4 million neonatal deaths:
An analysis of available cause-of-death data and systematic country estimates with a focus on "birth asphyxia"

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Volume I of II

(Volume II provides selected associated publications)

I, Joy Elizabeth Lawn,

confirm that the work presented in this thesis is my own.
Where information has been derived from other sources,
I confirm that this has been indicated in the thesis.
Where the work has been undertaken in collaboration with others
this is indicated in

the introductory section on scope and extent of the thesis

Abstract

BACKGROUND: Of the world's four million neonatal deaths, 99% occur in low/middle-income countries, but most information relates to the 1% dying in high-income countries. Reliable cause-of-death data are lacking. The aim of this thesis is to develop programmatically-relevant, national estimates for neonatal cause-of-death, focusing on "birth asphyxia" to illustrate specific challenges in the available data and for systematic national estimates.

OBJECTIVES:

1. Review estimation methods, giving implications for neonatal cause-of-death estimation.
2. Propose programmatic categories for neonatal cause-of-death, reviewing measurement options for intrapartum-related outcomes ("birth asphyxia").
3. Identify and analyse existing neonatal cause-of-death data.
4. Estimate intrapartum-related neonatal deaths for all countries, comparing single-cause and multi-cause models.
5. Summarise priorities for improving neonatal cause-of-death estimates and input data.

DATA INPUTS: Case definitions were reviewed for neonatal cause-of-death and intrapartum-related outcomes. Six programmatically relevant cause-of-death categories were defined, plus a residual "other neonatal" category. Two sources of neonatal cause-of-death data were examined: Vital Registration (VR) datasets for countries with high coverage (>90%) based on a new analysis from 83 countries; and published/unpublished studies identified through systematic searches. Inclusion criteria for representativeness and comparability were applied. Data from 44 countries with VR (96,797 neonatal deaths) and from 56 studies (29 countries, 13,685 neonatal deaths) met inclusion criteria, despite screening almost 7,000 abstracts. These data represent <3% of the world's neonatal deaths. Thus estimation is necessary for global level information. No useable data were identified from Central and North-West Africa, or Central Asia.

MODELLING: Methods were developed to estimate intrapartum-related neonatal deaths (single-cause), and then simultaneously estimate seven causes of neonatal death (multi-cause). Applying these proportions to the numbers of neonatal deaths in 192 countries gives a global estimate of intrapartum-related neonatal deaths of 0.90 (0.65-1.17) million using single-cause and 0.91 (0.60-1.08) million using multi-cause methods.

DISCUSSION: The multi-cause model has become WHO's standard method for neonatal cause-of-death estimates. However, complex statistical models are not a panacea. More representative data are required. Simplified case definitions and consistent hierarchical cause-of-death attribution would improve comparability, especially for intrapartum-related deaths.

[332 words]

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1. Lawn JE, Shibuya K, Stein C. No cry: Global estimates of intrapartum-related stillbirths and neonatal deaths. *Bull.World Health Organ* 2005; 83: 409-17.

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12. Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006; 367:1487-1494.

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I dedicate this thesis to reducing newborn deaths, especially the 1.2 million a year in Africa, having narrowly missed being an African newborn death myself following an obstructed labour in a bush hospital of Northern Uganda.

