

1.5 Timeline of the PhD

A timeline depicting major events in the course of the PhD is shown in Figure 1.1.

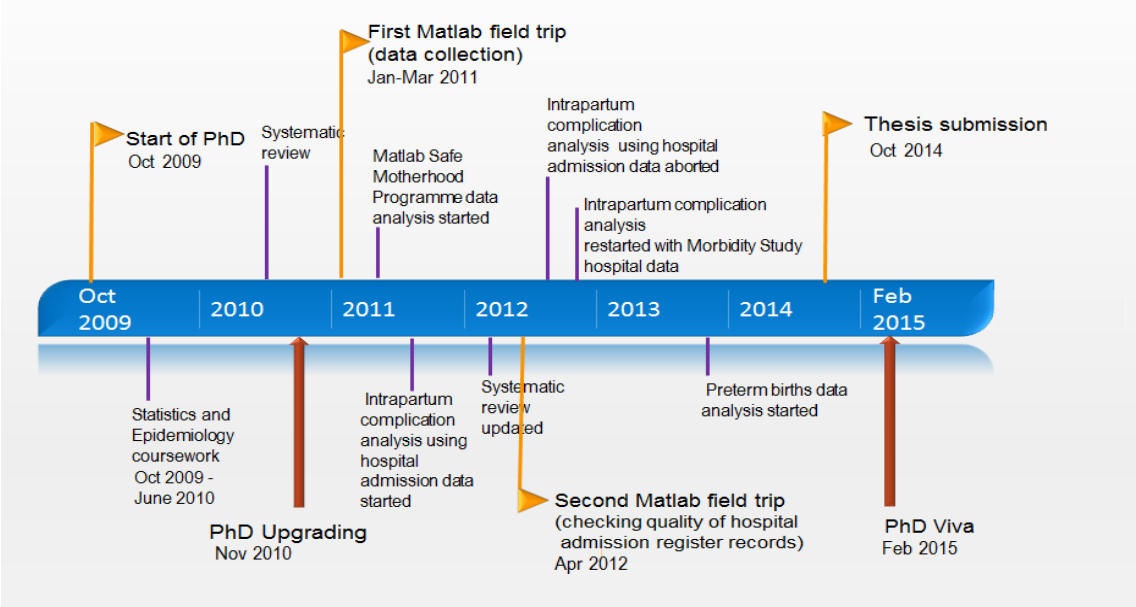


Figure1.1: Timeline of the PhD

Chapter 2. Background

2.1 Definitions

The WHO International Classification of Diseases, Tenth Revision (ICD-10) recommends stillbirths be defined as 'the death of a foetus that has reached a birth weight of 1000g, or, if missing, a gestational age of 28 weeks, or, if missing, crown-to-heel length of 35cm' (Figure 2.1) (Cousens et al. 2011; Lawn et al. 2011; World Health Organization 2004a). For international comparison, WHO recommends this definition of 28 weeks' gestation for stillbirths to account for any variability in registering births and deaths between 20 and 27 weeks' gestation (WHO 2006). Early neonatal deaths are deaths in the first seven days of life while late neonatal deaths are deaths between the eighth and twenty-eighth days of life (Lawn et al. 2011; WHO 2006) (Figure 2). Perinatal deaths comprise stillbirths and early neonatal deaths (WHO 2006; Barfield 2011). According to historical datasets, the ratio of stillbirth rate to early neonatal death rate in countries with high early neonatal death rate (>20 deaths/1000 live births) is 1.2:1 (and might be possibly more than 1.2:1) if there is no underreporting of stillbirths (WHO 2006).

Stillbirths are further categorized into antepartum ('macerated') stillbirths or intrapartum ('fresh') stillbirths. Antepartum stillbirths occur in-utero more than 12 hours before delivery and have evidence of foetal skin disintegration (Engmann et al. 2009; Lawn et al. 2005). Intrapartum deaths usually occur as a result of oxygen deprivation and injury during labour and delivery, have no evidence of skin disintegration and are not the result of congenital abnormalities (Engmann et al. 2009; Lawn et al. 2005).

Preterm births are defined by WHO as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period (LMP) (World Health Organization 1977). Figure 2.2 shows the periods of time associated with preterm births, stillbirths and perinatal deaths. Depending on gestational age, preterm births are further divided into extremely preterm (<28 weeks), very preterm (28-<32 weeks) and moderate and late preterm (32-<37 weeks) (Blencowe et al. 2012). Preterm births can also be differentiated phenotypically into spontaneous preterm births (spontaneous onset of labour) and provider-initiated preterm births (induced labour or Caesarean sections) (Goldenberg et al. 2012; Blencowe et al. 2013).

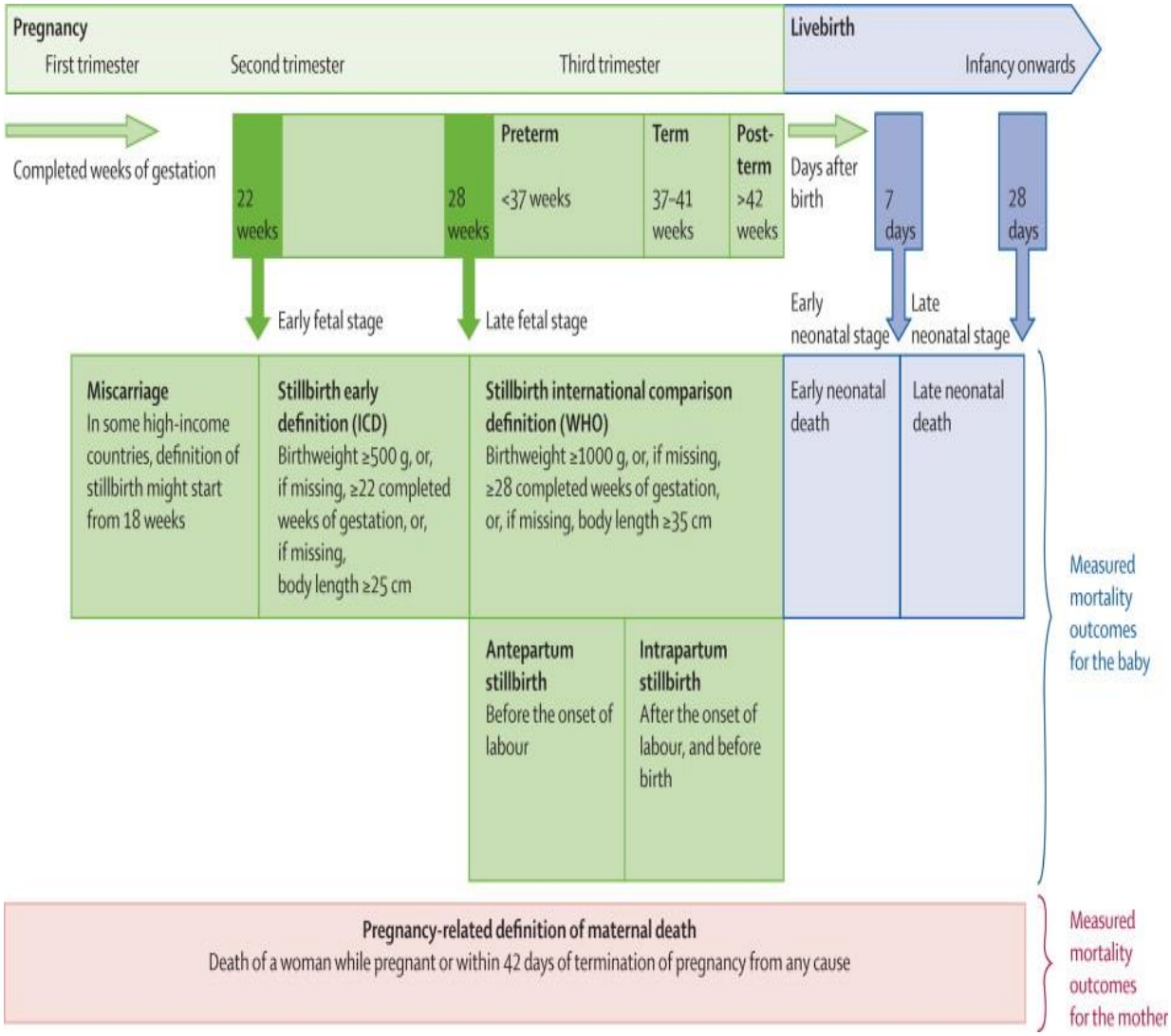


Figure 2.1: The epidemiological time periods of preterm births, stillbirths, early neonatal deaths and late neonatal deaths. Definitions are from the International Classification of Diseases, (ICD-10). Source: Lawn et al. 2011

2.2 Burden

Despite three decades of global attention to child survival interventions (Rohde et al. 2008; Black et al. 2003) and two decades of attention to safe motherhood (Campbell & Graham 2006; Rosenfield & Maine 1985) stillbirths, early neonatal deaths and late neonatal deaths are still at unacceptably high levels (Goldenberg et al. 2011; Lozano et al. 2011; Lawn et al. 2011; World Health Organization & UNICEF 2012). Stillbirths had no presence in the Millennium Development Goals (MDGs) or Global Burden of Disease assessments (United Nations Statistics Division 2008; Wang et al. 2014) and continue to be invisible in the post-2015 global development agenda (Lawn et al. 2014; United Nations 2013). Globally, attention has only very

recently focused on stillbirths (Lawn et al. 2011; Froen et al. 2011) and preterm births (Howson et al. 2012; Behrman & Butler 2007).

MDG 4 is to reduce under-5 mortality by two-thirds between 1990 and 2015 (United Nations Statistics Division 2008). However, the smallest reduction in under-5 child deaths in developing countries has been in the rates of early neonatal death and stillbirths (Wang et al. 2014; Lozano et al. 2011; Darmstadt et al. 2003; Darmstadt et al. 2014; Lawn, Lee et al. 2009) (Figure 2.1). Statistical estimates suggest that the reduction was smallest for stillbirths (1.1% annual decline during 1995-2009) (Lawn et al. 2011) compared to reductions in early and late neonatal mortality (1.7% and 2.7% annual declines over 1990-2011) (Lozano et al. 2011) in least developed countries. In the case of preterm births, recent information on time trends in countries with adequate data appears to suggest that preterm births increased between 1990 and 2010 (Blencowe et al. 2012).

With the end of the MDG era approaching, the Lancet Every Newborn series has set new goals for newborn health for 2035 for stillbirths and neonatal deaths (<10 stillbirths per 1000 total births and <10 neonatal deaths per 1000 live births) (Lawn et al. 2014). In order to achieve these rates, current rates of change need to double globally and more so in countries with the highest burden (Lawn et al. 2014; Lawn et al. 2011).

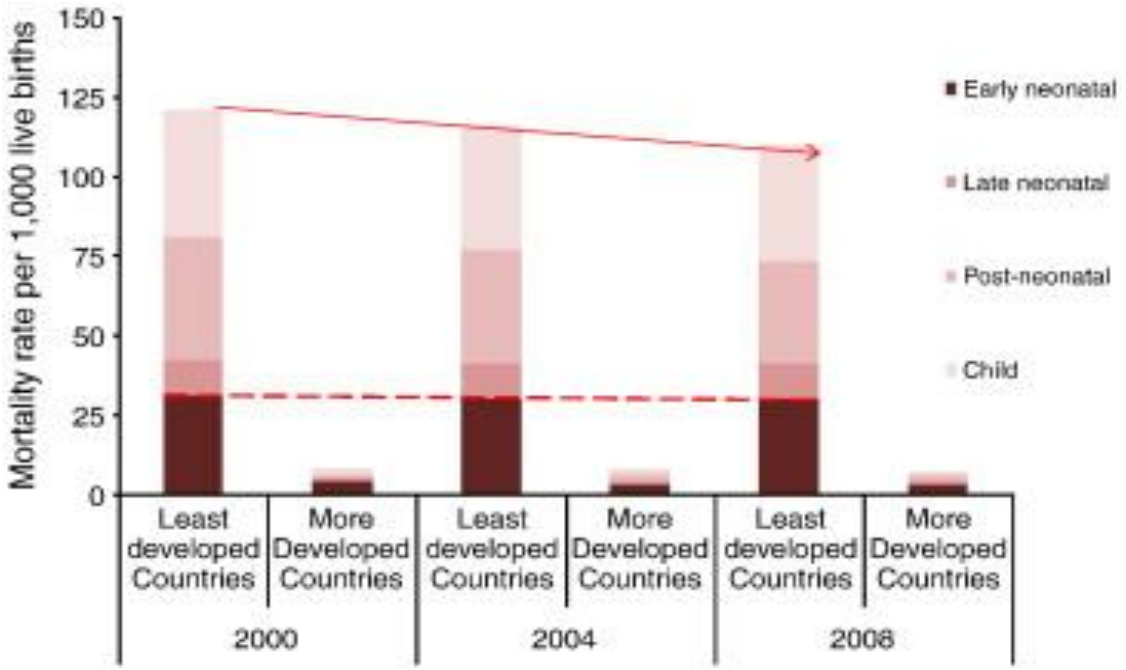


Figure 2.2: Time trends in early, late and post-neonatal mortality 2000-2008, showing lack of progress in reducing first-week deaths in least developed countries (shown by the dotted line). Source: Lawn, Lee et al. 2009

In 2012, 2.9 million babies died within 28 days of birth while 1 million children did not survive their first day of life (Save the Children 2014). The main causes of neonatal deaths in 2012 were preterm birth complications (1.0 million, 34%), intrapartum-related conditions (formerly called birth asphyxia; 0.7 million, 25%) and infections (mainly sepsis, meningitis and pneumonia; 0.6 million, 22%) (Lawn et al. 2014). Intrapartum complications in the labour and delivery period accounted for 1.2 million stillbirths, in addition to 0.7 million deaths of babies who were born at full-term (Lawn et al. 2014).

The most recent global estimates of perinatal mortality in 2004 showed that of the 5.9 million perinatal deaths, 98% of stillbirths and first week deaths took place in developing countries, where 90% of all babies are delivered (Ahman & Zupan 2007). The regions of South Asia and Africa saw the highest numbers and the highest rates of intrapartum deaths (Lawn, Lee et al. 2009) and were also the areas where 60% of the annual 15 million preterm births took place, with Africa having the highest rates (Blencowe et al. 2013; Lawn et al. 2014). Half (51%) of all stillbirths occur in India, Pakistan, China, and Bangladesh, the country in which this doctoral research is set (Stanton et al. 2006). It is thought that partial reduction in preterm births can possibly be attained through the use of antenatal steroids (Bhutta et al. 2014) though these are still largely unavailable in the places where most preterm births occur. However, there has been recent controversy (Azad et al. 2014) regarding the use of antenatal steroids after a large study found harmful results with an additional 3.5 neonatal deaths in 1000 women treated

(Althabe et al. 2015). Intrapartum deaths, considered to be greatly related to place of delivery and care at delivery, might be avoided with improved access to essential obstetric care and adequate skilled care. However, high coverage and good quality of these services are also thought to be essential in achieving reductions (Lee et al. 2011; Yakoob et al. 2011; WHO 2006; Ronsmans et al. 2003). The evidence for such interventions and the reductions possible from these and others will be addressed later. Small for gestational age babies are also at risk of increased mortality, with 2.8 million babies born in 2010 (Katz et al. 2013a). However they are beyond the objectives and scope of this thesis.

There is a general consensus on the conspicuous dearth of data, constituting a key research gap, in the evaluation of the impact of intervention packages on stillbirth and neonatal survival (Bhutta et al. 2009; Cousens et al. 2011). Lack of knowledge in this area has been observed particularly in regions where the highest burden exists (Bhutta et al. 2009; Haws et al. 2007). This is factually demonstrated by the finding that 3% of global stillbirth publications relate to low-income countries (LICs) where 90% of stillbirths occur (Froen et al. 2009). These are also areas with a scarcity of reliable data (Cousens et al. 2011) which underlines the need for good quality data and research leading to better assessment of the burden and possible approaches to address its reduction.

2.3 Global initiatives and programmes for newborn health:

Launched in 1987, the Safe Motherhood Initiative (Maine & Rosenfield 1999) advocated family planning, antenatal care, safe delivery, essential obstetric care, basic maternity care, primary health care and equity for women. Of these, essential obstetric care included actions that were and still are most effective in substantially reducing maternal deaths (Maine & Rosenfield 1999). The Matlab Safe Motherhood Programme in Bangladesh, discussed in this thesis, (Chapter 4) was launched in Matlab in 1987 in response to this initiative. As maternal health and child health gradually merged for ease of distributing services and accessing the affected, new partnerships and initiatives emerged in the last decade, mobilising action worldwide for maternal and child health. These include the Gates Foundation-supported Saving Newborn Lives (SNL), the Child Health Epidemiology Reference Group (CHERG), the Every Woman Every Child initiative, followed in 2012 by the Born Too Soon movement and in 2013 by the WHO and UNICEF Every Newborn Action Plan (Darmstadt et al. 2014). Most recently, two of the five objectives of the Every Newborn Action Plan focus on a) investing in care around the time of labour, delivery and first days of life and b) improving maternal and newborn care (Mason et al. 2014), themes that will be discussed throughout the thesis.

2.4 Difficulty in estimating perinatal deaths in developing countries

The difficulty in quantifying the number of perinatal deaths in low and middle income countries (LMICs) starts from their invisibility in government agendas. This is evidenced by the absence of pregnancy loss data and in complexities in defining, measuring and classifying perinatal deaths (WHO 2006; Lawn, Yakoob et al. 2009; McClure et al. 2006; Smith & Fretts 2007). It is further evidenced by the fact that areas with the highest risks, South Asia and sub-Saharan Africa, have the least information available via population studies and health and demographic surveys (Cousens et al. 2011). Very few demographic surveillance sites in the developing world gather pregnancy loss data (Lawn et al. 2010).

2.4.1 Issues of definition

Underestimation of stillbirths occurs due to different definitions being used in different countries and due to changes in definitions over time (Stanton et al. 2006; Kramer et al. 2002; Di Mario et al. 2007). In developed countries such as the USA, stillbirths have different definitions from the WHO definition and are based on birth weights from 350g to 1000g and on gestational ages which can range from 20 to 28 weeks (Lawn, Gravett, et al. 2010). Even the perinatal period of seven completed days can have two interpretations: day of birth plus six days and day of birth plus seven days, both of which are used (Bakketeig et al. 1984).

Defining preterm births can also be problematic, as there are very high mortality risks at lower gestational ages and some risk still persists at 37-38 weeks, between the preterm and term births (Goldenberg et al. 2012; Kramer et al. 2012). The lower and higher cut-offs of gestational age for preterm birth are based on arbitrary weeks (20/22 weeks to 37 weeks) and evidence-based definitions of preterm births suggest different cut-offs (16 weeks 0 days and 38 weeks 6 days) (Goldenberg et al. 2012; Kramer et al. 2012). The rationale for the lower cut-off suggested by Karmer et al. 2012 is because of the reason that although most countries base their preterm birth rates on live births (usually excluding stillbirths) from 20 (or 22) weeks, aetiological risk factors (e.g. bacterial vaginosis and miscarriage) for births at 14-23 weeks do not differ from those of preterm births at 20-25 weeks. Hence, Kramer et al. 2012 suggests that second trimester births should be included as preterm births. Whether or not stillbirths should be included or excluded is another concern in determining prevalence rates for preterm births (Kramer et al. 2012) though both stillbirths and live births are required to understand the true public health burden of preterm births (Goldenberg et al. 2012)

The needs for standard definitions for reporting preterm births and for consistency in reporting pregnancy outcomes has been highlighted in the literature (Howson et al. 2012; Lawn, Gravett, et al. 2010). When no lower age limit is set, this may result in live birth/stillbirth misclassification (Blencowe et al. 2013). As the ICD-10 encourages the inclusion of all live births, the lack of a lower limit can complicate matters, as in high-income countries (HICs) babies can survive at very low gestational ages (some HICs set this at 22 weeks) due to improved intensive neonatal care (Blencowe et al. 2013). In HICs, babies alive at 22 to 24 weeks maybe considered viable while in LICs with poor resources and neonatal technology those born at <32 weeks may be perceived as non-viable births (Blencowe et al. 2013). This is seen from South Asia community studies with high overall preterm rates (14-20%) where few extremely preterm births (<28 weeks) are reported (2% of preterm births) compared to higher percentages (5.3%) reported in HICs. Additionally, upper gestational age limits maybe higher than standard cut-offs, up to 38 completed weeks (Blencowe et al. 2013).

2.4.2 Issues of ascertainment

There is also significant difficulty in ascertaining stillbirths and early neonatal deaths in births not attended by a health professional (Stanton et al. 2006). Even health professionals may have difficulty in distinguishing between a stillbirth and a very early neonatal death by failing to understand the very slight movement of the ribcage denoting the intake of breath after birth. This can happen when infants die soon after birth, particularly asphyxiated or neurologically depressed live-born infants (Kramer et al. 2002).

There are also issues related to the correct ascertainment of preterm births. These relate to the method of gestational age assessment used (ultrasound, LMP, best obstetric estimate, fundal height and post-birth assessment) (Kramer et al. 2012). This is further discussed in Chapter 5. The perception of viability of a birth, may also result in an extremely preterm live birth being misclassified as a stillbirth (Sanders et al. 1998) and therefore not counted as a preterm births. Better case ascertainment for extremely preterm births (<28 weeks) is seen in HICs than in LICs where very low proportions of extremely preterm births are reported (Howson et al. 2012).

2.4.3 Issues of non-recording

Data show that there is less recording of the death of babies if they die in the first hours after birth (Lawn, Lee et al. 2009) or if they are small in size (Lumbiganon et al. 1990). Non-recording of stillbirths is also seen (Stanton et al. 2006; Chen et al. 1998). This tendency of under-reporting stillbirths (WHO 2006) is also seen in vital registration data in HICs where it is

estimated to be 20% or more (Lawn, Yakoob et al. 2009; Casterline 1989) and is noted in middle-income countries like Thailand (Lumbiganon et al. 1990). Assessment of global DHS data showed the DHS pregnancy-calendar based stillbirth estimates to be 30% less than population-based studies (Stanton et al. 2006).

The recording of preterm births may depend on the perception of viability, and socio-economic factors. It has been well-documented that live preterm births as well as stillbirths, born closer to the lower gestational age threshold (16 to 28 weeks) are under-registered (Froen et al. 2009). In developing countries live preterm births may counted as stillbirths because of the perception of non-viability or in order to protect the mother from blame (Blencowe et al. 2013) while maternity benefits, burial costs for a birth but not a miscarriage, and higher hospital fees for births compared to miscarriages may also contribute to under-reporting (Lumley 2003). Extreme preterm births are also seen to be more underreported in South Asia than in developed countries (Blencowe et al. 2013). Moreover, some reports on preterm birth provide birth rates and numbers only in terms of live births and sometimes live singleton births (Blencowe et al. 2012; Lee et al. 2013; Vogel et al. 2014). By excluding multiple births from the population at risk, (Vogel et al. 2014; Lee et al. 2013) information on preterm births resulting from multiple pregnancies can be lost (Blondel et al. 2006); while excluding stillbirths (Blencowe et al. 2012) results in loss of information on the preterm births that result from misclassification between stillbirths and (extremely preterm) live births (Blencowe et al. 2013; Kramer et al. 2002; Sanders et al. 1998).

All preterm births (including multiple births and stillbirths) need to be counted in order to give a true understanding of the actual public health burden of preterm births (Goldenberg et al. 2012; Blencowe et al. 2013).

2.5 Risk factors for perinatal deaths and preterm births

Empirical studies detailing risk factors for perinatal deaths, early neonatal deaths, stillbirths and preterm births have looked at proximal and distal factors. My conceptual framework (Figure 2.3) outlines the complex relationship between these factors as well as factors acting at community and individual level.

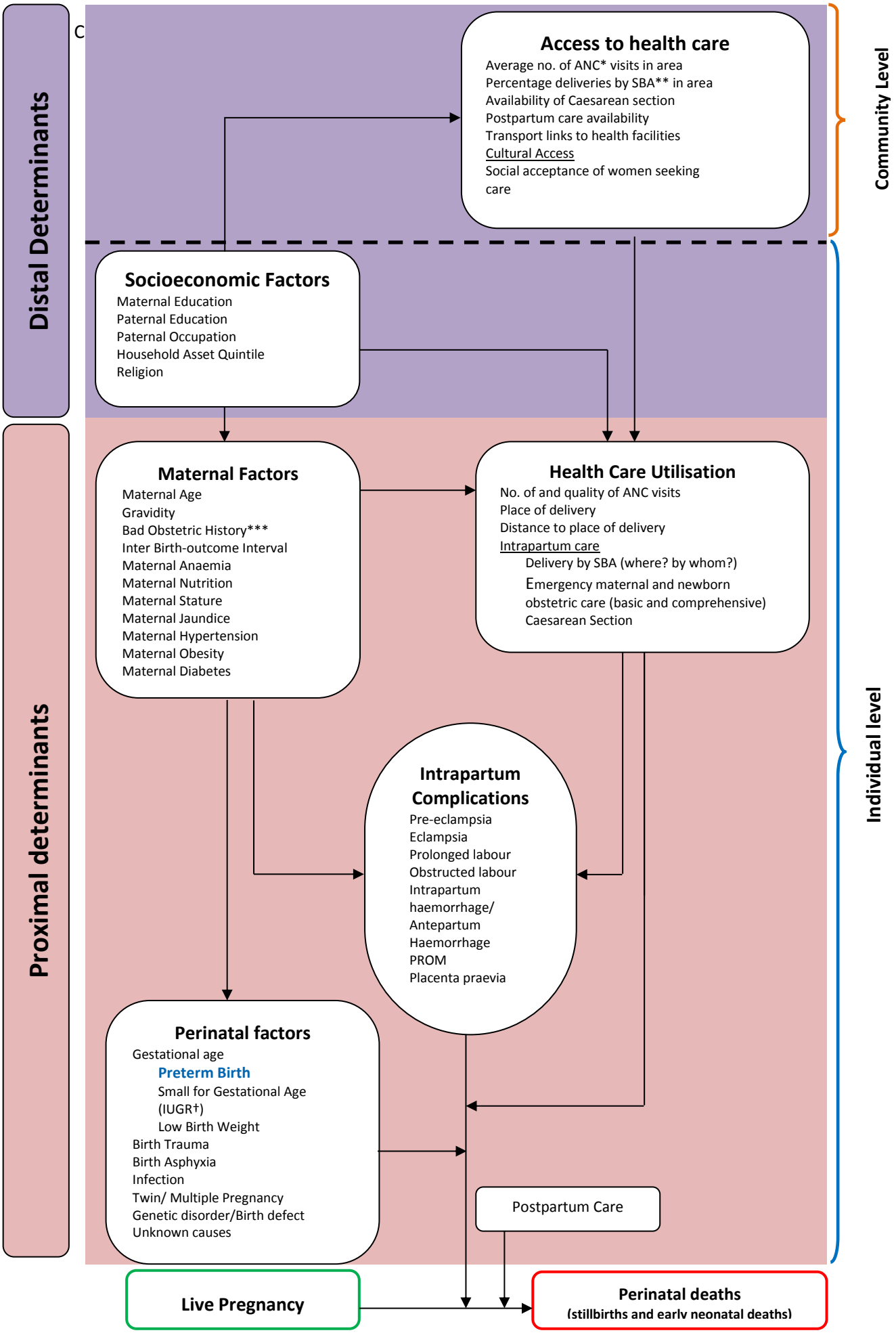


Figure 2.3: Conceptual framework showing the relationship between perinatal deaths and risk factors.*ANC=Antenatal care,**SBA=Skilled Birth Attendant, ***Bad Obstetric History= history of stillbirth, abortion, miscarriage, Caesarean section and obstructed labour. †IUGR= Intrauterine growth retardation.

Though many of the risk factors for perinatal deaths and preterm deaths overlap, they are discussed here separately for convenience.

2.5.1 Risk factors for perinatal deaths

The greatest risk for perinatal death is being born in a developing country (Say et al. 2006; Stanton et al. 2006; Smith & Fretts 2007). Studies have shown that lower socioeconomic status increases risks for perinatal deaths (Di Mario et al. 2007; Ronsmans et al. 2010; Cruz-Anguiano et al. 2004; Jammeh et al. 2010; Gazi et al. 1999). Women of higher socioeconomic status have greater access to health care, more deliveries with skilled birth attendants and more Caesarean sections than their poor counterparts (Achadi et al. 2007; Ronsmans et al. 2006).

Poor, uneducated women are also more likely to have maternal risk factors linked to increased perinatal deaths such as severe anaemia (Mavalankar et al. 1991), poor nutrition (Mavalankar et al. 1991), short inter-pregnancy intervals (<6 months) (DaVanzo et al. 2007), higher parity (Gazi et al. 1999), poor obstetric history (Hutcheon & Platt 2008; Kramer et al. 2000) and greater extremities of maternal age (Fauveau et al. 1990). Within maternal risk factors, studies have suggested that intrapartum risk factors (e.g. obstructed labour, malpresentation) have stronger associations with perinatal death than those identified during pregnancy (e.g. anaemia, pre-eclampsia, antepartum vaginal bleeding), which in turn have stronger risk associations than pre-pregnancy factors (e.g. maternal age, parity, undesired pregnancy, no partner) (Lawn et al. 2005; Kusiako et al. 2000; Chalumeau et al. 2000; Vanneste et al. 2000).

Perinatal risk factors such as low birth weight (Baqui et al. 2006; Lawn et al. 2005), preterm birth (Ngoc et al. 2006; Baqui et al. 2006), being small for gestational age (Katz et al. 2013b), birth asphyxia or birth injury (Lee et al. 2008; Baqui et al. 2006), multiple births (Cnattingius & Stephansson 2002), male sex (Engmann et al. 2009) and male sex of prior pregnancy (Nielsen et al. 2010) also increase risks for early neonatal deaths and stillbirths. Infections contribute only 10-25% of stillbirths in HICs while in LICs, syphilis and malaria, where prevalent, and chorioamnionitis are considered major contributors to infection-related early stillbirths with the first two diseases causing 40% and 32% of early stillbirths respectively (Goldenberg et al. 2010). Congenital abnormalities are thought to contribute to 5-15% of stillbirths (Lawn, Gravett, et al. 2010).

The risk factors for late neonatal mortality are not discussed in detail here. However, briefly, poor maternal socio-economic conditions, poor maternal health and nutrition, early childbearing , frequent pregnancies, preterm births, discarding colostrum, poor breastfeeding

and infections such as tetanus, meningitis, sepsis, pneumonia and diarrhoea are risk factors for deaths in the later part of the neonatal period (WHO 2006).

In 2012 the causes of neonatal deaths as estimated from statistical models were: complications from preterm births (34%), intrapartum-related conditions (previously known as birth asphyxia), (25%) and infections (mainly pneumonia, sepsis and meningitis) (22%) (Lawn et al. 2014). This modelling exercise was based on WHO statistical estimates for 194 countries and used verbal autopsy data for high-mortality (under-five mortality rate >35/1000 live births) countries. The models estimated that predominant causes for the early neonatal period were intrapartum-related conditions (29%) and preterm birth (40%) while infections (sepsis, pneumonia, tetanus and diarrhoea) dominated (44%) the late neonatal period followed by preterm births (21%). In the case of stillbirths, information on causes in high-burden countries (stillbirth rate>25/1000 births) was very limited and the results for the causes of intrapartum stillbirths came from a single unpublished verbal autopsy study in LAMB hospital in rural Bangladesh. These were: maternal complication (e.g. haemorrhage) identified (71%), other specific foetal condition (non-defined) (17%), foetal growth restriction or placental insufficiency, congenital anomaly (4%) and infection (2%) (Lawn, Lee et al. 2009).

2.5.2 Risk factors for preterm births

There is very little knowledge on the causes and mechanisms of preterm births (Howson et al. 2013). Depending on the type of initiation, preterm births can be broadly divided into: (i) provider-initiated or non-spontaneous preterm births and (ii) spontaneous preterm births i.e. babies born as a result of preterm labour or preterm rupture of membranes.

Provider-initiated preterm births can result from (a) medical induction or Caesarean section because of foetal or obstetric indications (Howson et al. 2012; Goldenberg et al. 2012) or from (b) delivery of what is considered a term baby due to errors in gestational age ascertainment (Mukhopadhaya & Arulkumaran 2007). The risk factors associated with spontaneous preterm births are poorly understood. Spontaneous preterm births constitute half (45-50%) of all preterm births and have unidentified aetiology (Menon 2008). These births are thought to result from multiple risk factors (described below) interacting through complex pathophysiological mechanisms to initiate preterm births (Menon 2008; Muglia & Katz 2010; Gravett et al. 2010). Infection may be responsible for up to 25% of spontaneous preterm births (Muglia & Katz 2010). Other risk factors (e.g. genetic factors, maternal age, undernutrition and diseases) are described later.

Globally, the proportion of preterm births from different causes varies between HICs and LICs (Muglia & Katz 2010). Secondary and tertiary-level facility studies in HICs suggest that the proportion of preterm births from preterm labour, rupture of membranes and provider-initiation (40-45%, 25-40% and 30-35%) were different to the proportion in facility studies in Latin America and some LICs (70%, 16-21% and 11-15%) with LICs having a higher proportion of preterm labour and lower proportion of provider-initiated pre term births than HICs (Gravett et al. 2010; Blencowe et al. 2013). In another recent and very large facility-based WHO study of 14,551 preterm births in 22 LMICs, the distribution of spontaneous preterm births and provider-initiated preterm births was found to be 77% and 22.6% respectively in nine Asian countries (including India, Nepal and Sri Lanka) (Vogel et al. 2014).

Maternal infections such as urinary tract infections, bacterial vaginosis, malaria, syphilis, and HIV have been found to be associated with greater risks of preterm births with the first three increasing risks by 1.2, 1.5 and 1.7 times (Vogel et al. 2014; Gravett et al. 2010). Cervical insufficiency brought on by cervical shortening as a result of ascending intrauterine infection and inflammatory processes also increases risks for preterm birth (Gravett et al. 2010).

Pre-eclampsia and pre-gestational diabetes were also found to increase risks for preterm births by 1.4 and 1.3 times, respectively and these conditions can aggravate maternal complications and increase provider-initiated preterm birth (Vogel et al. 2014; Blencowe et al. 2013). It is estimated that 15% to 25% of preterm deliveries are due to maternal and foetal complications. The main cause is thought to be hypertensive disease in pregnancy and severe intrauterine growth restriction (IUGR) that is associated with maternal hypertensive diseases (Tucker & McGuire 2004; Goldenberg et al. 2008).

Maternal genetic factors also feature prominently in preterm births. Mothers who were born preterm were found to have a 1.5 times higher risk of preterm birth and mothers with previous preterm births were found to have a 2.5 times higher risk (Muglia & Katz 2010; Goldenberg et al. 2008). Previous poor reproductive history of cervical incompetence, abortion and Caesarean section can also increase risks for preterm birth (Di Renzo et al. 2011).

Other maternal factors such as extremes of maternal age (<18 yrs and ≥35 yrs) increase preterm birth risks by 2.5 times and 1.1 times respectively (Tough et al. 2002; Hediger et al. 1997; da Silva et al. 2003). Maternal undernutrition (BMI< 18.5 kg/m2) and overnutrition can increase preterm birth risks by 1.3 and 1.1 times, respectively (Han et al. 2011; Dean et al. 2013). Increased risks are also seen for maternal stress and depression (Gravett et al. 2010),

excess physical labour and standing for long periods of time (Muglia & Katz 2010) and lifestyle factors such as smoking and alcohol and drug abuse (Dean et al. 2013; Requejo et al. 2013).

Short birth or inter-pregnancy intervals appear to be associated with higher risks of spontaneous preterm births (Conde-Agudelo et al. 2006; Kozuki et al. 2013; Dean et al. 2013). In one meta-analysis of five cohort studies from LMICs, women with birth intervals of <18 months were at 1.6 times greater risk of preterm births than those with birth intervals of 36-<60 months (Kozuki et al. 2013). Another meta-analysis of eight cohort, cross-sectional and case-control studies from HICs and LMICs showed that inter-pregnancy intervals of <6 months were at 1.4 times greater risk than intervals of 18-23 months (Conde-Agudelo et al. 2006).

Factors related to the foetus also increase risks for preterm births. Multiple pregnancy causing uterine over-distension, is an additional risk factor for preterm births and these pregnancies are at nearly 10 times more risk for preterm births than singleton births (Blondel et al. 2006; Goldenberg et al. 2008). The sex of the foetus is also a risk factor with male foetuses at higher risk of preterm birth and dying sooner than females born at the same gestational age (Kent et al. 2012; Brettell et al. 2008; Zeitlin 2002).

2.5.3 Intrapartum complications

Intrapartum complications refer to the complications that take place during labour and delivery (Lawn et al. 2005). These include dystocia, haemorrhage and hypertensive diseases, multiple pregnancy, anaemia and infection and increase the odds of perinatal mortality with the magnitude of increased risk varying by the type of complication. The strength of evidence on the effect of intrapartum complications on perinatal outcomes is explored in detail in Chapter 6.

2.5.4 Intrapartum care

Intrapartum care is the care of a woman and her baby during the labour and delivery period. The aim is to provide skilled childbirth care[2] and the use of basic and comprehensive emergency obstetric care (BEmOC and CEmOC)[3] (Yakoob et al. 2011; Lee et al. 2011). These provisions are also discussed in detail later.

The evidence for intrapartum care is discussed here. It is assumed that quality intrapartum care reduces perinatal mortality, but the evidence base is weak and relies mostly on a few studies. These are mainly observational studies and cluster-randomized control trials (RCTs), due to the ethical issues of randomly allocating care at the individual level.

[2] Skilled childbirth care is defined by WHO as care provided by "an accredited health professional – such as a midwife, doctor or nurse – who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth and the immediate postnatal period, and in the identification, management and referral of complications in women and newborns." (World Health Organization 2004b)

[3] Basic emergency obstetric care (**BEmOC**) consists of 7 signal functions: parenteral antibiotics, parenteral oxytocics, parenteral anticonvulsants, manual removal of retained placenta, removal of retained products of conception by manual vacuum aspiration and assisted vaginal delivery. Comprehensive emergency obstetric care (**CEmOC**) consists of the previous 7 functions plus Caesarean section and blood transfusion.(World Health Organization 2004b)

Observational studies

a) Ecologic studies:

An ecologic study by Goldenberg et al. (Goldenberg et al. 2007), which looked at the relationship between Caesarean sections (a component of CEmOC) and stillbirth rates, observed a decrease in stillbirths of 1.6/1000 births with each 1% increase in Caesarean section from 0 to 8%. Reduction declined after 8% for LICs having less than 15% Caesarean section rates. Another review by McClure et al. of 188 countries, supported this finding by showing that, in developing countries, intrapartum stillbirth rates showed a sharp decline when Caesarean sections increased from 0 to 10%, with little change after those levels (McClure et al. 2007).

Maternal mortality and perinatal mortality share overlapping risk factors (Lawn, Lee et al. 2009; Di Mario et al. 2007) such as absence of skilled birth attendance (SBA). In a large review (Scott & Ronsmans 2009) nine out of ten ecologic studies showed a reduction in maternal mortality rate with an increasing proportion of births attended by a health professional and one study showed a linear relationship between the variables in developing countries only when the proportion of births with a health professional had reached 40%. As risk factors overlap, this suggests that perinatal mortality also declines with SBA. However, ecologic studies that observe associations at the population level do not necessarily represent the association that exists at the individual level.

b) Before and after studies

In developed countries, historical data suggest that a large decline in the proportion of intrapartum stillbirths is the result of better foetal monitoring, access to emergency obstetric care and willingness to perform Caesarean sections (Goldenberg et al. 2007). A Matlab, Bangladesh study (Ronsmans et al. 2008) assessed the decline in perinatal deaths over time after implementation of an intensive maternal and child health intervention programme. Faster declines in stillbirths and early neonatal deaths were seen in the intervention area than in the comparison area leading the authors to conclude that the programme had had an effect on accelerating the decline of perinatal deaths.

c) Associations at individual-level

A Matlab, Bangladesh observational study showed that stillbirth rates and early neonatal rates are highest in women seeking comprehensive obstetric care compared to those not seeking care at all (Ronsmans et al. 2010). This seemingly contradictory finding is also echoed for

maternal mortality in countries like Indonesia, Pakistan and Mexico where less than one-third of births are attended by health professionals (Scott & Ronsmans 2009; Ronsmans 2009; Midhet et al. 1998). The results may reflect the fact low uptake occurs because women only seek professional care when they are very ill and it is too late to prevent maternal deaths or that care in poor countries is inadequate or late (Scott & Ronsmans 2009). Maternal mortality is seen to fall with increased care only when at least three-quarters of the population seek care, a rate seen only in the wealthiest women (Ronsmans 2009) and this is likely to also be the case in perinatal deaths.

d) Cohort studies:

Within the context of the developed world two components of care, the place of delivery and the skill level of the provider have been observed to have an impact on risks of perinatal and neonatal death. A Netherlands cohort-study showed that low-risk women delivering at home with a midwife had significantly higher risks (RR- 2.33; 95% CI: 1.12-4.83) of intrapartum deaths than high-risk women delivering in hospital with an obstetrician (Evers et al. 2010). A large meta-analysis of cohort studies (Wax et al. 2010) showed that planned home-births had double the odds (OR-1.98; 95% CI:1.19-3.28; 12 studies) of neonatal deaths than planned hospital births and caused an extra death in every 900 births. However, there appeared to be no effect on perinatal deaths in this study (OR-0.95; 95% CI: 0.77-1.18). These findings serve to further highlight the risks faced by poor women in developing countries who deliver at home without skilled providers and the complexities involved in the relationship between care and perinatal deaths.

Cluster-randomized control trials

One cluster-randomized control trial (cluster RCT) in rural Pakistan (Jokhio et al. 2005) in 1998-1999 allocated traditional birth attendants trained in antenatal care, intrapartum care, delivery practices and complication referral to intervention sub-districts. Intervention area women were also given three pregnancy visits and had access to newly set-up outreach clinics staffed by obstetricians. This resulted in significant reductions in stillbirth, perinatal and late neonatal deaths (31%, 30% and 29% respectively). In another cluster RCT of community interventions conducted in rural Pakistan over two years from 2006 to 2008 (Bhutta et al. 2011), government community health workers (CHWs) linked with TBAs provided two antenatal care visits and a postnatal visit within 4 days of birth. They promoted antenatal and essential newborn care, maternal nutrition and rest, early exclusive breastfeeding, danger sign recognition, and provided oral antibiotics for pneumonia. Control villages received only promotional messages on antenatal care and newborn care from CHWs. Stillbirths, early neonatal and late neonatal mortality reduced by 21%, 14% and 17% respectively in the villages with the intervention compared to control villages. In another cluster RCT study in rural India between 2004 and 2005 (Kumar et al. 2008) intervention villages received essential new born care (birth preparedness, clean delivery and cord care, danger sign recognition, birth feeding promotion) from CHWs while control villages received the usual government care. Stillbirths, early neonatal and late neonatal death reductions of 35%, 41% and 68% respectively were seen in the intervention area compared to the control area.

However, the results may be seen in a more critical light when it is borne in mind that the magnitude of effect from RCTs may not reflect the magnitude obtained in real-life situations. RCTs are not thought to be the most appropriate design when the intervention and the causal chain between the intervention and outcome are complex (Victora et al. 2004) as in the case of care and perinatal outcomes.

2.6 Interventions suggested for the reduction of perinatal mortality and preterm births

The evidence for interventions at community and facility levels that can result in reduced perinatal and preterm births is discussed in detail in Chapters 4 and 5. Interventions have been briefly highlighted here according to those provided during the continuum of care.

2.6.1 Interventions in the preconception and antenatal period

These consist of: prevention of unintended and adolescent pregnancies; pregnancy spacing; optimisation of maternal weight and provision of micronutrients; screening and managing or immunisation for infections (bacterial vaginosis, tetanus, syphilis) and management of chronic diseases (diabetes and hypertension). For preterm births specifically, antenatal corticosteroids and antibiotics for premature rupture of membranes are suggested but these are unavailable or of very low coverage in LICs.

2.6.2 Interventions during labour and delivery

These consist of SBA and timely basic and comprehensive emergency care (BEmOC and CEmOC).

2.6.3 Interventions for immediate newborn care and postnatal care for small and ill newborn babies

These consist of: (a) immediate newborn care (delayed cord clamping, antiseptic cord-care, thermal care and vitamin K administration); (b) neonatal resuscitation and (c) prevention and management of infections and care for small and ill infants by antibiotics preventing pneumonia, sepsis and meningitis, extra thermal care (including kangaroo mother care (KMC)), topical emollient care and secondary and tertiary level hospital care.

2.7 Reaching mothers and neonates in greatest need

In order to achieve substantial reduction in stillbirths and perinatal deaths, poor and marginalized mothers and neonates need to be able to access good quality care.

Reaching the mothers and neonates in the greatest need has been attempted through community-based delivery strategies, antenatal and postnatal visits by CHWs, community mobilisation and increasing demand for maternal and newborn services through women's groups, inclusion of newborn services within integrated management of childhood illnesses

and financial incentives and vouchers for facility delivery (Bhutta et al. 2014). The first three strategies are discussed here in further detail.

Community -based delivery platforms with linkages to referral health facilities in the locality can improve stillbirth, perinatal and neonatal survival through changes in household behaviours and practices such as: usage of clean delivery kits, increasing facility-birthing, early breastfeeding and care-seeking for newborn illnesses (Bhutta et al. 2014).

CHWs have been shown to play an important role in improving birth outcomes and reducing neonatal mortality by (i) providing antenatal and postnatal visits which complement facility-based care and (ii) improving family contact with health systems during critical times (Bhutta et al. 2014). Performance of these functions by these outreach workers has resulted in neonatal mortality reduction of up to 40% (Lassi et al. 2010). However, the effectiveness will depend on the actual services provided by the CHWs, along with appropriate frequency of visits and quality of services provided.

In the community, initiatives by facilitator-led women's groups to identify and prioritise maternal and newborn health issues, and develop strategies to address the issues, have had impacts on neonatal mortality. A meta-analysis of women's groups studies has shown that the groups have been linked to 23% reduction in neonatal mortality though non-reductions have been seen when coverage has been low (Prost et al. 2013). These groups can empower communities by changing household practices and increasing demand and planning for maternal and newborn care.

2.8 Contribution of the private health sector to delivery care provision

Though global and regional policies are focused mostly on the public sector, increasingly, women are delivering within the private health sector and this has become apparent in countries such as India, China and Sri-Lanka where increasing numbers of non-medically indicated provider-initiated preterm births (primarily due to Caesarean sections) are taking place (Darmstadt et al. 2014; Vogel et al. 2014). The number of women in developing countries to have Caesarean sections for a variety of reasons is also increasing (Muula 2007). Information on private health facilities and services is mostly unavailable in developing countries such as Bangladesh (Mridha et al. 2009) and this is an important consideration in understanding the effective measures in reduction of perinatal mortality. The most recent

Bangladesh DHS showed that 59.0% of all institutional births took place in private facilities (NIPORT et al. 2013) and details regarding these deliveries are largely unknown.

2.9 Timing of perinatal deaths

In 2012, 73% of global neonatal deaths occurred during the first week of life with 36% (1 million) occurring on the first day of life (Save the Children 2013). Grouped data from 47 DHS datasets suggested that early neonatal deaths vary in timing during the first week of life with 25-45% occurring in the first 24 hours and three quarters of all neonatal deaths taking place in the first week (Lawn et al. 2005) (Figure 2.4). In the Nepal Sarlahi study (Figure 2.5) (Lawn et al. 2009) and elsewhere (Baqui et al. 2006), this pattern is also seen with the majority of deaths occurring during the first 48 hours and almost all within the first week. While attention has been focused on the direct clinical causes and timings of these deaths, very little has been done on the risk factors during the continuum of mortality in the first month of life. The effect and pattern of risk factors, disaggregated by time since birth, on mortality outcomes in the first week of life has not been explored. It is also not known whether risk factors show the same effects on stillbirths as on early neonatal deaths.

Recently a prospective study of maternal, foetal and neonatal deaths in 220,235 prospective-enrolled women was undertaken in 106 communities in six LMIC countries (Argentina, Guatemala, India, Kenya, Pakistan and Zambia) (Saleem et al. 2014). Results from this study showed that most of the stillbirths (70%) were intrapartum, occurring at and around delivery. Deaths on the first, second and third to seventh days of life contributed to 34%, 14% and 28% respectively (76%) of all neonatal deaths. These findings highlight the need for better study and understanding of the differences, if any, in the risk factors for stillbirths and deaths in first month of life.

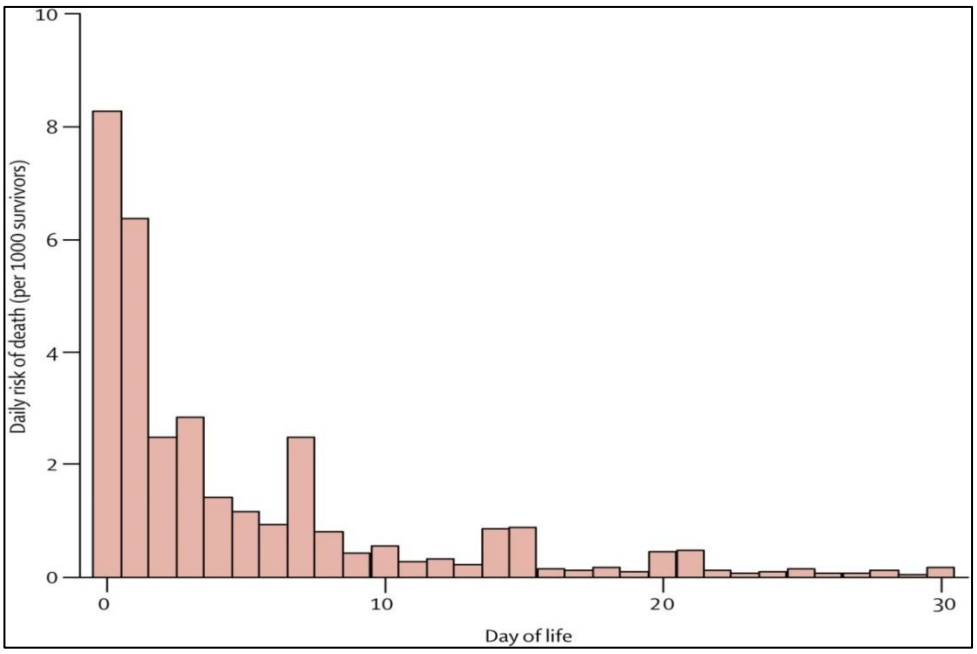


Figure 2.4: Daily risk of death during first month of life (based on analysis of 47 Demographic and Health Surveillance datasets from 1995–2003). Source: Lawn et al. 2005

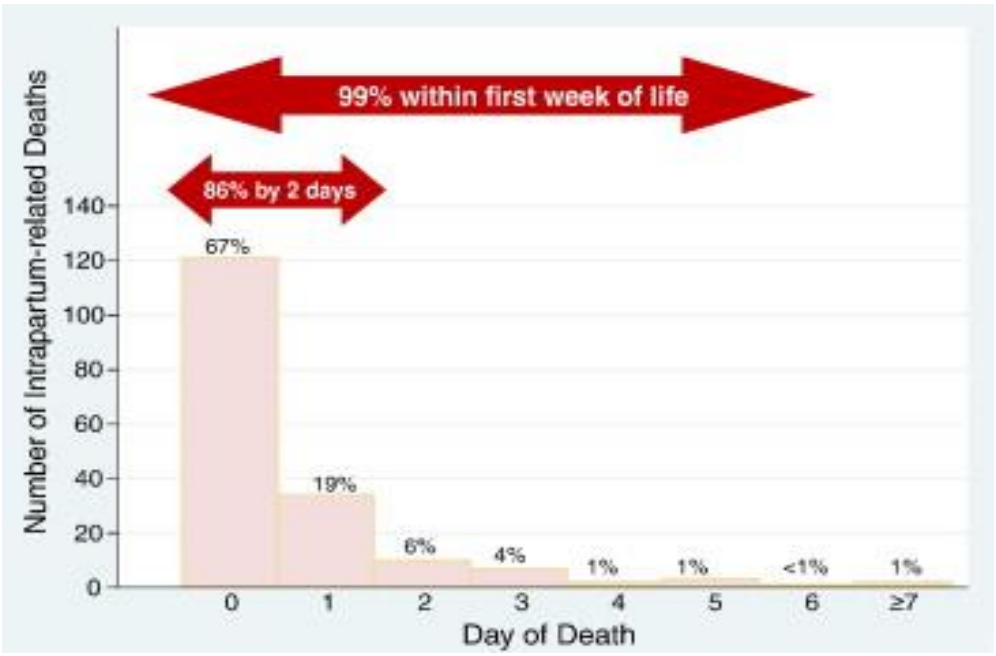


Figure 2.5: The timing of intrapartum early neonatal deaths in rural Sarlahi, Nepal.
Source: Lawn, Lee et al. 2009

2.10 Rationale for the thesis

There is little high-quality, population-based data for stillbirths and early neonatal deaths globally, even in developed countries (Stanton et al. 2006) and reliance on expert opinion drives much of the research on estimating reductions from interventions. The dearth of data on preterm births from LMICs has been highlighted recently with the first global and regional estimates for preterm births published as late as 2009 (Howson et al. 2013). Community surveys which are often self-reported can lack validity while relying only on hospital-based data may be misleading as most deliveries take place at home in many developing countries (Say et al. 2006). Statistically-modelled estimates at country level suggest that three South Asian countries (Bangladesh, India, Pakistan) have almost half of the world's stillbirths, numerically most of the world's 1.2 million labour and delivery related early neonatal deaths and the highest number of preterm births (Blencowe et al. 2013). However, there is a serious paucity of empirical evidence in the form of population-based, methodologically sound studies that (a) investigate the levels of perinatal deaths and preterm births and (b) explore the contribution of intrapartum complications and preterm births to perinatal deaths in South Asia. The few studies that are available globally and in South Asian countries do not assess the impact on stillbirth and early neonatal death separately and almost none examine the impact of labour complications alongside preterm births on perinatal mortality. There is also no knowledge available on the potential variability, if any, of the impact of complications and care on the early neonatal period by the day since birth. It is these gaps in knowledge that the following thesis aims to address.

Chapter 3. Systematic review of the rates of stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths in community-based studies in South Asia

3.1 Introduction

The global burden of stillbirths, early neonatal and late neonatal deaths and the difficulties related to the assessment of these deaths has been discussed previously (Chapter 2). Globally, the evidence base for empirical rates for these mortalities is weak (WHO, 2007). Mortality rate data from developing regions such as South Asia are mostly modelled (WHO, 2007, Stanton et al., 2006). Estimates in use for stillbirths (WHO, 2006b, Stanton et al., 2006, Cousens et al., 2011, Lawn et al., 2011, WHO, 2007) early neonatal (Lozano et al. 2011; Wang et al. 2014), late neonatal (Lozano et al. 2011; Wang et al. 2014) and perinatal mortality(WHO, 2006b, WHO, 2007) rely heavily on statistical models.

Global estimates of early and late neonatal death rates for 2000 were produced by Lozano et al. by using complex models that utilized vital registration data , surveillance systems and birth histories (Lozano et al., 2011). Stillbirth rates for the South Asian region (for 2009) and for 129 countries (for 2008) by Cousens et al. and Lawn et al., respectively, used regression models. In these models there was input of national and sub-national data from vital registration (in countries where available), Demographic and Health Surveys (DHSs) and published studies (Cousens et al., 2011; Lawn et al., 2011). Stanton and colleagues produced country-specific stillbirth rates (for 2000) from (a)regression models which predicted rates in the absence of studies (Afghanistan, Bhutan, Maldives and Sri Lanka) and (b) from adjusted data sources where empirical observations from studies were adjusted using a regression model (Bangladesh, India, Nepal, and Pakistan) (Stanton et al., 2006). The World Health Organization (WHO) published stillbirth, early neonatal and perinatal mortality rates for 2000 and 2004. These were produced from regression models with input of data from: country-specific under-five mortality rates that utilized DHS, national survey data and reports from the United Nations (UN) and World Health Organization, and stillbirth and early neonatal death ratios predicted for the region (WHO, 2006a; WHO, 2007). The most recent data on early neonatal and late neonatal deaths for the year 2013 for the Global Burden of Disease Study 2013 (Wang et al.

2014) are based on rates obtained from statistically modelled estimates of under-five mortality rates in 188 countries.

Epidemiologically, stillbirths are considered to equal or outnumber early neonatal deaths (WHO, 2006a) with high-income countries (HICs) showing ratios of stillbirth rates to early neonatal death rates (ranging from 1.7:1 to 1.9:1). Low-income countries (LICs) which usually have elevated early neonatal mortality (>20/1000 births), show a median ratio of 1.2:1 (WHO, 2006a). This ratio of 1.2:1 is confirmed by historical vital registration data from countries transitioning from high to low mortality e.g. Denmark, England and Sweden. However, it may be possible that the real ratio is different where mortality is high, though this seems unlikely from historical precedence. The WHO suggests that when data-poor, high-mortality countries show low ratios of 1 or below this may imply the presence of stillbirth underreporting, which is of major concern (WHO, 2006a). Stanton and colleagues reported low ratios with only 5 of 49 DHSs presenting ratios >1. Furthermore, they report the sub-Saharan regional ratio to be 0.55, which is implausibly low, and, on the other hand, Moldova is reported to have a very high ratio of 3.2, suggesting misclassification between stillbirths and early neonatal deaths (Stanton et al., 2006, Lawn et al., 2010)

To date, there is no body of work synthesizing empirical data on stillbirths, early neonatal, late neonatal and perinatal deaths for South Asian countries. In this chapter, I aim to better understand these mortality levels in South Asia by reviewing existing literature presenting population-based data in studies published from Jan 2000 to March 2012. I will produce summary mortality estimates using forest plots and document the methodology. I also aim to understand the level to which stillbirths are possibly underreported in: sub-national and national studies, the constituent countries and in South Asia.

3.2 Objectives:

Overall Objective:

To systematically review studies in order to obtain reliable estimates for the rates of stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths in South Asia.

Specific Objectives:

1. To obtain summary estimates for the above-mentioned mortality rates by calculating rates directly from data in published population-based studies. Rates will be calculated at regional level for the whole of South Asia and at national levels for the eight constituent countries (Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka and Maldives).

2. To compare the summary estimates obtained in the review with estimates available in the current literature.

3. To obtain the ratios of stillbirth rates to early neonatal death rates at the regional and national level for each of the eight countries of South Asia and for the whole of South Asia.

3.3 Methods

3.3.1 Search Strategy

Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka are the eight countries comprising the UNICEF South Asia region that I included in this systematic review . I ran the search on MEDLINE, Global Health, EMBASE and Popline databases on 12th March 2012 to identify studies published from 2000 until this date. Combinations of the following terms were adapted according to the search methodology of each database: *perinatal mortality, stillbirth mortality, early neonatal mortality, late neonatal mortality, infant mortality, Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka and South Asia.* The full search strategy is shown elsewhere (Appendix IA).

I searched Ovid Medline, Global health, Embase and Popline databases, the Measure DHS website and country-specific INDEPTH websites. INDEPTH is a global network of health and

demographic surveillance system (HDSS) field sites in Africa, Asia and Oceania producing longitudinal data. I conducted searches in English, checked titles and abstracts returned by databases to ensure relevance of the articles and checked bibliographies of retained papers for further eligible studies. I obtained country-specific DHS (Demographic and Health Survey) reports published within my stipulated time period to obtain DHS data and excluded any publications using DHS data from the same reports in their analysis. Of the available INDEPTH website data, only the Matlab site data was eligible but was excluded as the website provided information on neonatal, infant, and child mortality outcomes and not on stillbirth, early neonatal, late neonatal and perinatal mortality outcomes. The latter outcomes were available from eligible Matlab publications identified via the database searches.

In order to obtain international published estimates of mortality rates for the countries of South Asia that I would compare my review rates to, I identified publications reporting data on global and regional mortality estimates during the database searches. I also searched for publications from: database auto-alerts, email-alerts from perinatal/newborn websites and bibliographies of publications. The mean years corresponding to the published rates were those that were stated in the publications.

3.3.2 Study Selection

At first, I screened titles and abstracts of studies against eligibility criteria (described later), and included studies provisionally if there was not enough information for acceptance. I then screened the full-texts of studies. I consulted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and adapted their flow-diagram (Moher et al. 1999) to summarize my selection procedure.

3.3.3 Eligibility criteria

Inclusion criteria

The inclusion criteria are as follows:
Mortality outcome measures– stillbirths, early neonatal deaths, perinatal deaths and late neonatal death, regardless of study definitions.

Multiple studies/DHS reports-more than one study or more than one DHS report from each country could be included provided that raw data (numerators and denominators) for

mortality rates were reported. Studies from the same time period could be included. If the same study population was reported in several publications, the publication reporting the most information on mortality outcomes was used.

Study Design- cross-sectional, cohort, case-control or randomized control trial studies in South Asia reporting raw data for community-based estimates enabling mortality rate calculations of the mortality outcomes listed previously.

Study populations-pregnancies/births within the study period or within a defined recall period (e.g. 5-year recall period prior to interview for the DHSs).

Publication period- studies published from January 2000 till 12th March 2012. I chose the year 2000 so as to include research published since the establishment of the Millennium Development Goals (September 2000). However it should be noted that in some cases where a journal article or report was published on or after January 2000, the actual study period in which the study data was collected could have been from a time-period before the year 2000.

Languages- no restrictions placed on languages during database searches, however only articles published in English and Bengali were screened for the review.

Exclusion criteria

The exclusion criteria are as follows:
Mathematical models- studies that reported rates from mathematical/statistical models and extrapolation of rates.

Inappropriate study populations-

a. Facility-based studies.
b. Birth sub-groups (e.g. low-birth weight infants only)
c. Pregnant women sub-groups with specific illnesses (e.g. chronic renal insufficiency or diabetes)
d. Displaced/refugee South Asian populations or migrant populations of South Asian descent living outside South Asia.

Non-relevant mortality outcomes-Studies which measured mortality outcomes not of interest for the review (e.g. pooled neonatal deaths for the 1st month of life, deaths at 6 months, infant deaths, under-five deaths, etc.) or other outcomes (e.g. developmental milestones, weight, growth).

Publications such as: reviews, letters or editorials, protocols and conference proceedings/abstracts which were not considered to yield complete information on the study. Only full-length, full-text studies were used.

Published studies using DHS data- published studies reporting rates using DHS data (to avoid duplication of information as I calculated DHS rates myself from DHS report data).

Duplicate source or overlapping time period-I selected studies reporting the largest number of outcomes if studies had duplicate data or overlapping time periods.

Studies were not excluded because of small number (e.g. 20 or less) of deaths or high percentage (e.g. 20% or more) of missing data as this would exclude small but possibly relevant studies from the review. There were no guidelines available on the minimum number of outcomes in a study and while sample-size calculations do exist there is no guidance on minimum outcomes per study for meta-analyses. The number of outcomes and missing data were recorded for each study.

3.3.4 Data Extraction and Review Terminology

After data selection, I extracted study data using standardized data-extraction sheets in Excel (section 3.4.2). I consulted my supervisor (Professor Carine Ronsmans) only if I required a second opinion on study selection or on any complex data-extraction issue.

For each study I extracted data on: study setting, study design, data collection period, study population, pregnancy and birth ascertainment, gestational age assessment, death ascertainment, and definitions of types of mortality reported in the study (e.g. stillbirth, early neonatal death, late neonatal death etc.). I also extracted raw data for the numbers of deaths in each study (any or all of the following: stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths) and raw data for the corresponding denominators in order to calculate mortality rates. I calculated mortality rates, percentage followed-up or response rate and the mean year corresponding to the mortality rate. Even if the study reported their own rates and

even if these rates were adjusted for cluster-design or stratification, for my purpose, I calculated all the (unadjusted) rates myself. The rationale for this decision was that, by this process all the rates calculated for all the studies in the review had pre-defined numerators (e.g. stillbirths) and denominators (e.g. total births or all stillbirths and live births) and hence consistency for the numerators and denominators and so for the rates (e.g. stillbirths per 1000 total births)was ensured. If information was not available for a criterion, this was indicated in the appropriate cell.

I decided that the study design was that which yielded the outcome rates- e.g. for a cohort study embedded in a randomized controlled trial, the study design would be 'cohort study' and not 'randomized controlled trial' as in Baqui et al. 2009 (Baqui et al., 2009). A study in which only one cross-sectional survey was conducted (e.g. National DHS) was considered to be a 'cross-sectional study'. I decided that there were two types of surveillance studies: (a) surveillances of births and mortality outcomes based on regular repeated cross-sectional assessments (e.g. every 3 months) in the same population during the study period e.g. Bhutta et al. (2011) and (b) surveillances of births and deaths where these outcomes were reported by informants over a set time period e.g. Manandhar et al. (2010). For studies where interventions were tested or evaluated, I considered the outcomes in the non-intervention arm as these rates were thought to be more representative of the general population.

I calculated the follow-up/response percentage for my outcomes of interest irrespective of those reported by the study. I calculated loss to follow-up if reported separately for the control group/minimum-intervention group e.g. Manandhar et al. (2004) otherwise I calculated the overall loss in the study.

Studies used different terms to describe the person ascertaining pregnancies, births, deaths, gestational age, and mortality outcomes. Most studies provided insufficient detail on the training, education and skills of CHWs or their equivalents to allow comparison of CHWs or equivalents across all studies. I divided these workers into 'government CHWs' and 'research CHWs'. I used 'government CHW' to describe CHWs employed and trained by the public sector (e.g. the Lady Health Workers (LHWs) of Pakistan or Angaanwadi workers of India). I used 'research CHW' to describe workers who were recruited and trained by the study. Training duration and content was not usually described by studies. Any study which did not specify whether data collection staff possessed qualifications equivalent to CHWs was described as

stated in the study text and distinguished by quotation marks e.g. 'trained evaluation team member' in Kumar et al. (2008).

Throughout this review I use 'national' studies to refer to studies that sample nationally from the entire population of the country e.g. the DHSs. 'Sub-national' studies refer to studies taking place in a country which do not involve sampling from the entire population of a country, but from a few households, villages, districts or several districts within a country.

Any 'deaths' that I refer to in this review are stillbirths, early neonatal deaths, late neonatal or perinatal deaths.

3.3.5 Quality Assessment of Studies

I assessed study quality by obtaining the overall risk-of-bias for each study in the review using the component approach suggested by the Cochrane collaboration (Higgins and Green, 2011) which was also in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). I assessed the risk-of-bias (low, high and unclear) of the following component criteria for each study: (1) ascertainment of pregnancy (2) ascertainment of birth (3) ascertainment of death and (4) definitions of all mortality outcomes measured by the study. Another PhD student (Clara Calvert) reviewed 5 studies independently where risk-of-bias was ambiguous and any differences identified were reconciled after discussion.

Risk-of-bias was categorized as low, high and unclear according to criteria shown in Table 3.1. In cases of ascertainment of pregnancies, births and deaths, importance was placed on whether the study design resulted in pregnancies, births and deaths being missed and hence could have led to rates being calculated which might not have represented the true rate in the population being studied. It was also important to note studies where definitions for mortality outcomes fulfilled basic criteria of conventional definitions (Chapter 2) and studies where definitions were inadequate or unclear.

Table 3.1: Risk-of-bias criteria

Level of Risk	Ascertainment of pregnancy	Ascertainment of birth	Ascertainment of death	Definitions of all mortality outcomes measured by the study
Low risk	A prospective or retrospective cohort study which follows pregnancies from early pregnancy and pregnancy identification is by valid and reported pregnancy identification methods (last menstrual period or LMP method, urine dip-stick test and ultrasound)	Pregnancies identified previously are followed up until birth	Pregnancies identified previously are followed up until death	Overall risk-of-bias for definitions is *low* when all mortality outcomes have definitions considered to be at low risk-of-bias. Low risk-of-bias definitions are: 1. Stillbirth - Gestational age cut-off (weeks or days) is specified in the stillbirth definition 2. Early neonatal death and late neonatal death- Numbers of days for deaths to occur in are specified as 7 or 8 completed days and as 28 or 29 completed days, respectively *. 3. Perinatal death- Both the definitions of constituent deaths (stillbirth and early neonatal death) of perinatal death are at low risk-of-bias.
High risk	A clinical record review; a cross-sectional study; or surveillance studies which are (a) based on repeated cross-sectional assessments or (b)where pregnancies are ascertained by community members on an ad-hoc basis.	Births reported or identified by: a clinical record review; a cross-sectional study; or surveillance studies which are (a) based on repeated cross-sectional assessments or (b) where births are ascertained by community members on an ad-hoc basis.	Deaths reported or identified by: a clinical record review; a cross-sectional study; or surveillance studies which are (a) based on repeated cross-sectional assessments or (b) where deaths are ascertained by community members on an ad-hoc basis.	Overall risk-of-bias for definitions is *high* when at least one mortality outcome has a definition considered to be at high risk-of-bias. High risk-of-bias definitions are: 1. Stillbirth - Gestational age cut-off (weeks or days) is *not* specified in the stillbirth definition 2. Early neonatal death and late neonatal death - Numbers of days for deaths to occur in are *not* specified in the early neonatal death and late neonatal death definitions 3. Perinatal death- Any or both the definitions of constituent deaths (stillbirth and early neonatal death) of PND are at high risk-of-bias

Table 3.1 (continued).

Level of Risk	Ascertainment of pregnancy	Ascertainment of birth	Ascertainment of death	Definitions of all mortality outcomes measured by the study
Unclear Risk	Insufficient or no information on all or any of the following: ascertainment of pregnancy, person identifying pregnancy and pregnancy identification method.	Insufficient or no information on all or any of the following: ascertainment of birth and person identifying birth	Insufficient or no information on all or any of the following: ascertainment of death and person identifying death	Overall risk-of-bias for definitions is *unclear* when there is: 1. No definition for stillbirth, early neonatal death, late neonatal death or perinatal death **OR** 2. If perinatal death definition is available, any or both the definitions of constituent deaths (stillbirth and early neonatal death) of perinatal death are at unclear risk-of-bias.

* Definitions for early and late neonatal deaths were those reported by each study and so there were differing cut-off points for deaths to occur in. See Appendix IA and section 3.4.2 "Definitions of early, late and perinatal deaths" for list of studies defining the number of completed days for early and late neonatal deaths to occur in.

A study was considered at overall low risk-of-bias if all criteria were at low risk-of-bias. A study was considered to be at overall unclear risk-of-bias if any criterion was at unclear risk-of-bias. A study was at high risk-of-bias as long as there was no criterion at unclear risk-of-bias and if at least one criterion was at high-risk-of-bias.

I considered ascertainment of pregnancies, births and deaths to be at high risk-of-bias if cross-sectional assessments or surveillance systems were used. This was because, in these methods, women or community informants may forget to report, or conceal or choose not to report a pregnancy, birth or death if revelation was taboo, if the birth outcome was socially undesirable or if the birth outcome was associated with shame/grief (Lawn,Yakoob et al. 2009; Haws et al. 2010). In rural Tanzania burial of late pregnancy loss is done secretly near the house by the woman or local healer while an intrapartum stillbirth or early neonatal death with few signs of maturity is buried secretly in forest or bush by local men or a healer (Haws et al. 2010). In some cultures including those in South Asia, pregnancy disclosure is limited to one's partner and one or two trusted females while suppressed grieving and mourning also increases the likelihood of concealment from researchers (Lawn, Yakoob et al. 2009). Hence in Bangladesh where pregnancy disclosure is considered taboo, I considered these studies less able to report the true rate of births or deaths. I did not consider a study with a short length of recall (e.g. 1 month) to be low-risk, since a short recall period was unlikely to increase reporting of concealed outcomes.

I considered the provision of definitions to be an important factor in deciding the level of risk-of-bias as clear cut-definitions provided by the study could possibly reduce misclassification between types of mortality outcomes compared to those that provided no or unclear definitions.

I did not consider the completeness of data outcomes (percentage followed-up/ response rate) to be a vital quality criteria compared to the four criteria above. This was because DHS studies frequently report response rates of >98% but also depend on women's recall. Cohort studies can also have known survival status for 95% of enrolled pregnancies, yet births can be reported by community informants who may underreport or misreport adverse outcomes if influenced by any of the social factors described before. Additionally DHS studies might

possibly be subject to bias with intentional misclassification of a mortality outcome as a stillbirth in order to avoid completion of extra questions required for a neonatal death.

3.3.6 Data Analysis

Mortality outcome definitions:

Definitions for stillbirths, early neonatal deaths and late neonatal deaths were those reported by each study and I present these in the tables detailing study characteristics. I defined perinatal deaths as the sum of stillbirths and early neonatal deaths. The standard DHS definitions for mortality outcomes are shown below (Table 3.2) while any minor variations within each DHS are shown elsewhere (Table 3.9). As the DHS did not report a definition for late neonatal death, I defined this as shown in Table 3.2.

Table 3.2: Demographic and health surveillance (DHS) definitions for birth and mortality outcomes

Birth and mortality outcomes	**Demographic and Health Surveillance (DHS) definition**
Stillbirth	Pregnancy losses occurring after 7 completed months' of gestation
Early neonatal death	Deaths of live births within the first seven days of life.
Perinatal death	Stillbirths and early neonatal deaths
Late neonatal death	Neonatal deaths* excluding early neonatal deaths
Births	Stillbirths and live births

*births in the first month of life (as reported by the studies)

Mortality Rates:

I defined and calculated my own mortality rates for all studies in the review as shown in Table 3.3. Published mortality rates (if any were stated in studies) were not used. I used rates, numerators and denominators that I defined apriori (Table 3.3) for all the eligible studies in order to maintain consistency throughout the analysis.

Table 3.3: Formulas for the rates for stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths for all studies retained in the systematic review

Name of rate	**Numerator**	**Denominator**	**Formula**
Stillbirth rate	No. of stillbirths	No. of births (live births + stillbirths)	Stillbirth rate = (No. of stillbirths/ No. of births) × 1000

Early neonatal death rate	No. of early neonatal deaths	No. of live births	Early neonatal death rate =(No. of early neonatal deaths/ No. of live births) × 1000
Late neonatal death rate	No. of late neonatal deaths	No. of live births excluding early neonatal deaths	Late neonatal death rate =(No. of late neonatal deaths/ No. of live births excluding early neonatal deaths) × 1000
Perinatal death rate	No. of perinatal deaths	No. of births (live births + stillbirths)	Perinatal death rate = (No. of perinatal deaths/ No. of births) × 1000

I extracted numerators and denominators from the text, tables and/or flowcharts of eligible studies. I obtained the mean year corresponding to death rate for each study by obtaining the year corresponding to the mid-point of the data collection period (prospective cohort studies) or of the time period during which the deaths occurred (cross-sectional studies and retrospective cohort studies).

For each mortality outcome, I obtained rates for each individual study and I also pooled rates by national and sub-national studies for each country and for South Asia. The pooled review rates for each country were compared to mathematically modelled rates and adjusted rates from the literature which corresponded to a similar period of years. I obtained the overall mean year (e.g. 2001) corresponding to each summary mortality rate (e.g. summary stillbirth rate) in my review by calculating the mean of all the (mean) years corresponding to death rates for all studies of that outcome (e.g. all stillbirth studies).

I created forest plots, pooled by country and for South Asia, from data extracted from retained studies using STATA 12.1v on the basis of meta-analysis of proportions and used a random effects model. From the forest plots I obtained: 95% confidence intervals, weights that each study contributed to the analysis, level of heterogeneity and pooled estimates for rates. I performed sub-group analyses for national and sub-national studies. With all the forest plots, I also ordered the studies on the basis of the mean year representative of the rate to see if there were any time trends in the rates obtained for a country or for South Asia but formal analytical methods such as the use of meta-regression to test for the effect of year on mortality rates were not used. I also checked to see if there was any difference between the mortality rates that I calculated compared to the mortality rates reported by the studies which adjusted for clustering or for the sampling strategy. I also noted if any rates were outliers

when compared to studies from the region. If any outlier rates were detected, they were not excluded as excluding studies with outlier rates introduces bias into the analysis (Higgins and Green, 2011). However, sensitivity analyses with and without outlier rates were conducted to see the effects of outlier rates on the overall rate.

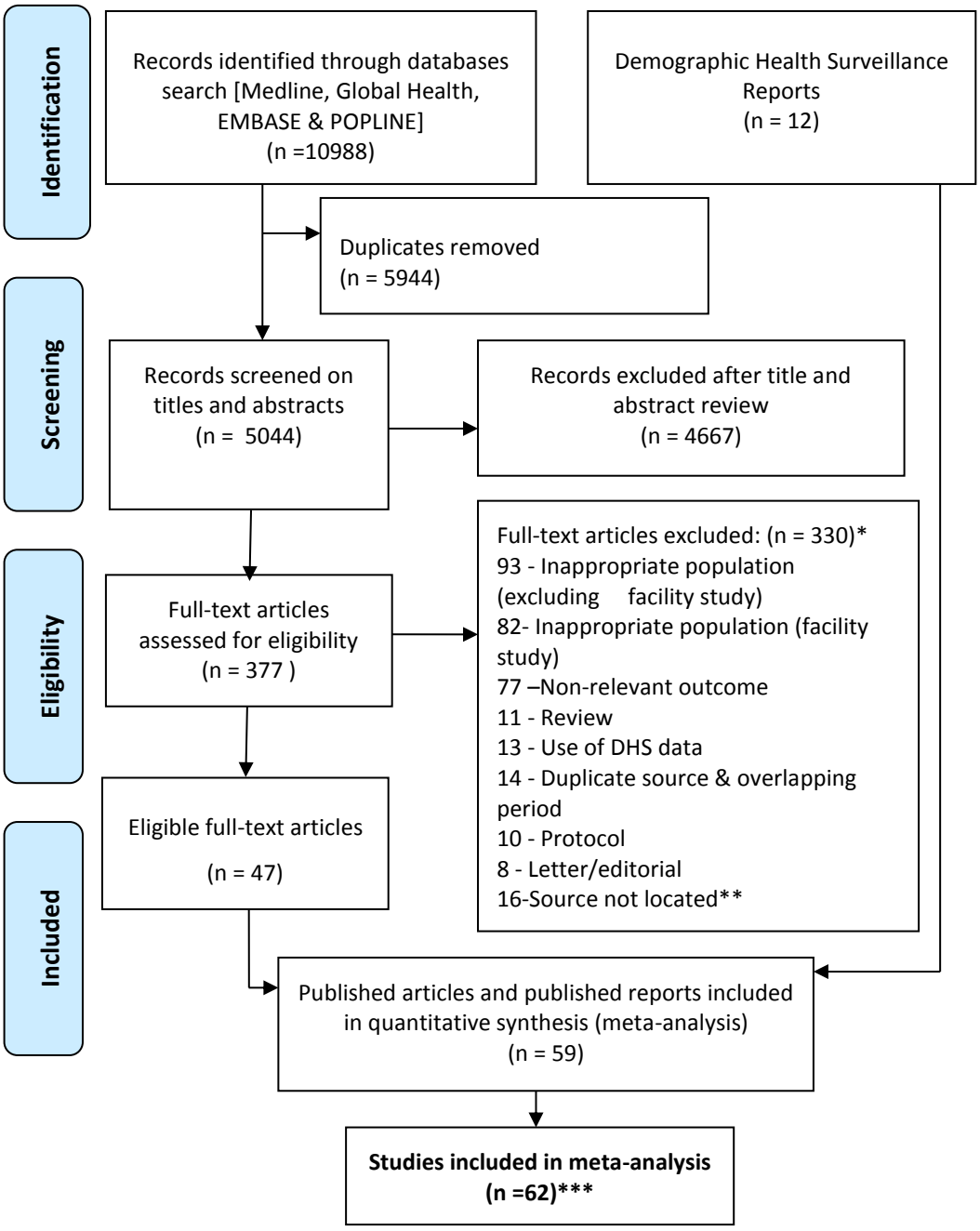
I assessed heterogeneity among the studies by using the I^2 statistic as well as the p-value of the chi-square test of heterogeneity as recommended by the Cochrane handbook for systematic reviews (Higgins et al., 2003, Higgins and Green, 2011). I considered cut-off values for I^2 statistic interpretation according to Higgins and Green (2011) where: 0% to 40% heterogeneity is considered not important; 30% to 60% is considered moderate heterogeneity; 50% to 90% is considered substantial heterogeneity and 75% to 100% is considered considerable heterogeneity. However, it should be noted that the ranges overlap and that the importance of the value of I^2 is also dependent on the direction and magnitude of effects seen and also on the p-value obtained (Higgins & Green 2011).
Since a random effects model is appropriate when heterogeneity exists among studies(Higgins & Green 2011), I used a random effects model for this review as the studies were considered to vary greatly within and between countries.

I also obtained the ratios of stillbirth rates to early neonatal death rates for South Asia and its constituent countries from pooled rates obtained from: (a) sub-national and national studies (b) sub-national studies and (c) national studies.

3.4 Results

3.4.1 Search strategy results

The search strategy identified 10988 publications of which 5944 were duplicates and were discarded (Figure 3.1). The remaining 5044 publications were screened by title and abstract. Of these 5044 publications, 377 full-text articles were assessed for eligibility. The number of eligible publications retained was 59 and these yielded a total of 62 eligible studies for the review. Of the 59 publications, 47 were journal publications (representing 50 study populations) while 12 were National Demographic and Health Survey (DHS) reports (representing 12 nationally representative study populations) from Afghanistan, Bangladesh, India, Maldives, Nepal, Pakistan, and Sri Lanka. No studies could be identified for Bhutan.



*Articles may have been excluded for multiple reasons. **Full-text unavailable from journal websites, the British Library or after two email non-responses from publisher/author. ***62 studies obtained from 59 publications

Flowchart modified from the PRISMA flowchart from "Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. MJ 2009, 339:b2535 " (Moher et al., 2009)

Figure 3.1: Flowchart showing the flow of information through the different phases of the systematic review during the study selection process.

3.4.2 Description of studies

The systematic review identified 62 studies of which there were 12 national studies and 50 sub-national studies. Table 3.4 below summarises the majority of study characteristics of the studies eligible for the review. Study characteristics are tabulated in detail later (Tables 3.5-3.9)

Table 3.4: Summary table for characteristics of all studies from South Asia

	Afghanistan	Bangladesh	India	Maldives	Nepal	Pakistan	Sri Lanka	**South Asia***
No. of studies	**1**	**17**	**21**	**1**	**11**	**10**	**1**	**62**
Area of coverage								
Sub-national	0	13	20	0	8	9	0	**50**
National	1	4	1	1	3	1	1	**12**
Setting								
Urban	0	1	3	0	0	2	0	**6**
Rural	0	12	14	0	8	4	0	**38**
Mixed	1	4	4	1	3	4	1	**18**
Study type								
Cohort	0	11	10	0	6	7	0	**34**
Cross-sectional	1	5	9	1	3	2	1	**23**
Surveillance	0	1	1	0	1	1	0	**4**
Unclear	0	0	1	0	0	0	0	**1**
Study population								
Live births and stillbirths	1	15	21	1	10	10	1	**59**
Live births only	0	2	0	0	1	0	0	**3**
Loss to follow-up/ response rate								
Reported	1	13	13	1	9	8	1	**46**
Not reported	0	4	8	0	2	2	0	**16**
Mortality outcomes measured								
Stillbirth	1	15	20	1	9	10	1	**57**
Early neonatal death	1	11	10	1	9	4	1	**37**
Late neonatal death	1	9	6	1	6	4	1	**28**
Perinatal death	1	9	11	1	7	5	1	**35**

*No studies were obtained for Bhutan

The country contributing the largest number of studies was India (21) followed by Bangladesh (17). The country-wise distribution of national and sub-national studies is shown in Table 3.5,

with Bangladesh and India having the greatest number of sub-national studies and Bangladesh and Nepal providing the highest number of national studies. The majority of studies (38/62) were from a rural or mostly rural setting, a third was from mixed areas and only six were from urban areas. One Pakistan study (Gustavson et al. 2005) reported an urban rate, a rural rate and a mixed setting rate.

Regarding study design, over half were cohort studies (34/62). Cross-sectional studies constituted around a third of all studies (23/62). There were also four surveillance studies, three of births and deaths reported by informants (Azad et al. 2010; Manandhar et al. 2010; Tripathy et al. 2010) and one based on repeated cross-sectional assessments (Bhutta, Soofi, et al. 2011). There was one study for which the study design was unclear but which could be possibly a retrospective record review (Sinha 2006).

Almost all studies (59/62) examined study populations of live births as well as stillbirths, with only 3 studies assessing live births exclusively (Arifeen et al., 2012, Baqui et al., 2009, Katz et al., 2003). Loss to follow-up was calculated for cohort studies and the response rate was calculated for cross-sectional studies. Loss to follow-up or the response rate was reported for three-fourths of all studies (Table 3.4). Out of all the studies the lowest response rate (70.0%) in a cross-sectional study was reported by Bamji et. al.(Bamji et al., 2008a) and the lowest percentage of the population followed up (57.7%) in a cohort study was reported by Niswade et al., 2011 (Tables 3.5-3.9). Only one study, Jehan et al., 2009, reported that the baseline characteristics for respondents lost to follow-up were similar to those of respondents followed up.

Almost all the sub-national and national studies reported stillbirths (57/62) while more than half reported early neonatal deaths (37/62) and perinatal deaths (35/62) with late neonatal deaths reported the least (28/62). All 12 national studies provided information on stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths.

The study characteristics of the eligible sub-national and national studies are described in Tables 3.5-3.8 and 3.9, respectively. The tables are stratified by risk-of-bias for each study and provide information on study setting, study population, method of ascertainment (of pregnancies, births and deaths), definitions (for stillbirths, early neonatal deaths and late neonatal deaths) and follow-up or response rate. The quality assessment of studies by categorising studies according to risk-of-bias is described later (Table 3.11).

All the deaths included in this review occurred during varying time periods ranging from 1975 to 2010 (Tables 3.5-3.9). The mean year for each study corresponding to the calculated death rate(s) ranged from 1985 to 2008.

Table 3.5: Characteristics of sub-national studies from Bangladesh retained in the systematic review, reporting stillbirths, early neonatal deaths and late neonatal deaths.

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
Studies at low risk-of-bias (2/13)									
Rahman et al. 2011	Matlab sub-district, Chandpur district (2005-06; 2008-09) Rural	Prospective cohort study of pregnancies to women in the study area.	10107 stillbirths and live births	●Pregnancy: research CHW visits households monthly (two-monthly from 2007) and notes LMP date (additional urine spot test from 2007) ●Birth: research CHW visits households monthly/two-monthly	●Research CHW visits households monthly/two-monthly	Birth of a dead foetus after 28 weeks of gestation	Deaths within 7 days of birth	_	Not reported
Ronsmans et al. 2008	Matlab sub-district, Chandpur district (1975-02) Rural	Retrospective cohort of pregnant women residing in the study area	97802 stillbirths and live births	●Pregnancy: research CHW visits households monthly and notes down LMP date ●Birth: research CHW visits households monthly	Research CHW visits households monthly	Foetal death after 28 weeks of gestation but before delivery of the head.	Deaths in the first 7 days of life	Deaths during 8-28 days of life	Not reported
Studies at high risk-of-bias (3/13)									
Azad et al. 2010	Bogra, Faridpur and Moulavibazar districts (2005-07) Rural	Surveillance study of births and deaths within an RCT	15257 stillbirths and live births	●Birth: monthly reporting by traditional birth attendant and verified by interviewers. Recently delivered women also identify other births in the area. ●GA assessment not reported	●Monthly reporting by traditional birth attendant and verified by interviewers	Foetal death after 28 weeks of gestation but before delivery of the baby's head.	Deaths within 0-6 days of birth	Deaths from 7-28 days after birth	Survival status obtained for 82.0% of enrolled births

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition		Follow-up/response (%)
Baqui et al. 2009	Beanibazar, Zakiganj and Kanaighat sub-districts, Sylhet district (2004-05) Rural	Prospective cohort of women aged 15-49 years becoming pregnant within RCT	3392 live births	●Pregnancy: research CHW visits households every 2 months and notes LMP date ●Birth: reported by community informants	Research CHW visits on Days 1, 3, 7 and on any one day between Days 29-35.	_	Deaths within 6 days of birth	Deaths from 7-27 days after birth	●Survival status known for 84.2% of enrolled pregnancies ●Survival status known for 100% of enrolled live births.
(Baqui et al. 2008)	Beanibazar, Zakiganj and Kanaighat sub-districts, Sylhet district (2003-05) Rural	Prospective cohort of women aged 15-49 years becoming pregnant within RCT	15914 stillbirths and live births	●Pregnancy: research CHW visits households every 2 months and notes LMP date ●Birth: reported by community informants	Reported by community informants	Foetal death with a GA of 28 weeks or more on the basis of the LMP	_	_	Survival status known for 84.2% of enrolled pregnancies
Studies at unclear risk-of-bias (10/13)								
(Mercer et al. 2006)	12 sub-districts, 12 districts (not named) (2001-03) Rural	Retrospective cohort study of pregnant married women aged 15-49 years residing in the study area	33615 stillbirths and live births	●Pregnancy: research CHW visits households every 2 months. PI method not reported ●Birth: Birth and immunization records	●Birth and immunization records	No definition	_	_	Not reported

Table 3.7 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
Bari et al. 2002	1 district each from Dhaka, Rajshahi, Chittagong and Khulna divisions (1992-93) Rural	Prospective cohort study of pregnant women of less than 6 weeks' pregnancy	924 stillbirths and live births	●Pregnancy and birth: monthly home visits. ●Pregnancy detection method unclear and person reporting births and pregnancies not reported	●Monthly home visits (Person reporting deaths not reported)	No definition	Deaths within 7 days of birth	_	●Survival status known for 98.7% of enrolled pregnancies ●Survival status known till 7 days for 100% of live births.
Osendarp et al. 2000	Dhaka city, Dhaka district (1996) Urban	Prospective cohort of women with 12 to 16 weeks of pregnancy and with no serious medical condition within RCT	232 stillbirths and live births	●Pregnancy and birth: unclear (by 'an established PI system') ●GA assessed by LMP date	Unclear	No definition. Includes infants who died shortly after birth (time not specified)	_	_	●Survival status known for 80.0% of enrolled pregnancies
(Arifeen et al. 2012)	Beanibazar, Zakiganj and Kanaighat sub-districts, Sylhet district (2007-09) Rural	Prospective cohort of live births to married women within RCT*	12022 live births	●Pregnancy: research CHW** visits households every 2 months and notes LMP*** date ●Birth: reported by family informant and confirmed by research CHW	●Research CHW visits on Days 1, 3, 6, 9, 15 and also on any one day between Days 28-35.	_	Deaths within 7 days of birth	Not reported	Survival status till 28 days known for 95.6% of live births

Table 3.8 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
(Darmstadt et al. 2010)	Mirzapore sub-district, Tangail district (2004-06) Rural	Cross-sectional study of women having at least one pregnancy outcome during 2003-05 within RCT	5350 stillbirths and live births	Women's recall	Women's recall	No definition	_	_	87.8% of all eligible women responded
(Rahman et al. 2010)	Matlab sub-district, Chandpur district (2002-04) Rural	Prospective cohort of women with pregnancies less than 14 weeks and no severe illness within RCT	2561 stillbirths and live births	●Pregnancy: research CHW visits households monthly and PI by urine test (additionally confirmed by ultrasound-time not reported) ●Birth: specially trained 'team' visit pregnant women monthly.	●Specially trained 'team' visit monthly	Birth of a dead foetus after 28 weeks of gestation	_	_	Survival status known for 91.3% of enrolled pregnancies.
(Sloan et al. 2008)	42 sub-sub-districts, Dhaka and Sylhet divisions (Not reported) Rural	Prospective cohort of births to pregnant women aged 12-50 years within RCT	2129 stillbirths and live births	●Pregnancy: research CHW visits households every 3 months. PI* method not reported. ●Birth: Unclear	Reported by research CHW (frequency of visit not reported)	No definition	Deaths in the first 7 days of life	Deaths during 8-28 days of life	Survival status known for 99.96% of enrolled births (pregnancies not reported)

Table 3.9 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition		Follow-up/response (%)
(Cherry et al. 2008)	600 villages in Dhaka, Barisal, Chittagong and Sylhet divisions (2001-03) Rural	Prospective cohort of pregnant women living within study area	30984 stillbirths and live births	●Pregnancy: female 'paramedics' visits households (frequency not reported). PI method not reported. ●Birth: Unclear	Unclear	Neonates observed to breathe but failing to establish viable respiration	_	_	Not reported

*RCT-randomized controlled trial **CHW-community health worker ***LMP-last menstrual period †PI- pregnancy identification ‡GA-gestational age

Table 3.10: Characteristics of sub-national studies from India retained in the systematic review, reporting stillbirths, early neonatal deaths and late neonatal deaths.