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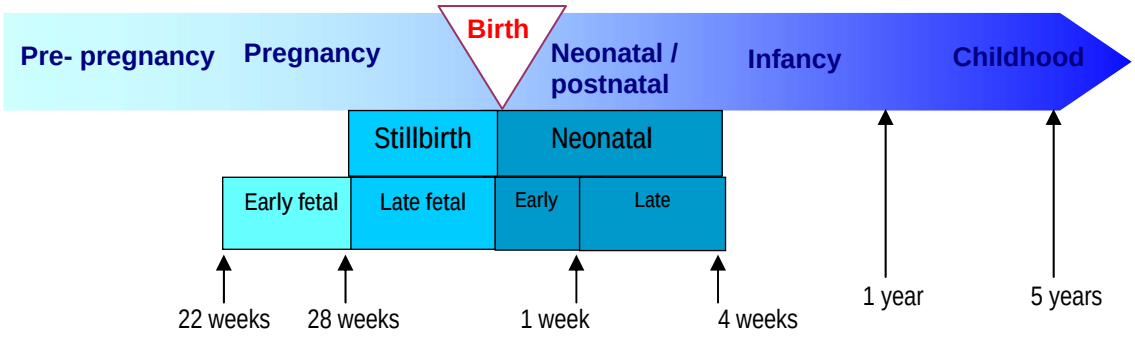
Definitions

Epidemiological Definitions

Figure 1.0 Epidemiological time periods and definitions



Adapted from Lawn JE et al 2001[1]

Stillbirths: *Stillbirth rate* for international comparison is the annual number of babies born dead after 28 weeks of gestation (late fetal deaths) per 1,000 total births.

According to the International Classification of Diseases, Revision 10 a stillbirth, or late fetal death, is death of a fetus weighing at least 500 g (or, if birth weight is unavailable, after 22 completed weeks gestation, or with a crown-heel length of 25 cm or more).[2] For the purposes of international comparison, it is recommended that stillbirth be defined as a late fetal death weighing at least 1000 g (or a gestational age of 28 completed weeks or a crown-heel length of 35 cm or more).[3] Birthweight is prioritised over gestational age because it is believed to be more reliably reported.

Newborns: *Neonatal mortality rate* is the number of neonatal deaths (deaths in the first 28 days of life) per 1,000 live births.

Early neonatal deaths are those that occur within the first week of life (day 0 to 6.9).

Late neonatal deaths are deaths occurring between the second and fourth weeks, i.e. from days 7 to 28.

Newborn refers to the newborn baby and does not have a defined duration, but is often assumed to refer to the first month of life.

Throughout this thesis the day of birth is referred to as day zero.

Small babies: Low birthweight refers to babies born with a birth weight of less than 2,500 g. This can be due to:

- *Poor growth in utero* – babies who are born after the full number of weeks of gestation (37 to 42 weeks gestation, or term births) but are smaller than expected based on accepted

growth standards (small for gestational age). This may be due to a number of causes, including small maternal size, obstetric causes (such as twins or multiple pregnancy, hypertension in pregnancy), infections, poor maternal nutrition or overwork.

- *Preterm or born too early* – babies are born before the normal 37 weeks of gestation. Preterm babies generally have a much higher risk of death than babies born at full term who are of normal size, and a risk that is 3 to 10 times higher than full term babies who were growth restricted.[4]
- Some babies are both preterm and have poor growth in-utero – this applies to many twins or other multiple births. Malaria in pregnancy can cause preterm birth, in-utero growth restriction or both.

Time periods: *Postnatal* is the period after birth for both mother and baby. The exact period is not well defined, but in this review we will assume that it is 6 weeks after birth.
Postpartum describes the same time period, but refers specifically to the mother.
Perinatal is the period that includes some of the end of pregnancy and some or all of the first month of life, and can refer to 10 different time periods depending on the cut-offs used. Perinatal is also used to refer to some, but not all causes of neonatal deaths in the International Classification of Diseases[2]; however, this grouping does not include sepsis, pneumonias or congenital abnormalities. Hence the term can cause confusion, and this thesis will refer to the actual period (e.g. late fetal), the outcome (e.g. stillbirth, neonatal death), or the specific cause-of-death.

Geographical Regions

Throughout this review, countries are the units of analysis. A variety of regional groupings of countries are commonly used. In this thesis the most commonly used regional grouping is the six WHO regions: AFR (Africa), AMR (Americas), EUR (Europe), EMR (Eastern Mediterranean), SEA (South East Asia), and WPR (Western Pacific).[5] For some methodological work the 14 WHO sub-regions promoted by the first phase of the Global Burden of Disease are used (table B1 in the appendix).