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
Studies at high risk-of-bias (3/20)									
(More et al. 2009)	48 slums, Mumbai city (2005-06) Urban	Cross-sectional study of births and deaths in 1 year (Oct 05- Sep 06) within RCT	5687 stillbirths and live births	●Birth: reported by community informants. Verified by interviewer home visits (visit frequency not reported) ●GA assessment not reported.	●Reported by community informants. Verified by interviewer home visits (visit frequency not reported)	Deaths after 22 weeks of gestation and before birth.	_	_	●Survival status known till 28 days for 84.7% of all births
(Darmstadt et al. 2006)	2 districts, Uttar Pradesh state (Not reported) Rural	Cross-sectional study of births and deaths in ever-married women aged 13-49 years in the two years preceding the study.	13522 stillbirths and live births	●Women's recall	●Women's recall	Births after 28 weeks of gestation that failed to cry, move or breathe	Deaths within 0-6 days of birth	Deaths within 7-27 days of birth	Survival status known for 86% of all eligible women's pregnancies
(Nath et al. 2004)	Belgaum district (Not reported) Rural	Cross-sectional study of births and deaths in married women residing in the study area	320 stillbirths and live births	●Women's reproductive lifetime recall	●Women's reproductive lifetime recall	Foetal losses after 28 weeks of gestation	_	_	Not reported

Table 3.6 (continued).

Studies at unclear risk-of-bias (17/20)									
Author Publication Year	**Region (Time period corresponding to data) Setting**	**Study Design**	**Study population**	**Ascertainment of pregnancy/ birth**	**Ascertainment of death**	**Definition**			**Follow-up/response (%)**
						Stillbirth	**Early neonatal death**	**Late neonatal death**	
(Manna et al. 2011)	Darjeeling and Jalpaiguri districts (2007-08) Rural	Cross-sectional study of married women aged 18-42 years living in the study area	4031 stillbirths and live births	●Women's recall (recall period not reported)	●Women's recall (recall period not reported)	_	_	_	Not reported
(McClure et al. 2011) (India site)	Nagpur city, Belgaum district and Orissa state (2005-10) Mixed	Prospective cohort of pregnant women from 24-28 weeks of gestation	72293 stillbirths and live births	●Pregnancy: Unclear. PI* method not reported. ●Birth: reported by birth attendants (TBA**, family & health facility), community informants and registry administrators. ●GA assessed by LMP date	●reported by birth attendants (TBA, family & health facility), community informants and registry administrators.	Gestation with no evident signs of life (breathing, crying, heartbeat, movement). Birth weight ≥ 1000g (measured by scales/estimation).	_	_	Not reported
(Niswade et al. 2011)	Ramtek subdistrict, Nagpur district (2006-07) Rural	Prospective cohort of all pregnant women of tribal and non-tribal areas with high neonatal mortality levels	562 stillbirths and live births	●Pregnancy: Unclear. Research CHWs visit households (visit frequency and PI method not reported) ●Birth: reported by local government CHW or TBA.	●Study research assistant visits at birth, Days 1, 7, 28 and 2nd and 4th months.	No definition.	_	_	●Survival status known for 57.7% of enrolled pregnancies.

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Tripathy et al. 2010)	Saraikela Kharswan, West Singhbhum and Keonjhar districts (2005-08) Rural	Surveillance. Monthly cross-sectional assessment of all births and newborn deaths to 15-49 year old women during 2005-08 within RCT***	9089 stillbirths and live births	●Births: monthly reporting by community informants (TBA or active village member).Interviewer verifies 6 weeks after delivery.	●Monthly reporting by community informants (TBA or active village member).Interviewer verifies 6 weeks after delivery.	No definition.	Deaths within 6 days of birth	Deaths within 7-28 days of birth	●Survival status known till 28 days for 98.2% of all births
(Subramoney et al. 2010)	Mumbai city (Not reported) Urban	Prospective cohort of pregnant women of 3 to 7 months' gestation living in the study area	924 stillbirths and live births	●Pregnancy: research CHW visits households (visit frequency not reported) (PI method not reported) ●Birth: Unclear. ●GA assessed by LMP date. Verified by medical records if available.	●Unclear	Newborn who did not breathe or show any other evidence of life at birth after 20 weeks of gestation.	_	_	●Survival status known for 79.2% of enrolled pregnancies.
(Tielsch et al. 2009)	2 districts, Tamil Nadu (1998-2000) Rural	Prospective cohort of pregnant women within RCT	13294 stillbirths and live births	●Pregnancy: Unclear ●Birth: reported by community informants. Verified by research CHW within 72h of delivery. ●GA assessed by LMP date	●Reported by community informants. Deaths (stillbirths) verified by research CHW within 72h of delivery.	No definition	_	_	●Survival status known for 93.8% of enrolled pregnancies.

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Benjamin et al. 2009)	Ludhiana district (2006-07) Mixed	Prospective cohort of pregnant women in the study area	1431 stillbirths and live births	●Pregnancy and birth: Unclear	●Unclear	No definition	No definition	_	●Survival status known for 92.2% of enrolled pregnancies. ●Survival status till 7 days known for 100% of births
(George et al. 2009)	Kaniyambadi subdistrict, Vellore district (1986-2005) Rural	Prospective cohort of pregnancies, deliveries, births and deaths† in the study area	49806 stillbirths and live births	●Pregnancy and birth: research CHW visits households weekly and notes LMP date. Verified by fortnightly nurse visits followed by fortnightly doctor visits.	●Research CHW visits households weekly. Verified by fortnightly nurse visits followed by fortnightly doctor visits.	GA between 20 and 50 weeks of gestation or a birth weight ≥ 400g. Birth weight measurement not reported.	No definition	_	Not reported
(Bamji et al. 2008)	Medak district (1998-2003) Rural	Cross-sectional study of births and deaths in a 5 year period in the study area	380 stillbirths and live births	●Women's recall	●Women's recall	No definition	_	_	70% of all eligible women responded

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Kumar et al. 2008)	Shivgarh village, Sultanpur district (2004-05) Rural	Prospective cohort of pregnant women within RCT	1143 stillbirths and live births	●Pregnancy: 'trained evaluation team' member visits households 3-monthly and notes LMP date. Reports by pregnant women and community informants. ●Birth: Daily reports by community informants. Verified by 'trained evaluation team' in 2 home visits (during and after study period).	●Daily reports by community informants. Verified by 'trained evaluation team' in 2 home visits (during and after study period). Ascertainment unclear.	Births after 190 days from date of LMP that did not move, breathe or cry at birth	Deaths within 0-6 days of birth	Deaths within 7-28 days of birth	●Survival status known for 98.9% of enrolled pregnancies. ●Survival status known till 28 days for 100% of live births
(ICMR Young Infant Study Group 2008)	Andhra Pradesh, Orissa, Bihar, Rajasthan and Maharashtra states (2002-03) Rural	Cross-sectional study of births and deaths occurring in 1 year in the study areas	30473 stillbirths and live births	●Recall (person interviewed unclear)	●Recall (person interviewed unclear)	No definition	Deaths within 7 days of birth	Deaths within 2nd to 4th weeks of life.	Not reported
(Tielsch et al. 2007)	2 sub-districts, Tamil Nadu state (1998-2001) Rural	Prospective cohort of pregnant women within RCT	13294 stillbirths and live births	●Pregnancy: Unclear. PI method not reported. ●Birth: reported by community informants ('when birth occurs')	●Reported by community informants	No definition	_	_	●Survival status known for 99.1% of enrolled pregnancies.
(Singh & Arora 2007)	Chandigarh union territory (2004) Rural	Prospective cohort of pregnant women	216 stillbirths and live births	●Pregnancy: Unclear. Research CHW visits household monthly in 11.7% of pregnancies. No visits in remainder. PI method not reported. ●Birth: Unclear	●Unclear	No definition	_	_	●Survival status known for 81.3% of enrolled pregnancies.

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Sinha 2006)	Delhi city (1997-98) Urban	Unclear. (Retrospective record review of pregnancies, births and deaths)	799 stillbirths and live births	●Research CHWs register all pregnancies and births but methods are unclear	●Research CHWs register all deaths but methods are unclear	No definition	Deaths within 7 days of birth	_	Not reported
(Ehrenstein et al. 2006)	South 24-Parganas district (1995-96) Rural	Cross-sectional study of births and deaths in married women aged 20-40 years in a previous study and similar women of the household and neighbourhood	558 stillbirths and live births	●Women's reproductive lifetime recall	●Women's reproductive lifetime recall	No definition	_	_	99% of all eligible women responded
(Bang et al. 2002)	10 districts, Maharashtra state (1998-2000) Mixed	Cross-sectional study of births and deaths in 1999 (1 year recall), prospective cohort of pregnancies (1999-2000) and three 4-mthly surveys(2000)	9688 stillbirths and live births	●Pregnancy: Unclear. Research CHW visits households once in 6 months. PI and GA assessment methods not reported. ● Birth: 1 year recall for household survey. CHW and TBA reports births to research CHW. Verified by research CHW supervisor visit (time not reported)	●1 year recall for household survey. CHW and TBA reports births to research CHW. Verified by research CHW supervisor visit (time not reported)	Foetal death after 28 weeks of gestation.	Deaths within 7 days of birth	_	Not reported

Table 3.6 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Bang et al. 2001)	Gadchiroli district, Maharashtra state (1995-96) Rural	Prospective cohort of pregnant women	584 stillbirths and live births	●Pregnancy: Unclear. Listing of pregnant women by research CHW (visit frequency not reported).PI and GA assessment by LMP date. Research CHW visits pregnant women thrice, every 1 month in third trimester. ● Birth: Unclear .Research CHW attended labour and reported some births. Different male CHWs also 'reported prospectively' and detected missed births in 6-monthly cross-sectional surveys	●Research CHW visited on Days 1,2,3,5,7,14,21 and 28. Different male CHWs also 'reported prospectively' and detected missed deaths in 6-monthly cross-sectional surveys	Delivery of a baby that showed no breathing, crying or muscular movements at birth. (≥28 weeks' gestation)	Deaths within 0-6 days of birth	Deaths within 7-27 days of birth	Not reported

*PI- pregnancy identification **TBA- traditional birth attendant ***RCT-randomized controlled trial ŧdeaths- refers to newborn deaths in this review

Table 3.11: Characteristics of sub-national studies from Nepal retained in the systematic review, reporting stillbirths, early neonatal deaths and late neonatal deaths.

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
Studies at low risk-of-bias (4/8)									
(Lee, Darmstadt, et al. 2009)	Sarlahi district (1999-01) Rural	Prospective cohort study of women likely to get pregnant within RCT	4273 live births and stillbirths	●Pregnancy: research CHW visits households 5-weekly, notes LMP date and provides urine test for women not menstruating for 30 days. ● Birth: research CHW visits households fortnightly until 3 months after delivery. Verified by anthropometrist within 72h of delivery	●Research CHW visits households fortnightly until 3 months after delivery. Death verified by anthropometrist within 72h of delivery.	GA† of 28 weeks or more	_	_	●Survival status known for 99.7% of enrolled pregnancies
(Manandhar et al. 2004)	24 sub-districts, Makwanpur district (2001-03) Rural	Prospective cohort of married women aged 15-49 years, likely to get pregnant and within RCT	3303 live births and stillbirths	●Pregnancy: research CHW visits households monthly and notes LMP date (considered pregnant if non-menstruating for 3 months) ●Birth: reported by research CHW at 7 months of gestation and 1 month after delivery	●reported by research CHW at 7 months of gestation and 1 month after delivery	Foetal death after 28 weeks of gestation but before delivery of the head.	Deaths within 7 completed days of birth.	Deaths within 7- 28 completed days of birth	●Survival status known for 95.0% of enrolled pregnancies. ●Survival status known till 1 month for 100% of live births
Christian et al. 2003	Sarlahi district (1999-2000) Rural	Prospective cohort of women of reproductive age likely to get pregnant and within RCT	916 live births and stillbirths	●Pregnancy: research CHW visits households 5-weekly, notes LMP date and provides urine test for women not menstruating for 30 days ●Birth: research CHW visits households twice every week until 3 months after delivery	● Research CHW visits households twice every week until 3 months after delivery	GA of 28 weeks or more	Deaths within the first 7 days of life.	_	●Survival status known for 99.9% of enrolled pregnancies. ●Survival status known till 6 months for 99.8% of live births

Table 3.7 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Katz et al. 2003)	Sarlahi district (1994-97) Rural	Prospective cohort of women of reproductive age within RCT	15469 live births	●Pregnancy and birth: research CHW visits households weekly and asks about menstruation in the past week	●Research CHW visits households weekly and at 3 months after delivery	_	Deaths within the first 7 days of life.	Deaths within 8-28 days of birth	●Survival status known till 6 months for 92.6% of live births
Studies at high risk-of-bias (1/8)									
(A. C. Lee, Mullany, et al. 2011)	Sarlahi district (2002-06) Rural	Prospective cohort of women with 6 months of pregnancy within a RCT*	24531 live births and stillbirths	●Pregnancy: research CHW** visits households monthly and notes LMP*** date ●Birth: reported by family informants. Confirmed by research CHWs.	● Reported by family informants. Confirmed by research CHWs by visits on Days 1, 2,3,4,6,8,10,12,14, 21 and 28.	Infant born without any signs of life (i.e. crying, breathing or movement) at or above 28 weeks' gestation	Deaths in the first week of life	_	●Survival status known for 92.9% of enrolled pregnancies. ●Survival status known till 28 days for 100% of live births
Studies at unclear risk-of-bias (3/8)									
(Maskey et al. 2011)	Bara district (2003-05) Rural	Cross-sectional study of births and deaths from pregnant mother immunisation lists, research CHW- led pregnant women groups and peer memory (2 year recall)	2025 live births and stillbirths	●Women's recall	●Women's recall	No definition	No definition	_	Not reported

Table 3.7 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Manandhar et al. 2010)	Dhanusha district, Janakpur zone (2006-08) Rural	●Surveillance of births and deaths occurring in 2 years in the study area	25982 live births and stillbirths	●Birth: reported by community informants. Verified by research CHW visit 6 weeks after delivery.	●Reported by community informants. Verified by research CHW visit 6 weeks after delivery.	No definition	No definition	No definition	Not reported
(Katz et al. 2008)	Sarlahi district (1992-2000) Rural	Prospective cohort study of women likely to get pregnant within two RCTs	10171 live births and stillbirths	●Pregnancy: research CHW visits households weekly (1st trial) and 5-weekly (2nd trial), notes LMP date (both trials) and provides urine test (2nd trial) for women not menstruating for 30 days. ● Birth: reported by research CHW in weekly visits (1st trial). Visit frequency unclear (2nd trial)	●Reported by research CHW in weekly visits till birth, and at 3 month and 6 month (1st trial). Visit frequency unclear (2nd trial)	Deliveries where the infant did not move or cry after delivery after 28 weeks of gestation	_	_	●Survival status known for 98.5% of enrolled pregnancies.

*RCT- randomized controlled trial **CHW – community health worker***LMP-last menstrual period †GA- gestational age

Table 3.12: Characteristics of sub-national studies from Pakistan retained in the systematic review, reporting stillbirths, early neonatal deaths and late neonatal deaths.

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
Studies at unclear risk-of-bias (9/9)									
(McClure et al. 2011) (Pakistan site)	Thatta district (2005-10) Rural	Prospective cohort of women from 24-28 weeks' gestation	45765 stillbirths and live births	●Pregnancy: Unclear. PI* method not reported. ●Birth: reported by birth attendants (TBA**, family & health facility), community informants and registry administrators. ●GA*** measured by LMP† method	●reported by birth attendants (TBA, family & health facility), community informants and registry administrators.	Gestation in which no signs of life (breathing, crying, heartbeat, movement) are evident. Birth weight ≥ 1000g (measured by scales/estimation).	_	_	Not reported
(Bhutta, Soofi, et al. 2011)	Hala and Matiari subdistricts, Sindh province (2006-08) Rural	3-monthly cross-sectional assessments of births and deaths in preceding 3 months within RCT‡.	11568 stillbirths and live births	Women's recall	Women's recall	No definition	Deaths from Day 0-7 of birth	Deaths from Day 8-28 of birth	●Survival status known for 98.6% of enrolled pregnancies. ●Survival status known till 1 month for 100% of live births

Table 3.8 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Saleem et al. 2010)	Punjab, Sindh, Baluchistan and North West Frontier Province (1990-94) Mixed	Cross-sectional study of women aged 15-52 years with minimum 1 pregnancy during reproductive life.	15099 stillbirths and live births	Women's reproductive lifetime recall.	Women's reproductive lifetime recall.	No definition (as reported by women)	_	_	Not reported
(Jehan et al. 2009)	Latifabad town, Hyderabad city (2003-05) Urban	Prospective cohort of women aged ≥16 years, of 20-26 weeks' gestation, no serious medical condition and planning to deliver in the study area.	1280 stillbirths and live births	●Pregnancy: Unclear. Government CHWˆ visits households (visit frequency not reported) ●Birth: Reported by home birth attendants and health facilities. Confirmed by research physician and nurse visit within 48 h of delivery and on Day 28. ●GA assessed by LMP date and ultrasound	●Reported by home birth attendants and health facilities ●Confirmed by research physician and nurse visit within 48 h of delivery and on Day 28.	Foetus born without a heartbeat, respiratory effort or movement or any other sign of life.	Deaths of live born infants occurring on or before 7 days of age.	Deaths from Day 8 to 28.	●Survival status known for 94.0% of enrolled pregnancies. ●Survival status known till 28 days for 87.6% of live births
Bhutta et al. 2009	Karachi city and Sindh district (Not reported) Mixed	Prospective cohort study of women of ≤16 weeks' gestation within RCT	832 stillbirths and live births	●Pregnancy: by household census and fortnightly research CHW household visits. PI method not reported. ●Birth: Research CHWs visit fortnightly and 'liase' with government CHWs and TBAs. ●GA assessed by LMP date and ultrasound	●Research CHWs visit fortnightly and on Days 7, 14 and 28.	GA: ≥28 weeks	Deaths in the first 7 days of life.	Deaths within 8-28 days of life.	●Survival status known for 84.4% of enrolled pregnancies. ●Survival status known till 28 days for 97.9% of live births

Table 3.8 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Jokhio et al. 2005)	7 sub-districts, Sindh province (1998-99) Rural	Prospective cohort study of pregnant women within RCT	8989 stillbirths and live births	●Pregnancy and birth: government CHW visits households monthly ● GA assessment unclear.	●Government CHW visits households monthly	Foetuses born after 6 months that never showed signs of life	_	_	●Survival status known for 99.9% of enrolled pregnancies. ●Survival status known till 42 days for 100% of live births
(Gustavson 2005)a	Lahore city (1984-86) Mixed	Prospective cohort study of women with 5th months' pregnancies	1512 stillbirths and live births	●Pregnancy and birth: Unclear. PI method not reported.	●Unclear	No definition	_	_	●Survival status unclear for enrolled pregnancies ●Survival status known for 70% of births (all settings) till 12 years of age.
(Gustavson 2005)b	Lahore city (1984-86) Urban	Prospective cohort study of women with 5th months' pregnancies	1014 stillbirths and live births	●Pregnancy and birth: Unclear. PI method not reported.	●Unclear	No definition	_	_	●Survival status unclear for enrolled pregnancies ●Survival status known for 70% of births (all settings) till 12 years of age.

Table 3.8 (continued).

Author Publication Year	Region (Time period corresponding to data) Setting	Study Design	Study population	Ascertainment of pregnancy/ birth	Ascertainment of death	Definition			Follow-up/response (%)
						Stillbirth	Early neonatal death	Late neonatal death	
(Gustavson 2005)c	Lahore city (1984-86) Rural	Prospective cohort study of women with 5th months' pregnancies	498 stillbirths and live births	●Pregnancy and birth: Unclear. PI method not reported.	●Unclear	No definition	_	_	●Survival status unclear for enrolled pregnancies ●Survival status known for 70% of births (all settings) till 12 years of age.

*PI-pregnancy identification **TBA- traditional birth attendant ***GA- gestational age †LMP- last menstrual period ‡RCT-randomized controlled trial^CHW-community health worker

Table 3.13: Characteristics of national studies from South Asia retained in the systematic review, reporting stillbirths, early neonatal deaths and late neonatal deaths.

Study Publication Year	Setting, Country, (Time period corresponding to data)	Study Design	Study population	Ascertainment of pregnancy, birth and death	Definition				Response (%)
					Stillbirth	Early neonatal death	Late neonatal death	Perinatal death	
Studies at high risk-of-bias (All)									
Afghanistan Mortality Survey 2010 (2011)(Afghan Public Health Institute Central Statistics et al. 2011)	Urban and rural areas, Afghanistan (2005-10)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age 1**2-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Pregnancy losses occurring after 7 completed months' of gestation	Deaths of live births within the first **7** days of life.	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.20%
Bangladesh Demographic and Health Survey 2007 (2009)(NIPORT et al. 2009)	Urban and rural areas, Bangladesh (2002-07)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **10-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.40%
Bangladesh Demographic and Health Survey 2004 (2005)(NIPORT et al. 2005)	Urban and rural areas, Bangladesh (1999-2004)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **10-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.60%

Table 3.9 (continued).

Study Publication Year	Setting, Country, (Time period corresponding to data)	Study Design	Study population	Ascertainment of pregnancy, birth and death	Definition				Response (%)
					Stillbirth	Early neonatal death	Late neonatal death	Perinatal death	
Bangladesh Demographic and Health Survey 1999-2000 (2001)(NIPORT et al. 2001)	Urban and rural areas, Bangladesh (1994-2000)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **10-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths of live births at age **0 to 7** days.	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	96.90%
Bangladesh Maternal Health Services and Maternal Mortality Survey 2001 (2003)(NIPORT 2003)	Urban and rural areas, Bangladesh (1996-2001)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **13-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths of live births at age **0 to 7** days.	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	97.20%
National Family Health Survey (NFHS-3), 2005-2006: India (2007)(International Institute for Population Sciences IIPS & Macro 2007)	Urban and rural areas, India (2000-06)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	94.50%
Maldives Demographic and Health Survey 2009 (2010)(Macro. 2010)	Urban and rural areas, Maldives (2004-09)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	85.30%

Table 3.9 (continued).

Study Publication Year	Setting, Country, (Time period corresponding to data)	Study Design	Study population	Ascertainment of pregnancy, birth and death	Definition				Response (%)
					Stillbirth	Early neonatal death	Late neonatal death	Perinatal death	
Nepal Demographic and Health Survey 2001 (2002)(Ministry of Health [Nepal] and ORC Macro. 2002)	Urban and rural areas, Nepal (1996-2001)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.20%
Nepal Demographic and Health Survey 2006 (2007) (Ministry of Health and Population (MOHP) [Nepal] and Macro International Inc. 2007)	Urban and rural areas, Nepal (2001-06)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.40%
Nepal Demographic and Health Survey 2011 (2012)(Ministry of Health and Population (MOHP) [Nepal] and ICF International Inc. 2012)	Urban and rural areas, Nepal (2006-10)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	98.10%
Pakistan Demographic and Health Survey 2006-2007 (2008)(National Institute of Population Studies (NIPS)[Pakistan] & Macro International 2008)	Urban and rural areas, Pakistan (2001-07)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Pregnancy losses occurring after 7 completed months' of gestation	Deaths of live births within the first **7** days of life.	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	95.00%

Table 3.9 (continued).

Study Publication Year	Setting, Country, (Time period corresponding to data)	Study Design	Study population	Ascertainment of pregnancy, birth and death	Definition				Response (%)
					Stillbirth	Early neonatal death	Late neonatal death	Perinatal death	
Sri Lanka Demographic and Health Survey 2006-2007 (2009)(Department of Census and Statistics (DCS) and Ministry of Healthcare and Nutrition (MOH). 2009)	Urban and rural areas, Sri Lanka (2002-06)	Cross-sectional	Pregnancies of 7+ months' duration in all ever-married women of age **15-49** years in the total sample of the households who were usual residents or present in the house on the night before the survey	Interviews based on women's recall	Foetal deaths in pregnancies lasting seven or more months	Deaths at age **0-6** days among live-born children	Neonatal deaths excluding early neonatal deaths	Stillbirths and early neonatal deaths	97.50%

Ascertainment of pregnancies, births and deaths:

In the majority of sub-national studies, pregnancies were ascertained by a research CHW visiting households and noting down the LMP (last menstrual period) date (Tables 3.5 to 3.8) while for national studies the number of completed months of pregnancy from women's recall was reported (Table 3.9). Frequency of visits was reported for most studies. Births and deaths were usually reported by key informants (generally family informants or traditional birth attendants) in the community and were frequently confirmed by research community health workers on their planned post-delivery visits. Methods for ascertaining pregnancies, births, and deaths were unclear in some studies.

Definitions of stillbirths and the ascertainment of gestational age:

Almost half of all studies (24/57) reporting on stillbirths did not report definitions for stillbirths (See Appendix IA for study names).The definitions used for stillbirths varied across the studies (Tables 3.5 to 3.8) with the definition in one study (Osendarp et al., 2000) including 'infants who died shortly after birth' though the time period for this was not specified.

Gestational age cut-offs were specified for half of all studies (31/57) and only in 18 of 45 sub-national stillbirth studies (See Appendix IA for study names). Minimum birth weight limits were mentioned in the definitions of very few studies (3/57)(McClure et al., 2011) (McClure et al., 2011)(George et al., 2009) and weight measurement/estimation was reported as used in gestational age assessment in only two studies (McClure et al., 2011), (McClure et al., 2011).

Of the 18 sub-national studies that included gestational age as a criterion in their stillbirth definition, only 5 studies set the minimum gestational age earlier than 28 weeks. These were: 20 weeks (Subramoney et al., 2010, George et al., 2009), 22 weeks (More et al., 2009), 6 months (Jokhio et al., 2005) and 190 days (Kumar et al., 2008). The last two studies had cut-offs that I assumed corresponded to ~ 26 and ~27 weeks, respectively.

Definitions of early neonatal deaths, late neonatal deaths and perinatal deaths:

Definitions for early and late neonatal deaths utilised differing numbers of days as cut-off points. The first day of birth was defined by studies as Day 0 or Day 1. The numbers of days that I describe below refer to number of completed days from birth for each study.

Of the 37 studies which reported early neonatal deaths, only four (Maskey et al., 2011, Manandhar et al., 2010), (Benjamin et al., 2009),(George et al., 2009) did not report the definitions. All the national studies and the majority of sub-national studies (16/25) (See Appendix IA for study names) defined early neonatal deaths as deaths within seven days of birth, with some limiting deaths to within 6 completed days of birth (2/25)(Baqui et al. 2009; Tripathy et al. 2010) or 8 completed days (Bhutta et al., 2011).

Of the 28 studies reporting late neonatal deaths, two sub-national studies did not report the definitions (Manandhar et al. 2010; Arifeen et al. 2012). Most of the sub-national studies reporting definitions (8/13) defined the late neonatal time period as 8-28 completed days after birth (See Appendix IA for study names). Variations of the time period were: 7-28 completed days (Tripathy et al. 2010; Kumar et al. 2008; Manandhar et al. 2004) and 2nd week to 4th week (ICMR Young Infant Study Group 2008).

For each study, perinatal deaths were defined as the total of stillbirths and early neonatal deaths and the definitions for stillbirths and early neonatal deaths were those defined in each study.

3.4.3 Summary of results of study quality assessment:

Quality assessment is shown in detail for each study elsewhere (Appendix IB: Tables 1-4). Of the 62 studies in the systematic review, the numbers of studies at low, high and unclear risk of bias were: 4, 19 and 39, respectively.

Of the 57 South Asian studies reporting on stillbirths, only 4 were considered to be at low risk for bias. Studies at low risk-of-bias were also few for studies on early neonatal deaths (4/36), late neonatal deaths (3/28) and perinatal deaths (4/35). Numbers of low risk-of-bias studies further reduced when these were stratified by country (Table 3.10).

For studies at high risk-of-bias, the most frequently observed reason for studies being at high risk-of-bias was that studies were cross-sectional in nature (fifteen studies). The second most common reason was that birth and death outcomes were reported by community informants (four studies).

Almost half of all studies at unclear risk-of-bias were categorised as such because information on ascertainment of mortality outcomes was unclear or was not reported. The second and third most frequent reasons for studies being at unclear risk-of-bias were that: studies did not report definitions for outcomes, and that pregnancy identification methods were either not identified or reported. Only three studies were considered to be at unclear risk of bias because the person ascertaining the mortality outcomes was not specified. However, of these three studies(Rahman et al. 2010; Bari et al. 2002; Kumar et al. 2008), one additionally did not report the definition for stillbirth (Bari et al. 2002) while ascertainment of deaths was also unclear in another (Kumar et al. 2008).

Table 3.14: Number of studies categorized as high risk-of-bias, low- risk-of-bias and unclear risk-of-bias for the countries of South Asia.

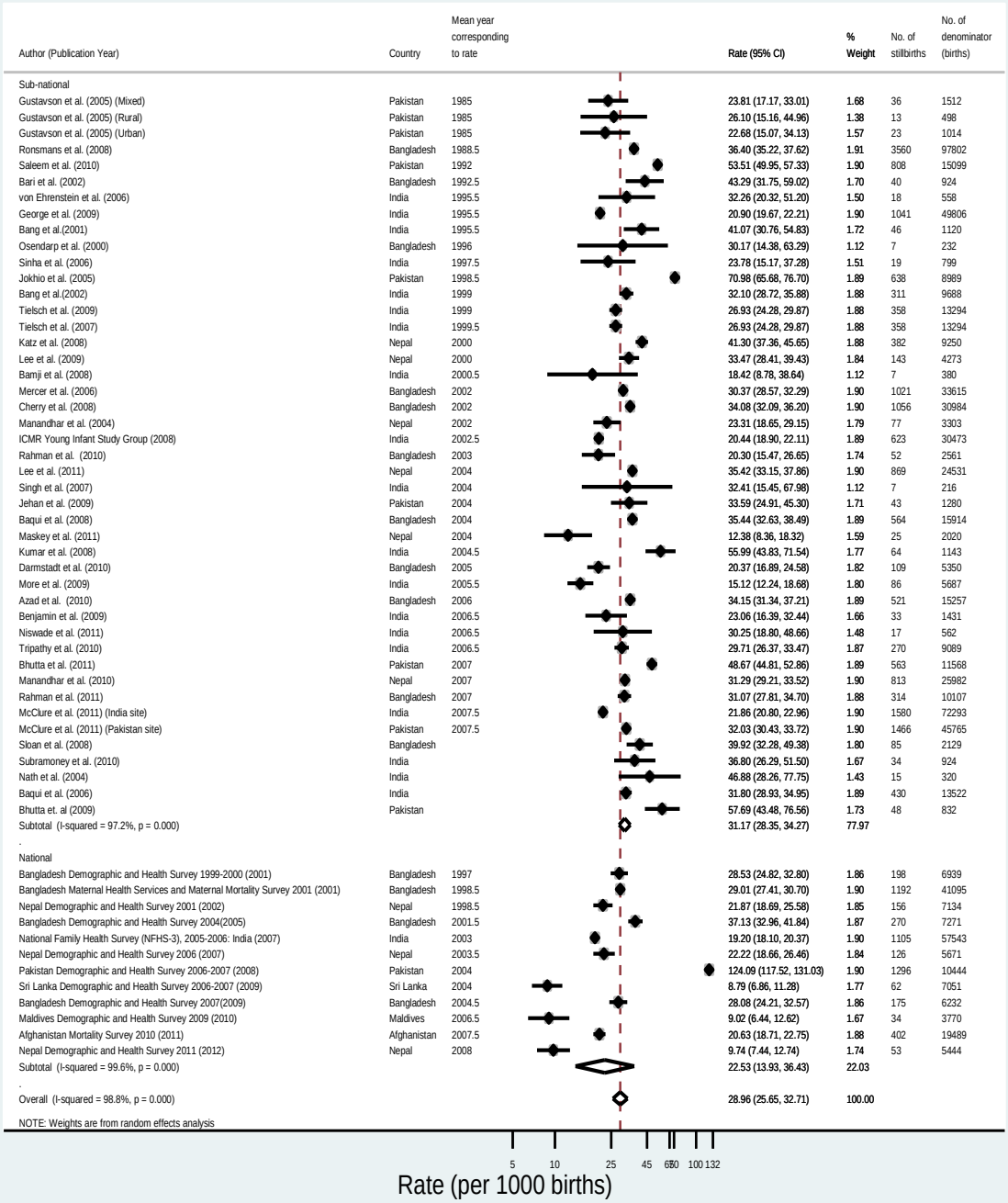
	Studies for stillbirth rate				**Studies for early neonatal death rate**				**Studies for late neonatal death rate**				**Studies for perinatal death rate**			
	Risk-of -bias				**Risk-of -bias**				**Risk-of -bias**				**Risk-of -bias**			
	All	**Low**	**High**	**Unclear**	**All**	**Low**	**High**	**Unclear**	**All**	**Low**	**High**	**Unclear**	**All**	**Low**	**High**	**Unclear**
Afghanistan	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
Bangladesh	15	2	6	7	11	2	6	3	9	1	6	2	9	2	5	2
India	20	0	3	17	10	0	3	7	6	0	3	3	11	0	8	3
Maldives	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
Nepal	9	2	4	3	8	2	4	2	6	2	3	1	7	2	3	2
Pakistan	10	0	1	9	4	0	1	3	4	0	1	3	5	0	1	4
Sri Lanka	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
South Asia	**57**	**4**	**19**	**34**	**36**	**4**	**17**	**15**	**28**	**3**	**16**	**9**	**35**	**4**	**20**	**11**

3.4.4 Mortality rates of the systematic review by outcome type:

Stillbirths

The overall pooled stillbirth rate for South Asia (Figure 3.2) was 29.0/1000 births (95% CI: 25.6-32.7). However, there was strong evidence of substantial heterogeneity between the studies (I^2=98.8%, p<0.0001), suggesting that a pooled rate for South Asia does not capture the diversity of rates observed. The studies are ordered by the average year corresponding to the rate for each study from this forest plot no trends in reduction in rates over time are seen for South Asia. Formal analyses for trends in reduction (e.g. testing the significance of non-linear fits of the relationship between year and mortality rates) had not been performed. Reduction in stillbirth rates over time was also not seen for any of the country-specific forest plots. Within each country heterogeneity between the studies was also very high ranging from I^2 values of 88.5% (Bangladesh) to 99.4% (Pakistan) (Appendix IB: Figures 1-7).

There was almost no difference between the mortality rates (of any type of mortality outcome) that I calculated for studies and mortality rates presented by studies that adjusted for clustering or adjusted for the sampling strategy. For example, Kumar et al. 2008 presented the cluster-adjusted perinatal death rate of 113.2/1000 births which was not significantly different from the (non-adjusted) rate that I calculated of 114.6/1000 births (95%CI: 96.6-136.0). In another example, the Bangladesh DHS 2007 survey reported an adjusted perinatal death rate of 55.0/1000 births while the corresponding (non-adjusted) rate that I calculated was 55.2/1000 births (95%CI: 49.7-61.4). The largest difference in rates was in the study by More et al. 2009 where the authors reported a stillbirth rate of 16.5/1000 births and I calculated a rate of 15.1/1000 births (95%CI: 12.24-18.68).

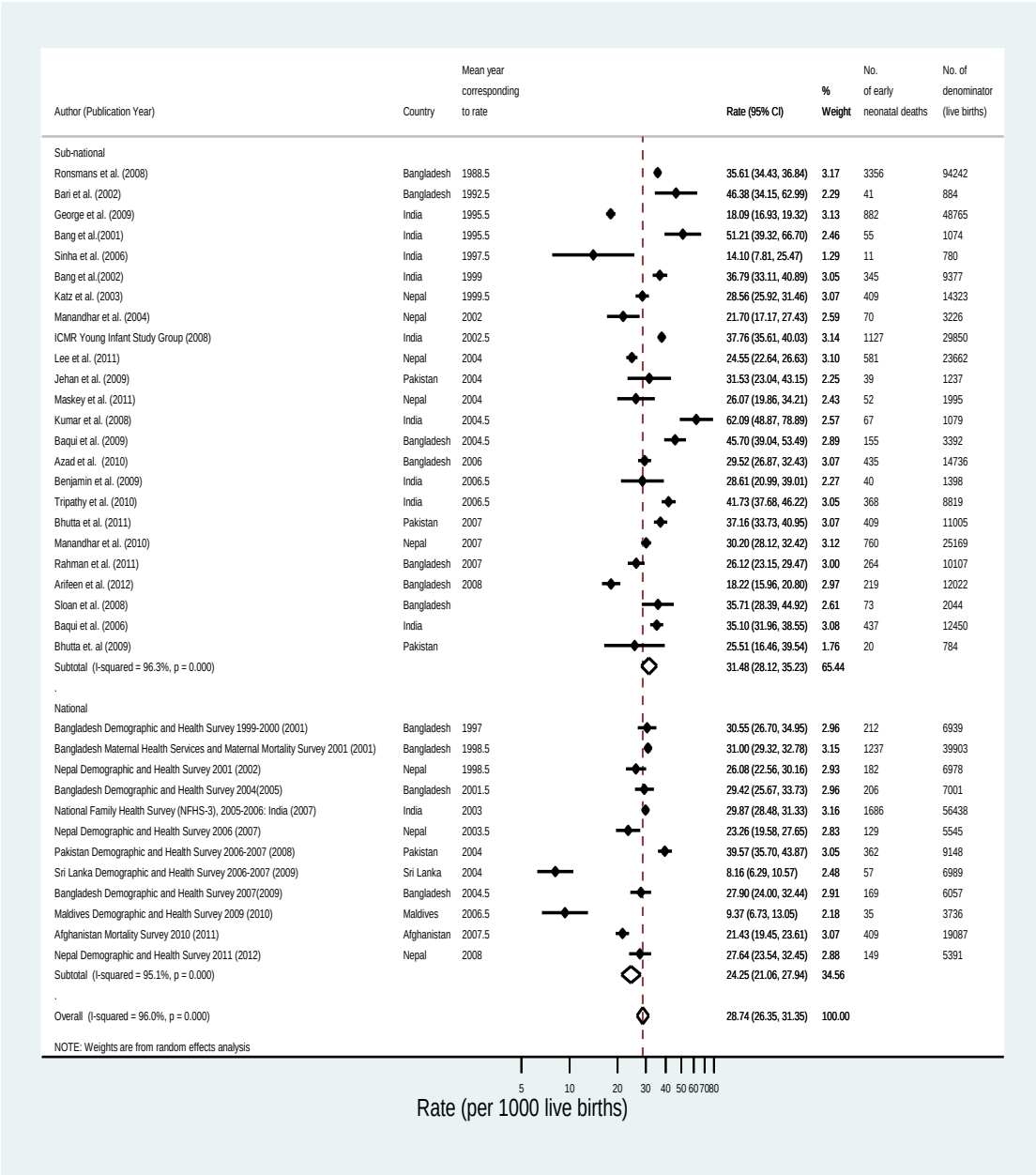


(Rates are shown on a logarithmic scale)

Figure 3.2: Forest plot showing stillbirth rates for South Asia

Early neonatal deaths:

The pooled early neonatal mortality rate for South Asia (Figure 3.3) was found to be 28.5/1000 live births (95% CI: 26.2-31.0) among highly heterogeneous studies (I^2=95.5%). No trends in reduction of rate over time were seen for South Asia or constituent countries except possibly Bangladesh (Appendix IB: Figure 9). Within countries, study heterogeneity was also high, ranging from 42.5% (Nepal) to 93.4% (Bangladesh)(Appendix IB: Figures 8-14).

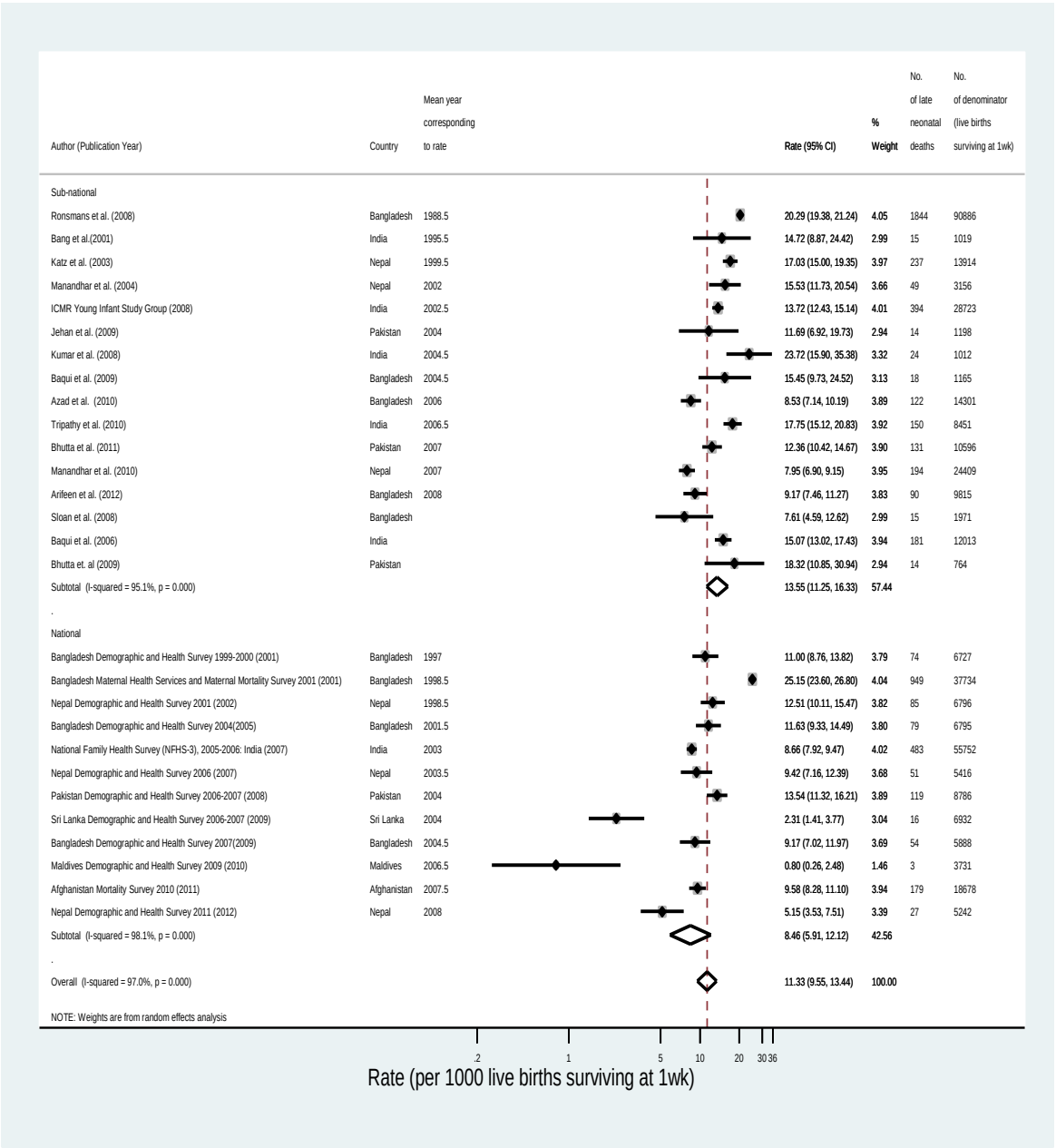


(Rates are shown on a logarithmic scale)

Figure 3.3: Forest plot showing early neonatal death rate for South Asia

Late neonatal deaths:

The summary rate for late neonatal deaths for South Asia (Figure 3.4) was 11.3/1000 live births surviving at 1 week (95%CI: 9.55-13.4) but substantial heterogeneity was present between the studies (I^2=97.0%, p<0.0001). Discernible trends over time were not observed from the forest plot for South Asia. However, rates appeared to decline over time for Bangladesh and Nepal (Appendix IB: Figures 16 and 19). Heterogeneity of studies within countries was high (Appendix IB: Figures 15-21).

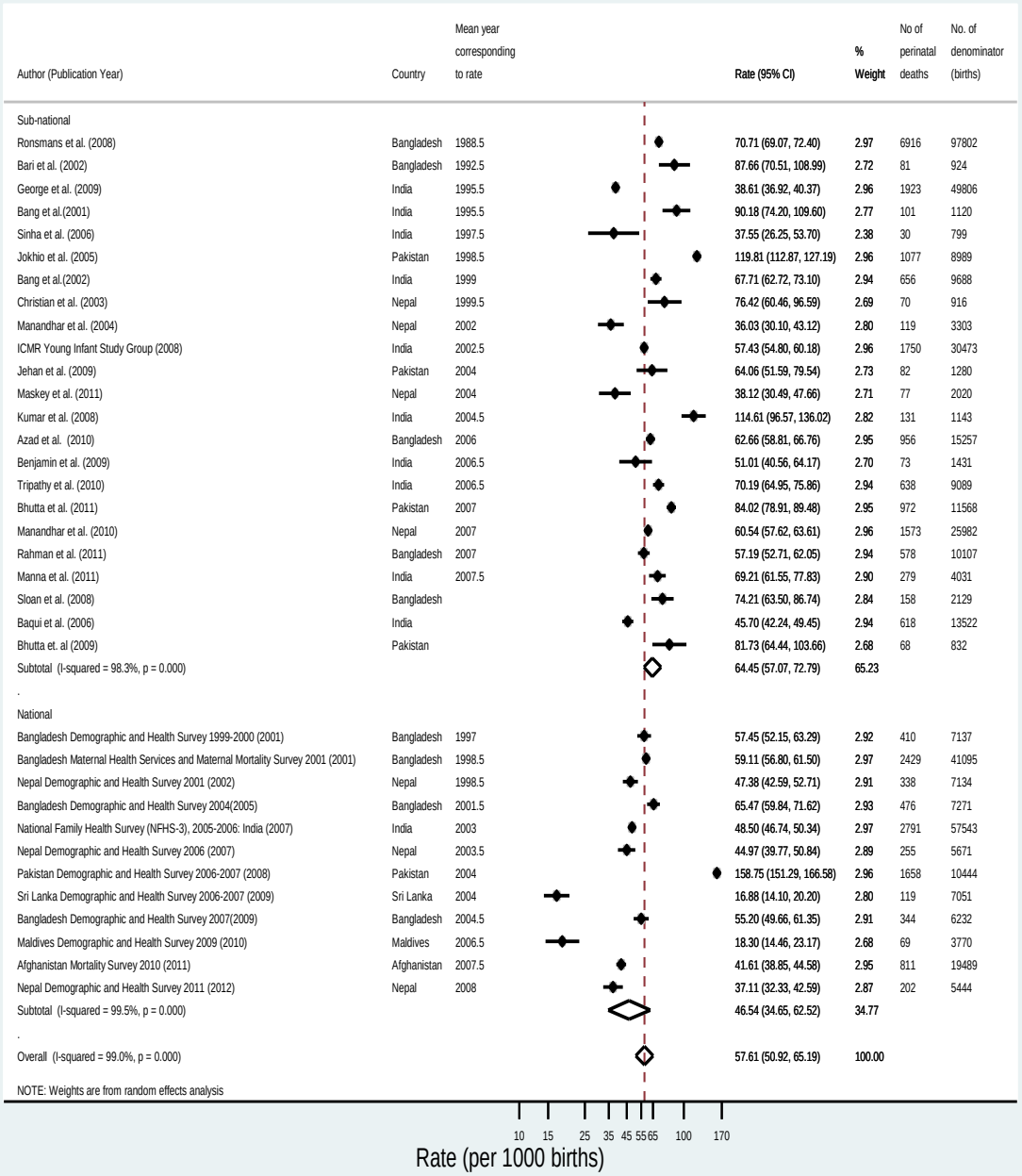


(Rates are shown on a logarithmic scale)

Figure 3.4: Forest plot showing the late neonatal death rate for South Asia

Perinatal deaths:

The pooled perinatal death rate in South Asia (Figure 3.5) of 56.6/1000 births (95% CI: 51.5-62.3) was from highly heterogeneous studies (I^2=99.0%, p<0.0001).Like the other mortality rates, perinatal death rates showed no clear trend over time for the region or individual countries and the country-specific rates showed high heterogeneity between studies (Appendix IB: Figures 22-28)



(Rates are shown on a logarithmic scale)

Figure 3.5: Forest plot showing the perinatal death rate for South Asia

Mortality rates for each outcome are shown in Figures 3.6 to 3.9 according to national, sub-national and pooled rates for each country.

From non-overlapping confidence levels in Figure 3.6 sub-national stillbirth rates appear statistically higher than national rates for India and Nepal. Pakistan conversely has an unusually high national rate (124.1/1000 births). Bangladesh's national and sub-national rates are seen to be statistically similar. For Bangladesh, India, Nepal and Pakistan, high heterogeneity was found among sub-national studies for each country and within national studies for Bangladesh and Nepal (Appendix IB: Figures 1-7).

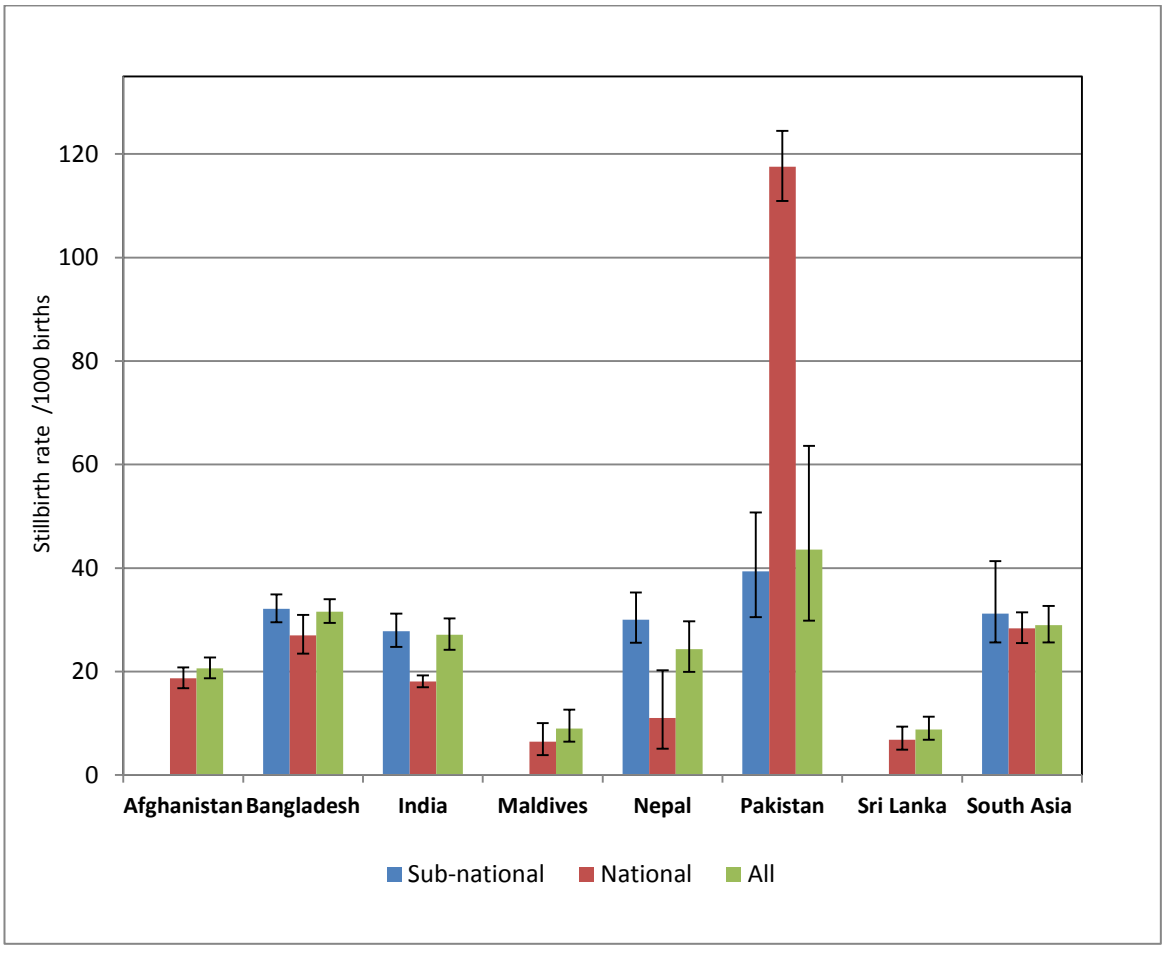


Figure 3.6: National and sub-national stillbirth rates in countries of South Asia (1985-2008)

For the four countries with both national and subnational rates for early neonatal deaths, sub-national rates were not significantly different from national rates (Figure 3.7) as suggested by overlapping CIs. For sub-national studies there was strong evidence for between-study heterogeneity for Bangladesh (I^2 =95.6%), India (I^2 = 98.5%) and Nepal (I^2=78.7%) and moderate evidence of heterogeneity for Pakistan (I^2 =42.4%) (Appendix IB: Figures 8-14). Among the national studies there was no evidence for between-study heterogeneity in case of Bangladesh and Nepal (Appendix IB: Figures 9 and 12).

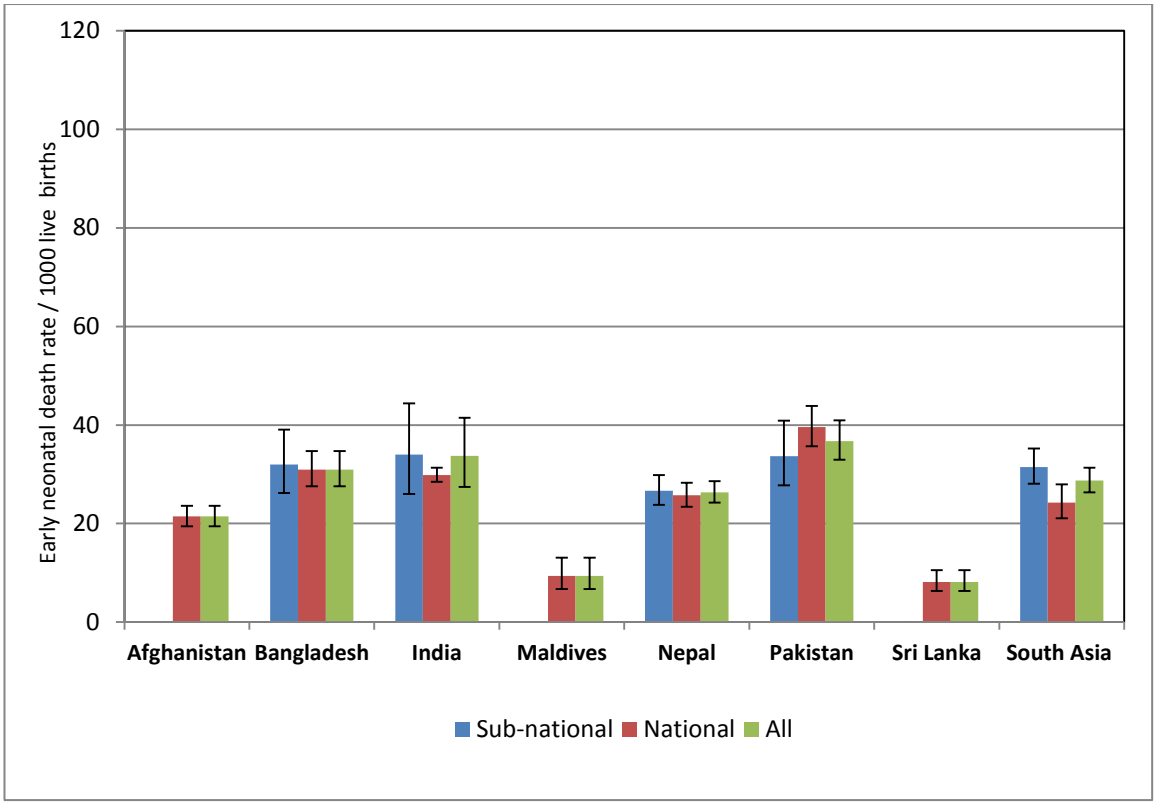


Figure 3.7: National and sub-national early neonatal death rates in countries of South Asia (1988-2008)

From Figure 3.8 it was seen that sub-national late neonatal death rates for Bangladesh, Nepal and Pakistan were not significantly different from their national rates (overlapping CIs) except for India which had a significantly higher sub-national rate. For all countries except India, sub-national or national rates were not significantly different from the overall pooled country rate. Heterogeneity was significantly high for all countries among and between sub-national and national studies (except for Pakistan where I^2 = 3.5% among sub-national studies) (Appendix IB: Figures 15-21).

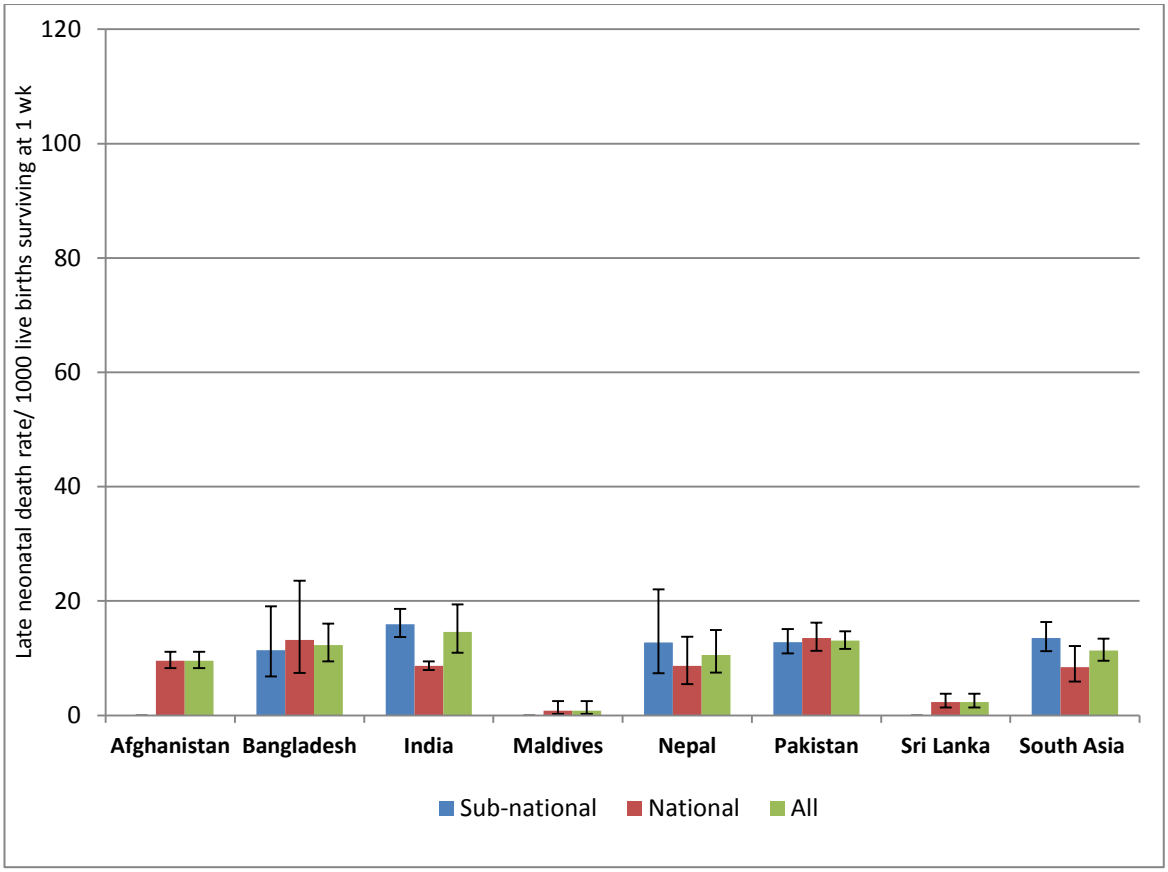


Figure 3.8: National and sub-national late neonatal death rates in countries of South Asia (1988-2008)

Differences between the high national and sub-national perinatal deaths rates were not significant for Bangladesh, Nepal and India) (Figure 3.9).Pakistan however, showed a very high national rate of 158.8/1000 births (95% CI: 151.3-166.6) significantly different from its sub-national rate (Figure 3.12).High heterogeneity was again seen for all countries, within and between the national and sub-national studies (Appendix IB: Figures 22-28).

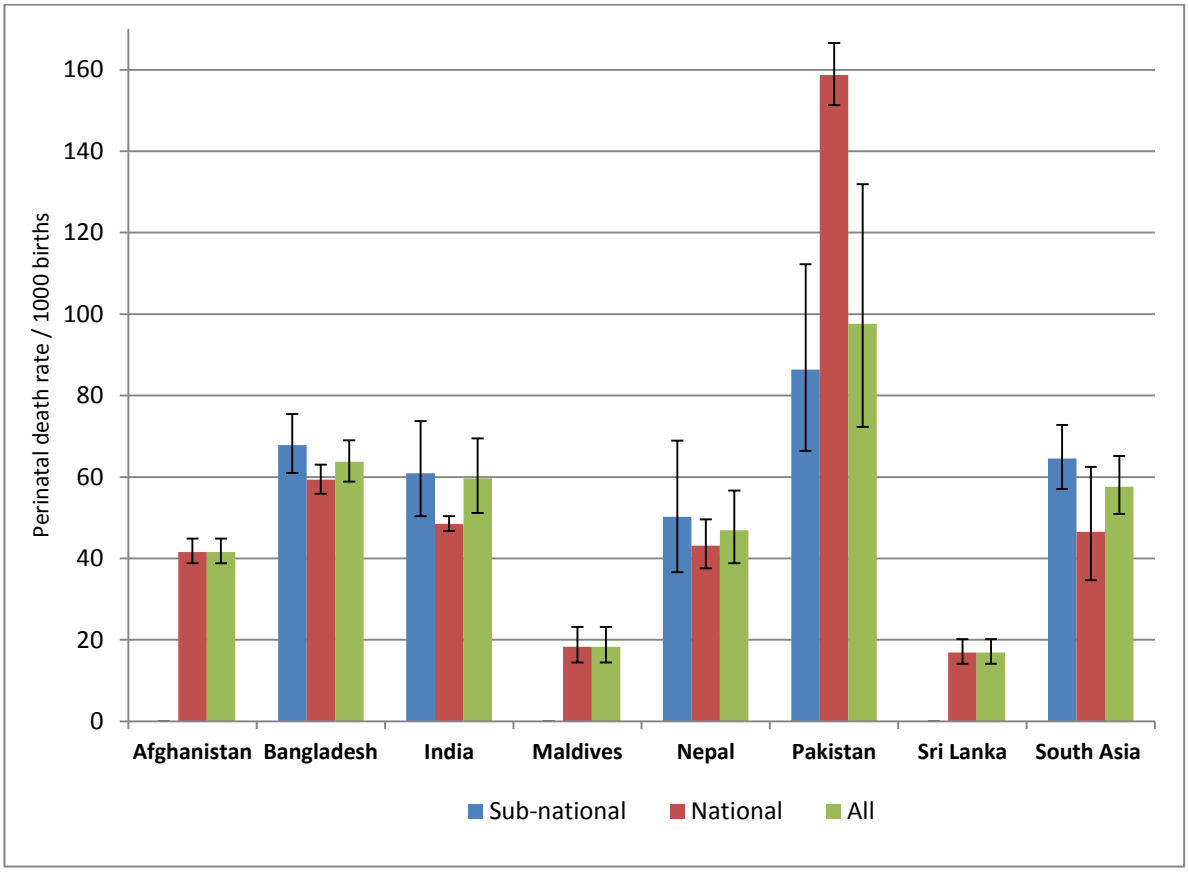


Figure 3.9: National and sub-national perinatal death rates in countries of South Asia (1988-2008)

These high levels of heterogeneity in the review suggest that all the pooled rates at national, sub-national and country level should be treated with caution.

Outlier rates:

Rates calculated from the Pakistan DHS 2006-2007 and the Nepal DHS 2011 appeared to be outliers. The Pakistan DHS 2006-2007 presented very high stillbirth (124.1/1000 births) and perinatal death (158.8/1000 births) rates for a DHS survey in the region and when compared to rates obtained from Pakistan's sub-national studies (Appendix IB: Figure 45). The Nepal DHS 2011 produced a very low stillbirth rate (9.74/1000 births) compared to the rates obtained

from the two earlier Nepal DHSs and when compared to the sub-national rate (Appendix IB: Figure 46). Sensitivity analyses for Pakistan and Nepal performed with and without the relevant DHS did not result in any significant changes in the rates for the countries (Appendix IB: Figures 29-36 and 45-46). Additionally, removal of one or both DHSs did not affect pooled rates for South Asia (Appendix IB: Figures 37-44).

3.4.5 Mortality Rates by Study Quality

Figures 3.10-3.13 show the rates for the four mortality outcomes stratified on levels of risk-of-bias for the studies. In Figure 3.10 it can be seen that for Bangladesh and Nepal, the rates from low risk-of-bias studies (33.9 and 28.2/1000 births, respectively) were not significantly different from rates seen in high and unclear risk-of-bias studies (32.0 and 20.1/1000 births; 30.1 and 27.4/1000 births). In India, which had no low risk-of bias studies, the rate for the high risk of bias studies (26.6/1000 births) was statistically similar to the rate for unclear risk-of-bias studies (29.1/1000 births). For Pakistan, the single high risk national study was extremely different from the studies that were at unclear risk-of-bias. Afghanistan, Maldives and Sri Lanka contributed only one study each and hence risk-of bias stratified rates are not meaningful for these countries. For the whole of South Asia, rates from low, high and unclear risk-of-bias studies are statistically similar to each other. The forest plots that provided these rates are shown elsewhere (Appendix IB: Figures 47, 51, 55, 59 and 63).

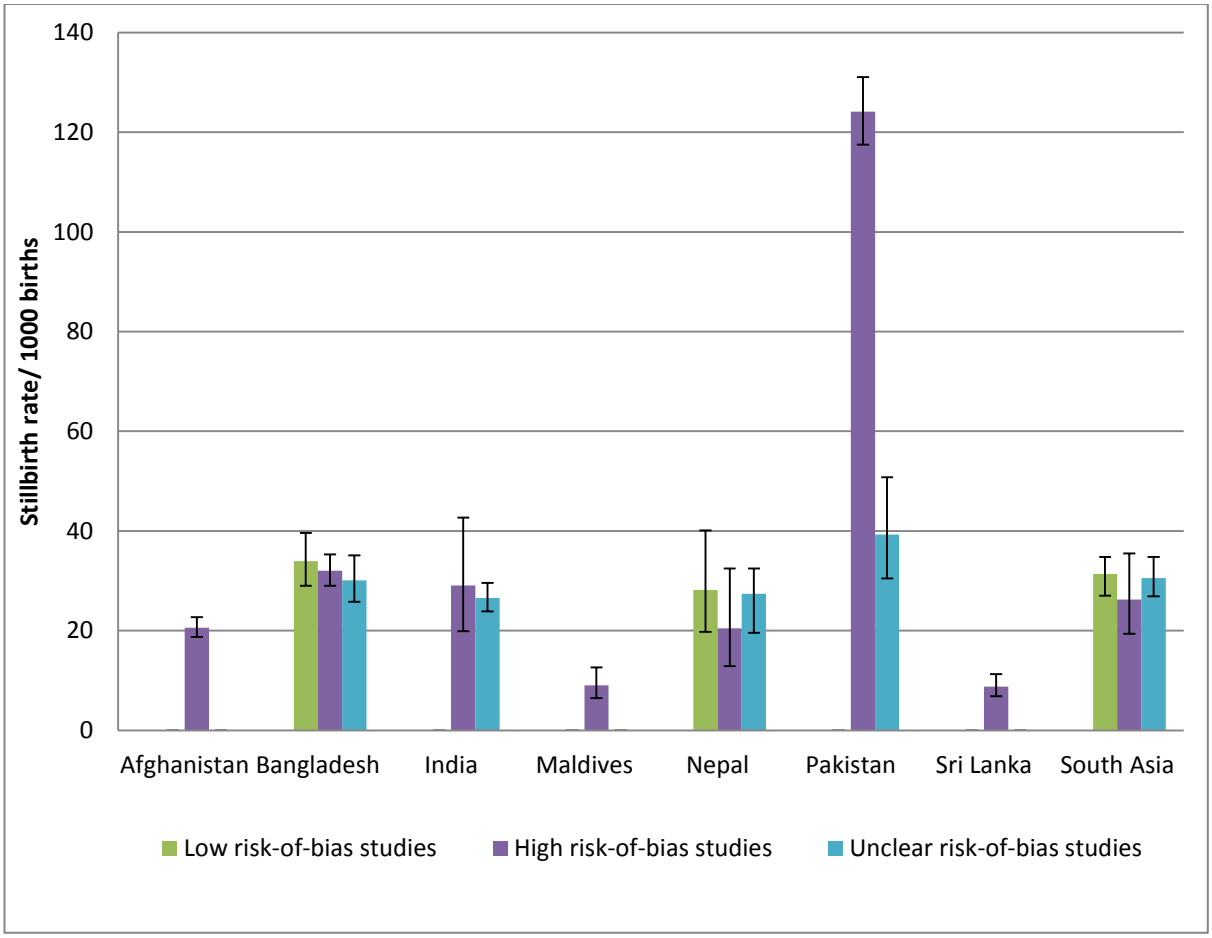


Figure 3.10: Stillbirth rates obtained from studies stratified on levels of risk-of-bias.

The stratification by study quality for studies reporting early neonatal deaths (Figure 3.11), revealed very similar patterns to those reported for stillbirth rates. As seen from overlapping confidence intervals, early neonatal death rates from low risk-of-bias studies (where available), high risk-of bias studies or unclear risk-of-bias studies, were not statistically different from each other. Forest plots which provided these rates are shown elsewhere (Appendix IB: Figures 48, 52, 56, 60 and 64).

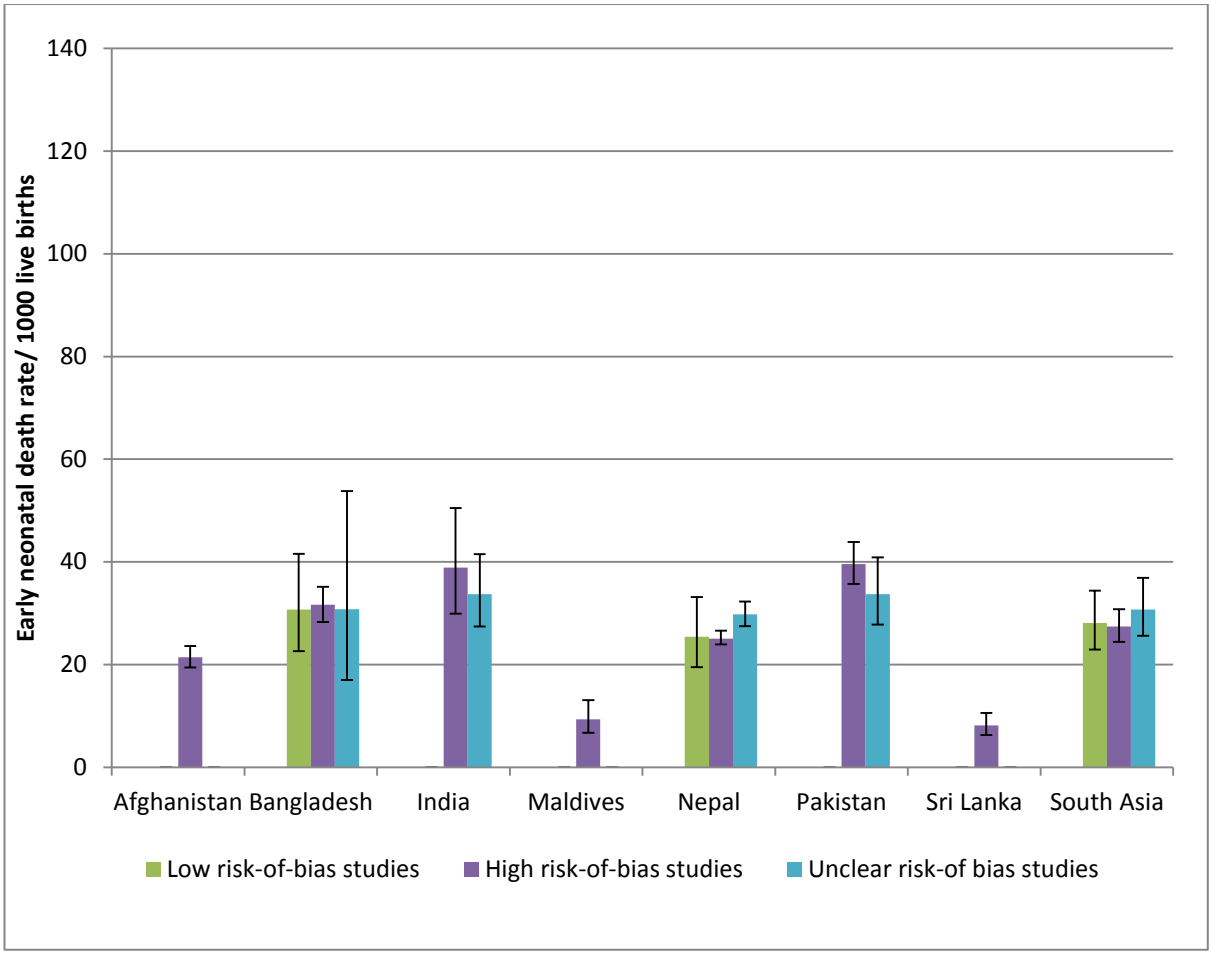


Figure 3.11: Early neonatal death rates obtained from studies stratified on levels of risk-of-bias.

This finding, where rates from studies stratified on levels of risk-of-bias do not differ statistically from each other was also seen for all countries in case of late neonatal death rates (Figure 3.12) and for perinatal death rates (with the exception of one high risk-of-bias national study from Pakistan) (Figure 3.13).

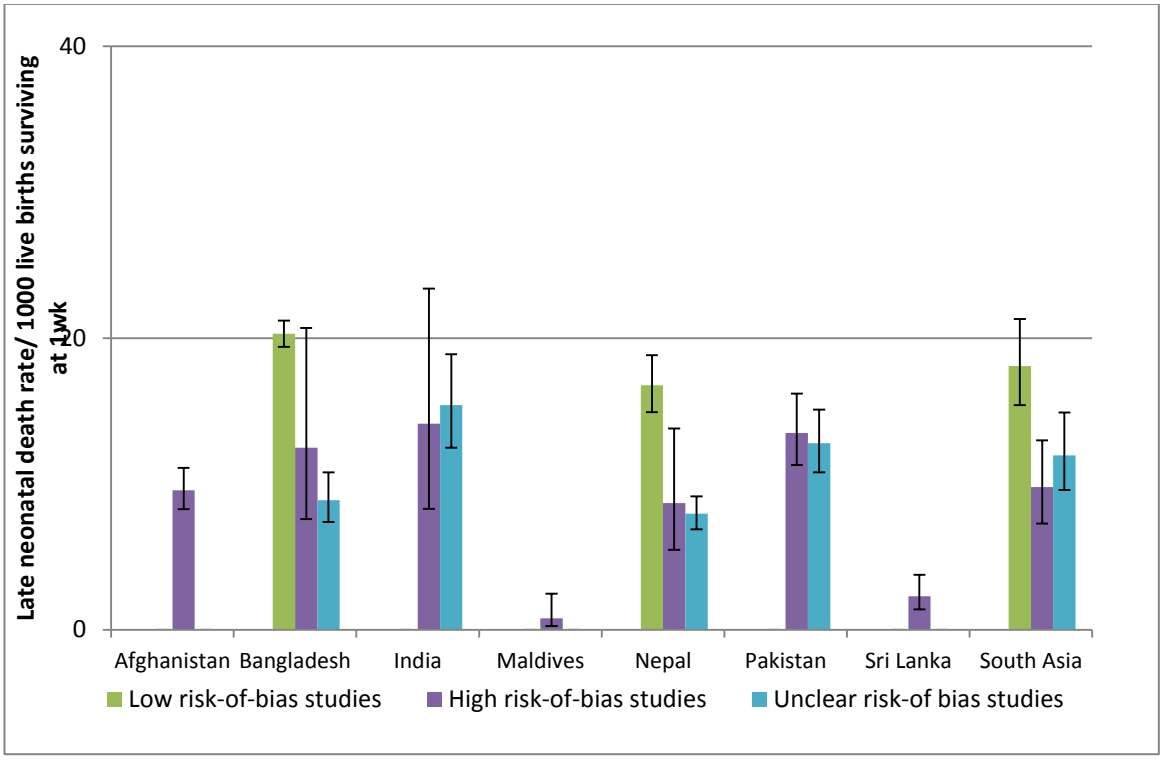


Figure 3.12: Late neonatal death rates obtained from studies stratified on levels of risk-of-bias.

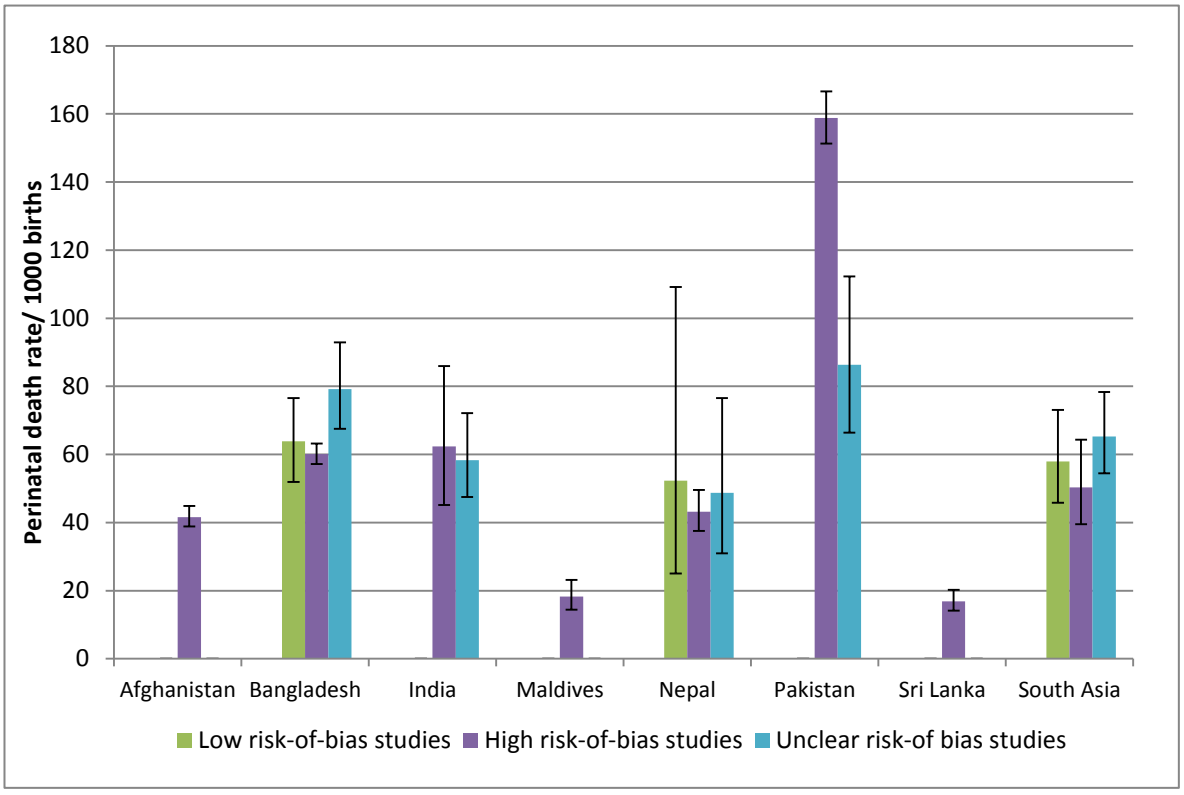


Figure 3.13: Perinatal death rates obtained from studies stratified on levels of risk-of-bias.

3.4.6 Comparison between countries:

Stillbirth rates:

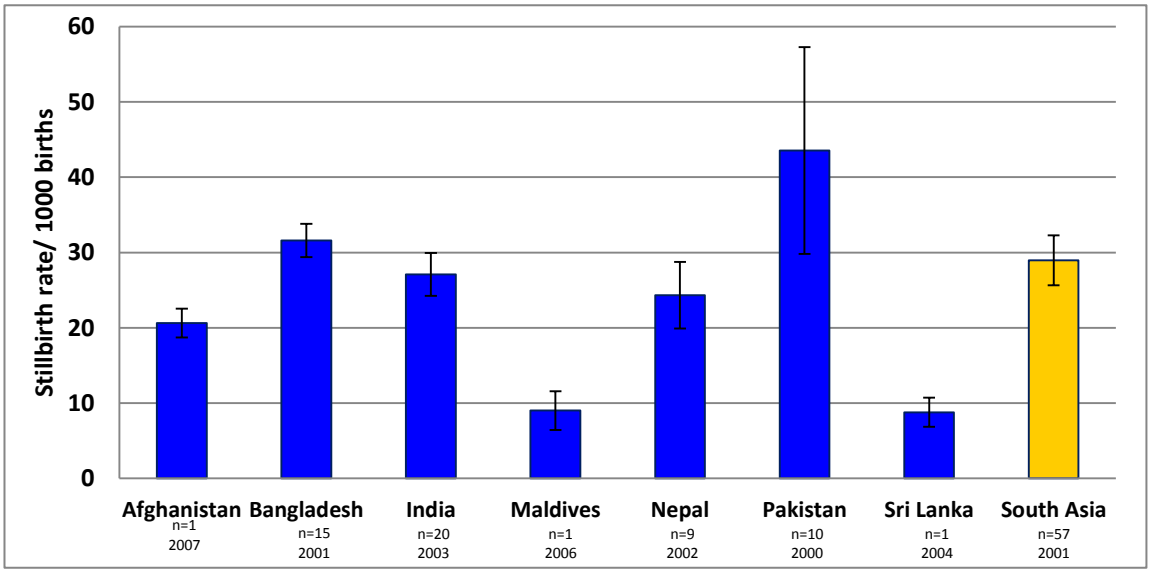


Figure 3.14: Country-wise pooled stillbirth rates in South Asia (1985-2008)

The summary stillbirth rate for South Asia was 29.0/1000 births (95% CI: 25.7-32.7) (Figure 3.14). Afghanistan, Bangladesh, India and Maldives had stillbirth rates of 20.6/1000 births, 31.6/1000 births, 27.1/1000 births and 9.0/1000 births respectively. Nepal had a pooled rate of 24.3/1000 births while Pakistan had the highest rate of 43.6/1000 births. Sri Lanka had the lowest rate of 8.8/1000 births. From the overlapping confidence intervals seen, Bangladesh, India and Nepal showed high rates statistically similar to each other. By eyeballing confidence intervals, the lower confidence interval of Pakistan overlapped with the upper CIs of Nepal, India and Bangladesh but it is possible that the rate for Pakistan was much higher than those from these three countries though this was not tested statistically. These four countries were the ones driving the high summary estimate for South Asia. Maldives and Sri Lanka had statistically similar low rates while Afghanistan's rate was similar to that for Nepal. As rates were variable for the countries within South Asia, the presentation of pooled rates for each country is more meaningful than a pooled rate for South Asia.

Early neonatal death rates:

Figure 3.15 shows the summary early neonatal death rates for South Asia. Afghanistan, Bangladesh and India had rates of 21.4/1000 live births, 30.9/1000 live births and 33.7/1000 live births, respectively (Figure 3.15). Nepal had a rate of 26.4/1000 live births. As in the case of stillbirth rates, the highest early neonatal death rate (36.7/1000 live births, 95% CI: 32.9-40.9) was seen in Pakistan while the lowest rate was seen in Sri Lanka (8.16/1000 live births, 95% CI: 6.3-10.6). The latter rate was statistically similar to the rate in Maldives (9.37/1000 live births). From eyeballing confidence intervals, Bangladesh, India and Pakistan possibly had similar high rates and though there is some overlap, Nepal's rate was likely to be comparatively lower though this was not statistically tested. Afghanistan's moderate rate did not appear similar to any other country's rate.

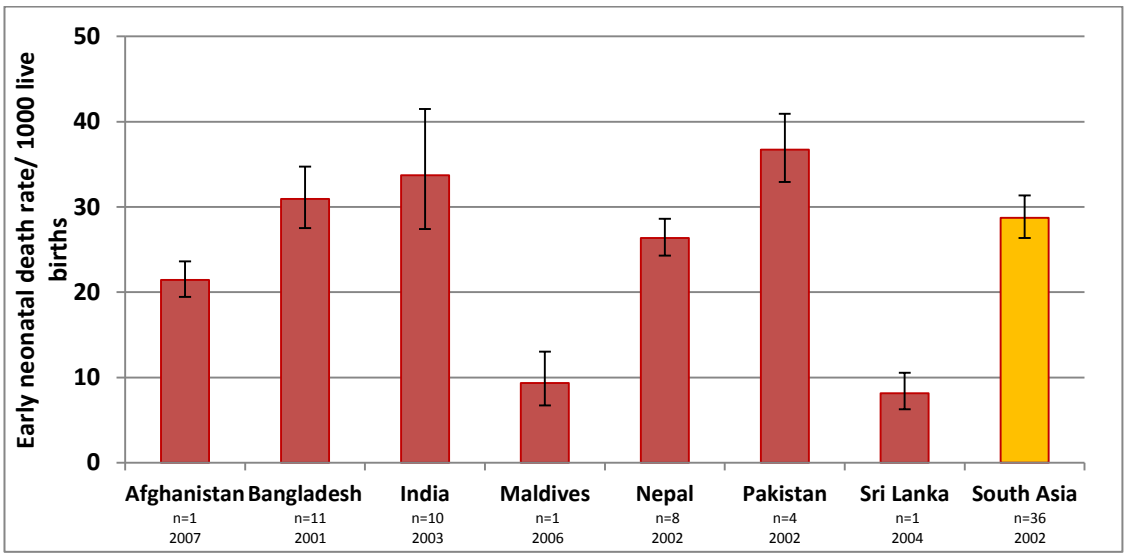


Figure 3.15: Country-wise pooled early neonatal death rates in South Asia (1988-2008)

Late neonatal death rates:

The pooled late neonatal death rates for Afghanistan, Bangladesh, Pakistan and Nepal are shown in Figure 3.16. The lowest summary late neonatal death rate (0.80/1000 live births surviving at 1 week) was obtained for the Maldives while the highest rate (14.6/1000 live births surviving at 1 week) was seen in India. Sri Lanka had the second lowest rate (2.3/ live births surviving at 1 week). Bangladesh, India, Nepal had similar high rates which did not appear different from one another from eyeballing confidence intervals while Afghanistan appeared to have a lower rate compared to Pakistan though these apparent differences were not statistically tested. The low rates for Maldives and Sri Lanka were statistically similar.

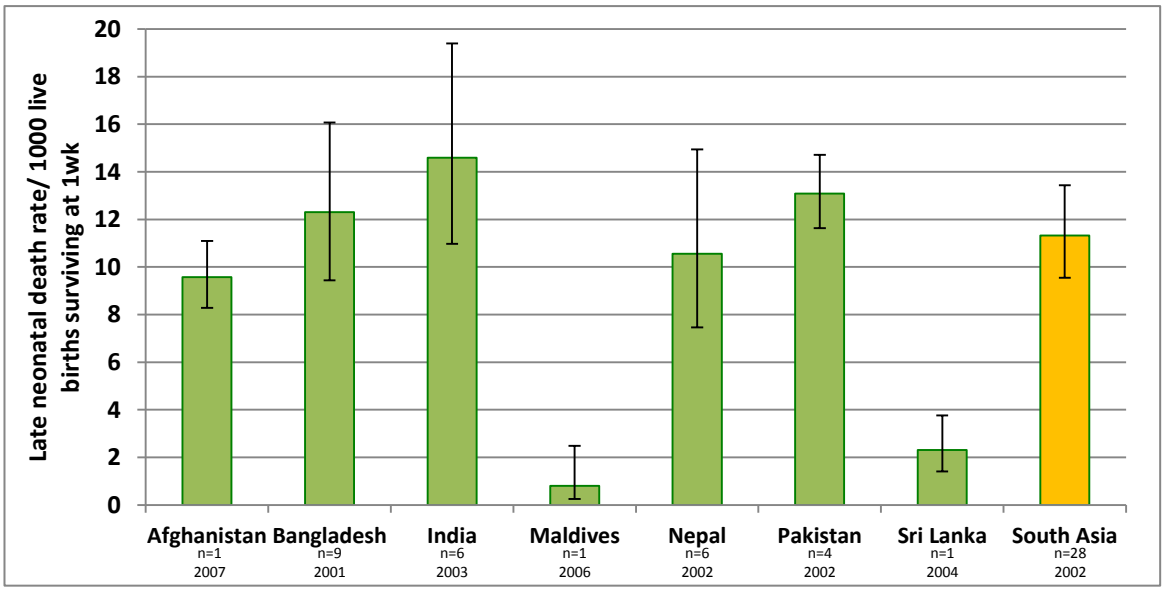


Figure 3.16: Country-wise pooled late neonatal death rates in South Asia (1988-2008)

Perinatal death rates:

Pooled perinatal death rates for Afghanistan, Bangladesh, India and Nepal were found to be 41.6/1000 births, 63.7/1000 births, 59.6/1000 births and 46.9/1000 births, respectively (Figure 3.17). The lowest pooled perinatal death rate was for Maldives at 18.3/1000 births (95% CI: 14.5-23.1) while Sri Lanka had the second lowest rate of 16.9/1000 births. The highest perinatal death rate was seen in Pakistan (97.7/1000 births, 95% CI: 72.3-131.9).