Data collection systems

Civil registration: As defined by the UN is the continuous, permanent, compulsory, and universal recording of the occurrence and characteristics of vital events (livebirths, deaths, fetal deaths, marriages, and divorces) and other civil status events pertaining to the population as provided by decree, law, or regulation, in accordance with the legal requirements in each country. It establishes and provides legal documentation of such events and a source of vital statistics.[6]

Demographic surveillance site: The continuous registration of all demographic events, in a geographically defined population; usually research purposes. Cause-of-death analysis through verbal autopsy may be linked to the surveillance.[6] INDEPTH network is the largest network of Demographic surveillance sites including at least 37 sites in 19 countries, mainly in Africa, collectively monitoring 1,800,000 people at household-level. http://www.indepth-network.org/

International Classification of Disease: The international standard diagnostic classification for epidemiological and health management purposes. The latest version is International Classification of Disease revision 10 (ICD 10), published by WHO in 1993.[2] Three-digit codes or even more detailed four-digit codes are listed and then a condensed classification suggested.[7] Around two-thirds of causes of death in the neonatal period have codes in the Perinatal chapter and all these are combined as "Perinatal causes".

Sample registration system: The longitudinal registration of demographic events, including cause-of-death by verbal autopsy, in a nationally representative sample of clusters (e.g. China, India).[6]

Verbal autopsy: A structured interview with caregivers or family members of households after a death occurs; used to establish probable cause-of-death in the absence of direct medical certification.

Vital event*:* As defined by the UN, is the occurrence of a live birth, death, fetal death, marriage, divorce, adoption, recognition of parenthood, annulment of marriage, or legal separation.[6]

Vital registration: All sanctioned modes of registering individuals and reporting on vital events. These modes can include registration activities through complementary systems that are not part of the civil formal registration system and do not produce legal birth or death certificates.

Vital statistics: Summary measures of vital events drawn from all of sources of vital events data. Particularly in developing country settings, where civil registration functions poorly or not at all, the UN acknowledges that many data sources and systems are used to derive estimates of vital statistics.

Vital statistics system: As defined by the UN, is the total process of (1) obtaining information by civil registration or enumeration on the frequency or occurrence of specified and defined vital events, and relevant characteristics of the events themselves; and (2) of compiling, processing, analysing, evaluating, presenting, and disseminating these data in statistical form.

Estimation modelling terminology

Single cause proportionate model: A statistical model to estimate the proportion of deaths due to a single cause-of-death (e.g., intrapartum-related neonatal deaths or neonatal tetanus) in a defined population by age-at-death such as neonatal, or by place such as national or by other criteria.

Multi-cause proportionate model: A statistical model to estimate the proportionate distribution of all deaths from all causes in a defined population. For example all major causes of death within the neonatal period for a specific population such as national level.

"Corner cause" in multi-cause modelling: One cause is selected to be the corner cause, and must be represented in each input dataset. A ratio of each of the other causes of death against this corner cause is converted to a log ratio. Regression modelling is applied to develop estimation equations for each log ratio of cause to the corner cause. Then all the equations are estimated simultaneously and the output constrained to a total of 1.0. The corner cause is estimated as the remainder after all the other proportions have been predicted.