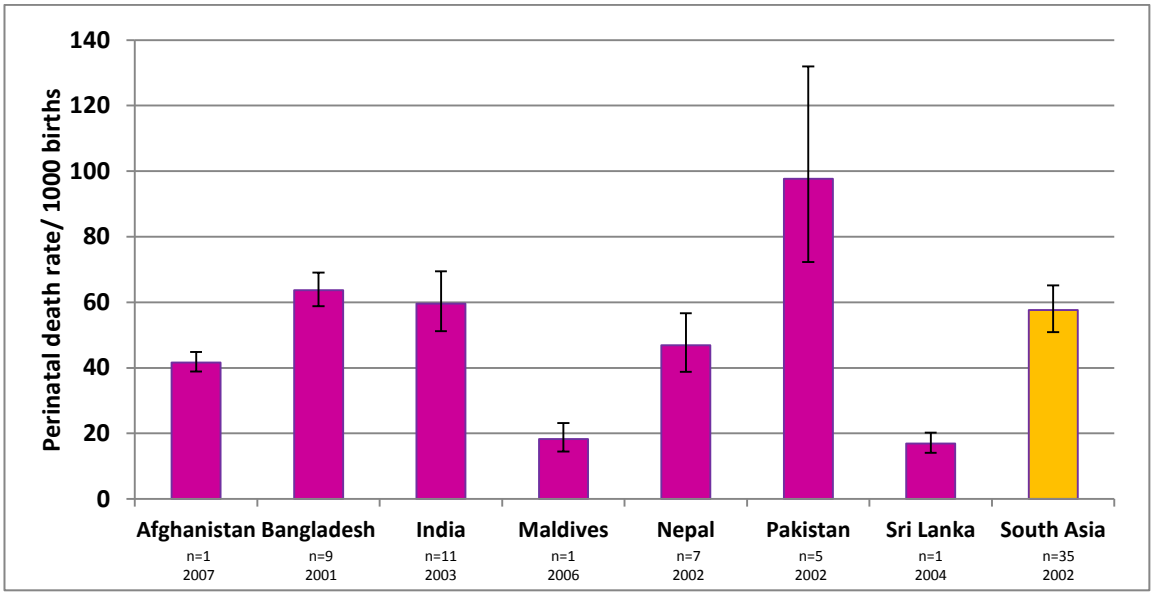


Figure 3.17: Country-wise pooled perinatal death rates in South Asia (1988-2008)*

3.4.7 Summary estimates obtained in review compared to estimates in literature:

Data sources for comparison against review rates:

During the search process, I identified six studies presenting country-specific or regional rates for my four mortality outcomes. These were: two reports by the WHO for the year 2000 and 2004 (WHO, 2006a) (WHO, 2007) using regression modelling (for stillbirth rates for Afghanistan, Bhutan, India and Sri Lanka) and DHS surveys (for early neonatal death rates and perinatal death rates). Four studies produced rates for 2000, 2008 and 2009 from statistical models using empirical data from studies and surveys (Stanton et al., 2006, Lozano et al., 2011) (Lawn et al., 2011, Cousens et al., 2011). Of the six studies, only one provided estimates for late neonatal mortality(Lozano et al. 2011). The mortality rates and the years that these rates corresponded to, were those specified within the publications. In 2014, the Global Burden of Disease Study 2013 published modelled estimates of early and late neonatal death rates in 188 countries for 2013 (Wang et al. 2014). These have not been included with the comparison rates, as the 2013 rates differed by a decade from the years that the systematic review rates represented.

Stillbirth rates:

Figure 3.18 depicts the summary stillbirth rates from the systematic review for each country. These corresponded to the median year of 2001 (rates between 1985-2008) for the countries of South Asia and are also pooled for the whole of South Asia. There was substantial variation noticed, as my rates did not appear to be uniformly higher or lower than the comparison rates. It was noticed that even the comparison rates were not consistently higher or lower than each other and sometimes differed substantially from each other even when they represented rates for the same year. For example, the WHO rates (WHO, 2006a) and Stanton et al., 2006 rates for the year 2000 for Nepal (23/1000 births vs. 54.6/1000 births) and Pakistan (22/1000 births vs. 41.4/1000 births) are seen to differ greatly. The WHO 2000 rates are higher than the systematic review rates in case of Afghanistan, India and Maldives. The Stanton et al., 2006 stillbirth rates are higher than the systematic review stillbirth rates across all the countries. The greatest difference between my review rate and that of published international rates is seen for Afghanistan. The absence of confidence intervals for the majority of the comparison rates makes it difficult to speculate on whether these differences were statistically significant

or not. However, it is to be noted that there is no order or pattern observed for the substantial variation exhibited among all rates. The Lawn et al., 2011 and Cousens et al., 2011 estimates were for the later years of 2008 and 2009, respectively, and hence comparisons were not drawn, though the rates have been shown (Figure 3.18).

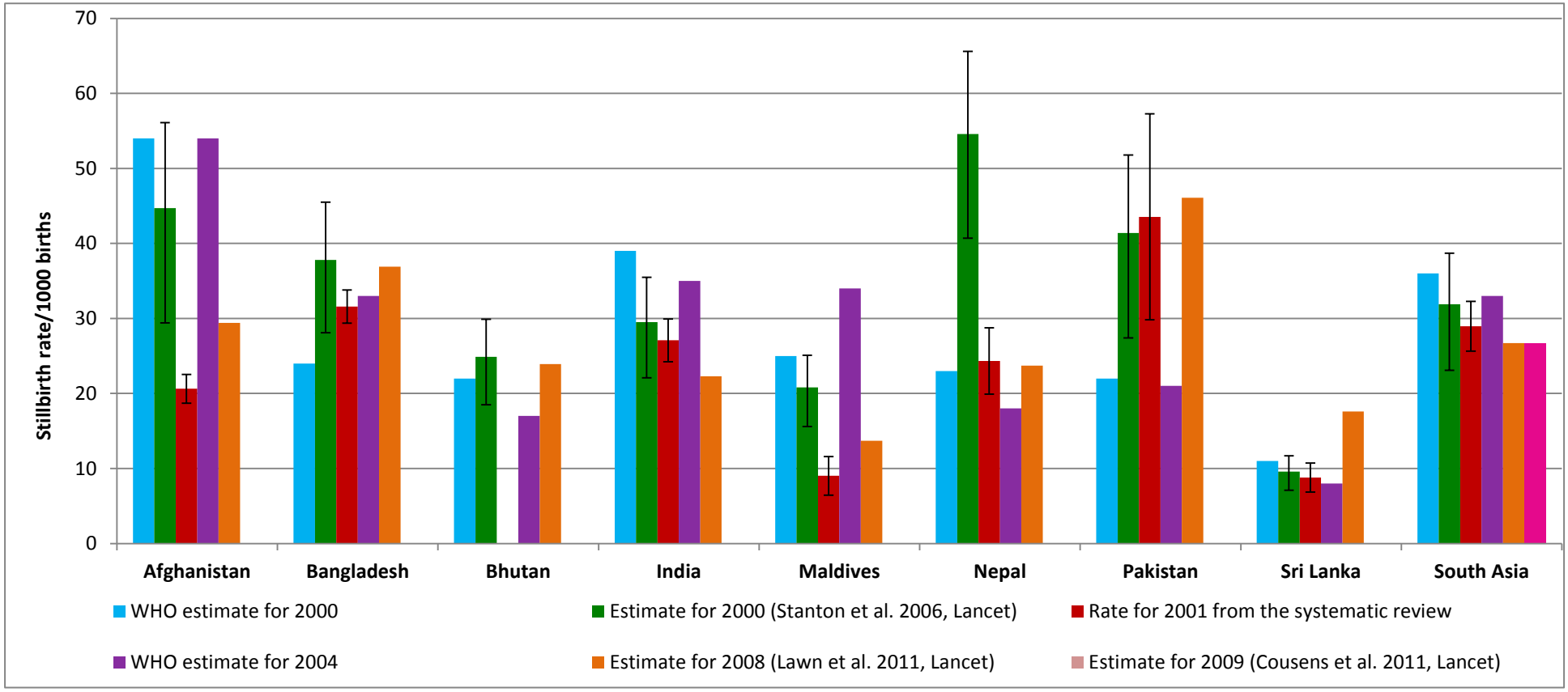


Figure 3.18: Stillbirth rates for South Asia: empirical and estimated rates

Early neonatal death rates:

Overall, the pooled early neonatal death rates obtained from all the South Asian countries in the systematic review which corresponded to the median year of 2002 (rates between 1988-2008), appear to be largely similar to the published rates of international studies. However, Afghanistan and Maldives are the exceptions (Figure 3.19).

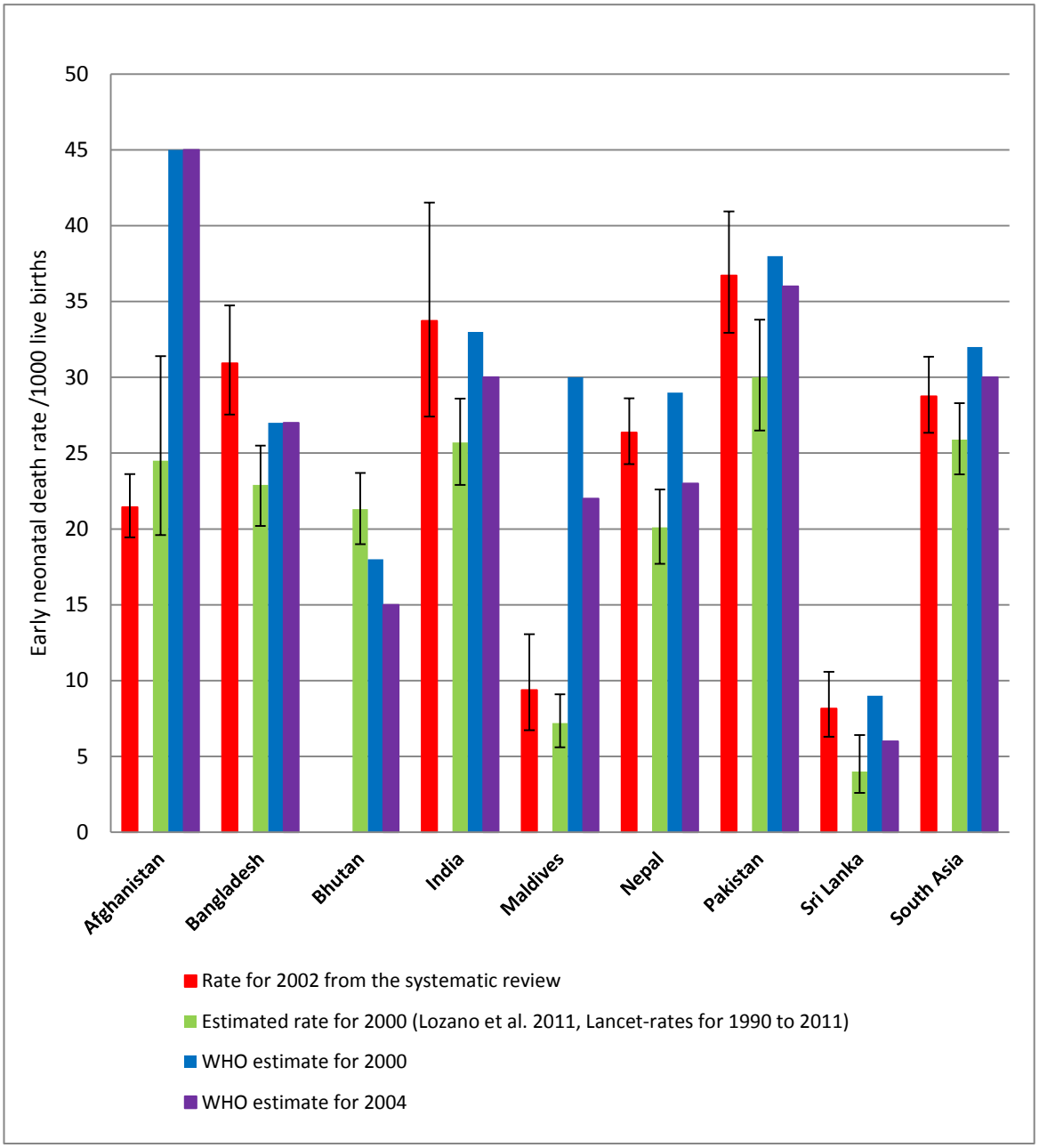


Figure 3.19: Early neonatal death rates for South Asia: empirical and estimated rates

Late neonatal death rates:

Late neonatal death rates obtained from my systematic review are also seen to be higher than the Lozano et al., 2011 estimates with the exception of Afghanistan and Maldives (Figure 3.20). The largest difference seen between the two sources was for India (review rate: 16.1/1000 live births excluding early neonatal deaths vs. Lozano et al., 2011 rate: 7.3/1000 live births excluding early neonatal deaths). The WHO estimates for 2000 and 2004 were not available for late neonatal deaths.

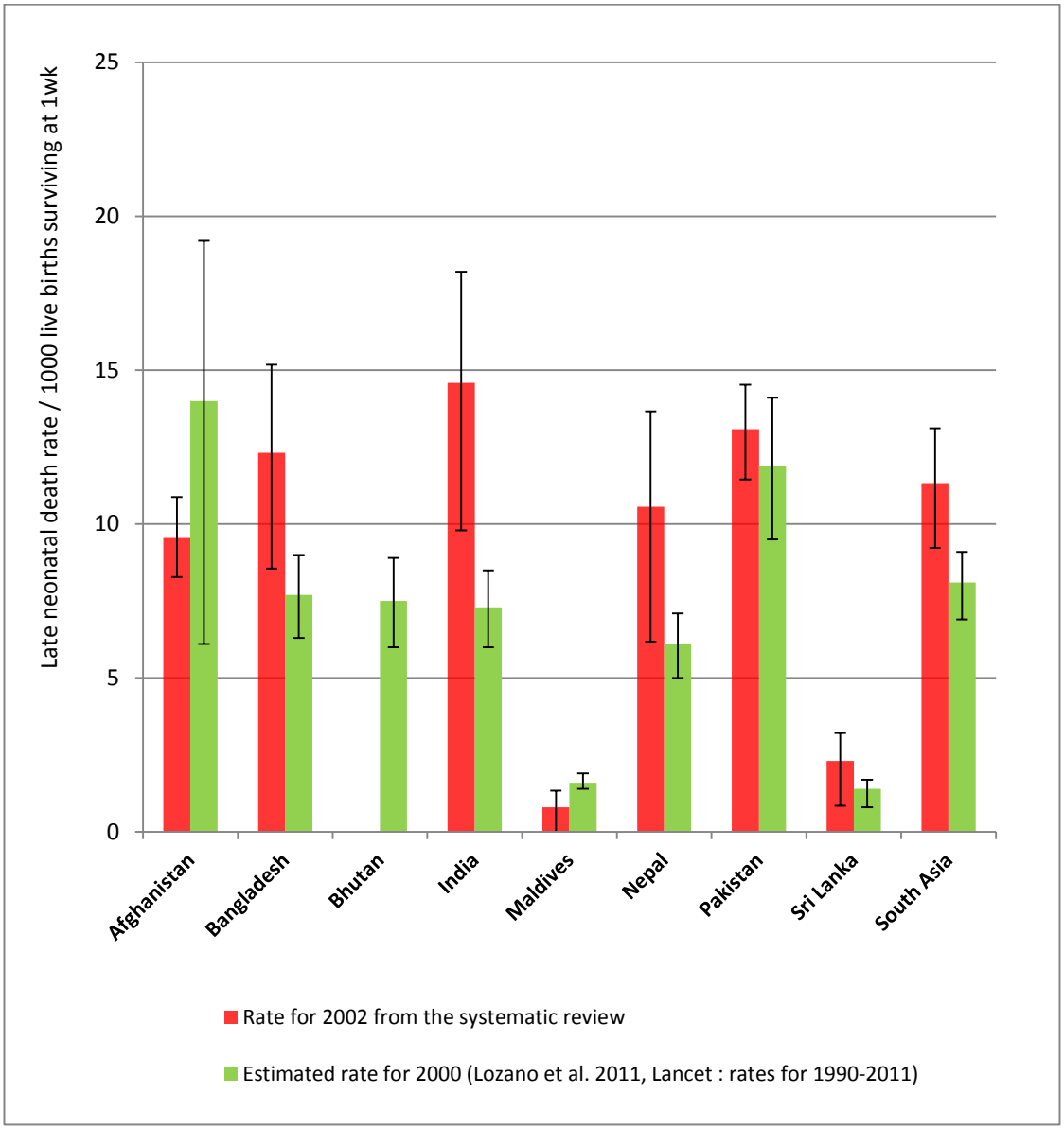


Figure 3.20: Late neonatal death rates for South Asia: empirical and estimated rates

Perinatal death rates:

The review rates for perinatal deaths were compared to the WHO estimates for 2000 and 2004 (Figure 3.21). From the graph it can be seen that review rates appeared similar to both the WHO estimates for Bangladesh, India, Nepal and Sri Lanka. Review rates appeared noticeably lower in case of Afghanistan and Maldives and much higher in case of Pakistan.

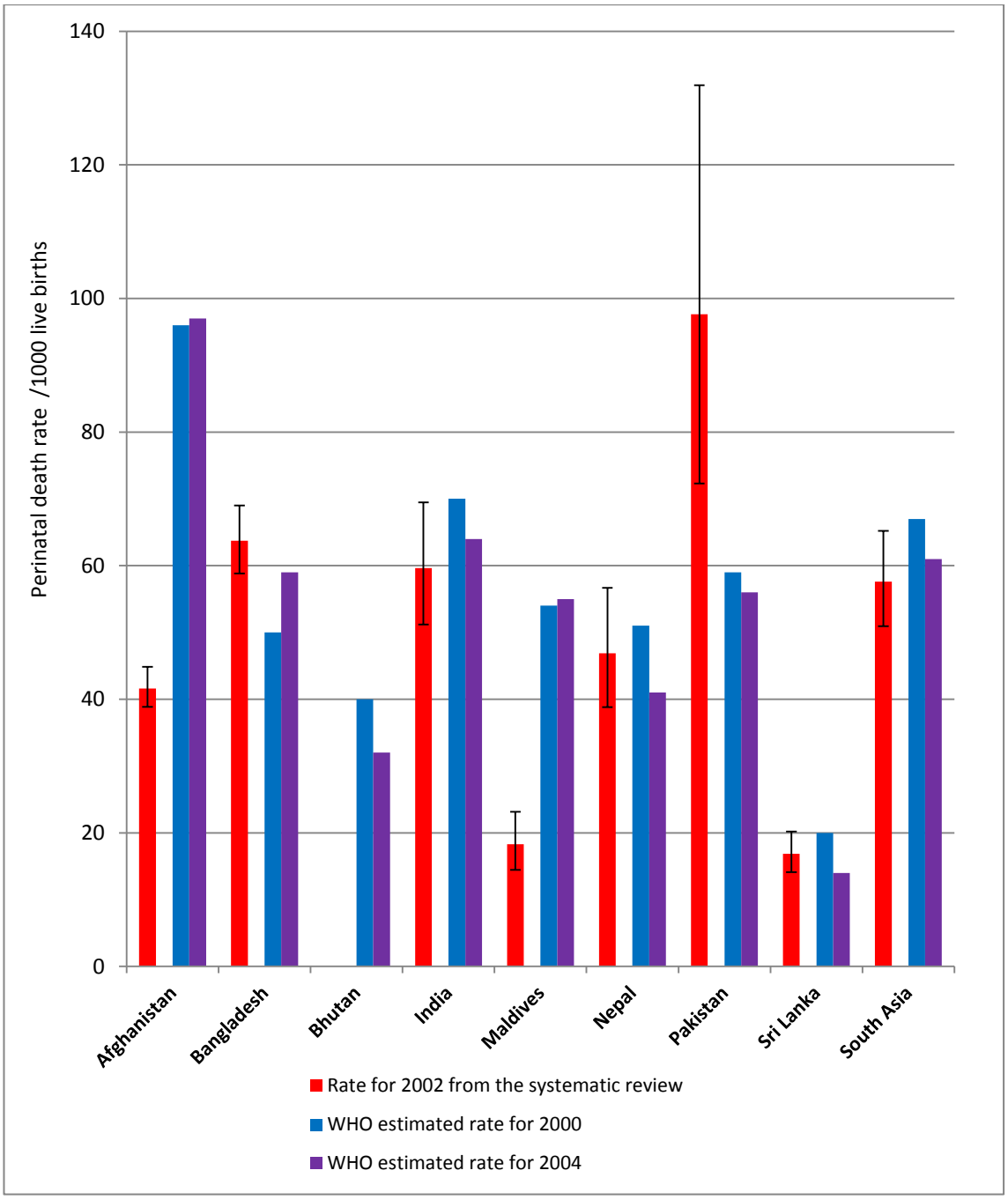


Figure 3.21: Perinatal death rates from South Asia: empirical and estimated rates

3.4.8 Ratios of stillbirth rate to early neonatal mortality rate:

Table 3.12 shows the ratios for summary stillbirth rate to summary early neonatal death rate for each country. The ratios obtained for each country (sub-national and national studies) range from the lowest value of 0.82 in India, to around a value of 1 for Afghanistan, Bangladesh, Maldives, Nepal and Sri Lanka, to the highest value of 1.17 in Pakistan. The WHO ratio of 1.2 implies non-underreporting of stillbirths. The WHO ratio of 0.6 or 0.8 (depending on country- see Note in Table 3.11) implies potentially high underreporting of stillbirths in this region assumed by the WHO to have early neonatal mortality rates above 20/1000 live births (WHO 2006). The review ratios for underreporting of stillbirths are found to be within the WHO ratio range (0.8 to 1.2) for high underreporting and no underreporting.

Table 3.15: Comparison of the ratios for stillbirth rate to early neonatal mortality rate according to different sources

Country	**Ratio of stillbirth rate to early neonatal mortality rate**		
	Systematic review (sub-national and national studies)	**Systematic review (sub-national studies)**	**Systematic review (national studies)**
Afghanistan	0.96	_	0.96
Bangladesh	1.05	1.06	1.00
Bhutan	_	_	_
India	0.82	0.83	0.64
Maldives	0.96	_	0.96
Nepal	0.95	1.16	0.66
Pakistan	1.19	1.17	3.14
Sri Lanka	1.08	_	1.08
South Asia	1.01	1.03	0.83

Note: The WHO suggests that Bangladesh, Bhutan, India, Maldives, Nepal have a ratio (of stillbirth rate to early neonatal mortality rate) of 0.8. Afghanistan and Pakistan have a WHO ratio of 0.6. There was no data provided by the WHO on a ratio for Sri Lanka. Source: Neonatal and Perinatal Mortality. Country, Regional and Global Estimates 2000. *Geneva: World Health Organization*. WHO 2006.

3.5 Discussion

In this systematic review of 62 studies, I find that the rates of stillbirths, early neonatal deaths, late neonatal deaths and perinatal deaths are very high in South Asia. The rates from my systematic review are in the range of modelled and adjusted estimates reported in the literature and there is no definite pattern of review rates being consistently higher or lower than the comparison rates with the caveat that rates compared are not for exactly the same year, differing by a maximum of 2 years. The underreporting of stillbirths estimated by the review falls within the expected range of underreporting for the region. The quality of the studies as obtained was generally poor with very few studies from South Asia were found to be at low-risk-of-bias, though this might have been due to using very stringent risk-of-bias criteria.

Within South Asia mortality levels vary greatly by country. Bangladesh, India, Nepal and Pakistan showed consistently high levels for all mortality rates followed closely by Afghanistan. Sri Lanka and Maldives presented persistently low mortality rates. The highest and lowest rates for stillbirths, early neonatal deaths and perinatal deaths were found in Pakistan and Sri Lanka, respectively. Late neonatal deaths were the highest and lowest in India and Maldives, respectively.

The comparison of perinatal mortality rates may be more informative than comparing countries on their stillbirth and early neonatal death rates. Pooling of stillbirths and early neonatal deaths into perinatal rates is epidemiologically valid, as risk factors for stillbirths and early neonatal deaths are thought to be the same (primarily poor intrapartum care and/or pre-term birth)(Lawn et al. 2014) and as this overcomes the problem of misclassification between stillbirth and early neonatal deaths. Different causes and risk factors for late neonatal deaths (sepsis and infection)(Lawn et al. 2014) warrant comparisons to be made separately from perinatal deaths.

In this review, I also looked at whether there was consistency between the rates obtained from national studies and sub-national studies. For all countries, except for India and Pakistan, the difference between national and sub-national rates did not reach significance at the 5% level, making national and sub-national rates consistent with each other. In India, I found that sub-national rates for stillbirths, late neonatal deaths and perinatal deaths were significantly

higher than the corresponding national rates. It was not clear why national and sub-national rates differed for India while this was not seen in other countries, except Pakistan. It could be speculated that India, a vast country with a variety of cultures is more heterogeneous than other countries. The national rate for India might possible mask a lot of regional variation which would not be expected for smaller, more homogenous countries such as the Maldives or Bangladesh. The available sub-national studies, limited by the number of studies and geographical scope were most probably not able to pick up on differences in rates across the whole of India. Hence this might have led to differences in rates for sub-national studies and the national study. Pakistan's national rates for stillbirths and perinatal deaths were based on a single DHS study and were substantially higher than corresponding sub-national rates. This was unusual as DHSs are generally known to underreport rather than over-report stillbirths and hence the unusually high rates obtained from a DHS study with standardized procedures could not be explained.

This chapter showed that high levels of heterogeneity were present between the countries in South Asia. Even after stratifying studies by country and by national and sub-national studies within countries, substantial heterogeneity was still observed within countries, and within national and sub-national studies in the countries. Heterogeneity between the countries of South Asia is expected because of differences in populations and cultures, different levels of progress with respect to health systems, different levels of government budgets allocated to and different types of policies aimed at reducing stillbirth and neonatal deaths. Heterogeneity may arise within countries because of dissimilarities in the quality and availability of antenatal, delivery, postnatal services and maternal and child health services. Sociocultural differences may also be present within countries regarding contraception, childbearing, delivery practices, family size, age at first birth and these could lead to differences in mortality levels. Heterogeneity may also be present within the national studies of a country because even where methodology (e.g. for the DHS) is standardized, the time periods assessed are different and the populations assessed also change over time. The heterogeneity seen within sub-national studies in a country is expected as it reflects differences in regions, study populations, time periods, and study design and methodology. It is also possible that poor quality of studies could result in heterogeneity as populations that are very similar and have very similar mortality rates might be reported as having very different rates by studies differing in quality. This might happen because of the differences between good-quality and poor-quality studies

in ascertaining pregnancies, births and deaths and in defining mortality outcomes of very similar populations. The overall high levels of heterogeneity indicate that these pooled country-specific rates and the pooled rates obtained for South Asia have to be interpreted with caution.

This systematic review might have possible limitations.

1) Studies might have been missed in this review. However as (a) the most recently recommended guidelines (PRISMA) for conducting systematic reviews were followed (b) the review process was rigorous, explicit, reproducible and prospectively defined, and search terms were predetermined and as (c) all available sources were explored, it is unlikely that studies were missed.

2) It is also possible that the risk-of-bias assessment for the studies was not ideal, with the quality criteria for low risk-of-bias studies too stringent. This might have resulted in few studies (4/62) that were at low risk-of-bias. It might also be possible that this quality assessment exercise was unable to capture the true quality of the studies. The quality of studies might have not been assessed fully, as certain aspects of studies could not be assessed due to lack of or poor quality of information. These were: qualifications of the person ascertaining outcomes, possible misclassification between stillbirths and early neonatal deaths, issues related to reporting outcomes and sampling issues. Many studies did not report or only partially reported education, skills and the training of the person involved in ascertaining pregnancies, births, types of deaths and gestational ages and so it was difficult to assess studies in terms of qualifications of personnel involved in data collection. Of the three studies (3/62) which did not provide clear information on the person ascertaining pregnancies, births and deaths (Rahman et al. 2010; Bari et al. 2002; Kumar et al. 2008) only one study (Rahman et al. 2010) was considered to be at unclear-risk-of bias solely because of this reason. In light of studies from the region it was likely the persons in these three studies were equivalent to CHWs. Ignoring the identity of the person ascertaining outcomes would have resulted in only one unclear-risk study (Rahman et al. 2010) becoming low-risk. This change is seen to have no effect on the rate likely to be affected (i.e. stillbirth rate in low risk-of-bias studies from Bangladesh). Possible misclassification between stillbirths and early neonatal deaths could result from: (a) largely unskilled birth attendants (TBAs, relatives, and mothers) in these studies being unable to differentiate between the two types of deaths when reporting to

CHWs or (b) possible benefits for the mother or the avoidance of stigma or blame for the birth attendant or mother. Poor study definitions are likely to have increased misclassification between early pregnancy loss and stillbirths, and between early and late neonatal deaths. In the review only half of all stillbirth studies defined stillbirths (24/57) with few studies which specified the minimum birth weight (3/57) in the definition or which measured/estimated birth weights (2/57). However, any quality assessment is subjective. By selecting ascertainment methods of pregnancies, births, deaths and definitions to represent the completeness of numerator and denominator which I considered to be the most vital determinants of rate, I expected that the most important determinants of rate had been included in this quality assessment. As quality assessment is a subjective process, a sample of studies which I considered to be ambiguous for quality was assessed by another reviewer and any differences were reconciled. Since the results from the quality assessment of the studies showed that the rates did not differ between low, high or unclear risk-of-bias studies, this suggested that the overall quality of all the studies was likely to be poor and unlikely to be all of acceptable quality because of poor ascertainment of pregnancies, births and deaths and unclear definitions obtained in many of the studies.

3) A potential weakness likely to have very little effect was the decision to not exclude studies on the basis of minimal number (e.g. 20) of outcomes (stillbirth, early neonatal deaths, perinatal deaths) or minimal cut-off (e.g. 20%) for missing data. This was decided as no international guidelines could be found recommending restriction of studies based on a minimum number of outcomes and because exclusion would have reduced the already low number of relevant South Asian studies. Of the 6 international studies(Cousens et al., 2011, Lawn et al., 2011, Lozano et al., 2011, Stanton et al., 2006, WHO, 2006a, WHO, 2007) only two studies (Lawn et al., 2011, Cousens et al., 2011) restricted studies to a minimum of 10 outcomes. However, no reasons for restriction were provided by the two studies.

4) My systematic review rates were not cluster-adjusted or adjusted for the sampling strategy of the study as were some rates presented by some individual studies. However, as there was very little difference between my rates and the rates published by the studies, this difference was unlikely to affect national, sub-national or country estimates.

5) Underreporting of stillbirths, which could not be controlled, was present in the studies, as evidenced from the review ratios for stillbirth rate to early neonatal death rate (SBR:ENMR). However, the ratios were within the range of the WHO country-specific values obtained when highest (0.6-0.8) and lowest (1.2) levels of underreporting of stillbirths are assumed. Stillbirth underreporting was expected, as earlier deaths such as miscarriages and stillbirths are underreported more than early neonatal or infant deaths (Lawn et al., 2010, WHO, 2006a). Underreporting may also result from data-collection methods, with evidence that Demographic and Health Survey (DHS) data can underreport stillbirths by around 30% compared to population based-studies (Stanton et al., 2006).

6) Formal testing of the trends of the reduction in mortality rates over time was not performed. This could be done by performing specific analyses (e.g. using meta-regression method with STATA, possibly separating the data by year within each study and by testing the significance of non-linear fits of the relationship between year and mortality).However the number of studies with many years of data was low. Formal statistical assessment of the difference between mortality rates could be performed instead of eyeballing confidence intervals, which may overlap by chance.

There were several strengths of the systematic review.

1) The systematic review was comprehensive, encompassing all community based studies from South Asia that reported numerators and denominators for stillbirths, early neonatal deaths, late neonatal deaths and/or perinatal deaths published from 2000. It is unlikely that any relevant studies were missed. All the search terms were clearly specified, and abstracts were available in English for a few non-English studies though none were eligible.

2) Community representativeness was rigorously maintained by identifying and excluding all facility-based studies.

3) Rates were calculated from numerators and denominators and according to predetermined definitions to maintain consistency throughout the analysis.

4) Additionally, the quality assessment of studies was adopted from recommendations of the Cochrane collaboration and PRISMA statement with rates stratified according to risk-of-bias for each study.

From this review, the urgent need for more empirical studies of good quality with strict definitions of outcomes and rigorous methodology on assessing mortality levels was highlighted, especially for countries of South Asia with the greatest burdens. There are two major recommendations from this review.

1) Recommendations for sub-national studies:

Though cohort studies provide good estimates of mortality rates when conducted well, these are expensive and also non-representative due to their small scale. The recommendations for cohort studies focus less on conducting more studies and more on improving studies already planned. Recommendations are to:

(i) Ensure that the ascertainment of pregnancies, births and deaths enables the capture of all pregnancies, births and deaths for proper assessment of mortality rates. This can be achieved through registering all pregnant women early in their pregnancy with valid and reported methods of pregnancy identification (last menstrual period method, urine dip-stick test and ultrasound) and following them up through their pregnancy till birth or death.

(ii) Use better definitions for stillbirths early and late neonatal deaths, which involves reporting gestational age cut-off values and if possible birth weight for stillbirths and specifying the number of completed days in which early and late neonatal deaths take place.
(iii)In case of cross-sectional studies and surveillance studies the ad-hoc reporting of birth or outcomes by community informants is to be strongly discouraged, with preference for CHWs using women's recall of birth and death outcomes.

2) Recommendations for national studies:

The routine reporting of all pregnancies, births and deaths (vital registration) for LICs would be ideal. However, as many women in these countries still do not deliver in facilities and as births go mostly unregistered, this might be currently unfeasible in the short-term. In the absence of vital registration for LICs, the national DHSs provide estimates that are representative for the

whole country. It is very difficult to improve the quality of DHS mortality rates, which from their very design suffer from the effects of recall bias, heaping of deaths on certain days corresponding to complete weeks, months or years and the secreting of undesirable birth and mortality outcomes. Though the underreporting of stillbirths in DHS studies is very difficult to improve and hampers the measurement of country-representative stillbirth rates, it is likely that the rates for early and late neonatal deaths are better at estimating the burden at country-level because of possibly less under-reporting due to the lower stigma associated with the death of a live born baby. However misclassification between stillbirths and early neonatal deaths and early and late neonatal deaths is always of concern. There is no information on the extent to which women conceal very early neonatal or late neonatal deaths. The recommendation from this review for DHS studies is that despite the shortcomings mentioned above, DHS data should continue to be collected and used as a source of valuable country-representative mortality rates in LICs lacking vital registration.

Pakistan, Bangladesh and India are three of the five countries that account for more than half global stillbirths (1.8 million)and neonatal deaths (2.4 million)(Lawn et al., 2011). While there are overall reductions in under-five mortality, the proportion of neonatal deaths has actually increased from 36% to 40% in the last decade (Countdownto2015). Stillbirths and early neonatal mortality are the most difficult to reduce in under-five deaths (Save the Children 2013; Darmstadt et al. 2014; Wang et al. 2014; J. Lawn , Lee et al. 2009). This review highlights the burden of high stillbirths and early neonatal death rates in these countries as well as in Nepal and Afghanistan. Underreporting of stillbirths is seen in these countries and the very recent separation of stillbirths from perinatal mortality is seen from the low visibility of these deaths in national systems of enumeration and reporting. The mortality rates in my review of population-based studies provide more representative estimates for South Asia and its countries than those available from statistical models. Recommendations described above for national and sub-national studies will improve the monitoring and assessment of these deaths in the South Asian countries that bear the greatest burden.

Chapter 4. The Contribution of the Safe Motherhood Programme to Stillbirths, Early Neonatal Deaths and Late Neonatal Deaths in Matlab

4.1 Introduction

The global burden of stillbirth, perinatal and neonatal mortality has been discussed before (Chapter 2). The reduction of perinatal deaths and preterm births is a complex, multi-faceted problem and suggestions for reductions involve multi-disciplinary interventions at global, country and grassroots levels. Reduction strategies including improvements in education and inequity, involvement of policy leaders and community stakeholders, improvement in quality of health services and increased demand from mothers and newborns have been discussed elsewhere in the literature (Dickson et al. 2014; Knippenberg et al. 2005; Lawn et al. 2013). This introduction will describe evidence-based interventions which are currently thought to reduce mortality and fall within the continuum of care for girls, pregnant mothers and newborns (Mason et al. 2014).

The most recent systematic review of interventions which are effective at reducing stillbirths and neonatal mortality during the antepartum, intrapartum and post-natal period was conducted for the Lancet Every Newborn series by Bhutta et al. 2014. This review identified available systematic reviews and conducted new reviews for some interventions (hygienic practices including use of clean birth kits and the cessation of smoking, alcohol and drug use in pregnancy). The review built on five evidence reviews of effective interventions on stillbirths and neonatal mortality in the Lancet (Bhutta et al. 2013; Bhutta et al. 2011; Darmstadt et al. 2005; Bhutta et al. 2008; Jones et al. 2003). Prior to that, reviews assessing the effect of different intervention packages on stillbirth and neonatal mortality had been descriptive and could not provide an overall estimate of reduction due to the scarcity of studies (Bhutta et al., 2009; Darmstadt et al., 2005; Haws et al., 2007; Schiffman et al., 2010). The reviews included in Bhutta et al 2014 covered the effect of interventions on stillbirths, perinatal and neonatal mortality and the interventions and outcomes are described separately for each review. Information on the effect of interventions on stillbirth or perinatal deaths in LMICs was provided by an earlier Lancet review (Darmstadt et al. 2005) if not covered by the Bhutta et al. review. The latter review noted that facility-based interventions were more likely to improve survival than community-based care though the former were more costly. The Every Newborn

review (Bhutta et al. 2014) estimated that the maximum number of stillbirths could be averted by care during labour and delivery, including complication management (70% stillbirths averted) followed by enhanced antenatal care (ANC) focused on detection of complications (10%). A greater reduction in neonatal deaths was estimated to be achieved by intrapartum interventions for obstetric complications (41% reduction) than by care of small and ill neonates (30%) care of healthy neonates (12%) and essential newborn care (10%). However, as seen below, the evidence base for these interventions comprises a few studies of variable quality.

Interventions administered during the continuum of care that are considered to reduce stillbirth and neonatal mortality include: (1) preconception and ANC interventions (2) skilled birth attendance and basic and emergency obstetric care, (3) essential newborn care and care for small and ill neonates (Bhutta et al. 2014; Lawn et al. 2013; Darmstadt et al. 2005; Bhutta et al. 2012; World Health Organization & UNICEF 2013). Evidence for these interventions is described below:

(1) Interventions in the preconception and antenatal period include: nutritional and micronutrient supplementation, anti-tetanus immunisation, antibiotics for maternal infections during pregnancy and detection of possible risk factors and pregnancy complications. A systematic review (Imdad 2012) evaluated the effect of studies providing balanced energy protein supplementation (protein <25% of total energy) compared to routine diet or no intervention. Studies included: randomized controlled trials (RCTs), quasi-randomised studies and before-and-after designs in low and high income countries (LICs and HICs) and 16 studies were eligible. The meta-analysis results showed a 38% reduction in stillbirths (RR-0.62; 95%CI: 0.40-0.98; 4 studies) though the effect was non-significant for neonatal mortality (RR-0.63; 95%CI: 0.37-1.06; 3 studies). The quality of evidence for both outcomes according to GRADE criteria (GRADE 2014) was reported as ‘low’.

A recent review of iron supplementation (Peña-Rosas et al. 2012) of 43 RCTs from LICs and HICs showed that daily oral supplementation (iron dose: 9-90 mg) versus placebo or no iron had no effect on neonatal mortality (RR-0.90; 95%CI: 0.68-1.19; 4 studies). The quality of studies was ‘low’. The non-significant effect of iron supplementation was supported in an earlier review (Darmstadt et al. 2005) where meta-analysis of five community based iron supplementation programmes in LICs showed no effect on stillbirth and neonatal deaths. A systematic review showed that folic acid supplementation reduced neural tube defects by up

to 62% (95% CI: 49%-71%) and this was based on one RCT and three cohort studies in HICs and MICs (Blencowe et al. 2010). There was no effect of iron combined with folic acid on neonatal mortality (RR-0.81;95%CI:0.81-1.30; 1 study) (Bhutta et al. 2014) and no effect of folic acid on stillbirth reduction (RR-0.78; 95%CI:0.34-1.78; 3 studies) (Darmstadt et al. 2005).

A meta-analysis of one RCT and one cohort study (Blencowe, Lawn, et al. 2010) showed that tetanus toxoid immunisation, when given as two doses in pregnant women, reduced neonatal deaths by 62% (RR-0.38;95%CI:0.27-0.55;1 study). The studies were from LMICs and the evidence was reported to be of 'moderate' quality. An earlier review of studies using tetanus toxoid in pre-pregnant and pregnant women in Bangladesh and India found significant reductions of 44% in stillbirths (1 study) and 33-58% in neonatal deaths (3 studies) (Darmstadt et al. 2005).

A systematic review (Brocklehurst et al. 2013) of 21 RCTs from LMICs and HICs estimated the effect of antibiotics, prescribed for bacterial vaginosis, on perinatal mortality and observed no effect (RR-0.71;95%CI: 0.36-1.39; 4 studies). Syphilis screening and management resulted in a great reduction in stillbirths (95%CI: 66-90%; 8 studies) and perinatal deaths (95%CI: 35-51%;2 studies) in areas where syphilis was prevalent (Blencowe et al. 2011).

Reviewers in the Bhutta et al. 2014 study suggested that the quality of studies was low to moderate for the interventions and few eligible studies were from LICs. The Darmstadt et al. 2005 reviewers noted that their study lacked large trials, was based on a few efficacy trials and that only ten trials targeting interventions for neonatal survival were from LICs or MICs. Hence evidence for these interventions is based on a few studies.

Early studies and recent evaluations show low quality of evidence for screening for women with high risk maternal characteristics (e.g. extremes of age or parity, short stature, poor obstetric history) to predict complicated pregnancies (Lee, Lawn, et al. 2009). Focused ANC is warranted for conditions associated with increased perinatal or maternal death (>3 times increased risk) such as young primiparous mothers (<16 years), malpresentation, and pregnancy complications (e.g. late pregnancy vaginal bleeding, hypertensive disorders and severe anaemia) (Lee, Lawn, et al. 2009; Dean et al. 2013). ANC, by increasing detection and treatment of maternal risk factors (including chronic diseases such as diabetes and hypertension) and possible pregnancy complications can avert intrapartum stillbirth and early

neonatal deaths (Lee et al. 2009; Dean et al. 2013). ANC is also an opportunity to promote skilled attendance at delivery, breast feeding, early post-natal care and optimal pregnancy spacing (Partnership for MNCH 2006)

(2) Skilled birth attendance (SBA) and basic and comprehensive emergency obstetric care (BEmOC and CEmOC) (Chapter 2), are considered to have substantial effects on stillbirths and neonatal mortality during the continuum of care.

Two parallel systematic reviews and meta-analyses by Yakoob et al. 2011 and Lee et al. 2011 tried to measure the impact of SBA, BEmOC and CEmOC on stillbirths and perinatal mortality, respectively. Studies included RCTs, quasi-randomised studies, other intervention studies (e.g. before-after), and observational studies. Interventions included skilled attendance by midwife, doctor or nurse, as defined by WHO (World Health Organization 2004b)(Chapter 2) and BEmOC and CEmOC as defined earlier (Chapter 2). Outcomes considered were stillbirths, early neonatal deaths and perinatal deaths.

Results from the Yakoob et al. 2011 meta-analysis to assess the effect of improved SBA on stillbirths showed a reduction of 23% (95% CI: 15% to 31%) based on two before-and-after studies without control groups that compared two time periods (Ibrahim et al. 1992) (Ronsmans et al. 2008). One of these studies in rural Sudan (Ibrahim et al. 1992) upgraded the skills and resources of village midwives (who collected pregnancy, delivery and newborn event data) in the middle of the 3-year study period. Upgrading consisted of: setting up weekly midwife-led ANC clinics, midwife-led referral systems to hospitals and midwife involvement in primary health care. A 25% stillbirth reduction was observed for the third year relative to the first two years (which had similar rates). In the second study in Matlab, Bangladesh (Ronsmans et al. 2008) SBA improved between 1975 and 2001. Improvements in this time period involved distribution of safe delivery kits to women, coverage of homebirths with trained midwives initiated from 1987 till 1996 (including free transport to referral facilities from 1987 onwards), and from 1996 onwards, facility-based strategy for deliveries. Midwives provided ANC, and basic obstetric and newborn care. During the study period, SBA increased from 0% to 27% while stillbirths were reduced by 24%.

The Lee et al. meta-analysis for early neonatal and perinatal outcomes found four eligible studies including those above and two more in rural Java, Indonesia and rural China in which community midwives (Ronsmans et al. 2008; Alisjahbana et al. 1995; Yan 1989; Ibrahim et al.

1992) or village doctors (Yan 1989) were trained in intrapartum monitoring and management with links to referral facilities. These were all before-after-studies which compared earlier time periods to later time periods. In the 1983-1986 rural China study (Yan et al., 1989), village doctors and midwives were trained to identify risk (blood pressure assessment), managed risks (external cephalic version) or referred mothers to a county hospital where the neonatal ward had been improved and reached up to 96% of pregnant women. In the 1992-1993 Java study village midwives and physicians were trained on danger signs, case management for pregnancy, labour, delivery, post-partum care and newborn care. Traditional birth attendants (TBAs) were also trained for pregnancy complication detection and referral. The Lee et al. 2011 meta-analysis showed that improved community-based skilled attendance reduced early neonatal mortality by 13% (95%CI: 3%-21%) and perinatal mortality by 12% (95%CI: 5%-18%). The quality of evidence was judged by the reviewers to be of 'moderate' quality, mainly because before-and-after study designs were used.

In order to assess the effect of emergency obstetric care on stillbirths, early neonatal deaths and perinatal deaths, Lee et al. 2011 included studies that tested the effect of emergency obstetric care packages on stillbirth and perinatal mortality. Emergency obstetric care was described as childbirth care packages using BEmOC/CEmOC or studies reporting the major functions of these two types of care. Studies included quasi-experimental, case-control, before-and-after, historical and cross-sectional studies and RCTs with standard practice as the comparison group. However, the review authors reported that the nine eligible studies were of low quality and heterogeneous in terms of the interventions included in BEmOC and CEmOC, making them unsuitable for meta-analysis. Hence expert opinion obtained via a Delphi panel of 21 experts for Lee et al. 2011 and of 27 experts for Yakoob et al. 2011 estimated that BEmOC and CEmOC could result in possible stillbirth reduction of 45% and 75%, respectively (Yakoob et al. 2011). Reductions in intrapartum neonatal deaths due to BEmOC and CEmOC were 40% and 85%, respectively (Lee et al. 2011). However, these reductions were based on the assumption that universal coverage (99%) of BEmOC and CEmOC services was available. Whether expert opinion is a valid method to ascertain the magnitude of mortality reductions associated with interventions is uncertain.

A Matlab study in rural Bangladesh (Ronsmans et al. 2010) assessed the impact of BEmOC and CEmOC care compared to no trained care on stillbirths and early neonatal deaths. This study obtained data from a health and demographic surveillance system running since 1961 and observed that skilled care at birth increased from 5.2% to 52.6% between 1987 and 2005. As

more women sought SBA, perinatal mortality rates decreased significantly over time (from 1987-1991 to 2002-2005) in women receiving BEmOC (stillbirths: 41.7 vs. 22.8/1000 births; early neonatal deaths: 39.1 vs. 27.7/1000 live births). This was also seen in the same period for women receiving CEmOC (stillbirths: 13.8 vs. 7.6/1000 births; early neonatal deaths: 83.8 vs. 33.9/1000 live births), suggesting that increasing uptake of BEmOC and CEmOC contributed to reductions in stillbirth and perinatal mortality. The effect of Caesarean section rates on stillbirth reduction was discussed earlier (Chapter 2).

(3) Essential newborn care consists of clean delivery and cord-cutting, neonatal resuscitation, warmth, breastfeeding, and proximity and access to the mother (UNICEF 2004). Care for small and ill neonates involves neonatal resuscitation, prevention of hypothermia (wrapping and kangaroo mother care), skin emollient therapy, recognition and management of neonatal infections (pneumonia and sepsis) and respiratory distress management (Bhutta et al. 2014).

In a systematic review (Blencowe et al. 2011) of the effect of clean birth practices on neonatal mortality, the very low quality of studies reviewed resulted in the authors obtaining estimates from a 30-member Delphi expert panel. Clean practices included hand washing, clean delivery surface, clean perineum, clean cord cutting, and skin and cord care. The Delphi estimates suggested that clean practices could result in 15% fewer neonatal deaths (IQR: 10-20%) at home and 27% fewer deaths (IQR: 24-34%) in facilities. In a systematic review, delayed cord clamping showed no effect on neonatal mortality in term neonates (McDonald et al. 2013). A Cochrane review of 34 RCTs in LICs and HICs on the effect of umbilical antiseptics (Imdad et al. 2013) showed that neonatal mortality was reduced by 23% (95%CI: 6-37%) and supported their use in community and primary care facilities in LICs.

A meta-analysis of three prospective cohort studies in LMICs (Debes et al. 2013) not included in the Bhutta 2014 review, showed that early (within 24 hrs of birth) exclusive breastfeeding was linked to 44% reduction in neonatal mortality (95%CI: 22-57%). The quality of the studies was reported as moderate. The review also reported that early or late initiation did not change mortality risk in exclusively breastfed children.

Bhutta et al. 2014 conducted a systematic review of the effect of delayed bathing, head covering or skin-to-skin on neonatal mortality, but no studies on effect on mortality were obtained. Therefore a Delphi panel of 26 experts was formed which suggested that the three

thermal practices could avert 20% (IQR: 15-25%) of neonatal deaths due to preterm complications. A Cochrane systematic review (Conde-Agudelo et al. 2011) and meta-analysis of seven RCTs in LICs and HICs compared kangaroo mother care (KMC) to usual hospital care in low birth weight (LBW) babies. Skin-to-skin contact between mothers and babies is the main component of KMC. Meta-analysis results showed that mortality at discharge from the hospital or at 40-41 weeks of life was 40% lower (95%CI:7 -61%) for babies who received KMC than those receiving conventional neonatal care. The review supported the use of KMC in LBW babies in resource-limited settings. In another meta-analysis (Salam et al. 2013) of three RCTs from LICs, skin emollient use (sunflower, coconut, soybean or mineral oil) was associated with a 27% (95%CI: 6-44%) reduction of neonatal mortality in preterm babies if applied within 96 hours of birth and for at least a week.

Bhutta et al. 2014 conducted a systematic review of studies assessing the effect of immediate newborn assessment and basic resuscitation on stillbirth, perinatal and neonatal mortality. The interventions were implemented by lay-workers within communities and outreach home-based packages. Studies included RCTs, quasi-experimental studies and observational studies. Community-based neonatal resuscitation was found to reduce perinatal mortality by 11% (95%CI: 2%-20%; 5 studies), early neonatal mortality by 15% (95%CI: 6%-24%; 7 studies) and neonatal mortality by 26% (95%CI: 8%-41%; 4 studies). Effects on stillbirths (6 studies), and late neonatal mortality (4 studies) were non-significant. Facility-based neonatal resuscitation, on the other hand, was found to reduce neonatal mortality by 30% (RR-0.70; 95%CI: 0.59-0.84). The last finding was from a meta-analysis (Lee et al. 2011) of three studies in India, Bulgaria and Zambia which examined the effect of resuscitation training on intrapartum-related neonatal deaths in hospitals and delivery centres in urban areas.

A systematic review (Zaidi et al. 2011) assessed the effects of oral or injectable antibiotics for pneumonia or sepsis at home or at first-level facilities. Studies included were RCTs, studies with non-randomized concurrent controls and observational studies with no control group. Antibiotics were those administered for pneumonia or sepsis in the community and pneumonia or sepsis was defined by the authors of the studies. A meta-analysis of four non-randomized, concurrent control trials in India, Pakistan, Nepal and Tanzania which assessed oral antibiotics for pneumonia found a 25% reduction in neonatal mortality (RR-0.75;95%CI:0.64-0.89) for pneumonia. No studies were found for the effect of oral antibiotics on sepsis. In two community-based studies (one RCT and one observational study) (Baqui et al.

2008; Bang et al. 1999) injectable antibiotics as part of community-based neonatal care packages resulted in significant neonatal mortality reductions of 44% and 34%, but the interpretation of the results is difficult as the reductions are the effect of multiple co-interventions.

In other studies not included in the above review, postnatal home visits have also been associated with neonatal mortality reduction. These visits, delivered in rural Bangladesh by community health visitors (Baqui et al. 2009) within the first two days of life have also been found to reduce neonatal mortality by 67% compared to no visits, if given on the first day of life, by 60% if given on the second day of life, but no effect if given later. The visits consisted of essential newborn care messages, assessment of illness and referral to higher facilities based on a WHO algorithm and provision of gentamicin and penicillin injections to ill neonates if referral was refused. A study in rural India by Bang et al. (Bang et al. 2005) observed tremendous reductions in early neonatal mortality (64%) and late neonatal mortality (80%) in the intervention area relative to the comparison area over a 10-year period when village health workers visited homes. They diagnosed newborn illness by algorithms, followed by use of oral and injectable antibiotics. Impact of postnatal visits in similar settings may depend on content, quality and coverage of interventions included.

The Bhutta et al. 2014 review also included high-tech interventions (ventilation and lung surfactants) that reduced mortality from respiratory distress, but these have not been described here because they are not relevant to the setting studied here.

Studies looking at interventions impacting survival along the entire continuum of neonatal survival are few, as noted in my systematic review (Chapter 3) and as highlighted in international reviews on the topic (Haws et al. 2007; Lassi et al. 2010; Kerber et al. 2007). Additionally, no research was found to provide information on whether the effect of interventions was the same for all days in the first week of life or whether the effect varied by day since birth within the early neonatal period. It was surprising to note that there was no research on the difference of effects for different types of interventions, though it is acknowledged that causes of death are different in this period, with early deaths resulting more from birth asphyxia and later deaths resulting more from sepsis or pneumonia (Baqui et al. 2006; Engmann et al. 2012).

This paucity of studies was again seen in a recent Cochrane review (Lassi et al. 2010) which evaluated the effect of packages of community-based interventions, rather than single interventions, on mortality outcomes. Outcomes were: stillbirths, early and late neonatal deaths, perinatal deaths and maternal deaths. Studies included were community-based RCTs or quasi-RCTs in rural areas of LICs including Bangladesh, India, Nepal and Pakistan. Study intervention packages were those which included routine newborn care and additional training of outreach workers (CHWs, facilitators or TBAs) during pregnancy, delivery and the post-partum period. The additional training was training other than that usually received from governments or NGOs and usually comprised a combination of: antenatal, delivery and postnatal care; essential newborn care; management and referral of sick babies; behaviour change communication and community mobilisation. In this review intervention packages consisting of community mobilization and antenatal and postnatal home visits by community health workers resulted in a 25% (95%CI: 15-33 %) reduction in stillbirths, 19% (95% CI: 6-31%) reduction in early neonatal deaths and 26% (95% CI: 7-40%) reduction in late neonatal deaths. Perinatal mortality was reduced by 28% (95%CI: 12- 41%). Results for the four outcomes were based on meta-analyses from four studies (Kumar et al. 2008; Bhutta et al. 2008; Bhutta et al. 2011; Jokhio et al. 2005). Meta-analysis of three studies (Azad et al. 2010; Manandhar et al. 2004; Tripathy et al. 2011) showed that community support groups or women's groups resulted in early neonatal death reduction (24%; 95%CI: 2-42%) though effects were non-significant for stillbirths, perinatal and late neonatal deaths. However, a recent meta-analysis of seven women's groups studies suggested that effects on stillbirths were non-significant while reductions in perinatal and early and late neonatal mortality were significant (24%, 24% and 25%) (Prost et al. 2013).

It should be noted that the Lassi et al. review evaluated the effect of packages that differed greatly in terms of the interventions used, the training of outreach workers and timings and durations of the intervention. Hence the meta-analysis results of different interventions grouped as one intervention (e.g. intervention packages consisting of community mobilization and antenatal and postnatal home visits by community health workers) should be interpreted with caution.

In summary, the available evidence on interventions resulting in reduction of stillbirth and perinatal mortality relies on very few studies, mostly of low to moderate quality and also on Delphi estimates from panels of experts. The complex issues in understanding and defining intervention packages and their impact on specific mortality outcomes suggests that there is

an urgent need for quality implementation research in countries where the majority of the deaths occur. The following cohort study in Matlab, rural Bangladesh, will address gaps in the research by comparing and tracking mortality outcomes over two decades to see the impact of a safe motherhood intervention package on stillbirths and newborn survival. The mortality outcomes over the continuum of newborn survival (stillbirth and early neonatal death, disaggregated by day since birth, and late neonatal death) will be explored to compare the effects of a Safe Motherhood intervention package on survival during the continuum of early life. This study will address the knowledge gap as to whether the effect of the Matlab Safe Motherhood Programme on mortality is unchanged throughout the early neonatal period or whether it is varies by day since birth in the first seven days of life. The presence of a comparison area in addition to the intervention area, both covered by Matlab's long-term demographic surveillance system, enables us to assess trends in socio-demographic factors and care-seeking patterns. This will help us to better understand and measure the effect of interventions on survival during the earliest period life when stillbirths and newborn mortality occur, in an area with one of the greatest global burdens of such deaths.

4.2 Objectives

Overall Objective

The overall objective is to examine the contribution of the Matlab Safe Motherhood Programme to the levels and trends in mortality for stillbirths, early neonatal deaths, early neonatal deaths (disaggregated by day since birth) and late neonatal deaths in a rural cohort in Matlab, Bangladesh.

Specific Objectives

1) To examine levels and trends in the rates of stillbirths, early neonatal deaths, early neonatal deaths (disaggregated by day since birth) and late neonatal deaths in two areas of a rural cohort in Matlab, Bangladesh from 1987-2009. One of the two areas has the Matlab Safe Motherhood Programme.

2) To examine the levels and trends in uptake of delivery care in the two areas of Matlab by:

i. Type of birth attendant
ii. Place of delivery
iii. Mode of delivery

3) To examine the socio-demographic determinants of stillbirths, early neonatal deaths (disaggregated by day since birth) and late neonatal deaths. The socio-demographic determinants to be examined will be:

i. Time period
ii. Area of residence
iii. Maternal formal education
iv. Household asset quintile
v. Religion
vi. Maternal age
vii. Gravidity

4) To examine if there are differences in mortality rates over time in the two areas and if so, whether the differences are explained by the socio-demographic changes taking place in Matlab over the study period or by the presence of the Safe Motherhood Programme.

4.3 Methods

4.3.1 Study design:

This is a retrospective cohort study of all women living in the ICDDR,B (International Centre for Diarrhoeal Disease Research, Bangladesh) and the Government service areas in Matlab, who had pregnancies ending in a live birth or a stillbirth between January 1987 and December 2009.

4.3.2 The Matlab Health and Demographic Surveillance System (HDSS)

The research organization, ICDDR,B, has been operating a health and demographic surveillance system (HDSS) in the rural sub-district of Matlab since 1966. The Matlab study area comprises two halves which are similar in geographical terrain and population. One half (ICDDR,B service area) has received extensive maternal, child health and family planning services since 1977 from ICDDR,B in addition to government health and family planning services. The other half (Government service area) receives only government services (Figure 4.1). These services are described in sections 4.3.4-4.3.6.

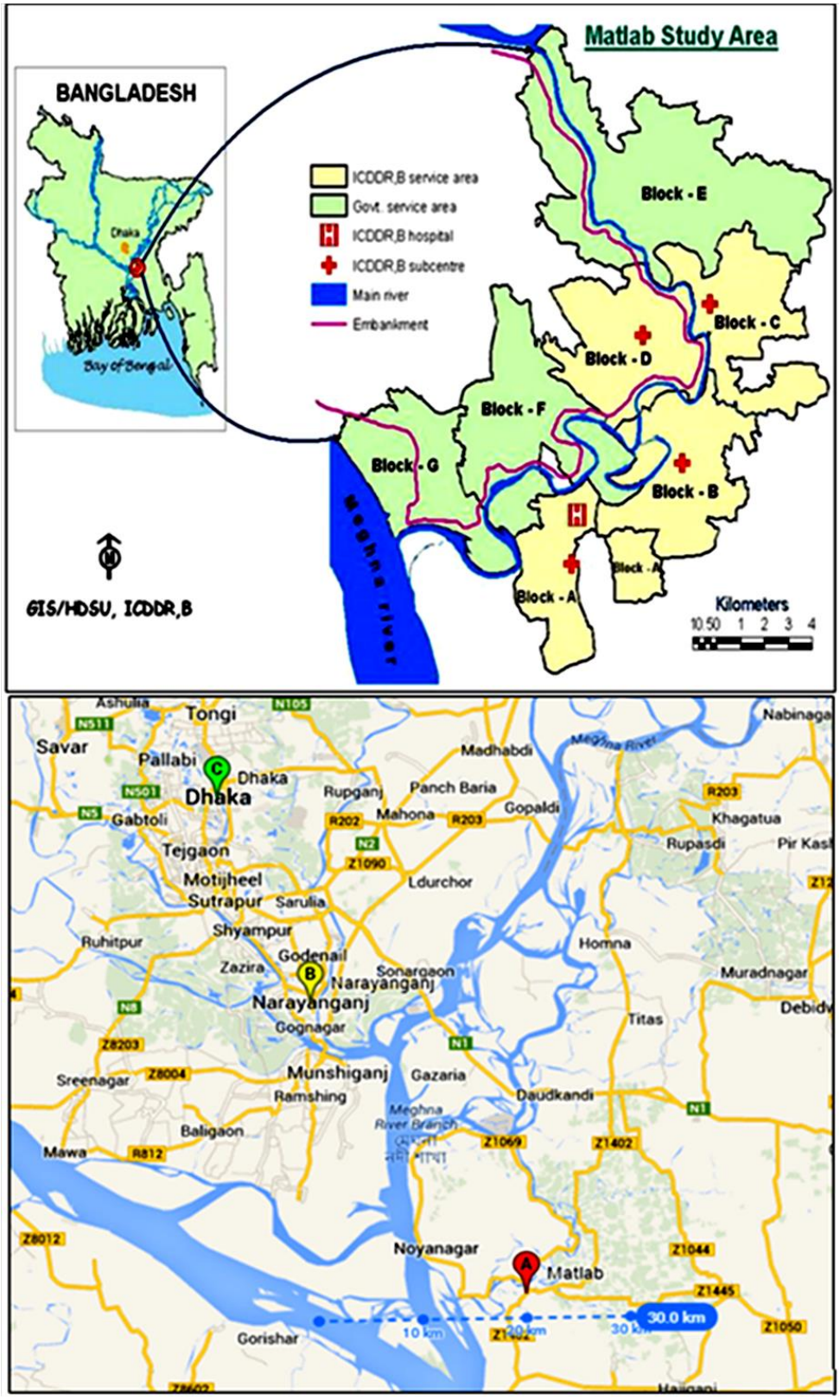


Figure 4.1: Maps showing a) ICDDR,B and the Government service areas which constitute the Health and Demographic Surveillance (HDSS) area of Matlab, Bangladesh and b) the location of Matlab relative to Narayanganj town and the capital, Dhaka, places women from Matlab and Chandpur travel to in order to access high-level care (Images: ICDDR,B and Google Maps)

4.3.3 Study area and population:

Matlab, located 55 km southeast of the capital Dhaka, is within Bangladesh's Chandpur district. Predominantly an agricultural area, the sub-district is typical of many rural and riverine-deltaic areas of Bangladesh (Figure 4.2).

The mid-year population for 2009 in the surveillance area was 223,285 with similar numbers of residents living in the ICDDR,B (114230) and Government (109055) service areas (ICDDRB 2011). The surveillance area covers 142 villages (184 km^2) and has a high population density (~1200 individuals/km^2)(Bos 2004).

Nearly 90% of the population is Muslim. The next largest minority group comprises Hindus. Principal occupations are rice cultivation, fish-farming and fishing.

The educational status of women in Matlab has changed considerably over time. The percentage of pregnant women with one or more years of schooling increased from 31% in 1976-80 to 73% in 2001-2005 in the ICDDR,B service area, with a corresponding increase of 27% to 72% in the Government area (Chowdhury et al. 2007).

BRAC (Bangladesh Rural Advancement Committee), an NGO, initiated micro-credit programmes in both areas in 1992 and access to these and other NGO programmes is equal in both areas. (Ahmed et al. 2001).

The commercial and administrative centre of the surveillance area is Matlab Bazaar which houses the Matlab Health Research Centre (MHRC), ICDDR,B's Matlab headquarters. The main ICDDR,B headquarters are in Dhaka. The MHRC contains the ICDDR,B Hospital, a 30-bed maternity hospital (designated 'H' in Figure 4.1) and the demographic and health surveillance system offices.

Figure 4.2: Images of the villages in the Matlab study area. (Photographs: Suchismita Roy)

4.3.4 Family planning and fertility rates in Matlab

Government family planning services, which provide free contraceptives, have been operational in Matlab since 1975 and this, alongside early pregnancy terminations by vacuum aspiration, has resulted in declining fertility levels. Intensification of service provision in the ICDDR,B area from 1978 has resulted in a steeper decline in fertility rates in the ICDDR,B service area than the Government service area (Rahman et al. 2001) (Figure 4.3). Details of family-planning services in the two areas are noted elsewhere (Appendix II). Fertility rates relevant for our study period are from 1987 onwards, and differences in rates between the

ICDDR,B (4.2 live births /woman)and Government (5. 3 live births /woman) service areas had almost ceased to exist by 2005 (2.7 and 2.8 live births/woman, respectively) (Chowdhury et al. 2009).

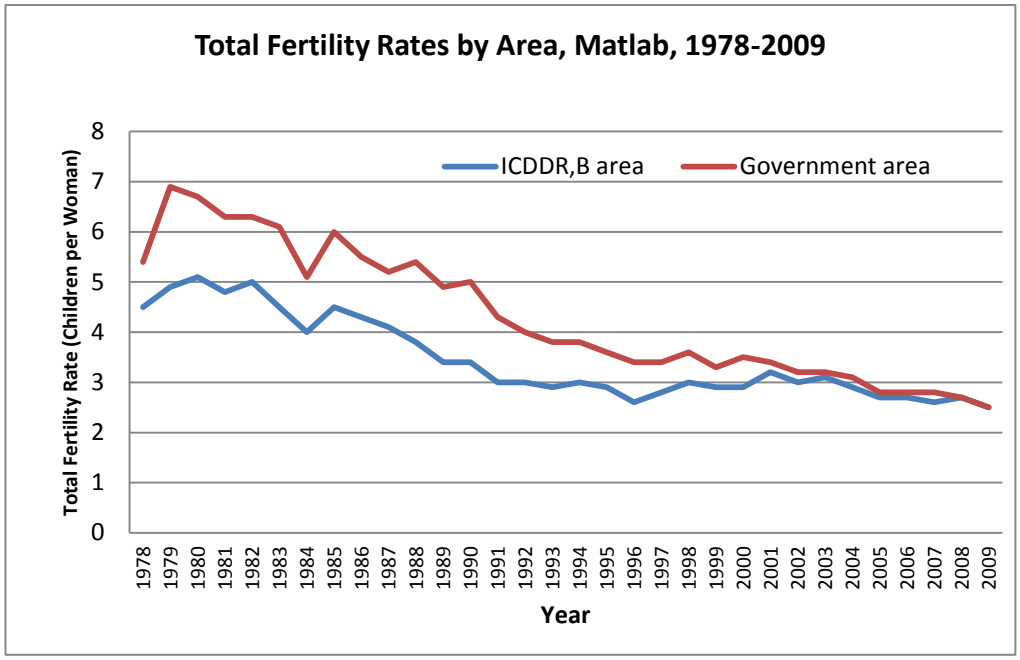


Figure 4.3: Trends in the number of live births per woman (total fertility rate) in the ICDDR,B and Government service areas in Matlab (1978-2009)

Source: HDSS Annual Reports and Matlab Demographic Workbook, version July-2009-v2)

4.3.5 Public and private sector health facilities in Matlab and beyond:

Inside the Government service area of the Matlab surveillance area, maternity care services at the 31-bed government sub-district health complex (Matlab *Upazila/Thana* Health Complex) are accessible to residents of both areas(Rahman et al. 2011). This facility is staffed by 9-10 physicians for serving a population of 200,000 people and basic emergency obstetric care is available. The lowest level of governmental health facility is the sub-sub- district health facility (sub-district or *Union* Health and Family Welfare Centre) which serves 20,000 people via a paramedic trained in midwifery and a health assistant and provides antenatal care, delivery services as well as family planning and child care/immunisation services (National Encyclopedia of Bangladesh 2014) (Rahman et al. 2011).

The only trained delivery attendants inside the surveillance area are the ICDDR,B's midwives/paramedics and corresponding government service providers and the only private hospital is the 30-bed ICDDR, B hospital (Chowdhury et al. 2006).

Chandpur Town is located a 40 minutes' drive south of Matlab. Two government hospitals there (Chandpur District Hospital -150 beds; and Chandpur Maternal and Child Welfare Centre-13 beds) provide Caesarean sections and blood transfusions. Private care in Chandpur Town dramatically increased after 2004 and now 26 private hospitals and clinics provide varying degrees of delivery services (Huda et al. 2012; Anwar et al. 2004). Women also deliver in Narayanganj Town health facilities, north of Matlab (Ronsmans et al. 1997; A. Rahman et al. 2009) and some travel to Dhaka, and elsewhere for high-level care and delivery (Figure 4.1).

4.3.6 ICDDR,B's Matlab Maternal and Child Health Services:

From 1982, in addition to its intensified family planning, half of the ICDDR,B service area was provided with free maternal and neonatal services such as: tetanus and measles immunisations, and simple antenatal screening. These services were provided by community health workers (CHRWs) from the locality during fortnightly household visits (Phillips et al. 1982; Chowdhury et al. 2007). By 1986, these services were rolled out to the entire ICDDR,B service area and included full immunization services for children and pregnant women, oral rehydration therapy, vitamin-A doses, nutrition education and acute respiratory infection treatment (Ronsmans et al. 2008).

In 1987, a Safe Motherhood Programme was piloted in the ICDDR,B area to increase skilled birth attendance at home-births as nearly all births took place at home. The ICDDR,B hospital was established in Matlab Town with four fixed-site health centres ('sub-centres') located within the ICDDR,B service area providing free services(Figures 4.4-4.5). A midwife and paramedic (both trained) were posted in two sub-centres, on call 24 hours a day ,to provide antenatal, delivery and postnatal care at home-births. Training included treatment of minor pregnancy and delivery complications, performing normal delivery and referral of serious patients to the ICDDR,B hospital (Ronsmans et al. 1997; Fauveau et al. 1991; Fauveau et al. 1990). Free transfers 24 hours a day to the ICDDR,B Hospital or to higher-level Chandpur facilities (40 minutes' journey) were available by ambulance or speedboat (Chowdhury et al. 2007; Huda et al. 2012).

In 1990, midwives and paramedics were posted to the two remaining sub-centres and the programme was expanded to the entire ICDDR,B service area. During our study period (1987-2009) the four sub-centres provided coverage to 23,000-28,000 people with 90% of all women living within 3 kilometres of a sub-centre (Chowdhury et al. 2006). In 1996, the home-birth strategy was replaced with a facility-birth strategy whereby midwives only delivered babies in upgraded sub-centres(Ronsmans et al. 2010; Chowdhury et al. 2009).

In mid- 2007, a new programme called the MNCH (Maternal Neonatal and Child Health) package was added to the Safe Motherhood Programme which strengthened existing interventions and added new ones to complete a continuum of care from pregnancy to the post-partum stage (Pervin et al. 2012; Rahman et al. 2011). Among the interventions strengthened were ANC visits, skilled obstetric care at birth, essential newborn care and referral for complications, while new interventions included antibiotics for premature rupture of membrane, corticosteroids for women at risk of preterm birth, pregnancy and post-partum home visits and birth-preparedness (Details of ANC visits and other services: Appendix II: Tables 1-2).

Figure 4.4: ICDDR,B subcentre. From top to bottom: i)a rickshaw-van to transport women from home to sub-centres ii)sub-centre building iii) paramedic attending a mother and baby iv) midwife providing ANC and v)delivery-room in the sub-centre (Photographs: Suchismita Roy)

Figure 4.5: ICDDR,B Matlab hospital. From top to bottom i)ambulance for transport to higher referral facilities ii) ICDDR,B Matlab hospital building iii)nurse-midwife checking foetal heart rate iv) delivery-room v) cut-out representing cervical dilatation and vi) 1 day-old baby (Photographs: Suchismita Roy)

From 1987 midwives have maintained a record (kept as a card) of all pregnancy and post-delivery visits for each ICDDR,B service area pregnancy. Initially, cards were only provided for women who were seen by midwives but in 1993 the system was extended to all women identified as pregnant by CHRWs. CHRWs confirmed pregnancies if two consecutive periods were missed or after 2007, by positive urine dipstick test. The cards included information on past obstetric history, ANC, labour/delivery, pregnancy outcome, newborn condition and postnatal care with additional pictorial messages on pregnancy danger-signs and nutrition from 1996 (Figure 4.6).

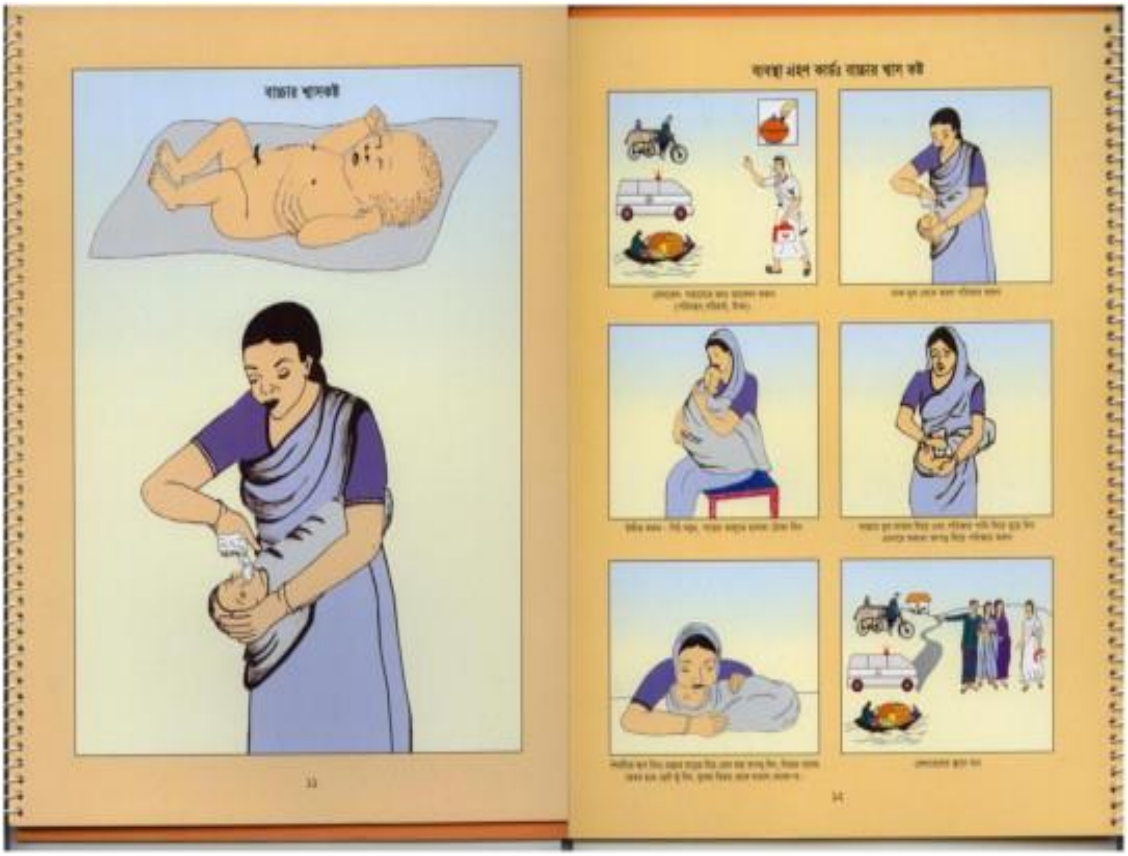


Figure 4.6: Pictorial messages on cards received by pregnant women

Maternal and newborn services provided at home, sub-centres and the ICDDR,B hospital have changed over the study period (1987-2009).

Services at home and subcentre:

From 1987 to 1996, when trained midwives attended home births they provided antenatal and basic obstetric and newborn care, progress-monitoring of labour, drying/wrapping of the baby, placing baby on mother's breast for breastfeeding facilitation, antibiotic eye prophylaxis and application of suction when necessary (Ronsmans et al. 2008). They also organized referral and

accompanied patients to ICDDR,B hospital if necessary and visited home-birthing women within 48 hours of delivery (Fauveau.V 1994). Between 1996 and 2001 as home-births with trained midwives were stopped and the facility-birthing strategy started, the ICDDR,B subcentres were upgraded to provide basic obstetric ,antenatal and postnatal care (Chowdhury et al. 2006). The services provided till 2009 included: ANC, post-natal care, ultrasonography (from 2001) (Neufeld et al. 2009), active management of the third stage of labour by oxytocis, normal delivery, initial treatment of complications (e.g. antibiotics for infection, saline infusion for haemorrhage and sedatives for pre-eclampsia and eclampsia), oxygen via mask, newborn resuscitation by CPR (cardio pulmonary resuscitation) and Ambu-bag (Huda et al. 2012). Newborns with complications were given initial emergency treatment, including antibiotics, and were referred to the ICDDR,B hospital. From 2007 (when the MNCH programme was introduced) more services were added: routine ultrasonogram and deworming, maternal and newborn infection prevention protocols, referral of preterm/small babies to ICDDR,B hospital for kangaroo mother care, early detection and referral of maternal and newborn complications and extra visits for preterm babies (Rahman et al. 2011).

Services at ICDDR,B hospital:

From 1987 the newly established ICDDR,B hospital offered basic obstetric and newborn care and in addition to conducting normal delivery, the following services were recorded (Fauveau.V 1994): early administration of anti-eclampsia drugs (not specified), stimulation of labour for prolonged labour, external or internal version for breech deliveries, uterine evacuation for retained placenta, vaginal packing for cervical tear, stitching for vaginal tear, fluids for haemorrhagic shock and antibiotics for infection prevention. Newborn interventions included early clearing of the airways, warming, early colostrum feeding and simple resuscitation procedures. More recently, from 1996 -2009, the ICDDR,B hospital has provided all the services provided at the sub-centres in addition to more intensive management and treatment of complications. These procedures include: magnesium sulphate administration for pre-eclampsia/eclampsia, assisted vaginal delivery by vacuum extraction, manual removal of placenta and removal of retained products of conception from the uterus, (Ronsmans et al. 2010; Huda et al. 2012) qualifying it as a basic emergency obstetric care (BEmOC) facility. Patients with complications requiring surgery (Caesarean sections and hysterectomies) and blood transfusion are transferred free to Chandpur facilities. Simple laboratory tests if needed, are conducted free of cost at the Matlab ICDDR,B hospital.

4.3.7 Data sources:

Health and demographic surveillance data collected by the ICDDR, B from 1987- 2009 were analysed for the retrospective cohort study.

Figure 4.7: ICDDR,B community health research worker recording information from a pregnant woman during a routine home visit.(Photograph: Suchismita Roy)

Vital events and census information:

The Matlab Health and Demographic Surveillance System (HDSS) has collected vital events data in both areas since 1966 and conducted three socio-economic censuses. Details are presented below.

Vital Events Data:

The Demographic Surveillance System has been continuously recording vital events in the ICDDR,B and Government service areas since 1966.

Female CHRWs visit households in their designated villages to record pregnancy outcomes (live births, stillbirth, abortions and miscarriages), deaths, migration (into and out of the surveillance area), marriages and divorces and changes in head of household (Figure 4.7).

These household visits occurred fortnightly from 1966-1996, monthly from 1997 onwards and every two months from 2007 onwards. Senior male health assistants accompany CHRWs every two months on their visits to verify data collected. CHRWs are local married women, usually employed for many years, considered to be trustworthy and in a good position to obtain reliable intimate pregnancy outcomes information (Rahman et al. 2009). There are 61 and 30 CHRWs in the ICDDR,B and Government servicer areas, respectively. The number of households visited daily by each CHRW varies by each service area (ICDDR,B: 20-25 vs. Government: 50-55) (Razzaque & Streatfield 1998) because of health services provided in the ICDDR,B service area (Ronsmans et al. 2008).

ICDDR,B provides each household with a Family Register which is updated manually by the CHRW if there are any changes in the composition of the family. Additional information on vital events is recorded on specialized forms (birth, death, migration, marriage, divorce, change of household head) during interviews with household members on joint visits by the CHRW and her senior health assistant. Illegitimate pregnancies are very rare in Matlab and are a sensitive issue so although these births are recorded, due to privacy concerns they are removed from the final datasets given to ICDDRB staff researchers or external researchers for purposes of analyses.

Census Data:

Information for the three censuses (1982, 1996 and 2005) was recorded by CHRWs on: occupation (maternal and paternal), religion (maternal and paternal), education (maternal and paternal), contraception (maternal and paternal), and household assets. ICDDR,B generated household asset scores corresponding to asset quintiles (poorest quintile=asset score 1 and richest quintile= asset score 5) at each of the three censuses based on: materials for roof, floor, wall of dwelling, type of latrine, land owned, electricity supply, ownership of radio, television, cow, etc. (Chowdhury et al. 2007).

Data for pregnancy outcomes, early and late neonatal deaths

Information on pregnancy outcomes (live birth, stillbirth, abortion and miscarriage), multiple births and date of birth were obtained from the birth form and the date of death from a death form. Unique ID numbers of the women, men and live children were used to link socio-demographic, health and pregnancy information for analysis (Razzaque & Streatfield 1998).

Data for delivery care: delivery location, birth attendant and mode of delivery

Information on delivery location and mode of delivery was available and recorded on the birth forms from 2002 and 2004. The type of birth attendant was recorded from 1987 to 2009 but there is no information for 1999-2001 as data collection was halted for this period.
The different categories for these delivery care characteristics are listed later (section 4.3.10)

4.3.8 Data structure

The Matlab HDSS recorded the information for each pregnancy outcome with its corresponding retrospective reproductive history in birth files. This history consists of number of: living daughters/sons, dead daughters/sons and foetal losses (stillbirths and spontaneous/induced abortions). A Matlab woman with two live births, one stillbirth and one abortion would therefore have four records in the birth file, each bearing her unique ID number.

4.3.9 Data Quality:

The Matlab surveillance data is generally thought to be of reasonably high quality (Chowdhury et al. 2007; Ronsmans et al. 2010).There are several reasons for this.

Pregnancy is ascertained on each visit by the same familiar CHRW. The prospective recording of pregnancy and pregnancy outcomes on these regular visits by recording the last menstrual period date with confirmation by three periods missed (pre- 2007) or urine-dipstick (2007 onwards) makes it less likely that pregnancies and outcomes are missed as all pregnancies are tracked from identification to miscarriage/abortion or delivery unlike e.g. key informant surveillance systems. As key informants depend on women notifying them if they are pregnant or have had a favourable/unfavourable pregnancy outcome, pregnancies and outcomes may be missed if women (and their families) choose to conceal the pregnancy itself and its outcome from key informants and other people living in the same community. Stillbirth under-reporting is also less likely because pregnancies are recorded and tracked from the start (pregnancy confirmation). Misclassification between stillbirths and early neonatal deaths because of errors in women's self-reports may still occur in both the ICDDR,B and Government service areas. ICDDR,B CHRWs try to limit this by explaining ICDDR,B definitions for stillbirths and live births to mothers before recording the answers.

Fortnightly (till the end of 1996), monthly (from 1997) and two-monthly (from 2007) recording of deaths reduces recall bias for dates of death. There is no misclassification between early and

late neonatal deaths as this is calculated by researchers from birth and death dates. These birth and death dates are recorded during CHWR visits with accuracy and completion checked during random household visits by CHRW supervisors and data quality checks described below.

If women were unable to report delivery locations to CHRWs (e.g. unconscious or severely ill during transfer) another household member was allowed to answer. If place of delivery was not on the form, the name was recorded for later coding by ICDDR,B staff. Researchers coded facilities into public/private facilities with support from ICDDR,B staff to avoid misclassification in these categories by women.

Misclassification caused by women being unable to differentiate between their birth attendants is possible as providers rarely introduce themselves to birthing women and women do not regularly seek care outside the home. During the study period birth attendants in the ICDDR,B service area consisted of TBAs or trained midwives at home births (till end of 1995) and trained nurse-midwives and doctors in facilities. So ICDDR,B service women might have misclassified these categories of birth attendants. For the Government service area there were no designated trained midwives for home deliveries and so misclassification could have occurred between TBAs, nurse-midwives and doctors. However it was likely that misclassification was non-differential as ICDDR,B and Government service area women probably misclassified birth attendants to the same extent.

Data collected by CHRWs are subject to regular, random checks by a quality control team from Dhaka visiting households. The data are also checked fortnightly by CHRW supervisors. Computerised data-entry in Matlab has automated checks for range and inconsistency, while consistency checks are made with the longitudinal data already collected (Razzaque & Streatfield 2002).

4.3.10 Definitions:

Definitions for Pregnancy and Mortality Outcomes

The following definitions of pregnancy outcomes are from the ICDDR,B field worker's instruction manuals in the local language, Bengali.

Stillbirth – The production of a lifeless foetus after seven completed months of gestation (Note: CHRWs do not always confirm seven months' gestation though they are required to do so. The instruction manual does not explain how this duration is to be calculated)

Live birth - The complete expulsion or extraction from the mother of a baby, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached. Each product of such a birth is considered live born.

Abortion - The expulsion of a dead foetus from the time a woman is known to be pregnant until seven completed months of gestation. An abortion may be involuntary in which case it is described as 'spontaneous'(also known as a miscarriage) or deliberate in which case it is known as 'induced'.

Birth- Indicates a live birth or stillbirth.

Delivery- Process of birthing. Also refers to the event irrespective of the number of newborn (e.g. in the case of a twin pregnancy, one delivery may consist of two babies)

Where no Matlab definitions were available, I have defined outcomes as given below.

Neonatal deaths - Deaths within the first 28 days of life.

Day 0 Deaths – Deaths occurring on the day of birth.

Day 1-2 Deaths - Deaths occurring in the second and third days of life.

Day 3-6 Deaths - Deaths occurring in the fourth to seventh days of life.

Early neonatal deaths - Deaths within the first full seven days of life.

Late Neonatal Deaths - Deaths occurring in the eighth to twenty-eighth days of life.

Since only the date of death was noted on the birth forms and not the actual time of death or delivery, the age of a child at death (obtained from subtracting date of death from date of birth) could cover a range of hours as shown in Table 4.1.

Table 4.1: Possible range of hours that newborns might have been alive prior to death.

Death	**Difference between death date and birth date(day/s)**	**Possible range of hours that the newborn might have been alive prior to death**
Day 0	0	0 min - 23 h 59 min (24 h)
Day 1-2	1 to ≤ 2	1 min - 47 h 59 min (48 h)
Day 3-6	3 to ≤ 6	48 h - 167 h 59 min (168 h)
Early Neonatal	0 to ≤ 6	0 min - 167 h 59 min (168 h)
Late Neonatal	>6 to ≤ 27	168 h - 671 h 59 min (672 h)

Definitions and Categories for Birth Attendants

Categories:

1. Doctor
2. Nurse/Midwife/ Paramedic
3. Traditional birth attendant/Other
4. Unknown attendants

Note: If more than one birth attendant present at a birth, the most highly trained person was considered to be the birth attendant

Definitions:

I have constructed my own definitions for the categories of birth attendants and for the CHRWs, unless referenced otherwise.

Skilled Birth Attendant- doctor, nurse, nurse/midwife or paramedic who conducts the delivery of a baby.

Doctors- specialists in gynaecology and obstetrics or general physicians

Nurse-midwives/midwives- health professional who has completed 10 years of schooling, 3 years of nursing training and 1 year midwifery training. Provides antenatal and postnatal care, basic emergency obstetric care, newborn resuscitation, menstrual regulation, abortion care and family planning services (Mridha et al. 2009).

Paramedic:

Family Welfare Visitor (FWV): female government health professional with 10 years of schooling and 18 months of training on maternal and child health, family planning and contraception. Provides antenatal and postnatal care and a few basic emergency obstetric care services: intravenous antibiotic/oxytocin administration and basic neonatal resuscitation. Can also provide: menstrual regulation, abortion care and family planning services including intra-uterine device (IUD) insertion and injectable contraceptives (Mridha et al. 2009).

The Lady Family Planning Visitor (LFPV): Matlab equivalent of FWV with the same schooling and training. Has an additional 6-week ICDDR,B training. Provides the same services as a FWV and is posted in ICDDR,B sub-centres (Mridha et al. 2009).

Non-Professional Birth Attendant- traditional birth attendant (trained or untrained), unlicensed/'quack' doctor, traditional healer (*kabiraj, hakim* or spiritual healer) or pregnant

woman, her relatives or neighbours irrespective of whether or not they conduct deliveries as a means of livelihood.

> **Traditional Birth Attendant (TBA)-** A person who assists the mother during childbirth and who initially acquired her skills by delivering babies herself or by working with other traditional birth attendants (World Health Organization 1978). Most TBAs in Bangladesh and Matlab are older, usually illiterate women and some may have received training from the government (Ronsmans et al. 1997).

Definition for Community Health Research Worker

Community Health Research Worker (CHRW)- A married woman living in a surveillance area village with at least eight years of schooling, prior or current experience of contraception usage and at least one child. She has eight weeks ICDDR,B training to perform regular household visits, record vital events and to additionally provide maternal and child services if operating in the ICDDR,B service area (Nag 1992; Fauveau.V 1994).

Definitions and Categories for Delivery Location

Categories:

1. Home - of the pregnant woman or her relative
2. Public Facilities
3. Private Facilities
4. ICDDR,B Facilities

Definitions: I have constructed my own definitions for the categories of delivery locations.

Home- of the pregnant woman or her relative. Deliveries in transit were also considered to be home deliveries.

Public Health Facilities - Owned and administered by the government. These include: District hospitals, District Maternity and Child Welfare Centres, Sub-district (*Thana/Upazila*) Health Complexes, Sub-sub-district (*Union*) Health and Family Welfare Centres.

Private Health Facilities -Owned and administered by one or more private individuals, or private businesses. Depending on the facility, these may offer different levels of maternal and child health services. NGO-run hospitals, clinics and health centres are included.

ICDDR,B Health Facilities- Owned and administered by ICDDR,B. These include ICDDR,B hospital and sub-centres. Though technically private health facilities, these have been categorized separately.

4.3.11 Definitions and categories for Mode of Delivery

Categories:

1. Vaginal delivery
2. Caesarean section
3. Instrumental delivery (forceps delivery and/or suction-cup vacuum delivery)

Definitions: I have constructed my own definitions for the categories of mode of delivery.

Vaginal delivery - all non-Caesarean deliveries and all non-instrumental deliveries of Matlab mothers.

Caesarean section - delivery of a baby through a surgical incision made in the mother's abdomen and uterus.

Instrumental delivery - birth that requires use of forceps or vacuum extraction by a suction cap in order to complete delivery of the baby.

4.3.12 Definitions and Categories for Socio-Demographic Characteristics

Definitions: I have constructed my own definitions for socio-demographic characteristics.

Year - Any calendar year from 1987-2009 in which a pregnant woman in the Matlab study area has had a pregnancy outcome (live birth, stillbirth, miscarriage or abortion).

Area of Residence - One of two areas in the Matlab surveillance area where the pregnant woman resides: Government service area and the ICDDR,B service area

Maternal Formal Education (Year) - Number of years of formal education received by the mother in a secular institution: 0 (reference), 1-5 years, 6-10 years, 11-16 years, Unknown. The ICDDR,B and I consider education in religious institutes to be equivalent to 0 years formal education.

Household Asset Score/Quintile - ICDDR,B generated an asset quintile for a household each time a socio-economic census was conducted (1982, 1996, and 2005). The lowest quintile (asset score-1) represented the poorest households and the highest quintile (asset score-5) represented the least poor households. When assigning mother's household asset quintile to a

delivery, I used the census closest in time to the delivery date (e.g. a delivery on 10th Jan 2008 would have the 2005 census asset quintile and not the 1996 census asset quintile).

Maternal Age - the age of the mother at the time of having a live birth, stillbirth, miscarriage or abortion: <20 years, 20-29 years , 30-39 years and 40+ years.

Gravidity - Number of times a woman has been pregnant irrespective of the duration and outcome of the pregnancy, including her current or index pregnancy at the time of pregnancy confirmation**:** 1, 2-3, 4-6 and 7+.

4.3.13 Analysis:

Description of sample

I included live births and stillbirths to women registered in the Matlab surveillance area from 1987 to 2009. I excluded abortions (spontaneous and induced) and infants aged 28 days or less who migrated out of the surveillance area during 1987-2009. I performed analyses where the unit of analysis was a delivery and not a birth.