Abbreviations

CHERG	Child Health Epidemiology Reference Group
CHW	Community health worker
DHS	Demographic and Health Surveys
DSS	Demographic surveillance sites
GBD	Global Burden of Disease
HIV	Human immunodeficiency virus
HMIS	Health Management Information System
ICD	International classification of diseases
IMR	Infant mortality rate
IUGR	Intra-uterine growth retardation
LBW	Low birth weight
LMP	Last menstrual period
MDG	Millennium Development Goal
MICS	Multiple Indicator Cluster Survey
MNCH	Maternal, newborn and child health
NE	Neonatal encephalopathy
NMR	Neonatal mortality rate
SBR	Stillbirth rate
TBA	Traditional birth attendant
UNICEF	United Nations Children's Fund
VA	Verbal autopsy
VLBW	Very low birth weight
VR	Vital registration
WFS	World Fertility Surveys
WHO	World Health Organization

Introduction

Scope of the thesis

This thesis comprises part of a wider body of epidemiological work to advance the data and national level estimates for rates, numbers and cause-of-death for both causes neonatal deaths and stillbirths. The work included in the thesis focuses on neonatal cause-of-death and is drawn from two major streams of work led by the investigator. The first stream of work was undertaken between 2002 and 2005, to generate improved national estimates for neonatal deaths due to birth asphyxia for the Global Burden of Disease (GBD), which also resulted in estimates of intrapartum stillbirths. The second stream of work was undertaken between 2004 and 2007, to produce the first set of systematic, national level estimates for cause-of-death in the neonatal period, in collaboration with the Child Health Epidemiology Reference Group (CHERG) and commissioned by the World Health Organisation. At the start of the work for this thesis credible estimates and visibility were lacking and the publication of these estimates, particularly through *The Lancet* Neonatal series contributed to increased visibility of the global problem of newborn deaths.

My focus here is on two core questions. Firstly, how to produce systematic national level estimates for cause of neonatal deaths based on current data? Secondly, how to improve future estimates and strengthen the input data on neonatal cause-of-death? In order to gain more depth I have selected one cause of neonatal death that is of public health importance and is particularly challenging to define and measure – "birth asphyxia" or intrapartum-related neonatal death. The thesis is primarily on the epidemiological inputs and outputs and not on the detailed statistics of the modelling methods, but a description of the main steps involved particularly for the multi-cause model is essential for discussion of potential strengths and limitations of the multi-cause estimation results and also for implications for future estimation methods.

Associated topics not covered in this thesis

There are important areas of perinatal epidemiology that will not be covered in detail in this thesis, despite the associated new work by this investigator and colleagues. The focus here is on proportionate mortality *within* the envelope of neonatal deaths estimated to occur in each country. The numbers of deaths and validity of neonatal mortality rate estimates raise major questions, but the improvement of these data is not the focus of this thesis, although sources of national data for neonatal mortality rates and numbers are summarised. In addition despite systematic country level estimates[8], stillbirths remain even more neglected than neonatal deaths on the global agenda, but are not detailed in this thesis. Stillbirths are estimated to account for at least 3.2 million deaths[8] and are closely linked to neonatal deaths, particularly the obvious linkage of intrapartum stillbirths and neonatal deaths related to birth asphyxia. Finally, intervention priorities from the epidemiology will be highlighted, but interventions to reduce

neonatal deaths are not in the scope of the thesis although the main purpose of improved epidemiological estimates and data is to help guide public health prioritisation for interventions.

Role of the investigator

Given the novel work being undertaken and complexity of modelling required in global estimates, and the requirement for critical appraisal for each assumption, no investigator can undertake credible estimates on their own. Many individuals and agencies have been involved, but the final responsibility for each stage of both these sets of estimates was mine including designing the overall approach, gaining consensus around the case definitions, compiling the input datasets, writing the papers and reports and ensuring the overall quality. In both estimation processes the modelling was undertaken in association with a statistician but as the lead investigator I was involved with the many cycles of refining the various models.

For the single-case estimates of intrapartum related neonatal deaths the searches and the database construction was undertaken by me and I highlight Dr Kenji Shibuya, previously of WHO, for expert inputs and developing the multiple regression model used for countries without vital registration data. For the neonatal multiple cause-of-death work, I had the assistance of several assistants hired through WHO funding whom I supervised in undertaking parts of the searches, locating publications and helping to abstract data, especially for double data abstraction. Katarzyna Wilckynska-Ketende worked with me for around 6 months part-time in this role and a number of others added inputs for shorter periods. Professor Simon Cousens of the London School of Hygiene and Tropical Medicine, one of the supervisors on this thesis, undertook the complex modelling required which involved multiple interactions over the period of around a year. His hard work and willingness to try multiple approaches to improve the modelling, and critical appraisal were essential to success.