Choice of denominators

Conventionally, stillbirth, early neonatal death and late neonatal death outcomes are analysed among all births (Bhutta, Soofi, et al. 2011; Ellis et al. 2011; More et al. 2009; George et al. 2009; Bang et al. 1999) and not deliveries. Ronsmans et al. further restricted their analysis to singleton births in Matlab (Ronsmans et al. 2008).

I based mortality rates on deliveries rather than births as the focus of this thesis is on deliveries, the care obtained during deliveries as well as the complications experienced during delivery. I dealt with multiple births by assigning one birth outcome for each delivery. In case of multiple births with different birth outcomes, I assigned outcomes in the following hierarchical order: stillbirth, early neonatal death, late neonatal death and live birth (Tables 4.2 and 4.3).

Table 4.2: Combinations of birth outcomes in 1442 deliveries of twins in Matlab (1987-2009)

Combinations of Birth Outcomes in Deliveries of Twins	Birth Outcome Assigned
Both infants alive at 1 month	Live birth
1 infant alive at 1 month + 1 Stillbirth	Stillbirth
1 infant alive at 1 month + 1 Early Neonatal Death	Early Neonatal Death
1 infant alive at 1 month + 1 Late Neonatal Death	Late Neonatal Death
2 Stillbirths	Stillbirth
1 Stillbirth+ 1 Early Neonatal Death	Stillbirth
1 Stillbirth + 1 Late Neonatal Death	Stillbirth
2 Early Neonatal Deaths	Early Neonatal Death
1 Early Neonatal Death + 1 Late Neonatal Death	Early Neonatal Death

Table 4.3: Combinations of birth outcomes in 18 deliveries of triplets in Matlab (1987-2009)

Combinations of Birth Outcomes in Deliveries of Triplets	Birth Outcome Assigned
All three infants alive at 1 month	Live birth
2 infants alive at 1 month + 1 Stillbirth	Stillbirth
2 infants alive at 1 month + 1 Early Neonatal Death	Early Neonatal Death
2 infants alive at 1 month + 1 Late Neonatal Death	Late Neonatal Death
1 infant alive at 1 month + 1 Early Neonatal Death + 1 Stillbirth	Stillbirth
1 infant alive at 1 month + 1 Early Neonatal Death + 1 Late Neonatal Death	Early Neonatal Death
3 Stillbirths	Stillbirth
2 Stillbirths + 1 Early Neonatal Death	Stillbirth
1 Stillbirth + 2 Early Neonatal Deaths	Stillbirth
3 Early Neonatal Deaths	Early Neonatal Death
1 Early Neonatal death + 2 Late Neonatal Deaths	Early Neonatal Death
3 Late Neonatal Deaths	Late Neonatal Death

I calculated the six mortality rates by dividing the number of deaths by the population initially at risk and multiplied the result by 1000 (Table 4.4). Although epidemiologically these mortality rates are risks, as they do not take into account person-time, I have designated them as rates in accordance with the convention followed in the stillbirth and neonatal literature (Stanton et al. 2006; Ahman & Zupan 2007; Cousens, Blencowe et al. 2011). Though the denominators for the mortality rates are deliveries (Table 4.4), in later analyses, I will use the word ‘births’ instead of ‘deliveries’ for ease of use in indicating denominators.

Table 4.4: Numerators and denominators for calculation of death rates

Rate	Numerator (No. of deaths)	Denominator (Population at risk)
Stillbirth	Stillbirths	All deliveries
Early Neonatal Death	Early Neonatal Deaths	All deliveries with a live birth
Day 0 Death	Day 0 Deaths	All deliveries with a live birth
Day 1-2 Death	Day 1-2 Deaths	All deliveries with a baby alive at Day 1
Day 3-6 Death	Day 3-6 Deaths	All deliveries with a baby alive at Day 3
Late Neonatal Death	Late Neonatal Deaths	All deliveries with a baby alive at Day 7

Statistical Analysis

Univariate Analysis

I performed statistical analyses using STATA version 12 (StataCorp. 2011) and tabulated and produced frequency analyses for all variables.

I checked the degree and distribution of missing data for each variable. I excluded deliveries with ≤10 missing observations from the analysis (e.g. if eight deliveries had missing information on religion, they were removed) and grouped >10 missing observations in the 'unknown' category (e.g. if 30 deliveries had missing information on maternal education these deliveries were categorised as 'unknown' for maternal education).

Bivariate Analysis:

To examine whether the choice of study population (i.e. deliveries rather than births or singleton births) might have affected mortality rates, I compared the rates of stillbirths, early neonatal deaths and late neonatal deaths for all deliveries, all births and all singleton births over time.

I plotted trends over time in the number of deliveries and mortality rates for the ICDDR,B and the Government service areas separately. I also presented trends in socio-demographic characteristics (maternal formal education, household asset quintile, religion, maternal age and gravidity) over time. I used time as a linear continuous variable in the analyses I performed to see if socio-demographic variables changed over time. I used linear regression to obtain estimates of annual slopes (coefficients) for change in the mean years of maternal education, mean years of maternal age and gravidity for each area (all of which were continuous variables). I also obtained the p-value for interaction between time and area by including the interaction term in the linear regression model. I used the stata 'lincom' command to obtain 95% confidence intervals. I also performed a logistic regression for the categorical variable of

religion and an ordered logistic regression for the ordered categorical variable of household asset quintile to obtain annual change in odds ratios over the study period for the two areas. I also added an interaction term between time and area within the model to see if the changes were different in the two areas over time . If interaction was not significant at the 0.05 significance level, I presented a single odds ratio for the socio-demographic variable.

To understand whether birth attendant types varied by delivery locations in the two areas, I cross-tabulated birth attendants and delivery locations. As traditional birth attendants to not generally deliver women in facilities in Bangladesh, if a facility birth attendant was identified as a TBA I recoded the attendant as a nurse. I also produced time trends for percentages of Caesarean sections and instrumental deliveries in the two areas.

I obtained crude associations between each of the outcomes and socio-demographic exposures using logistic regression. I adjusted for clustering of deliveries in any one woman (executed by the 'xtlogit' command) as children born to the same mother over the study might have similar exposures and outcomes compared to children born to different mothers.

Multivariate Analysis

In the multivariate analysis, I used a statistical-based approach by building logistic regression models to obtain adjusted odds ratios. I selected the socio-demographic factors listed above , and then built logistic regression models using the backward-step selection method (Kirkwood & Sterne 2003). I fitted the logistic regression model for each mortality outcome with all the exposure variables. I omitted each variable in turn and recorded the p-value for each likelihood ratio test for the full model and the model with the omitted variable. Next, I omitted the variable with the highest likelihood ratio test p-value (≥ threshold significance value of 0.2) and fitted a new model with the remaining exposure variables. I repeated the procedure to find the next variable to be omitted from the model and repeated the steps until the p-value for the omission of each variable was <0.2. I used the p-value threshold of 0.2, as advised by Kirkwood and Sterne, instead of the traditional threshold for statistical significance of 0.05.

I explored whether the area of residence (ICDDR,B service area or Government service area) modified the effect of time on the outcomes by adding an interaction term for time and area of residence.

4.4 Results:

4.4.1 Description of study sample:

Initially the study covered records of 152,496 pregnancies, 132,030 live births and 4,470 stillbirths between 1987 and 2009 (Table 4.5). There were 3,852 early neonatal deaths and 1,360 late neonatal deaths. The number of Day 0, Day 1-2 and Day 3-6 deaths were 1589, 1395 and 868, respectively.

Only 478 infants (0.35% of all births) ≤28 days old had migrated out of the Matlab surveillance area in the 23 years of the study. They were excluded from the analysis alongside abortions #and miscarriages.

Table 4.5: Distribution of pregnancy outcomes in Matlab (1987-2009)

Pregnancy Outcome	Number	Percent (%)
Abortion	6,241	4.09
Miscarriage	9,755	6.40
Stillbirth	4,470	2.93
Live birth	132,030	86.58
Total	152,496	100

Figure 4.8 shows the distribution of stillbirths and neonatal deaths by day since birth in all births in Matlab. Stillbirths constituted 46% of all deaths occurring from 7 months of pregnancy till 28 days of life. Early neonatal deaths contributed 30% of all deaths in this period while late neonatal deaths contributed only 18%.

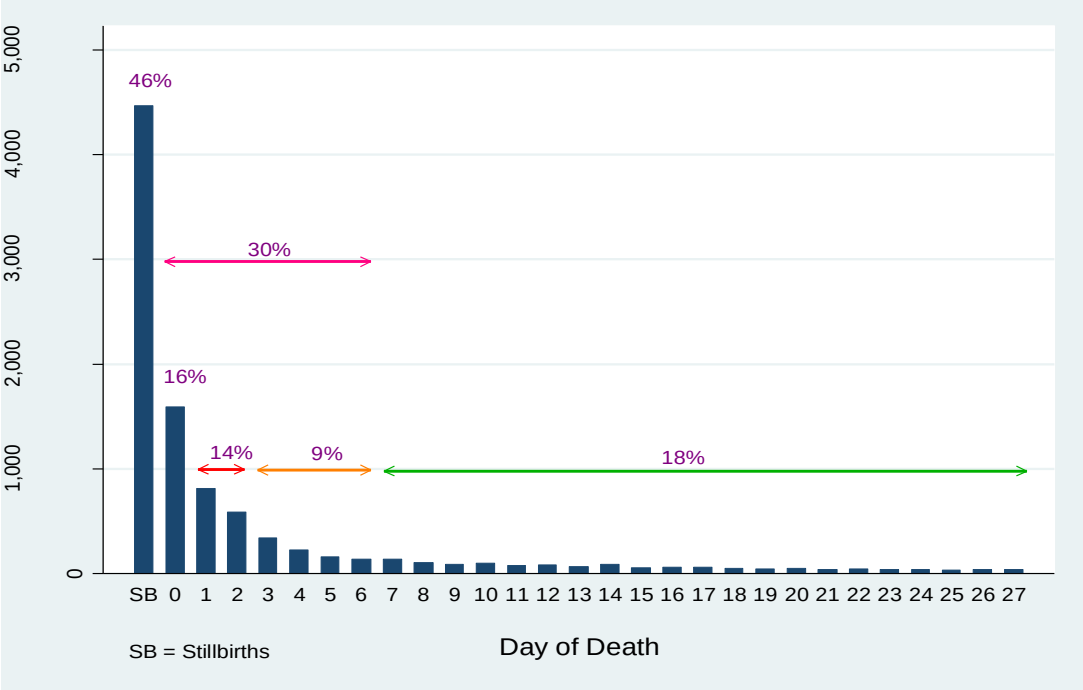


Figure 4.8: Stillbirths and neonatal deaths (by day since birth) in all births in Matlab (1987-2009)

4.4.2 Multiple Births and Pregnancy Outcomes:

Multiple births (twins and triplets) represented 2.15% of all births and 1.06% of all deliveries in Matlab (Table 4.6).

Table 4.6: Distribution of singleton and multiple births among all births and among all deliveries in Matlab (1987-2009)

	All Births		All Deliveries	
	Number	Percent	Number	Percent
Singletons	133,109	97.87	133,109	98.93
Twins	2,848	2.09	1,424	1.06
Triplets	54	0.04	18	0.01
Total	136,011	100	134,551	100

The distribution of pregnancy outcomes in all deliveries with multiple births is shown in Tables 4.7 and 4.8. In about half (55.3%) of twin deliveries both babies were alive at the end of their first month (Table 4.7). All three babies survived their first month in only 5.6% of all triplet deliveries. The remainder of the babies in twin and triplet deliveries were stillborn, experienced early neonatal death, late neonatal deaths or a combination of all three death outcomes (Tables 4.7 and 4.8).

Table 4.7: Combinations of birth outcomes in 1424 deliveries of twins in Matlab (1987-2009)

Combinations of Birth Outcomes in Deliveries of Twins	N=1424	Percentage (%) of N	Birth Outcome Assigned
Both infants alive at 1 month	787	55.3	Live birth
1 infant alive at 1 month + 1 Stillbirth	134	9.4	Stillbirth
1 infant alive at 1 month + 1 Early Neonatal Death	119	8.4	Early Neonatal Death
1 infant alive at 1 month + 1 Late Neonatal Death	54	3.8	Late Neonatal Death
2 Stillbirths	41	2.9	Stillbirth
1 Stillbirth+ 1 Early Neonatal Death	48	3.4	Stillbirth
1 Stillbirth + 1 Late Neonatal Death	9	0.6	Stillbirth
2 Early Neonatal Deaths	180	12.6	Early Neonatal Death
1 Early Neonatal Death + 1 Late Neonatal Death	32	2.2	Early Neonatal Death

Table 4.8: Combinations of birth outcomes in 18 deliveries of triplets in Matlab (1987-2009)

Combinations of Birth Outcomes in Deliveries of Triplets	N=18	Percentage (%) of N	Birth Outcome Assigned
All three infants alive at 1 month	1	5.6	Live birth
2 infants alive at 1 month + 1 Stillbirth	2	11.1	Stillbirth
2 infants alive at 1 month + 1 Early Neonatal Death	2	11.1	Early Neonatal Death
2 infants alive at 1 month + 1 Late Neonatal Death	1	5.6	Late Neonatal Death
1 infant alive at 1 month + 1 Early Neonatal Death + 1 Stillbirth	2	11.1	Stillbirth
1 infant alive at 1 month + 1 Early Neonatal Death + 1 Late Neonatal Death	1	5.6	Early Neonatal Death
3 Stillbirths	1	5.6	Stillbirth
2 Stillbirths + 1 Early Neonatal Death	1	5.6	Stillbirth
1 Stillbirth + 2 Early Neonatal Deaths	1	5.6	Stillbirth
3 Early Neonatal Deaths	4	22.2	Early Neonatal Death
1 Early Neonatal death + 2 Late Neonatal Deaths	1	5.6	Early Neonatal Death
3 Late Neonatal Deaths	1	5.6	Late Neonatal Death

Table 4.9 shows the frequencies with which stillbirths, early neonatal deaths and late neonatal deaths occur deliveries with multiple (twin and triplet) and singleton births. For all three mortality outcomes, the percentages of deaths are highest in triplets, lower in twins and lowest in singletons.

Table 4.9: Distribution of stillbirths, early neonatal deaths and late neonatal deaths in 134, 551 deliveries with singleton and multiple births in Matlab (1987-2009)

	Delivery			
	Singleton % (n)	**Twin** % (n)	**Triplet** % (n)	**Total** % (n)
Stillbirth	3.15 (4187)	16.29 (232)	27.78 (5)	3.29 (4424)
Early Neonatal Death	2.46 (3272)	17.98 (256)	38.89 (7)	2.63 (3535)
Late Neonatal Death	0.89 (1189)	3.65 (52)	11.11 (2)	0.92 (1243)

I used Figures 4.9, 4.10 and 4.11 to explore differences, if any, in mortality rates and trends when analysis was done on all deliveries versus all births or all singleton births. No differences in trends were seen for any outcomes. Rates did not differ substantially except for early neonatal death rates, which were slightly lower for all deliveries were compared to all births (Figure 4.10). These graphs indicate that an analysis based on all deliveries instead of all births should not greatly bias results in terms of magnitude or trends, except for a possible slight underestimation of early neonatal death rates.

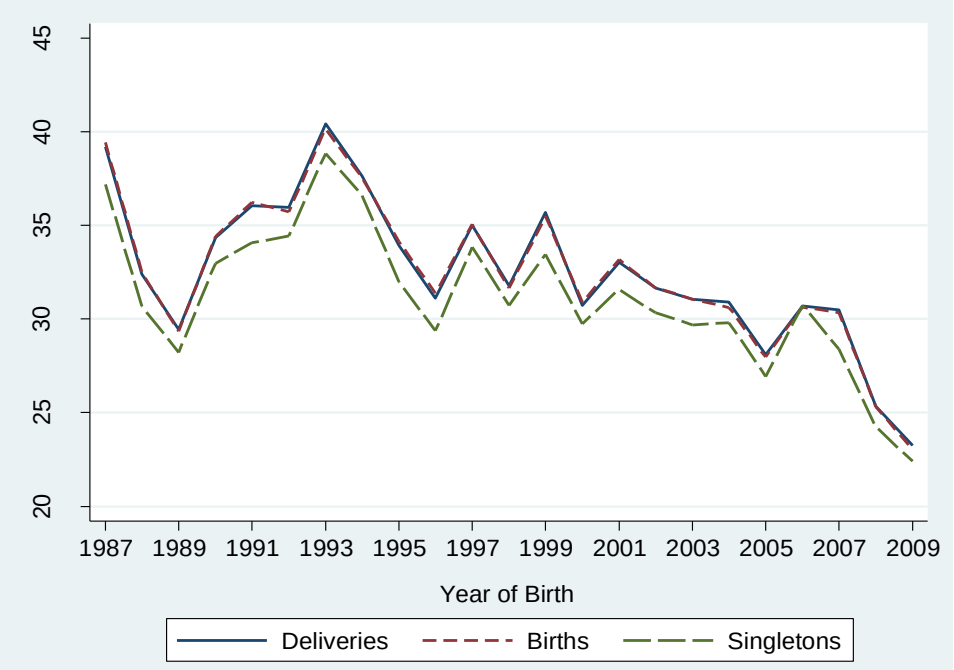


Figure 4.9: Stillbirth Rates from All Deliveries, All Births and All Singleton Births in Matlab, 1987-2009

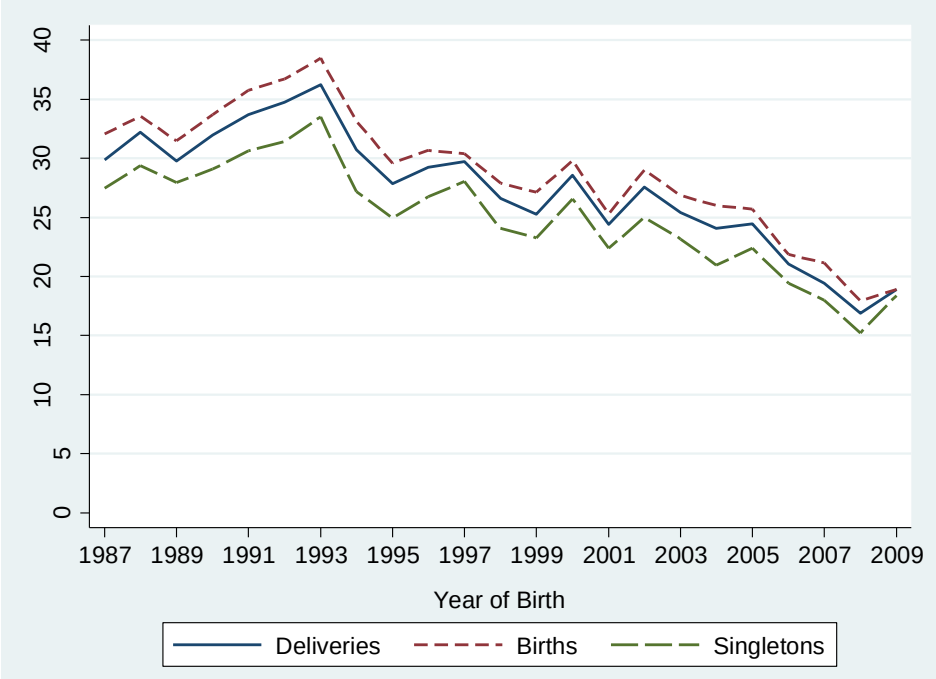


Figure 4.10: Early Neonatal Death Rates from All Births, All Deliveries, and All Singletons in Matlab, 1987-2009

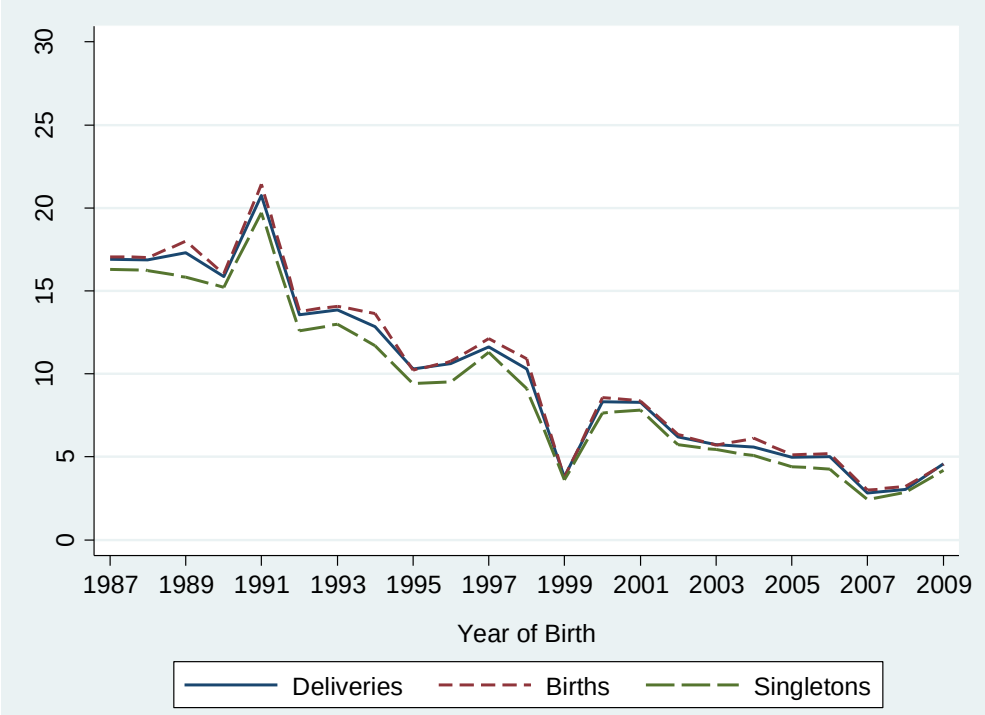


Figure 4.11: Late Neonatal Death Rates from All Births, All Deliveries, and All Singletons in Matlab, 1987-2009

4.4.3 Final Sample Size and Denominators

The final sample consists of 134,551 deliveries, 4424 stillbirths, 3535 early neonatal deaths and 1243 late neonatal deaths. There were 1462, 1262, and 811 Day 0, Day 1 to 2 and Day 3 to 6 deaths respectively. Eight deliveries which had missing religion information (including seven with missing maternal education information) were excluded from the analysis.

4.4.4 Area-wise Deliveries over time:

Figures 4.12 and 4.13 show the annual number of deliveries for the ICDDR,B and Government service areas in Matlab. Between 1987 and 2009, the ICDDR,B service area (Figure 4.12) had a lower number of annual deliveries than the Government service area (Figure 4.13). From 2005 annual deliveries appeared to decrease in the Government area though they appeared stable in the ICDDR,B area.

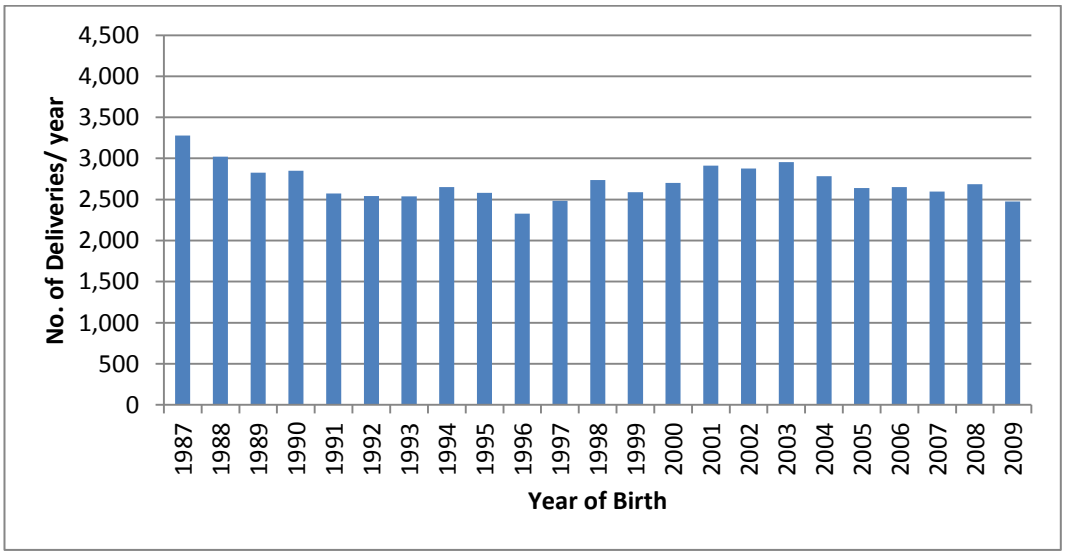


Figure 4.12: Trends in all deliveries in ICDDR,B Service Area in Matlab (1987-2009)

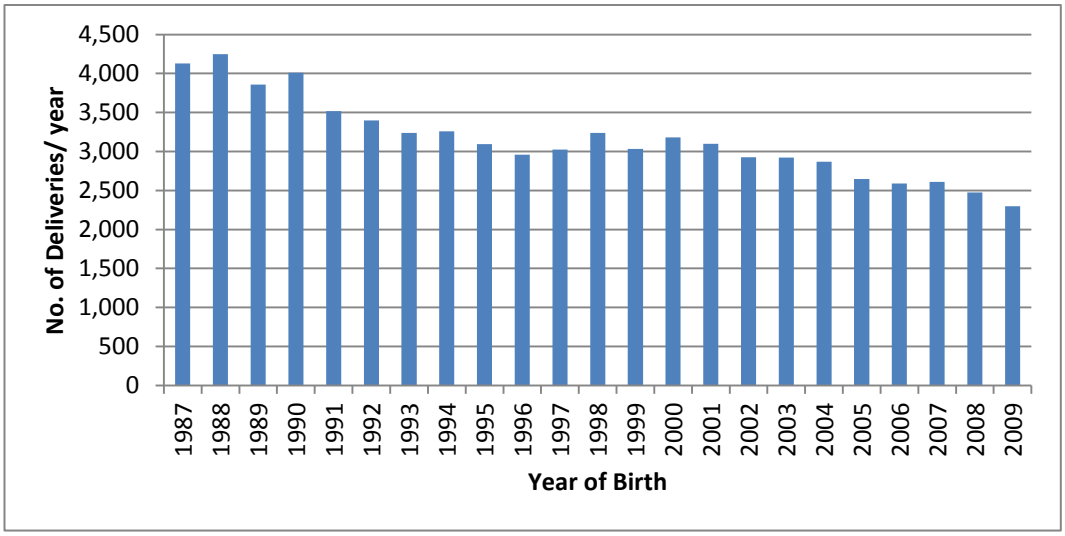
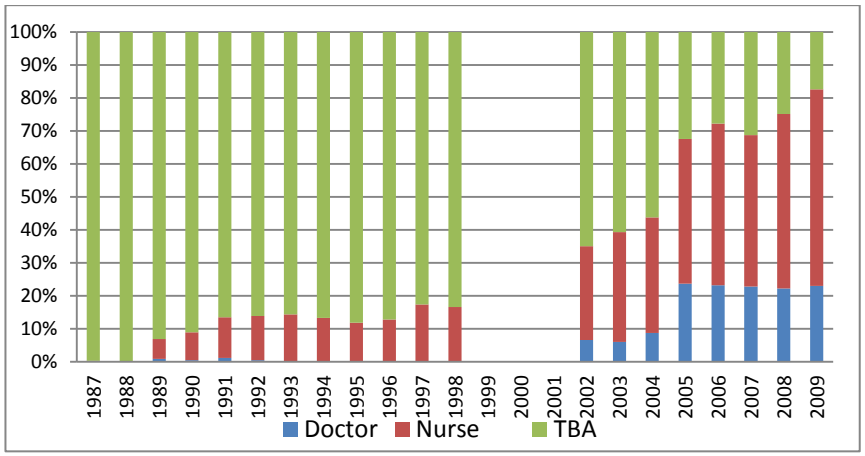


Figure 4.13: Trends in all deliveries in the Government service area in Matlab (1987-2009)

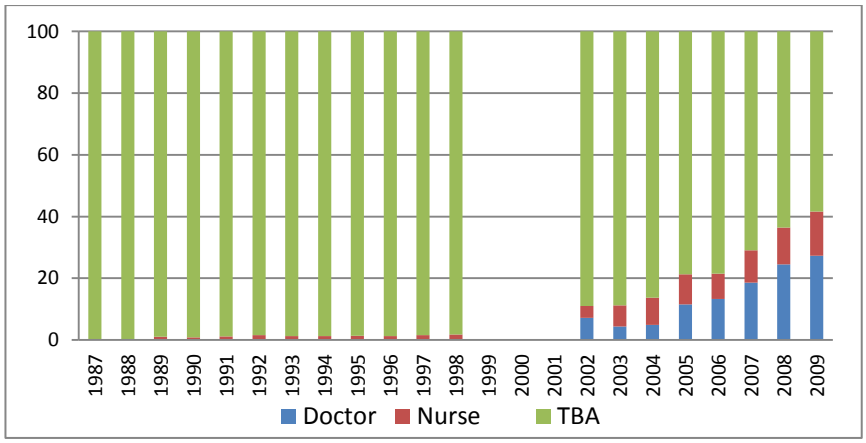
4.4.5 Uptake in Professional Delivery Care:

In 1987, most women in both the ICDDR,B and the Government service areas gave birth at home with a traditional birth attendant (Figures 4.14 and 4.15). No births were attended by a health professional in either area in 1987. However, by 2009, skilled birth attendance was 82.6% in the ICDDR,B service area compared to 37.8% in the Government service area. In 2009, traditional birth attendants were conducting most of the deliveries (58.4%) in the Government service area while this had decreased to only 17.4% of deliveries in ICDDR,B service area.



*the HDSS did not collect data on skilled birth attendance during 1999-2001

Figure 4.14: Trends in deliveries with birth attendants in ICDDR,B Service Area, Matlab (1987-2009)



*the HDSS did not collect data on skilled birth attendance during 1999-2001

Figure 4.15: Trends in deliveries with birth attendants in Government service area, Matlab (1987-2009)

Tables 4.10 and 4.11 show the distribution of birth attendants by delivery location in the two areas from 2002-2009. In both areas, most births in the public sector and in the ICDDR,B area were attended by nurses or paramedics while most births in the private sector were attended by doctors. There were 222 deliveries in ICDDR,B facilities which were to women of the Government service area (Table 4.11) suggesting that Government service area women occasionally approach ICDDR,B facilities for delivery and are not turned away. As in 63.5% of these 222 deliveries the most highly skilled birth attendant was a doctor in ICDDR,B facilities (where usually nurses/paramedics perform most of the deliveries), it is probable that these Government service area women had severe urgent complications requiring a doctor in addition to a nurse/paramedic.

Table 4.10: Distribution of birth attendants according to delivery location in ICDDR,B service area in Matlab (2002-2009)

	Delivery Location				
		Health Facility			
Birth Attendant	**Home** No. of deliveries (%)	**Public** No. of deliveries (%)	**Private** No. of deliveries (%)	**ICDDR,B** No. of deliveries (%)	**All** No. of deliveries (%)
Traditional Birth Attendant	8669 (84.6)	0 (0)	0 (0)	0 (0)	8669 (40.3)
Nurse/Midwife/ Paramedic	200 (1.95)	1311 (69.8)	320 (20.1)	7422 (95.5)	9253 (43.1)
Doctor	1373 (13.4)	567 (30.2)	1276 (80.0)	350 (4.5)	3566 (16.6)
All	10242 (100)	1878 (100)	1596 (100)	7772 (100)	21488 (100)

Table 4.11: Distribution of birth attendants according to delivery location in the Government service area, Matlab (2002-2009)

	Delivery Location				
		Health Facility			
Birth Attendant	**Home** No. of deliveries (%)	**Public** No. of deliveries (%)	**Private** No. of deliveries (%)	**ICDDR,B** No. of deliveries (%)	**All** No. of deliveries (%)
Traditional Birth Attendant	16474 (90.6)	0 (0)	0 (0)	0 (0)	16472 (77.6)
Nurse/Midwife/ Paramedic	355 (2.0)	1207 (63.2)	276 (30.7)	81 (36.5)	1919 (9.04)
Doctor	1347 (7.4)	702 (36.8)	642 (69.9)	141 (63.5)	2832 (13.3)
All	18174 (100)	1909 (100)	918 (100)	222 (100)	21223 (100)

From Figures 4.16 and 4.17 it can be seen that from 2002-2009 the increase in facility deliveries was higher in the ICDDR,B service area (32% to 77%) than in the Government service area (10% to 25%). The majority of ICDDR,B service area births (55%) in 2009 were in ICDDR,B facilities followed by increasing deliveries in private facilities in both areas from 2004.

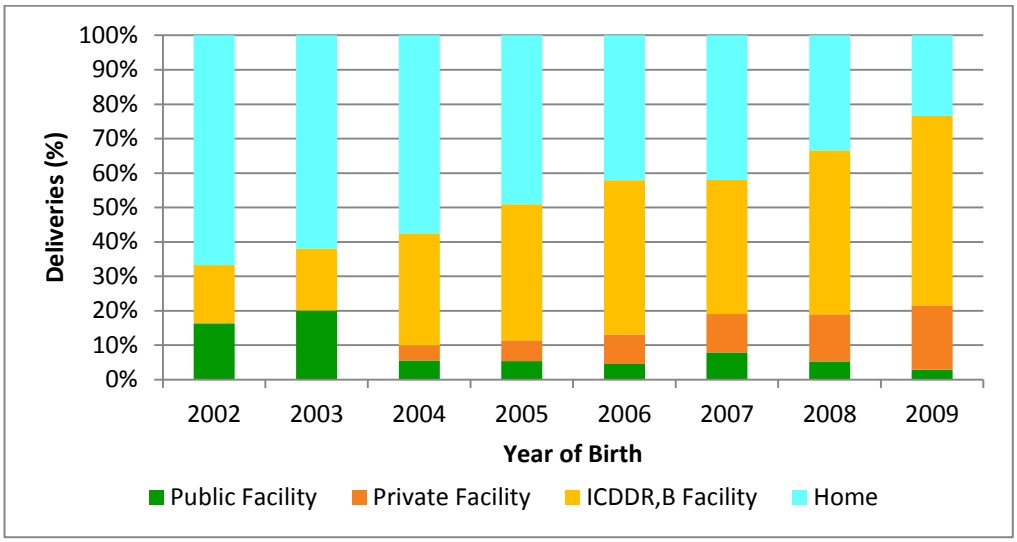


Figure 4.16: Trends in deliveries according to delivery location in ICDDR,B Service Area, Matlab (2002-2009)

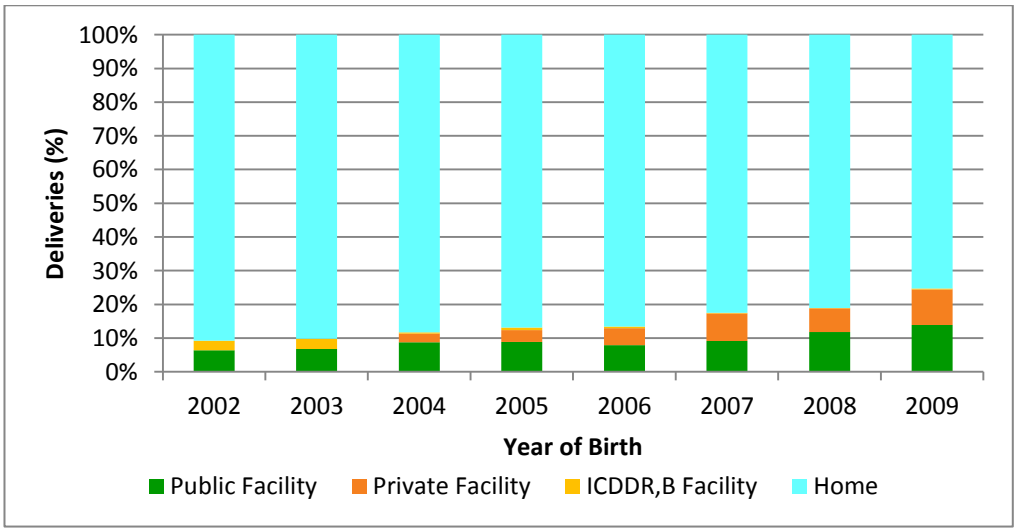


Figure 4.17: Trends in deliveries according to delivery location in Government service area, Matlab (2002-2009)

4.4.6 Trends in Caesarean Sections and Instrumental Deliveries:

Figures 4.18 and 4.19 show the uptake of Caesarean sections and instrumental delivery in the two areas during 2004-2009. The two areas saw rapid increases in Caesarean sections during this period from 6.1% to 17.6% in the ICDDR,B service area compared to a slower increase from 3.4% to 11.7% in the Government service area. Instrumental deliveries which were very low in both areas, (but higher in the ICDDR,B service area) declined and almost stopped as Caesarean sections increased.

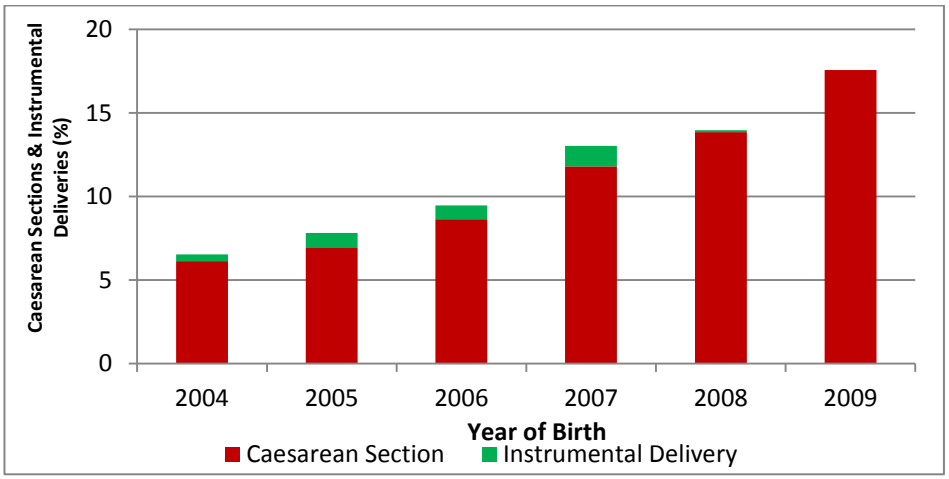


Figure 4.18: Trends in Caesarean deliveries and instrumental deliveries in ICDDR,B Service Area, Matlab (2004-2009)

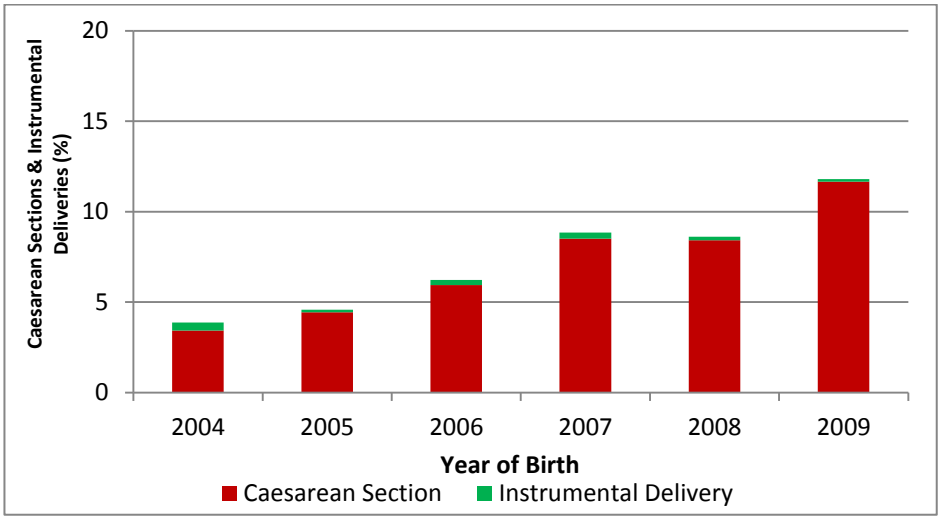


Figure 4.19: Trends in Caesarean deliveries and instrumental deliveries in Government service area, Matlab (2004-2009)

4.4.7 Changes in demographic and socio-economic status over time in the two areas:

The Matlab area has seen improvements in demographic and socio-economic indicators over the study period. Figure 4.20 shows the changes taking place in the ICDDR,B and Government service areas.

Maternal education increased dramatically over time for both areas (Figure 4.20a) rising from 1987 levels of 1.5 and 1.8 mean years of maternal education in the Government and ICDDRB service areas respectively, to corresponding levels of 6.0 and 6.4 years in 2009. The estimated slopes (Figure 4.20a) show annual increases in mean years of maternal education in each area (Government service area: 0.227 per year vs. ICDDRB area: 0.220 per year). The statistically significant interaction between time and area (p=0.006) confirmed that the increase was marginally higher in the Government service area than in the ICDDRB service area.

The mean maternal age did not change dramatically over 1987-2009 in either area (Figure 4.20b). There was an annual decline of only 0.006yr (95%CI: -0.005 to -0.007) in the Government service area compared to an annual increase of 0.082yr (95%CI: 0.054 to 0.109) and the changes were different for the two areas (p= 0.002).

The mean gravidity was seen to decrease significantly in women of both areas over 1987-2009 (Figure 4.20c). In 1987 women were more frequently pregnant (Government service area: 4.1 times; ICDDRB service area: 3.6 times) than in 2009 (2.5 and 2.3 times, respectively). Levels of higher gravidity were always greater in the Government service area (p<0.001).

In case of religion, the annual odds of being Hindu reduced slowly over time (OR=0.984, 95%CI: 0.982 – 0.987) in both areas (Figure 4.20d) but the decline over time did not differ by area (p=0.185).

Households in both areas appeared to be getting richer over time, but the annual increase in wealth was small (Figure 4.20e).The odds of an annual increase in one household asset quintile was 0.9% (OR: 1.009; 95%CI: 1.007-1.011) and this was the same for both areas (p=0.245).

In terms of socio-demographic characteristics, differences for some characteristics between the two areas were found to be highly statistically significant (p<0.001). Though a large study population can result in even minor differences having high statistical significance, it is unlikely that this is the case for Matlab as the differences observed are large.

Figure 4.20: Changes in socio-demographic characteristics in the Government and ICDDR,B service areas over time (1987-2009)

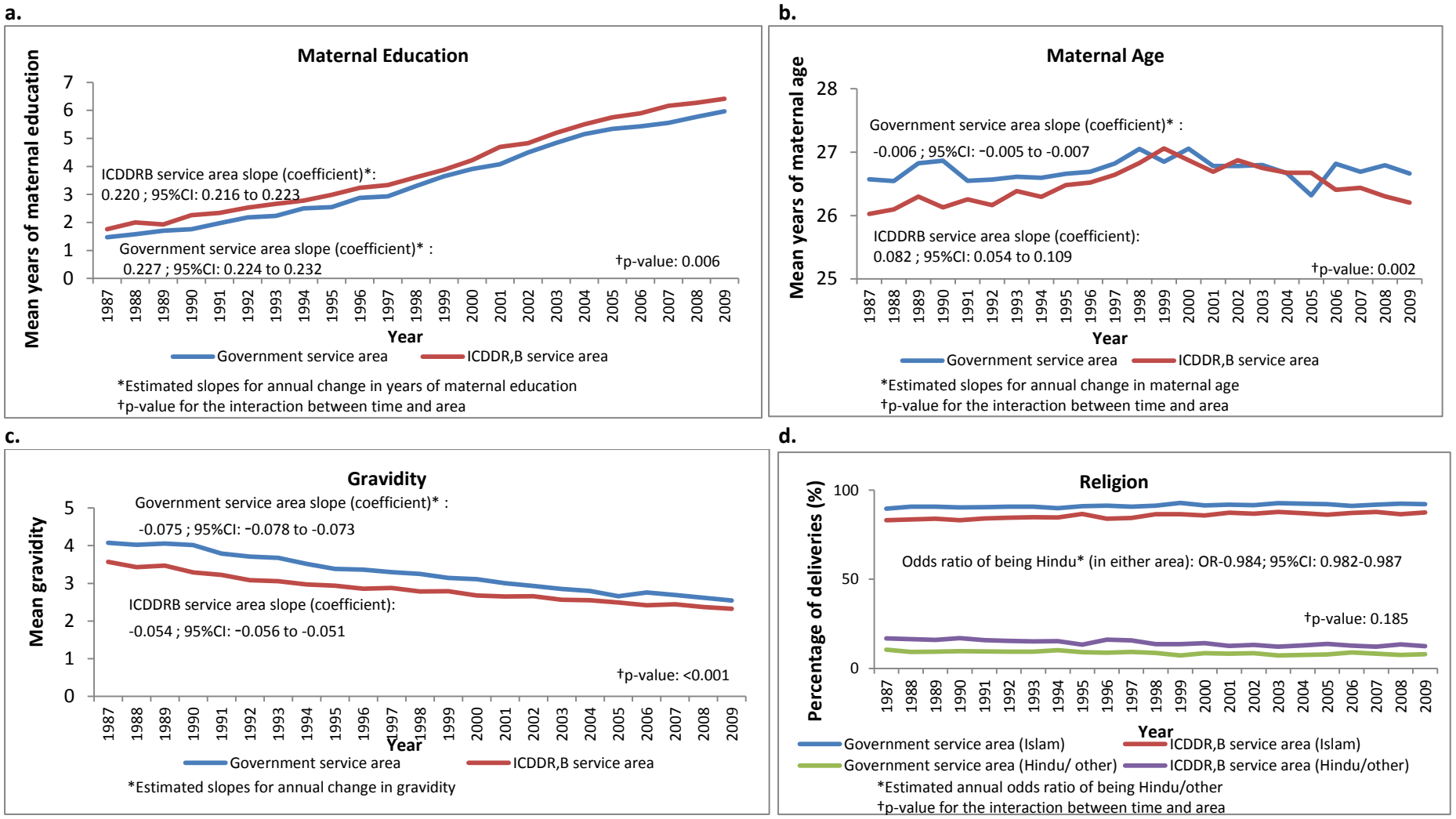
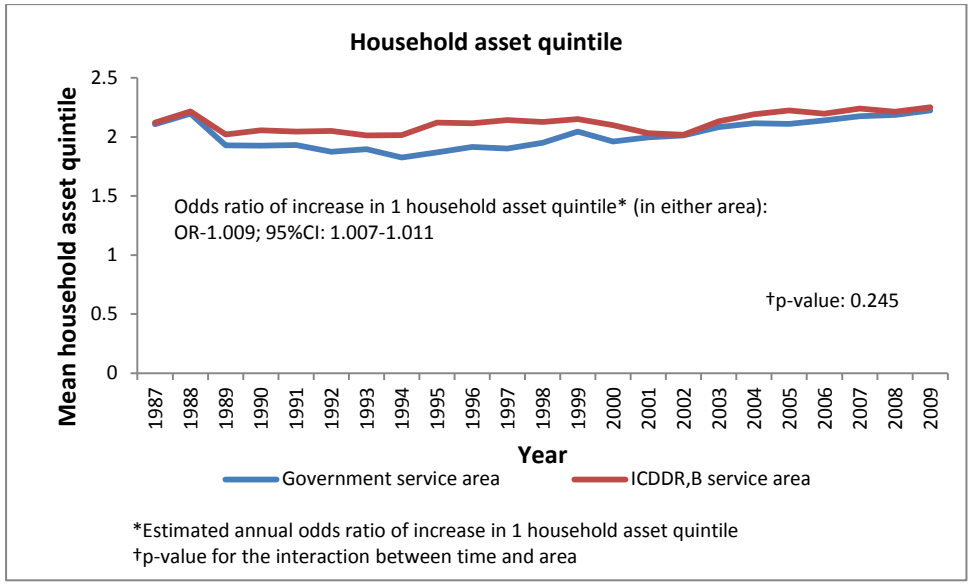


Figure 4.20 (continued)

e.



4.4.8 Trends in outcomes over the study-period

Trends in stillbirth rates, early neonatal death rates and late neonatal death rates by intervention area during 1987-2009 are shown in Tables 4.12- 4.13 and Figures 4.15-4.20. The overall rates for stillbirths, early neonatal deaths and late neonatal deaths in the Matlab surveillance area in this period were 32.7/1000 births, 27.5/1000 live births and 10.0/1000 babies alive at Day 7. Rates for Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths were 11.3/1000 live births, 9.8/1000 babies alive at Day 1 and 6.4/1000 babies alive at Day 3, respectively. Perinatal deaths rates are shown elsewhere (Appendix II: Table 3).

Table 4.122: Year-wise stillbirth rates, early neonatal death rates and late neonatal death rates in ICDDR,B service area and Government service area, Matlab (1987-2009)

Year of Birth	ICDDR,B Service Area			Government service area		
	Stillbirth Rate[a] (n)	Early Neonatal Death Rate[b] (n)	Late Neonatal Death Rate[c] (n)	Stillbirth Rate[a] (n)	Early Neonatal Death Rate[b] (n)	Late Neonatal Death Rate[c] (n)
1987	36.9 (121)	28.8 (91)	11.4 (35)	41.2 (170)	30.8 (122)	20.0 (72)
1988	38.0 (115)	29.6 (86)	9.54 (27)	28.5 (121)	34.2(141)	21.1 (84)
1989	29.1 (82)	29.3 (80)	10.9 (29)	29.9 (115)	30.3 (113)	20.1 (73)
1990	35.5 (101)	32.4 (89)	12.4 (33)	33.7 (135)	31.8 (123)	17.1 (64)
1991	34.6 (89)	30.2 (75)	15.3 (37)	37.3 (131)	36.4 (123)	22.0 (72)
1992	32.7 (83)	36.7 (90)	9.7 (23)	38.6 (131)	33.4 (109)	14.9 (47)
1993	35.0 (89)	29.4 (72)	10.5 (24)	44.8 (145)	41.7 (129)	14.2 (44)
1994	32.5(86)	25.0 (64)	9.6 (23)	42.1 (137)	35.6 (111)	15.6 (47)
1995	27.2 (70)	19.5 (49)	6.1 (15)	39.7 (123)	35.0 (104)	12.5 (36)
1996	33.9 (79)	28.5 (64)	8.7 (19)	29.0 (86)	29.9 (86)	10.7 (28)
1997	32.7 (81)	24.2 (58)	7.3 (17)	36.8 (111)	34.8 (101)	15.3 (43)
1998	26.3 (72)	25.9 (69)	8.1 (21)	36.5 (118)	27.3 (85)	11.2 (34)
1999	28.7 (74)	21.5 (54)	1.2 (3)	42.0 (127)	28.6 (83)	6.0 (17)
2000	33.8 (91)	23.5 (61)	6.7 (17)	28.4 (90)	33.1 (102)	8.7 (26)
2001	34.8 (101)	18.9 (53)	4.2 (12)	31.6 (98)	29.7 (89)	10.6 (31)
2002	28.6 (82)	26.9 (75)	5.2 (14)	35.1 (102)	28.5 (80)	7.3 (20)
2003	20.3 (60)	24.6 (71)	6.0 (17)	42.1 (123)	26.5 (74)	4.8 (13)
2004	27.0 (75)	22.6 (61)	4.9 (13)	35.0 (100)	25.7 (71)	6.3 (17)
2005	27.0 (71)	20.7 (53)	4.0 (10)	29.5 (78)	28.5 (73)	5.6 (14)
2006	28.9 (76)	19.2 (49)	4.4 (11)	32.9 (85)	23.2 (58)	4.6 (11)
2007	24.2 (62)	16.8 (42)	1.6 (4)	36.9 (96)	22.8 (57)	3.9 (10)
2008	19.6 (52)	12.7 (33)	2.3 (6)	32.1 (79)	21.8 (52)	3.8 (9)
2009	16.0 (39)	11.7 (28)	3.4 (8)	31.5 (72)	27.1 (60)	4.6 (10)
Overall	29.8(1851)	24.2(1467)	7.45(420)	35.5(2573)	30.7(2146)	12.6(823)

[a]per 1000 births. Number of births in each area in every year is 2200+.

[b]per 1000 live births. Number of live births in each area in every year is 2100+.

[c]per 1000 babies alive at Day 7. Number of babies alive at Day 7 in each area in every year is 2100+.

Table 4.133: Year-wise Day 0 death rates, Day 1 to 2 death rates and Day 3 to 6 death rates in ICDDR,B service area and Government service area, Matlab (1987-2009)

Year of Birth	ICDDR,B Service Area			Government service area		
	Day 0 Rate[a] (No.)	Day 1 to 2 Death Rate[b] (No.)	Day 3 to 6 Death Rate[c] (No.)	Day 0 Death Rate[a] (No.)	Day 1 to 2 Death Rate[b] (No.)	Day 3 to 6 Death Rate[c] (No.)
1987	9.5 (30)	13.1 (41)	6.5 (20)	7.1 (28)	10.4 (41)	13.4 (52)
1988	12.0 (35)	9.7 (28)	6.3 (18)	12.4 (51)	10.6 (43)	10.9 (44)
1989	11.0 (30)	10.0 (38)	8.2 (22)	10.2 (38)	10.3 (38)	10.1 (37)
1990	12.4 (34)	10.0 (27)	8.9 (24)	13.4 (52)	8.1 (31)	9.8 (37)
1991	12.9 (32)	9.0 (22)	8.6 (21)	12.7 (43)	11.7(39)	12.1 (40)
1992	15.1 (37)	12.8 (31)	8.4 (20)	11.6 (38)	13.0 (42)	7.5 (24)
1993	12.2 (30)	10.7 (26)	5.8 (14)	16.5 (51)	16.4 (50)	8.7 (26)
1994	7.4 (19)	10.2 (26)	6.8 (17)	12.2 (38)	14.3 (44)	8.6 (26)
1995	7.8 (20)	5.6 (14)	5.3 (13)	13.1 (39)	11.6 (34)	9.7 (28)
1996	12.9 (29)	10.3 (23)	4.6 (10)	9.7 (28)	11.6 (33)	8.5 (24)
1997	9.6 (23)	9.7 (23)	4.3 (10)	13.4 (39)	12.9 (37)	8.1 (23)
1998	10.1 (27)	8.7 (23)	6.5 (17)	13.2 (41)	9.8 (30)	4.3 (13)
1999	12.8 (32)	6.9 (17)	2.0 (5)	13.8 (40)	11.5 (33)	3.2 (9)
2000	12.7 (33)	6.6 (17)	4.3 (11)	14.3 (44)	12.2 (37)	6.0 (18)
2001	9.6 (27)	4.0 (11)	5.1 (14)	12.0 (36)	10.5 (31)	6.8 (20)
2002	11.5 (32)	9.4 (26)	5.5 (15)	12.1 (34)	10.8 (30)	4.4 (12)
2003	9.0 (26)	10.1 (29)	4.2 (12)	13.9 (39)	9.8 (27)	2.2 (6)
2004	11.9 (32)	8.2 (22)	2.6 (7)	10.1 (28)	8.1 (22)	6.6 (18)
2005	7.0 (18)	8.7 (22)	4.8 (12)	13.6 (35)	11.1 (28)	3.6 (9)
2006	9.0 (23)	7.1 (18)	2.8 (7)	9.6 (24)	10.1 (25)	3.7 (9)
2007	6.4 (16)	7.2 (18)	2.4 (6)	13.2 (33)	5.7 (14)	4.1 (10)
2008	7.0 (18)	3.5 (9)	1.9 (5)	8.0 (19)	8.9 (21)	4.7 (11)
2009	5.4 (13)	4.2 (10)	2.1 (5)	12.7 (28)	10.1 (22)	4.6 (10)
Overall	10.2 (616)	8.6(510)	5.2(305)	12.1(846)	10.9(752)	7.4(506)

[a]per 1000 babies alive at Day 1. Number of babies alive at Day 1 in each area in every year is 2100+.

[b]per 1000 babies alive at Day 3. Number of babies alive at Day 3 in each area in every year is 2100+.

[c]per 1000 babies alive at Day 7. Number of babies alive at Day 7 in each area in every year is 2100+.

Trends in stillbirths over time are shown in Figure 4.21 and Table 4.14. Rates were seen to be lower in the ICDDR,B service area than the Government service area. Stillbirths declined with increasing levels of formal education.

Stillbirths declined by 1% annually (95% CI: 1% -2%) over the entire area from 1987-2009 and the overall stillbirth rate in the ICDDR,B area was significantly lower than that in the Government area (29.8/1000 births vs. 35.5/1000 births; p<0.0001). Adjustment for socio-demographic variables did not lead to any changes in the time-trends or the area differentials.

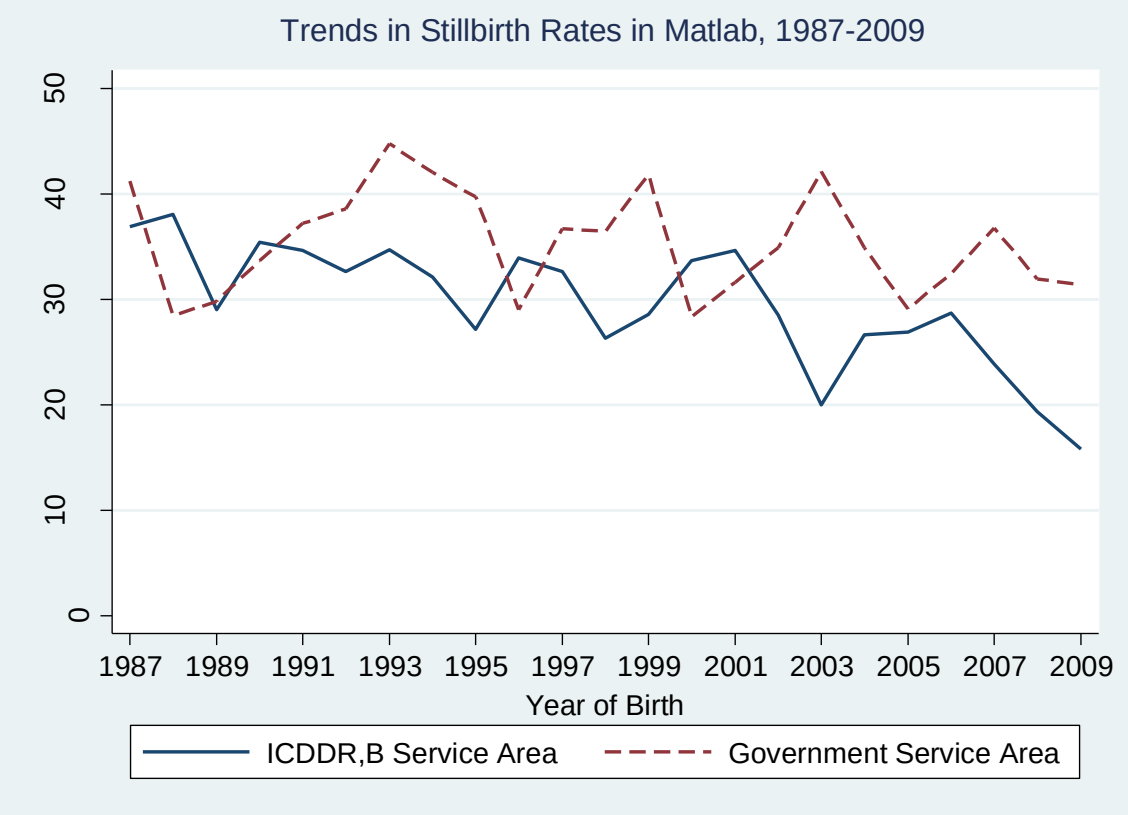


Figure 4.21: Trends in stillbirth rates in all deliveries in Matlab, 1987-2009

Table 4.144: Stillbirths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of births (Number of stillbirths)	Stillbirths per 1000 deliveries	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs [a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.99 (0.98-0.99)	<0.0001	0.99 (0.98-0.99)	<0.0001
Area of Residence						
ICDDR,B Service Area	62071 (1851)	29.82	0.82 (0.77-0.88)	<0.0001	0.84 (0.78-0.90)	<0.0001
Government service area (Reference)	72480 (2573)	35.50	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	57538 (2071)	35.99	1.00	_	1.00	_
1-5	34701 (1119)	32.25	0.89 (0.82-0.97)	0.007	0.94 (0.86-1.02)	0.164
6-10	35672 (1046)	29.32	0.80 (0.74-0.87)	<0.0001	0.87 (0.79-0.95)	0.003
11-16	3011 (83)	27.57	0.75 (0.59-0.95)	0.018	0.76 (0.60-0.98)	0.031
Unknown	3629 (105)	28.93	0.79 (0.63-0.98)	0.032	0.85 (0.68-1.07)	0.163
Household asset quintile						
Most poor (Reference)	22484 (778)	34.60	1.00		_	_
Very poor	24747 (837)	33.82	0.98 (0.88-1.09)	0.663	_	_
Poor	24276 (852)	35.10	1.03 (0.93-1.15)	0.557	_	_
Less poor	25964 (805)	31.00	0.90 (0.81-1.00)	0.053	_	_
Least poor	25664 (790)	30.78	0.89 (0.80-0.99)	0.038	_	_
Unknown	11416 (362)	31.71	0.92 (0.80-1.05)	0.205	_	_
Religion						
Islam (Reference)	119205 (3900)	32.72	1.00		_	_
Hinduism/Other	15346 (524)	34.15	1.04 (0.94-1.15)	0.480	_	_
Maternal Age						
<20	16171 (539)	33.33	1.16 (1.05-1.28)	0.003	0.90 (0.81-1.01)	0.072
20- 29 (Reference)	82220 (2447)	29.76	1.00	_	1.00	_
30-39	33235 (1236)	37.19	1.25 (1.16-1.35)	<0.0001	1.34 (1.22-1.48)	<0.0001
40+	2925 (202)	69.06	2.52 (2.14-2.97)	<0.0001	2.39 (1.97-2.90)	<0.0001
Gravidity						
1	35864 (1329)	37.06	1.44 (1.33-1.56)	<0.0001	1.58 (1.44-1.72)	<0.0001
2-3 (Reference)	52950 (1419)	26.80	1.00	_	1.00	_
4-6	34804 (1105)	31.75	1.16 (1.07-1.26)	0.001	0.96 (0.87-1.05)	0.364
7+	10933 (571)	52.23	1.97 (1.76-2.19)	<0.0001	1.23 (1.07-1.42)	0.005
All	**134551 (4424)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, maternal education, maternal age and gravidity

Trends in early neonatal deaths over time are shown in Figure 4.22 and Table 4.15. Mortality rates were higher in the Government service area than the ICDDR,B service area and declined in both areas over time. Maternal age and gravidity showed similar U-shaped relationships to early neonatal mortality, as seen for stillbirths, and higher maternal education was associated with a reduction in early neonatal mortality rates.

There was an annual decline of 1% (95% CI: 1% -3%) in early neonatal deaths in Matlab with significantly lower rates in the intervention area than the Government service area (24.2/1000 live births vs. 30.7/1000 live births; p<0.0001).

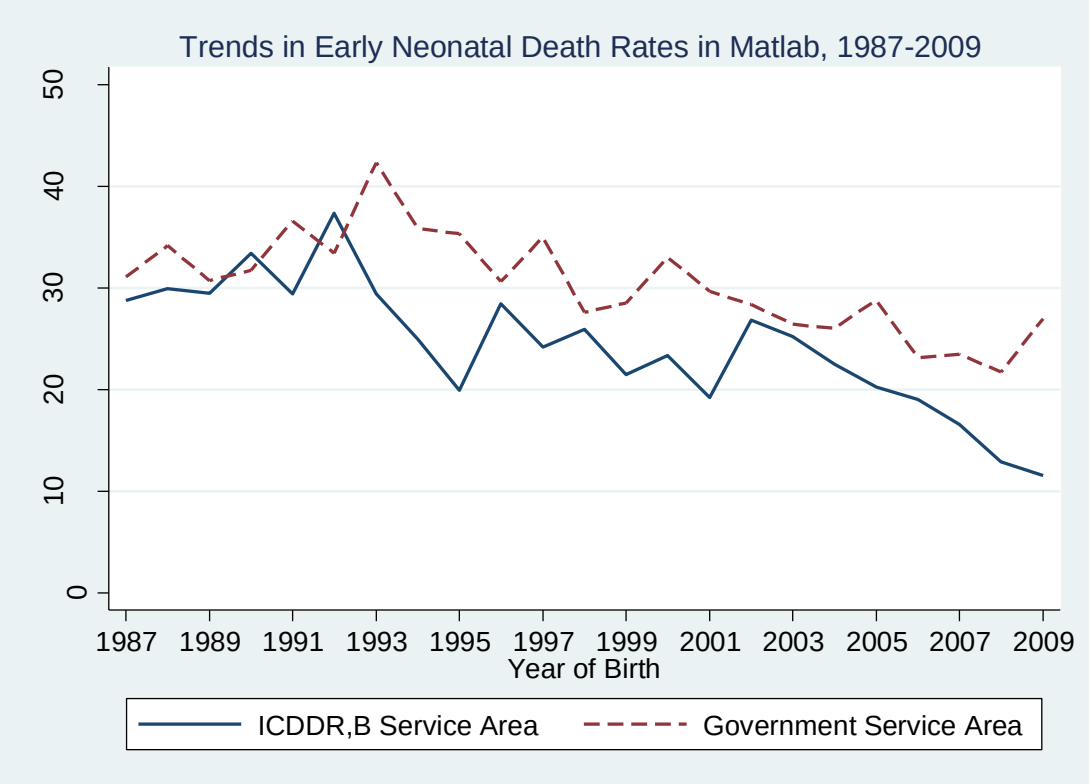


Figure 4.22: Trends in early neonatal death rates in all deliveries in Matlab, 1987-2009

Table 4.155: Early neonatal deaths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of live births (Number of early neonatal deaths)	Early neonatal deaths per 1000 live births	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs[a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.98 (0.97-0.98)	<0.0001	0.99 (0.97-0.99)	<0.0001
Area of Residence						
ICDDR,B Service Area	60220 (1467)	24.36	0.78 (0.73-0.84)	<0.0001	0.80(0.74-0.86)	<0.0001
Government service area (Reference)	69907 (2146)	30.70	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	55467 (1706)	30.76	1.00	_	1.00	_
1-5	33582 (970)	28.88	0.93 (0.86-1.02)	0.116	0.97 (0.89-1.06)	0.501
6-10	34626 (802)	23.16	0.74 (0.68-0.81)	<0.0001	0.82 (0.74-0.92)	<0.0001
11-16	2928 (57)	19.47	0.62 (0.47-0.81)	0.001	0.79 (0.59-1.06)	0.118
Unknown	3524 (78)	22.13	0.69 (0.54-0.88)	0.003	0.76 (0.59-0.98)	0.032
Household asset quintile						
Most poor (Reference)	21706 (672)	30.96	1.00	_	1.00	_
Very poor	23910 (694)	29.03	0.94 (0.84-1.05)	0.281	0.94 (0.84-1.06)	0.304
Poor	23424 (667)	28.48	0.92 (0.82-1.04)	0.172	0.93 (0.83-1.05)	0.236
Less poor	25159 (684)	27.19	0.88 (0.99-0.81)	0.027	0.91 (0.81-1.02)	0.099
Least poor	24874 (566)	22.75	0.73 (0.65-0.83)	<0.0001	0.79 (0.69-0.89)	<0.0001
Unknown	11054 (330)	29.85	0.97 (0.85-1.12)	0.695	1.03 (0.89-1.18)	0.729
Religion						
Islam (Reference)	115305 (3155)	27.36	1.00		_	_
Hinduism/Other	14822 (458)	30.90	1.13 (1.02-1.26)	0.021	_	_
Maternal Age						
<20	15632 (653)	34.89	1.73 (1.57-1.90)	<0.0001	1.44 (1.29-1.60)	<0.0001
20- 29 (Reference)	79773 (2035)	22.10	1.00	_	1.00	_
30-39	31999 (822)	26.53	1.00 (0.91-1.08)	0.924	0.97 (0.87-1.08)	0.565
40+	2723 (103)	36.19	1.54 (1.24-1.90)	<0.0001	1.29 (1.01-1.64)	0.042
Gravidity						
1	34535 (1205)	41.77	1.65 (1.52-1.80)	<0.0001	1.50 (1.36-1.65)	<0.0001
2-3 (Reference)	51531 (1139)	25.51	1.00	_	1.00	_
4-6	33699 (894)	25.69	1.16 (1.28-1.00)	0.001	1.11 (1.28-1.22)	0.058
7+	10362 (375)	37.83	1.60 (1.41-1.82)	<0.0001	1.35 (1.15-1.59)	<0.0001
All	**130127 (3535)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, maternal education, household asset quintile, maternal age, previous live births and gravidity

From the late neonatal death trends shown in Figure 4.23 and Table 4.16, it can be seen that these deaths declined greatly in both areas during the study period.

Late neonatal deaths saw a relatively large decline of 6% per year (95% CI: 5%-7%) in Matlab. The lower rate of 7.5/1000 babies alive at Day 7 in the ICDDR,B area was statistically different ($p<0.0001$) from the rate of 12.6/1000 babies alive at Day 7 in the Government service area. Adjustment for socio-demographic variables did not alter annual decline or area differentials.

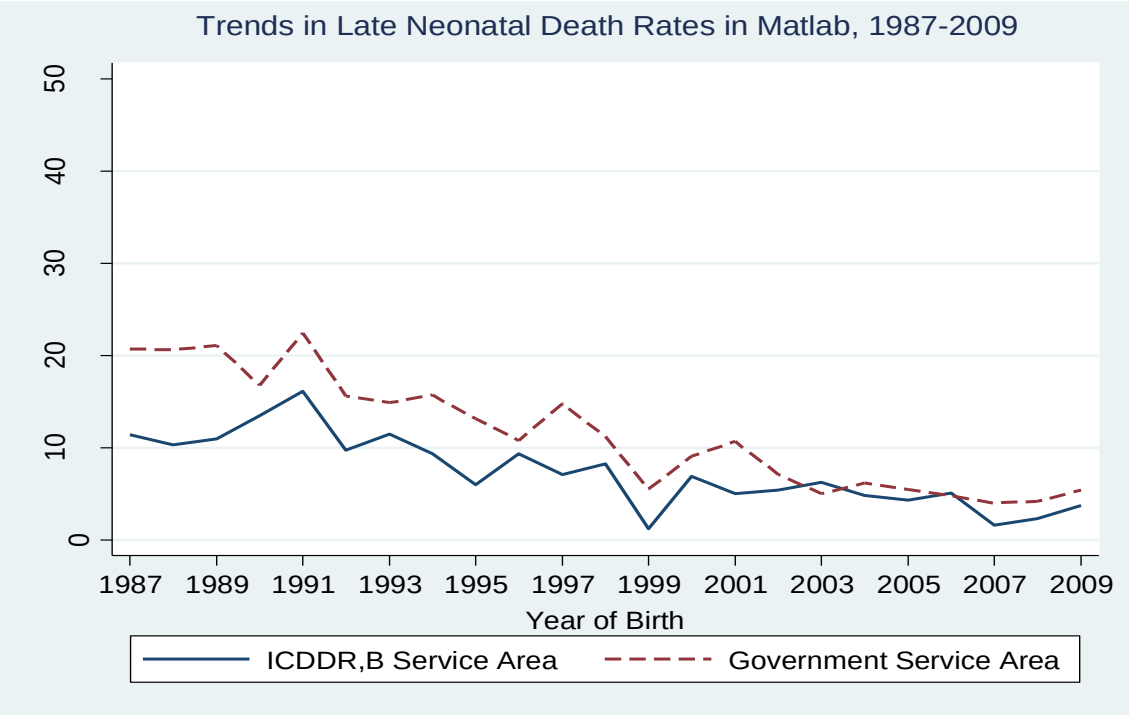


Figure 4.23: Trends in Late Neonatal Death Rates by Area in Matlab, 1987-2009

Table 4.166: Late neonatal deaths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of babies alive at Day 7 (Number of late neonatal deaths)	Late neonatal deaths per 1000 babies alive at Day 7	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs[a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.93 (0.92-0.93)	<0.0001	0.94 (0.93-0.95)	<0.0001
Area of Residence						
ICDDR,B Service Area	58753 (438)	7.45	0.59 (0.52-0.66)	<0.0001	0.62 (0.55-0.70)	<0.0001
Government service area (Reference)	67761 (856)	12.63	1.00	_	1.00	
Maternal formal education (completed years)						
0 (Reference)	53761 (713)	13.26	1.00	_	1.00	_
1-5	32612 (330)	10.12	0.76 (0.66-0.87)	<0.0001	0.91 (0.79-1.04)	0.175
6-10	33824 (202)	5.97	0.44 (0.38-0.52)	<0.0001	0.67 (0.55-0.80)	<0.0001
11-16	2871 (6)	2.09	0.16 (0.07-0.35)	<0.0001	0.26 (0.12-0.60)	0.001
Unknown	3446 (43)	12.48	0.94 (0.68-1.29)	0.704	0.98 (0.71-1.35)	0.905
Household asset quintile						
Most poor (Reference)	21034 (279)	13.26	1.00	_	1.00	_
Very poor	23216 (267)	11.50	0.87 (0.73-1.03)	0.098	0.87 (0.73-1.04)	0.121
Poor	22757 (247)	10.85	0.82 (0.69-0.98)	0.026	0.85 (0.71-1.01)	0.071
Less poor	24475 (202)	8.25	0.62 (0.52-0.75)	<0.0001	0.67 (0.56-0.81)	<0.0001
Least poor	24308 (190)	7.82	0.59 (0.49-0.71)	<0.0001	0.70 (0.57-0.85)	<0.0001
Unknown	10724 (109)	10.16	0.77 (0.61-0.96)	0.020	0.83 (0.66-1.04)	0.105
Religion						
Islam (Reference)	112150 (1127)	10.05	1.00	_	_	_
Hinduism/Other	14364 (167)	11.63	1.16 (0.98-1.37)	0.082	_	_
Maternal Age						
<20	14979 (211)	14.09	1.47 (1.26-1.72)	<0.0001	_	_
20- 29 (Reference)	77738 (756)	9.72	1.00	_	_	_
30-39	31177 (296)	9.49	0.97 (0.84-1.11)	0.642	_	_
40+	2620 (31)	11.83	1.21 (0.84-1.75)	0.308	_	_
Gravidity						
1	33330 (422)	12.66	1.61 (1.40-1.85)	<0.0001	1.78 (1.55-2.05)	<0.0001
2-3 (Reference)	50392 (403)	8.00	1.00	_	1.00	_
4-6	32805 (318)	9.69	1.20 (1.03-1.39)	0.020	0.97 (0.83-1.13)	0.690
7+	9987 (151)	15.12	1.87 (1.54-2.26)	<0.0001	1.21 (0.99-1.48)	0.056
All	**126514 (1243)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, maternal education, household asset quintile, and gravidity

Figure 4.24 and Table 4.17 show trends for Day 0 deaths. Day 0 rates in both areas are largely unchanged over the years. Household asset quintile was significantly associated with decreased Day 0 death rates but only at the highest asset quintile.

Day 0 deaths declined by 1% (95% CI: 0%-1%) though this was not significant. Death rates were significantly lower in the ICDDR,B service area than the Government service area (10.2/1000 live births vs. 12.1/1000 live births; p=0.004).

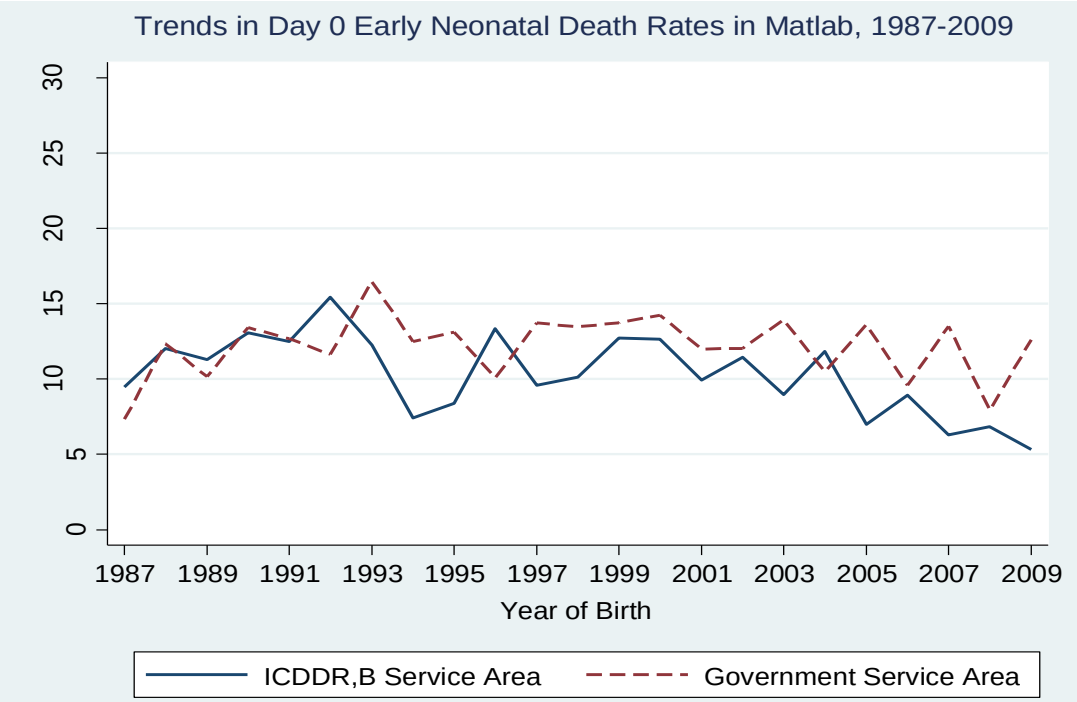


Figure 4.24: Trends in Day 0 death rates by area in Matlab, 1987-2009

Table 4.177: Day 0 deaths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of live births (Number of Day 0 deaths)	Day 0 deaths per 1000 live births	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs [a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.99 (0.98-1.00)	0.022	0.99 (0.99-1.00)	0.092
Area of Residence						
ICDDR,B Service Area (Reference)	60220 (616)	10.23	0.84 (0.75-0.94)	0.002	0.85 (0.76-0.95)	0.004
Government service area (Reference)	69907 (846)	12.10	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	55467 (654)	11.79	1.00	_	_	_
1-5	33582 (396)	11.79	0.99 (0.87-1.14)	0.927	_	_
6-10	34626 (361)	10.43	0.88 (0.77-1.01)	0.068	_	_
11-16	2928 (23)	7.86	0.65 (0.43-1.01)	0.054	_	_
Unknown	3524 (28)	7.95	0.66 (0.45-0.99)	0.044	_	_
Household asset quintile						
Most poor (Reference)	21706 (288)	13.27	1.00	_	1.00	_
Very poor	23910 (269)	11.25	0.85 (0.71-1.01)	0.057	0.84 (0.70-1.00)	0.049
Poor	23424 (269)	11.48	0.87 (0.73-1.03)	0.112	0.86 (0.72-1.02)	0.081
Less poor	25159 (278)	11.05	0.83 (0.70- 0.99)	0.038	0.82 (0.69-0.98)	0.025
Least poor	24874 (234)	9.41	0.71 (0.59-0.85)	<0.0001	0.70 (0.59-0.84)	<0.0001
Unknown	11054 (124)	11.22	0.84 (0.68-1.05)	0.122	0.85 (0.68-1.06)	0.157
Religion						
Islam (Reference)	115305 (1283)	11.13	1.00	_	_	_
Hinduism/Other	14822 9(179)	12.08	1.08 (0.91-1.28)	0.365	_	_
Maternal Age						
<20	15632 (294)	18.81	1.94 (1.68-2.23)	<0.0001	1.67 (1.42-1.97)	<0.0001
20- 29 (Reference)	79773 (803)	10.07	1.00	_	1.00	_
30-39	31999 (326)	10.19	1.01 (0.88-1.15)	0.920	0.94 (0.79-1.11)	0.46
40+	2723 (39)	14.32	1.46 (1.04-2.04)	0.029	1.23 (0.84-1.80)	0.28
Gravidity						
1	34535 (506)	14.65	1.70 (1.49-1.94)	<0.0001	1.42 (1.22-1.64)	<0.0001
2-3 (Reference)	51531 (457)	8.87				
4-6	33699 (361)	10.71	1.18 (1.02-1.36)	0.021	1.20 (1.03-1.41)	0.02
7+	10362 (138)	13.32	1.46 (1.20 -1.79)	<0.0001	1.42 (1.10-1.82)	0.01
All	**130127 (1462)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, household asset quintile, maternal age and gravidity

Day 1-2 death trends (Figure 4.25 and Table 4.18) showed decline over the study period.

Day 1-2 deaths declined significantly by 2% per year (95% CI: 1% to 3%) and rates were significantly higher in the ICDDR, B service area. Adjustment for the socio-demographic confounders could not explain the differential rates in the two areas.

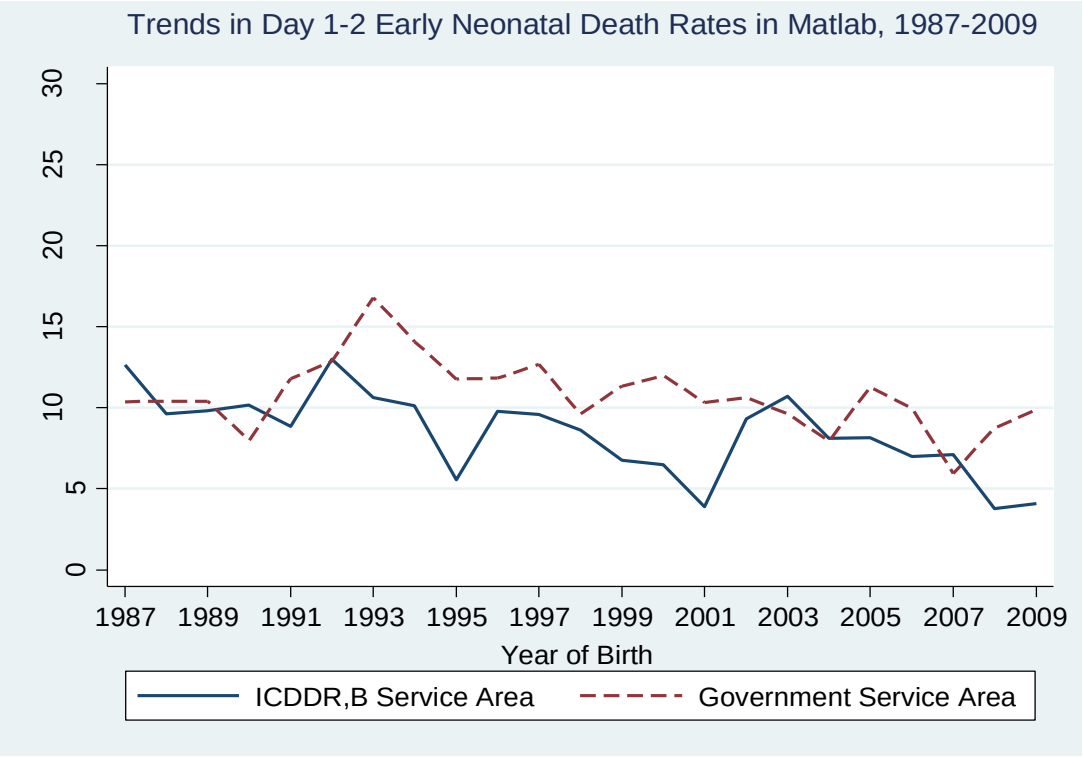


Figure 4.25: Trends in Day 1 to 2 neonatal death rates by area in Matlab, 1987-2009

Table 4.188: Day 1 to 2 deaths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of babies alive on Day 1 (Number of Day 1-2 deaths)	Day 1-2 deaths per 1000 babies alive on Day 1	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs [a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.98 (0.97-0.99)	<0.0001	0.98 (0.97-0.99)	<0.0001
Area of Residence						
ICDDR,B Service Area (Reference)	59604 (510)	8.56	0.78 (0.70-0.88)	<0.0001	0.80 (0.71-0.90)	<0.0001
Government service area (Reference)	69061 (752)	10.89	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	54813 (574)	10.47	1.00	_		
1-5	33186 (349)	10.52	1.01 (0.88-1.15)	0.949	_	_
6-10	34265 (287)	8.38	0.80 (0.69-0.92)	<0.0001	_	_
11-16	2905 (22)	7.57	0.72 (0.47-1.11)	0.137	_	_
Unknown	3496 (30)	8.58	0.80 (0.55-1.17)	0.244	_	_
Household asset quintile						
Most poor (Reference)	21418 (223)	10.41	1.00	_	1.00	_
Very poor	23641 (261)	11.04	1.06 (0.89-1.28)	0.503	1.06 (0.88-1.27)	0.560
Poor	23155 (235)	10.15	0.98 (0.81-1.18)	0.801	0.97 (0.80-1.17)	0.715
Less poor	24881 (231)	9.28	0.89 (0.74-1.08)	0.231	0.88 (0.73-1.06)	0.183
Least poor	24640 (188)	7.63	0.73 (0.60-0.89)	<0.0001	0.73 (0.60-0.89)	<0.0001
Unknown	10930 (124)	11.34	1.10 (0.88-1.37)	0.416	1.14 (0.91-1.43)	0.250
Religion						
Islam (Reference)	114022 (1115)	9.78	1.00	_	_	_
Hinduism/Other	14643 (147)	10.04	1.03 (0.86-1.23)	0.759	_	_
Maternal Age						
<20	15338 (222)	14.47	1.68 (1.44-1.96)	<0.0001	1.34 (1.12-1.59)	0.001
20- 29 (Reference)	78970 (694)	8.79	1.00	_	1.00	_
30-39	31673 (312)	9.85	1.12 (0.98-1.28)	0.103	1.11 (0.93-1.32)	0.243
40+	2684 (34)	12.67	1.46 (1.03-2.08)	0.034	1.28 (0.86-1.91)	0.219
Gravidity						
1	34029 (437)	12.84	1.79 (1.55-2.06)	<0.0001	1.67 (1.43-1.95)	<0.0001
2-3 (Reference)	51074 (373)	7.30	1.00	_	1.00	_
4-6	33338 (321)	9.63	1.31 (1.12-1.52)	<0.0001	1.20 (1.01-1.42)	0.035
7+	10224 (131)	12.81	1.74 (1.42-2.14)	<0.0001	1.41 (1.08-1.82)	0.010
All	**128665 (1262)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, household asset quintile, maternal age and gravidity

From Figure 4.26 and Table 4.19, Day 3-6 death trends declined in both areas and rates were found to be significantly greater in the Government service area.

Day 3-6 death rates declined by 6% per year (95% CI: 5%-7%) in Matlab and rates were again significantly lower in the ICDDR,B area than the Government service area.

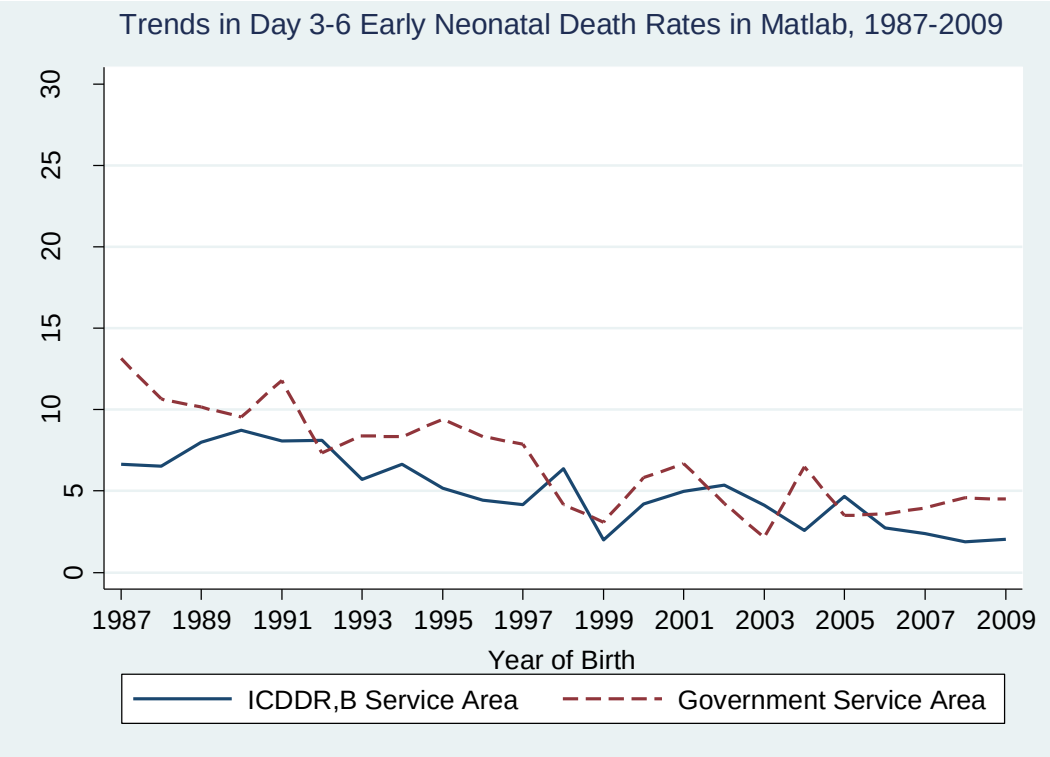


Figure 4.26: Trends in Day 3 to 6 neonatal death rates by area in Matlab, 1987-2009

Table 4.19: Day 3 to 6 deaths according to time, area and socio-demographic characteristics of women in Matlab (1987-2009)

Socio-demographic characteristics	Number of babies alive on Day 3 (Number of Day 3-6 deaths)	Day 3-6 deaths per 1000 babies alive on Day 3	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs [a b] (95 % CI)	P-values (Wald test)
Year of Birth	_	_	0.94 (0.93-0.95)	<0.0001	0.94 (0.93-0.95)	<0.0001
Area of Residence						
ICDDR,B Service Area	59094 (305)	5.16	0.78 (0.70-0.88)	<0.0001	0.70 (0.60-0.81)	<0.0001
Government service area (Reference)	68309 (506)	7.41	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	54239 (440)	8.11	1.00	_	1.00	_
1-5	32837 (200)	6.09	0.75 (0.63-0.89)	0.001	0.83 (0.69-0.99)	0.035
6-10	33978 (141)	4.15	0.51 (0.42-0.61)	<0.0001	0.62 (0.50-0.77)	<0.0001
11-16	2883 (11)	3.82	0.47 (0.26-0.85)	0.013	0.64 (0.34-1.18)	0.150
Unknown	3466 (19)	5.48	0.67 (0.42-1.07)	0.097	0.69 (0.43-1.10)	0.119
Household asset quintile						
Most poor (Reference)	21195 (152)	7.17	1.00	_	1.00	_
Very poor	23380 (147)	6.29	0.88 (0.70-1.11)	0.271	_	_
Poor	22920 (148)	6.46	0.90 (0.72-1.14)	0.384	_	_
Less poor	24650 (156)	6.33	0.89 (0.71-1.11)	0.290	_	_
Least poor	24452 (132)	5.40	0.75 (0.60-0.95)	0.019	_	_
Unknown	10806 (76)	7.03	0.99 (0.75-1.30)	0.917	_	_
Religion						
Islam (Reference)	112907 (690)	6.11	1.00	_	1.00	_
Hinduism/Other	14496 (121)	8.35	1.37 (1.13-1.67)	0.002	1.33 (1.09-1.63)	0.005
Maternal Age						
<20	15116 (131)	8.67	1.39 (1.15-1.69)	0.001	1.19 (0.95-1.48)	0.135
20- 29 (Reference)	78276 (491)	6.27	1.00	_	1.00	_
30-39	31361 (160)	5.10	0.81 (0.68-0.97)	0.021	0.86 (0.69-1.08)	0.206
40+	2650 (29)	10.94	1.76 (1.20-2.57)	0.004	1.53 (0.97-2.42)	0.066
Gravidity						
1	33592 (262)	7.80	1.44 (1.21-1.71)	<0.0001	1.44 (1.19-1.75)	<0.0001
2-3 (Reference)	50701 (277)	5.46	1.00	_	1.00	_
4-6	33017 (186)	5.63	1.02 (0.85-1.23)	0.823	0.91 (0.74-1.12)	0.375
7+	10093 (86)	8.52	1.55 (1.22-1.99)	<0.0001	1.10 (0.79-1.53)	0.562
All	**127403 (811)**					

[a]All odd ratios are adjusted for clustering of births to the same mother
[b]Adjusted for time period, area of residence, maternal education, religion, maternal age and gravidity

Tables 4.20 and 4.21 summarise the reductions in different mortality outcomes in the two areas over the 23 years of the study. Stillbirths declined by 46% [4](95%CI: 34%-66%) between 1987 and 2009 in the ICDDR,B service area compared to no decline in the Government service area. The 57% decline in early neonatal deaths in the ICDDR,B service area was significantly greater than the 28% seen in the Government service area. The large declines in late neonatal deaths, 81% and 79% in the ICDDR,B and Government service areas respectively, were similar for both areas.

Table 4.190: Reduction in stillbirths, early neonatal deaths and late neonatal deaths in the ICDDR,B and Government service areas in Matlab (1987-2009)

Year of birth	Area of residence			
	ICDDR,B Service Area		**Government Service Area**	
	Crude OR (95% CI)	p-value	Crude OR (95% CI)	p-value
Stillbirths				
1987-1990	1.00	_	1.00	_
1991-1994	0.96 (0.82-1.11)	0.558	1.24 (1.09-1.41)	0.001
1995-1998	0.84 (0.71-0.98)	0.028	1.06 (0.93-1.22)	0.336
1999-2002	0.89 (0.76-1.03)	0.123	1.03 (0.89-1.17)	0.724
2003-2006	0.71 (0.60-0.83)	<0.0001	1.05 (0.91-1.21)	0.483
2007-2009	0.54 (0.45-0.66)	<0.0001	1.00 (0.84-1.17)	0.974
Early neonatal deaths				
1987-1990	1.00	_	1.00	_
1991-1994	0.99 (0.84-1.17)	0.907	1.15 (1.01-1.32)	0.034
1995-1998	0.79 (0.66-0.94)	0.007	0.98 (0.85-1.13)	0.813
1999-2002	0.73 (0.61-0.87)	<0.0001	0.93 (0.80-1.07)	0.288
2003-2006	0.70 (0.58-0.83)	<0.0001	0.79 (0.68-0.93)	0.003
2007-2009	0.43 (0.34-0.54)	<0.0001	0.72 (0.60-0.87)	<0.0001
Late neonatal deaths				
1987-1990	1.00	_	1.00	_
1991-1994	1.02 (0.80-1.32)	0.842	0.84 (0.71-1.01)	0.063
1995-1998	0.65 (0.49-0.87)	0.004	0.61 (0.51-0.76)	<0.0001
1999-2002	0.40 (0.29-0.56)	<0.0001	0.40 (0.32-0.50)	<0.0001
2003-2006	0.44 (0.32-0.61)	<0.0001	0.25 (0.19-0.34)	<0.0001
2007-2009	0.19 (0.11-0.32)	<0.0001	0.21 (0.15-0.31)	<0.0001

[4] Due to the large sample size and relatively rare outcomes the odds ratios approximates a percentage (%) reduction (i.e. approximates the relative risk) even though it shows the percentage (%) reduction in the odds of the outcome.

Day 0 deaths declined by 46% (95% CI: 24%-61%) between 1987 and 2009 in the ICDDR,B area while they remained unchanged in the government service area. The 55% reduction in Day 1 to 2 deaths in the ICDDR,B service area was significant compared to the non-significant decline of 18% (crude OR: 0.82; 95%CI: 0.60-1.11) in the Government service area. The large reductions of 72% and 60% in Day 3 to 6 deaths in the two areas were not significantly different.

Table 4.201: Reduction in Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths in the ICDDR,B and Government service areas in Matlab (1987-2009)

Year of birth	Area of residence			
	ICDDR,B Service Area		**Government Service Area**	
	Crude OR (95% CI)	p-value	Crude OR (95% CI)	p-value
Day 0 deaths				
1987-1990	1.00	_	1.00	_
1991-1994	1.05 (0.81-1.36)	0.704	1.22 (0.98-1.52)	0.073
1995-1998	0.88 (0.67-1.16)	0.368	1.13 (0.90-1.42)	0.282
1999-2002	1.02 (0.79-1.32)	0.881	1.20 (0.96-1.43)	0.110
2003-2006	0.81 (0.61-1.06)	0.120	1.08 (0.84-1.37)	0.539
2007-2009	0.54 (0.39-0.76)	<0.0001	1.02 (0.77-1.34)	0.889
Day 1 to 2 deaths				
1987-1990	1.00	_	1.00	_
1991-1994	0.99 (0.76-1.29)	0.932	1.41 (1.12-1.75)	0.073
1995-1998	0.79 (0.60-1.04)	0.098	1.16 (0.91-1.47)	0.282
1999-2002	0.62 (0.46-0.83)	0.001	1.14 (0.90-1.44)	0.110
2003-2006	0.79 (0.60-1.04)	0.092	0.98 (0.76-1.27)	0.539
2007-2009	0.45 (0.31-0.66)	0	0.82 (0.60-1.11)	0.889
Day 3 to 6 deaths				
1987-1990	1.00	_	1.00	_
1991-1994	0.97 (0.71-1.35)	0.873	0.84 (0.66-1.06)	0.139
1995-1998	0.68 (0.48-0.97)	0.036	0.68 (0.53-0.89)	0.004
1999-2002	0.56 (0.40-0.81)	0.002	0.46 (0.34-0.62)	<0.0001
2003-2006	0.47 (0.31-0.69)	<0.0001	0.36 (0.26-0.51)	<0.0001
2007-2009	0.28 (0.16-0.48)	<0.0001	0.40 (0.27-0.59)	<0.0001

4.4.9 Time Trends by Area

Interactions between time and area were significant for stillbirths and early neonatal deaths, but not for late neonatal deaths (Table 4.22). When early neonatal deaths were disaggregated by day since birth, interactions between time and area were significant for Day 0 deaths and Day 1-2 deaths but not for Day 3-6 deaths.

Stillbirths declined by 2% per year in the ICDDR,B area (95% CI: 1% - 3%) but not in the Government service area.

Early neonatal deaths also declined, by 3% per year in the ICDDR,B area (95% CI: 3% - 4%) compared to 2% per year in the Government service area (95% CI: 1% - 2%) and the decline was faster for the ICDDR,B service area.

For late neonatal deaths the 6% decline in the ICDDR,B area (95% CI: 4% to 7%) and the 7% decline in the Government area (95% CI: 6% -8%) were not statistically different (p=0.243).

In case of disaggregated early neonatal deaths, Day 0 deaths declined 2% annually in the intervention area (95% CI: 1%-3%) with no decline seen in the comparison area.

The annual decline of 3% in the ICDDR,B area (95% CI: 2%- 4%) for Day 1-2 deaths was faster than that of 1% in the Government service area (95% CI: 0% -2%).

Day 3-6 deaths declined swiftly and significantly in both the ICDDR,B (6%; 95% CI: 3%-7%) and Government (4%; 95% CI: 3%-6%) service areas but the speed of decline was the same (p=0.573) for both areas.

Table 4.212: Annual trends in stillbirths, early neonatal deaths, late neonatal deaths, Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths in ICDDR,B and Government service areas, Matlab (1987-2009)

	Crude odds ratio (95% CI)	P-value (Wald Test)	Adjusted odds ratio (95% CI)	P-value (Wald Test)	P-value for interaction between time and area of residence
Stillbirth trend per year[1]					
ICDDR,B Service Area	0.98 (0.97-0.98)	<0.0001	0.98 (0.97-0.99)	<0.0001	<0.0001
Government service area	1.00 (0.99-1.00)	0.236	1.00 (0.99-1.00)	0.386	
Early neonatal death trend per year[2]					
ICDDR,B Service Area	0.97 (0.95-0.98)	<0.0001	0.97 (0.96-0.97)	<0.0001	0.007
Government service area	0.98 (0.98-0.99)	<0.0001	0.99 (0.98-0.99)	0.002	
Late neonatal death trend per year [3]					
ICDDR,B Service Area	0.93 (0.92-0.95)	<0.0001	0.94 (0.93-0.96)	<0.0001	0.243
Government service area	0.92 (0.91-0.93)	<0.0001	0.93 (0.92-0.94)	<0.0001	
Day 0 death trend per year[4]					
ICDDR,B Service Area	0.98 (0.97-0.99)	0.001	0.98 (0.97-0.99)	0.005	0.005
Government service area	1.00 (0.99-1.01)	0.843	1.00 (0.99-1.01)	0.707	
Day 1 to 2 death trend per year[5]					
ICDDR,B Service Area	0.97 (0.96-0.98)	<0.0001	0.97 (0.96-0.98)	<0.0001	0.014
Government service area	0.99 (0.98-1.00)	0.077	0.99 (0.98-1.00)	0.085	
Day 3 to 6 death trend per year[6]					
ICDDR,B Service Area	0.95 (0.93-0.96)	<0.0001	0.95 (0.93-0.97)	<0.0001	0.573
Government service area	0.94 (0.93-0.96)	<0.0001	0.96 (0.94-0.97)	<0.0001	

Adjusted for: [1] maternal education, maternal age and gravidity; [2]maternal education, household asset quintile, maternal age and gravidity; [3]maternal education, asset quintile and gravidity; [4]household asset quintile, maternal age, and gravidity; [5]household asset quintile, maternal age and gravidity; and [6]maternal education, religion, maternal age and gravidity.

4.5 Discussion

This study reported very high rates for stillbirths (32.7 /1000 births), early (27.5 /1000 live births) and late neonatal deaths (10.0/1000 babies alive at Day 7) over the last 23 years but stillbirths and neonatal deaths have been declining dramatically. Stillbirths, early and late neonatal deaths declined by 46%, 57% and 81%, respectively, over 23 years in the study area. Large reductions in deaths on the first day (46%) and on the second and third days (55%) after birth were also seen during this period. The patterns of decline for stillbirths and very early (Day 0-2 deaths) neonatal deaths are different from patterns for deaths occurring 3 to 6 days after birth and late neonatal mortality. Stillbirths and Day 0 deaths declined annually in the ICDDR,B service area compared to no decline in the Government service area. Day 1 to 2 deaths declined in both areas but the decline was faster in the ICDDR,B service area than the Government service area. The decline seen for Day 3-6 deaths and late neonatal deaths was much steeper than that for stillbirths and very early neonatal deaths but there was no difference between the two areas. The results did not change after demographic and socio-economic factors changes were taken into consideration.

The differential decline in stillbirths and very early (Day 0-2 deaths) neonatal deaths in the intervention and Government service areas suggests that the Safe Motherhood Programme may have contributed to the decline. The programme may have contributed in a number of ways, including (1) improved intrapartum care and increased access to intrapartum care, and (2) greater coverage of and better quality of ANC.

(1) Findings from studies in Matlab on causes of neonatal deaths show that birth asphyxia is the single largest cause of death in the early neonatal period while sepsis/meningitis is the single largest cause for the late neonatal period (Chowdhury et al. 2010; Ronsmans et al. 2008; Chowdhury et al. 2005). The progression in causes of deaths from birth asphyxia to sepsis/pneumonia by day since birth is also seen in a community-based study in rural India (Baqui et al. 2006). This rural study also found that 87% of all stillbirths were fresh and that most of the first day deaths were due to birth asphyxia or complications of preterm delivery (Baqui et al. 2006). Since birth asphyxia is associated with poor intrapartum delivery care and poor newborn care (Lawn, Lee et al. 2009) it is plausible that the Matlab Safe Motherhood Programme contributed to the decline in stillbirths and very early (Day 0-2 deaths) neonatal deaths by increasing trained birth attendance, health facility deliveries and Caesarean sections. This is supported by a recent Matlab study by Rahman and colleagues (Rahman et al. 2011) which reported a decline in birth asphyxia and infection-related deaths after strengthening of

the Matlab Safe Motherhood Programme. A quick and efficient referral system is also invaluable in getting women to specific care when needed (Lee, Lawn, et al. 2009). Intrapartum care in ICDDR,B facilities consisted of skilled obstetric care at birth, essential and emergency newborn care, case management of newborn complications and referral to higher facilities for maternal and newborn complications with free transport.

(2) The increased coverage and better quality of ANC in the ICDDR,B service area may also explain the differentials seen. In Matlab the increase in coverage of antenatal care visits (≥3) between 2002-2009 was greater in the ICDDR,B service area (40% to 81%) than the Government service area (16% to 27%) (Pervin et al. 2012). The quality of ANC in the ICDDR,B service area was possibly better as an earlier study showed doubled odds of perinatal mortality for 0 or 1 ANC visit compared to 3+ visits in the ICDDR,B service area whereas a non-significant effect was shown in the Government service area (Pervin et al. 2012). The ICDDR,B ANC benefited from elements absent in the Government ANC namely: (1) specific guidelines for components within the ANC package (2) foundational and refresher training for providers including a manual (3) counselling on interventions including danger signs (4) linkages between community and facilities to improve referrals for complications and (5) regular monitoring, evaluation and supervision of services offered (Pervin et al. 2012). Additionally, government facilities lacked routine ultrasound examination, risk tracking, protocols on preterm and post-term delivery management and newborn thermal care provision (Rahman et al. 2011).

Studies in Matlab and elsewhere (Chowdhury et al. 2010; Ronsmans et al. 2008; Chowdhury et al. 2005; Baqui et al. 2006), have shown that Day 3-6 and late neonatal deaths are largely due to sepsis, meningitis and pneumonia (Lawn, Lee et al. 2009). These infections can be managed through oral and injectable antibiotics administered as soon as the disease is detected. Community-based pneumonia/sepsis management by antibiotics, ideally through frequent and regular post-partum home visits, can avert up to 35% of neonatal mortality and has been recommended as an evidence-based and cost-effective intervention to reduce neonatal deaths (Darmstadt et al. 2005)

The dramatic decline in neonatal mortality after 4 days of life, with no difference between the intervention and comparison areas, suggests that the Safe Motherhood Programme did not contribute to these later deaths and that they might be explained by other interventions (e.g. antibiotics and oral rehydration salts) in Matlab, described later.

In the ICDDR,B service area postpartum home visits at 0, 3, 7 and 28 days were introduced in mid- 2007, reaching high coverage (81.8%) by 2008-2009 (Rahman et al. 2011). Post-partum visits promoted exclusive breastfeeding, cord and skin care and extra care for preterm and low birthweight infants (referral to the kangaroo mother care unit with thermal protection, skin-to-skin care, frequent breastfeeding advice, and monitoring follow-up visits to the kangaroo mother care unit). Visits also promoted facility-based care for babies, care-seeking and danger sign recognition. There were no post-partum home visits in the Government service area during the study period (personal communication, Anisur Rahman). However, the presence of these visits in the ICDDR,B service area and absence in the Government service area is unlikely to have affected late neonatal mortality reduction. Significant reductions in Day 3 to 6 and late neonatal deaths were seen in both areas from 1995-1998 onwards, prior to initiation of post-partum visits in the ICDDR,B service area and reductions were no different in the two areas in the period 2007-2009. It is possible that the ICDDR,B home visits did not result in a greater reduction of mortality as the home visits did not include administration of injectable antibiotics to ill babies. These were given to ill babies and babies whose parents refused referral in the post-partum home visits of two studies in the Gadchiroli district of India and in the Sylhet district of Bangladesh which showed reductions in neonatal mortality (Bang et al. 2005; Baqui et al. 2009).

The most likely explanation for the non-differential decline in Day 3-6 and late neonatal deaths is the wide availability of antibiotics, oral rehydration salts, and other medicines dispensed from village-level pharmacies and village doctors in both areas (Ronsmans et al. 2008). The earlier decline in early and late neonatal deaths during the 1980s in Matlab was linked to reductions in neonatal tetanus (Fauveau et al. 1990) supporting the role of maternal immunisation in neonatal mortality reduction (Darmstadt et al. 2005).

Though balanced protein energy supplementation is found to reduce perinatal mortality, a large study in Matlab showed that prenatal food and multiple micronutrient supplementation had no effect on infant development and stillbirths, early neonatal deaths and late neonatal deaths (Tofail et al. 2008; Ronsmans et al. 2009) This was supported by two systematic reviews (Haider et al. 2011; Ronsmans et al. 2009). Malaria, STIs and HIV/AIDs, infections linked to perinatal mortality, are very uncommon in Matlab (Hawkes et al. 2002)

The associations between socio demographic determinants and stillbirths and neonatal mortality were consistent with patterns seen in the literature for: year of birth and area of residence (Ronsmans et al. 2008; Rahman et al. 2007), extremes of maternal age (Marston &

Cleland 2004) gravidity (Rahman et al. 2007), religion and household asset quintile (Ronsmans et al. 2008; Kusiako et al. 2000). Adjustment for socio-demographic variables did not alter the time trends and area differentials for mortality. This suggests that the area-wise trends and differences could not be explained by changes in these characteristics over time. It was surprising that changes in maternal education did not explain part of the trends over time, given that education increased dramatically over time and is an independent predictor of stillbirths and early mortality in previous studies(Olsen & Madsen 1999; Stephansson 2001) as well as in mine where it is also an independent predictor for late neonatal mortality.

The strengths of this study include: prospective ascertainment of pregnancies and their outcomes, a large sample of 134,551 births, adjustment for a large number of confounders and very small loss to follow-up for a cohort study of such duration and size (0.99%) (Appendix II: Table 4). There were several possible limitations, however, including (1) residual confounding (2) inability of the asset score to detect change in wealth over time (3) stillbirth and Day 0 death misclassification (4) missing data and (5) birth attendant misclassification.

The quasi-experimental study design assumes that the two areas are similar in core characteristics except for the intervention under study. I adjusted the analysis for important socio-demographic variables, but some residual confounding may still have occurred. For example, short (≤6 months) and long (>6 years) inter-birth intervals negatively impact stillbirths and neonatal mortality (Yakoob et al. 2009; Conde-Agudelo et al. 2006; Dean et al. 2013). Two Matlab studies showed that between 1982 and 2002, births in the Government service area occurred after shorter birth intervals (<15 months) than in the ICDDR,B service area (DaVanzo et al. 2004; Chowdhury et al. 2009). However, a Matlab study that assessed trends of stillbirths, early neonatal and late neonatal mortality showed that adjustment for preceding birth intervals in addition to the socio-demographic factors present in this study did not result in any changes in the trends (Ronsmans et al. 2008). Although I have tried to adjust for as many confounders as possible, the possibility of residual confounding cannot be ruled out and hence it is possible that the different trends between the two areas are due to inherent differences between the two areas rather than to the intervention.

The asset score used in this study could not detect changes in wealth over time. This is because socio-economic quintiles were obtained from previously computed quintiles based on household assets at the time of each of the three censuses. Hence though each pregnancy was linked to the most relevant census quintile, within each of the three censuses, the population was always divided into five equal groups and so relative change in wealth over time for a

household could not be determined. An earlier Matlab study (Chowdhury et al. 2007) which used principal component analysis to generate asset scores and allowed for changes in asset variables (e.g. latrine type, material of walls and roof, ownership of lamp/ watch/ bicycle/ boat/ cow, remittance etc.) with each pregnancy, showed a dramatic decline in poverty. The poorest households declined from 33% in 1976-1980 to only 1% by 2001-2005. However, female education is a valid proxy for maternal wealth in Bangladesh (Pitchforth et al. 2007), and since adjustment for education did not change the results, it is unlikely that being able to measure actual wealth increase would have changed the results.

Any misclassification between stillbirths and Day 0 deaths is likely to affect the overall levels of mortality, but since it is non-differential in the two areas, it is unlikely to affect the magnitude of the odds ratios.

The low-level missing data present for maternal education (2.7%) and asset quintiles (8.5%) were retained in 'unknown' categories to avoid creating selection bias and corresponding rates and odds ratios were presented.

Where possible, misclassification of birth attendant type because of women's self-reports were recoded. Any residual misclassification is likely to be non-differential in the two areas and hence unlikely to bias the results.

The study suggests that the Safe Motherhood Programme, with its strengthening of antenatal and delivery care, may have contributed to a fall in stillbirths (46%), Day 0 and Day 2-3 deaths (46% and 55%). These results are consistent with those reported in the literature.

In an earlier Matlab study (Ronsmans et al. 2008) stillbirths, early and late neonatal deaths declined by 24% , 39% and 73% over 28 years (1975-2002) in the ICDDR,B service area; these figures are consistent with the declines seen in my study. A recent Matlab paper (Rahman et al. 2011) also suggested that the Safe Motherhood Programme had reduced perinatal mortality; however, the focus was on perinatal mortality and the strengthened programme after 2007 (Rahman et al. 2011). Results showed that perinatal mortality was significantly lower (36%) in the ICDDR,B service area in 2008-2009 compared to 2005-2006, and that the corresponding 12% decline in the Government service area was non-significant. The authors, surprised to note that skin-to-skin contact did not reduce very preterm and/or low-birth weight related neonatal deaths, suggested that the contact given was not sufficient to prevent these deaths. Decline in perinatal mortality was attributed to greater care-seeking behaviour and increased quality of care at the Matlab sub-centres and Matlab hospital.

Other studies from South Asia that compared community-based intervention packages with control or usual care showed reductions in stillbirth and perinatal outcomes. Reductions in stillbirths, early and late neonatal deaths in the ICDDR,B service area compared to the Government service area in my study were 46%, 29% and 2% respectively. A Cochrane systematic review (Lassi et al. 2010) provided meta-analysis results of effects of community based interventions on perinatal mortality (Chapter 2). The magnitude of reductions in Matlab was consistent with the corresponding reductions of 25%, 19% and 26% seen in the Cochrane review. Three studies in the meta-analysis (Bhutta et al. 2011; Kumar et al. 2008; Jokhio et al. 2005) with interventions most similar to the Matlab study interventions have been described earlier (Chapter 2, section 2.5.4). The reductions for stillbirths, early neonatal and late neonatal mortality in these studies were 21%, 14% and 17% (Bhutta et al. 2011), 35%, 41% and 68% (Kumar et al. 2008) and 31%, 30% and 29% (Jokhio et al. 2005).

Overall, the decline in mortality observed in these three studies in the region supports the findings seen in Matlab. However, it should be noted that my Matlab study differed from these studies as the decline in late neonatal mortality (89% and 79% in the ICDDR,B and Government service areas respectively over the study time period) was much greater than the declines seen in the three studies above (17%, 68% and 29%).

The decline observed in Matlab is also supported by literature described earlier on the effect of SBA, BEmOC and CEmOC on stillbirths and perinatal mortality (Yakoob et al. 2011; Lee et al. 2011).

Stillbirth, early and late neonatal death rates in the Government service area are consistent with national rates, those seen in the region and other studies conducted in Bangladesh. The Bangladesh Demographic and Health Survey (DHS) 2007 rates for 2002-2007 for stillbirths and early neonatal mortality in rural areas were 30.6/1000 births and 28.9/1000 live births (NIPORT 2009) which correspond to rates obtained for the Government service area during the same period, 35.2/1000 births and 25.9/1000 live births, respectively. The national DHS late neonatal mortality rate of 7.6/1000 babies alive at Day 7 was similar to the Government service area rate of 5.1/1000 babies alive at Day 7. Azad and colleagues (2010) reported stillbirth, early neonatal death and late neonatal death rates of 34.1/1000 births, 29.5/1000 live births and 8.3/1000 live births respectively in 2005-2007 in three rural districts of Bangladesh which corresponded to the Government service area rates obtained for the 2005-2007 time period. Rates were also consistent with other rural studies in Bangladesh

(Chowdhury et al. 2005; Ronsmans et al. 2008) and were similar to those obtained in Pakistan by Bhutta et al. 2011 and in India by Tripathy et al. 2010.

It has been suggested that findings obtained in Matlab in a research-sensitized population are less generalizable to developing countries with non-sensitized populations. However, though the ICDDR,B service area showed a facility delivery rate of 76.6% in 2009, the Government service area had a facility delivery rate of 24.6% in 2009 which is very similar to Bangladesh's national rate of 23% in 2010. This has been achieved to an extent by the ICDDR,B strictly ensuring that the Government service area people use their own services and facilities to prevent 'cross- contamination' by usage of the ICDDR,B services and facilities. The Matlab area is still representative of rural Bangladesh geographically and culturally, and the socio-demographic and delivery trends in its Government area closely follow that of the rest of the country.

The study findings suggest that the indicators for perinatal mortality might be revisited. Stillbirths, Day 0 and Day 1-2 deaths appear to respond similarly to antenatal detection of risk factors, essential obstetric and newborn care and to referral and emergency care, while Day 3-6 and late neonatal deaths appear to respond to interventions involving care-seeking and improved management of newborn illness. Studies in Bangladesh and other developing countries are needed to see if these patterns are also observed elsewhere.

This study has two implications for the organisation of care for women and neonates in Bangladesh and other low income countries. First, the Matlab Safe Motherhood Programme shows how investment in comprehensive antenatal and professional delivery care can impact on stillbirths and very early neonatal mortality. The government of Bangladesh has provided basic delivery centres (Rahman et al. 2011) similar to ICDDR,B sub-centres and encourages ANC visits and SBA at delivery. The ANC visits and SBA programmes at government and private facilities should be further strengthened by evidence-based practices, improved monitoring of the programs, set protocols for improved management of maternal and newborn complications and strengthened referral linkages to higher facilities.

Second, this study also showed that a dramatic decline in late neonatal deaths can be achieved when formal post-partum visits are absent but antibiotics and oral rehydration salts are available close to the woman's home. Informal care providers such as drug-retailers and unqualified/semi-qualified village doctors play an important role in providing treatment for newborn illness (Ahmed & Hossain 2006; Mahmood et al. 2010; Ronsmans et al. 1996).

Government training of informal care providers on common neonatal illness recognition, primary treatment and referral to facilities could increase the contribution of these partners in reducing late neonatal mortality.

Chapter 5. The Contribution of Preterm Births to Stillbirths, Early Neonatal Deaths and Late Neonatal Deaths in Matlab

5.1 Introduction

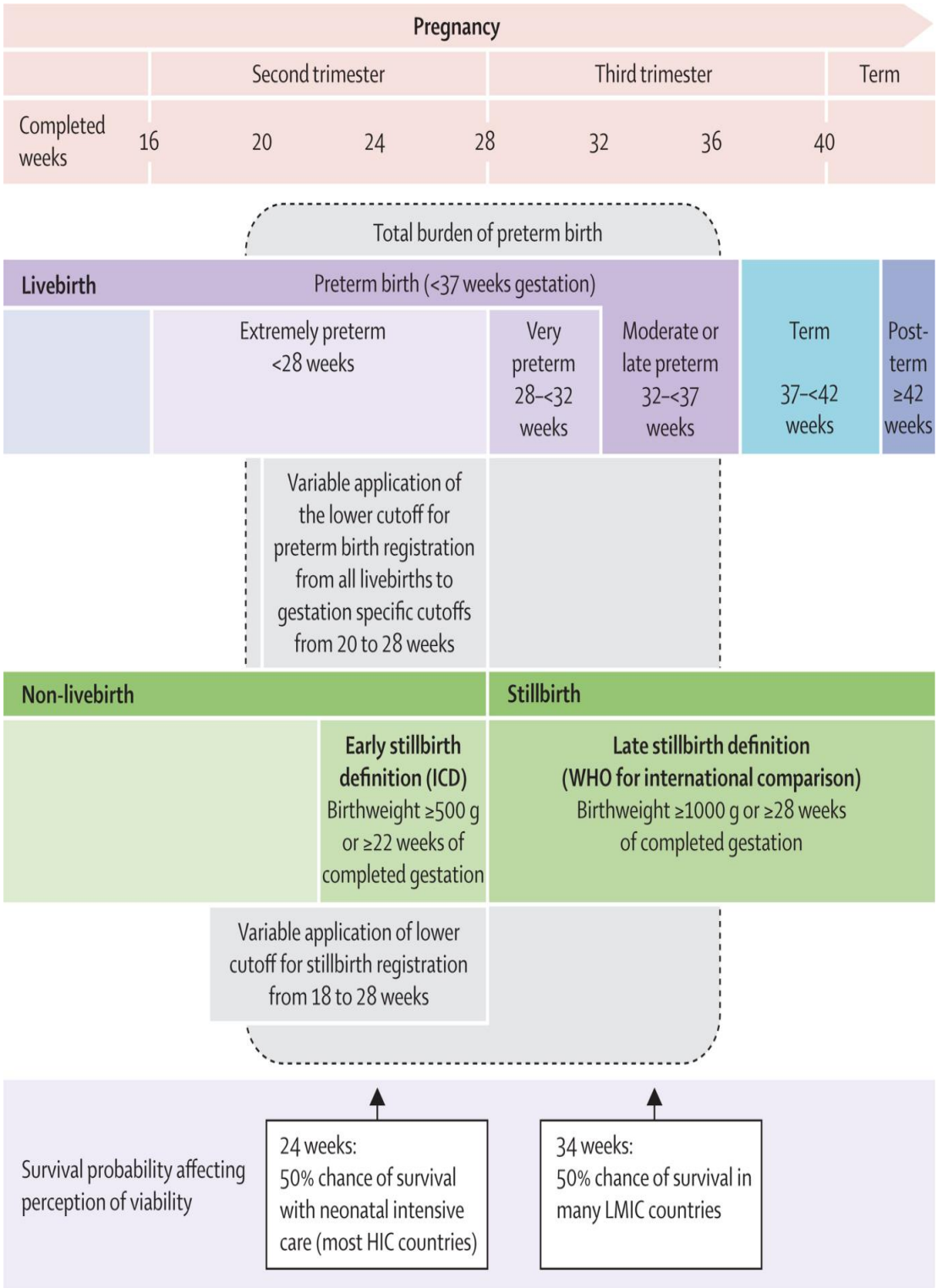
Preterm birth is the biggest cause of neonatal death and the second biggest cause of death after infectious diseases (pneumonia, diarrhoea and malaria) in children under 5 years (Darmstadt et al. 2014; Blencowe et al. 2013; Liu et al. 2012). Direct contributory factors for neonatal deaths in 2010 were: pre-term birth complications (1.08 million), intrapartum complications (0.7 million) and sepsis or meningitis (0.4 million) (Liu et al. 2012; Blencowe et al. 2013). Preterm babies are at a higher risk of dying from infections, and so, indirectly preterm births resulted in 0.83 million neonatal deaths in 2010 (Liu et al. 2012; Blencowe et al. 2013; Lawn et al. 2005). In 2010, 1 in 10 babies worldwide was born preterm (before 37 weeks of gestation) resulting in 15 million global preterm births, 60% of which were in South Asia and sub-Saharan Africa (Blencowe et al. 2012). India, Pakistan and Bangladesh have the first, fourth and seventh highest numbers of preterm births (3.5M, 0.8M and 0.4M) globally (Blencowe et al. 2012). The highest prevalences are also seen in South-eastern Asia and South Asia (13.5 % and 13.3%) followed by sub-Saharan Africa (12.3%) while a prevalence of 8.6% is seen in developed countries (Blencowe et al. 2012). Currently preterm complications result in 1 million neonatal deaths annually (Lawn et al. 2013). The UN-led Every Woman Every Child initiative aims to halve preterm-related neonatal deaths between 2010 and 2025 (Lawn et al. 2013) while the 2014 WHO and UNICEF Every Newborn Action Plan (Mason et al. 2014) lists the care of small and ill neonates in its five-point action plan and strongly encourages recording and tracking of preterm birth rates. Most preterm births occur at 32 to 36 weeks of gestation (84%) (Blencowe et al. 2013).

In Bangladesh, although preterm birth prevalence was not reported nationally, 11.3% of neonatal deaths were considered to be due to preterm birth (from physicians' review of verbal autopsy data) while 17.7% of babies born were reported by mothers as 'very small' or 'smaller than average' at birth (NIPORT et al. 2013). Other studies from Bangladesh present preterm birth rates from 14.0% to 22.3% (Shah et al. 2014; Baqui et al. 2013; Kusiako et al. 2000; Blencowe et al. 2012) with a rate of 14.8% seen in Matlab in recent years (Rahman et al. 2011).

These figures attest to the high burden and the need to reduce preterm births in Bangladesh and Matlab, the site where the research for this chapter is based.

Preterm births are defined by WHO as any birth before 37 completed weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period (LMP) (World Health Organization 1977). Preterm births are divided into: extremely pre-term (<28 weeks), very pre-term (28 to <32 weeks), moderate pre-term (32 to <34 weeks) and late pre-term (34 to <37 weeks) births (Figure 5.1) (Blencowe et al. 2012; Katz et al. 2013a).

Figure 5.1 shows the timing for the different categories of preterm births in relation to the 40+ week pregnancy period, and to the definitions for early (≥ 22 weeks) and late (>28 weeks) stillbirths (Blencowe et al. 2012). There are definitional and measurement issues associated with the variation in cut-offs of lower limits for preterm births (20-28 weeks) and stillbirths (18-28 weeks and even 16-28 weeks (Froen et al. 2009)) and because of differences in perceptions of viability for preterm births in low-income and high-income countries (LICs and HICs) (Figure 1). These were discussed in detail earlier in Chapter 2.



*Source: Blencowe et al 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet.2012;10:2162–2172

Figure 5.1: An overview of the definitions and the variable cut-offs applied to preterm births in relation to pregnancy and stillbirths.*Source: (Blencowe et al. 2012)

Chapter 5. Preterm births in Matlab

The dearth of knowledge on the causes and mechanisms of preterm births, and the information available on possible contributory risk factors for preterm births were discussed earlier (Chapter 2).

It is thought that three-quarters of preterm deaths (32 to 36 weeks) could be prevented by basic essential newborn care without the need for neonatal intensive care (Blencowe et al. 2013; Lawn et al. 2013; Morken 2012). Because of the large numbers of preterm babies at 34-36 weeks among preterm babies, these babies are likely to have the greatest public health impact and are of importance in planning interventions such as Kangaroo Mother Care (KMC), essential newborn care and care of the moderate preterm baby (Blencowe et al. 2013). However, the evidence for these interventions is only based on a few studies.

The most recent evidence for the effect of interventions on preterm births has been presented by the Lancet Every Newborn series review (Bhutta et al. 2014) described earlier (Chapter 4) which identified systematic reviews to evaluate the effect of interventions on preterm births, stillbirths, perinatal and neonatal mortality. This review suggested that some interventions might be effective at preventing preterm births or deaths from preterm birth. These were: (i) antibiotics for lower genital tract infections (ii) maternal calcium supplements for hypertension (iii) low-dose aspirin in pregnant women (iv) antenatal corticosteroids and (v) care of the preterm baby including KMC. The reviews discussed here are included in the Bhutta et al. review unless specified otherwise.

(i) A Cochrane review (Swadpanich et al. 2008) evaluated the effect of lower genital tract infection screening and management on preterm births and low birth weight. Infections included bacterial vaginosis, trichomonas and candidiasis. Routine antibiotics were administered before 20 weeks' pregnancy. Only one non-hospital based RCT from antenatal clinics in Austria was eligible and showed a 45% reduction (95%CI: 25-61%) in preterm births. This study was reported to be of 'high' quality. Another Cochrane review of nine RCTs from HICs and LMICs (Thinkhamrop et al. 2002) found that administering prophylactic antibiotics during the second and third trimester of pregnancy versus no treatment or placebo had no effect on preterm delivery (RR-0.96; 95%CI: 0.7- 1.33; 6 studies). It did, however, reduce the risk of preterm pre-labour rupture of membranes (pPROM). The quality of the studies was considered 'satisfactory' but authors suggested that the sample size in one sub-group of women in the preterm birth sample might not have been large enough to demonstrate differences. Possible reasons why antibiotics might not prevent preterm births are that antibiotics may not effectively treat or prevent chorioamnionitis and that other factors (diet ,

smoking and genetic variations in inflammatory responses) might affect risks of infection-related preterm birth regardless of antibiotic usage (Iams et al. 2008)

(ii)A systematic review on the effect of balanced protein energy supplementation on birth outcomes in countries in HICs and LMICs showed no effect on the risk of preterm birth (RR-0.96; 95%CI: 0.80-1.16; 6 studies) (Imdad & Bhutta 2012b). Another review by the same authors of maternal calcium supplementation for hypertension (Imdad & Bhutta 2012a) showed a 34% (95%CI:3-40%; 11 studies) reduction in preterm births in 15 RCTs from HICs and LMICs when calcium supplements (0.5-2g/day) were taken till delivery. The methodological quality of the studies was not reported.

(iii) In the Bhutta et al. study a Cochrane review and meta-analysis of RCTs (Duley et al. 2007) showed that anti-platelet drugs (low-dose aspirin with or without other antiplatelet drugs) given to women at risk of pre-eclampsia reduced preterm birth reduction of 8% (95%CI: 3-12%; 29 studies). The authors reported that the quality of the studies varied from 'poor' to 'high'.

(iv) In HICs antenatal steroids have been given to women at risk of preterm labour to accelerate foetal lung maturity since the 1990s (Roberts & Dalziel 2006) but this is not routine practice in LICs where only 5-10% of eligible mothers receive treatment (Requejo et al. 2013). Though the Bhutta et al. 2014 review could not identify any reviews or studies assessing the effect of steroids on preterm birth itself, 44 studies in several reviews, including one Cochrane review (Roberts & Dalziel 2006), assessed the effect on neonatal morbidity and mortality of giving antenatal steroids to mothers at risk of preterm labour. Neonatal mortality among preterm babies (<36 weeks) was reduced by 31% (95%CI: 19 -42%) in the Cochrane review of 18 studies, 14 of which were in HICs. The control group in HICs was routine care (ventilation and surfactant) while in LICs it was little or no medical care. Studies were reported to be of 'high' quality and antenatal steroids were recommended for scale-up in LICs.

Another review (Cousens et al. 2010), which updated a previous Cochrane review, identified 18 RCTs, mostly from HICs, which evaluated antibiotic usage (given alone or combined with antenatal steroids and surfactant) for premature preterm rupture of membranes (pPROM). Although a non-significant reduction of 10% in neonatal mortality (RR-0.9; 95%CI: 0.7-1.1; 15 studies) was observed, significant reductions in respiratory distress (12%) and post-natal infection (39%) were seen. Studies were of 'low' quality for neonatal mortality reduction and 'low to moderate' for morbidity. In LICs where other interventions (steroids, surfactants, ventilation and antibiotic therapy) are limited, antibiotics for pPROM could be useful.

(v) In a 2004 review, Bhutta et al. 2014 found little evidence for the effectiveness of hospital-based care packages for care of ill or preterm infants in high, middle and low income countries as the focus is on trials for single interventions. However, the authors conducted a Delphi consultation of 27 experts which suggested that packages of secondary level hospital (KMC, warmth, feeding/fluids, oxygen and management of infections/jaundice) and tertiary level hospital care (surfactant, positive airway pressure and ventilation) could prevent 70% and 90% respectively of preterm-related deaths. However, it is not known whether expert opinion consensus is a valid measure of evidence of an intervention. A Cochrane systematic review (Conde-Agudelo et al. 2011) and meta-analysis of seven RCTs in LICs and HICs described earlier (Chapter 4) found 40% (95%CI:7-61%) lower mortality at discharge or at 40-41 weeks for LBW babies receiving KMC than those receiving conventional care. In another review (Lawn et al. 2010) that assumed that babies <2000g were preterm (~ 32-34 weeks gestation), and where KMC was started within a week of birth, meta-analysis results from three RCTs in hospitals in Colombia, India and Ethiopia showed that KMC was associated with 51% reduced neonatal mortality (95%CI:18-72%; 3 studies) in these preterm births compared to conventional care (incubator or more limited care). Although both these reviews supported the use of KMC in LBW babies in resource-limited settings, it was acknowledged that this type of care was not available at scaled-up levels in LICs.

An earlier report on preterm births, The Born Too Soon report (Howson et al. 2012) suggested interventions for the preconception period, and for the pregnancy and labour period that could possibly reduce preterm births. In the preconception period interventions suggested were: prevention of adolescent and unintended pregnancies, optimal birth-spacing, optimization of pre-pregnancy weight, nutrition promotion and micronutrient supplementation, rubella vaccination and screening/management of mental health issues, STIs and chronic diseases (diabetes, hypertension and anaemia). Interventions suggested for the pregnancy period were: basic antenatal care packages for all women which included treatment of infections (e.g. tuberculosis, malaria, bacterial vaginosis and bacteraemia); screening of women at risk of preterm births, including those with previous preterm births, multiple pregnancies, cervical anomalies and pregnancy disorders (e.g. diabetes, hypertension, bleeding); maternal calcium supplementation for hypertension; vaginal progesterone; maternal antenatal corticosteroids; and antibiotics for pPROM. For women who were in preterm labour, the use of tocolytic drugs (which inhibit uterine contractions) was suggested. However the absence or very low use of antenatal corticosteroids, vaginal progesterone,

cervical cerclage and tocolytics in LICs was acknowledged along with the paucity of research on the effect of these interventions within packages (Howson et al. 2012).However though interventions are recommended, the evidence of the effect of specific interventions (e.g. antenatal corticosteroids, progesterone, tocolytics and cervical cerclage) and prenatal care in low-risk and high-risk women on reducing the risk of preterm births is mixed and highlights the need for further studies (Iams et al. 2008).

Interventions suggested by the United Nations to reduce preterm birth mortality involve four high impact low-coverage commodities: antenatal corticosteroids, chlorhexidine cord care, resuscitation devices and injectable antibiotics (Lawn et al. 2013). These are currently unavailable at scaled-up levels and the current levels are not considered to be effective in LICs (Lawn et al. 2013). Moreover, as mentioned earlier (section 2.2) antenatal corticosteroids are controversial (Azad et al. 2014) and when given to women at risk of preterm births, have resulted in increased risk of neonatal deaths (Althabe et al. 2015).

Information on the prevalence of preterm births in Bangladesh is drawn from very few studies and includes modelled estimates. The evidence from available studies is described here. In the majority of these studies stillbirths are excluded and preterm birth status of these stillbirths is unknown.

The most recent national, regional and country estimates for preterm births were obtained for 2010 by a number of research institutes including WHO (Blencowe et al. 2012). The preterm birth prevalence estimate for Bangladesh for 2010 was estimated at 14.0% of live births. This figure was obtained from a statistical model based on preterm birth data from three published studies (Kusiako et al. 2000; Arifeen et al. 2000; Klemm et al. 2008) and one unpublished study from Bangladesh, which are described further below.

The most recent estimate from a study using empirical data was from an RCT which took place between 2007 and 2009 in three districts of rural Sylhet and compared two regimens of umbilical cord cleansing in women receiving maternal and newborn interventions (Shah et al. 2014). The preterm (≥28 and <37 completed weeks) birth prevalence was found to be 22.3% among the 32,126 live births in the study (including multiple births) for whom LMP dates were known. Gestational age was prospectively ascertained by women's recall of LMP date in 2-monthly home visits. Stillbirths were excluded from the study.

In an earlier population and earlier time period (2004-2005) in the same study area as Shah et al. (2014), an RCT provided maternal and newborn interventions (Baqui et al. 2013).This study estimated the burden of preterm births (≥28 and <37 completed weeks) among 10,585 live births including multiple births in one of the RCT intervention arms which received interventions at home. Gestational age was prospectively ascertained as in Shah et al. (2014) The preterm prevalence of 19.4% for 2004-2005 excluded stillbirths and so might not be considered representative of the total population at risk for preterm birth.

Another randomised controlled trial (Klemm et al. 2008) compared newborn vitamin A supplements versus placebo in rural areas of northwest Bangladesh and found a preterm birth (<37 weeks) prevalence of 23.3% for 2005 among all the 15937 live births in the trial. In this study gestational age was assessed prospectively by LMP date recall in 5 weekly home visits to identify pregnant women (twins were included).

A Matlab retrospective cohort study (Kusiako et al. 2000) investigated the role of labour complications in perinatal deaths and preterm births (≥28 and <37 completed weeks or <259 days), between 1987 and 1993, in an area covered by a Safe Motherhood (maternity care) Programme. Gestational age was determined prospectively from women recalling LMP dates in routine monthly home visits by CHWs. Preterm birth prevalence was found to be 20.0% among 3865 births (live births and stillbirths) between 1987-1993 in the study. In this study, analyses performed with and without twins did not alter the findings. Preterm birth prevalence was also found to be similar in women delivering at home and those delivering with a midwife.

Another prospective cohort study between 1993 and 1995 which studied infant growth patterns in urban slums in Dhaka city (Arifeen et al. 2000), obtained a preterm (<37 completed weeks) birth prevalence of 16.8% for 1994 among the 1654 singleton live births enrolled into the study. Gestational age was assessed for the majority of live births by the LMP method and by newborn examination for the remainder (15%).

A preterm birth prevalence of 8.7% for 2006 in a rural area in Parbatipur sub-district in Northern Bangladesh was reported by Blencowe et al. (2012) from unpublished data (Day, LAMB hospital). Information on gestational age assessment method and whether or not stillbirths or multiple births were included was not given.

Although the national Demographic and Health Survey of Bangladesh (BDHS 2011) did not report preterm birth prevalence from gestational age assessment, women self-ascertained that for the 5 years preceding the survey, 17.7% of babies born were 'very small' or 'smaller than average' at birth (NIPORT 2013). However self-ascertainment of size at birth cannot be considered a valid estimate of preterm birth and 'small size' at birth may also be seen because of intrauterine growth retardation of term babies.

The evidence for prevalence for preterm births in Bangladesh was obtained from a few sub-national studies where the denominator in the vast majority of the prevalence estimates excludes stillbirths. National estimates are from statistical models or self-ascertainment by women. This suggests that further work is necessary in the measurement of true preterm birth prevalence in Bangladesh which includes all prospectively ascertained pregnancies and births and takes into account stillbirths as well as live births.
The relationship between lower gestational age at birth and increased mortality has been documented before (Katz et al. 2013a; Kramer 2000; Copper et al. 1993). However, there is very little information on whether the relationship between gestational age and mortality is similar for stillbirths, early and late neonatal deaths and within the early neonatal time period for a single population. The higher mortality seen in preterm babies arises from the fact that preterm babies are more likely than term babies to develop serious and deadly complications such as respiratory distress syndrome, brain haemorrhage, necrotizing enterocolitis (severe infection of the bowels). Pre-term babies often have poorer immunity, leading to episodes of pneumonia, sepsis and meningitis (Fraser et al. 2004; Behrman & Butler 2007; Saigal & Doyle 2008). In low-resource countries, such as Bangladesh, where intensive care units are scarce and access is limited, better access to basic essential newborn care coupled with early identification and immediate treatment with appropriate drugs is needed to prevent these deaths.

The measurement of preterm births is complex for many reasons: variations in definitions of preterm birth, stillbirth/preterm birth misclassification, inclusion of stillbirths and multiple pregnancies and gestational age assessment (Blencowe et al. 2013). All issues except gestational age assessment have been discussed before (Chapter 2).

Variations in gestational age can occur because of multiple methods of assessment: early first trimester ultrasound (gold standard), uterine fundal height, LMP date method (most widely used), birth weight as a surrogate for gestational age (preterm birth is equivalent to birth

weight ≤ 2500g), newborn examination (from skin texture, wrist flexion and other signs) and best obstetric estimate (based on combination of LMP date method, fundal height measurement and ultrasound (Engle 2004)). LMP-based gestational ages can be relatively imprecise because of (i) variation of the menstrual cycle (ii) conception occurring up to several days after ovulation and not on the same day as assumed by this method and (iii) error in recalling LMP date (Kramer et al. 2012). Ultrasound based gestational ages are 2-3 days shorter than LMP-based ages (corresponding to ovulation on Day 16-17 vs. Day 14) and yield higher rates of preterm births (Kramer et al. 2012; Yang et al. 2002). Ultrasound itself is not an error-free method as, together with errors from insufficient standardization and quality control of the operators, it assumes that all foetuses with the same measurements are of the same gestational age and so does not account for growth differences between foetuses (Kramer et al. 2012; Morin et al. 2005). These methods can all lead to differences in gestational age (Kramer et al. 2012) and therefore in the numbers of births recorded as preterm.

The determinants of preterm births for LICs are not well known, and very few studies have quantified preterm birth burden in these countries with accurate gestational age measurements and even fewer with time trend data (Howson et al. 2012; Beck et al. 2010; Chang et al. 2013). Little information is available on the effect of preterm births on stillbirths and on the continnuum of mortality outcomes in the neonatal period. There is an urgent global need for research on the effect of packages of effective interventions on preterm births. Few interventions effective for preterm birth reduction are used in LICs and the evidence for most interventions used in LICs and HICs is based on a few studies. Recent recommendations include calls for high quality research on understanding reasons for low coverage and the adaptation of effective strategies for reducing preterm births (Lawn et al. 2013; Behrman & Butler 2007).

This study has access to a large sample of population based data with good prospective measurement of LMP date for the last 5 years. Demographic surveillance sites with recording of background characteristics and pregnancy registration are important data sources for preterm births and stillbirths (Lawn et al. 2010). Matlab is one of the few INDEPTH sites recording stillbirths (Lawn et al. 2010). This study with its Safe Motherhood Programme operating alongside an adjacent area of government services provides important opportunities to explore the burden of, and context-specific trends in, preterm birth prevalence in rural Bangladesh.

5.2 Objectives

Overall Objective

The overall objective is to examine the contribution of preterm births to stillbirths and neonatal deaths in a rural cohort in Matlab, Bangladesh between 2005 and 2009.

Specific Objectives

1) To examine the distribution of gestational age at birth and the distribution of preterm births in a rural cohort in Matlab, Bangladesh.

2) To examine the socio-demographic determinants of preterm births in Matlab. The socio-demographic determinants to be examined will be:
   viii. Year of birth
   ix. Area of residence
   x. Maternal formal education
   xi. Household asset quintile
   xii. Religion
   xiii. Maternal age
   xiv. Gravidity

3) To examine the association between gestational age and stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths.

4) To examine whether there are any differences in preterm birth rates in the two areas (with and without the Safe Motherhood Programme) over time and if so, whether the differences are explained by the socio-demographic changes taking place in Matlab over the study period.

5) To measure the contribution of preterm births to stillbirths, early neonatal deaths, specific day-wise early neonatal deaths and late neonatal deaths by calculating the population attributable risk percentage of preterm births for these mortality outcomes.

5.3 Methods

5.3.1 Study design

This is a retrospective cohort study of all women living in the ICDDR,B service area and the Government service area in rural Matlab, Bangladesh who had pregnancies ending in a live birth or a stillbirth between 1st January 2005 and 31st December 2009.

5.3.2 Data sources, collection and quality:

The Matlab Demographic and health surveillance programme has been described extensively in Chapter 4 (section 4.3).

Information on the data source, collection and data quality for the LMP date (which will be used to measure gestational age) has not been covered in Chapter 4 and hence this is detailed here.

5.3.3 Definitions and categorization of variables:

LMP date

The LMP (last menstrual period) date is the first day of the last menstrual period as reported by the mother to the CHRW (community health research worker) on her monthly/bimonthly visit to the woman's home. The LMP date has been routinely collected from all women in both the ICDDR,B and Government service areas since 2005 in monthly CHRW home visits. Before 2005 LMP date collection was absent in the Government service area and not routinely collected during CHRW visits in the ICDDR,B service area. Since 2007 these home visits have taken place every two months. CHRWs asked women if they had menstruated since the last visit and if so, they were asked to recall the date of the first day of the last menstrual period which was noted down. A woman was considered to be pregnant if she reported a non-menstruation period of 6-weeks to the CHRW and from 2007 (ICDDR,B service area) and 2010 (Government service area) pregnancies were confirmed by CHRWs performing on-site urine strip-tests.

Gestational age and gestational age categories

I calculated gestational age in days by deducting the date of birth from the date of the last menstrual period and dividing by 7 to obtain the gestational age at birth in weeks. Gestational ages that were improbable (0-21 weeks and 46-94 weeks; section 5.4.1) were considered to be outliers and removed from the final sample. I decided that the range for probable gestational

age was from 22- 45 weeks. I chose the 22-week cut-off to include extremely preterm stillbirths and live births and to exclude early foetal losses which are considered to occur until the widely accepted upper limit of 21 completed weeks. I set the upper gestational age limit as 45 weeks because, according to Mongelli et al., 99% of all births calculated by LMP are delivered by 44 weeks and 5 days (45 weeks) while 99% of all pregnancies dated by ultrasonography are delivered by 42 weeks and 2 days (Mongelli et al. 1996). As I use LMP dating in my study, a 45-week upper limit would ensure inclusion of all births.

Preterm births

I considered preterm births to be those occurring at a gestational age of 22 to 36 completed weeks, i.e. less than 259 days. This was based on preterm birth definitions according to WHO and current usage in scientific and clinical research (World Health Organization 2013; Blencowe et al. 2012; Howson et al. 2012; Lawn, Gravett, et al. 2010). The terminology used (Blencowe et al. 2012; Howson et al. 2012; Katz et al. 2013a) for various gestational age groups is shown below in Table 5.1.

Table 5.1: Birth categories according to gestational age group (weeks)

Birth type	**Gestational age group (weeks)**
Extremely preterm	22-27
Very preterm	28-31
Moderate preterm	32-33
Late preterm	34-36
Term	37-41
Post-term	42-45

I considered preterm birth prevalence to be:

$$\text{Preterm birth prevalence} = \frac{\boldsymbol{the\ number\ of\ pre\ term\ births}}{\boldsymbol{all\ \ stillbirths\ and\ livebirths\ (22\ weeks\ onwards)}} \times \mathbf{100}$$

Birth outcomes and mortality outcomes

I consider birth outcomes to mean live births and stillbirths. I consider mortality outcomes to include stillbirths, early neonatal deaths, late neonatal deaths and day-wise early neonatal deaths (Day 0, Day 1 to 2 and Day 3 to 6 deaths).

Population attributable risk percent

The population attributable risk percent (PAR%) of preterm births is the percentage of deaths in the Matlab study population that is attributable to babies being born preterm (and potentially could be eliminated if preterm births were eliminated).

This is calculated by:

Population attributable risk percent (PAR%) = $\frac{aOR-1}{aOR+\frac{1}{P_e}-1} x100$

where,

aOR (adjusted odds ratio) is the odds of death in preterm births (exposed individuals) divided by the odds of death in term babies (unexposed individuals) adjusted for confounders.

P_e is the proportion of preterm birth among the population at risk. This is different for different mortality outcomes: for example to calculate the PAR% of preterm births among early neonatal deaths, I used the proportion of preterm births among all live births, as live births are the exposed population. The different P_e appropriate for the different mortality outcomes is shown in Table 5.2 below.

Table 5.2: The different proportion of preterm births among population at risk (Pe) for calculation of population attributable risk percentage of preterm births for all mortality outcomes in Matlab.

Mortality outcome	**Population at risk of preterm birth**	**Proportion of population exposed, P_e (proportion of preterm births among population at risk)**
Stillbirths	Births (stillbirths and live births)	preterm births, *n* / births, *n*
Early neonatal deaths	Live births	preterm births, *n* / live births, *n*
Late neonatal deaths	Babies alive at Day 7	preterm births, *n* / babies alive at Day 7 , *n*
Day 0 deaths	Live births	preterm births, *n* / live births, *n*
Day 1 to 2 deaths	Babies alive at Day 1	preterm births, *n* / babies alive at Day 1 , *n*
Day 3 to 6 deaths	Babies alive at Day 3	preterm births, *n* / babies alive at Day 3 , *n*

5.3.4 Data Analysis:

The study included live births and stillbirths from 1st January 2005 to 31st Dec 2009 to women registered in the Matlab surveillance area. The dataset I used for this analysis is a sub-set of the 1987-2009 birth dataset used earlier (Chapter 4). The unit of analysis for this study was deliveries rather than births as detailed in section 4.3.13. All exposures and outcomes were as defined in Chapter 4.

I tabulated birth outcomes and mortality outcomes for all births by gestational age.

I provided graphical presentations for: the annual preterm birth prevalence from 2005 to 2009 for the ICDDR,B and Government service areas, the overall prevalence in the two areas, and the preterm birth prevalence found from other Bangladesh studies.

I calculated odds ratios for the association between socio-demographic exposures and preterm births using logistic regression. I adjusted for birth clustering by using a random effects logistic regression model, as children born to the same mother during the study time period were likely to have similar exposure and outcomes compared to children of other mothers. I presented crude and adjusted odds ratios. I also used logistic regression to examine the association between preterm births and six mortality outcomes. I assessed for confounders as described in Chapter 4. I did not adjust for multiple hypotheses testing in my analyses but do acknowledge that with many statistical significance tests there is the risk of false positive significances just by chance and so was wary of over-interpreting borderline significant results.

I plotted the strength of association found between preterm births and mortality outcomes in Matlab with other estimates found in the literature.

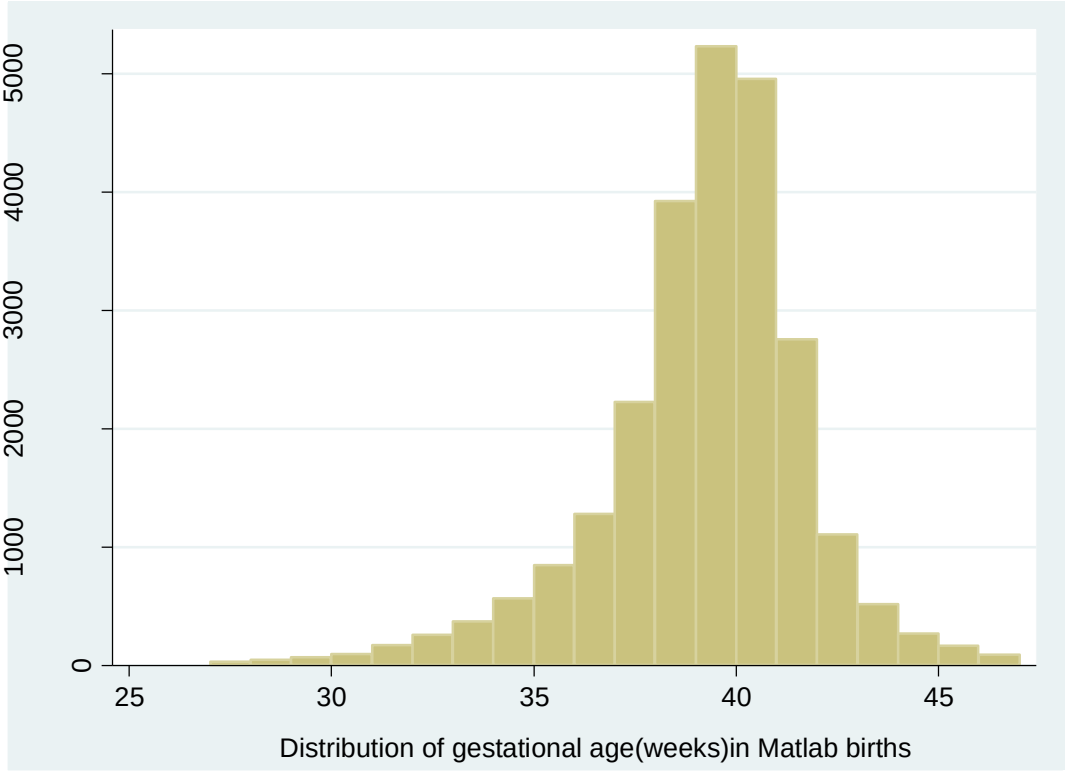
I tested for interaction between year of birth and area of birth to see whether trends over time for preterm births varied by area. Interaction was tested by modelling time as a) a categorical variable and b) as a continuous variable in the logistic regression models.

Finally, I calculated the population attributable risk percentage of preterm birth for the six mortality outcomes.

5.4 Results

5.4.1 Description of study sample

There were 25,438 births between 2005 and 2009 in Matlab. Gestational age was missing for 54 births (0.21% of all births). Of the 25,384 births of known gestational age, very few had births with unrealistic outlier gestational ages (0-21 weeks and 46-99 weeks) (112 [0.44%] and 234 [0.92%], respectively). The final sample consisted of 25,038 births ranging from 22 to 45 weeks (Figure 5.2). Median and mean gestational ages were 39.4 weeks and 39.0 weeks, respectively.



*Gestational ages were missing for 54 births

Figure 5.2: The distribution of gestational ages in Matlab (2005-2009) for 25,384 births of known gestational age*

5.4.2 Prevalence of preterm births

There were 3855 preterm births (22 – 36 weeks) in Matlab between 2005 and 2009. Preterm birth prevalence was 15.5% among all births. The largest contribution to preterm births was from late preterm births (68.5%) (Table 5.3), while moderate preterm and very preterm contributed a quarter of the total (17.3% and 11.2% respectively) and extremely preterm births were rare (3.0%).

Table 5.3 : Distribution of births and preterm births according to gestational age groups in 25038 births in Matlab (2005-2009)

	Gestational age group (weeks)	Number (n)	Prevalence (%)*
Births			
Extremely preterm	22-27	115	0.46
Very preterm	28-31	431	1.72
Moderate preterm	32-33	667	2.66
Late preterm	34-36	2,642	10.55
Term	37-41	19,105	76.3
Post-term	42-45	2,078	8.3
Total	22-45	25,038	100
Preterm births			
Extremely preterm	22-27	115	3.0
Very preterm	28-31	431	11.2
Moderate preterm	32-33	667	17.3
Late preterm	34-36	2,642	68.5
Total	22-36	3,855	100.0

*may not add up to 100 because of rounding

5.4.3 Preterm birth prevalence over time

Overall the prevalence of preterm births declined from 17.0% in 2005 to 13.8% in 2009 (3.2% reduction). In the Government service area prevalence reduced from 17.4% to 14.8% (2.6% reduction), while in the ICDDR,B service area the reduction was from 16.6% to 12.8% (3.8% reduction) (Figure 5.3). The largest decline was found among late preterm births in both areas (Figure 5.4).

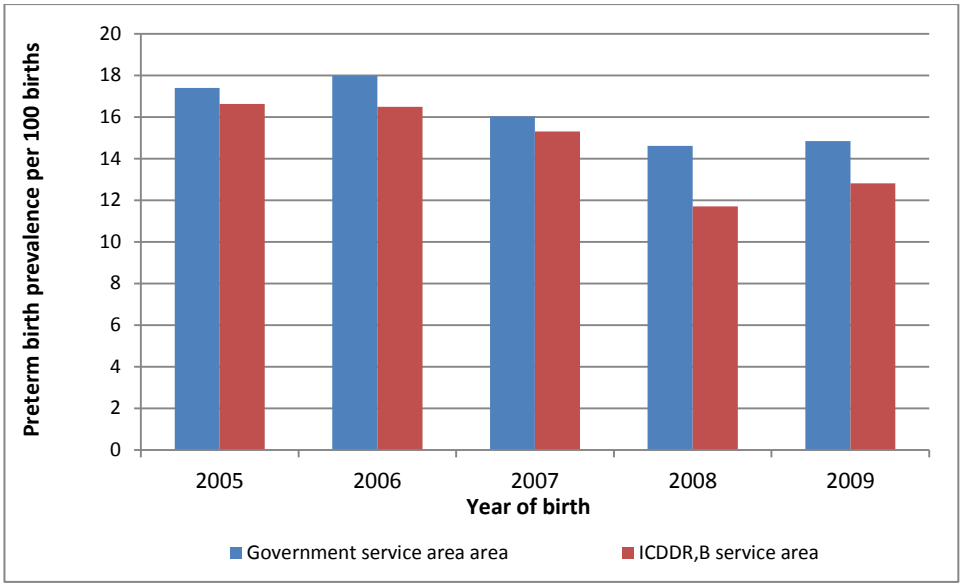


Figure 5.3: Annual prevalence for preterm births (n=3855) in 25038 births in the Government service area and the ICDDR,B service area in Matlab (2005-2009).

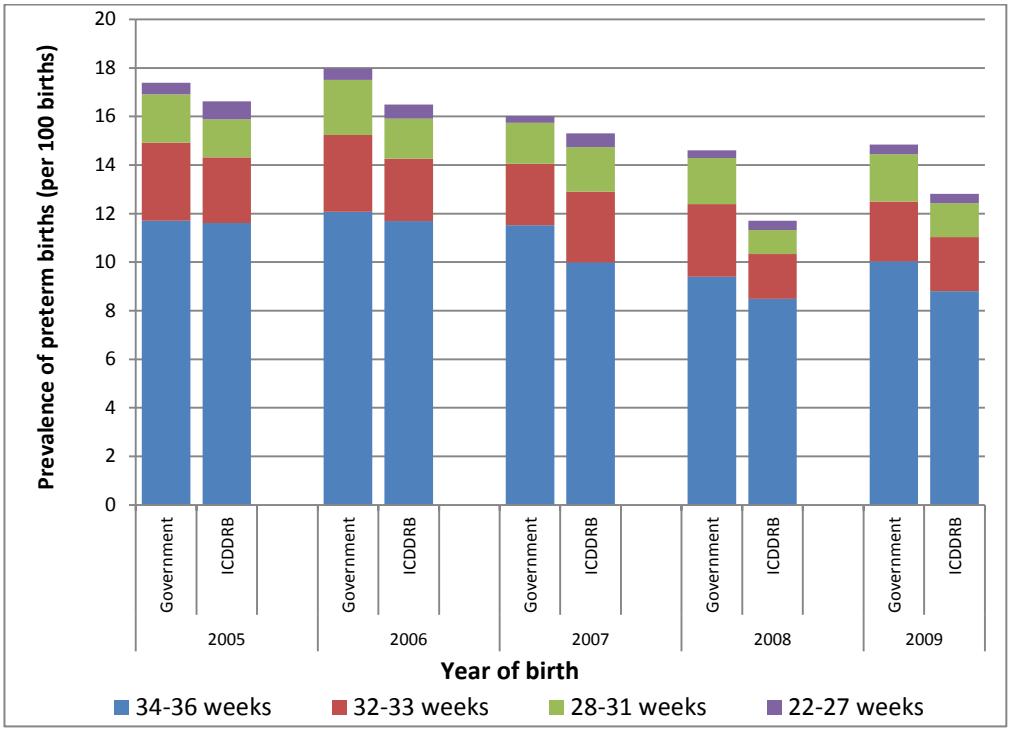


Figure 5.4: Annual prevalence for preterm births by gestational age group for preterm births (n=3855) in 25,038 births in the Government service area and the ICDDR,B service area in Matlab (2005-2009)

.

5.4.4 Association between socio-demographic characteristics and preterm births

Table 5.4 shows the prevalence of preterm births among socio-demographic categories, as well as crude and adjusted odds ratios of the association between preterm births and socio-demographic factors.

Overall, preterm births declined over time but not uniformly. In 2006 the odds of preterm births were no lower than in 2005 (adjusted OR-1.01; 95% CI: 0.79-1.09) and although a decline in preterm births was observed in 2007 compared to 2005 (adjusted OR-0.90; 95%CI: 0.78-0.99) this 10% reduction in odds was not significant. In 2008 and 2009, odds of preterm births were 29% and 33% lower than in 2005 (adjusted ORs: 0.71; 95%CI: 0.63-0.81 and 0.67; 95%CI: 0.68-0.88) and the results were highly statistically significant (p values <0.0001) suggesting that most of the reduction occurred in the latter years of the study.

Preterm rates were lower in the ICDDR,B service area than the Government service area (14.6 /100 births vs. 16.2/100 births) and this difference was significant (adjusted OR-0.91; 95%CI:0.85-0.99, p=0.03)

Preterm births decreased dramatically with increasing levels of formal education, from 20.0% in women with 0 years of schooling to 10.3% in women with 11-16 years of schooling (p<0.0001). Similarly, preterm birth prevalence also decreased with increased household asset quintiles declining from 20.5% in the most poor quintile to 11.9% in the least poor quintile (p<0.0001).

After adjusting for socio-demographic variables, no change was seen in the odds ratios over time.

I tested an interaction between area of birth and time, using time as a continuous variable (Table 5.5) and as a categorical variable (Table 5.6). Table 5.5 shows that the annual decline in preterm births was rapid in both areas (declining by 11% and 7% per year in the ICDDR,B and Government service areas respectively), and the interaction between time and area was non-significant (likelihood ratio test p=0.214) providing no evidence that the pace of decline was different in the two areas. From Table 5.6 it can be seen that the yearly trends in preterm birth decline reached significance only from 2008 onwards. This decline was seen in the Government area as well as the ICDDR,B service area and there was no difference in the magnitude of decline between the two areas (likelihood ratio test p=0.554) (Table 5.6).

Table 5.4: Preterm births (22 to 36 completed weeks' gestational age at birth) according to time, area and socio-demographic characteristics of women in 25,038 births in Matlab (2005-2009).

Socio-demographic characteristics	Number of births (Number of preterm births)	Preterm births per 100 births	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs[a b] (95 % CI)	P-values (Wald test)
Year of Birth						
2005	4240 (869)	17.0	1.00	_	1.00	_
2006	4270 (889)	17.2	1.02 (0.90-1.14)	0.803	1.01 (0.79-1.09)	0.910
2007	4249 (789)	15.7	0.89 (0.79-1.01)	0.062	0.90 (0.78-0.99)	0.068
2008	4387 (662)	13.1	0.71 (0.63-0.80)	<0.0001	0.71 (0.63-0.81)	<0.0001
2009	4038 (646)	13.8	0.76 (0.67-0.86)	<0.0001	0.67 (0.58-0.88)	<0.0001
Area of Residence						
ICDDR,B Service Area	12693 (1853)	14.6	0.87 (0.81-0.94)	0.001	0.91 (0.85-0.99)	0.032
Government Service Area (Reference)	12345 (2002)	16.2	1.00	_	1.00	_
Maternal formal education (completed years)						
0 (Reference)	4712 (944)	20.0	1.00	_	1.00	_
1-5	6375 (1085)	17.0	0.79 (0.71-0.89)	<0.0001	0.93 (0.83-1.04)	0.221
6-10	12862 (1698)	13.2	0.57 (0.51-0.63)	<0.0001	0.83 (0.74-0.93)	0.002
11-16	1037 (107)	10.3	0.42 (0.33-0.53)	<0.0001	0.67 (0.52-0.86)	0.002
Unknown	52 (21)	40.4	3.19 (1.63-6.27)	0.001	1.82 (0.92-3.59)	0.084
Household asset quintile						
Most poor (Reference)	3606 (740)	20.5	1.00	_	1.00	_
Very poor	4221 (729)	17.3	0.79 (0.69-0.90)	<0.0001	0.84 (0.74-0.96)	0.009
Poor	4336 (694)	16.0	0.70 (0.62-0.81)	<0.0001	0.80 (0.70-0.92)	0.001
Less poor	4950 (666)	13.5	0.57 (0.50-0.65)	<0.0001	0.67 (0.59-0.77)	<0.0001
Least poor	5475 (649)	11.9	0.48 (0.42-0.55)	<0.0001	0.61 (0.52-0.70)	<0.0001
Unknown	2450 (377)	15.4	0.67 (0.58-0.79)	<0.0001	0.85 (0.72-0.99)	0.051
Religion						
Islam (Reference)	22388 (3500)	15.6	1.00		1.00	_
Hinduism/Other	2650 (355)	13.4	0.82 (0.72-0.93)	0.003	0.81 (0.71-0.93)	0.002
Maternal Age						
<20	3314 (463)	14.0	1.00 (0.89-1.13)	0.992000	1.12(0.98-1.28)	0.098
20- 29 (Reference)	14993 (2087)	13.9	1.00	_	1.00	_
30-39	6221 (1141)	18.3	1.44 (1.32-1.58)	<0.0001	1.11 (1.00-1.24)	0.052
40+	510 (164)	32.2	3.41 (2.71-4.31)	<0.0001	2.04 (1.58-2.63)	<0.0001
Gravidity						
1	8048 (1019)	14.6	0.84 (0.77-0.93)	<0.0001	0.87 (0.78-0.97)	0.015
2-3 (Reference)	11348 (1654)	12.7	1.00	_	1.00	_
4-6	4996 (987)	19.8	1.51 (1.35-1.64)	<0.0001	1.21 (1.08-1.36)	0.001
7+	646 (195)	30.2	2.86 (2.39-3.62)	<0.0001	1.76 (1.39-2.23)	<0.0001
All	25038 (3855)	15.4				

[a]All odds ratios are adjusted for clustering of births to the same mother
[b]Adjusted for year of birth, area of residence, maternal education, asset quintile, religion, maternal age and gravidity

Table 5.5: Annual trends in preterm births in the ICDDR,B and Government service areas in Matlab (2005-2009).

	Crude odds ratio (95% CI)	p-value (Wald test)	Adjusted odds ratio* (95% CI)	p-value (Wald test)	p-value for interaction between time and area of residence
Annual trend of preterm births (2005-2009)					
ICDDR,B service area	0.89 (0.85-0.93)	<0.0001	0.90 (0.86-0.93)	<0.0001	0.214
Government service area	0.93 (0.89-0.96)	<0.0001	0.93 (0.89-0.96)	<0.0001	

*adjusted for: maternal education, household asset quintile, religion, maternal age and gravidity

Table 5.6: Yearly trends in preterm births in the ICDDR,B and Government service areas in Matlab (2005-2009).

	Crude odds ratio (95% CI)	p-value (Wald test)	Adjusted odds ratio* (95% CI)	p-value (Wald test)	p-value for interaction between time and area of residence
Yearly trend of preterm births					
2005 (reference year)					0.554
ICDDR,B service area	1.00	_	1.00	_	
Government service area	1.00	_	1.00	_	
2006					
ICDDR,B service area	0.99 (0.83-1.17)	0.879	0.99 (0.84-1.17)	0.918	
Government service area	1.02 (0.87-1.20)	0.775	1.01 (0.86-1.18)	0.92	
2007					
ICDDR,B service area	0.87 (0.73-1.03)	0.102	0.88 (0.74-1.05)	0.144	
Government service area	0.89 (0.76-1.05)	0.157	0.89 (0.76-1.04)	0.149	
2008					
ICDDR,B service area	0.63 (0.52-0.76)	<0.0001	0.64 (0.53-0.77)	<0.0001	
Government service area	0.78 (0.66-0.92)	0.003	0.78 (0.66-0.92)	0.003	
2009					
ICDDR,B service area	0.70 (0.58-0.84)	<0.0001	0.72 (0.60-0.86)	<0.0001	
Government service area	0.78 (0.66-0.92)	0.003	0.78 (0.66-0.93)	0.005	

*adjusted for: maternal education, household asset quintile, religion, maternal age and gravidity

5.4.5 Gestational age and mortality outcomes

Mortality rates according to gestational week are shown in Tables 5.7 and 5.8. Early gestational ages of 22 to 25 weeks have very few births and deaths, and the rates at these gestational ages have to be interpreted with caution.

Table 5.7: Rates for stillbirths, early neonatal deaths and late neonatal deaths according to each gestational week at birth in 25,038 births, 24, 339 live births and 23, 849 babies alive at Day 7 in Matlab (2005-2009)

	Stillbirth rate			Early neonatal death rate			Late neonatal death rate		
Gestational age (weeks)	No. of deaths	No. of births	Rate per 1000 births	No. of deaths	No. of live births	Rate per 1000 live births	No. of deaths	No. of babies alive at Day 7	Rate per 1000 babies alive at Day 7
22	0	6	0.0	1	6	166.7	0	5	0.0
23	0	10	0.0	3	10	300.0	0	7	0.0
24	0	11	0.0	2	11	181.8	0	9	0.0
25	4	20	200.0	10	16	625.0	1	6	166.7
26	3	35	85.7	15	32	468.8	2	17	117.6
27	6	33	181.8	9	27	333.3	1	18	55.6
28	10	53	188.7	17	43	395.3	1	26	38.5
29	11	70	157.1	16	59	271.2	2	43	46.5
30	7	97	72.2	14	90	155.6	4	76	52.6
31	21	174	120.7	22	153	143.8	2	131	15.3
32	30	261	114.9	18	231	77.9	8	213	37.6
33	34	377	90.2	10	343	29.2	6	333	18.0
34	24	572	42.0	20	548	36.5	5	528	9.5
35	46	853	53.9	25	807	31.0	7	782	9.0
36	51	1,283	39.8	19	1,232	15.4	5	1213	4.1
37	68	2,228	30.5	36	2,160	16.7	7	2124	3.3
38	72	3,927	18.3	48	3,855	12.5	12	3807	3.2
39	88	5,233	16.8	49	5,145	9.5	9	5096	1.8
40	91	4,958	18.4	71	4,867	14.6	10	4796	2.1
41	59	2,759	21.4	43	2,700	15.9	8	2657	3.0
42	37	1,111	33.3	21	1,074	19.6	1	1053	0.9
43	16	523	30.6	10	507	19.7	0	497	0.0
44	11	273	40.3	5	262	19.1	1	257	3.9
45	10	171	58.5	6	161	37.3	1	155	6.5
All	**699**	**25,038**	**27.9**	**490**	**24,339**	**20.1**	**93**	**23849**	**3.9**

Table 5.8: Rates for Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths according to each gestational week at birth in 24,339 live births, 24,117 babies alive at Day 1 and 23,932 babies alive at Day 3 in Matlab (2005-2009)

	Day 0 death rate			**Day 1 to 2 death rate**			**Day 3 to 6 death rate**		
Gestational age (weeks)	No. of deaths	No. of live births	Rate per 1000 live births	No. of deaths	No. of babies alive at Day 1	Rate/1000 babies alive at Day 1	No. of deaths	No. of babies alive at Day 3	Rate/1000 babies alive at Day 3
22	1	6	166.7	0	5	0.0	0	5	0.0
23	1	10	100.0	2	9	222.2	0	7	0.0
24	1	11	90.9	0	10	0.0	1	10	100.0
25	7	16	437.5	1	9	111.1	2	8	250.0
26	11	32	343.8	2	21	95.2	2	19	105.3
27	2	27	74.1	5	25	200.0	2	20	100.0
28	10	43	232.6	5	33	151.5	2	28	71.4
29	7	59	118.6	7	52	134.6	2	45	44.4
30	5	90	55.6	8	85	94.1	1	77	13.0
31	10	153	65.4	8	143	55.9	4	135	29.6
32	12	231	51.9	5	219	22.8	1	214	4.7
33	4	343	11.7	3	339	8.8	3	336	8.9
34	12	548	21.9	5	536	9.3	3	531	5.6
35	11	807	13.6	10	796	12.6	4	786	5.1
36	8	1232	6.5	4	1224	3.3	7	1220	5.7
37	13	2160	6.0	17	2147	7.9	6	2130	2.8
38	17	3855	4.4	21	3838	5.5	10	3817	2.6
39	23	5145	4.5	17	5122	3.3	9	5105	1.8
40	31	4867	6.4	29	4836	6.0	11	4807	2.3
41	19	2700	7.0	18	2681	6.7	6	2663	2.3
42	8	1074	7.4	10	1066	9.4	3	1056	2.8
43	5	507	9.9	3	502	6.0	2	499	4.0
44	1	262	3.8	2	261	7.7	2	259	7.7
45	3	161	18.6	3	158	19.0	0	155	0.0
All	**222**	**24339**	**9.1**	**185**	**24117**	**7.7**	**83**	**23932**	**3.5**

Figures 5.5 and 5.6 show the mortality rates for stillbirths, early neonatal deaths and late neonatal deaths by each gestational week at birth while Figures 5.7 and 5.8 show these mortality rates by gestational age groups.

Shorter gestational age at birth (from 25 weeks onward) was associated with higher mortality for all outcomes. Mortality rates at lower gestational age (25 weeks of gestation) were higher for early neonatal deaths (625 per 1000 live births at 25 weeks) than stillbirths and late neonatal deaths (200 per 1000 births and 167 per 1000 babies alive at Day 7) (Figure 5.5). Deaths in the first day of life were particularly high at 438 per 1000 babies alive at Day 1 at 25 weeks (Figure 5.6).

When gestational ages were grouped (Figures 5.7 and 5.8) the same pattern was seen with mortality rates decreasing with longer gestational ages. Among all mortality outcomes the highest rates were seen for early neonatal deaths (453 per 1000 live births) at 25-27 weeks while stillbirth and late neonatal death rates (148 per 1000 births and 98 per 1000 babies alive at Day 7) were also highest for children in the lowest gestational age group. First day death rates (267 per 1000 babies alive at Day 1) were also greatest at 25-27 weeks. The rates, numerators and denominator have been tabulated and shown elsewhere (Appendix III: Tables 2 and 3).

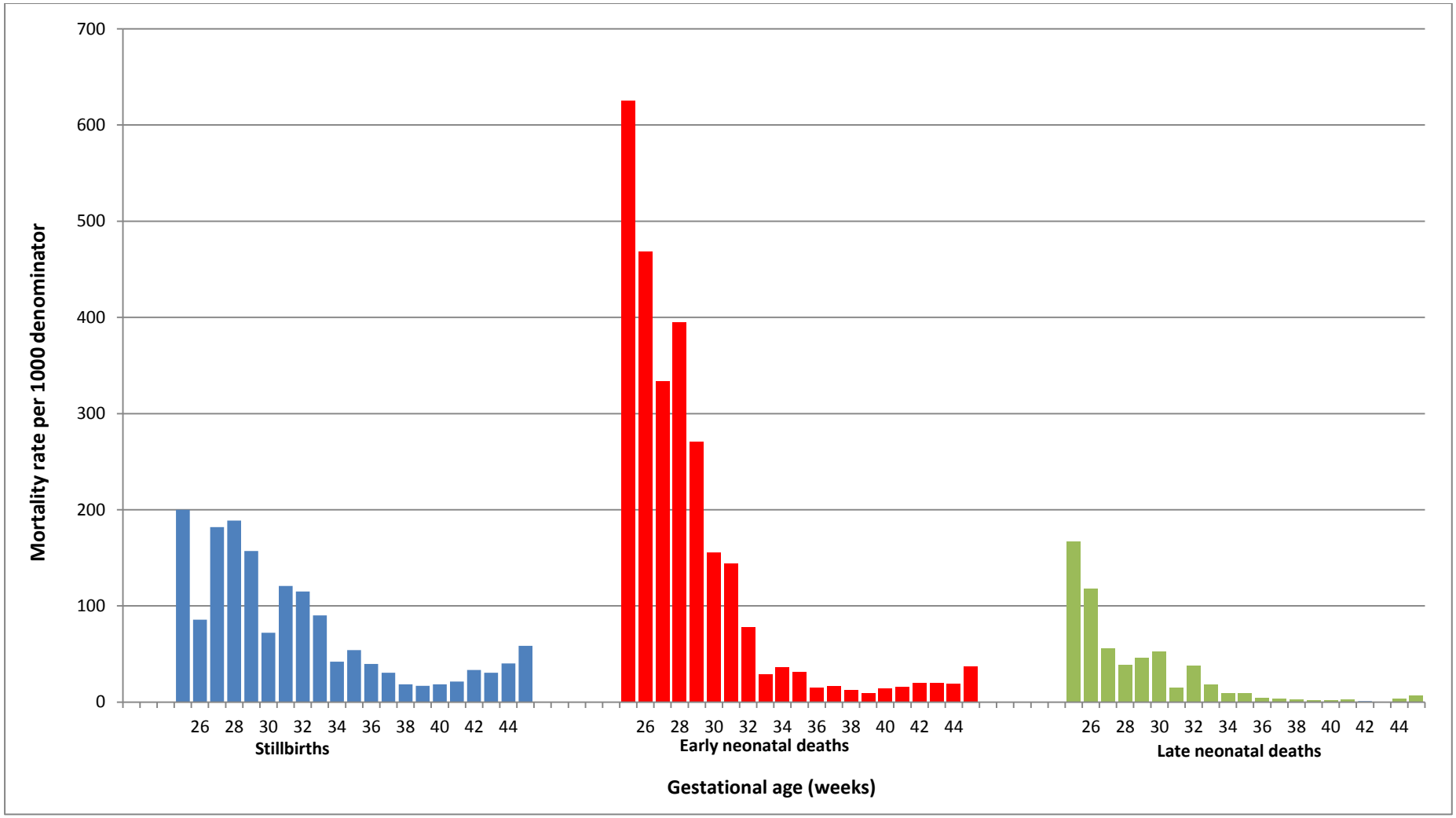


Figure 5.5: Mortality rates (25 weeks onwards) for stillbirths, early neonatal deaths and late neonatal deaths by gestational week at birth in Matlab (2005-2009)

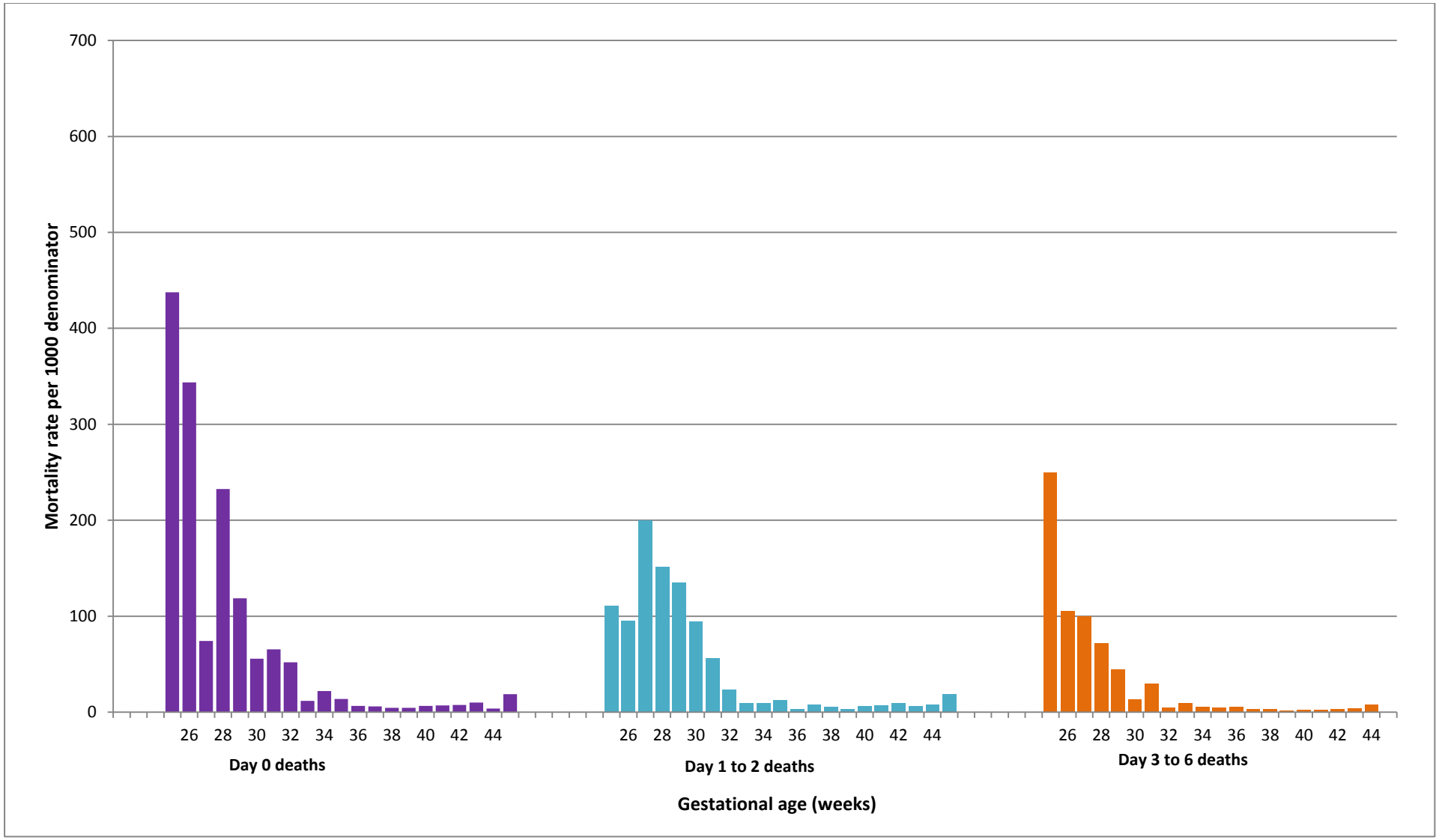


Figure 5.6: Mortality rates (25 weeks onwards) for Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths by gestational week at birth in Matlab (2005-2009)

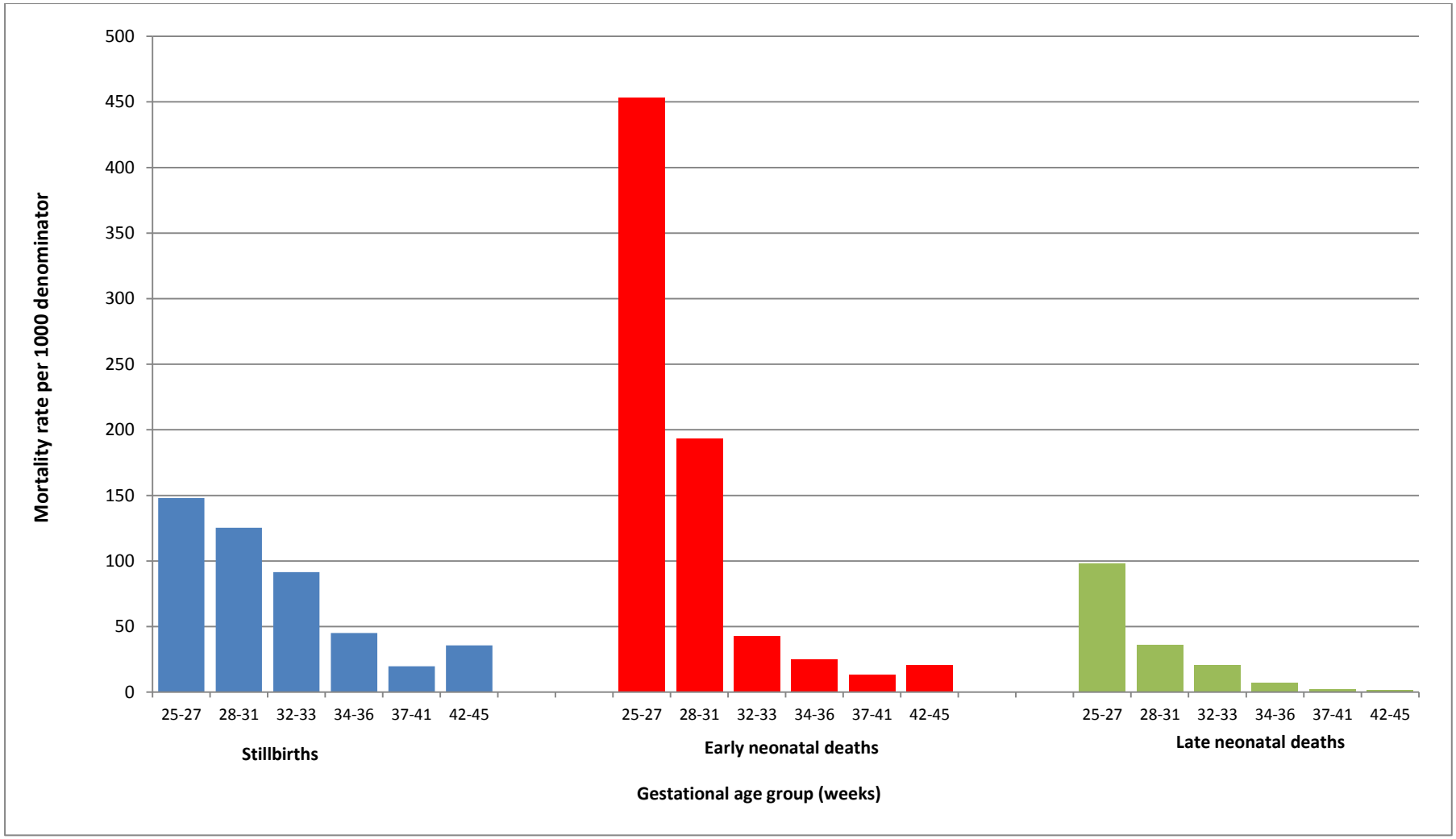


Figure 5.7: Mortality rates (25 weeks onwards) for stillbirths, early neonatal deaths and late neonatal deaths by gestational age group (weeks) at birth in Matlab (2005-2009)

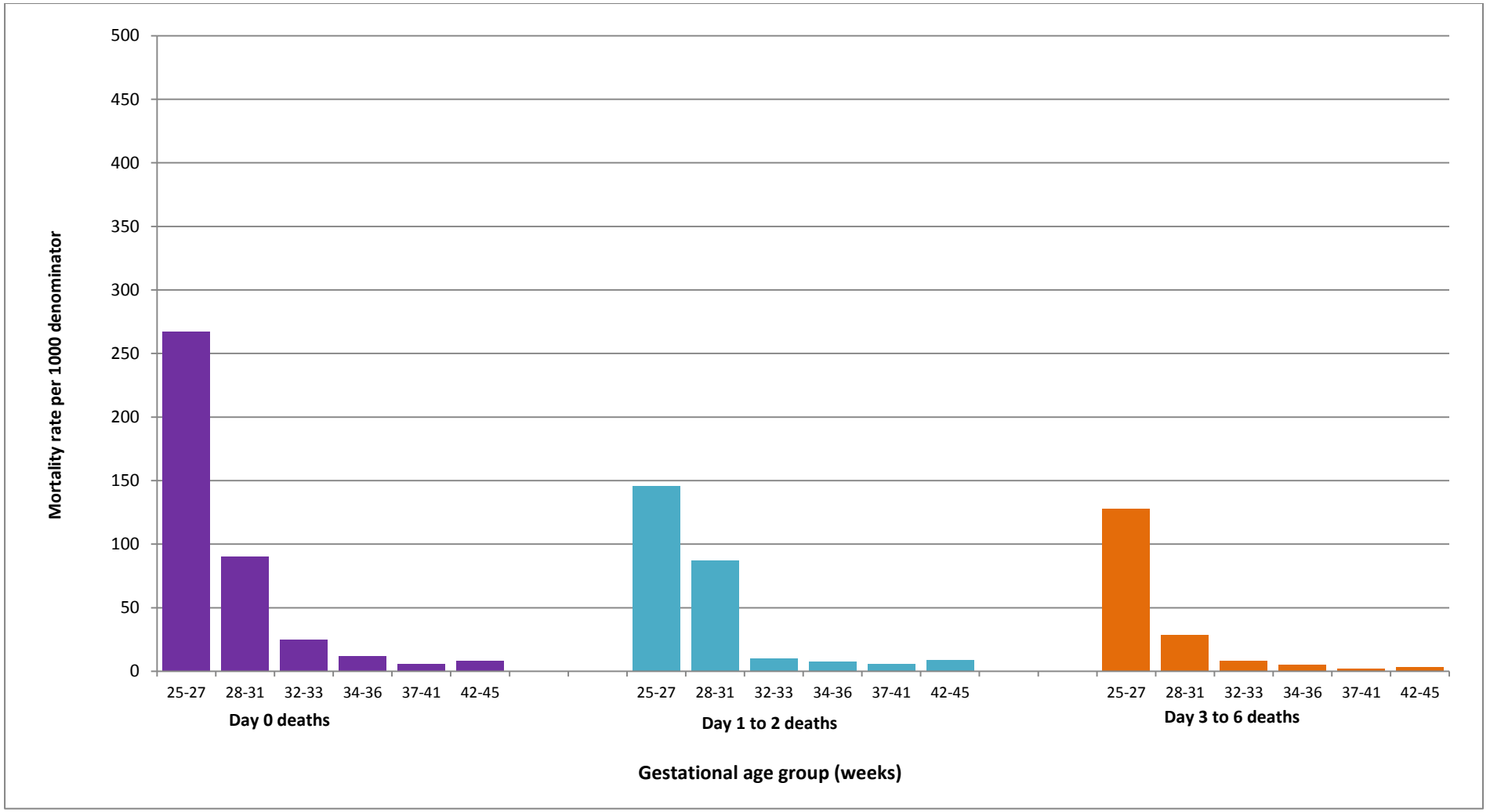


Figure 5.8: Mortality rates (25 weeks onwards) for Day 0 deaths, Day 1 to 2 deaths and Day 3 to 6 deaths by gestational age group (weeks) at birth in Matlab (2005-2009)

5.4.6 Association between gestational age and mortality

Table 5.9 shows the relationship between mortality outcomes and gestational age in Matlab from 2005-2009. Figure 5.9 shows the adjusted odds ratios plotted for all mortality outcomes.