Invaluable and insightful review was provided by the CHERG, and particularly Professor Bob Black (John Hopkins Bloomberg School of Public Health), at several meetings hosted by WHO and UNICEF. These meetings also provided opportunities to hear from groups working on estimates for other causes of child death such as malaria or diarrhoea which were invaluable to me as the leader of the neonatal estimates.

I developed the figures and tables in this thesis apart from the following:

- Figure 1.4 which is cited to the United Nations (WHO)
- Several figures were developed with Simon Cousens notably Figures 5.6 and 5.7
- I am grateful to Igor Rudan for assistance with the maps in Fig 5.3 and 7.2.
- The layout of several graphics were improved by *The Lancet* and I have used these versions with references to the relevant publications where appropriate.

Thesis structure

The thesis begins with a brief review of the world's four million neonatal deaths. The Millennium Development Goal 4 for child survival has helped to focus attention on neonatal deaths, which account for an increasing proportion of under five deaths since progress in reducing neonatal deaths has been slower than for postnatal deaths. However, an important gap affecting attention and public health planning was the lack of programmatically relevant neonatal cause-of-death estimates.

Chapter Two sets out the aim and objectives of the thesis.

Chapter Three summarises recent advances in the science of systematic epidemiological estimates, and implications for undertaking neonatal cause-of-death estimates. Systematic steps for estimation are defined which form the basis of the rest of the thesis.

Chapter Four proposes six programmatically relevant case definitions for cause-of-death in the neonatal period, with a residual seventh category. These standard categories allow multiple ICD 9 and 10 codes to be mapped onto these seven comparable cause-of-death groups so that comparisons can be made between countries with varying data sources. Case definitions and measurement options for intrapartum-related related outcomes ("birth asphyxia") are reviewed in more detail.

Chapter Five reports the identification, and review of available, comparable data for the selected cause-of-death categories reporting on a new analysis of Vital Registration data for multiple countries, and systematic searches for useable published data. The quantity and quality of useable data are described, with a focus on the data for intrapartum-related outcomes.

Chapter Six describes the methods developed and applied to estimate national level proportionate mortality for the neonatal period using a single cause model for intrapartum-related outcomes, and multi-cause modelling methods.

Chapter Seven provides results from these two modelling exercises and compares the results for intrapartum-related estimates from the single and multi-cause models.

Chapter Eight sets out the overall findings, the strengths and limitations of the existing data and methods as well as highlighting priorities for improving the data and questions for further analysis and research.

Finally, Chapter Nine gives brief overall conclusions.

The appendices include a list of the papers published to date in relation to the research presented in this thesis, as well as associated chapters and books. Relevant presentations are also listed. In addition the appendix contains supplementary data tables and the study data abstraction form.

The companion bound volume (Volume II) includes copies of selected associated peer reviewed papers and a chapter published y the investigator in association with the work in this thesis.