Stillbirths were strongly associated with gestational age. The odds ratios did not change after adjusting for socio-demographic exposures. The strengths of association of socio-demographic characteristics with stillbirths and other mortality outcomes were similar to that observed earlier in Chapter 4 and hence are not shown here.

Early neonatal death rates declined dramatically with increasing gestational age and this remained significant for all gestational age groups even after adjustment for time, socio-demographic factors of area of residence and gravidity. Odds of dying in the first week of life were almost 49 times higher for babies with a gestational age of 22-27 weeks at birth than 37-41 weeks at birth (OR= 48.68 , 95% CI:28.07-84.40, p<0.0001).

This relationship of gestational age with mortality was also seen for late neonatal deaths, though not as strongly. Even so, odds of late neonatal death were 14 times higher at 22-27 weeks than 37-41 weeks (OR= 14.31, p<0.0001).

Among all mortality outcomes, low gestational age affected Day 0 deaths the most. Babies of 22-27 weeks gestational age had 53 times greater odds of death on their first day than babies who were born at term. Day 1 to 2 deaths and Day 3 to 6 deaths showed similar but less strong relationships with gestational age as with the other mortality outcomes.

Table 5.9 : Mortality outcomes according to gestational age and socio-demographic characteristics of women in Matlab (2005-2009).

Gestational age (weeks)	Denominator (No. of mortality outcomes)	Mortality per 1000 denominator	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs[a b] (95 % CI)	P-values (Wald test)
Stillbirths						
22-27	115 (13)	113.0	7.31 (3.68-14.54)	<0.0001	7.31 (3.59-14.91)	<0.0001
28-31	431 (54)	125.3	8.85 (6.10-12.86)	<0.0001	8.85 (5.99-13.07)	<0.0001
32-33	667 (61)	91.5	5.82 (4.17-8.13)	<0.0001	5.61 (3.97-7.93)	<0.0001
34-36	2642 (119)	45.0	2.49 (1.97-3.14)	<0.0001	2.39 (1.88-3.04)	<0.0001
37-41	19105 (378)	19.8	1.00	_	1.00	_
42-45	2078 (74)	35.6	1.91 (1.45-2.51)	<0.0001	1.86 (1.41-2.46)	<0.0001
All	25038 (699)	27.92				
Early neonatal deaths						
22-27	102 (40)	392.2	40.85 (27.22-61.31)	<0.0001	48.68 (28.07-84.40)	<0.0001
28-31	377 (73)	193.6	15.60 (11.80-20.67)	<0.0001	16.42 (11.69-23.08)	<0.0001
32-33	606 (26)	42.9	3.10 (2.05-4.68)	<0.0001	3.06 (2.01-4.67)	<0.0001
34-36	2523 (62)	24.6	1.84 (1.39-2.43)	<0.0001	1.82 (1.37-2.42)	<0.0001
37-41	18727 (247)	13.2	1.00	_	1.00	_
42-45	2004 (42)	21.0	1.58 (1.13-2.19)	0.007	1.53 (1.09-2.13)	0.013
All	24339 (490)	20.1				
Late neonatal deaths						
22-27	62 (4)	64.5	14.93 (5.28-42.1)	<0.0001	14.31 (5.04-40.61)	<0.0001
28-31	304 (11)	36.2	10.85 (5.58-21.09)	<0.0001	10.44 (5.34-20.42)	<0.0001
32-33	580 (12)	20.7	7.59 (4.00-14.39)	<0.0001	7.20 (3.77-13.74)	<0.0001
34-36	2461 (17)	6.9	2.68 (1.54-4.69)	0.001	2.62 (1.50-4.60)	0.001
37-41	18480 (46)	2.5	1.00	_	1.00	_
42-45	1962 (3)	1.5	0.60 (0.19-1.93)	0.390	0.59 (0.18-1.90)	0.380
All	23849 (93)	3.9				
Day 0 deaths						
22-27	102 (23)	225.5	46.13 (28.08-75.78)	<0.0001	53.81 (27.17-106.53)	<0.0001
28-31	377 (34)	90.2	15.80 (10.59-23.58)	<0.0001	16.38 (10.50-25.57)	<0.0001
32-33	606 (15)	24.8	4.24 (2.46-7.34)	<0.0001	4.28 (2.45-7.48)	<0.0001
34-36	2523 (30)	11.9	2.12 (1.41-3.19)	<0.0001	2.12 (1.41-3.21)	<0.0001
37-41	18727 (103)	5.5	1.00	_	1.00	_
42-45	2004 (17)	8.5	1.52 (0.91-2.55)	0.11	1.49 (0.89-2.49)	0.134
All	24339 (222)	9.1				
Day 1 to 2 deaths						
22-27	79 (10)	126.6	18.49 (8.87-38.50)	<0.0001	20.31 (9.20-44.8)	<0.0001
28-31	343 (30)	87.5	14.41 (9.05-22.9)	<0.0001	14.29 (8.58-23.80)	<0.0001
32-33	591 (6)	10.2	1.70 (0.74-3.90)	0.212	1.59 (0.68-3.69)	0.283
34-36	2493 (19)	7.6	1.35 (0.82-2.21)	0.234	1.29 (0.96-2.67)	0.311
37-41	18624 (102)	5.5	1.00	_	1.00	_
42-45	1987 (18)	9.1	1.63 (0.98-2.70)	0.058	1.60 (0.96-2.67)	0.07
All	24117 (185)	7.7				

Gestational age (weeks)	Denominator (No. of mortality outcomes)	Mortality per 1000 denominator	Crude ORs[a] (95 % CI)	P-values (Wald test)	Adjusted ORs[a b] (95 % CI)	P-values (Wald test)
Day 3 to 6 deaths						
22-27	69 (7)	101.4	29.42 (12.92-66.96)	<0.0001	31.24 (13.54-72.01)	<0.0001
28-31	313 (9)	28.8	9.68 (4.68-20.01)	<0.0001	10.65 (5.12-22.15)	<0.0001
32-33	585 (5)	8.5	3.42 (1.35-8.69)	0.009	3.61 (1.42-9.21)	0.007
34-36	2474 (13)	5.3	2.24 (1.40-4.19)	0.011	2.32 (1.25-4.35)	0.008
37-41	18522 (42)	2.3	1.00	_	1.00	_
42-45	1969 (7)	3.6	1.53 (0.69-3.42)	0.295	1.51 (0.68-3.36)	0.317
All	23932 (83)	3.5				

[a]All odd ratios are adjusted for clustering of births to the same mother

[b]Adjusted for: *stillbirths*-gestational age, year of birth, area of residence, maternal education, maternal age and gravidity; *early neonatal deaths*-gestational age, year of birth, area of residence and gravidity; *late neonatal deaths*-gestational age and gravidity; *day 0, day 1 to 2 and day 3 to 6 deaths*-gestational age, area of residence, maternal age and gravidity.

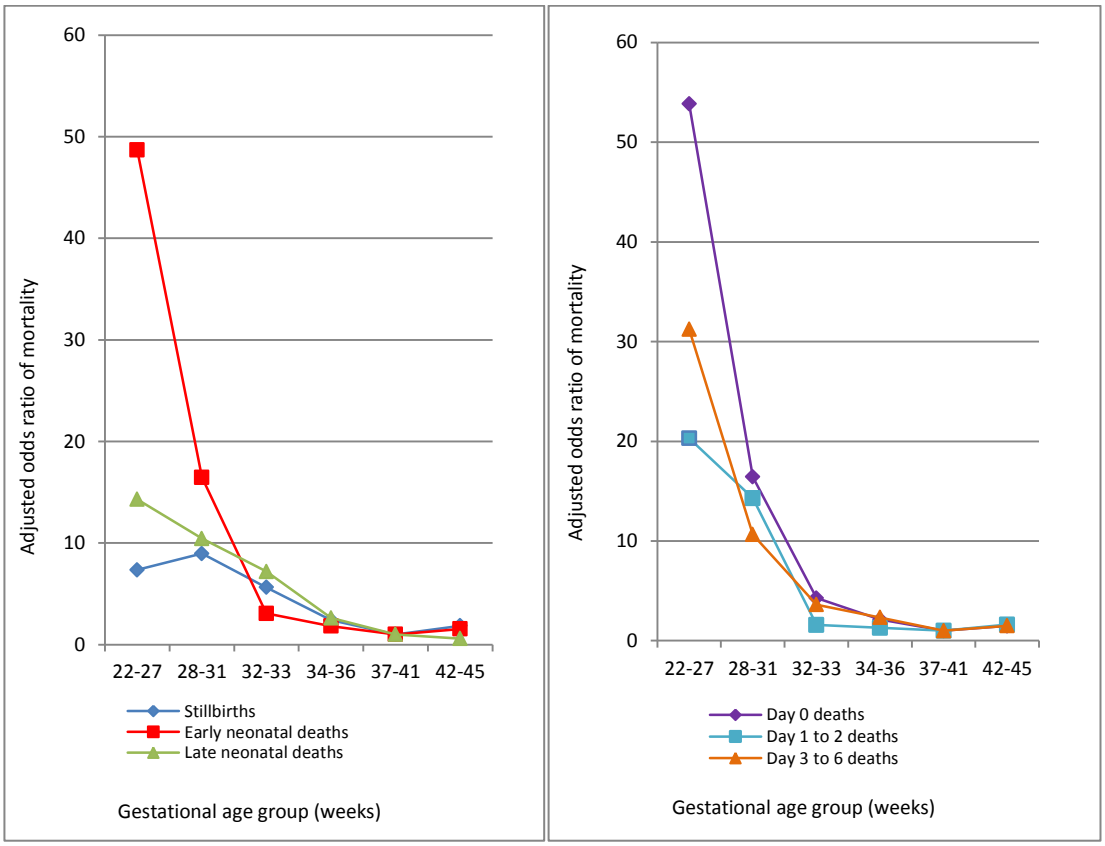
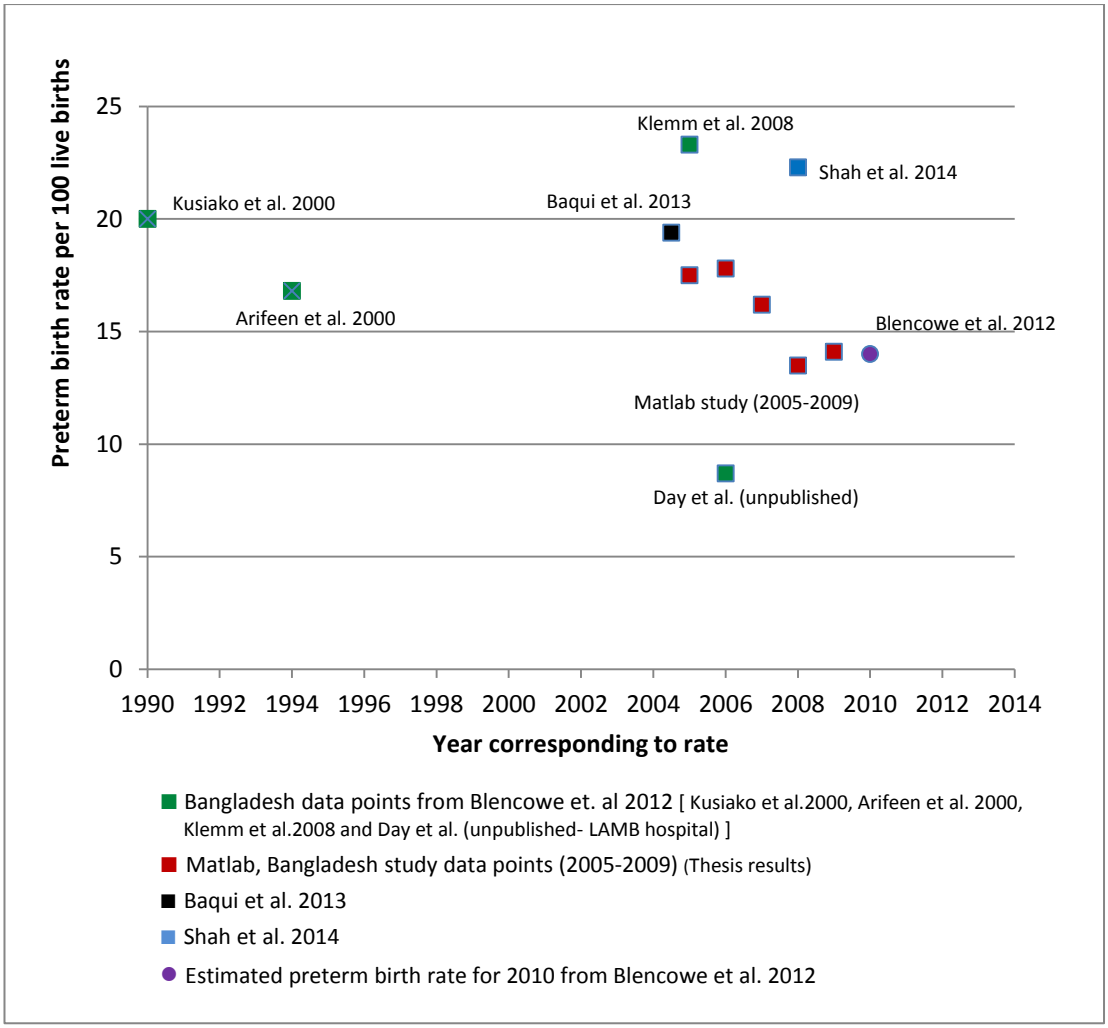


Figure 5.9: Adjusted odds ratios for mortality outcomes by gestational age group (weeks) at birth in Matlab (2005-2009).

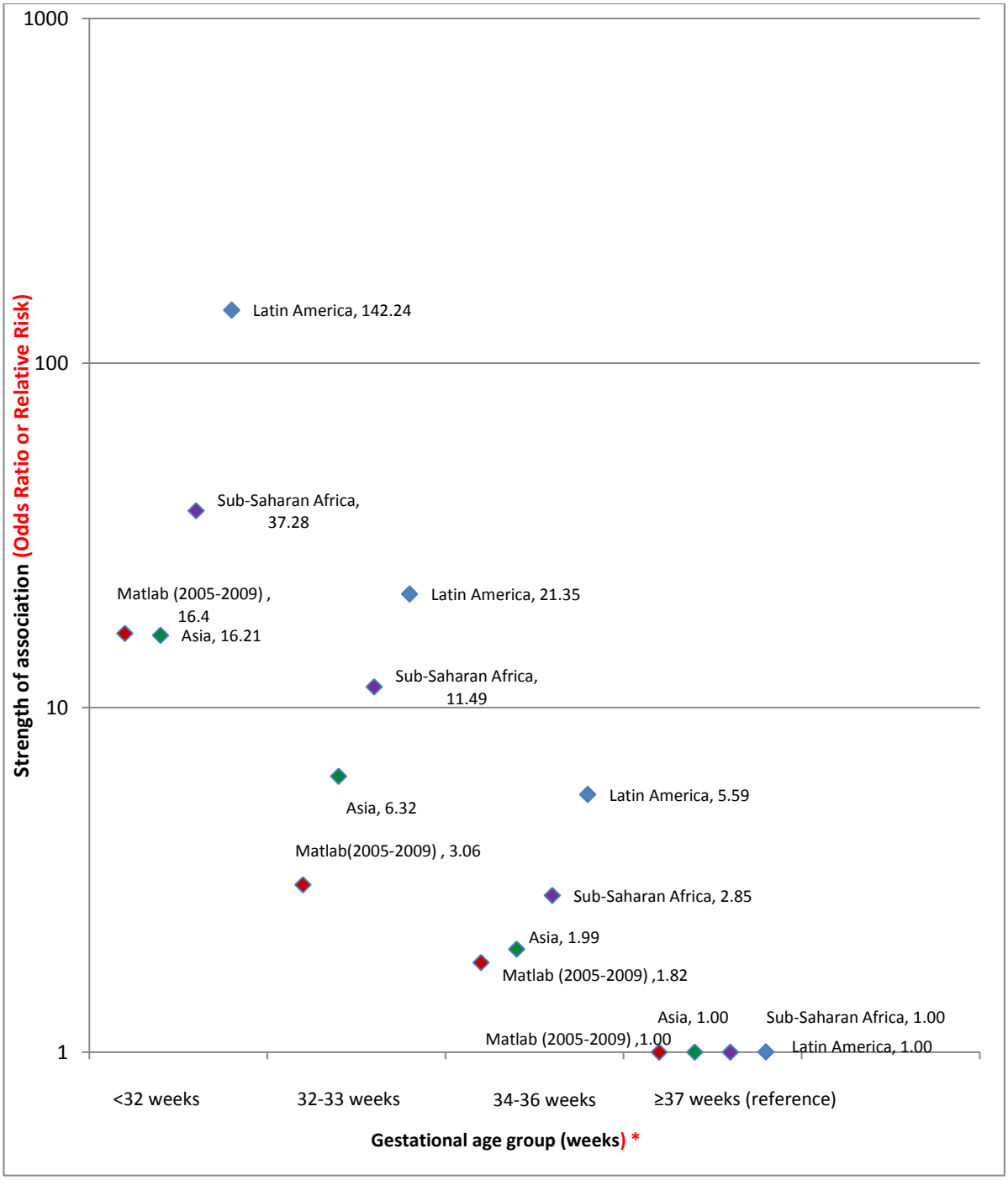
Figure 5.10 compares preterm birth rates in Matlab between 2005 and 2009 with rates obtained from Bangladeshi studies (Kusiako et al. 2000; Arifeen et al. 2000; Klemm et al. 2008) included in the global and national estimations of preterm births by Blencowe et al. 2012. Details of these and other published (Baqui et al. 2013; Shah et al. 2014) and unpublished (Day et al., LAMB hospital) Bangladesh studies have been discussed earlier in this chapter (see Introduction). Rates from these studies and those estimated by Blencowe et al. 2012 for 2010 ranged from 8.7% to 23.3% and the rates obtained from my study fell within this range. However, a time trend could not be detected from these rates, suggesting that preterm births were declining in Bangladesh.

The comparison of the strength of association between preterm birth and early neonatal mortality by weeks of gestational age for Matlab with published estimates by (Katz et al. 2013a) for Asia, Sub-Saharan Africa and Latin America is shown in Figure 5.11. These published estimates for early and late neonatal death outcomes are based on 20 datasets from these regions and estimates for Asia are based on datasets from Bangladesh, India, Nepal, Pakistan, Philippines and Thailand. The adjusted odds estimates for early neonatal deaths in Matlab (2005-2009) are consistent with the adjusted estimates for Asia (adjusted for land ownership, occupation, maternal and paternal education, maternal age and gravidity in the Katz et al. 2013 study). Figure 5.12 shows the comparison for late neonatal deaths and the Matlab results are also consistent with results for Asia.



Graph adapted from Blencowe et al. 2012, "National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications" Lancet, Vol. 379, pp. 2162–2172. Note: In order to be consistent with Blencowe et al. 2012 estimates, Matlab estimates (thesis results) used in this graph have been converted to rate per 100 live births from rate per 100 births used elsewhere in the thesis.

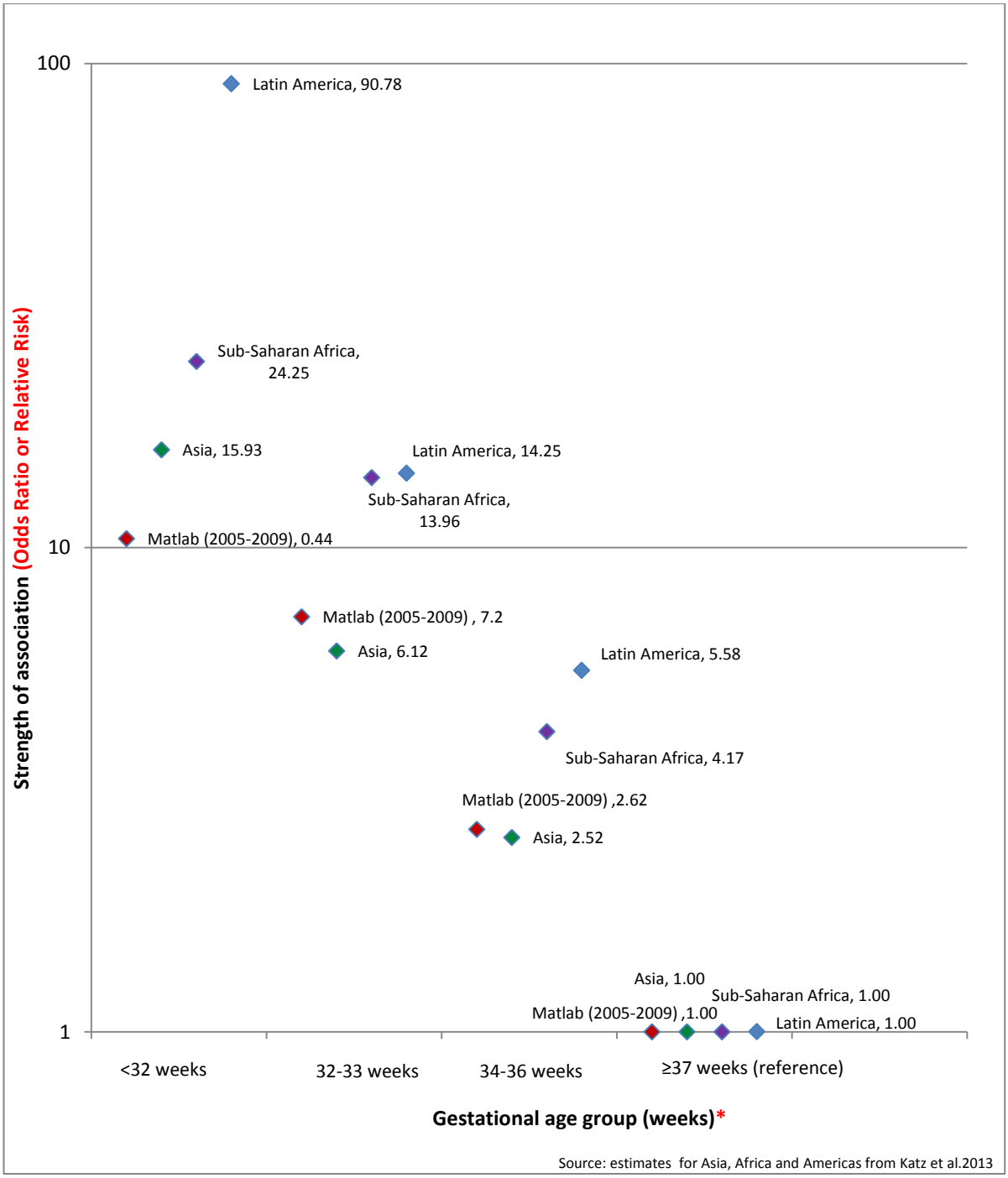
Figure 5.10: Comparison of Matlab preterm birth rates with rates from other Bangladesh studies.



Graph adapted from Katz J. et al. 2013, "Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis", Lancet, Vol. 382:9890, pp 417-25.

***Note:** Matlab data for 28-31 weeks and 37-41 weeks, were used for gestational age groups of <32 weeks and ≥37 weeks in this graph. The Matlab data were representative for 2005-2009 while the Katz et al. 2013 study estimates were representative for 1982-2008. Katz et al. 2013 and the Matlab study presented relative risks and odds ratios, respectively.

Figure 5.11: Comparison of strength of association between preterm birth and early neonatal mortality by gestational age groups (weeks) for Matlab, Bangladesh with published estimates for Asia, Sub-Saharan Africa and Latin America.



Graph adapted from Katz J. et al. 2013, "Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis", Lancet, Vol. 382:9890, pp 417-25.

***Note:** Matlab data for 28-31 weeks and 37-41 weeks, were used for gestational age groups of <32 weeks and ≥37 weeks in this graph. The Matlab data were representative for 2005-2009 while the Katz et al. 2013 study estimates were representative for 1982-2008. Katz et al. and the Matlab study presented relative risks and odds ratios, respectively.

Figure 5.12: Comparison of strength of association between preterm birth and late neonatal mortality by gestational age groups (weeks) for Matlab, Bangladesh with published estimates for Asia, Sub-Saharan Africa and Latin America.

Table 5.10 shows the population attributable risk percentage of preterm births for each mortality outcome. Approximately 30% of mortality was attributable to preterm births, regardless of age at death. Extremely preterm births are responsible for between 2.8% of stillbirths and 18.1% of Day 0 deaths. Very preterm births are responsible for between 10.7% of late neonatal deaths and 19.3% of early neonatal deaths. Moderate and late preterm births are responsible for 13.1% and 14.3%, respectively, of late neonatal deaths.

Table 5.10: Percentage of mortality outcomes attributable to preterm births in Matlab (2005-2009)

	Population attributable risk percent (PAR%)				
	Preterm (22-36 weeks)	Extremely preterm (22-27 weeks)	Very preterm (28-31 weeks)	Moderate preterm (32-33 weeks)	Late preterm (34-36 weeks)
Stillbirths	29.7	2.8	11.9	10.9	12.8
Early neonatal deaths	32.0	16.7	19.3	4.9	7.8
Late neonatal deaths	34.0	3.3	10.7	13.1	14.3
Day 0 deaths	37.1	18.1	19.2	7.6	10.4
Day 1 to 2 deaths	23.2	5.9	15.9	1.4	2.9
Day 3 to 6 deaths	31.6	8.0	11.2	6.0	12.0

5.5 Discussion:

This study found that the preterm birth prevalence is high in rural Bangladesh: 15.5% of all births are preterm with 10.6% and 2.7% late and moderately preterm, respectively. Very preterm births and extremely preterm births are rare (1.7% and 0.5% of births). Women who are the least educated, poorest, oldest and have had the greatest number of pregnancies have the highest prevalence of preterm birth. The differentials were particularly strong for maternal education where the risk of preterm birth for the most educated women was half that of women with no education. Preterm births are associated with very high rates of stillbirths and neonatal mortality. The population attributable risk percent for preterm births is around 30% for stillbirths, early and late neonatal deaths and is highest (37%) in Day 0 deaths.

The preterm birth prevalences of 13.8% (2009) to 17.0% (2005) seen in my study are consistent with those reported in previous Bangladesh studies (8.6 to 23.3%) and the WHO estimates for Bangladesh and South Asia (14.0% and 13.3%) described earlier (Introduction).The proportions of late and moderate preterm births (68.5% and 17.3% respectively) in my study are also the same as proportions found in the two rural Sylhet studies described earlier [69.6% and 17.1% (Baqui et al. 2013); 55.1% and 31.8% (Shah et al. 2014)]. The proportions in my study are also in line with the combined value for late and moderate preterm births reported from the global meta-analysis of data points from 41 countries (84.3%) (Blencowe et al. 2012).

Maternal education had a dramatic effect on preterm birth prevalence. Prevalence was halved from 20.0/100 births in women with no education to 10.3/100 births in women with 11-16 years of education. When adjusted for other factors, this corresponded to a 33% reduction (58% reduction when unadjusted) in preterm births for the highest-educated women compared to uneducated women. This effect is consistent with that found elsewhere in Bangladesh and in Pakistan. In the Sylhet study described earlier (Shah et al. 2014) women with 5 or more years of schooling had a 27% reduction in preterm births compared to those with 0-4 years of schooling. In a prospective cohort study in Karachi, Pakistan (Shaikh et al. 2011) women with ten or more years education had preterm prevalence of 9.8/100 births compared to 15.0/100 births in women with no or ‘some’ schooling (where ‘some’ schooling was undefined). In this study, women with higher education levels were seen to have 39% less preterm births though this reduction was not significant.

A number of factors might contribute to the strong association between preterm birth and maternal education. Women with secondary education may be more likely to access antenatal care, space their births, optimize their pre-pregnancy weight, identify and manage risk factors (e.g. by using antibiotics for infections and anti-hypertensives for hypertensive diseases of pregnancy) and access better care during labour (Dean et al. 2013). The strong association seen between education and prematurity prevalence in Matlab could be partly explained by educated women (i) accessing ANC more often, (ii) increasing their birth-spacing or because of (iii) information bias. (i) In both areas of Matlab, percentages of antenatal care visits (0-1, 2 and 3+ visits) increased significantly with rising levels of maternal education (Pervin et al. 2012).(ii) In Matlab more than half of all births (58.2%) following short birth intervals (24-35 weeks) were seen to occur in women with no education (DaVanzo et al. 2004). One of the major global recommendations for reducing preterm birth prevalence (Howson et al. 2012) includes providing antenatal care services for all women (screening for infectious diseases, correction of weight, birth preparedness) and for women at risk of preterm birth (by anticipating and managing previous and current pregnancy disorders e.g. hypertension, bleeding and multiple pregnancy).(iii) It is also possible that educated women reported their LMP dates differently from uneducated women but it is unlikely that this reporting error was present as a study in the USA showed that women reported their LMP dates accurately regardless of education level (high-school, some post high-school education and at least a college degree) (Wegienka & Baird 2005). However as the lowest level of education in the USA study was high school education (12 years of education), the effect of no education on recalling LMP dates accurately is not known.

The lowest socioeconomic status was associated with the highest risk of preterm birth in my study, an association also seen in England between 1994 and 2003 where mothers in the most deprived decile had a very preterm prevalence of 16.4/1000 births compared to 8.5/1000 births in the least deprived decile (Smith et al. 2007). However after adjusting for other socio-demographic factors such as education in Matlab, there appeared to be no significant effect of increased wealth on preterm birth reduction. Absence of effect was seen in all but the poorest wealth quintile.

The U-shaped relationship found between maternal age and preterm birth prevalence corresponds to similar findings in previous studies (Fraser et al. 1995; Hediger et al. 1997; da Silva et al. 2003; Tough et al. 2002). Extremes in gravidity are seen to increase preterm birth risks significantly in this population after adjustment for socio-demographic factors and this is

also seen elsewhere (López & Bréart 2013). However, a large meta-analysis for the relationship between parity and preterm births suggested that residual confounding (e.g. poor access to care, financial instability, or high fertility at the end of the reproductive period) and not biological mechanisms are predominantly responsible for the relationship (Kozuki et al. 2013). In my study, however, adjustment for wealth, age and other demographic factors only attenuated the risks for preterm births associated with high gravidity.

The prevalence of preterm birth fell in Matlab from 2005 to 2009 (17.0% to 13.8%), both in the Government (17.4% to 14.8%) and the ICDDR, B service areas (16.6% to 12.8%).
The odds ratios for yearly decline in preterm births did not change after adjusting for socio-demographic characteristics over time, suggesting that changing socio-demographic characteristics were not responsible for the decline. The pace of decline was similar in both areas. Possible reasons for the decline are discussed later.

The rates for stillbirths and neonatal mortality declined monotonically with longer gestational age, whatever the time since birth. These findings are consistent with what has been found in the region and elsewhere for stillbirths (Ngoc et al. 2006; Smith 2001), early neonatal mortality (Ngoc et al. 2006; Katz et al. 2003), perinatal mortality (Kusiako et al. 2000), late neonatal mortality (Katz et al. 2003)and neonatal mortality (Smith 2001; Mohangoo et al. 2011; Baqui et al. 2013).

My findings suggest that a third of stillbirths (29.7%), early neonatal deaths (32.0%), and late neonatal deaths (34.0%) are attributable to prematurity. Assuming that the association between preterm birth and mortality is causal, a third of neonatal deaths could be eliminated if preterm births could be prevented. Causality is plausible, because according to the criteria for causality (Lucas & McMichael 2005) prematurity precedes mortality, is related to mortality by a biological gradient (or dose-response), the strength of association (odds ratio) with mortality is high, findings are consistent with those of previous studies in the region and elsewhere (Liu et al. 2012; Baqui et al. 2013; Kusiako et al. 2000) and analogous studies of LBW with mortality have shown similar effects (Yasmin et al. 2001; Copper et al. 1993). My findings are consistent with those found in other studies from Matlab (27.3% of perinatal deaths during 1987-1993) and Sylhet (33% of neonatal deaths during 2004-2005) (Kusiako et al. 2000; Baqui et al. 2013). The 2011 Bangladesh DHS reported that only 11.3% of neonatal deaths were attributable to preterm birth, but this is likely to be an underestimate as preterm birth was

ascertained by verbal autopsy of dead babies instead of by gestational age measurement for all babies (NIPORT et al. 2013).

This study has a number of unique strengths, including the large sample of stillbirths and live births, preterm births, and early and late neonatal deaths. First, the large sample size ensures that there was enough power to test the study associations. Second, data were prospectively collected and loss to follow up was low. The main reason for loss to follow-up in Matlab is out-migration (Rahman et al. 2013) and during 2005-2009, 10.5/1000 females of all ages in Matlab migrated out (Appendix III: Table 4), roughly corresponding to a loss-to follow up of 1.05% which is likely to be even lower for pregnant women. This loss to follow-up is extremely small for a cohort study and unlikely to introduce bias. Third, there were very few births with missing LMP dates (0.21%) while births with missing socio-demographic characteristics (household asset quintile-9.8% and maternal education-0.21%) were retained as unknown categories in the analysis. Fourth, the analytic sample included the total population at risk of preterm births (i.e. stillbirths and live births) and hence the results represented the total population and not just a subset of live births. Lastly, the study was community based, thereby providing estimates of the prevalence of preterm births and the associations of gestational age with mortality that are representative of a population.

The study has a number of limitations, including (1) gestational age measurement method (2) misclassification between stillbirths and early neonatal deaths (3) exclusion of births with extremes of gestational age and (4) residual confounding.

First, gestational age was measured by LMP dating. As women recalled LMP dates during one- or two-monthly visits during pregnancy, recall bias for LMP date is likely to be lower than when it is checked during or after birth. LMP dating may underestimate preterm births compared to ultrasonography dating (Mongelli et al. 1996). LMP dating underestimated ultrasound-based gestational ages by only one day in a tertiary hospital in Bangladesh (Rosenberg et al. 2009). It is therefore possible that the preterm prevalence of 15.5% is an underestimate of the actual burden of prematurity, but as recall bias for LMP dates is likely to be low, the effect of this on the prevalence reported is likely to be small. A very recent study in Matlab which compared gestational ages assessed by reported LMP dates and by ultrasound during 2008-2010 found a very high correlation for the two methods (Anisur Rahman, manuscript in preparation),

suggesting that the gestational ages measured by LMP dates were not likely to be very different from those measured by ultrasound.

Second, I expect some misclassification between stillbirths and early neonatal death because the majority of these births are at home with traditional birth attendants and differentiation is difficult (Chapter 4). However, this misclassification is likely to be non-differential for preterm and term infants and so unlikely to affect the results.

Third, the number of births with extremely large or small gestational ages was very small (1.36%) and excluding these births from the analysis was unlikely to introduce bias.

Fourth, residual confounding might not have been adjusted for. Factors not included in the analysis included maternal body mass index (BMI) (Kosa et al. 2011) and anaemia (Zhang et al. 2009), maternal and foetal complications (Lawn, Lee et al. 2009), and short inter-pregnancy intervals (Smith et al. 2003; DeFranco et al. 2007) which are associated with increased risk of preterm births (outcome) and also independently associated with the socio-demographic variables (exposure) analysed here (Hossain et al. 2012; Ahmed et al. 2003; Wandabwa 2004; Centers for Disease Control and Prevention 1998). Adjustment for these factors could have possibly attenuated the strength of association seen between socio-demographic factors and preterm births but was unlikely to have any effect on preterm birth prevalence. Inter-pregnancy interval and BMI by gestational age were not calculated or analysed because of time limitations in the PhD. The next chapter explores the role of maternal complications in relation to preterm births, stillbirths and neonatal mortality.

The majority of preterm births in South Asia, Bangladesh and this study are moderate to late preterm (Beck et al. 2010; Blencowe et al. 2012; Baqui et al. 2013) and these births do not need expensive intensive care units for survival (Morken 2012). However the recommendations for reduction of preterm births often include antenatal corticosteroids, vaginal progesterone and tocolytics which are unavailable or have very low coverage in LICs.

In my study, the reduction of preterm births in both areas from 2005-2009 appears to be driven by the reduction of late preterm births, suggesting that these pregnancies are possibly being extended by a few weeks and reaching term status. It is possible that the change in LMP ascertainment over the study period of 2005-2009 (one month recall during 2001-2006 and two month recall from 2007 onwards) might have resulted in changes in gestational age over the time period which might have resulted in the sharp decline observed from 2008. Increase

in LMP recall periods have resulted in women tending to report the LMP date before the actual LMP date in a US study (Wegienka & Baird 2005) when different recall periods were compared (0-<1 weeks, 1-<2 weeks, 2- <3 weeks and 3 weeks or longer, where the maximum period was 56 days). This might have led to gestational ages in Matlab being overestimated after mid-2007 resulting in the reduction seen in preterm births in both areas from 2008.

Matlab has seen an increase in ANC uptake over the study period in both the areas. Uptake of three or more antenatal care visits increased during the period 2005-2009 in both areas (from 40% to 81% in the ICDDR,B service area and from 16% to 27% in the Government service area) (Pervin et al. 2012) and this is consistent with increases in ANC uptake seen nationally. In the most recent (2011) national DHS 67.9% of women had at least one ANC visit (26% with 4 or more visits) compared to 63% (22% with 4 or more visits) for the 2007 DHS (NIPORT et al. 2013; NIPORT et al. 2009). It is possible that by identifying and treating mothers at greater risk of pre-term birth, the increased antenatal care uptake in both areas of Matlab is partly responsible for the reduction in preterm births by delaying preterm labour. The Sylhet study described earlier supports this suggestion and shows that at least one ANC visit versus none was associated with a 25% reduction in preterm births (95%CI: 22-28%) (Shah et al. 2014). It is also possible that improved ANC visits resulted in knock-on effects of better awareness of complications and care-seeking for these when necessary, enabling prompt management of complications. There were increases in the percentages of women with education between 2005 and 2009; however, it is unlikely that the change was sufficiently substantial to result in less closely-spaced pregnancies which might have reduced the number of preterm births. Girls who finish their education are likely to have fewer adolescent pregnancies which result in preterm births (World Health Organization 2011b) though this is unlikely to be the case in Matlab. In Matlab, the number of births to young mothers (<20 years or less) did not change between 2005 (13.3%) and 2009 (13.0%) (Data not shown). Though I was not able to assess the reduction (if any) over time of maternal undernutrition in Matlab, it has been estimated that the number of chronic energy deficient (BMI <18.5 kg/m2) non-pregnant mothers of children below 5 years decreased from 35.5% in 2005 in rural Bangladesh to 25.5% in 2010 (Helen Keller International 2005; Helen Keller International 2010). It is possible that improvement in maternal BMI in Matlab contributed to the decline in preterm births. The Sylhet study also supported this possibility by showing almost 1.5 times greater preterm birth risks in the thinnest women (mid upper arm circumference<21.4 cm) than the least thin women. However it should be noted that a systematic review and meta-analysis described earlier on balanced

protein energy supplementation in pregnancy on preterm births showed no effect on risks of preterm births (Imdad & Bhutta 2012b).

The reduction from 2008 in preterm births in both areas may be because of improvements in ANC, nutrition, education and better care-seeking, but why this would result in preterm reduction after 2008 is unknown. It might be speculated that certain antibiotics, drugs or services became more accessible from that point (though there is no information on this) or, analogous to the threshold effect of caesarean section on reduction of stillbirths discussed earlier (Chapter 4), levels of antenatal care, nutrition or education may have reached coverage levels from which preterm reductions were apparent. It is uncertain whether the improvements in the factors described above could have resulted in the decline seen in preterm births in both areas from 2007 onwards.

The previous chapter showed that the Safe Motherhood Programme resulted in great reductions in stillbirth and very early neonatal mortality while it showed no effect on the reduction of preterm births. When initially launched, the Matlab Safe Motherhood Programme was not designed to reduce preterm births or preterm-related deaths. Strengthening of the programme in 2007 attempted to implement evidence-based interventions such as antibiotics for pPROM and injectable antenatal corticosteroid treatment for women at risk of preterm labour or in preterm labour. KMC was also provided for preterm babies. These interventions were part of an effort to reduce perinatal and preterm deaths and improve survival for preterm babies (Chapter 4-Appendix II: Table 1) (Rahman et al. 2011). The coverage of these additional interventions in the Matlab ICDDR,B service area was unknown for the study period and it is not known whether providers routinely implemented these interventions in women at risk of preterm birth. It is possible that in Matlab, antibiotics for pPROM or antenatal corticosteroids were not used or were not used in a manner to result in greater preterm reduction in the ICDDR,B service area. However, there is no data available to assess drug usage. Additionally, skin-to-skin care in the 6-bed KMC unit was found to be insufficient to reduce mortality in preterm babies (Rahman et al. 2011). Reduction in preterm births was only seen from 2008 onwards and was evident in both areas. The results for the interaction between time and area of residence showed that there was no effect of the Safe Motherhood Programme on preterm birth reduction between 2005 and 2007. In summary, there was no evidence of improved services from 2007 onwards, so the decline in preterm births in both

areas after 2007 is largely unexplained by improvement of services and might be a result of change in the recall period of LMP date after mid-2007.

It is possible that greater gains in preterm birth reduction could be achieved through antenatal corticosteroids, antibiotics for pPROM, tocolytic agents, vaginal progesterone and other HIC interventions mentioned at the beginning of this chapter. However only a few of these preventative interventions (antibiotics for pPROM and antenatal corticosteroids) have been recommended for scale-up in LICs and further research on uptake, delivery and context-specific reasons for low coverage is necessary before policy recommendations for scaling up in LICs can be made (Bhutta et al. 2014; Lawn et al. 2013).

Prevention of preterm birth is primarily understood to be a knowledge-gap for both LICs and HICs while ensuring survival of preterm babies is an action-gap that LICs need to bridge (Lawn et al. 2013).

The reduction in mortality for babies already born preterm is thought to be possible to achieve through optimization of newborn survival techniques such as essential newborn care, resuscitation, breastfeeding, preventing hypothermia, kangaroo mother care and community-based management of preterm babies with pneumonia (Darmstadt et al. 2005; Lawn et al. 2013).

From my study there was no indication that the presence of the Safe Motherhood Programme resulted in the reduction of preterm birth prevalence in the ICDDR,B service area in Matlab through the increased uptake of ANC and emergency obstetric care. Hence it is not possible to make recommendations on the reduction of preterm birth prevalence based on the findings of this study. Until interventions effective in reducing the prevalence of preterm births are available, the reduction of mortality in preterm babies should be possibly focused on in Matlab. Reduction in preterm-related newborn mortality can be effected through the interventions recommended in the literature for newborn survival through newborn care, thermal and feeding support, and management of illnesses (Darmstadt et al. 2014). Currently, these activities must be emphasized at all levels of care, in order to reduce the burden of preterm-related mortality in Bangladesh and other LICs.

Chapter 6. The impact of intrapartum complications on perinatal mortality

6.1 Introduction:

The effect of labour and delivery complications, known as intrapartum complications, on increased neonatal mortality has recently become highly visible globally and calls have been made for this burden to be addressed (Bhutta et al. 2014; Lawn et al. 2014).

It has been suggested that at least 15% of pregnant women around the world are likely to develop serious and sudden obstetric complications during birth, and that these women require access to good quality obstetric care to ensure survival for themselves and their child (World Health Organization 2009; United Nations Children's Fund 1997). However there has been no validation for this number or evidence available that supports the widespread use of this number except for the prevalence of obstetric complications found by an Indian study (Bang et al. 2004). Statistical models estimate that globally, a quarter (1.2 million) of stillbirths and one-fourth (0.9 million) of early neonatal deaths, mostly in South Asia, may be due to unspecified labour and delivery events (Lawn et al. 2005; Lawn, Lee et al. 2009) but the true contribution of intrapartum complications to perinatal and neonatal mortality has not been established. This information is immensely important for public health programmes designed to manage and treat intrapartum complications and thus reduce perinatal and neonatal mortality.

Current research on newborn intrapartum deaths is scarce. Most information on the number of deaths from intrapartum complications has relied on statistical models generated by Lawn et al. 2005. The authors calculated intrapartum neonatal death numbers by multiplying the proportion of neonatal deaths related to intrapartum events (predicted from regression models for countries without vital registration data) with WHO estimates for neonatal death numbers. Intrapartum stillbirth numbers were obtained by multiplying intrapartum stillbirth rates (from eligible studies) with country-wise WHO live-birth estimates for 2000 (Lawn et al. 2005). The authors did not provide estimates for early neonatal deaths. The evidence for the strength of association between intrapartum complications with perinatal or neonatal mortality is scarce with the bulk of the evidence in low-income countries (LICs) provided by just a few studies (Lawn et al. 2005; Lawn, Lee et al. 2009; Rudan et al. 2005). There are no reviews (including Cochrane) or meta-analyses on the effect of different types of intrapartum complications on perinatal or neonatal mortality in LICs. The only systematic review and meta-

analysis is on studies from high-income countries (HICs) (Flenady et al. 2011). This review explored the role of a few intrapartum complications on stillbirths and this too was based on very few studies for each complication examined.

I searched the available literature to obtain studies that investigated the association between intrapartum complications and perinatal mortality. I reviewed studies previously obtained for the systematic review (Chapter 3) in South Asia, snowballed' studies from the bibliography of relevant studies and searched online for studies. I searched Google scholar and PubMed with combinations of broad search terms e.g. "labour complications", "intrapartum complications", "perinatal mortality" and with and without "developing countries" or "low-income countries". Perinatal outcomes included perinatal deaths, stillbirths and early neonatal deaths. As the focus of this chapter is an LIC, HIC studies were not searched for specifically and were represented by one HIC review. Only studies that presented effect estimates (odds ratios or risk ratios) were included. Studies published before 2000 or in a language other than English were not included.

I obtained nine studies (Tables 6.1 and 6.2). Study characteristics, definitions of intrapartum complications and strength of association reported in the studies were tabulated for six population-based studies (Tables 6.1-6.1 D) and three facility-based studies (Tables 6.2 -6.2 D). Among the six population-based studies, three were from Bangladesh (Kusiako et al. 2000; Cherry et al. 2008; Bari et al. 2002) including a previous Matlab study (Kusiako et al. 2000), one was from India, one was from six West African countries (Burkina Faso, Ivory Coast, Mali, Mauritania, Niger and Senegal) (Chalumeau et al. 2000), and one review was from 5 HICs (Australia, Canada, Netherlands, the UK and the USA) (Flenady et al. 2011).

Overall, from the nine studies reviewed, two large studies provided strong evidence for the association of intrapartum complications with perinatal mortality and the studies were located in HICs (Flenady et al. 2011) or a mixture of high, middle and low-income countries (Vogel et al. 2014). Few studies provided strong evidence from LICs.

Of the six population-based studies, five were cohort studies, with three prospective studies (Bari et al. 2002; Chalumeau et al. 2000; Bang et al. 2004) and two retrospective studies (Kusiako et al. 2000; Cherry et al. 2008). The sixth was a review of population-based studies (including cross-sectional, retrospective and prospective cohort and case-control studies) (Flenady et al. 2011). Of the five cohort studies, the three prospective studies (Bari et al. 2002;

Chalumeau et al. 2000; Bang et al. 2004) were designed to collect data for study purposes while the two retrospective studies (Kusiako et al. 2000; Cherry et al. 2008) used previously collected data obtained for routine purposes. The mortality outcome of interest in three studies was perinatal deaths (Kusiako et al. 2000; Chalumeau et al. 2000; Bari et al. 2002) in two it was stillbirths (Cherry et al. 2008; Flenady et al. 2011) and in one both stillbirth and perinatal deaths (Bang et al. 2004) .

Ascertainment of pregnancy, births and deaths was mostly from household visits, though this was unclear in one Bangladesh study (Cherry et al. 2008) and in the India study (Bang et al. 2004). Ascertainment of pregnancy, births and deaths was very good for the HIC review on stillbirths (Flenady et al. 2011).

Ascertainment of intrapartum complications varied substantially. Kusiako et al. relied on hospital and midwifery records (Kusiako et al. 2000) while Chalumeau et al. used hospital records (four-fifths of births) as well as women's self-reports for the home births (less than a fifth of all births) (Chalumeau et al. 2000). In one systematic review, eligible studies used national birth databases, birth and perinatal registries and linked hospital records (Flenady et al. 2011). The Bang et al. study used complications as observed by community health workers at home during labour and delivery, though it was unclear how complications were ascertained in the hospital births (5.1%)(Bang et al. 2004). Bari et al. 2012 used women's self-reported intrapartum complications for all births (Bari et al. 2002). The method of ascertainment of complications in the retrospective Cherry et al. study was unclear (possibly from interviews)(Cherry et al. 2008).

From the population-based studies, strong evidence was found for the association of dystocia with perinatal mortality (Table 6.1 C). Prolonged labour increased the odds of perinatal mortality several fold in all studies, apart from two (Bari et al. 2002; Bang et al. 2004). Obstructed labour increased the odds greatly (up to 24 times) in the previous Matlab study. Breech and non-breech malpresentation were only reported in the Matlab study but the high odds ratios reported were consistent with those reported for non-cephalic malpresentation in West Africa (Chalumeau et al. 2000) and for all types of malpresentation in India (Bang et al. 2004). Hypertensive diseases of pregnancy, particularly eclampsia, were also associated with several-fold increases in mortality (between 1.3 times and 6.4 times) in four studies. The Matlab study and the Bari et al. study found haemorrhage to have no effect on perinatal

mortality, though the West African study (Chalumeau et al. 2000) and one Bangladesh study(Cherry et al. 2008) reported high odds ratios. Infection was not investigated in any of the population-based studies. Multiple pregnancies, explored in only two studies, showed four to five-fold increases in the odds of mortality. Anaemia, explored in only the Matlab study, was not associated with perinatal mortality, although the diagnosis was clinical and not from blood haemoglobin tests.

In interpreting the results of the above studies, the role of information bias, selection bias, and adjustment for confounders must be considered. Information bias may affect the strength of association presented. For studies with self-reported complications, ascertainment of complications occurred after birth, hence women remembered their complications differently depending on whether the child was stillborn, died soon after birth or was alive at the time of the interview; this led to overestimated odds ratios between intrapartum complications in cases of poor survival outcomes. For some studies (e.g. those using hospital records) it was not possible to verify whether intrapartum complications were noted before or after the occurrence of stillbirth or early neonatal death. If complications were noted prior to the death, then misclassification of complications would be non-differential but non-differentiality of this exposure would not necessarily lead to an underestimate of the odds ratio, as non-differentiality, in addition with other factors can lead to an overestimate of the odds ratio or the same odds ratio as well (Jurek et al. 2005). If misclassification was differential, i.e. complications recalled differently for a stillbirth than for a live birth, the odds ratios obtained would be overestimates of the true strength of association. Misclassification of outcomes is also possible. If health providers or mothers considered a child as a stillbirth instead of a live birth because the mother experienced complications during birth, this would have led to overestimates of odds ratios for intrapartum stillbirths.

Selection bias might have also affected the studies reviewed but is unlikely to have affected results greatly. Of the 5 population-based studies, the Matlab study population might not have been representative as it excluded women not seen by a midwife and those delivering in cities outside the research area. However, as perinatal mortality rates which could be calculated for included and excluded woman did not differ between the two groups and as loss to follow-up was very also low, the odds ratios were probably representative of women in the study area. The low loss to follow-up in most studies made any selection bias unlikely.

Regarding adjustment for confounders, care needs to be taken in separating factors that truly confound the association between intrapartum complications and perinatal mortality, factors that may be on the causal pathway, and factors that are risk factors for perinatal mortality but do not confound the association between intrapartum complications and perinatal mortality. Socio-demographic characteristics, preterm gestation, and delivery location may confound the association as these are associated with the exposure (labour complications) and are risk factors for the outcome (perinatal mortality). On the other hand, foetal complications such as foetal distress (e.g. meconium-staining of liquor), foetal hypoxia or birth asphyxia, (Kaye 2003; Buchmann & Pattinson 2006; Ellis et al. 2000), umbilical cord compression and cord prolapse (Royal College of Obstetricians and Gynaecologists 2008; Hofmeyr & Lawrie 2012) may be on the causal pathway between labour complications (e.g. prolonged or obstructed labour, breech or other malpresentation) and perinatal mortality. Disorders of the amniotic fluid and membranes e.g. polyhydramnios and ruptured membranes (Royal College of Obstetricians and Gynaecologists 2006; US National Library of Medicine 2014) could also be on the causal pathway between certain labour complications (e.g. infection or multiple pregnancy) and perinatal mortality. In the association between a specific intrapartum complication and perinatal mortality, whether or not another labour complication acts as a confounder or as an intermediate variable present on the causal pathway, depends on the labour complication being studied. For example, in the relationship between dystocia and perinatal mortality, multiple pregnancy is a confounder as it is associated with dystocia (having twins increases risk of dystocia) while also being a risk factor for perinatal mortality independent of dystocia (twins are at higher risk of perinatal death than singletons). In the relationship between multiple pregnancy and perinatal mortality, however, dystocia is on the causal pathway from multiple pregnancy to perinatal mortality (twins can lead to dystocia leading to perinatal death) but here dystocia is not associated with multiple pregnancy (i.e. having dystocia does not result in twins). In another example, haemorrhage has no role in the relationship between hypertensive diseases of pregnancy and perinatal mortality as it is not associated with hypertensive diseases of pregnancy nor is it on the causal pathway between hypertensive diseases and perinatal mortality. More details on this are presented in the Methods section (Table 6.3).

In the studies reviewed, adjustment was variable (Tables 6.1 C-6.1 D). Most studies adjusted for socio-demographic characteristics. Only the Matlab study adjusted for other labour complications and preterm gestation, but not for delivery location. The Matlab study may also have over-adjusted for antepartum pre-eclampsia and per-vaginal bleeding, which were

already present as intrapartum complications. Vogel et al. adjusted for foetal presentation as a confounder for all maternal labour complications but did not adjust for other labour complications. The Chalumeau et al. study was unable to assess eclampsia and pre-eclampsia (proteinuria results were inaccurate), and preterm gestation and hence unable to adjust for these factors (Chalumeau et al. 2000). As adjustment was different for different studies, I compared studies on the basis of crude odds ratios.

Table 6.1: Study characteristics of **population-based studies** investigating the strength of association between intrapartum complications and perinatal mortality

Study	Region (Time period) Setting	Study design	Study population	Mortality outcome(s) studied	Definitions of mortality outcome(s)	Ascertainment of pregnancy/ birth/death	Ascertainment of intrapartum complications
(Kusiako et al. 2000)	Matlab sub-district, Bangladesh (1987-1993) Rural	Retrospective cohort study of all women seen by a midwife antenatally and during childbirth for births after 28 weeks of gestation	3865 stillbirths and live births	Perinatal deaths	Death of a foetus after 28 weeks' gestation or of a neonate during the first seven days of life.	●Pregnancy: research CHW visits households monthly and notes down LMP date ●Birth: research CHW visits households monthly ●Death: as for 'Birth'	From midwife records and hospital records
(Chalumeau et al. 2000)	Neighbourhoods in capital cities of Burkina Faso, Ivory Coast, Mali, Mauritania, Niger and two towns and one city in Senegal (1994-1996) Urban	Prospective cohort study of all pregnant women living in defined study areas	19870 stillbirths and live births	Perinatal deaths	Not reported. Reference to missing vital status on 7th day of life for 2.3% births.	●Pregnancy: social workers, midwives, and nurses visit households to identify pregnancies (non-reported method) and within the second trimester, around 8 months of pregnancy, at delivery and before 60 days post-delivery. ●Birth and death: from questionnaires filled daily by midwives in wards for hospital births and from interview with the mother and relatives for home deliveries.	Questionnaires filled daily by midwives in wards for hospital births and from interview with the mother and relatives within a few days of birth for home deliveries.
(Bari et al. 2002)	1 district each from Dhaka, Rajshahi, Chittagong and Khulna divisions, Bangladesh (1992-93) Rural	Prospective cohort study of pregnant women of less than 6 weeks' pregnancy	924 stillbirths and live births	Perinatal deaths	SB*: No definition END**: Deaths within 7 days of birth	●Pregnancy and birth: monthly home visits (role of visitor not reported). ●Pregnancy detection method unclear and role of person reporting births and pregnancies not reported ●Death-post-partum visit within one month of birth	Interview with mother during home visit

Study	Region (Time period) Setting	Study design	Study population	Mortality outcome(s) studied	Definitions of mortality outcome(s)	Ascertainment of pregnancy/ birth/death	Ascertainment of intrapartum complications
Bang et al. 2004	39 villages in Gadchiroli district, Maharashtra state, India (1995-1996) Rural	Prospective cohort of pregnant women in study area	772 stillbirths and live births	Perinatal deaths and stillbirths	PND***: stillbirths and deaths within 0-6 days SB: Delivery of a baby that showed no breathing, crying or muscular movements at birth. (≥28 weeks' gestation)	●Pregnancy: Unclear. Listing of pregnant women by research CHW (visit frequency not reported) and asked about LMP date. Research CHW visits pregnant women thrice, every 1 month in third trimester. ● Birth: Unclear. Research CHW attended labour when called by mother and reported some births. Different male CHWs also 'reported prospectively' and detected missed births in 6-monthly cross-sectional surveys. ●Death: Research CHW visited on Days 2,3,5,7,14,21 and 28. Deaths also detected by different male CHWs as for 'Birth' above.	From observational records made by CHW during delivery by traditional birth attendants. For hospital births (5.1%) ascertainment was unclear as "partly observed by CHW"
(Cherry et al. 2008)	600 villages in Dhaka, Barisal, Chittagong and Sylhet divisions, Bangladesh (2001-03) Rural	Retrospective cohort study of pregnant women living within study area	30984 stillbirths and live births	Stillbirths	Neonates observed to breathe but failing to establish viable respiration	●Pregnancy: female 'paramedic' visits households (frequency not reported). ●Birth: Unclear (possibly interview) ●Death: Unclear (possibly interview)	Unclear (possibly interview)
(Flenady et al. 2011)	Australia, Canada, Netherlands, UK and USA (1998-2009) Urban and rural.	Systematic review of 96 population-based studies (including cross-sectional, retrospective and prospective cohort and case-control studies), addressing risk factors for stillbirths	96 study populations of mothers with risk factors (demographic, lifestyle related, medical conditions and pregnancy complications) for stillbirths	Stillbirths	Study stillbirth definitions included gestation of 20 weeks or more, or a birth weight of at least 400g	●Pregnancy, birth and death: from national databases, birth and perinatal registries and linked birth/death/ maternal data and hospital records	From national databases, birth and perinatal registries and linked birth/death/maternal data and hospital records

*SB- stillbirth **END- early neonatal death ***PND- perinatal death

Table 6.1 A: Definitions of intrapartum complications in **population-based studies** investigating the strength of association between intrapartum complications **(dystocia and hypertensive diseases of pregnancy)** and perinatal mortality

Study	**Intrapartum complications**									
	Dystocia						**Hypertensive diseases of pregnancy**			
	Prolonged labour	**Obstructed labour**	**Malpresentation**				**Pre-eclampsia**	**Eclampsia**	**Other**	**All**
			Breech	**Non-breech**	**Non-cephalic**	**All**				
Kusiako et al. 2000	Not defined	Not defined	Yes	Not defined	_	_	Diastolic blood pressure≥ 90 mmHg with moderate-to-severe tibial oedema or proteinuria	Not defined	_	No
Chalumeau et al. 2000	Labour length> 12 hr	_	_	_	Brow, face, compound , shoulder and breech presentations	_	Clinical diagnosis	Clinical diagnosis	Diastolic blood pressure ≥90mmHg	Yes
Bari et al. 2002	Not defined	Not defined	_	_	_	_	_	_	_	_
Bang et al. 2004	Labour length> 24 hr from the onset of mild pains to the birth of the baby	_	_	_	_	Face, shoulder, hand, leg or breech presentation	_	_	_	_
Cherry et al. 2008	Not defined	_	_	_	_	_	_	_	_	_

Flenady et al. 2011	_	_	_	_	_	_	Not defined	Not defined	Not defined	_

Table 6.1 B: Definitions of intrapartum complications in **population-based studies** investigating the strength of association between intrapartum complications **(haemorrhage, infection, multiple pregnancy and** anaemia) and perinatal mortality

Study	**Intrapartum complications**									
	Haemorrhage						**Infection**	**Multiple pregnancy**	**Anaemia**	**Grouped intrapartum complications**
	Placenta praevia	**Placental abruption**	**Placenta accreta/ increta/percreta**	**Ruptured uterus**	**Other haemorrhage**	**All**				
Kusiako et al. 2000	_	_	_	_	_	Not defined	_	Yes	Clinical diagnosis	Yes
Chalumeau et al. 2000	_	_	_	_	_	_	_	_	_	No
Bari et al. 2002	_	_	_	_	_	Not defined	_	_	_	No
Bang et al. 2004	_	_	_	_	_	_	_	_	_	No
Cherry et al. 2008	_	_	_	_	_	Not defined	_	Yes	_	No
Flenady et al. 2011	_	Not defined	_	_	_	_	_	_	_	_

Table 6.1 C: The strength of association between intrapartum complications **(dystocia and hypertensive diseases of pregnancy)** and perinatal mortality in **population-based studies** investigating this relationship.

Study	**Confounders adjusted for**	**Intrapartum complications (crude OR** and adjusted OR**)~**									
		Dystocia						**Hypertensive diseases of pregnancy**			
		Prolonged labour	**Obstructed labour**	**Malpresentation**				**Pre-eclampsia**	**Eclampsia**	**Other**	**All**
				Breech	**Non-breech**	**Non-cephalic**	**All**				
Kusiako et al. 2000	Maternal age, parity, poor obstetric history, anthropometric measurements, pregnancy signs and symptoms (anaemia, pre-eclampsia, fever, jaundice and vaginal bleeding), gestational length, complications during labour.	**3.5 [2.6-4.8]** 2.5 [1.8-3.7]	**23.8 [6.7-85.0]** 26.4 [6.6-105.0]	**9.6 [6.4-14.7]** 8.3 [5.3-13.2]	**17.0 [8.3-33.5]** 16.6 [7.6-36.1]	_	_	**2.5 [1.7-3.7]** _	**6.4 [3.0-13.8]** 7.9 [3.3-18.8]	_	_
Chalumeau et al. 2000	Socio-economic status, poor obstetric history, anthropometric factors, other complications	**2.1 [1.7-2.4]** 2.6 [1.7-4.0]	_	_	_	**6.2 [4.8-7.8]** 4.8 [3.5-6.5]	_	_	_	**5.5 [4.1-7.3]** 2.6 [1.7-4.0]	_
Bari et al. 2002	Maternal age, socio-economic status, parity, history of anaemia, delivery mode, delivery location, birth attendant type, special food intake during pregnancy, colostrum provision (for END), antenatal haemorrhage, labour complications.	**NR** † 1.5 [0.6-3.5]	**NR** 0.9 [0.4-1.9]	_	_	_	_	_	_	_	_

Study	**Confounders adjusted for**	**Intrapartum complications (crude OR** and adjusted OR)**~**								
		Dystocia						**Hypertensive diseases of pregnancy**			
		Prolonged labour	**Obstructed labour**	**Malpresentation**				**Pre-eclampsia**	**Eclampsia**	**Other**	**All**
				Breech	**Non-breech**	**Non-cephalic**	**All**				
Bang et al. 2004	None	PND*: **1.0 [0.4-2.6]** SB**: **1.7 [0.5-5.6]**	_	_	_	_	PND: **8.7 [4.8-15.7]** SB: **10.9 [4.5-26.9]**	_	_	_	_
Cherry et al. 2008	Maternal age, socio-economic status, parity, infant sex, multiple pregnancy, gestational length, history of stillbirth, delivery place and birth weight (visual estimation).	**11.9 [9.8-14.4]** 6.5 [5.0-8.4]	_	_	_	_	_	_	_	_	_
Flenady et al. 2011	Age, smoking, parity, race, medical conditions, infant sex, and antenatal care	_	_	_	_	_	_	**NR** 1.6 [1.1-2.2] (meta-analysis of 3 studies)	**NR** 2.2 [1.5-3.2] (single study- study not identified)	**NR** 1.3 [1.1-1.6] (meta-analysis of 4 studies)	_

*PND- perinatal deaths **SB- stillbirths ~Except for Bang et al. 2004 which reports relative risks (RR) †NR=Not Reported

Table 6.1 D: The strength of association between intrapartum complications **(haemorrhage, infection, multiple pregnancy and anaemia)** and perinatal mortality in **population-based studies** investigating this relationship.

Study	**Intrapartum complications (crude OR** and adjusted OR**)~**									
	Haemorrhage						**Infection**	**Multiple pregnancy**	**Anaemia**	**Grouped intrapartum complications**
	Placenta praevia	**Placental abruption**	**Placenta accreta/ increta/percreta**	**Ruptured uterus**	**Other**	**All**				
Kusiako et al. 2000	_	_	_	_	_	**1.4 [0.8-2.3]** _	_	**3.7 [2.0-6.8]** _	**1.7 [0.9-3.1]** _	**_** 5.36 [4.1-7.1]
Chalumeau et al. 2000	_	_	_	_	_	**13.0 [9.3-18.2]** 4.7 [2.7-8.0]	_	_	_	_
Bari et al. 2002	_	_	_	_	_	**NR†** 0.7 [0.2-2.1]	_	_	_	_
Bang et al. 2004	_	_	_	_	_	_	_	_	_	_
Cherry et al. 2008	_	_	_	_	_	**11.5 [8.2-16.1]** 1.7 [1.2-2.7]	_	**5.2 [3.2-8.4]** 3.0 [1.7-5.7]	_	_
Flenady et al. 2011	_	**15.4 [NR†]** 18.9 [16.9-20.8] (single study)	_	_	_	_	_	_	_	_

†NR=Not Reported

All three facility-based studies were cross-sectional (Table 6.2). Studies took place at a rural district hospital in Kenya (Weiner et al. 2003), two rural hospitals in the Gambia which provided comprehensive obstetric care (Jammeh et al. 2010) and at secondary and tertiary hospitals which performed Caesarean sections in 29 countries (Vogel et al. 2014). Of the three facility studies, data were collected specifically for study purposes for only one study (Weiner et al. 2003), while the other two obtained data from routine hospital records (Jammeh et al. 2010) and from a previous WHO study exploring maternal deaths and mothers who almost died (Vogel et al. 2014). Only the Vogel et al. study provided definitions for all the complications that were examined (Tables 6.2 A-6.2 B). It was not clear whether complications were recorded before or after outcomes and so differential misclassification of complications could have occurred. More adverse complications could be noted for stillbirths compared to live births, for example, and this might have resulted in elevation of odds ratios observed.

Intrapartum complications increased perinatal mortality odds. Among hypertensive disorders, pre-eclampsia increased odds of perinatal mortality by 3 to 4 times (Weiner et al. 2003; J P Vogel et al. 2014) while eclampsia increased them by 11 to 13 times (Weiner et al. 2003; J P Vogel et al. 2014). Combined haemorrhagic disorders resulted in a 24-fold increase in odds of perinatal mortality (Weiner et al. 2003) while the Vogel et al. study showed that ruptured uterus, placental abruption, placenta praevia and deformities of the placenta resulted in a 78-fold to four-fold increase (Table 6.2 C). Infection was only assessed by the Vogel et al. study and was associated with elevated mortality in both stillbirths (ORs ranging from 1.2-5.3) and early neonatal deaths (ORs ranging from 4.4-7.0). Anaemia increased the odds of perinatal mortality from two-fold (Weiner et al. 2003) to almost eight-fold (Vogel et al. 2014). Generally, facility-based studies tended to report higher magnitudes for strength of association between intrapartum complications and perinatal mortality than population-based studies.

From the very few studies reviewed, intrapartum complications appear to increase perinatal mortality while the magnitude varies, depending on the type of complication. Dystocia and haemorrhage were found to have the highest magnitude of effect, though hypertensive diseases of pregnancy were also found to elevate perinatal mortality. Increases in perinatal mortality were seen for multiple pregnancies, and the effects of anaemia and infection also suggested an increase. However, even the HIC systematic review is based on only a few studies for each complication (three for pre-eclampsia and one each for eclampsia and placental abruption) and complication definitions or criteria are not provided in the review. In LIC cases,

the evidence comes from a few studies, including those where ascertainment of pregnancy, birth, deaths and intrapartum complications is unreliable or of poor quality, and complications are mostly undefined. Furthermore, definitional issues, described later, also need to be taken into consideration. From the literature available, there appears to be an association between different intrapartum complications and perinatal mortality, but the evidence for this, particularly from LICs, is not strong and is based on very few studies.

Table 6.2: Study characteristics of **facility-based studies** investigating the strength of association between intrapartum complications and perinatal mortality

Study	**Region (Time period) Setting**	**Study design**	**Study population**	**Mortality outcome(s) studied**	**Definitions of mortality outcome(s)**	**Ascertainment of pregnancy/ birth/death**	**Ascertainment of intrapartum complications**
(Weiner et al. 2003)	District hospital in Kilifi district, Kenya [1996-1997] Rural	Cross-sectional study of women who gave birth at the hospital	910 stillbirths and live births	Perinatal deaths	Stillbirths (no further details) and deaths in the first week of life	●Pregnancy, birth and death: from hospital records	From hospital records
(Jammeh et al. 2010)	2 rural hospitals with comprehensive obstetric care in North and South Bank regions, The Gambia (July-2008 to Dec 2008) Rural	Retrospective cross-sectional study of all women giving birth in the hospital at or after 28 weeks of gestation	1519 stillbirths and live births	Stillbirths	Death of an infant in the uterus at ≥28 weeks of gestation or ≥ 1000 g.	●Pregnancy, birth and death: from hospital records	From hospital records
(J P Vogel et al. 2014)	359 secondary and tertiary facilities which deliver >1000 deliveries per year and perform Caesarean sections in 29 countries (2010-2011) Capital cities and provinces Urban and rural	Cross-sectional facility-based study of all women giving birth and those who died or almost died ('near miss') from pregnancy and delivery complications (including abortion or ectopic pregnancy)	308392 stillbirths and live births	Stillbirths Early neonatal deaths	SB: foetal death of birth weight ≥ 1000g, or if birth weight unknown, at ≥ 28 weeks of gestation. END: neonatal death: death of a live born neonate by discharge/ day 7 of life.	●Pregnancy, birth and death: at discharge from the hospital from records filled by medical staff	From hospital records

*SB- stillbirth **END-early neonatal death

Table 6.2 A: Definitions of intrapartum complications in **facility-based studies** investigating the strength of association between intrapartum complications **(dystocia and hypertensive diseases of pregnancy)** and perinatal mortality

Study	**Intrapartum complications**									
	Dystocia						**Hypertensive diseases of pregnancy**			
	Prolonged labour	**Obstructed labour**	**Malpresentation**				**Pre-eclampsia**	**Eclampsia**	**Other**	**All**
			Breech	**Non-breech**	**Non-cephalic**	**All**				
Weiner et al. 2003	Not defined	Not defined	_	_	_	Yes	Not defined	Not defined	_	_
Jammeh et al. 2010	Not defined	Not defined	_	_	_	_	Not defined	Not defined	_	_
Vogel et al. 2014	_	_	_	_	_	_	Hypertension (blood pressure greater than 140/90mmHg) associated with proteinuria in women previously normotensive.	Convulsions and/or coma unrelated to other cerebral conditions in women with signs and symptoms of pre-eclampsia. Seizures are of grand mal type and may first appear before labour, during labour, or up to 48 hours postpartum.	Blood pressure greater than 140/90, diagnosed prior to the onset of pregnancy or before the 20th week of gestation.	No

Table 6.2 B: Definitions of intrapartum complications in **facility-based studies** investigating the strength of association between intrapartum complications **(haemorrhage, infection, multiple pregnancy and anaemia)** and perinatal mortality.

Study	**Intrapartum complications**									
	Haemorrhage						**Infection**	**Multiple pregnancy**	**Anaemia**	**Grouped intrapartum complications**
	Placenta praevia	**Placental abruption**	**Placenta accreta/ increta/percreta**	**Ruptured uterus**	**Other haemorrhage**	**All**				
Weiner et al. 2003	_	_	_	_	_	Antepartum haemorrhage and/or placental abruption. Placenta praevia excluded	_	_	_	Yes
Jammeh et al. 2010	Not defined	Not defined	_	_	_	_	_	_	Haemoglobin level <9g/dl	Yes
Vogel et al. 2014	Low implantation of the placenta, where it is partially or completely placed over the internal ostium of the uterus	Premature separation of the placenta	Abnormally adherent placenta with variable degrees of myometrium penetration	Breach of the myometrial wall which may be complete or incomplete	Haemorrhage primarily caused by an obstetric condition and not classifiable	No	Pyelonephritis (bacterial infection of one or both kidneys), sepsis (bacterial/ fungal infection) with tachycardia and hypotension. Pneumonia, peritonitis, post-operative abdominal infections.	_	Haemoglobin level <7mg per dl	No

Table 6.2 C: The strength of association between intrapartum complications **(dystocia and hypertensive diseases of pregnancy)** and perinatal mortality in **facility-based studies** investigating this relationship.

Study	**Confounders adjusted for**	**Intrapartum complications (crude OR** and adjusted OR**)**									
		Dystocia						**Hypertensive diseases of pregnancy**			
		Prolonged labour	**Obstructed labour**	**Malpresentation**				**Pre-eclampsia**	**Eclampsia**	**Other**	**All**
				Breech	**Non-breech**	**Non-cephalic**	**All**				
Weiner et al. 2003	Gravidity, previous stillbirths, education, antenatal care visits, haemoglobin and body mass index	**2.7 [1.6-4.8]** see ~	Same as for prolonged labour	_	_	_	_ ~7.9 [3.9-15.9]	**3.3 [1.7-6.5]** see ~~	**13.0 [4.1-41.2]** see ~~	_	_ ~~1.9 [0.8-4.9]
Jammeh et al. 2010	Maternal age, parity, area of residence, referred or not, antenatal care, delivery mode, partograph use, multiple pregnancy and birth weight	_	_	_	_	_	_	_	_	_	_
Vogel et al. 2014	Maternal age, marital status, maternal education, number of previous births, number of previous Caesarean sections, foetal presentation, congenital malformation, infant sex, gestational age, facility level and country	_	_	_	_	_	_	SB*: **3.6 [NR†]** 2.3 [1.8.-2.8] END**: **3.9 [NR]** **1.7**[1.4-2.2]	SB: **12.0 [NR]** 3.3 [2.3-4.6] END: **11.5 [NR]** 4.8 [3.2-6.2]	SB: **3.2 [NR]** 1.3 [1.0.-1.7] END: **3.8 [NR]** 0.9 [0.5-1.6]	_ _

†NR=Not Reported *SB- stillbirth **END-early neonatal death

Table 6.2 D: The strength of association between intrapartum complications **(haemorrhage, infection, multiple pregnancy and anaemia)** and perinatal mortality in **facility-based studies** investigating this relationship.

Study	**Intrapartum complications (crude OR** and adjusted OR**)**									
	Haemorrhage						**Infection**	**Multiple pregnancy**	**Anaemia**	**Grouped intrapartum complications**
	Placenta praevia	**Placental abruption**	**Placenta accreta/ increta/percreta**	**Ruptured uterus**	**Other**	**All**				
Weiner et al. 2003	_	_	_	_	_	**24.3 [6.2-94.2]** 61.9 [14.0-274.2]	_	_	**2.2 [1.1-4.3]** 1.0 [0.4-2.7]	_
Jammeh et al. 2010	_	_	_	_	_		_	_	_	**11.7 [8.6-16.1]** 6.7 [3.8-11.6]
Vogel et al. 2014	SB*: **5.4 [NR†]** 1.2 [0.8-1.8] END**: **5.8 [NR]** 1.2 [0.8-1.6]	SB: **33.2 [NR]** 12.4 [8.2-18.8] END: **3.8 [NR]** 0.9 [0.5-1.6]	SB: **3.2 [NR]** 1.3 [1.0.-1.7] END: **15.2 [NR]** **4.0** [2.7-5.9]	SB: **78.3 [NR]** 45.3 [23.2-88.2] END: 10.7 **[NR]** 4.2 [1.9-9.5]	SB: **5.8 [NR]** 1.5 [0.9.-2.57] END: **5.4 [NR]** 3.2 [1.8-9.5]	_ _	Pyelonephritis: SB: **1.3 [NR]** 1.2 [0.2-9.1] END: **4.4 [NR]** 1.7 [0.9-3.0] Other/sepsis: SB: **5.3 [NR]** 2.7 [1.9.-4.0] END: **7.0 [NR]** 2.3 [1.3-4.0]	_	SB: **7.7 [NR]** 2.6 [2.2-3.1] END: **4.0 [NR]** 1.4 [1.1-1.8]	_

†NR=Not Reported *SB- stillbirth **END-early neonatal death

Available studies have been hampered by the absence of standardized definitions for intrapartum complications. This is described below.

There is no standard conceptualisation or definition of intrapartum complications. First, while it is understood that intrapartum complications consist of labour and childbirth complications (Lawn, Lee et al. 2009), it is not clear whether these refer only to maternal obstetric or also to foetal complications. Recent papers related to intrapartum complications and mortality reduction do not clarify this issue (Bhutta et al. 2014; Lawn et al. 2014; Lee et al. 2011; Yakoob et al. 2011). Among the studies tabulated above (Tables 6.1-6.2) most involve only maternal complications (Vogel et al. 2014; Kusiako et al. 2000; Weiner et al. 2003). Weiner et al.(2003), listed foetal abnormalities under intrapartum complications. Recent recommendations suggest that foetal congenital abnormalities should be excluded from deaths related to intrapartum events (Lawn, Lee et al. 2009), possibly because these deaths are not results of adverse intrapartum events.

Second, within the broad categories of maternal and foetal complications, there is no consensus on which conditions qualify as maternal or foetal complications. For example, malpresentation, e.g. breech or transverse lie, can be considered either a poor positioning of the foetus leading to adverse foetal outcomes (foetal complication) or a condition endangering a safe vaginal delivery (maternal complication). The International Classification of Diseases (Tenth Revision) (World Health Organization 2004a) considers malpresentation to be a pregnancy and childbirth complication, but no further clarification is presented.

Third, the definitions of specific complications have been variable. For example, intrapartum haemorrhage has been defined as ‘intrapartum haemorrhage’(Kusiako et al. 2000) and also as ‘antepartum haemorrhage’(Weiner et al. 2003). Vogel et al., in the WHO multi-country study, have defined haemorrhage as related to specific complications (e.g. ‘placenta praevia’, 'placental abruption’) (Vogel et al. 2014). Prolonged labour definitions have also been inconsistent with the WHO definitions that suggested durations of more than 8 and 12 hours for the first and second stages of labour, respectively (World Health Organization 2008). The studies used the terms ‘prolonged labour’(Kusiako et al. 2000), ‘labour length >12 hrs’ (Chalumeau et al. 2000) and labour length >24 hrs (Bang et al. 2004) with no clarification on the stage of labour. The confusion caused by the inconsistent terminology and lack of specificity regarding maternal complication definitions has also been highlighted elsewhere (Koblinsky et al. 2012; Prual et al. 2000)

Fourth, maternal medical conditions (e.g. anaemia, malaria, tuberculosis, diabetes etc.) while not essentially obstetric complications, may complicate delivery (Koblinsky et al. 2012) and impact on perinatal survival (Vogel et al. 2014; Kusiako et al. 2000; Loto & Awowole 2012; Macintosh et al. 2006; Lumbiganon et al. 2014). However there is no consensus on whether these conditions constitute intrapartum complications. Vogel et al. (2014)considered anaemia to be a maternal complication while others categorised it as an antepartum factor (Lawn, Lee et al. 2009; Kusiako et al. 2000).

Evidence for the association between intrapartum complications and perinatal mortality is based on studies that suffer from definitional issues as well as methodological issues. The strength of association from LICs relies on very few well-conducted studies. My study in Matlab allows the exploration of all major intrapartum complications that take place during deliveries at rural facilities in Bangladesh, in a cohort with good follow-up. This rural population also has data on preterm gestation and socio-demographic characteristics, all obtained from a routine demographic and health surveillance system, which has been running in the community for half a century. This study, which has access to intrapartum complications diagnosed by hospital staff, presents a unique and timely research opportunity to explore the effect of intrapartum complications on perinatal mortality in a poor rural community in Bangladesh, where women increasingly deliver in health facilities.

6.2 Objectives:

Overall Objective

The overall objective is to examine the contribution of intrapartum complications to perinatal deaths in a rural cohort in Matlab, Bangladesh.

Specific Objectives

1) To examine perinatal mortality, socio-demographic characteristics and length of gestation by highest level of care accessed in a cohort of women in Matlab, Bangladesh.
2) To examine perinatal mortality, delivery location and socio-demographic characteristics by whether or not data on intrapartum complications are available in women who deliver at health facilities.
3) To examine the prevalence of intrapartum complications in women delivering at health facilities.
4) To examine the prevalence of intrapartum complications by delivery location, socio-demographic characteristics and preterm gestation in births for which any intrapartum complication was present or absent.
5) To examine the strength of association between intrapartum complications and perinatal deaths in women delivering at health facilities.

6.3 Methods:

6.3.1 Study design

This is a retrospective cohort study of all women living in the ICDDR,B service area in Matlab, Bangladesh, who have had pregnancies ending in a live birth or a stillbirth between 1st January 2007 and 31st December 2008.

6.3.2 Data sources, collection and quality:

I described the Matlab demographic and health surveillance programme (HDSS) and definitions for socio-demographic variables previously in Chapter 4 (section 4.3). I also defined preterm births and categorised gestational age into groups including an 'unknown' group as described earlier in Chapter 5. As in preceding chapters, all deliveries were termed 'births' irrespective of single or multiple birth outcomes.

The recording procedure for antepartum complications in the ICDDR,B hospital underwent an administrative change in mid-2007 (onset of the MNCH programme described in Chapter 4) and not all the information recorded in the antenatal care records was fully entered into datasets. This information included proteinuria results and blood pressure measurements (for diagnosis of preeclampsia) as well as blood sugar measurements (for diabetes). As complete information on antepartum complications was unavailable at the time of this study, I was unable to measure the impact on perinatal mortality.

I obtained data on intrapartum complications from a study (Matlab Maternal Morbidity Study) by (Huda et al. 2012) which investigated intrapartum complications in the ICDDR,B service area among women delivering in Matlab and Chandpur hospitals during 2007-2008. In this study, community health workers made home-visits to all the ICDDR,B service area women who delivered between 2007-2008 to ask about stillbirths or early neonatal death, and about the facilities visited before, during and after delivery. This information was independent of data recorded during routine HDSS surveillance. Using this information, a physician conducted record-reviews of all admissions of these women during labour or up to 42 days postpartum in the following hospitals: the Matlab ICDDR,B hospital, one public Matlab hospital, and two public and 26 private hospitals in Chandpur. Information on complications was not available for women delivering outside Matlab and Chandpur. Information was extracted from admission registers, as well as individual patient records, where available. A maximum of two facility visits for each woman was recorded in this study. The complications were those

recorded by health professionals in the relevant facility and were further coded according to the International Classification of Diseases (Tenth version) (World Health Organization 2010)

Mortality outcomes:

I obtained information on stillbirths and early neonatal deaths, as defined in Chapter 4. The sample of births was too small, however, to enable mortality outcomes to be broken down into stillbirths and early neonatal deaths. Perinatal mortality was, therefore, the only mortality outcome that I used in my study.

Where births recorded in the Huda et al. 2012 study did not link with the HDSS dataset, I obtained mortality outcomes from community health worker home visits and facility records.

Intrapartum complications:

I defined intrapartum complications as those detected during the time of labour and delivery. I only examined maternal complications (including anaemia and multiple pregnancy) as the focus of this study is on the impact of maternal labour complications on perinatal mortality. I considered foetal complications and disorders of the amniotic fluid and membranes to be on the causal pathway between labour complications and perinatal mortality. I excluded information on post-partum complications (including cervical or perineal tear, post-partum haemorrhage and puerperal sepsis) as these were not temporally related to mortality. I also did not consider mode of delivery (including Caesarean section) as an intrapartum complication, as it lies on the causal pathway between intrapartum complications and perinatal mortality. Congenital anomalies (e.g. anencephaly) were not included in intrapartum complications in order to be consistent with a recent recommendation (Lawn, Lee et al. 2009).

Information on complications in the Huda et al. 2012 study dataset (Huda et al. 2012) was available under ‘initial diagnoses’, ‘final diagnoses’ and ‘indications for surgery/any major obstetric interventions’. I extracted data on complications from: (i) the ‘final diagnoses’ and (ii) ‘the indications for surgery/any major obstetric interventions’ (i.e. emergency or elective Caesarean section, hysterectomy, hysterotomy, laparotomy, craniotomy or symphysiotomy). I used ‘final diagnoses’ as this detected greater numbers of complications than ‘initial diagnoses’ and as I considered final diagnoses to provide better information on the complication.

The Huda et al. 2012 study entered standardized information on complications under ‘final diagnosis’ and ‘indication for surgery’, including a standardised text variable as well as the ICD

code. Their dataset allowed for up to five diagnoses for the 'final diagnosis' and the 'indications for surgery'. The Huda et al. 2012 study code plan is shown in Appendix IV. The dataset contained information on a maximum of two records per woman if the woman had made two hospital visits. As data on the hospital's name was unavailable for the second visit, it was not known if women with two records had visited two different hospitals or had visited the same hospital twice.

I grouped complications as shown below, with any Huda et al. 2012 dataset text presented in quotation marks. Information on anaemia was obtained from haemoglobin levels, where available, and on multiple pregnancy from the HDSS information.

Any intrapartum complication - diagnosis of any of the intrapartum complications listed below.

Dystocia - diagnosis of any of: cephalo-pelvic disproportion, malpresentation, obstructed labour or prolonged labour.

Cephalo-pelvic disproportion : "cephalo-pelvic disproportion (CPD)", "big baby" or "floating head (high head)".

Malpresentation:

Non-breech malpresentation: "malpresentation, unspecified", "malpresentation, unstable lie", "compound presentation/ occipitoposterior" or "transverse or oblique lie".

Breech malpresentation: "breech presentation" or "spontaneous breech delivery".

Obstructed labour: "obstructed labour due to malposition & malpresentation of foetus", "obstructed labour due to malposition & malpresentation, unspecified", "obstructed labour due to unusually large foetus", "obstructed labour, unspecified" or "ruptured uterus during labour".

Prolonged labour: "prolonged labour, prolonged 1st stage of labour" or "prolonged labour, prolonged 2nd stage of labour".

Hypertensive diseases of pregnancy: diagnosis of any or a combination of: eclampsia, pre-eclampsia or other hypertensive diseases of pregnancy

Eclampsia: "eclampsia"

Pre-eclampsia: "pre-eclampsia"

Other hypertensive disorders of pregnancy: "pregnancy induced hypertension (PIH)" or "unspecified maternal hypertension (HTN)"

Haemorrhage: "placenta praevia", "placenta accrete or malformation of placenta", "antepartum haemorrhage, unspecified" or "obstetric shock".

Infection:"chorioamnionitis", "urinary tract infection in pregnancy (UTI)" or "septicaemia during labour"

Anaemia: includes moderate and severe anaemia. Mild anaemia is excluded. Anaemia is measured by haemoglobin levels and defined as haemoglobin levels of <10 g/dl.

Multiple pregnancy: as identified from HDSS data (twins or triplets).

Definition of prevalence for intrapartum complication:

$$\text{Prevalence of intrapartum complication} = \frac{\text{the number of births with the complication}}{\text{all stillbirths and livebirths}} \times 100$$

The denominator contains births with non-realistic gestational ages of <22 weeks and >50 weeks which I categorised under 'unknown' preterm births. These were not excluded from the analysis as I did not wish to further reduce the small sample of births available for analysis.

Missing data:

My study assumed that data missing for a certain complication (e.g. "placenta praevia") in a birth obtained from "final diagnosis" or "indication of surgery" was equivalent to the absence of that particular complication, provided the woman had some other information on complication recorded in the dataset (e.g. "pregnancy-induced hypertension" or "single spontaneous vertex delivery"). This is because it is common practice in Bangladeshi hospitals to record only the complications present in a birth and not the complications that are absent. Births with missing data on haemoglobin level were assumed to be unknown because the large majority of births had no information. Where data on multiple pregnancy were missing the

birth was considered to be singleton. Births with missing gestational age data were categorised as 'unknown'.

Delivery location:

Deliveries taking place en route to any health facility where deliveries were conducted were considered to be home deliveries. Delivery locations (from lowest to highest level of care) are listed below:

1. Home
2. ICDDR,B sub-centre
3. ICDDR,B Matlab hospital
4. Matlab and Chandpur hospitals

   These included:

   a. Matlab sub-district (*Thana/Upazila*) hospital (only public hospital in Matlab; 31 bed; conducts uncomplicated vaginal deliveries)
   b. Chandpur Maternal and Child Welfare Centre (public hospital; 10 bed; conducts Caesarean sections)
   c. Chandpur District Hospital (public hospital in Chandpur; 200 bed; conducts Caesarean sections)
   d. Chandpur district hospitals and clinics-at least 26 (private hospitals; majority conduct Caesarean sections)
5. Hospitals beyond Chandpur

   These included:

   a. Narayanganj District Hospital (public hospital; 200 bed; conducts Caesarean sections) and Narayanganj Town hospitals and clinics (public and private hospitals)
   b. Dhaka City hospitals and clinics (public and private hospitals)

6.3.3 Analysis:

I linked all HDSS records and intrapartum complication records by unique identifiers consisting of the mother's registration number and the delivery date.

I used different samples for (i) analyses related to the description of the initial sample and (ii) analyses relating to intrapartum complications.

Analyses relating to the description of the initial sample

To examine the percentage distribution of births at different delivery locations, I used the sample of births to women in the ICDDR,B service area during 2007-2008 from the Huda et al. 2012 study. I then presented perinatal mortality rates by delivery location and obtained 95% confidence intervals (obtained by the prtesti command in Stata) to explore whether there was any statistically significant difference in perinatal mortality rates by delivery location. I also assessed whether the distribution of socio-demographic characteristics of women and occurrence of preterm gestation differed significantly by place of delivery, using a chi-square test. In this analysis, the sample consisted of fewer births than the analysis by delivery location, as it contained only births for which HDSS socio-demographic characteristics were available.

Analyses relating to intrapartum complications

For this analysis, my initial sample consisted of births taking place at the Matlab ICDDR,B hospital and the hospitals at Matlab and Chandpur since these were the only sites for which information on complications were collected by Huda et al. I divided births into 1) those where data were available for intrapartum complications and 2) those where data were unavailable for intrapartum complications. Data were considered available if records were available for these births at the hospitals.

I checked if there were any biases between births with available and unavailable intrapartum complication data. I assessed whether perinatal mortality rates differed significantly by data availability by using 95% confidence intervals (obtained by the prtesti command in Stata) and used chi-square tests to assess whether delivery location, socio-demographic characteristics and preterm gestation differed significantly by data availability. The sample for the latter analysis consisted only of births for which HDSS socio-demographic characteristics and preterm gestation were known.

Multiple imputation of data for births with missing information on preterm gestation (17 of 4317 births, 0.4% births) and socio-demographic characteristics (500 of 4817 births, 10.4% births) which could have provided a larger sample size was not performed due to time restrictions in the PhD.

I assessed perinatal mortality rates among emergency Caesarean section deliveries, comparing births with and without intrapartum complications. This analysis was done because births by emergency Caesarean section but with no intrapartum complications could potentially be births with complications for which intrapartum complications had not been noted. I also compared perinatal death rates in births with and without a history of previous Caesarean sections because Caesarean section births could potentially have similar complications to the preceding Caesarean section birth. In order to explore the quality of recording of complications by hospitals, I explored perinatal mortality rates in births with and without foetal distress (a foetal and not maternal obstetric complication) to check if perinatal mortality was significantly higher, as would be expected, in births with foetal distress.

I explored the prevalence of intrapartum complications, whether present as a single complication or as multiple complications. I also obtained the prevalence of births with a single complication and with two, three and four complications occurring in a birth, for all the births, and presented the most common combinations of complications.

I assessed the percentage of women who had two hospital visits for the same pregnancy.

I presented the prevalence of intrapartum complications according to delivery location, socio-demographic characteristics and pre-term gestation.

I used a random-effects logistic regression model to account for the clustering of births to one mother (using the 'xtlogit' command with the're' option in Stata) and obtained crude and adjusted odds ratios for the association between intrapartum complications and perinatal mortality, as well as that between preterm gestation and perinatal mortality. I obtained adjusted odds ratios for (a) the relationship between any intrapartum complications and perinatal mortality and for (b) 'grouped' intrapartum complications and perinatal mortality. For (b) adjusted odds ratios were obtained for 'groups' of similar complications: dystocia, hypertensive diseases of pregnancy, haemorrhage, infection, multiple pregnancy and anaemia. The aim of the grouping was to reduce misclassification between complications with similar presentation in the absence of set definition criteria in the hospitals (i.e. prolonged labour and

obstructed labour were grouped together under ‘dystocia’, and eclampsia and pre-eclampsia were grouped under ‘hypertensive diseases of pregnancy’).

For (a), I considered delivery location, socio-demographic characteristics and preterm gestation to be potential confounders and adjusted for these in my logistic regression model for adjusted odds ratios. For (b), in addition to the confounders mentioned in (a), other labour complications could act as confounders or could be present on the causal pathway between the complication studied and perinatal mortality. This depended on which particular ‘grouped’ labour complication was acting as the exposure, as shown in Table 6.3. In the adjusted analysis for each group of complications, I adjusted for another intrapartum complication if I considered it to be a confounder. I did not adjust for it if I thought it was on the causal pathway (Table 6.3) on the basis of my clinical knowledge. If I did not consider a group of complications to be confounded by other intrapartum complications, I adjusted only for the confounders mentioned in (a).

Table 6.3: Labour complications as possible confounders or possibly present on the causal pathway in the association between particular labour complications and perinatal mortality

Exposure	Other labour complication likely to be a **confounder***	**Outcome**
Dystocia	Multiple pregnancy	Perinatal mortality
Infection	Dystocia	Perinatal mortality
Anaemia	Haemorrhage	Perinatal mortality
Exposure	Other labour complication likely to be on **causal pathway**	**Outcome**
Dystocia	Infection	Perinatal mortality
Multiple pregnancy	Dystocia	Perinatal mortality
Haemorrhage	Anaemia	Perinatal mortality

*The confounder remained in the final regression model (for obtaining the adjusted odds ratio) only if it achieved a likelihood ratio test p-value of ≤0.2 in the final model

For both (a) and (b) I used a backward stepwise selection method to obtain the final adjusted model for obtaining adjusted odds ratios, retaining only the variables that achieved a likelihood ratio test p-value of ≤0.2 in the final model, as described in detail earlier (Chapter 4 section 4.3.13).

6.4 Results:

6.4.1 Description of sample

There were 5486 pregnancies in the ICDDR,B service area between 2007-2008, of which 669 ended in abortions or miscarriages. Exclusion of the latter resulted in a total of 4817 births. Perinatal mortality outcomes were known for all births while HDSS data on socio-demographic characteristics were available for 4317 (89.6%) births.

The place of delivery for the initial sample of 4817 births is shown in Table 6.4. The majority of births were at health facilities (62.5%) with just over a third (37.5%) taking place at home. One third of births (29.2%) were at the ICDDRB Matlab Hospital and 5% were at hospitals outside Chandpur.

Table 6.4: Delivery locations for 4817 Matlab births (2007-2008)

Delivery location	**No. of births (%)**
Home	1807 (37.5)
ICDDRB subcentres	689 (14.3)
ICDDRB Matlab Hospital	1408 (29.2)
Hospitals in Matlab and Chandpur*	686* (14.2)
Hospitals beyond Chandpur	227 (4.7)
Total	4817 (100)

*Of the 686 births, 29 took place at a Matlab government hospital (Matlab Thana Health Complex) while the remaining births took place in Chandpur facilities.

Table 6.5 shows that perinatal mortality rates increased, with higher levels of health facilities. The lowest perinatal mortality rate was observed in the ICDDR,B subcentre (21.8 deaths/ 1000 births; 95%CI: 10.9-32.7) while the highest perinatal death rate was seen in hospitals beyond Chandpur (88.1/1000 births; 95% CI: 51.2-125.0). Perinatal mortality rates at the Matlab and Chandpur Hospitals (53.9/1000 births; 95%CI: 37.0-70.8) were higher than those at the ICDDR,B Matlab hospital (38.4/1000 births; 95% CI:35.8-40.9) though there was no statistically significant difference (p=0.101).

Table 6.5: Perinatal mortality according to delivery location (highest level of care reached) in 4817 Matlab births (2007-2008)

Delivery location	No. of births (No. of perinatal deaths)	Perinatal mortality rate (per 1000 births)
Home	1807 (57)	31.5 (23.5-39.6)
ICDDRB subcentre	689 (15)	21.8 (10.9-32.7)
ICDDRB Matlab Hospital	1408 (54)	38.4 (35.8-40.9)
Matlab and Chandpur Hospitals	686 (37)	53.9 (37.0-70.8)
Hospitals beyond Chandpur	227 (20)	88.1 (51.2-125.0)
All	4817 (183)	38.0 (32.6-43.4)

Table 6.6 shows the distribution of socio-demographic characteristics of women giving birth and the occurrence of preterm gestation by delivery location. Women delivering in hospitals beyond Chandpur were the most educated, wealthiest and had the least number of pregnancies while women delivering at home were the poorest, least educated and had the highest number of pregnancies. Preterm births were more common in women delivering in hospitals beyond Chandpur and in those delivering at home compared to other locations.

Table 6.6: Socio-demographic characteristics of women and preterm gestation according to delivery-location in 4317 Matlab births (2007-2008)*

Socio-demographic characteristic	Location of delivery					Chi-squared test p-value
	Home n (%)	ICDDR,B subcentres n (%)	ICDDR,B Matlab Hospital n (%)	Hospitals in Matlab and Chandpur n (%)	Hospitals beyond Chandpur n (%)	
Maternal formal education (completed years)						
0	369 (23.3)	108 (16.6)	164 (12.7)	66 (11.2)	10 (5.4)	p<0.0001
1-5	491 (30.7)	159 (24.5)	291 (22.5)	73 (12.4)	20 (10.8)	
6-10	710 (44.3)	371 (57.2)	773 (59.8)	379 (64.5)	109 (58.9)	
11-16	31 (1.9)	11 (1.7)	63 (4.8)	70 (11.9)	46 (24.9)	
Unknown	1 (0.06)	0 (0)	2 (0.2)	0 (0)	0 (0)	
Household asset quintile						
Most poor	327 (20.4)	79 (12.2)	136 (10.5)	41 (7.0)	6 (3.2)	p<0.0001
Very poor	305 (19.1)	119 (18.3)	175 (13.5)	73 (12.4)	15 (8.1)	
Poor	316 (19.7)	113 (17.4)	213 (16.5)	88 (15.0)	21 (11.4)	
Less poor	260 (16.2)	156 (24.1)	220 (17.0)	100 (17.0)	36 (19.5)	
Least poor	221 (13.8)	125 (19.3)	354 (27.4)	221 (37.6)	80 (43.2)	
Unknown	173 (10.8)	57 (8.8)	195 (15.1)	65 (11.1)	27 (14.6)	
Religion						
Islam	1395 (87.1)	536 (82.6)	1169 (83.0)	502 (85.4)	145 (78.4)	p<0.0001
Hinduism/ Other	207 (12.9)	113 (17.4)	124 (9.6)	86 (14.6)	40 (21.6)	
Maternal Age						
<20	205 (12.8)	97 (15.0)	198 (15.3)	96 (16.3)	27 (14.6)	p<0.0001
20- 29	912 (56.9)	385 (59.3)	788 (60.9)	345 (58.7)	101 (54.6)	
30-39	451 (28.2)	160 (24.7)	285 (22.0)	140 (23.8)	49 (26.5)	
40+	34 (2.1)	7 (1.1)	22 (1.7)	7 (1.2)	8 (4.3)	
Gravidity						
1	841 (52.5)	316(48.7)	627 (48.5)	232 (39.5)	85 (46.0)	p<0.0001

Socio-demographic characteristic	Location of delivery					Chi-squared test p-value
	Home n (%)	ICDDR,B subcentres n (%)	ICDDR,B Matlab Hospital n (%)	Hospitals in Matlab and Chandpur n (%)	Hospitals beyond Chandpur n (%)	
2-3	375 (23.4)	215 (33.1)	434 (33.1)	266 (45.2)	72 (38.9)	
4-6	340 (21.2)	107 (16.5)	216 (15.7)	84 (14.3)	26 (14.1)	
7+	46 (2.9)	11 (1.7)	16 (1.2)	6 (1.1)	2 (1.1)	
Preterm birth (22 to 37 weeks gestational age)						
Yes	249 (15.5)	66 (10.2)	134 (10.4)	62 (10.5)	39 (21.1)	p<0.0001
No	1348 (84.1)	581 (89.5)	1152 (89.1)	523 (88.9)	146 (78.9)	
Unknown	5 (0.3)	2 (0.3)	7 (0.5)	3 (0.5)	0 (0)	
Total (4317)	1602 (100)	649 (100)	1293 (100)	588 (100)	185 (100)	

*Socio-demographic and pre-term gestation information was not available for 500 of 4817 births

6.4.2 Results related to intrapartum complications:

Of the 4817 births covered in this study, 2094 births took place at the ICDDR,B Matlab hospital or the Matlab and Chandpur hospitals included in the Huda et al. 2012 study.

Births taking place at the Matlab ICDDR,B hospital and Matlab and Chandpur hospitals had a perinatal mortality rate (43.5 deaths/ 1000 births; 95% CI: 34.7-52.2) similar to that of the 4817 births taking place in the ICDDR,B service area (38.0 deaths/ 1000 births; 95% CI: 32.6-43.4). Among the 2094 births, information on any intrapartum complication was available for 1927 births (92.0%) (Table 6.7).

Perinatal mortality rates were much higher in births with no available intrapartum complication data (89.8 deaths/ 1000 births; 95% CI: 46.5-133.1) than births with available data (39.4 deaths/ 1000 births; 95%CI: 30.6-48.1) but the difference was not statistically significant (Table 6.7).

Table 6.7: Perinatal mortality by data availability for intrapartum complications in 2094 Matlab births (2007-2008)

	Data on any intrapartum complication				p-value
	Available		Unavailable		
	No. of births (No. of perinatal deaths)	Rate per 1000 births (95% CI)	No. of births (No. of perinatal deaths)	Rate per 1000 births (95% CI)	
Perinatal mortality rate	1927 (76)	**39.4 (30.6-48.1)**	167 (15)	**89.8 (46.5-133.1)**	0.062

Table 6.8 shows the data availability for births at the ICDDR,B Matlab hospital (93.9%) and at the Matlab and Chandpur hospitals (88.2%).

Table 6.8: Data availability on intrapartum complications according to delivery location in 2094 Matlab births (2007-2008)

	Data on any intrapartum complication		
	Available	Unavailable	All
	No. of births (% of total births)	No. of births (% of total births)	No. of births (% of total births)
Delivery location			
ICDDRB Matlab Hospital	1322 (93.9)	86 (6.1)	1408 (100)
Matlab and Chandpur Hospitals	605 (88.2)	81 (11.8)	686 (100)

*Percentage of 2094 births. Percentages may not add up to 100 because of rounding.

Socio-demographic characteristics of mothers or preterm births were not significantly different for births with available or unavailable intrapartum complication data (all chi-squared test p-values >0.05) (Table 6.9).

Table 6.9: Socio-demographic characteristics and preterm gestation by data availability on intrapartum complications in 1881 Matlab births (2007-2008)†

Socio-demographic characteristic	Data on any intrapartum complication		Chi-squared test p-value
	Available No. of births (%)*	Unavailable No. of births (%)*	
Maternal formal education (completed years)			
0	220 (12.6)	10 (7.7)	0.443
1-5	340 (19.4)	24 (18.5)	
6-10	1068 (61.0)	84 (64.6)	
11-16	121 (6.9)	12 (9.2)	
Unknown	2 (0.1)	0 (0)	
Household asset quintile			
Most poor	164 (9.4)	13 (10.0)	0.941
Very poor	232 (13.3)	16 (12.3)	
Poor	276 (15.8)	25 (19.2)	
Less poor	299 (17.1)	21 (16.2)	
Least poor	537 (30.7)	38 (29.2)	
Unknown	243 (13.9)	17 (13.1)	
Religion			
Islam	1562 (89.2)	109 (83.9)	0.061
Hinduism/ Other	189 (11.0)	21 (16)	
Maternal Age			
<20	273 (15.6)	21 (16.2)	0.484
20- 29	1056 (60.3)	77 (59.2)	
30-39	393 (22.4)	32 (24.6)	
40+	29 (1.7)	0 (0)	
Gravidity			
1	646 (36.9)	54 (41.5)	0.443
2-3	804 (45.9)	55 (42.3)	
4-6	279 (15.9)	21 (16.2)	
7+	22 (1.3)	0 (0)	
Preterm birth (22 to 37 weeks gestational age)			
No	1558 (89.0)	117 (90.0)	0.78
Yes	183 (10.5)	13 (10.0)	
Unknown	10 (0.6)	0 (0)	
Total (1881)	**1751 (100.0)**	**130 (100.0)**	

*percentages may not add up to 100 because of rounding
†information on socio-demographic characteristics and preterm birth not available in 213 of 2094 births.

Regarding missing data, of the births with intrapartum complication data (1927 births), information on perinatal outcomes was missing for 176 births (8.7%) but information for all

these missing outcomes was provided from the Huda et al. 2012 study. Missing data on intrapartum complications was very high ranging from a minimum 45.0% for anaemia to 93.6% for prolonged labour, and to a maximum of 98.6% for haemorrhage and the complication was assumed to be absent in these cases. Information missing on anaemia for 868 births (45.0%) and was categorized as 'unknown'. Information on multiple pregnancy was missing for 23 births (1.2%) and these births were considered to be singletons. Preterm birth information was missing for 186 births (9.7%) and these were categorized as 'unknown'.

The majority of the 1927 births had only one facility visit (87.6%) while there were two facility visits per birth for 239 births (12.4%).

Table 6.10 shows the list of complications that I consider as intrapartum complications and those that I exclude. The table also shows the exact textual description of conditions recorded by investigators under 'final diagnosis' and 'indication of surgery' in the Huda et al. 2012 study. Among the 1927 births with intrapartum complication data, a quarter were found to have had any of the intrapartum complications listed (24.3/100 births).

The most common intrapartum complication was dystocia (13.2/100 births) followed by anaemia (5.7/100 births) and hypertensive diseases of pregnancy (4.4/100 births) (Table 6.10). Within dystocia, prolonged labour was seen most commonly (6.4%) followed by obstructed labour (3.8%) and malpresentation (2.3%). Infection and haemorrhage during labour and delivery were seen in 1.7% and 1.4% of births while multiple pregnancy was found in 1.2% of births. Preterm births constituted 9.5% of all births in this sample. Foetal distress and cord around the neck were observed in 7.7% and 6.3% of births, respectively. Caesarean sections and emergency Caesarean sections took place in 20.8% and 14.3% of all births.

Table 6.10: Prevalence of intrapartum complications, preterm birth and other complications for 1927 births delivered at the Matlab ICDDR,B hospital and Matlab and Chandpur hospitals (2007-2008).

	No. of births with complication/condition present, N	**Prevalence† (per 100 births)**
Intrapartum complications		
Any intrapartum complication	**469 ^**	**24.3**
Dystocia *	**255 ***	**13.2**
Cephalo-pelvic disproportion (as a single or multiple complication)	**32**	**1.7**
Cephalo-pelvic disproportion (CPD)	25	1.3
Big Baby	4	0.2
Floating head(high head)	3	0.2
Malpresentation (as a single or multiple complication)	**53**	**2.8**
Non-breech malpresentation	**23**	**1.2**
Malpresentation, unspecified	1	0.1
Malpresentation, unstable lie	8	0.4
Compound presentation/ occipitoposterior	5	0.3
Transverse or oblique lie	9	0.5
Breech malpresentation ~	**30 ~**	**1.6**
Breech presentation	27	1.4
Spontaneous breech delivery	7	0.4
Obstructed labour (as a single or multiple complication)	**73**	**3.8**
Obstructed labour due to malposition & malpresentation of foetus	3	0.2
Obstructed labour due to malposition & malpresentation, unspecified	7	0.4
Obstructed labour due to unusually large foetus	2	0.1
Obstructed labour, unspecified	58	3.0
Ruptured uterus during labour	3	0.2
Prolonged labour (as a single or multiple complication)	**124**	**6.4**
Prolonged labour, prolonged 1st stage of labour	109	5.7
Prolonged labour, prolonged 2nd stage of labour	15	0.8
Hypertensive diseases of pregnancy *	**84 ***	**4.4**
Eclampsia	**8**	**0.4**
Pre-eclampsia (as a single or multiple complication)	**37**	1.9
Other hypertensive disorder (as a single or multiple complication)	**45**	**2.3**
Pregnancy induced hypertension (PIH)	8	0.4
Unspecified maternal hypertension (HTN)	37	1.9
Haemorrhage	**27**	**1.4**
Placenta praevia	14	0.7
Placenta accreta/Malformation of placenta	1	0.1
Antepartum haemorrhage, unspecified	10	0.5
Obstetric shock	2	0.1
Infection	**33**	**1.7**
Chorioamnionitis	2	0.1
Urinary tract infection in pregnancy (UTI)	30	1.6
Septicaemia during labour	1	0.1

	No. of births with complication/condition present, N	Prevalence† (per 100 births)
Twin pregnancy (not used to determine multiple pregnancy)	20	1.0
Multiple delivery, Multiple delivery, all spontaneous (not used to determine multiple pregnancy)	7	0.4
Anaemia (not extracted from 'final diagnosis/indication of surgery'- extracted from haemoglobin level <10 g/dl)	**109**	**5.7**
Multiple Pregnancy (not extracted from 'final diagnosis/indication of surgery'- extracted from HDSS information)	**23**	**1.2**
Conditions considered not to be intrapartum complications		
Preterm birth		
Premature delivery (not used to determine preterm birth)	35	1.8
Preterm births (not extracted from 'final diagnosis/indication of surgery'- extracted from HDSS information)	**183**	**9.5**
Foetal distress	**148**	**7.7**
Foetal distress	144	7.5
Foetal distress due to meconium in amniotic fluid	4	0.2
H/O Caesarean section	**43**	**2.2**
H/O Previous C/S	39	2.0
Failed trial of labour, unspecified	4	0.2
Delivery by emergency Caesarean section	275	14.3
Caesarean section (emergency AND elective) for current delivery (not extracted from 'final diagnosis/indication of surgery'- from specific question)	401	20.8
Delivery by Caesarean hysterectomy	3	0.2
Single delivery by C/S, Delivery by elective C/S	43	2.2
Cord complication, Cord prolapse	5	0.3
Cord around the neck (non-threatening condition)	122	6.3
Puerperal sepsis (infection occurs after delivery)	1	0.1
Polyhydramnios	5	0.3
Disorders of amniotic fluid &membrane	58	3.0
Other unspecified disorder of amniotic fluid & membrane (leaking membrane)	183	9.5
Premature rupture of membrane	155	8.0
Maternal distress during labour & delivery, FTP, IUGR, LP, LA Pain, Bandl's ring, V.V.F (full term pregnancy, intrauterine growth retardation, lumbar pain, lower abdominal pain, Bandl's ring, vesico-vaginal fistula)	1634	84.8
Single spontaneous delivery, Spontaneous vertex delivery	1302	67.6
Spontaneous delivery, unspecified	11	0.6
IUD	30	1.6
Anencephaly	3	0.2
Post-dated/post term	480	24.9
Cervical tear	6	0.3
Perineal tear, 1st degree	156	8.1

	No. of births with complication/condition present, N	Prevalence† (per 100 births)
Perineal tear, 2nd degree	30	1.6
Perineal tear, 3rd degree	4	0.2
Perineal tear, unspecified (Laceration)	23	1.2
PPH (postpartum haemorrhage),retained placenta NOS(not otherwise specified)	7	0.4
PPH (postpartum haemorrhage) unspecified	4	0.2
Retained placenta without haemorrhage	2	0.1
Diabetes mellitus in pregnancy, unspecified	1	0.1

† Prevalence was calculated in 1927 births.

^ The sum of births with any complication (469) is less than the sum of constituent complications (539) of dystocia, hypertensive diseases of pregnancy, haemorrhage, infection, anaemia and multiple pregnancy because births with any complication, by definition, include the presence of one or more constituent complications.

*Constituent complications under broad categories of complications (e.g. dystocia or hypertensive diseases of pregnancy) may add up to more than the category total as the broad category is defined as the presence of any one (and at least one in case of multiple complications) constituent complication. For example, there are 255 cases of dystocia but a total of 282 cases of constituent complications (cephalo-pelvic disproportion, malpresentation, obstructed labour, and prolonged labour). Within these 282 cases, 22 cases are combinations of complications constituting dystocia (i.e. cephalo-pelvic disproportion and prolonged labour-10, obstructed labour and prolonged labour-9, cephalo pelvic disproportion and obstructed labour-2 and malpresentation and obstructed labour-1). In case of hypertensive diseases of pregnancy, the category total of 84 is less than the 94 constituent complications (eclampsia, pre-eclampsia and other hypertensive disorder).The 94 cases also include one combination case (pre-eclampsia and other hypertensive disorder).

~There are 30 cases of breech malpresentation as four of the 27 cases of breech presentation were also recorded as having spontaneous breech delivery.

Table 6.11 shows the distribution of single and multiple intrapartum complications in births with data on intrapartum complications. A single complication was experienced in 18.6% of all births, while two and three intrapartum complications were much less frequent (5.7% and 0.9% respectively) and no cases of four complications were found. Among births with single complications, the most common complication was dystocia, with prolonged labour the commonest complication constituting dystocia. Dystocia was present in over half (53.9%) of all births with a single complication, followed by anaemia (20.0%) and hypertensive diseases of pregnancy (12.2%). The most frequently observed combinations for two complications were cephalo-pelvic disproportion and prolonged labour (10 cases), followed by obstructed labour and prolonged labour (9 cases) and seven cases each of anaemia combined with either: prolonged labour, pre-eclampsia or other hypertensive disorders. Frequently observed combinations for three complications were: cephalo-pelvic disproportion, prolonged labour and obstructed labour (2 cases); cephalo-pelvic disproportion, prolonged labour and anaemia (2 cases) and prolonged labour, anaemia and other hypertensive disorders (2 cases).

Table 6.11: The distribution of births with single and multiple intrapartum complications in 1927 Matlab births (2007-2008)

	Births with available intrapartum complication data N (%)	**No complication N (%)**	**Any (at least one) complication N (%)**	**One complication N (%)**	**Two complications N (%)**	**Three complications N (%)**	**Four complications N (%)**
Intrapartum complication	1927 (100)	1458 (75.7)	469 (24.3)	359 (18.6)	110 (5.7)	18 (0.9)	0 (0.0)

The prevalence of intrapartum complications (Table 6.12) differed by delivery location, with at least one being experienced in half of all births (49.3/100 births; 95%CI: 45.2-53.2) delivered at Matlab and Chandpur hospitals compared to significantly fewer at the ICDDR,B Matlab hospital (12.9/100 births; 95%CI: 11.1-14.7).

The prevalence of intrapartum complications did not vary overall by socio-demographic characteristics. Unexpectedly, intrapartum complication prevalence appeared higher in Hindus, though the reason for this was not known. The lack of significant differences in intrapartum complication prevalence in older women could possibly be due to small numbers of these women. Prevalence was higher in births that were preterm, with 31 out of 100 experiencing an intrapartum complication (31.1/100 births; 95% 22.4-37.9) compared to 23 out of 100 term births (23.3/100 births; 95% CI: 21.2-25.4) and the difference was significant (p=0.004).

Table 6.12: The prevalence of intrapartum complications by delivery location, socio-demographic characteristics and preterm gestation in 1927 Matlab births (2007-2008).

	Births for which any intrapartum complication was present or absent		p-value
	No. of births (No. of births with complication)	Prevalence per 100 births (95% CI)	
Delivery location			
ICDDR,B Matlab Hospital	1322 (171)	12.9 (11.1-14.7)	<0.0001
Hospitals in Matlab and Chandpur	605 (298)	49.3 (45.2-53.2)	
Maternal formal education (completed years)			
0	220 (55)	25.0 (19.2-30.7)	0.489
1-5	340 (83)	24.4 (19.8-29.0)	
6-10	1068 (256)	23.9 (21.4-26.5)	
11-16	121 (30)	24.8 (17.1-32.4)	
Unknown	178 (45)	25.3 (18.9-31.8)	
Household asset quintile			
Most poor	164 (40)	24.4 (17.8-31.0)	0.904
Very poor	232 (53)	22.8 (17.4-28.2)	
Poor	276 (72)	26.1 (20.9-31.3)	
Less poor	299 (76)	25.4 (20.4-30.3)	
Least poor	537 (134)	24.9 (21.1-28.6)	
Unknown	419 (94)	22.4 (18.4-26.4)	
Religion			
Islam	1562 (362)	23.2 (21.0-25.2)	0.003
Hinduism/ Other	189 (62)	32.8 (26.1-39.5)	
Unknown	176 (45)	25.6 (19.1-32.0)	
Maternal Age			
<20	273 (63)	23.1 (18.1-28.1)	0.483
20- 29	1056 (252)	23.9 (21.3-26.4)	
30-39	393 (99)	25.2 (20.9-29.5)	
40+	29 (10)	34.5 (17.2-51.8)	
Unknown	176 (45)	25.6 (19.1-32.0)	
Gravidity			
1	646 (169)	26.2 (22.8-29.6)	0.369
2-3	804 (183)	22.8 (19.9-25.6)	
4-6	279 (64)	22.9 (18.0-27.9)	
7+	22 (8)	36.4 (16.3-56.4)	
Unknown	176 (45)	25.6 (19.1-32.0)	
Preterm birth (22 to 37 weeks gestational age)			
No	1558 (363)	23.3 (21.2-25.4)	0.004
Yes	183 (57)	31.1 (24.4-37.9)	
Unknown	186 (49)	26.3 (20.0-32.7)	
Total	**1927 (469)**	**24.3 (22.4-26.2)**	

Table 6.13 shows the crude odds ratios obtained for intrapartum complications and perinatal mortality. The presence of any intrapartum complication increased the odds of a perinatal death by 1.76 (crude OR-1.76; 95% CI: 1.08-2.84). Surprisingly, among all intrapartum complications, only haemorrhage and multiple pregnancy were associated with significantly increased odds of perinatal mortality (crude OR-9.28; 95%CI: 3.80-22.7 and crude OR-5.36 95%CI: 1.99-14.46, respectively). Dystocia (OR-1.37; 95%CI: 0.74-2.53) and hypertensive diseases of pregnancy (crude OR-0.89; 95%CI: 0.28-2.91) did not appear to increase the odds of perinatal deaths. Within dystocia, cephalo-pelvic disproportion, malpresentation and obstructed labour were associated with increased perinatal mortality (by 2.6 times, 1.5 and 1.5 times respectively), but prolonged labour had no effect (crude OR-1.02 ; 95%CI: 0.41-2.59). Within hypertensive diseases of pregnancy, eclampsia elevated crude odds ratios for these deaths 3.5 times (crude OR-3.51; 95%CI: 0.43-28.91). Surprisingly pre-eclampsia was protective for mortality (crude OR-0.67; 95% CI: 0.09-4.97) but the confidence interval was wide and includes 1. Infection (crude OR- 0.76; 95%CI: 0.11-5.63) and anaemia (crude OR-0.94; 95%CI: 0.33-2.67) were not found to be associated with perinatal mortality. Preterm births, as expected, increased the odds for perinatal deaths significantly (by five times) (crude OR- 4.80; 95%CI: 2.77-8.32, p<0.0001). The relationship between delivery location and perinatal mortality was significant in the crude analysis, with births at higher levels of care associated with greater perinatal mortality (crude OR-1.72; 95% CI: 1.07-2.73, p=0.023)(data not shown in the table).

Table 6.13: Strength of association (crude odds ratio) between intrapartum complications and perinatal mortality in 1927 births in Matlab (2007-2008)

	No. of births (No. of perinatal deaths)	**Perinatal death rate (per 1000 births)**	**Crude odds ratio [a] (95% CI)**	**P-value (Wald test)**
Any intrapartum complication				
Absent (Reference)	1458 (49)	33.6	1.00	
Present	469 (27)	57.6	1.76 (1.08-2.84)	0.022
Dystocia				
Absent (Reference)	1672 (63)	37.7	1.00	
Present	255 (13)	51.0	1.37 (0.74-2.53)	0.311
Cephalo-pelvic disproportion				
Absent (Reference)	1895 (73)	38.5	1.00	
Present	32(3)	93.8	2.58 (0.77-8.67)	0.125
Malpresentation				
Absent (Reference)	1874 (73)	39.0	1.00	
Present	53(3)	56.6	1.48 (0.45-4.86)	0.518

Breech malpresentation				
Absent (Reference)	1897 (75)	39.5	1.00	
Present	30 (1)	33.3	0.84 (0.11-6.24)	0.863
Other malpresentation				
Absent (Reference)	1904 (74)	38.9	1.00	
Present	23 (2)	87.0	2.35 (0.54-10.23)	0.253
Obstructed labour				
Absent (Reference)	1854 (72)	38.8	1.00	
Present	73 (4)	54.8	1.43 (0.51-4.04)	0.494
Prolonged labour				
Absent (Reference)	1803 (71)	39.4	1.00	
Present	124 (5)	40.3	1.02 (0.41-2.59)	0.958
Hypertensive diseases of pregnancy				
Absent (Reference)	1843 (73)	39.6	1.00	
Present	84 (3)	35.7	0.89 (0.28-2.91)	0.858
Eclampsia				
Absent (Reference)	1919 (75)	39.1	1.00	
Present	8 (1)	125.0	3.51 (0.43-28.91)	0.243
Pre-eclampsia				
Absent (Reference)	1890 (75)	39.7	1.00	
Present	37 (1)	27.0	0.67 (0.09-4.97)	0.697
Other hypertensive disorder				
Absent (Reference)	1882 (74)	39.3	1.00	
Present	45 (2)	44.4	1.13 (0.27-4.78)	0.862
Haemorrhage				
Absent (Reference)	1900 (69)	36.3	1.00	
Present	27 (7)	259.3	9.28 (3.80-22.7)	<0.0001
Infection				
Absent (Reference)	1894 (75)	39.6	1.00	
Present	33 (1)	30.3	0.76 (0.11-5.63)	0.786
Multiple pregnancy				
Absent (Reference)	1898 (75)	37.4	1.00	
Present	29 (1)	172.4	5.36 (1.99-14.46)	0.001
Anaemia				
Absent (Reference)	950 (37)	38.9	1.00	
Present	109 (4)	36.7	0.94 (0.33-2.67)	0.908
Unknown	868 (35)	40.3	1.04 (0.33-2.67)	0.881
Preterm birth (22 to 37 weeks of gestation)				
Absent (Reference)	1558 (41)	26.3	1.00	
Present	183 (21)	114.8	4.80 (2.77-8.32)	<0.0001
Unknown	186 (14)	75.3	3.01 (1.61-5.64)	0.001
Total	**1927 (76)**	**39.4**		

[a] Adjusted for clustering of births to one mother

Adjusted odds ratios for the strength of association of intrapartum complications with perinatal mortality are shown in Table 6.14. The strength of association between any intrapartum complication in a birth and perinatal deaths lessened from the crude odds ratio of 1.76 (95%CI: 1.08-2.84) to an adjusted value of 1.41 (95%CI: 0.82-2.41). Effect estimates for haemorrhage and multiple pregnancy were attenuated but remained significant (adjusted OR-6.88; 95% CI: 2.67-17.72 and adjusted OR- 3.60; 95%CI: 1.25-10.30, respectively). The non-significant effects of dystocia, hypertensive diseases of pregnancy, infection and anaemia changed very little after adjustment was made for the confounders that remained relevant in the final adjusted models for each specific complication. The adjusted odds ratio for the effect of preterm gestation on mortality declined but remained statistically significant (adjusted OR-3.60; 95%CI: 2.00-6.48). There was no effect of delivery location on mortality, after adjustment for confounders (adjusted OR-1.38; 95%CI: 0.38-2.31).

Table 6.14: Strength of association (crude and adjusted odds ratios) between intrapartum complications and perinatal mortality in 1927 births in Matlab (2007-2008)

	No. of births (No. of perinatal deaths)	**Perinatal death rate (per 1000 births)**	**Crude odds ratio [a] (95% CI)**	**P-value (Wald test)**	**Confounders that are adjusted for in the final adjusted model [b]**	**Adjusted odds ratio [a] (95% CI)**	**P-value (Wald test)**
Any intrapartum complication							
Absent (Reference)	1458 (49)	33.6	1.00	_	Delivery location, asset quintile and preterm births	1.00	_
Present	469 (27)	57.6	1.76 (1.08-2.84)	0.022		1.41 (0.82-2.41)	0.212
Dystocia							
Absent (Reference)	1672 (63)	37.7	1.00	_	Preterm births, multiple pregnancy and asset quintile	1.00	_
Present	255 (13)	51.0	1.37 (0.74-2.53)	0.311		1.46 (0.72-2.98)	0.298
Hypertensive diseases of pregnancy							
Absent (Reference)	1843 (73)	39.6	1.00	_	Preterm births and asset quintile	1.00	_
Present	84 (3)	35.7	0.89 (0.28-2.91)	0.858		0.79 (0.24-2.63)	0.697
Haemorrhage							
Absent (Reference)	1900 (69)	36.3	1.00	_	Preterm births and asset quintile	1.00	_
Present	27 (7)	259.3	9.28 (3.80-22.71)	<0.0001		6.31 (2.45-16.25)	<0.0001
Infection							
Absent (Reference)	1894 (75)	39.6	1.00	_	Preterm births and asset	1.00	_

	No. of births (No. of perinatal deaths)	**Perinatal death rate (per 1000 births)**	**Crude odds ratio [a] (95% CI)**	**P-value (Wald test)**	**Confounders that are adjusted for in the final adjusted model [b]**	**Adjusted odds ratio [a] (95% CI)**	**P-value (Wald test)**
Present	33 (1)	30.3	0.76 (0.11-5.63)	0.786	quintile	0.87 (0.11-6.59)	0.891
Multiple pregnancy							
Absent (Reference)	1898 (75)	37.4	1.00	_	Preterm births and asset quintile	1.00	_
Present	29 (1)	172.4	5.36 (1.99-14.46)	0.001		3.60 (1.25-10.30)	0.017
Anaemia							
Absent (Reference)	950 (37)	38.9	1.00	_	Preterm births, haemorrhage, and asset quintile	1.00	_
Present	109 (4)	36.7	0.94 (0.33-2.67)	0.908		0.74(0.25-2.19)	0.586
Unknown	868 (35)	40.3	1.04 (0.33-2.67)	0.881		0.96 (0.58-1.55)	0.861
Preterm birth (22 to 37 weeks of gestation)							
Absent (Reference)	1558 (41)	26.3	1.00	_	Haemorrhage, any intrapartum complication and asset quintile	1.00	_
Present	183 (21)	114.8	4.80 (2.77-8.32)	<0.0001		4.40 (2.53-7.73)	<0.0001
Unknown	186 (14)	75.3	3.01 (1.61-5.64)	0.001		1.73 (0.80-3.75)	0.16
Total	**1927 (76)**	**39.4**					

[a] Adjusted for clustering of births to one mother

[b] Confounders adjusted for in the final adjusted model include only those variables that do not exceed a likelihood ratio test value of 0.2 on elimination during the construction of a backward stepwise regression model.

From Table 6.15, it was found that perinatal mortality rates were much higher in Caesarean section births with intrapartum complications (36.7 deaths per 1000 births; 95%CI: 11.7-61.6) compared to Caesarean section births without (10.9 deaths per 1000 births; 95% CI: 4.1-26.0), though the difference was not statistically significant (p=0.099).

Table 6.15: Perinatal mortality rates in non-Caesarean section births and Caesarean section births with and without intrapartum complications in 1927 births in Matlab (2007-2008).

	Caesarean section		
	No	Yes	
		Intrapartum complications	
		No	Yes
Number of births (No. of perinatal deaths)	1526 (66)	183 (2)	218 (8)
Perinatal deaths per 1000 births (95% CI)	43.3 (33.1-53.5)	10.9 (4.1-26.0)	36.7 (11.7-61.6)

Results (Table 6.16) suggested that women who had Caesarean sections had a lower perinatal mortality rate (24.9 deaths/1000 births) than women who did not (43.3 deaths /1000 births) but the difference was not significant. Perinatal mortality rates were higher in non-emergency (31.8 deaths per 1000 births; 95%CI: 1.1-62.3) than in emergency Caesareans sections (21.8 per 1000 births; 95% CI: 4.6-39.1) though the difference between the two groups was not statistically significant.

Table 6.16: Perinatal mortality rates in non-Caesarean section and Caesarean section births as well as in emergency Caesarean section and non-emergency Caesarean section births in 1927 births in Matlab (2007-2008)

	Caesarean section			p-value
	No	Yes		
Number of births (No. of perinatal deaths)	1526 (66)	401 (10)		0.094
Perinatal deaths per 1000 births (95% CI)	43.3 (33.1-53.5)	24.9 (9.6-40.2)		
		Emergency Caesarean section		p-value
		No	Yes	
Number of births (No. of perinatal deaths)		126 (4)	275 (6)	0.554
Perinatal deaths per 1000 births (95% CI)		31.8 (1.1-62.3)	21.8 (4.6-39.1)	

As there were no perinatal deaths in the 43 births with a history of Caesarean section, a perinatal mortality rate could not be calculated and hence it was not possible to compare rates for births with and without prior Caesarean sections. Surprisingly, there was no statistical difference between perinatal mortality rates in births with foetal distress (47.3/1000 births; 95%CI: 13.0-81.5) and without (38.8 /1000 births; 95%CI: 29.8-47.8) (p=0.402). Perinatal mortality rates were much higher in these births with cord complications than in those without complications (800/1000 births; 95%CI: 283.5-994.9 vs. 37.4/1000 births; 95%CI; 29.4-46.4; p <0.001) but as there were only five cases of cord complications, caution should be exercised in drawing conclusions based on these comparisons.

6.5 Discussion:

I found that, against expectations, only two intrapartum complications (haemorrhage and multiple pregnancy) were associated with increases in odds of perinatal mortality, while dystocia and hypertensive diseases of pregnancy had no effect on mortality.

Comparison with studies from my literature review suggests that the results from some complications are comparable, while others are different. The strength of association for haemorrhage (crudeOR-9.28 ; 95%CI: 3.8-22.7) was consistent with findings from studies from Bangladesh (Cherry et al. 2008) West Africa (Chalumeau et al. 2000), Kenya(Weiner et al. 2003), and HICs (Flenady et al. 2011; Vogel et al. 2014).The increased odds of perinatal deaths in twins seen in my study (crude OR-5.36; 95%CI: 2.0-14.5) was also consistent with the four-fold increase in odds ratios seen in the previous Matlab study by Kusiako et al. (crude OR- 3.7; 95%CI: 2.0-6.8) and the five-fold increase seen in another Bangladesh study (Cherry et al. 2008), the only other studies which measured the effect of multiple pregnancy as an intrapartum complication.

In my study, dystocia was not found to be associated with perinatal mortality either in the crude (crude OR-1.37; 95%CI: 0.74-2.53) or adjusted analysis (crude OR-1.48; 95%CI: 0.78-2.78). This is inconsistent with the findings from the studies that I reviewed. It is particularly inconsistent with the earlier Matlab study, where prolonged labour-(crude OR- 3.5 ; 95%CI: 2.6-4.8), obstructed labour (crude OR- 23.8; 95%CI: 6.7-85.0), breech presentation (crude OR - 9.6; 95% CI: 6.4-14.7), and other abnormal presentations (crude OR-17.0; 95% CI: 8.3-33.5) were associated significantly with perinatal mortality.

I also found no association between infection and perinatal mortality (crude OR-0.76; 95%CI:0.11-5.63). This is partially consistent with the findings from the WHO facility-based study, which showed no effect of kidney infection on stillbirths and early neonatal deaths (crude ORs 1.3 and 4.4 respectively; 95%CIs: not reported) but an effect for other infections including sepsis (crude ORs 5.4 and 3.2 respectively; 95%CIs:not reported) (Vogel et al. 2014) The Chalumeau et al. study reported that intrapartum fever >38^{o}C increased perinatal mortality by 2.6 times (95%CI: 1.4-5.0). My study defined infection as urinary tract infection and septicaemia during labour, which is not consistent with the definitions used by Vogel et al. and Chalumeau et al.

Contrary to expectations, I found that hypertensive diseases of pregnancy (crude OR- 0.89; 95%CI: 0.28-2.91) did not increase the odds of perinatal mortality significantly in my study. Other studies contradicted these findings with the previous Matlab study showing elevated odds of perinatal mortality for pre-eclampsia (crude OR-2.5; 95% CI: 1.7-3.7) and eclampsia (crude OR-6.4; 95%CI: 3.0-13.8) as did Vogel et al. (four-fold increase for pre-eclampsia and twelve-fold increase for eclampsia), Chalumeau et al. (six-fold increase for all hypertensive diseases) and to a lesser extent Flenady et al. (one and a half-fold increase for pre-eclampsia and two-fold increase for eclampsia). Only Weiner et al. reported non-association between all hypertensive diseases of pregnancy and perinatal mortality (Weiner et al. 2003)

Lastly, anaemia had no effect on perinatal deaths (crude OR-0.9; 95%CI: 0.3-2.7). This was also seen in the Matlab population-based study, but severe anaemia increased the odds of fresh stillbirths and early neonatal deaths in the WHO facility study and the Kenya facility-based study (Weiner et al. 2003).

There are some possible explanations as to why some of my findings are consistent with what has been found in the literature while others are not. Issues to consider include: the sample size and power, the role of selection bias (including study characteristics), and information bias (misclassification of exposure).

First, my sample of births excluded the poorest, least educated women delivering at home and at subcentres and the richest and most educated women delivering at hospitals beyond Matlab and Chandpur (56.5% of all births). Hence complications were missing for more than half the women in Matlab. The women in my sample were at mid-levels of socio-economic status, education levels and perinatal mortality rates compared to the women at the extremes of these measures who were excluded. The exclusion of births from higher level facilities, which had higher perinatal mortality, may have led to an exclusion of the most severe complications. In the absence of uniform definitions and criteria for severity of complications in the delivery locations of my study, births with the most severe forms of complications are likely to be seen at higher level facilities than in my sample. This small sample size of women would explain why the odds ratios obtained in my study show either no associations or underestimated odds ratios (with very low strength of associations and very wide confidence intervals) for the relationship between (possibly) less severe complications and perinatal

mortality. Moreover it is very likely that the small number of cases for each complication and small number of perinatal deaths was insufficient to obtain odds ratios nearing the true odds ratios. However, sample size of the number of women and number of births with complications was not within my control as I used all of the data on intrapartum complications that was available from the Morbidity Study. An example of small numbers is seen for hypertensive diseases of pregnancy (OR-0.89 ; 95%CI: 0.28-2.91) which had 1843 negative cases and 84 positive cases the latter of which had only three perinatal deaths. This is possibly the reason for the non-association seen between an intrapartum complication such as hypertensive diseases of pregnancy and perinatal mortality in my study which does not correspond to the high odds ratios from the literature discussed earlier. Small sample sizes could be responsible for the non-association seen and the wide confidence interval in dystocia (233 positive cases and only 13 perinatal deaths) and infection (33 positive cases and only one perinatal death) where a non-association was seen. The very small number of perinatal deaths for the complications means that there is a lack of power as even observing one or more extra perinatal deaths could have resulted in odds ratios that would have varied from my study odds ratios. Hence the small sample sizes affect the validity of my results. However, this cannot adequately explain why strong associations for perinatal mortality were found for haemorrhage (seven perinatal deaths) and multiple pregnancy (one death) and not for other complications.

Second, misclassification of exposure is a major concern in this study. Data on intrapartum complications were missing from 45.0% for anaemia to over 90% for other complications (e.g. 93.6% for prolonged labour and 98.6% for haemorrhage) and may have affected the validity of the results. Data for some intrapartum complications were missing for over 90% of births, and women with missing data may have been wrongly considered to have no complications. The treatment of missing data i.e. the assumption that those without data didn't have a complication might have also biased the results as described below. There are two possible hospital scenarios.

1) Owing to the standard clinical practice of doctors and nurses recording only the complications (e.g 'haemorrhage during delivery') on hospital treatment sheets of a patient and not recording the absence of complications (e.g. 'absence of haemorrhage during delivery') I assumed that where intrapartum complications were blank or 'missing', they were absent. It is possible this assumption may not create a major bias in the results as this selective recording is standard clinical practice and so the odds ratios for the association between labour

complications and perinatal mortality obtained using this assumption will not deviate much from the true odds ratios.

2) However, it is also possible that a birth without any recorded complication (i.e. delivery treatment record is 'blank') did not have it recorded (data 'missing') because the treatment record during a complicated birth was not filled in emergency situations or because tools to assess the complication (e.g. the partograph) were not applied. In this case misclassification of exposure is likely and will have been differential as complicated births were less likely to have their complications recorded. This second scenario is likely to have happened for these hospitals where data recording is not of priority.

In my study as I have made an assumption that those without data didn't have a complication, considering that possibly many births with complications did not have their complications recorded means that it is likely that my results are biased. My study results are biased in that they show low, underestimated odds ratios and non-associations compared to the high and significant true odds ratios for the association between that labour complication and perinatal mortality seen in all studies.

Data may be more likely to be missing for women with complications because complicated births were not recorded in emergency situations or because tools to assess the complication (e.g. the partograph) were not applied. Complications may also have been misclassified because the definitions were not standardised in hospital records. Data recording was not a priority in these hospitals. This high percentage of missing data assumed to be non-complications coupled with the small sample size of women with complications having perinatal deaths could result in an under-powered analysis resulting in the non-associations seen. The reason for the association seen for haemorrhage, but not for other complications might be that haemorrhage was better identified than other complications (e.g. dystocia and hypertensive diseases of pregnancy). Haemorrhage is easier to identify visually (blood visible or not) while dystocia (including cephalopelvic disproportion, malpresentation, obstructed and prolonged labour) requires skilled physical examination coupled with progress monitoring by partograph. Identification of hypertensive diseases of pregnancy requires measurements of blood pressure, tests for proteinuria and understanding of hyperreflexia. This might explain why haemorrhage was seen to increase odds of perinatal mortality by nine times (crude OR- 9.28; 95% CI: 3.80-22.71) while hypertensive diseases of pregnancy (crude OR- 0.89; 95%CI: 0.28-2.91) were not seen to increase the odds of perinatal mortality significantly. It is possible that adverse outcomes influenced the recording of complications (differential

misclassification), as there is no information on whether details of labour complications were completed before or after the birth and, in this case, the odds ratios seen would be overestimates. However, the majority of non-association results seen suggest that this is unlikely to have occurred to a great extent. The near-completeness of information on twins (from the HDSS) meant that misclassification was unlikely to be an issue in the case of multiple pregnancy and perinatal mortality.

Third, misclassification of outcome may have occurred. Information on perinatal mortality was nearly complete however, so there is almost no chance of misclassification between perinatal death and a live baby after 7 days due to any assumption in my study.

The rates for perinatal mortality were not different for births with and without foetal distress, supporting the possibility of widespread misclassifications in intrapartum complications.

The small sample sizes of 1927 births and very low numbers of perinatal deaths for specific complications has probably resulted in the wide confidence intervals seen for the low strength of associations obtained for the relatively rare outcome of perinatal mortality.

It is possible that there was incomplete adjustment for confounders in this study. Adjustment was performed for socio-demographic characteristics, delivery location, preterm gestation and additionally for other intrapartum complications in the case of specific intrapartum complications, but some conditions were not adjusted for. It was not possible to adjust for maternal malnutrition, even though the previous Matlab study that measured malnutrition found no effect on perinatal mortality, while non-adjustment for diseases such as diabetes (4% in Matlab women and representative of rural levels of 4-13%)(Islam & Alam 2009) is unlikely to have affected the study results. However, it is possible with the small sample sizes of the specific intrapartum complications and perinatal deaths for those complications that the study was too under-powered to allow for the above adjustments made to the analysis.

It is possible that the literature review might have missed relevant studies presenting different or similar odds ratios to those obtained in my study, thus adversely affecting the comparison of literature study findings with my study.

Labour complications can be difficult to identify and diagnose, even in HICs (Nystedt & Hildingsson 2014) where guidelines and evidence based-recommendations are often not followed clinically (Janakiraman & Ecker 2010). The correct diagnosis of obstetric complications (e.g. prolonged labour) requires substantial clinical skill and not all providers interpret clinical signs in the same way. Though the partograph has been introduced to standardise the diagnosis of (and actions for managing) prolonged labour, it is not often used (Pirkle et al. 2012) or is used incorrectly (World Health Organization 1994; Burkhalter et al. 2006). In a large study conducted in public-sector health facilities in two of Bangladesh's seven administrative divisions (Anwar et al. 2009), evidence-based practices were rarely used; partograph use was reported in less than a third of facilities in a high-performing division compared to 5% facilities in a low-performing division. One study which explored the issues arising with prolonged labour in three hospitals in Sweden (Nystedt & Hildingsson 2014) reported that diverse opinions on definitions among midwives and obstetricians and different guidelines at different hospitals, resulted in different interventions. It is quite likely that this scenario also occurs in LICs. The Swedish study also suggested that improved clinical skills were required for identifying and classifying prolonged labour (Nystedt & Hildingsson 2014). Hence the lack of a standard definition followed consistently by all hospitals and the difference in opinions on the definitions among providers suggests that misclassification between complications such as prolonged labour and obstructed labour (which have similar presentations clinically) is also possible. In LIC rural hospital settings definitional issues may be compounded by poor quality of services (Koblinsky et al. 2006) and poor retention of well-trained staff (Lehmann et al. 2008). In the Bangladesh study above (Anwar et al. 2009) on unannounced visits, only a third of doctors and half of nurses were present at their posts in the low-performing division compared to 60% and 100% presence in the high performing division. General doctors were also found in obstetrician posts and this was more in the low-performing division. Difficulty in clinical diagnosis and lack of appropriate clinical staff, equipment (e.g. dip-stick for measuring proteinuria in pre-eclampsia) and training (e.g. partograph use) which can prevent correct diagnosis, may lead to misclassification of intrapartum complications in hospital settings including those in my study.

The presence of diagnostic errors in hospitals in developing countries has also been highlighted in the literature. The WHO conducted a study of 15,584 records in 26 hospitals (oversampling large teaching hospitals and urban hospitals) in eight low-income and transitional countries in Africa and the Middle East (Wilson et al. 2012). It was found that 20% of unintended injury in

patients (defined as temporary or permanent disability, death or prolonged stay at a hospital as a result of healthcare management) was because of diagnostic error. Diagnostic error was described as improper diagnosis, non-timely diagnosis or failure to make a correct diagnosis from the information given. Hence it is possible that diagnostic errors in labour complications were also present in these rural hospitals in Matlab and Chandpur. However, as missing data on complications ranged from 45% to >90% for individual complications, the effect is more likely due to the fact that an assumption of no complication was made for the majority of cases and less for improper diagnosis.

The completeness of medical records is also of concern in developing countries (Pirkle et al. 2012) and attempts have been made to improve the situation by introducing training manuals for improving medical record keeping (WHO Regional Office for the Western Pacific 2006; International Records Management Trust 1999). An intervention study in a rural Ethiopian hospital assessed the accessibility and completeness of patient records before and after an intervention to improve patient registration and record management (Wong & Bradley 2009). This study found that post-intervention, completeness of available medical records increased from 6.5% (2 records/ 31 records) to 45.7% (16 records/35 records) ($p<0.01$). In this study though completeness of records was defined as the overall availability of registration number, patient information, physician note, nursing note, medication and investigative reports (if ordered), it is likely that diagnostic fields filled by physicians and nurses (notes) could be poorly filled in or unavailable and that this scenario was also possible in the rural hospitals in our study. This study also noted that it was difficult to convince medical staff to address recording issues during the pressing concerns of a cholera epidemic or during power cuts. The hospitals in my study, like the vast majority in Bangladesh, do not consider data-recording to be a priority activity and the Ethiopian study supports the possibility that data-recording is unlikely to be of high-priority during emergency situations.

WHO have also called attention to the poor quality of health facility data in developing countries. Health facility data are often the primary source of data at district level and are commonly used as cause of death data(World Health Organization 2011a). The poor quality of data from maternity registers and general hospital records (World Health Organization 2011a) was a result of poor use of standardized definitions based on ICD (World Health Organization 2010).

My study showed that the prevalence of labour complications was 24.3%. In the Kusiako et al. Matlab study of 1987-1993, the prevalence of labour complications was lower, at 12.0%, (Kusiako 2000). This substantial difference may be possibly explained by: (1) different time periods for the study (2) different samples of women and (3) different ascertainment of complications. (1) As these two studies (and the Huda et al. 2012 study), are the only studies in Matlab to ascertain prevalence of complications, it is not possible to understand if prevalence of complications in Matlab is rising over time or declining. However, in Matlab the percentage of stillbirths and early neonatal deaths receiving comprehensive emergency obstetric care increased from 2.2% and 2.0%, respectively, in 1987-1991 to 9.3% and 8.8% in 2002-2005 (Ronsmans et al. 2010). In 2007-2008 facility births were higher (62.3%) in my study compared to 1987-1993 when facility births were presumably lower than the earliest record in 2002 (33.3%). This suggests that over time, more complicated births have been reaching facilities and hence the higher prevalence might represent more complications being diagnosed. (2) The samples of women are different in these studies, with deliveries outside Matlab ICDDR,B facilities in higher-level facilities also included in my study. Hence it is possible that inclusion of higher-level facilities and correspondingly older Matlab women, with more preterm births, might have resulted in a higher prevalence of complications than for women delivering at home or at the ICDDR,B facilities in the Kusiako study who might have been at lower risk of complications. This is supported by my study finding which showed lower perinatal mortality rates in women delivering at home and Matlab facilities than for those delivering at higher facilities. (3) It is very possible that ascertainment of complications in the two studies was different, as neither study provided hospital staff and midwives with criteria for identifying complications that would enable standardization across each study. However, as differences in complication definitions between the two studies could not be assessed, it is not possible to speculate on whether this resulted in the difference in prevalence seen.

I compared the prevalence of complications in my study with that reported in the Disease Control Priorities (DCP)(Filippi et al.-In Press) report on global levels of maternal obstetric complications. No clear patterns were seen, as my study prevalences were not consistently higher or lower than those in the DCP report. The prevalences for haemorrhage and severe anaemia were similar to the global prevalences reported in the DCP while those for dystocia and hypertensive disorders were higher and lower, as seen below. The prevalences for obstructed labour (3.8%) and prolonged labour and obstructed labour together (10.2%) in my study were higher than those (1.9% and 8.7% respectively) obtained in an unpublished

systematic review of 16 population-based studies by Adler et al. The reason for this could not be speculated on because the methods have not been published. Global prevalences for pre-eclampsia and eclampsia from a systematic review of 129 studies in 40 countries worldwide, (Abalos et al. 2013) were 5.5% (95% CI: 1.9-10.9) and 1.1% (95% CI: 1.0-1.3) for the WHO SEARO region; both these values are higher than the results (1.9% and 0.4%) obtained for my study. However as Bangladesh was excluded from the 40 countries and as statistical modelling was done for data-deficient regions (including Bangladesh) it is possible that the prevalence obtained does not reflect that in Bangladesh. According to a systematic review by (Cresswell et al. 2013), prevalence for placenta praevia was found to be 0.5% worldwide and 0.8% in Asia (from six Asian studies excluding Bangladesh) and this was comparable to the 0.7% I obtained in my study. In this review, the authors found that geographical difference was the only study characteristic found to have significant influence on prevalence, with higher prevalence in Asian women possibly because of pelvic structure, higher prematurity rates and shorter gestational period. This might possibly explain the similar prevalence in my study. Prevalence of severe anaemia globally (0.9%), obtained from 257 population-based datasets from 107 countries (Stevens et al. 2013) was similar to that in my study (0.8%), and the prevalence in Southern Asia was also statistically similar (1.2%; 95%: 0.4-2.7).The authors defined severe anaemia as blood haemoglobin levels <7g/dl similar to my study and hence it is plausible that my findings correspond to the levels for South Asia. As only post-partum infection prevalence was reported in the DCP, this could not be compared with intrapartum infection prevalence in my study. Only Vogel et al. measured intrapartum infection in my literature review but the prevalence was unreported. The global prevalence of labour complications has been presented as 15% by WHO and UNFPA (United Nations Fund for Population Activities 2014) and this figure has been seen only in one Indian study by Bang et al. 2004 (17.7%; 95%CI: 15.0-20.4) though this included post-partum complications. If complications are considered mutually exclusive, prevalence may be as high as 31% (Filippi et al.- In Press). My prevalence for all labour complications of 24.3%, where complications are considered mutually exclusive, is between these two values of 15% and 31%.

This study identified issues as factors that affected assessment of the relationship between intrapartum complications and perinatal mortality: 1) lack of standardisation of obstetric diagnoses and (2) poor record keeping. However, there are potential solutions to these issues which are presented below.

(1) Standardisation of diagnoses can be addressed by ensuring national and local clinical guidelines set criteria for complications based on ICD (World Health Organization 2011a; World Health Organization 2014). Implementation of these guidelines could be improved by including physicians in their design and review, while hospital accreditation alongside performance-based remuneration for both public and private facilities is also known to improve quality of services (Peabody et al. 2006). (2) Training manuals for improving record-keeping in developing countries are available (WHO Regional Office for the Western Pacific 2006; International Records Management Trust 1999) and content can be customised for use in particular settings. In the Ethiopian study discussed earlier (Wong & Bradley 2009), a simple, custom-made computer database managed patient information while standardized medical records, standardized processes for file recording and filing, and staff training and supervision which emphasised the need for full completion of forms greatly improved record-keeping. Electronic devices such as personal digital assistants and mobile phones have also been found to be effective interventions in improving poor record keeping (Pirkle et al. 2012).
Strong governance and political will at hospital and policy level are needed to ensure that improvements occur at all levels. This would help in addressing the need for good quality data that could be used to calculate the burden of intrapartum complications and the steps required in the management of such complications to reduce perinatal mortality.

Chapter 7. Discussion

The main objective of this thesis was to gain a better understanding of the burden, trends and determinants of perinatal and neonatal deaths, as well as preterm births taking place in Bangladesh and South Asia. In particular it assessed the effect of the Matlab Safe Motherhood Programme on these outcomes in Matlab, Bangladesh. The main findings can be summarised in terms of four broad areas: (1) the burden of stillbirths, early neonatal deaths, late neonatal deaths and preterm births, (2) trends over time of stillbirths, early neonatal deaths, late neonatal deaths and preterm births, (3) the contribution of the Safe Motherhood Programme to stillbirths, early neonatal deaths, late neonatal deaths and preterm births and (4) implications for measurement of deaths in the neonatal period (especially in the early neonatal period) and the recording of intrapartum complications. A summary of the findings by thesis chapters and objectives is shown in Table 7.1 (Appendix V).

1. Burden of stillbirths, early neonatal deaths, late neonatal deaths and preterm births

The systematic review of population-based studies in South Asia found that mortality rates for stillbirths, early neonatal, late neonatal and perinatal deaths were very high in South Asia but were not uniformly high across all the seven countries. Perinatal mortality rates were high in Afghanistan (41.6 per 1000 births), Bangladesh (63.7 per 1000 births), India (59.6 per 1000 births), Nepal (46.9 per 1000 births) and Pakistan (97.7 per 1000 births) but relatively low in Maldives (18.3 per 1000 births) and Sri Lanka (16.9 per 1000 births). The perinatal death rate for Bangladesh places it alongside other South Asian countries with high perinatal mortality rates. This is the first systematic review of population-based studies in South Asia. All previous estimates for the different mortality outcomes for the countries of South Asia were obtained from statistical models (WHO, 2006a) (WHO, 2007)(Stanton et al., 2006, Lozano et al., 2011) (Lawn et al., 2011, Cousens et al., 2011). These modelled estimates of mortality rates were not consistently higher or lower than each other and sometimes differed substantially from each other even when they presented rates for the same year. For example, the WHO rates (WHO, 2006a) and Stanton et al., 2006 rates for the year 2000 for Nepal (23/1000 births vs. 54.6/1000 births) and Pakistan (22/1000 births vs. 41.4/1000 births) are very different. The pooled estimates from my systematic review were within the range found by modelled estimates in

the literature and confirmed the high rates of stillbirth, early neonatal and late neonatal mortality in the countries of South Asia.

The perinatal and neonatal mortality rates obtained in Matlab were consistent with rates reported from other studies in the country. The stillbirth rate in Matlab between 2002 and 2007 (35.2/1000 births) was very similar to Bangladesh's national rate reported in the 2007 DHS, covering 2002-2007 (30.6/1000 births) (NIPORT 2009). Similarly, early neonatal mortality rates (25.9/1000 live births in Matlab versus 28.9/1000 live births nationally) and late neonatal mortality rates (5.1/1000 babies alive at Day 7 in Matlab vs. 7.6/1000 babies alive at Day 7) were consistent with national rates. Government service area rates in 2005-2007 were also similar to those seen for the same time period in another Bangladesh study by Azad and colleagues where stillbirth, early neonatal death and late neonatal death rates were 34.1/1000 births, 29.5/1000 live births and 8.3/1000 live births respectively in 2005-2007. The Matlab Government service area is also similar to other areas in rural Bangladesh (Bangladesh DHS 2007) in terms of the percentage of health facility births (12.4% in Matlab versus 10.5% in rural areas, between 2002 and 2007), education of women (6 years of schooling or more) (46.8% in Matlab versus 32.8% in rural areas, between 2002 and 2007) and fertility (total fertility rate of 2.8% in Matlab versus 2.8% in rural areas, between 2002 and 2007). Percentages for two or more antenatal visits in Matlab and rural Bangladesh were 48.7% and 39.4%, respectively, for the same time period (NIPORT 2009; Pervin et al., 2012). The percentage of births in Matlab and rural Bangladesh (Bangladesh DHS 2007) delivered by a medically trained provider (14.6% in Matlab versus 13.2% in rural Bangladesh, between 2002 and 2007) and by Caesarean section (5.6% in Matlab between 2004 and 2007 versus 5.4% in rural areas between 2002 and 2007) were also similar. The findings from Matlab can therefore be considered representative of rural Bangladesh.

The preterm birth prevalence in Matlab was high, ranging from 17.0% in 2005 to 13.8% in 2009. These rates were consistent with those reported in earlier Bangladesh studies (14.1% to 23.3%) conducted in rural areas (Baqui et al., 2013; Klemm et al., 2008; Kusiako et al. 2000; Shah et al., 2014) and an urban slum (Arifeen et al. 2000) and with recent preterm prevalences (17.1% in 2005-2006 and 14.8% in 2008-2009) reported in Matlab (Rahman et al. 2011). The burden of preterm births was also comparable to modelled estimates for prevalence produced by WHO and other research institutions for 2010 for Bangladesh and South Asia (14.0% and 13.3%, respectively) (Blencowe et al. 2012). An unpublished study from Northern Bangladesh

(Day et al., LAMB hospital) included by Blencowe et al., 2012 reported a preterm prevalence of 8.6%. Hence, compared to published studies, the preterm birth prevalence observed in Matlab can be considered representative of rural Bangladesh. The Bangladesh DHS of 2011 (NIPORT 2013) did not report preterm birth prevalence. However, women self-ascertained that for the 5 years preceding the survey, 17.7% of babies born were 'very small' or 'smaller than average' at birth (NIPORT 2013), though it should be noted that self-reported size at birth is not a valid estimate of preterm birth and that term babies with intrauterine growth retardation may also be 'very small' at birth.

2. Trends in stillbirths, early neonatal deaths, late neonatal deaths and preterm births

There was no evidence from the systematic review that declines in rates of stillbirth, early and late neonatal death or perinatal death took place over time in South Asia or within its constituent countries. Declining trends were not seen even within the sub-national or national studies within each country. However, it was not possible to conclude that there was no decline in mortality rates within countries, as the systematic review was not designed to assess such trends over time. Within each country, the studies varied greatly, representing different sites, time periods, populations and study methodologies making comparison between rates over time difficult.

My study in Matlab shows evidence of clear trends in the reduction of mortality in the perinatal and neonatal periods over time. In the Matlab Government service area, annual declines in early (1%; 95%CI: 1% - 2%) and late neonatal death rates (7%; 95%CI: 6%-8%) were seen between 1987 and 2009, though no reduction was observed for the rates of stillbirth. In the ICDDR, B service area stillbirths showed an annual decline of 2% (95% CI: 1% - 3%) and there was a sharp annual decline in early (3%; 95%CI: 3% - 4%) and late neonatal death rates (6%; 95% CI: 4% to 7%). Within the early neonatal period, very early (Day 0-2) neonatal deaths declined only in the ICDDR,B service area while the declines seen in late early (Day 3-6) neonatal deaths were similar in both areas. The reductions in the Government service area, corresponded to an overall reduction of 28% and 79% between 1987 and 2009 in early and late neonatal mortality respectively. Information from Bangladesh's five DHS studies for 1995 to 2011 suggested that the declines seen for stillbirth, early and late neonatal mortality did not reach significance. Stillbirth mortality was 28.5/1000 births (95%CI: 24.8-32.8) in the 2000 DHS

and 25.7/1000 births (95%CI: 21.7-28.2) in the 2011 DHS. Early neonatal mortality was 30.6/1000 live births (95% CI: 26.7-35.0) in the 2000 DHS and 25.0/1000 live births (95% CI: 21.8-28.3) in the 2011 DHS. Late neonatal mortality rates for the corresponding DHSs were 11.0/1000 births surviving at 1 week (95%CI: 8.8-13.8) and 7.8/1000 births surviving at 1 week (95%CI: 5.9-9.6). This suggests that while the decline seen in the Matlab Government service area is significant, the decline over time for national DHS rates did not reach significance. Facility delivery rates and caesarean section rates for the Government service area and Bangladesh are very comparable between 2002 and 2009, as discussed before (Chapter 4) (NIPORT et al. 2005) (NIPORT et al. 2009)(NIPORT et al., 2013).

Preterm birth prevalences in Matlab declined from 17.0% in 2005 to 13.8% in 2009. The most recent modelled estimate for preterm prevalence by Blencowe et al. in Bangladesh for 2010 (14.0%) and preterm prevalences from earlier Bangladesh studies (8.6%-23.3%) (Arifeen et al., 2000; Klemm et al., 2008; Kusiako et al., 2000, Day et al., LAMB Hospital Bangladesh) suggested there was no decline in preterm births in Bangladesh from 1990 to 2010 (Blencowe et al. 2012). Preterm birth prevalences (19.4% and 22.3%) from studies published more recently than the earlier rates do not suggest that preterm births are declining in Bangladesh (Shah et al. 2014; Baqui et al. 2013). In Matlab, the sudden sharp declines seen since 2008 in both the ICDDR,B and Government service areas are unexplained, and the effect may be due to bias. The increase in recall period from one-month to two-months after mid-2007 in both areas of Matlab may have resulted in overestimation of gestational age after mid-2007 resulting in the sudden declines in preterm births seen from 2008. Increase in the recall period for last menstrual period (LMP) dates may have resulted in women tending to report the LMP date before the actual LMP date. The decline seen in both areas is possibly a result of information bias.

3. Contribution of the Safe Motherhood Programme to stillbirths, early neonatal deaths, late neonatal deaths and preterm births

The Matlab Safe Motherhood Programme was found to have contributed to the reduction in stillbirths and very early (Day 0-Day 2) neonatal deaths but not to late early neonatal deaths (Day 3-6) or late neonatal deaths. Stillbirths and very early (Day 0 and Day 1-2 deaths) neonatal deaths declined faster in the ICDDR,B service area (2%, 2% and 3% per year respectively) than in the Government service area (0%, 0% and 1% per year respectively). The declines in the

ICDDR,B and Government service areas for Day 3-6 deaths (6% vs. 4%) and late neonatal deaths (6% vs. 7%) were much steeper than those for stillbirths and very early neonatal deaths but there was no difference between the two areas. This suggests that the Matlab Safe Motherhood Programme was not responsible for the decline seen for Day 3-6 deaths and late neonatal deaths.

Core elements of the Matlab Safe Motherhood Programme may have contributed to the decline in stillbirths and very early neonatal deaths (Day 0-2). These include: increasing antenatal care (ANC) access (evidenced by the increase in the number of ANC visits); skilled birth attendance (SBA) by trained midwives in the sub-centres and nurse-midwives and doctors in the Matlab hospital; and timely access to emergency obstetric care and referral to higher facilities. Matlab ANC included: assessment and correction of pre-pregnancy weight, routine blood and urine tests for diabetes and hypertension, anaemia detection and iron folic acid supplementation, management of infections and chronic diseases, detection of pregnancy complications and information on obstetric and newborn danger signs to women. ANC, by increasing detection and treatment of maternal risk factors (including chronic diseases such as diabetes and hypertension) and possible pregnancy complications is known to avert intrapartum stillbirth and early neonatal deaths (Lee et al. 2009; Dean et al. 2013).
Delivery by a medically trained provider and provision of basic and emergency comprehensive care have been shown to reduce stillbirths and early neonatal deaths (Yakoob et al. 2011; Lee, Cousens, Darmstadt, et al. 2011). The midwives and doctors in Matlab were trained in: active management of the third stage of labour using oxytocis; initial treatment of complications (sedatives and magnesium sulphate for eclampsia, saline infusion for haemorrhage and antibiotics for infection); stitching and vaginal packing for cervical and vaginal tears; external and internal version for breech deliveries; manual removal of placenta and removal of retained placenta. They additionally referred women with obstetric complications to facilities which provided free specialised obstetric care and caesarean sections (with free transportation to the facility). The ICDDR,B service area, with its Safe Motherhood Programme, saw: an increase in the uptake of ANC (three or more visits) from 40% to 81% between 2005 and 2009, an increase in health facility deliveries from 32% to 77% between 2002 and 2009 and an increase in Caesarean sections from 6.1% to 17.6% between 2004 and 2009.
The effect of Matlab's Safe Motherhood Programme on reducing stillbirths and early neonatal deaths is supported by the literature. A review showed that training community midwives,

village doctors and physicians in pregnancy complication detection, intrapartum monitoring, delivery, postpartum care and referral reduces perinatal mortality and early mortality (Lee et al. 2011). Historical evidence from the UK and USA showed that shifts to facility deliveries from home deliveries and delivery by skilled birth attendants such as midwives, nurses and doctors during 1940-1970 resulted in a 50% reduction in neonatal mortality (Lawn et al. 2013). Historical datasets also showed that intrapartum stillbirths declined with increased access to emergency obstetric care including Caesarean sections (Goldenberg et al. 2007).

The Matlab Safe Motherhood Programme had no effect on declining preterm birth prevalences, suggesting that the increases in ANC, SBA and access to emergency care, which contributed to declines in stillbirths and early neonatal mortality, did not prevent preterm births. Preterm birth prevalence was lower in the ICDDR,B service area (14.6/100 births; 95%CI: 14.0-15.2) than the Government service area (16.2/100 births; 95%: 15.6-16.9) over the study period, but annual trends for the two areas did not show a greater magnitude of decline for the ICDDR,B service area. Preterm birth prevalence was halved in the most educated women (10.3/100 births) compared to women with no education (20.0/100 births). This large reduction in preterm births could possibly have been mediated by education in three ways. First, maternal infections, pre-eclampsia, pre-gestational diabetes, maternal under-nutrition and excess physical labour increase risks of preterm births (section 2.5.2). Thus, as educated women access more antenatal care than uneducated women in Matlab and elsewhere (Dean et al. 2013) (Pervin et al. 2012), detection and management of these conditions could have resulted in a lower preterm birth prevalence. However, the Matlab Safe Motherhood Programme shows that increasing ANC did not result in the reduction of preterm births and so it is doubtful that the difference in prevalence is due to increased ANC uptake.
Second, educated women have longer intervals between births than uneducated women as seen previously in Matlab (DaVanzo et al. 2004) and the increased birth-spacing could have resulted in reduced risks for preterm births (section 2.5.2). Third, it is possible that educated women report their LMP dates differently from uneducated women and the reduction is a result of information bias. A US study showed that women report their dates accurately regardless of education level (Wegienka & Baird 2005). The lowest level of education in the study was high-school education (12 years of education) and the effect of no education on recall of LMP dates is not known. Hence the effect of information bias cannot be ruled out.
ANC is a global recommendation for reducing preterm birth prevalence and improving outcomes for women at risk of preterm birth (Howson et al., 2012) and is thought to work

through: screening of infections, correction of weight , improvement of birth preparedness and through management of hypertension, bleeding and multiple pregnancies. However, evidence from reviews of studies on the specific interventions included in ANC visits suggests that many of these procedures, though recommended, do not actually result in the prevention of preterm births but do reduce stillbirth and early neonatal mortality (Bhutta et al., 2014; Iams et al., 2008). Only one study from Bangladesh described earlier (Shah et al. 2014) (Chapter 5) suggested that one ANC visit versus none resulted in a 14% reduction of preterm birth risk (95% CI:10-17%). However, a minimum of four ANC visits is recommended by WHO for ensuring the full-life saving potential for women and their children (Partnership for MNCH 2006) and so further studies might be required to understand the effect of one ANC visit on preterm birth reduction. The findings from Matlab do not seem to suggest that improvements in ANC visit frequency and quality (discussed in section 4.5) prevent preterm births and hence the recommendation for improved ANC is unlikely to reduce the number of preterm births. However preterm birth research is a relatively new research area in LICs and current studies focus on estimating the prevalence over short periods of time (e.g. 2 years). Studies conducting long-term tracking of preterm births over time alongside improvements in ANC in the country and region might be warranted.

My study did not assess the role of specific interventions that could possibly prevent preterm births (e.g. antibiotics for pPROM or tocolytic drugs to suppress labour contractions) (Requejo et al. 2013). The current literature suggests that using antibiotics for pPROM to delay the onset of labour by 48 hours and prevent newborn infections and using antenatal corticosteroids to prevent respiratory distress can reduce preterm-related mortality (Bhutta et al. 2014; Requejo et al. 2013). However the stagnant and high preterm birth prevalence between 1990 and 2010 in the USA and UK (Blencowe et al. 2012) where these drugs were available and used, suggests they may not be the answer to reducing preterm births. It is possible that any decline seen in preterm births in HICs is counteracted by steadily increasing rates of preterm births from non-essential Caesarean sections and multiple pregnancies from in-vitro procedures (Blencowe et al. 2012; Gyamfi et al., 2011). However, there is a lack of evidence on whether this is the case. LICs are different from HICs in that most preterm births result from spontaneous preterm labour (70% in LICs vs, 40% in HICs) and fewer are provider-initiated (11-16% in LICs vs 30-45% or up to 57% in HICs) (Gravett et al. 2010; Gyamfi et al., 2011). The limitations of the evidence on preventative interventions in LICs have resulted in calls for epidemiological research (Requejo et al. 2013). In Matlab, although antenatal corticosteroids and antibiotics for pPROM

have been included in the list of ANC services since 2007, their actual use and coverage has not been assessed and is unknown. Kangaroo mother care (KMC) in Matlab was not found to reduce preterm-related mortality in the small number of preterm babies admitted to the 6-bed KMC unit. The study authors suggested that the skin-to skin care provided was insufficient (Rahman et al. 2011). Until effective interventions in the prevention of preterm births are introduced, current efforts in Matlab might focus on improving the survival of preterm babies through the interventions for newborn survival recommended in the literature (resuscitation, thermal care, breastfeeding and illness management).

My findings did not show that the presence of intrapartum complication increased the odds of perinatal deaths other than haemorrhage and multiple births. Though this was unexpected given that the Safe Motherhood Programme is thought to have contributed to a reduction in perinatal mortality through better intrapartum care, the poor data quality is most probably responsible for the non-associations seen. Intrapartum complications were found to be present in a quarter of all births. WHO and UNFPA estimate that the prevalence of intrapartum complications to be 15% (United Nations Fund for Population Activities 2014) whereas the newest edition of Disease Control Priorities puts the figure at 31% (Filippi et al., 2014, in Press). Prevalences for specific intrapartum complications in my study were consistent with systematic review rates for placenta praevia and severe anaemia (Cresswell, Ronsmans, Calvert & Filippi, 2013) (Stevens et al. 2013) while those for hypertensive diseases and obstructed labour were lower and higher, respectively (Abalos et al., 2013) (Adler et al., unpublished). My study suggested that intrapartum complications were possibly misclassified due to lack of standardized definitions and poor record keeping and also that issues of small sample sizes and missing data contributed to the results seen. However, the finding that possibly a quarter of births in Matlab had intrapartum complications, supports the ongoing Safe Motherhood Programme strategy of reducing intrapartum stillbirths and perinatal deaths by identifying, managing and treating complications arising during the intrapartum period.

The Safe Motherhood Programme improved ANC services, upgraded health centres for delivery, posted trained midwives in the health centres who provide free antenatal and intrapartum care, provided the Matlab ICDDR,B hospital staffed with doctors and nurse-midwives and provided free transport to hospitals. It may be challenging to implement a similar strategy in other rural areas of Bangladesh, even though there are delivery centres similar to ICDDR,B subcentres and ICDDR,B hospital. At the sub-sub-district (or ‘union’) level

government delivery centres (Union Health and Family Welfare Centres) are staffed by one nurse-midwife for 20,000 people and offer ANC care, family planning, child care and delivery services. The ICDDR,B subcentres, staffed by a trained midwife and a paramedic, cover a similar population and perform similar services (Rahman et al. 2011). At the sub-district (or 'upazila' level) government hospitals (Upazila Health Complex) are 31-bedded, have 9-10 physicians, 11 nurses and cater for a population of 200, 000 people. This corresponds to the Matlab ICDDR,B 50–bed hospital staffed by 6 physicians and 9 nurses (Personal Communication- J.Pervin).

However, unlike the ICDDR,B service area, Government service area health facilities lack specific guidelines for components of ANC, foundational and refresher training for providers, counselling on evidence–based interventions and good linkages to referral facilities (Rahman et al. 2011). Although the public health facilities of Matlab, Chandpur and Bangladesh are required to provide ANC, delivery and caesarean sections free of charge, women and their families sometimes need to make additional unauthorized payments to access services or medicines and the availability of medication and health providers in public-sector health facilities is not always assured (Mridha et al., 2009). Additionally, transportation to referral facilities requires out-of-pocket payment from the families. Absenteeism, staff vacancies and appointment of general doctors to consultant obstetrician posts were found in public health facilities (Anwar et al., 2009). In 1993, nurses and doctors in sub-district hospitals were not found to be sufficiently trained in EmOC (GHWA WHO, 2008). The government training of skilled birth attendants at the union level and doctors and nurses at the sub-district level in emergency obstetric care reached only 60% of target levels between 2001 and 2007 while attrition rates of 35% were seen for these trained health professionals (GHWA WHO, 2008). The supervision of staff in Matlab's public health facilities is also inadequate with frequent absences of supervisors and staff (Personal communication- J. Pervin). Conversely, in Matlab ICDDR,B facilities all providers are trained in EmOC, with monthly supervision of sub-centre midwives at the sub-centres by doctors, and daily supervision of nurse-midwives by doctors at the ICDDR,B hospital. Staff are rapidly replaced when there are vacancies and attrition is very low with the four sub-centre midwives completing between 7 and 25 years of service. There is ongoing training throughout the year with week-long refresher courses in safe delivery practices and essential newborn care and resuscitation.

4. Measurement of deaths in the early neonatal period and the recording of intrapartum complications

My findings question the current distinction between early and late neonatal deaths. My results suggest that stillbirths and very early neonatal deaths (Day 0-2 deaths) are similar from an epidemiological point of view as they respond to antenatal care, SBA and emergency obstetric care. Late early neonatal deaths (Day 3-6) and late neonatal deaths are different from these early deaths. The breakdown of the early neonatal period into very early and late early neonatal deaths is a better method of categorising deaths that are epidemiologically similar. My results also question whether late early neonatal deaths should be included in assessments of the effects of programmes aimed at reducing perinatal mortality.

Mortality rates for stillbirths and neonatal mortality are reported in the current literature as pooled estimates for South Asia (WHO, 2006a) (WHO, 2007) (Stanton et al., 2006) (Lawn et al., 2011) (Cousens et al., 2011). My systematic review showed that pooling of rates for South Asia is simplistic, as the countries in the region vary greatly in terms of the mortality levels seen. As very low rates for all these mortality outcomes are seen in Sri Lanka and Maldives compared to the higher rates in Afghanistan, Bangladesh, India, Nepal and Pakistan, I suggest a new regional breakdown for South Asia, namely, South Asian Low Mortality Countries and South Asian High Mortality Countries. This breakdown should reflect the separation of low and high mortality rate countries in South Asia in future reports of regional mortality rate estimates.

In the case of the study on intrapartum complications, it was noted that there was poor recording of intrapartum complications in hospitals of Matlab and Chandpur, probably due to lack of standardisation of obstetric diagnoses and poor record keeping. The Safe Motherhood Programme showed reductions in stillbirths and Day 0-2 deaths resulting from improvements in ANC, SBA and emergency obstetric care, reductions that would be unlikely to be achieved if clinical skills were indeed poor. Improving the quality of record keeping in public and private clinics and hospitals in Matlab and Chandpur is important. Standardisation of diagnoses can be addressed by ensuring that national and local clinical guidelines set criteria for complications based on the International Classification of Diseases (ICD; version 10) (WHO, 2011; WHO 2014) while the WHO training manual for improved record keeping can be customized for local use (WHO Regional Office for the Western Pacific 2006; International Records Management Trust 1999). Poor medical record keeping can result from (a) incomplete charting due to lack of

documentation of required information (e.g. laboratory results), illegible handwriting or inaccurate information, as well as (b) poor archiving where records are missing or irretrievable. This can be improved by: standardization of medical records, standardized file recording and filing systems. In addition simple, low-cost electronic devices such as mobile phones and personal digital assistants linked to simple customized computer databases can be used to record data electronically (Wong & Bradley 2009) (Pirkle et al., 2012). Though electronic recording may be difficult to implement, standardization of physical medical records and improved filing are feasible in the hospitals and clinics of Matlab and Chandpur. Recommendations can also be taken from the literature which suggests that record keeping can improve if training is provided to all clinical staff, if hospital leaders review the quality of records kept to maintain accountability, and if the link between accurate record keeping and assessment of quality of care and epidemiology is stressed (Pirkle et al., 2012) .

Conclusion

Results from this thesis suggest that levels of stillbirths and mortality in the first month of life are still very high in most of the countries of South Asia and in Matlab, Bangladesh. However, the thesis also finds that a programme that encourages ANC visits, increases SBA and increases access to emergency obstetric and neonatal care with an efficient referral system in place can reduce stillbirths and very early neonatal mortality without the need for complex, high-tech interventions. There is also evidence that dramatic reductions in neonatal mortality from Day 3 to Day 27 can be achieved despite the absence of formal post-partum visits if oral rehydration salts, antibiotics, and other drugs are available near the woman's home. The reduction of preterm birth rates is challenging and until interventions for prevention of these births are introduced, it is more feasible to focus on reducing deaths in preterm babies. Great reductions in stillbirths and newborn mortality are achievable in rural areas of Bangladesh without the need for complicated, high-tech care. However, substantial and long-term investments in SBA, emergency obstetric and neonatal care and treatment and management of ill neonatal need to be made before these reductions are seen all over Bangladesh and in LICs with high stillbirth and neonatal mortality.

Recommendations:

Policy recommendations:

- This thesis reinforces messages found in the literature (Bhutta et al. 2014; Lawn et al. 2013) that investment in ANC, SBA, emergency obstetric and newborn care and referral systems can greatly reduce stillbirths and early neonatal mortality.

- Improvement of ANC and intrapartum care at government facilities might be achieved through: provision of specific guidelines, foundational and refresher training in ANC; emergency obstetric and newborn care and reduction of absenteeism through accountability. Enhanced links with, and free access to, referral facilities are also recommended. Although this will require good governance and substantial investment, the results from the Matlab Safe Motherhood Programme show that large reductions in stillbirth and early neonatal mortality are possible.

- When mortality levels for South Asia are reported, the levels should not be presented for the whole of South Asia but should be reported separately for South Asian Low Mortality Countries and South Asian High Mortality Countries.

- The reduction of preterm births is a challenge. Until effective interventions for prevention are found, the most feasible recommendation would be to reduce deaths from preterm-related conditions by improving the management of babies currently born preterm. This would involve following the recommendations for neonatal survival by ensuring that all preterm babies have access to good quality emergency neonatal care, thermal care and feeding, and that neonatal illnesses are managed promptly and effectively.

- The lack of international consensus on the lower limit of preterm births observed during the PhD suggests the need for the identification of an international lower limit for preterm births. This lower cut-off should take into account the difference in perceptions of viability of life in HICs and LICs by medical personnel, the difference in epidemiological and clinical cut-offs (16 weeks vs. 20/22 weeks), and also take into account the lower limits of gestational age for stillbirths and miscarriages.

Research Recommendations:

- There is extreme paucity of research on interventions that reduce the occurrence of preterm births in LICs and HICs. More research on interventions reducing preterm births is urgently needed as well as research on the delivery and uptake of these interventions by rural health facilities and rural women in LICs.

- Further research is needed on improving and evaluating the coverage of kangaroo mother care, as well as evaluating the effect of antibiotics for pPROM on preterm prevalence and preterm-related mortality in Matlab.

- Further studies from the country and other LICs are needed to validate the finding from this PhD that early neonatal period (Day 0-2) deaths are similar to stillbirths responding similarly to improved skilled birth attendance and emergency obstetric and newborn care, while reduction in late early neonatal period (Day 3-6) and late neonatal deaths is achievable via better access to drugs and oral rehydration salts.

- Further research on the trends in yearly reductions in mortality rates over time in studies from South Asia could be performed by using formal analytical methods. These methods could include: meta-regression in STATA to test for effect of year on the mortality rate, separation of the data by year within each study to obtain multiple data points and by testing the significance of non-linear fits of the relationship between year and mortality. However, as only a few studies took place over a number of years the number of studies available for this research would be low. Difference between mortality rates in the systematic review had been assessed by eyeballing confidence intervals, which may overlap by chance and so formal statistical methods of comparison of rates could be performed.

- There is need for qualitative research on quality of care processes and mechanisms such as why data collection on intrapartum complications is poor in rural health facilities of LICs. There is also need for research on methods which will improve the quality of record-keeping in these facilities.

- Further research with a much larger sample size of births with and without complications and with and without perinatal death outcomes is needed in Matlab to properly assess the association between intrapartum complications and perinatal mortality. Since data was missing for the analysis on intrapartum complications, until better methods of record-keeping are utilised, multiple imputation is a research recommendation for studies in countries where intrapartum data, socio-demographic variables and preterm gestation status is missing from records. This can provide an understanding of the effect of intrapartum complications on preterm births and mortality in the first month of life in rural hospital scenarios of developing countries.

- My study on the Matlab Safe Motherhood programme's contribution on newborn mortality was an observational study and the study design considered appropriate as it followed up the participants for rare mortality outcomes over a long time period and had very low loss-to-follow up. However, residual bias could be present as it is difficult to control for all confounding. Recommendations for study designs for future studies are given below. The Matlab Safe motherhood programme is not a real-life programme in that it has much greater quality control, more money and more supervision. More implementation research would be needed to assess whether a programme similar to the Matlab Safe Motherhood programme implemented by the government might be effective. In this case, a quasi-experimental study design similar to the Matlab study (but at larger scale) could be used or a cluster RCT study design could be used with the cluster unit depending on the unit at which the government may need to implement a scale-up (possibly at the government deli very centres at the sub-sub-district or 'union' level or at the sub-district level or 'upazila' level).

- Health economics research (e.g. cost-benefits analysis) is required to understand whether financial investment on improving and upgrading existing health facilities provides cost-effective returns in terms of reduction of deaths and better health outcomes. The cost of the Matlab Safe Motherhood programme was not assessed in my study and a cost-effectiveness analysis would be important if the findings from Matlab are to be replicated in high-burden areas in Bangladesh and in other countries. Investment areas could possibly include improvements in: addition of evidence-based antenatal care components; training and refresher training on emergency obstetric and newborn care of health personnel; better availability and retention of health personnel; and improved referral systems between higher and lower level health facilities.

- Qualitative research could also help in the adaptation of the Matlab Safe Motherhood programme elsewhere. There is no information on the factors allowing Matlab

women to overcome cultural barriers that are considered to prevent women from giving birth in health facilities in Bangladesh. Qualitative research into midwives' attitudes towards women could also be undertaken. A greater understanding of these issues could help in scaling up the programme in Bangladesh and elsewhere.

References:

Abalos, E., Cuesta, C., Grosso, A. L., Chou, D. & Say, L. (2013). Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *170*(1), 1–7. doi:10.1016/j.ejogrb.2013.05.005

Achadi, E., Scott, S., Pambudi, E. S., Makowiecka, K., Marshall, T., Adisasmita, A. & Ronsmans, C. (2007). Midwifery provision and uptake of maternity care in Indonesia. *Tropical Medicine & International Health*, *12*(12), 1490–1497. Retrieved from http://dx.doi.org/10.1111/j.1365-3156.2007.01957.x

Afghan Public Health Institute Central Statistics, Ministry of Public Health (APHI/MoPH) [Afghanistan], Indian Institute of Health Management Research (IIHMR) [India], and World Health Organization (WHO/EMRO). (2011). Afghanistan Mortality Survey 2010. Calverton, Maryland, USA: APHI/MoPH, ICF Macro, IIHMR and WHO/EMRO.

Ahman, E. & Zupan, J. (2007). *Neonatal and perinatal mortality 2004. Country, regional and global estimates*. Geneva, Switzerland: World Health Organization. Retrieved from http://whqlibdoc.who.int/publications/2007/9789241596145_eng.pdf

Ahmed, F., Mahmuda, I., Sattar, A. & Akhtaruzzaman, M. (2003). Anaemia and vitamin A deficiency in poor urban pregnant women of Bangladesh. *Asia Pacific Journal of Clinical Nutrition*, *12*(4), 460–6.

Ahmed, S. & Hossain, M. (2006). *Pilot Project on Capacity Development of the Unqualified/semi-qualified Allopathic Healthcare Providers*. Dhaka 1212, Bangladesh. Retrieved from http://research.brac.net/reports_details.php?scat=8&v=0&tid=457

Ahmed, S. M., Chowdhury, M. & Bhuiya, A. (2001). Micro-Credit and Emotional Well-Being: Experience of Poor Rural Women from Matlab, Bangladesh. *World Development*, *29*(11), 1957–1966. doi:10.1016/S0305-750X(01)00069-9

Alisjahbana, A., Williams, C., Dharmayanti, R., Hermawan, D., Kwast, B. E. & Koblinsky, M. (1995). An integrated village maternity service to improve referral patterns in a rural area in West-Java. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *48 Suppl*, S83–94.

Althabe, F., Belizán, J. M., McClure, E. M., Hemingway-Foday, J., Berrueta, M., Mazzoni, A. & Buekens, P. M. (2015). A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. *The Lancet*, *385*, 629–639. doi:10.1016/S0140-6736(14)61651-2

Anwar, I., Kalim, N. & Koblinsky, M., 2009. Quality of obstetric care in public-sector facilities and constraints to implementing emergency obstetric care services: evidence from high- and low-performing districts of Bangladesh. *Journal of Health, Population, and Nutrition*, 27(2), pp.139–55.

Anwar, I., Killewo, J. & Chowdhury, M., 2004. Bangladesh: Inequalities in Utilization of Maternal Health Care Services - Evidence from Matlab. *Health, Nutrition and Population (HNP) Discussion Paper. Reaching the Poor Program. Paper No.2. 2004.* Health, Nutrition and Population Division, Human Development Department, The World Bank.

Arifeen, S. El, Mullany, L. C., Shah, R., Mannan, I., Rahman, S. M., Talukder, M. R. R. & Baqui, A. H. (2012). The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial. *The Lancet*, *379*(9820), 1022–1028.

Arifeen, S. E., Black, R. E., Caulfield, L. E., Antelman, G., Baqui, A. H., Nahar, Q. & Mahmud, H. (2000). Infant growth patterns in the slums of Dhaka in relation to birth weight, intrauterine growth retardation, and prematurity. *The American Journal of Clinical Nutrition*, *72*(4), 1010–7.

Azad, K., Barnett, S., Banerjee, B., Shaha, S., Khan, K., Rego, A. R. & Costello, A. (2010). Effect of scaling up women's groups on birth outcomes in three rural districts in Bangladesh: a cluster-randomised controlled trial. *The Lancet*. 2010. Apr 3; 375(9721):1193-202

Azad, K. & Costello, A. (2014). Extreme caution is needed before scale-up of antenatal corticosteroids to reduce preterm deaths in low-income settings. *The Lancet Global Health*. doi:10.1016/S2214-109X(14)70020-8

Bakketeig, L., Hoffman, H. & Oakley, A., 1984. Perinatal mortality. Editor: Bracken MB. New York, NY: Perinatal epidemiology. pp.34-37. Oxford University Press.

Bamji, M. S., Murthy, P. V. V. S., Williams, L., & Rao, M. V. V. (2008). Maternal nutritional status & practices & perinatal, neonatal mortality in rural Andhra Pradesh, India. *Indian Journal of Medical Research*, 127(1), 44–51.

Bang, A., Reddy, M.H. & Deshmukh, M.D., 2002. Child mortality in Maharashtra. *Economic and Political Weekly,* 37(49), pp.4947–4965.

Bang, A. T., Bang, R. A., Sanjay, B., Mahesh, D. & Reddy, M. H. (2001). Burden of morbidities and the unmet need for health care in rural neonates - a prospective observational study in Gadchiroli, India. *Indian Pediatrics*, 38(9), 952–965.

Bang, A. T., Bang, R. A., Baitule, S. B., Reddy, M. H. & Deshmukh, M. D. (1999). Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *The Lancet*, 354(9194), 1955–61.

Bang, A. T., Reddy, H. M., Deshmukh, M. D., Baitule, S. B. & Bang, R. A. (2005). Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: effect of home-based neonatal care. *Journal of Perinatology : Official Journal of the California Perinatal Association*, 25 Suppl 1, S92–107.

Bang, R. A., Bang, A. T., Reddy, M. H., Deshmukh, M. D., Baitule, S. B. & Filippi, V. (2004). Maternal morbidity during labour and the puerperium in rural homes and the need for medical attention: A prospective observational study in Gadchiroli, India. *British Journal of Obstetrics and Gynaecology : An International Journal of Obstetrics and Gynaecology,* 111(3), 231–8.

Bangladesh Ministry of Health and Family Welfare, 2010. Health Care Network of Bangladesh under the Ministry of Health & Family Welfare. pp.1–6. Available at: http://dghs.gov.bd/dmdocuments/Bangladesh Health Network.pdf.

Banglapedia: National Encyclopedia of Bangladesh (2014). Reproductive healthcare services. *Banglapedia*. Dhaka 1212, Bangladesh.

Baqui, A. H., El-Arifeen, S., Darmstadt, G. L., Ahmed, S., Williams, E. K., Seraji, H. R. & Projahnmo Study Group (2008). Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial. *The Lancet*, *371*(9628), pp.1936–1944.

Baqui, A. H., Ahmed, S., El Arifeen, S., Darmstadt, G. L., Rosecrans, A. M., Mannan, I. & Black, R. E. (2009). Effect of timing of first postnatal care home visit on neonatal mortality in Bangladesh: A observational cohort study. *British Medical Journal*, *339*(7718), pp. 445–448.

Baqui, A. H., Rosen, H. E., Lee, A. C. C., Applegate, J. A., El Arifeen, S., Rahman, S. M. & Black, R. E. (2013). Preterm birth and neonatal mortality in a rural Bangladeshi cohort: implications for health programs. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *33*(12), pp.977–81.

Baqui, A. H., Darmstadt, G. L., Williams, E. K., Kumar, V., Kiran, T. U., Panwar, D. & Santosham, M. (2006). Rates, timing and causes of neonatal deaths in rural India: implications for neonatal health programmes. *Bulletin of the World Health Organization*, *84*(9), pp.706–713.

Barfield, W.D., 2011. Standard terminology for fetal, infant, and perinatal deaths. *Pediatrics*, 128(1), pp.177–81.

Bari, W., Chowdhury, R. I., Islam, M. A., Chakraborty, N. & Akhter, H. A. H. (2002). The differentials and determinants of perinatal mortality in rural Bangladesh. *The European Journal of Contraception and Reproductive Health Care*, *7*(4), pp.216–222.

Beck, S., Wojdyla, D., Say, L., Betran, A. P., Merialdi, M., Requejo, J. H & Van Look, P. F. A. (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World Health Organization*, *88*(1), pp.31–8.

Behrman, R.E. & Butler, A.S. eds., (2007). *Preterm Birth: Causes, Consequences, and Prevention.* Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes: National Academies Press (US). Washington D.C.

Benjamin, A.I., Paramita, S. & Shavinder, S. (2009). Perinatal mortality and its risk factors in Ludhiana: a population-based prospective cohort study. *Health and Population- Perspectives and Issues*, 32(1), pp.12–20.

Bhutta, Z. A., Arjumand, R., Farrukh, R., Sunil, H., Shujaat, Z., Hossain, S. M. & Shereen, B. (2009). A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. (Special Issue: Multiple micronutrient supplementation during pregnancy in developing country settings.). *Food and Nutrition Bulletin*, *30*(4 (Supplement)), pp.S496–S505.

Bhutta, Z. A., Ali, S., Cousens, S., Ali, T. M., Haider, B. A., Rizvi, A. & Black, R. E. (2008). Alma-Ata: Rebirth and Revision 6 Interventions to address maternal, newborn, and child survival: what difference can integrated primary health care strategies make? *The Lancet*, *372*(9642), pp.972–989.

Bhutta, Z. A., Das, J. K., Bahl, R., Lawn, J. E., Salam, R. A., Paul, V. K. & Walker, N. (2014). Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *The Lancet*, 384 (9940), pp. 347–370

Bhutta, Z. A., Darmstadt, G. L., Haws, R. A., Yakoob, M. Y. & Lawn, J. E. (2009). Delivering interventions to reduce the global burden of stillbirths: improving service supply and community demand. *BMC Pregnancy and Childbirth*, *9 Suppl 1*(Suppl 1), pp.S7.

Bhutta, Z. A., Das, J. K., Rizvi, A., Gaffey, M. F., Walker, N., Horton, S. & Black, R. E. (2013). Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *The Lancet*, *382*(9890),pp. 452–77.

Bhutta, Z. A., Memon, Z. A., Sajid, S., Salat, M. S., Cousens, S. & Martines, J. (2008). Implementing community-based perinatal care: results from a pilot study in rural Pakistan. *Bulletin of the World Health Organization*, *86*(6), pp.452–459.

Bhutta, Z. A., Soofi, S., Cousens, S., Mohammad, S., Memon, Z. A., Ali, I. & Martines, J. (2011). Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. *The Lancet*, *377*(9763), pp.403–12.

Bhutta, Z. A., Cabral, S., Chan, C.-W. & Keenan, W. J. (2012). Reducing maternal, newborn, and infant mortality globally: an integrated action agenda. *International*

Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, *119 Suppl*, pp.S13–7.

Bhutta, Z. A., Yakoob, M. Y., Lawn, J. E., Rizvi, A., Friberg, I. K., Weissman, E. & Goldenberg, R. L. (2011). Stillbirths: what difference can we make and at what cost?*The Lancet*, *377*(9776), pp.1523–38.

Black, R.E., Morris, S.S. & Bryce, J., 2003. Where and why are 10 million children dying every year? *The Lancet*, 361(9376), pp.2226–2234.

Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A.-B. & Lawn, J. (2013). Born Too Soon: The global epidemiology of 15 million preterm births. *Reproductive Health*, *10*(Suppl 1), S2. doi:10.1186/1742-4755-10-S1-S2

Blencowe, H., Cousens, S., Kamb, M., Berman, S. & Lawn, J. E. (2011). Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health*, *11 Suppl 3*, S9. doi:10.1186/1471-2458-11-S3-S9

Blencowe, H., Cousens, S., Modell, B. & Lawn, J. (2010). Folic acid to reduce neonatal mortality from neural tube disorders. *International Journal of Epidemiology*, *39 Suppl 1*, i110–21. doi:10.1093/ije/dyq028

Blencowe, H., Cousens, S., Mullany, L. C., Lee, A. C. C., Kerber, K., Wall, S. & Lawn, J. E. (2011). Clean birth and postnatal care practices to reduce neonatal deaths from sepsis and tetanus: a systematic review and Delphi estimation of mortality effect. *BMC Public Health*, *11 Suppl 3*, S11. doi:10.1186/1471-2458-11-S3-S11

Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A.-B., Narwal, R. & Lawn, J. E. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet*, *379*(9832), pp.2162–72. doi:10.1016/S0140-6736(12)60820-4

Blencowe, H., Lawn, J., Vandelaer, J., Roper, M. & Cousens, S. (2010). Tetanus toxoid immunization to reduce mortality from neonatal tetanus. *International Journal of Epidemiology*, *39 Suppl 1*, i102–9. doi:10.1093/ije/dyq027

Blondel, B., Macfarlane, A., Gissler, M., Breart, G. & Zeitlin, J. (2006). Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. *BJOG: An International Journal of Obstetrics and Gynaecology*, *113*(5), pp.528–35. doi:10.1111/j.1471-0528.2006.00923.x

Bos, E. (2004). Population and Health in Developing Countries. Volume 1. Population, Health, and Survival at INDEPTH Sites. INDEPTH Network. Ottawa: International Development Research Centre, 2002, pp. 356, ISBN: 0-88936-948-8. *International Journal of Epidemiology*, *33*(4),pp.916–917. doi:10.1093/ije/dyh220

Brettell, R., Yeh, P. S. & Impey, L. W. M. (2008). Examination of the association between male gender and preterm delivery. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *141*(2),pp. 123–6. doi:10.1016/j.ejogrb.2008.07.030

Brocklehurst, P., Gordon, A., Heatley, E. & Milan, S. J. (2013). Antibiotics for treating bacterial vaginosis in pregnancy. *The Cochrane Database of Systematic Reviews*, *1*, CD000262. doi:10.1002/14651858.CD000262.pub4

Buchmann, E. J. & Pattinson, R. C. (2006). Babies who die from labour-related intrapartum hypoxia: a confidential enquiry in South African public hospitals. *Tropical Doctor*, *36*(1), pp.8–10. doi:10.1258/004947506775598879

Burkhalter, B., Edson, W., Harvey, S. & Boucar, M. (2006). *Quality of obstetric care observed in 14 hospitals in Benin, Ecuador, Jamaica, and Rwanda. Operations Research Results.* Retrieved from http://www.popline.org/node/174216

Campbell, O. M. R. & Graham, W. J. (2006). Strategies for reducing maternal mortality: getting on with what works. *The Lancet*, *368*(9543), pp.1284–99. doi:10.1016/S0140-6736(06)69381-1

Casterline, J. B. (1989). Collecting data on pregnancy loss: a review of evidence from the World Fertility Survey. *Stud Fam Plann*, *20*(2),pp. 81–95.

Centers for Disease Control and Prevention. (1998). Risk factors for short interpregnancy interval--Utah, June 1996-June 1997. *MMWR. Morbidity and Mortality Weekly Report*, *47*(43), pp.930–4. Retrieved from file:///C:/ResQues3_Morb2013/Morb2013_MACU_29sep2013/Do Files_Morb2013_27Sep2013/WorkFigLog_Macu/PTB Word and Excel Docs/Preterm birth workdocs/PT articles/MMWR1998_Risk Factors for Short Interpregnancy Interval_ Utah, June 1996-June 1997.htm

Chalumeau, M., Salanave, B., Bouvier-Colle, M.-H., Bernis, L., Prua, A. & Bréart, G. (2000). Risk factors for perinatal mortality in West Africa: a population-based study of 20 326 pregnancies. *Acta Paediatrica*, *89*(9),pp. 1115–1121. Retrieved from http://dx.doi.org/10.1111/j.1651-2227.2000.tb03361.x

Chang, H. H., Larson, J., Blencowe, H., Spong, C. Y., Howson, C. P., Cairns-Smith, S. & Lawn, J. E. (2013). Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. *The Lancet*, *381*(9862), pp.223–34. doi:10.1016/S0140-6736(12)61856-X

Chen, L. M., Sun, C. A., Wu, D. M., Shen, M. H. & Lee, W. C. (1998). Underregistration of neonatal deaths: an empirical study of the accuracy of infantile vital statistics in Taiwan. *Journal of Epidemiology andCommunity Health*, *52*(5),pp. 289–292.

Cherry, N., Shaikh, K., McDonald, C. & Chowdhury, Z. (2008). Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra. *Bulletin of the World Health Organization*, *86*(3), pp.172–177. doi:S0042-96862008000300009 [pii]

Chowdhury, H. R., Thompson, S., Ali, M., Alam, N., Yunus, M. & Streatfield, P. K. (2010). Causes of neonatal deaths in a rural subdistrict of Bangladesh: implications for intervention. *Journal of Health, Population, and Nutrition*, *28*(4), pp.375–82.

Chowdhury, M. E., Ahmed, A., Kalim, N. & Koblinsky, M. (2009). Causes of maternal mortality decline in Matlab, Bangladesh. *Journal of Health, Population and Nutrition*, *27*(2), pp. 108–123.

Chowdhury, M. E., Akhter, H. H., Chongsuvivatwong, V. & Geater, A. F. (2005). Neonatal mortality in rural Bangladesh: an exploratory study. *Journal of Health, Population, and Nutrition*, *23*(1), pp.16–24.

Chowdhury, M. E., Botlero, R., Koblinsky, M., Saha, S. K., Dieltiens, G. & Ronsmans, C. (2007). Determinants of reduction in maternal mortality in Matlab, Bangladesh: a 30-year cohort study. *The Lancet*, *370*(9595), pp.1320–1328. doi:S0140-6736(07)61573-6 [pii] 10.1016/S0140-6736(07)61573-6

Chowdhury, M. E., Ronsmans, C., Killewo, J., Anwar, I., Gausia, K., Das-Gupta, S. & Borghi, J. (2006). Equity in use of home-based or facility-based skilled obstetric care in rural Bangladesh: an observational study. *The Lancet*, *367*(9507), pp.327–32. doi:10.1016/S0140-6736(06)68070-7

Chowdhury, S. N. M. & Moni, D. (2004). A situation analysis of the menstrual regulation programme in Bangladesh. *Reproductive Health Matters*, *12*(24 Suppl), pp.95–104.

Christian, P. (2003). Micronutrients and reproductive health issues: An international perspective. *Journal of Nutrition*, *133*(6), pp.1969S–1973S.

Cnattingius, S. & Stephansson, O. (2002). The epidemiology of stillbirth. *Seminars in Perinatology*, *26*(1), pp.25–30.

Conde-Agudelo, A., Belizán, J. M. & Diaz-Rossello, J. (2011). Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *The Cochrane Database of Systematic Reviews*, (3), CD002771. doi:10.1002/14651858.CD002771.pub2

Conde-Agudelo, A., Rosas-Bermúdez, A. & Kafury-Goeta, A. C. (2006). Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA : The Journal of the American Medical Association*, *295*(15), 1809–23. doi:10.1001/jama.295.15.1809

Copper, R. L., Goldenberg, R. L., Creasy, R. K., DuBard, M. B., Davis, R. O., Entman, S. S. & Cliver, S. P. (1993). A multicenter study of preterm birth weight and gestational age-

specific neonatal mortality. *American Journal of Obstetrics and Gynecology*, *168*(1 Pt 1), 78–84. doi:8420354

Cousens, S., Blencowe, H., Gravett, M. & Lawn, J. E. (2010). Antibiotics for pre-term pre-labour rupture of membranes: prevention of neonatal deaths due to complications of pre-term birth and infection. *International Journal of Epidemiology*, *39 Suppl 1*, pp.i134–43. doi:10.1093/ije/dyq030

Cousens, S., Blencowe, H., Stanton, C., Chou, D., Ahmed, S., Steinhardt, L. & Lawn, J. E. (2011). National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet*, *377*(9774), pp.1319–1330.

Cresswell, J. A., Ronsmans, C., Calvert, C. & Filippi, V. (2013). Prevalence of placenta praevia by world region: a systematic review and meta-analysis. *Tropical Medicine & International Health : TM & IH*, *18*(6), pp.712–24. doi:10.1111/tmi.12100

Cruz-Anguiano, V., Talavera, J. O., Vázquez, L., Antonio, A., Castellanos, A., Lezana, M. A. & Wacher, N. H. (2004). The importance of quality of care in perinatal mortality: a case-control study in Chiapas, Mexico. *Archives of Medical Research*, *35*(6), pp.554–562.

Da Silva, A. A. M., Simões, V. M. F., Barbieri, M. A., Bettiol, H., Lamy-Filho, F., Coimbra, L. C. & Alves, M. T. S. S. B. (2003). Young maternal age and preterm birth. *Paediatric and Perinatal Epidemiology*, *17*(4), pp.332–9.

Darmstadt, G. L., Bhutta, Z. A., Cousens, S., Adam, T., Walker, N. & de Bernis, L. (2005). Evidence-based, cost-effective interventions: how many newborn babies can we save? *Lancet*, *365*(9463), pp.977–88. doi:10.1016/S0140-6736(05)71088-6

Darmstadt, G. L., Choi, Y., Arifeen, S. E., Bari, S., Rahman, S. M., Mannan, I. & Bangladesh Projahnmo-2 Mirzapur Study Group (2010). Evaluation of a cluster-randomized controlled trial of a package of community-based maternal and newborn interventions in Mirzapur, Bangladesh. *PLoS ONE*, *5*(3), e9696.

Darmstadt, G. L., Kinney, M. V, Chopra, M., Cousens, S., Kak, L., Paul, V. K. & Lawn, J. E. (2014). Who has been caring for the baby? *The Lancet*. doi:10.1016/S0140-6736(14)60458-X

Darmstadt, G. L., Kumar, V., Yadav, R., Singh, V., Singh, P., Mohanty, S. & Santosham, M. (2006). Introduction of community-based skin-to-skin care in rural Uttar Pradesh, India. *Journal of Perinatology*, *26*(10), pp.597–604. doi:http://dx.doi.org/10.1038/sj.jp.7211569

Darmstadt, G. L., Lawn, J. & Costello, A. (2003). Advancing the state of the world's newborns. *Bulletin of the World Health Organization*, *81*(3), pp.224–225. doi:S0042-96862003000300014 [pii]

DaVanzo, J., Hale, L., Razzaque, A. & Rahman, M. (2007). Effects of interpregnancy interval and outcome of the preceding pregnancy on pregnancy outcomes in Matlab, Bangladesh. *BJOG: An International Journal of Obstetrics & Gynaecology*, *114*(9), pp. 1079–1087. Retrieved from http://dx.doi.org/10.1111/j.1471-0528.2007.01338.x

DaVanzo, J., Razzaque, A., Rahman, M., Hale, L. & Ahmed, K. (2004). *The effects of birth spacing on infant and child mortality, pregnancy outcomes, and maternal morbidity and mortality in Matlab, Bangladesh*. *RAND Labor and Population Working Paper Series WR-198;USAID Cooperative Agreement No. HRN-A-00-00-00003-00*. [Santa Monica, California], RAND, 2004 Oct. Retrieved from http://www.rand.org/pubs/working_papers/WR198.html

Dean, S. V, Mason, E., Howson, C. P., Lassi, Z. S., Imam, A. M. & Bhutta, Z. A. (2013). Born Toon Soon: Care before and between pregnancy to prevent preterm births: from evidence to action. *Reproductive Health*, *10*(Suppl 1), S3. doi:10.1186/1742-4755-10-S1-S3

Debes, A. K., Kohli, A., Walker, N., Edmond, K. & Mullany, L. C. (2013). Time to initiation of breastfeeding and neonatal mortality and morbidity: a systematic review. *BMC Public Health*, *13 Suppl 3*, S19. doi:10.1186/1471-2458-13-S3-S19

DeFranco, E. A., Stamilio, D. M., Boslaugh, S. E., Gross, G. A. & Muglia, L. J. (2007). A short interpregnancy interval is a risk factor for preterm birth and its recurrence. *American Journal of Obstetrics and Gynecology*, *197*(3), 264.e1–6. doi:10.1016/j.ajog.2007.06.042

Department of Census and Statistics (DCS) and Ministry of Healthcare and Nutrition (MOH). (2009). *Sri Lanka Demographic and Health Survey 2006-07.* Colombo, Sri Lanka: DCS and MOH.

Di Mario, S., Say, L. & Lincetto, O. (2007). Risk Factors for Stillbirth in Developing Countries: A Systematic Review of the Literature. *Sexually Transmitted Diseases*, *34*(7), pp.S11–S21 10.1097/01.olq.0000258130.07476.e3.

Di Renzo, G. C., Giardina, I., Rosati, A., Clerici, G., Torricelli, M. & Petraglia, F. (2011). Maternal risk factors for preterm birth: a country-based population analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *159*(2), pp.342–6. doi:10.1016/j.ejogrb.2011.09.024

Dickson, K. E., Simen-Kapeu, A., Kinney, M. V, Huicho, L., Vesel, L., Lackritz, E. & Lawn, J. E. (2014). Health-systems bottlenecks and strategies to accelerate scale-up in countries. *The Lancet,* 384 (9941), pp.438–454. doi:10.1016/S0140-6736(14)60582-1

Duley, L., Henderson-Smart, D. J., Meher, S. & King, J. F. (2007). Antiplatelet agents for preventing pre-eclampsia and its complications. *The Cochrane Database of Systematic Reviews*, (2), CD004659. doi:10.1002/14651858.CD004659.pub2

Ehrenstein, O. S. von, Mazumder, D. N. G., Hira-Smith, M., Ghosh, N., Yuan, Y., Windham, G. & Smith, A. H. (2006). Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *American Journal of Epidemiology*, *163*(7), pp.662–669.

Ellis, M., Azad, K., Banerjee, B., Shaha, S. K., Prost, A., Rego, A. R. & Barnett, S. (2011). Intrapartum-related stillbirths and neonatal deaths in rural Bangladesh: a prospective, community-based cohort study. *Pediatrics*, *127*(5), pp.e1182–90. doi:10.1542/peds.2010-0842

Ellis,M., Manandhar D. S., Wyatt, J., Bolam, A.J. & Costello, A.M. (2000). Stillbirths and neonatal encephalopathy in Kathmandu, Nepal: an estimate of the contribution of birth asphyxia to perinatal mortality in a low-income urban population. *Paediatric and Perinatal Epidemiology*, *14*(1), pp.39–52. doi:10.1046/j.1365-3016.2000.00233.x

Engle, W. A. (2004). Age terminology during the perinatal period. *Pediatrics*, *114*(5), 1362–4. doi:10.1542/peds.2004-1915

Engmann, C., Garces, A., Jehan, I., Ditekemena, J., Phiri, M., Mazariegos, M. & Wright, L. L. (2012). Causes of community stillbirths and early neonatal deaths in low-income countries using verbal autopsy: an International, Multicenter Study. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *32*(8), pp.585–92. doi:10.1038/jp.2011.154

Engmann, C., Matendo, R., Kinoshita, R., Ditekemena, J., Moore, J., Goldenberg, R. L., & Wright, L. L. (2009). Stillbirth and early neonatal mortality in rural Central Africa. *Int J Gynaecol Obstet*, *105*(2), pp.112–117. doi:S0020-7292(08)00580-8 [pii] 10.1016/j.ijgo.2008.12.012

Evers, A. C. C., Brouwers, H. A. A., Hukkelhoven, C. W. P. M., Nikkels, P. G. J., Boon, J., van Egmond-Linden, A. & Kwee, A. (2010). Perinatal mortality and severe morbidity in low and high risk term pregnancies in the Netherlands: prospective cohort study. *British Medical Journal (Clinical Research Ed.)*, *341*, pp.c5639.

Fauveau, V., Stewart, K., Khan, S. A. & Chakraborty, J. (1991). Effect on mortality of community-based maternity-care programme in rural Bangladesh. *The Lancet*, *338*(8776), pp.1183–1186. doi:0140-6736(91)92041-Y [pii]

Fauveau, V., Wojtyniak, B., Mostofa, G., Sarder, A. M. & Chakraborty, J. (1990). Perinatal Mortality in Matlab, Bangladesh: A Community-Based Study. *International Journal of Epidemiology*, *19*(3),pp. 606–612. doi:10.1093/ije/19.3.606

Fauveau.V. (1994). Matlab: Women, children and health. Ed. ICDDR, B.Dhaka. In Fauveau.V (Ed.), (pp. 1–160). ICDDR,B Mohakhali, Dhaka, Bangaldesh.

Filippi, V., Chou, D., Ronsmans, C., Graham, W. & Say, L. Levels and causes of maternal morbidity and mortality (In Press). In *Disease Control Priorities 3.* Retrieved from

http://www.dcp-3.org/volume/maternal-and-child-health/chapter/1/burden-mortality-and-morbidity-during-pregnancy-and

Flenady, V., Koopmans, L., Middleton, P., Frøen, J. F., Smith, G. C., Gibbons, K. & Ezzati, M. (2011). Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*, *377*(9774), pp.1331–40. doi:10.1016/S0140-6736(10)62233-7

Fraser, A. M., Brockert, J. E. & Ward, R. H. (1995). Association of young maternal age with adverse reproductive outcomes. *The New England Journal of Medicine*, *332*(17), pp.1113–7. doi:10.1056/NEJM199504273321701

Fraser, J., Walls, M. & McGuire, W. (2004). Respiratory complications of preterm birth. *British Medical Journal (Clinical Research Ed.)*, *329*(7472), pp.962–5. doi:10.1136/bmj.329.7472.962

Froen, J. F., Cacciatore, J., McClure, E. M., Kuti, O., Jokhio, A. H., Islam, M. & Shiffman, J. (2011). Stillbirths: why they matter. *The Lancet*, *377*(9774), pp.1353–1366. doi:10.1016/S0140-6736(10)62232-5

Froen, J. F., Gordijn, S., Abdel-Aleem, H., Bergsjo, P., Betran, A., Duke, C. & Shankar, A. (2009). Making stillbirths count, making numbers talk - Issues in data collection for stillbirths. *BMC Pregnancy and Childbirth*, *9*(1), 58.

Gazi, R., Goodburn, L. & Chowdhury, A. M. (1999). Risk factors for perinatal deaths in rural Bangladesh. *Journal of Health and Population in Developing Countries*, *2*(1), pp.70–77.

George, K., Prasad, J., Singh, D., Minz, S., Albert, D. S., Muliyil, J. & Kramer, M. S. (2009). Perinatal outcomes in a South Asian setting with high rates of low birth weight. *BMC Pregnancy and Childbirth*, *9*, 5. doi:10.1186/1471-2393-9-5

Global Health Workforce Alliance & World Health Organization. (2008). *Bangladesh trains health workers to reduce maternal mortality.* Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/workforcealliance/knowledge/case_studies/CS_Bangladesh_web_en.pdf

Goldenberg, R. L., Culhane, J. F., Iams, J. D. & Romero, R. (2008). Epidemiology and causes of preterm birth. *The Lancet*, *371*(9606), pp.75–84. doi:10.1016/S0140-6736(08)60074-4

Goldenberg, R. L., Gravett, M. G., Iams, J., Papageorghiou, A. T., Waller, S. A., Kramer, M. & Villar, J. (2012). The preterm birth syndrome: issues to consider in creating a classification system. *American Journal of Obstetrics and Gynecology*, *206*(2), pp.113–8. doi:10.1016/j.ajog.2011.10.865

Goldenberg, R. L., McClure, E. M. & Bann, C. M. (2007). The relationship of intrapartum and antepartum stillbirth rates to measures of obstetric care in developed and developing countries. *Acta Obstetricia et Gynecologica Scandinavica*, *86*(11), pp.1303–9. doi:10.1080/00016340701644876

Goldenberg, R. L., McClure, E. M., Bhutta, Z. A., Belizán, J. M., Reddy, U. M., Rubens, C. E. & Darmstadt, G. L. (2011). Stillbirths: the vision for 2020. *The Lancet*, *377*(9779), pp.1798–805. doi:10.1016/S0140-6736(10)62235-0

Goldenberg, R. L., McClure, E. M., Saleem, S. & Reddy, U. M. (2010). Infection-related stillbirths. *The Lancet*, *375*(9724), pp.1482–1490.

GRADE Working Group. (2014). Criteria for applying or using GRADE. Retrieved from http://www.gradeworkinggroup.org/intro.htm

Gravett, M., Rubens, C., Nunes, T. & Group, the G. R. (2010). Global report on preterm birth and stillbirth (2 of 7): discovery science. *BMC Pregnancy and Childbirth*, *10*(Suppl 1), S2.

Gustavson, K. H. (2005). Prevalence and aetiology of congenital birth defects, infant mortality and mental retardation in Lahore, Pakistan: a prospective cohort study. *Acta Paediatrica*, *94*(6), pp. 769–774.

Gyamfi-Bannerman, C., Fuchs, K. M., Young, O. M. & Hoffman, M. K. (2011). Nonspontaneous late preterm birth: etiology and outcomes. *American Journal of Obstetrics and Gynecology*, *205*(5), 456.e1–6. doi:10.1016/j.ajog.2011.08.007

Haider, B. A., Yakoob, M. Y. & Bhutta, Z. A. (2011). Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. *BMC Public Health*, *11 Suppl 3*, S19. doi:10.1186/1471-2458-11-S3-S19

Han, Z., Mulla, S., Beyene, J., Liao, G. & McDonald, S. D. (2011). Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. *International Journal of Epidemiology*, *40*(1), pp.65–101. doi:10.1093/ije/dyq195

Hawkes, S., Morison, L., Chakraborty, J., Gausia, K., Ahmed, F., Islam, S. S. & Mabey, D. (2002). Reproductive tract infections: prevalence and risk factors in rural Bangladesh. *Bulletin of the World Health Organization*, *80*(3), pp.180–8.

Haws, R. A., Mashasi, I., Mrisho, M., Schellenberg, J. A., Darmstadt, G. L. & Winch, P. J. (2010). “These are not good things for other people to know”: how rural Tanzanian women’s experiences of pregnancy loss and early neonatal death may impact survey data quality. *Social Science & Medicine (1982)*, *71*(10), pp.1764–72. doi:10.1016/j.socscimed.2010.03.051

Haws, R. A., Thomas, A. L., Bhutta, Z. A. & Darmstadt, G. L. (2007). Impact of packaged interventions on neonatal health: a review of the evidence. *Health Policy and Planning*, *22*(4), pp.193–215. doi:10.1093/heapol/czm009

Hediger, M. L., Scholl, T. O., Schall, J. I. & Krueger, P. M. (1997). Young maternal age and preterm labor. *Annals of Epidemiology*, *7*(6), pp.400–6. doi:9279449

Helen Keller International (HKI). (2010). *The Food Security and Nutrition Surveillance Project Round 1: January 2010-April 2010*.

Helen Keller International, & Institute of Public Health Nutrition (IPHN). (2005). *Bangladesh in Facts and Figures. 2004 Annual Report of the Nutritional Surveillance Project*. Helen Keller International; Dhaka, Bangladesh.

Higgins, J. P. T. & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Retrieved from www.cochrane-handbook.org.

Hofmeyr, G. J. & Lawrie, T. A. (2012). Amnioinfusion for potential or suspected umbilical cord compression in labour. *The Cochrane Database of Systematic Reviews*, *1*, CD000013. doi:10.1002/14651858.CD000013.pub2

Hossain, M. G., Bharati, P., Aik, S., Lestrel, P. E., Abeer, A. & Kamarul, T. (2012). Body mass index of married Bangladeshi women: trends and association with socio-demographic factors. *Journal of Biosocial Science*, *44*(4), 385–99. doi:10.1017/S002193201200003X

Howson, C., Kinney, M. & Lawn (Eds.), J. (2012). *Born Too Soon: The Global Action Report on Preterm Birth.* Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/entity/pmnch/media/news/2012/201204_borntoosoon-report.pdf

Howson, C. P., Kinney, M. V, McDougall, L. & Lawn, J. E. (2013). Born too soon: preterm birth matters. *Reproductive Health*, *10 Suppl 1*, p.S1. doi:10.1186/1742-4755-10-S1-S1

Huda, F. A., Ahmed, A., Dasgupta, S. K., Jahan, M., Ferdous, J., Koblinsky, M. & Chowdhury, M. E. (2012). Profile of maternal and foetal complications during labour and delivery among women giving birth in hospitals in Matlab and Chandpur, Bangladesh. *Journal of Health, Population, and Nutrition*, *30*(2), pp.131–42.

Hutcheon, J. A. & Platt, R. W. (2008). The impact of past pregnancy experience on subsequent perinatal outcomes. *Paediatric and Perinatal Epidemiology*, *22*(4),pp. 400–408. Retrieved from http://dx.doi.org/10.1111/j.1365-3016.2008.00937.x

Iams, J. D., Romero, R., Culhane, J. F. & Goldenberg, R. L. (2008). Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *The Lancet*, *371*(9607), pp.164–75. doi:10.1016/S0140-6736(08)60108-7

Ibrahim, S. A., Omer, M. I., Amin, I. K., Babiker, A. G. & Rushwan, H. (1992). The role of the village midwife in detection of high risk pregnancies and newborns. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *39*(2), pp.117–22.

ICMR Young Infant Study Group. (2008). Age profile of neonatal deaths. *Indian Pediatrics*, *45*(12), pp.991–994.

Imdad, A., Bautista, R. M. M., Senen, K. A. A., Uy, M. E. V, Mantaring, J. B. & Bhutta, Z. A. (2013). Umbilical cord antiseptics for preventing sepsis and death among newborns. *The Cochrane Database of Systematic Reviews*, *5*, CD008635. doi:10.1002/14651858.CD008635.pub2

Imdad, A. & Bhutta, Z. A. (2012a). Effects of calcium supplementation during pregnancy on maternal, fetal and birth outcomes. *Paediatric and Perinatal Epidemiology*, *26 Suppl 1*, pp.138–52. doi:10.1111/j.1365-3016.2012.01274.x

Imdad, A. & Bhutta, Z. A. (2012b). Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. *Paediatric and Perinatal Epidemiology*, *26 Suppl 1*, pp.178–90. doi:10.1111/j.1365-3016.2012.01308.x

International Centre for Diarrhoeal Disease Research Bangladesh (ICDDRB) (2011). *Health and Demographic Surveillance System–Matlab, v. 43. Registration of health and demographic events 2009, Scientific Report No. 114.* Dhaka: ICDDR,B.

International Institute for Population Sciences (IIPS), & Macro. (2007). *National Family Health Survey (NFHS-3), 2005–06: India: Volume I.* Mumbai: IIPS.

International Records Management Trust. (1999). *Managing public sector records: a study programme*. Retrieved from http://www.doc88.com/p-27635657627.html

Islam, S. M. S. & Alam, D. S. (2009). Type 2 diabetes and pre-diabetic conditions among adults aged 27-50 years in Matlab: A hidden public health burden. *Health and Science Bulletin*, *7*(2), pp.13–18.

Jammeh, A., Vangen, S. & Sundby, J. (2010). Stillbirths in rural hospitals in The Gambia: a cross-sectional retrospective study. *Obstetrics and Gynecology International*, *2010*, 186867. doi:10.1155/2010/186867

Janakiraman, V. & Ecker, J. (2010). Quality in obstetric care: measuring what matters. *Obstetrics and Gynecology*, *116*(3), pp.728–32. doi:10.1097/AOG.0b013e3181ea4d4f

Jehan, I., Harris, H., Salat, S., Zeb, A., Mobeen, N., Pasha, O. & Goldenberg, R. L. (2009). Neonatal mortality, risk factors and causes: a prospective population-based cohort study in urban Pakistan. *Bulletin of the World Health Organization*, *87*(2), pp.130–138.

Jokhio, A. H., Winter, H. R., & Cheng, K. (2005). An intervention involving traditional birth attendants and perinatal and maternal mortality in Pakistan. *New England Journal of Medicine*, *352*(20), pp.2091–2099. doi:http://dx.doi.org/10.1056/NEJMsa042830

Jones, G., Steketee, R. W., Black, R. E., Bhutta, Z. A. & Morris, S. S. (2003). How many child deaths can we prevent this year? *The Lancet*, *362*(9377), pp.65–71. doi:10.1016/S0140-6736(03)13811-1

Jurek, A. M., Greenland, S., Maldonado, G. & Church, T. R. (2005). Proper interpretation of non-differential misclassification effects: Expectations vs observations. *International Journal of Epidemiology*, *34*(3), pp.680–687. doi:10.1093/ije/dyi060

Katz, J., Khatry, S. K., LeClerq, S. C., Shrestha, S. R., West Jr, K. P. & Christian, P. (2008). Miscarriage but Not Stillbirth Rates Are Higher Among Younger Nulliparas in Rural Southern Nepal. *Journal of Adolescent Health*, *42*(6), pp.587–595.

Katz, J., Lee, A. C. C., Kozuki, N., Lawn, J. E., Cousens, S., Blencowe, H. & Black, R. E. (2013). Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *The Lancet*, *382*(9890), pp.417–25. doi:10.1016/S0140-6736(13)60993-9

Katz, J., West, K. P., Khatry, S. K., Christian, P., LeClerq, S. C., Pradhan, E. K. & Shrestha, S. R. (2003). Risk factors for early infant mortality in Sarlahi district, Nepal. *Bulletin of the World Health Organization*, *81*(10), pp.717–25.

Kaye, D. (2003). Antenatal and intrapartum risk factors for birth asphyxia among emergency obstetric referrals in Mulago Hospital, Kampala, Uganda. *East African Medical Journal*, *80*(3), pp.140–3.

Kent, A. L., Wright, I. M. R. & Abdel-Latif, M. E. (2012). Mortality and adverse neurologic outcomes are greater in preterm male infants. *Pediatrics*, *129*(1), pp.124–31. doi:10.1542/peds.2011-1578

Kerber, K. J., de Graft-Johnson, J. E., Bhutta, Z. A., Okong, P., Starrs, A., & Lawn, J. E. (2007). Continuum of care for maternal, newborn, and child health: from slogan to service delivery. *The Lancet*, *370*(9595), pp.1358–69. doi:10.1016/S0140-6736(07)61578-5

Kirkwood, B., & Sterne, J. (2003). *Essential Medical Statistics. 2nd Edition.* Wiley-Blackwell. Oxford, UK.

Klemm, R. D. W., Labrique, A. B., Christian, P., Rashid, M., Shamim, A. A., Katz, J. & West, K. P. (2008). Newborn vitamin A supplementation reduced infant mortality in rural Bangladesh. *Pediatrics*, *122*(1), pp.e242–50. doi:10.1542/peds.2007-3448

Knippenberg, R., Lawn, J. E., Darmstadt, G. L., Begkoyian, G. & Fogstad, H. (2005). Systematic scaling up of neonatal care in countries. *The Lancet*, *365*, pp.1087–1098.

Koblinsky, M., Chowdhury, M. E., Moran, A. & Ronsmans, C. (2012). Maternal morbidity and disability and their consequences: neglected agenda in maternal health. *Journal of Health, Population, and Nutrition*, *30*(2), pp.124–30.

Koblinsky, M., Matthews, Z., Hussein, J., Mavalankar, D., Mridha, M. K., Anwar, I. & van Lerberghe, W. (2006). Going to scale with professional skilled care. *The Lancet*, *368*(9544), pp. 1377–1386.

Kosa, J. L., Guendelman, S., Pearl, M., Graham, S., Abrams, B. & Kharrazi, M. (2011). The association between pre-pregnancy BMI and preterm delivery in a diverse southern California population of working women. *Maternal and Child Health Journal*, *15*(6), pp.772–81. doi:10.1007/s10995-010-0633-4

Kozuki, N., Lee, A., & Silveira , Mariangela F & Child Health Epidemiology Reference Group Small-for-Gestational-Age-Preterm Birth Working Group (2013). The associations of birth intervals with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis. *BMC Public Health*, *13*(S2). doi:10.1186/1471-2458-13-S3-S3

Kramer, M. S. (2000). The Contribution of Mild and Moderate Preterm Birth to Infant Mortality. *JAMA*, *284*(7), 843. doi:10.1001/jama.284.7.843

Kramer, M. S., Liu, S., Luo, Z., Yuan, H., Platt, R. W. & Joseph, K. S. (2002). Analysis of Perinatal Mortality and Its Components: Time for a Change? *American Journal of Epidemiology*, *156*(6), pp.493–497. doi:10.1093/aje/kwf077

Kramer, M. S., Papageorghiou, A., Culhane, J., Bhutta, Z., Goldenberg, R. L., Gravett, M. & Villar, J. (2012). Challenges in defining and classifying the preterm birth syndrome. *American Journal of Obstetrics and Gynecology*, *206*(2), pp.108–12. doi:10.1016/j.ajog.2011.10.864

Kramer, M. S., Séguin, L., Lydon, J. & Goulet, L. (2000). Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? *Paediatric and Perinatal Epidemiology*, *14*(3), pp.194–210.

Kumar, V., Mohanty, S., Kumar, A., Misra, R. P., Santosham, M., Awasthi, S. & Darmstadt, G. L. (2008). Effect of community-based behaviour change management on neonatal mortality in Shivgarh, Uttar Pradesh, India: a cluster-randomised controlled trial. *The Lancet*, *372*(9644), 1151–62. doi:10.1016/S0140-6736(08)61483-X

Kusiako, T., Ronsmans, C. & Van der Paal, L. (2000). Perinatal mortality attributable to complications of childbirth in Matlab, Bangladesh. *Bulletin of the World Health Orgaization*, *78*(5), pp.621–627.

Lassi, Z. S., Haider, B. A. & Bhutta, Z. A. (2010). Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. *The Cochrane Database of Systematic Reviews*, (11), CD007754. doi:10.1002/14651858.CD007754.pub2

Lawn, J., Shibuya, K. & Stein, C. (2005). No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. *Bulletin of the World Health Organization*, *83*(6), pp.409–17. doi:/S0042-96862005000600008

Lawn, J., Cousens, S. & Zupan, J., 2005. 4 million neonatal deaths: When? Where? Why? *The Lancet*, 365(9462), pp.891–900.

Lawn, J. E., Lee, A. C. C., Kinney, M., Sibley, L., Carlo, W. A., Paul, V. K., … Darmstadt, G. L. (2009). Two million intrapartum-related stillbirths and neonatal deaths: Where, why, and what can be done? *International Journal of Gynecology & Obstetrics*, *107*(Supplement 1), S5–S19.

Lawn, J., Yakoob, M., Haws, R., Soomro, T., Darmstadt, G., & Bhutta, Z. (2009). 3.2 million stillbirths: epidemiology and overview of the evidence review. *BMC Pregnancy and Childbirth*, *9*(Suppl 1), S2. Retrieved from http://www.biomedcentral.com/1471-2393/9/S1/S2

Lawn, J., Gravett, M. G., Nunes, T. M., Rubens, C. E. & Stanton, C. (2010). Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. *BMC Pregnancy and Childbirth*, *10 Suppl 1*, S1. doi:10.1186/1471-2393-10-S1-S1

Lawn, J., Mwansa-Kambafwile, J., Horta, B. L., Barros, F. C. & Cousens, S. (2010). "Kangaroo mother care" to prevent neonatal deaths due to preterm birth complications. *International Journal of Epidemiology*, *39 Suppl 1*, i144–54. doi:10.1093/ije/dyq031

Lawn, J., Blencowe, H., Pattinson, R., Cousens, S., Kumar, R., Ibiebele, I. & Stanton, C. (2011). Stillbirths: Where? When? Why? How to make the data count? *The Lancet*, *377*(9775),pp.1448–63. doi:10.1016/S0140-6736(10)62187-3

Lawn, J., Kinney, M. V, Belizan, J. M., Mason, E., McDougall, L., Larson, J. & Howson, C. P. (2013). Born Too Soon: Accelerating actions for prevention and care of 15 million newborns born too soon. *Reproductive Health*, *10*(Suppl 1), S6. doi:10.1186/1742-4755-10-S1-S6

Lawn, J., Blencowe, H., Oza, S., You, D., Lee, A. C., Waiswa, P. & Cousens, S. N. (2014). Progress, priorities, and potential beyond survival. *The Lancet*, 384 (9938), pp.189–205. doi:10.1016/S0140-6736(14)60496-7

Lee, A. C. C., Cousens, S., Darmstadt, G. L., Blencowe, H., Pattinson, R., Moran, N. F. & Lawn, J. (2011). Care during labor and birth for the prevention of intrapartum-related neonatal deaths: a systematic review and Delphi estimation of mortality effect. *BMC Public Health*, *11 Suppl 3*, S10. doi:10.1186/1471-2458-11-S3-S10

Lee, A. C. C., Cousens, S., Wall, S. N., Niermeyer, S., Darmstadt, G. L., Carlo, W. A. & Lawn, J. (2011). Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect. *BMC Public Health*, *11 Suppl 3*, S12. doi:10.1186/1471-2458-11-S3-S12

Lee, A. C. C., Darmstadt, G. L., Khatry, S. K., LeClerq, S. C., Shrestha, S. R. & Christian, P. (2009). Maternal-fetal disproportion and birth asphyxia in rural Sarlahi, Nepal. *Archives of Pediatrics and Adolescent Medicine*, *163*(7), pp.616–623. doi:http://dx.doi.org/10.1001/archpediatrics.2009.75

Lee, A. C. C., Lawn, J. E., Cousens, S., Kumar, V., Osrin, D., Bhutta, Z. A. & Darmstadt, G. L. (2009). Linking families and facilities for care at birth: what works to avert intrapartum-related deaths? *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *107 Suppl*, pp.S65–85, pp.S86–8. doi:10.1016/j.ijgo.2009.07.012

Lee, A. C. C., Mullany, L. C., Tielsch, J. M., Katz, J., Khatry, S. K., LeClerq, S. C. & Darmstadt, G. L. (2008). Risk factors for neonatal mortality due to birth asphyxia in Southern Nepal: a prospective, community-based cohort study. *Pediatrics*, *121*(5), pp.e1381–e1390.

Lee, A. C., Katz, J., Blencowe, H., Cousens, S., Kozuki, N., Vogel, J. P. & Black, R. E. (2013). National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *The Lancet Global Health*, *1*(1), pp.e26–e36. doi:10.1016/S2214-109X(13)70006-8

Lee, A. C., Mullany, L. C., Tielsch, J. M., Katz, J., Khatry, S. K., LeClerq, S. C. & Darmstadt, G. L. (2011). Community-based stillbirth rates and risk factors in rural Sarlahi, Nepal. *International Journal of Gynecology and Obstetrics*, *113*(3), pp.199–204. doi:http://dx.doi.org/10.1016/j.ijgo.2010.12.015

Lehmann, U., Dieleman, M. & Martineau, T. (2008). Staffing remote rural areas in middle- and low-income countries: a literature review of attraction and retention. *BMC Health Services Research*, *8*, p.19. doi:10.1186/1472-6963-8-19

Liu, L., Johnson, H. L., Cousens, S., Perin, J., Scott, S., Lawn, J. & UNICEF (2012). Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *The Lancet*, *379*(9832), pp.2151–2161. doi:10.1016/S0140-6736(12)60560-1

López, P. O. & Bréart, G. (2013). Sociodemographic characteristics of mother's population and risk of preterm birth in Chile. *Reproductive Health*, *10* p.26. doi:10.1186/1742-4755-10-26

Loto, O. M. & Awowole, I. (2012). Tuberculosis in pregnancy: a review. *Journal of Pregnancy*, *2012*, p.379271. doi:10.1155/2012/379271

Lozano, R., Wang, H., Foreman, K. J., Rajaratnam, J. K., Naghavi, M., Marcus, J. R. & Murray, C. J. L. (2011). Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. *The Lancet*, *378*(9797), pp. 1139–1165. doi:10.1016/s0140-6736(11)61337-8

Lucas, R. M. & McMichael, A. J. (2005). Association or causation: evaluating links between "environment and disease". *Bulletin of the World Health Organization*, *83*(10), pp.792–5. doi:/S0042-96862005001000017

Lumbiganon, P., Laopaiboon, M., Intarut, N., Vogel, J. P., Souza, J. P., Gülmezoglu, A. M. & Mori, R. (2014). Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health. *BJOG : An International Journal of Obstetrics and Gynaecology*, *121 Suppl*, pp.32–9. doi:10.1111/1471-0528.12647

Lumbiganon, P., Panamonta, M., Laopaiboon, M., Pothinam, S. & Patithat, N. (1990). Why are Thai official perinatal and infant mortality rates so low? *Int J Epidemiol*, *19*(4), pp. 997–1000.

Lumley, J. M. (2003). Unexplained antepartum stillbirth in pregnancies after a caesarean delivery. *The Lancet*, *362*(9398), pp.1774–1775.

Mahmood, S. S., Iqbal, M., Hanifi, S. M. A., Wahed, T. & Bhuiya, A. (2010). Are "Village Doctors" in Bangladesh a curse or a blessing? *BMC International Health and Human Rights*, *10*, p.18. doi:10.1186/1472-698X-10-18

Maine, D., & Rosenfield, A. (1999). The Safe Motherhood Initiative: why has it stalled? *American Journal of Public Health*, *89*(4),pp. 480–2.

Manandhar, D. S., Osrin, D., Shrestha, B. P., Mesko, N., Morrison, J., Tumbahangphe, K. M. & Costello, A. M. de L. (2004). Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial. *The Lancet (British Edition)*, *364*(9438), pp.970–979. doi:http://dx.doi.org/10.1016/S0140-6736(04)17021-9

Manandhar, S. R., Ojha, A., Manandhar, D. S., Shrestha, B., Shrestha, D., Saville, N. & Osrin, D. (2010). Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: a verbal autopsy study. *Kathmandu University Medical Journal (KUMJ)*, *8*(1), pp.62–72.

Manna, P. K., Debasis, D. & Debidas, G. (2011). Knowledge attitude and practices for antenatal care and delivery of the mothers of tea garden in Jalpaiguri and Darjeeling districts, West Bengal. *National Journal of Community Medicine*, *2*(1), pp.4–8.

Marston, C. & Cleland, J. (2004). *The effects of contraception on obstetric outcomes.* Geneva, Switzerland: World Health Organization.Retrieved from http://whqlibdoc.who.int/publications/2004/9241592257.pdf

Maskey, M. K., Baral, K. P., Rajani, S., Shrestha, B. D., Lang, J. & Rothman, K. J. (2011). Field test results of the motherhood method to measure maternal mortality. *Indian Journal of Medical Research*, *133*(1), pp.64–69.

Mason, E., McDougall, L., Lawn, J. E., Gupta, A., Claeson, M., Pillay, Y. & Chopra, M. (2014). From evidence to action to deliver a healthy start for the next generation. *The Lancet.* 384 (9941), p455–467 doi:10.1016/S0140-6736(14)60750-9

Mavalankar, D. V, Trivedi, C. R. & Gray, R. H. (1991). Levels and risk factors for perinatal mortality in Ahmedabad, India. *Bulletin of the World Health Organization*, *69*(4), pp.435–442.

McClure, E. M., Goldenberg, R. L. & Bann, C. M. (2007). Maternal mortality, stillbirth and measures of obstetric care in developing and developed countries. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *96*(2), pp.139–46. doi:10.1016/j.ijgo.2006.10.010

McClure, E. M., Nalubamba-Phiri, M. & Goldenberg, R. L. (2006). Stillbirth in developing countries. *International Journal of Gynecology & Obstetrics*, *94*(2), pp.82–90.

McClure, E. M., Pasha, O., Goudar, S. S., Chomba, E., Garces, A., Tshefu, A. & Goldenberg, R. L. (2011). Epidemiology of stillbirth in low-middle income countries: A Global Network Study. *Acta Obstetricia et Gynecologica Scandinavica*, *90*(12), pp.1379–1385. doi:10.1111/j.1600-0412.2011.01275.x

McDonald, S. J., Middleton, P., Dowswell, T. & Morris, P. S. (2013). Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *The Cochrane Database of Systematic Reviews*, *7*, CD004074. doi:10.1002/14651858.CD004074.pub3

Menon, R. (2008). Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. *Acta Obstetricia et Gynecologica Scandinavica*, *87*(6), pp.590–600. doi:10.1080/00016340802005126

Mercer, A., Haseen, F., Huq, N. L., Uddin, N. & Khan, M. H. (2006). Risk factors for neonatal mortality in rural areas of Bangladesh served by a large NGO programme. *Health Policy and Planning*, *21*(6), pp.432–443.

Midhet, F., Becker, S. & Berendes, H. W. (1998). Contextual determinants of maternal mortality in rural Pakistan. *Social Science & Medicine*, *46*(12), pp.1587–1598.

Ministry of Health [Nepal] and ORC Macro(2002). Nepal Demographic and Health Survey 2001. Calverton, Maryland, USA: Family Health Division, Ministry of Health and ORC Macro.

Ministry of Health and Population (MOHP) [Nepal] and ICF International Inc.,(2012). Nepal Demographic and Health Survey 2011. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland.

Ministry of Health and Population (MOHP) [Nepal] and Macro International Inc.,(2007). Nepal Demographic and Health Survey 2006. Kathmandu, Nepal: Ministry of Health and Population, New ERA, and Macro International Inc.

Ministry of Health and Family (MOHF) [Maldives}, & ICFMacro. (2010). Maldives Demographic and Health Survey 2009. Calverton, Maryland: Ministry of Health and Family (MOHF) [Maldives] and ICF Macro.

Mohangoo, A. D., Buitendijk, S. E., Szamotulska, K., Chalmers, J., Irgens, L. M., Bolumar, F., & Zeitlin, J. (2011). Gestational age patterns of fetal and neonatal mortality in Europe: results from the Euro-Peristat project. *PloS One*, *6*(11), p.e24727. doi:10.1371/journal.pone.0024727

Mongelli, M., Wilcox, M. & Gardosi, J. (1996). Estimating the date of confinement: ultrasonographic biometry versus certain menstrual dates. *American Journal of Obstetrics and Gynecology*, *174*(1 Pt 1), pp.278–81.

More, N. S., Bapat, U., Das, S., Barnett, S., Costello, A., Fernandez, A. & Osrin, D. (2009). Inequalities in maternity care and newborn outcomes: one-year surveillance of births in vulnerable slum communities in Mumbai. *International Journal for Equity in Health*, *8*, p.21. doi:10.1186/1475-9276-8-21

Morin, I., Morin, L., Zhang, X., Platt, R. W., Blondel, B., Bréart, G. & Kramer, M. S. (2005). Determinants and consequences of discrepancies in menstrual and ultrasonographic gestational age estimates. *BJOG : An International Journal of Obstetrics and Gynaecology*, *112*(2), pp.145–52. doi:10.1111/j.1471-0528.2004.00311.x

Morken, N.H. (2012). Preterm birth: new data on a global health priority. *The Lancet*, *379*(9832), pp.2128–30. doi:10.1016/S0140-6736(12)60857-5

Mridha, M., Anwar, I. & Koblinsky, M. (2009). Public-sector Maternal Health Programmes and Services for Rural Bangladesh. *Journal of Health, Population and Nutrition*, *27*(2), pp.124–138.

Muglia, L. J. & Katz, M. (2010). The enigma of spontaneous preterm birth. *The New England Journal of Medicine*, *362*(6),pp. 529–35. doi:10.1056/NEJMra0904308

Mukhopadhaya, N., & Arulkumaran, S. (2007). Reproductive outcomes after in-vitro fertilization. *Current Opinion in Obstetrics & Gynecology*, *19*(2), pp.113–9. doi:10.1097/GCO.0b013e32807fb199

Muula, A. S. (2007). Ethical and practical consideration of women choosing cesarean section deliveries without "medical indication" in developing countries. *Croatian Medical Journal*, *48*(1), pp.94–102.

Nag, M. (1992). *Family planning success stories in Bangladesh and India*. *Policy Research Working Papers WPS 1041*. Population and Human Resources Dept. World Bank. Washington, D.C.

Nath, A., Patil, C., & Naik, V. A. (2004). Prevalence of consanguineous marriages in a rural community and its effect on pregnancy outcome. *Indian Journal of Community Medicine*, *29*(1) p.3. Retrieved from http://medind.nic.in/iaj/iajai.shtml

National Institute of Population Research and Training (NIPORT) and ORC Macro (2001). Bangladesh Demographic and Health Survey 1999-2000. Dhaka, Bangladesh and Calverton, Maryland [USA]: National Institute of Population Research and Training, Mitra and Associates, and ORC Macro.

National Institute of Population Research and Training (NIPORT), ORC Macro, Johns Hopkins University and ICDDRB (2003). Bangladesh Maternal Health Services and Maternal Mortality Survey 2001. Dhaka, Bangladesh and Calverton, Maryland (USA): NIPORT, ORC Macro, Johns Hopkins University and ICDDR,B.

National Institute of Population Research and Training (NIPORT), Mitra and Associates, and Macro International (2009) Bangladesh Demographic and Health Survey 2007. Dhaka, Bangladesh and Calverton, Maryland, USA: National Institute of Population Research.

National Institute of Population Research and Training (NIPORT). Mitra and Associates. ICF International (2013). Bangladesh Demographic and Health Survey 2011. Dhaka, Bangladesh and Calverton, Maryland, USA.

National Institute of Population Research and Training (NIPORT), Macro ORC, & Mitra and Associates (2005). Bangladesh Demographic and Health Survey 2004. Dhaka, Bangladesh and Calverton, Maryland [USA].

National Institute of Population Studies (NIPS)[Pakistan] & Macro International. (2008). Pakistan Demographic and Health Survey 2006-07. Islamabad, Pakistan: National Institute of Population Studies and Macro International Inc.

Neufeld, L. M., Wagatsuma, Y., Hussain, R., Begum, M. & Frongillo, E. A. (2009). Measurement error for ultrasound fetal biometry performed by paramedics in rural Bangladesh. *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *34*(4), pp.387–94. doi:10.1002/uog.6385

Ngoc, N. T., Merialdi, M., Abdel-Aleem, H., Carroli, G., Purwar, M., Zavaleta, N. & Villar, J. (2006). Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries. *Bulletin of the World Health Organization*, *84*(9), pp.699–705. doi:S0042-96862006000900012 [pii]

Nielsen, H. S., Mortensen, L. H., Nygaard, U., Schnor, O., Christiansen, O. B., & Andersen, A.M. N. (2010). Sex of Prior Children and Risk of Stillbirth in Subsequent Pregnancies. *Epidemiology, 21*(1), 114–117.

Niswade, A., Zodpey, S. P., Suresh, U. & Bangdiwala, S. I. (2011). Neonatal morbidity and mortality in tribal and rural communities in Central India. *Indian Journal of Community Medicine*, *36*(2), pp.150–158. doi:http://dx.doi.org/10.4103/0970-0218.84137

Nystedt, A. & Hildingsson, I. (2014). Diverse definitions of prolonged labour and its consequences with sometimes subsequent inappropriate treatment. *BMC Pregnancy and Childbirth*, *14*(1) p.233. doi:10.1186/1471-2393-14-233

Olsen, O. & Madsen, M. (1999). Effects of maternal education on infant mortality and stillbirths in Denmark. *Scandinavian Journal of Public Health*, *27*(2), pp.128–36.

Osendarp, S. J., van Raaij, J. M., Arifeen, S. E., Wahed, M. A. & Baqui, A. H. (2000). A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. *American Journal of Clinical Nutrition*, *71*(1), pp.114–119.

Peabody, J., Taguiwalo, M. & Robalino, D. (2006). Improving the Quality of Care in Developing Countries. In D. Jamison, J. Breman, & A. Measham (Eds.), *Disease Control Priorities in Developing Countries.* (2nd edition.) Chapter 70.pp 1298-1307. Washington (DC): World Bank.

Peña-Rosas, J. P., De-Regil, L. M., Dowswell, T. & Viteri, F. E. (2012). Daily oral iron supplementation during pregnancy. *The Cochrane Database of Systematic Reviews*, *12*, CD004736. doi:10.1002/14651858.CD004736.pub4

Pervin, J., Moran, A., Rahman, M., Razzaque, A., Sibley, L., Streatfield, P. K. & Rahman, A. (2012). Association of antenatal care with facility delivery and perinatal survival - a population-based study in Bangladesh. *BMC Pregnancy and Childbirth*, *12*, 111. doi:10.1186/1471-2393-12-111

Phillips, J. F., Stinson, W. S., Bhatia, S., Rahman, M. & Chakraborty, J. (1982). The demographic impact of the family planning--health services project in Matlab, Bangladesh. *Studies in Family Planning*, *13*(5), pp.131–40.

Pirkle, C. M., Dumont, A. & Zunzunegui, M.-V. (2012). Medical recordkeeping, essential but overlooked aspect of quality of care in resource-limited settings. *International Journal for Quality in Health Care : Journal of the International Society for Quality in Health Care*, *24*(6), pp.564–7. doi:10.1093/intqhc/mzs034

Pitchforth, E., van Teijlingen, E., Graham, W. & Fitzmaurice, A. (2007). Development of a proxy wealth index for women utilizing emergency obstetric care in Bangladesh. *Health Policy and Planning*, *22*(5), pp.311–9. doi:10.1093/heapol/czm022

Prost, A., Colbourn, T., Seward, N., Azad, K., Coomarasamy, A., Copas, A. & Costello, A. (2013). Women's groups practising participatory learning and action to improve maternal and newborn health in low-resource settings: a systematic review and meta-analysis. *The Lancet*, *381*(9879), pp.1736–46. doi:10.1016/S0140-6736(13)60685-6

Prual, A., Bouvier-Colle, M. H., de Bernis, L. & Bréart, G. (2000). Severe maternal morbidity from direct obstetric causes in West Africa: incidence and case fatality rates. *Bulletin of the World Health Organization*, *78*(5), pp.593–602.

Rahman, A., Moran, A., Pervin, J., Khan, A., Yeasmin, S., Rashid, H. & Koblinsky, M. (2009). Perinatal Deaths in Matlab, Bangladesh: Preliminary Findings from an Integrated MNCH Programme. *12th Annual Scientific Conference (ASCON) 2009.Conference Proceedings.* Dhaka, Bangladesh.

Rahman, A., Moran, A., Pervin, J., Rahman, M., Yeasmin, S., Begum, H. & Koblinsky, M. (2011). Effectiveness of an integrated approach to reduce perinatal mortality: recent experiences from Matlab, Bangladesh. *BMC Public Health*, *11*(914)

Rahman, A., Persson, L.-Å., Nermell, B., El Arifeen, S., Ekström, E.-C., Smith, A. H. & Vahter, M. (2010). Arsenic exposure and risk of spontaneous abortion, stillbirth, and infant mortality. *Epidemiology*, *21*(6), 797–804. doi:10.1097/EDE.0b013e3181f56a0d

Rahman, A., Vahter, M., Ekstrom, E. C., Rahman, M., Golam Mustafa, A. H., Wahed, M. A. & Persson, L. A. (2007). Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. *American Journal of Epidemiology*, *165*(12), pp.1389–1396. doi:kwm025 [pii] 10.1093/aje/kwm025

Rahman, M., DaVanzo, J., & Razzaque, A. (2001). Do better family planning services reduce abortion in Bangladesh? *The Lancet*, *358*(9287), pp.1051–6. doi:10.1016/S0140-6736(01)06182-7

Rahman, M., DaVanzo, J., & Razzaque, A. (2009). Why are maternal mortality rates lower in the MCH-FP Area of Matlab, Bangladesh? The role of pregnancy outcomes. *Pathfinder International.* Dhaka, Bangaldesh.

Rahman, M., Sohel, N., Yunus, M., Chowdhury, M. E., Hore, S. K., Zaman, K. & Streatfield, P. K. (2013). Increased childhood mortality and arsenic in drinking water in Matlab, Bangladesh: a population-based cohort study. *PloS One*, *8*(1), e55014. doi:10.1371/journal.pone.0055014

Razzaque, A. & Streatfield, P. K. (1998). Matlab DSS, Bangladesh. International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B).1998.INDEPTH Monograph. Vol 1 Part C.

Razzaque, A. & Streatfield, P. K. (2002). Chp 27.pp 156-9. Matlab DSS, Bangladesh. In *Population and Health in Developing Countries*. IDRC 2002. Retrieved from website: http://web.idrc.ca/en/ev-43043-201-1-DO_TOPIC.html

Requejo, J., Merialdi, M., Althabe, F., Keller, M., Katz, J. & Menon, R. (2013). Born Too Soon: Care during pregnancy and childbirth to reduce preterm deliveries and improve health outcomes of the preterm baby. *Reproductive Health*, *10*(Suppl 1), S4. doi:10.1186/1742-4755-10-S1-S4

Roberts, D. & Dalziel, S. (2006). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *The Cochrane Database of Systematic Reviews*, (3), CD004454. doi:10.1002/14651858.CD004454.pub2

Rohde, J., Cousens, S., Chopra, M., Tangcharoensathien, V., Black, R., Bhutta, Z. A. & Lawn, J. E. (2008). 30 years after Alma-Ata: has primary health care worked in countries? *The Lancet*, *372*(9642),pp. 950–61. doi:10.1016/S0140-6736(08)61405-1

Ronsmans, C. (2009). Professional assistance during birth and maternal mortality in two Indonesian districts. *Bulletin of the World Health Organization*, *87*(6), pp.416–423. doi:10.2471/BLT.08.051581

Ronsmans, C., Chowdhury, M. E., Alam, N., Koblinsky, M. & Arifeen, S. El. (2008). Trends in stillbirths, early and late neonatal mortality in rural Bangladesh: the role of public health interventions. *Paediatric and Perinatal Epidemiology*, *22*(3), pp.269–279. doi.10.1111/j.1365-3016.2008.00939.x

Ronsmans, C., Chowdhury, M. E., Koblinsky, M. & Ahmed, A. (2010). Care seeking at time of childbirth, and maternal and perinatal mortality in Matlab, Bangladesh. *Bulletin of the World Health Organization*, *88*(4), pp.289–296. doi:10.2471/BLT.09.069385

Ronsmans, C., Etard, J. F., Walraven, G., Hoj, L., Dumont, A., de Bernis, L. & Kodio, B. (2003). Maternal mortality and access to obstetric services in West Africa. *Tropical Medicine and International Health*, *8*(10), pp.940–948. doi:1111 [pii]

Ronsmans, C., Fisher, D. J., Osmond, C., Margetts, B. M., Fall, C. H. D. & Maternal Micronutrient Supplementation Study Group (2009). Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects

on stillbirths and on early and late neonatal mortality. *Food & Nutrition Bulletin*, *30*(4 Suppl), pp.S547–55.

Ronsmans, C., Holtz, S. & Stanton, C. (2006). Socioeconomic differentials in caesarean rates in developing countries: a retrospective analysis. *The Lancet*, *368*(9546), pp.1516–23. doi:10.1016/S0140-6736(06)69639-6

Ronsmans, C., Vanneste, A. M., Chakraborty, J. & van Ginneken, J. (1997). Decline in maternal mortality in Matlab, Bangladesh: a cautionary tale. *The Lancet*, *350*(9094), pp.1810–1814. doi:S0140-6736(97)08012-4 [pii] 10.1016/S0140-6736(97)08012-4

Rosenberg, R. E., Ahmed, A. S. M. N. U., Ahmed, S., Saha, S. K., Chowdhury, M. A. K. A., Black, R. E. & Darmstadt, G. L. (2009). Determining gestational age in a low-resource setting: validity of last menstrual period. *Journal of Health, Population, and Nutrition*, *27*(3), pp.332–8.

Rosenfield, A. & Maine, D. (1985). Maternal mortality--a neglected tragedy. Where is the M in MCH? *The Lancet*, *2*(8446), pp.83–5.

Royal College of Obstetricians and Gynaecologists. (2006). *Preterm Prelabour Rupture of Membranes*. Retrieved from http://www.rcog.org.uk/files/rcog-corp/GTG44PPROM28022011.pdf

Royal College of Obstetricians and Gynaecologists. (2008). *Umbilical Cord Prolapse (Green-top 50) Guidelines*. Retrieved from http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT50UmbilicalCordProlapse2008.pdf

Rudan, I., Lawn, J., Cousens, S., Rowe, A. K., Boschi-Pinto, C., Tomasković, L. & Campbell, H. (2005). Gaps in policy-relevant information on burden of disease in children: a systematic review.*The Lancet*, *365*(9476), pp.2031–40. doi:10.1016/S0140-6736(05)66697-4

Saigal, S. & Doyle, L. W. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet*, *371*(9608), pp.261–9. doi:10.1016/S0140-6736(08)60136-1

Salam, R. A., Das, J. K., Darmstadt, G. L. & Bhutta, Z. A. (2013). Emollient therapy for preterm newborn infants--evidence from the developing world. *BMC Public Health*, *13 Suppl 3*, S31. doi:10.1186/1471-2458-13-S3-S31

Saleem, S., McClure, E. M., Goudar, S. S., Patel, A., Esamai, F., Garces, A. & Goldenberg, R. L. (2014). A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries. *Bulletin of the World Health Organization*, *92*(8), pp.605–612. doi:10.2471/BLT.13.127464

Sanders, M. R., Donohue, P. K., Oberdorf, M. A., Rosenkrantz, T. S. & Allen, M. C. (1998). Impact of the perception of viability on resource allocation in the neonatal

intensive care unit. *Journal of Perinatology: Official Journal of the California Perinatal Association*, *18*(5), pp.347–51.

Sarah, S., McClure, E. M., Rasool, B., Ameer, S., Goldenberg, R. L. & Pappas, G. (2010). Pregnancy behavior of Pakistani women over their reproductive life span. *Al Ameen Journal of Medical Sciences*, *3*(3), pp.228–236.

Save the Children. (2013). *Surviving the first day: State of the World's Mothers 2013. Save the Children.* Retrieved from http://www.savethechildren.org/site/c.8rKLIXMGIpI4E/b.8585863/k.9F31/State_of_the_Worlds_Mothers.htm

Save the Children. (2014). *Ending Newborn Deaths: Ensuring Every Baby Survives*. London. Retrieved from http://www.savethechildren.org/site/c.8rKLIXMGIpI4E/b.8989373/k.E376/Ending_Newborn_Deaths_Ensuring_Every_Baby_Survives.htm

Say, L., Donner, A., Gulmezoglu, A. M., Taljaard, M. & Piaggio, G. (2006). The prevalence of stillbirths: a systematic review. *Reproductive Health*, *3*(1), 1. Retrieved from http://www.reproductive-health-journal.com/content/3/1/1

Schiffman, J., Darmstadt, G. L., Agarwal, S., & Baqui, A. H. (2010). Community-based intervention packages for improving perinatal health in developing countries: a review of the evidence. *Seminars in Perinatology*, *34*(6), pp.462–76. doi:10.1053/j.semperi.2010.09.008

Scott, S. & Ronsmans, C. (2009). The relationship between birth with a health professional and maternal mortality in observational studies: a review of the literature. *Tropical Medicine & International Health : TM & IH*, *14*(12), pp.1523–33. doi:10.1111/j.1365-3156.2009.02402.x

Shah, R., Mullany, L. C., Darmstadt, G. L., Mannan, I., Rahman, S. M., Talukder, R. R. & Baqui, A. H. (2014). Incidence and risk factors of preterm birth in a rural Bangladeshi cohort. *BMC Pediatrics*, *14* (112). doi:10.1186/1471-2431-14-112

Shaikh, K., Premji, S. S., Rose, M. S., Kazi, A., Khowaja, S. & Tough, S. (2011). The association between parity, infant gender, higher level of paternal education and preterm birth in Pakistan: a cohort study. *BMC Pregnancy and Childbirth*, *11* (88). doi:10.1186/1471-2393-11-88

Singh, A. & Arora, A. K. (2007). The changing profile of pregnant women and quality of antenatal care in rural north India. *Indian Journal of Community Medicine*, *32*(2), pp.135–136.

Sinha, S. (2006). Outcome of antenatal care in an urban slum of Delhi. *Indian Journal of Community Medicine*, *31*(3), pp.189–191.

Sloan, N. L., Salahuddin, A., Mitra, S. N., Nuzhat, C., Mushtaque, C., Ubaider, R., & Winikoff, B. (2008). Community-based kangaroo mother care to prevent neonatal and infant mortality: a randomized, controlled cluster trial. *Pediatrics*, *121*(5), pp. e1047–e1059.

Smith, G. C. (2001). Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. *American Journal of Obstetrics and Gynecology*, *184*(3), pp.489–96. doi:10.1067/mob.2001.109735

Smith, G. C. S., & Fretts, R. C. (2007). Stillbirth. *The Lancet*, *370*(9600), pp.1715–1725.

Smith, G. C. S., Pell, J. P. & Dobbie, R. (2003). Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. *British Medical Journal (Clinical Research Ed.)*, *327*(7410),pp. 313. doi:10.1136/bmj.327.7410.313

Smith, L. K., Draper, E. S., Manktelow, B. N., Dorling, J. S. & Field, D. J. (2007). Socioeconomic inequalities in very preterm birth rates. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *92*(1), pp.F11–4. doi:10.1136/adc.2005.090308

Stanton, C., Lawn, J. E., Rahman, H., Wilczynska-Ketende, K. & Hill, K. (2006). Stillbirth rates: delivering estimates in 190 countries. *The Lancet*, *367*(9521), pp.1487–1494.

StataCorp. (2011). Stata Statistical Software: Release 12. College Station, TX: StataCorp LP. Retrieved from http://www.stata.com/stata12/

Stephansson, O. (2001). The influence of socioeconomic status on stillbirth risk in Sweden. *International Journal of Epidemiology*, *30*(6), pp.1296–1301. doi:10.1093/ije/30.6.1296

Stevens, G. A., Finucane, M. M., De-Regil, L. M., Paciorek, C. J., Flaxman, S. R., Branca, F. & Ezzati, M. (2013). Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. *The Lancet Global Health*, *1*(1), pp.e16–e25. doi:10.1016/S2214-109X(13)70001-9

Subramoney, S., d'Espaignet, E. T. & Gupta, P. C. (2010). Higher risk of stillbirth among lower and middle income women who do not use tobacco, but live with smokers. *Acta Obstetricia et Gynecologica Scandinavica*, *89*(4), pp. 572–577.

Swadpanich, U., Lumbiganon, P., Prasertcharoensook, W. & Laopaiboon, M. (2008). Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. *The Cochrane Database of Systematic Reviews*, (2), CD006178. doi:10.1002/14651858.CD006178.pub2

The Partnership for Maternal Newborn and Child Health. (2006). Opportunities for Africa's newborns: Practical data, policy and programmatic support for newborn care

in Africa. Joy Lawn & Kate Kerber, Save the Children and BASICS. *Opportunities for Africa's newborns* (p. 250). WHO on behalf of The Partnership for Maternal Newborn and Child Health. Retrieved from http://www.who.int/pmnch/media/publications/aonsectionIII_2.pdf

Thinkhamrop, J., Hofmeyr, G. J., Adetoro, O., & Lumbiganon, P. (2002). Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality. *The Cochrane Database of Systematic Reviews*, (4), CD002250. doi:10.1002/14651858.CD002250

Tielsch, J. M., Darmstadt, G. L., Mullany, L. C., Khatry, S. K., Katz, J., LeClerq, S. C. & Adhikari, R. (2007). Impact of newborn skin-cleansing with chlorhexidine on neonatal mortality in southern Nepal: a community-based, cluster-randomized trial. *Pediatrics*, *119*(2),pp. e330–40. 8

Tielsch, J. M., Katz, J., Thulasiraj, R. D., Coles, C. L., Sheeladevi, S., Yanik, E. L. & Lakshmi, R. (2009). Exposure to indoor biomass fuel and tobacco smoke and risk of adverse reproductive outcomes, mortality, respiratory morbidity and growth among newborn infants in south India. *International Journal of Epidemiology*, *38*(5), pp.1351–1363. doi:http://dx.doi.org/10.1093/ije/dyp286

Tofail, F., Persson, L. A., El Arifeen, S., Hamadani, J. D., Mehrin, F., Ridout, D. & Grantham-McGregor, S. M. (2008). Effects of prenatal food and micronutrient supplementation on infant development: a randomized trial from the Maternal and Infant Nutrition Interventions, Matlab (MINIMat) study. *American Journal of Clinical Nutrition*, *87*(3), pp.704–711.

Tough, S. C., Newburn-Cook, C., Johnston, D. W., Svenson, L. W., Rose, S. & Belik, J. (2002). Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. *Pediatrics*, *109*(3) pp.399–403.

Tripathy, P., Nair, N., Barnett, S., Rajendra, M., Borghi, J., Shibanand, R. & Costello, A. (2010). Effect of a participatory intervention with women's groups on birth outcomes and maternal depression in Jharkhand and Orissa, India: a cluster-randomised controlled trial.*The Lancet (British Edition)*, *375*(9721), pp.1182–1192. doi:http://dx.doi.org/10.1016/S0140-6736(09)62042-0

Tripathy, P., Nair, N., Mahapatra, R., Gope, R. K., Rath, S., Bajpai, A. & Prost, A. (2011). Community mobilisation with women's groups facilitated by Accredited Social Health Activists (ASHAs) to improve maternal and newborn health in underserved areas of Jharkhand and Orissa: study protocol for a cluster-randomised controlled trial. *Trials*, *12* (182). doi:http://dx.doi.org/10.1186/1745-6215-12-182

Tucker, J. & McGuire, W. (2004). Epidemiology of preterm birth. *British Medical Journal (Clinical Research Ed.)*, *329*(7467), pp.675–8. doi:10.1136/bmj.329.7467.675

UNICEF (2004). *What Works for Children in South Asia. Newborn care: An overview*. UNICEF. Kathmandu, Nepal. Retrieved from http://www.unicef.org/rosa/Newborn.pdf

United Nations (2013). The Report of the High-Level Panel of Eminent Persons on the Post-2015 Development Agenda. A new global partnership:Eradicate poverty and transform Economies through sustainable Development.United Nations Publications. New York, USA. Retrieved June 25, 2014, from http://www.un.org/sg/management/pdf/HLP_P2015_Report.pdf

United Nations Children's Fund (1997). *Guidelines for monitoring the availability and use of obstetric services*. United Nations Children's Fund Publications. New York,USA. Retrieved from http://www.childinfo.org/files/maternal_mortality_finalgui.pdf

United Nations Fund for Population Activities. (2014). *Disease Control Priorities*. UNFPA Publications. Seattle, Washington, USA. Retrieved September 21, 2014, from http://www.unfpa.org/public/mothers/pid/4383

United Nations Statistics Division. (2008). Official list of MDG indicators. Retrieved June 25, 2014, from website: http://unstats.un.org/unsd/mdg/Host.aspx?Content=Indicators/OfficialList.htm

US National Library of Medicine. (2014). Premature rupture of membranes. Retrieved from website: http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000512.htm

Vanneste, A. M., Ronsmans, C., Chakraborty, J. & De Francisco, A. (2000). Prenatal screening in rural Bangladesh: from prediction to care. *Health Policy Planning*, *15*(1), pp.1–10.

Victora, C. G., Habicht, J.-P., & Bryce, J. (2004). Evidence-based public health: moving beyond randomized trials. *American Journal of Public Health*, *94*(3), pp.400–5.

Vogel, J. P., Lee, A. C. & Souza, J. P. (2014). Maternal morbidity and preterm birth in 22 low- and middle-income countries: a secondary analysis of the WHO Global Survey dataset. *BMC Pregnancy and Childbirth*, *14*(1) p.56. doi:10.1186/1471-2393-14-56

Vogel, J. P., Souza, J. P., Mori, R., Morisaki, N., Lumbiganon, P., Laopaiboon, M. & Gülmezoglu, A. M. (2014). Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG : An International Journal of Obstetrics and Gynaecology*, *121 Suppl*, pp.76–88. doi:10.1111/1471-0528.12633

Wandabwa, J. (2004). *Investigation of risk factors for severe maternal morbidity and progression to mortality. A case control and follow up study in Mulago Hospital complex, Uganda.* PhD Thesis. London School of Hygiene and Tropical Medicine, University of London. Retrieved from http://researchonline.lshtm.ac.uk/682332/1/416034.pdf

Wang, H., Liddell, C. A., Coates, M. M., Mooney, M. D., Levitz, C. E., Schumacher, A. E. & Murray, C. J. L. (2014). Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet, 384(9947):957-79. doi:10.1016/S0140-6736(14)60497-9

Wax, J. R., Lucas, F. L., Lamont, M., Pinette, M. G., Cartin, A. & Blackstone, J. (2010). Maternal and newborn outcomes in planned home birth vs planned hospital births: a metaanalysis. *American Journal of Obstetrics and Gynecology*, *203*(3), pp.243.e1–8. doi:10.1016/j.ajog.2010.05.028

Wegienka, G. & Baird, D. D. (2005). A comparison of recalled date of last menstrual period with prospectively recorded dates. *Journal of Women's Health (2002)*, *14*(3), pp.248–52. doi:10.1089/jwh.2005.14.248

Weiner, R., Ronsmans, C., Dorman, E., Jilo, H., Muhoro, A. & Shulman, C. (2003). Labour complications remain the most important risk factors for perinatal mortality in rural Kenya. *Bulletin of the World Health Organization*, *81*(8), pp.561–6. doi:10.1590/S0042-96862003000800005

WHO (2006). Neonatal and Perinatal Mortality. Country, Regional and Global Estimates 2000. *Geneva: World Health Organization*.

WHO Regional Office for the Western Pacific. (2006). *Medical Records Manual: A Guide for Developing Countries*. Retrieved from http://www.wpro.who.int/publications/docs/MedicalRecordsManual.pdf?ua=1

Wilson, R. M., Michel, P., Olsen, S., Gibberd, R. W., Vincent, C., El-Assady, R. & Larizgoitia, I. (2012). Patient safety in developing countries: retrospective estimation of scale and nature of harm to patients in hospital. *British Medical Journal (Clinical Research Ed.)*, *344*, p. e832. doi:10.1136/bmj.e832

Wong, R. & Bradley, E. H. (2009). Developing patient registration and medical records management system in Ethiopia. *International Journal for Quality in Health Care: Journal of the International Society for Quality in Health Care*, *21*(4), pp.253–8. doi:10.1093/intqhc/mzp026

World Health Organization (1977). WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstetricia et Gynecologica Scandinavica*, *56*(3), pp.247–53.

World Health Organization (1978). *Primary Health Care: Report of the International Conference on Primary Health Care, Alma-Ata.* Geneva: 63 (Health for All Series No.1). Retrieved from http://whqlibdoc.who.int/publications/9241800011.pdf

World Health Organization (1994). World Health Organization partograph in management of labour. World Health Organization Maternal Health and Safe Motherhood Programme. *The Lancet*, *343*(8910), pp.1399–404.

World Health Organization (2004a). International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010. 2nd edition. Retrieved from http://www.who.int/classifications/icd/ICD-10_2nd_ed_volume2.pdf

World Health Organization (2004b). *Making pregnancy safer: The critical role of the skilled attendant: A joint statement by WHO, ICM and FIGO.* Geneva, Switzerland: World Health Organization. Retrieved from http://whqlibdoc.who.int/publications/2004/9241591692.pdf?ua=1

World Health Organization (2008). *Managing prolonged and obstructed labour. Education material for teachers of midwifery.* (Education.). Geneva, Switzerland: World Health Organization. Retrieved from http://whqlibdoc.who.int/publications/2008/9789241546669_4_eng.pdf?ua=1

World Health Organization (2009). *Monitoring emergency obstetric care: a handbook*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.unfpa.org/webdav/site/global/shared/documents/publications/2009/obstetric_monitoring.pdf

World Health Organization (2010). World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems - Instruction Manual. World Health Organization. Retrieved from http://www.who.int/classifications/icd/icdonlineversions/en/index.html

World Health Organization (2011a). *Country Health Information Systems: A review of the current situation and trends*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/healthmetrics/news/chis_report.pdf

World Health Organization (2011b). *Preventing early pregnancy and poor reproductive outcomes among adolescents in developing countries: WHO guidelines*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/maternal_child_adolescent/documents/preventing_early_pregnancy/en/

World Health Organization (2013). Preterm birth. Factsheet No. 363. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/mediacentre/factsheets/fs363/en/

World Health Organization (2014). International Classification of Diseases (ICD). eneva, Switzerland: World Health Organization. Retrieved April 30, 2014, from http://www.who.int/classifications/icd/en/

World Health Organization & UNICEF (2012). *Countdown to 2015. Building a Future for Women and Children:The 2012 Report*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.countdown2015mnch.org/documents/2012Report/2012-complete-no-profiles.pdf

World Health Organization, & UNICEF (2013). *Countdown to 2015: Accountability for Maternal, Newborn & Child Survival. The 2013 Update*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/woman_child_accountability/ierg/reports/Countdown_Accountability_2013Report.pdf

Yakoob, M. Y., Ali, M. A., Ali, M. U., Imdad, A., Lawn, J. E., Van Den Broek, N. & Bhutta, Z. A. (2011). The effect of providing skilled birth attendance and emergency obstetric care in preventing stillbirths. *BMC Public Health*, *11 Suppl 3*, S7. doi:10.1186/1471-2458-11-S3-S7

Yakoob, M. Y., Menezes, E. V, Soomro, T., Haws, R. A., Darmstadt, G. L. & Bhutta, Z. A. (2009). Reducing stillbirths: behavioural and nutritional interventions before and during pregnancy. *BMC Pregnancy and Childbirth*, *9 Suppl 1*(Suppl 1), S3. doi:10.1186/1471-2393-9-S1-S3

Yan, R. Y. (1989). How Chinese clinicians contribute to the improvement of maternity care. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *30*(1), pp.23–6.

Yang, H., Kramer, M. S., Platt, R. W., Blondel, B., Bréart, G., Morin, I. & Usher, R. (2002). How does early ultrasound scan estimation of gestational age lead to higher rates of preterm birth? *American Journal of Obstetrics and Gynecology*, *186*(3), pp.433–7.

Yasmin, S., Osrin, D., Paul, E. & Costello, A. (2001). Neonatal mortality of low-birth-weight infants in Bangladesh. *Bulletin of the World Health Organization*, *79*(7),pp.608–14. doi:S0042-96862001000700005

Zaidi, A. K. M., Ganatra, H. A., Syed, S., Cousens, S., Lee, A. C. C., Black, R. &Lawn, J. E. (2011). Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health*, *11 Suppl 3*, S13. doi:10.1186/1471-2458-11-S3-S13

Zeitlin, J. (2002). Fetal sex and preterm birth: are males at greater risk? *Human Reproduction*, *17*(10), pp.2762–2768. doi:10.1093/humrep/17.10.2762

Zhang, Q., Ananth, C. V, Li, Z. & Smulian, J. C. (2009). Maternal anaemia and preterm birth: a prospective cohort study. *International Journal of Epidemiology*, *38*(5), pp.1380–9. doi:10.1093/ije/dyp243