Chapter 1

Counting neonatal deaths and making them count

1.1. Neonatal deaths count

1.1.1 Counting the world's newborn deaths

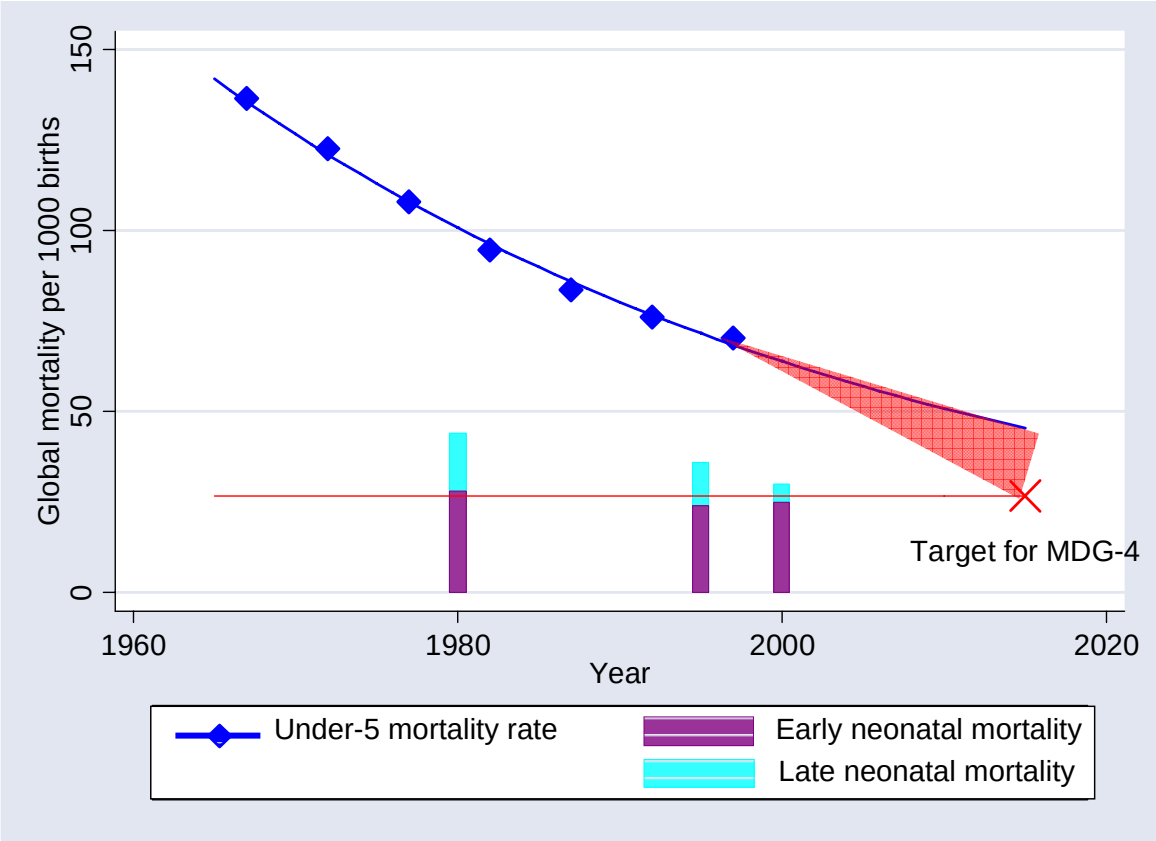
Each year some 130 million babies are born[9] and an estimated 4 million die in their first 4 weeks of life, the neonatal period.[10] A similar number of babies are stillborn—dying in-utero during the last three months of pregnancy.[8] Most of these deaths (99%) occur in low- and middle-income countries,[10] and approximately half occur at home.[4] In poor communities, many babies die unnamed and unrecorded, reflecting the perceived inevitability of these deaths.[11] In contrast, the 1% of neonatal deaths that occur in rich countries are the subject of confidential enquires and public outcry if services are considered substandard.[12] The majority of published trials of neonatal interventions focus on these relatively few deaths in rich countries. The "Inverse Care Law," first described in Britain in the 1960s, still holds today:

> "The availability of good medical care tends to vary inversely with the need for it in the population served."[13]

For newborn survival, this law could appropriately be extended to the "Inverse Information and Inverse Care Law": those communities with the most neonatal deaths have the least information on them and the least access to cost-effective interventions to prevent them.

Global demand for information on neonatal deaths is growing with the recent recognition that an increasing proportion of global under-five mortality occurs in the first 28 days of life. The second half of the twentieth century witnessed a remarkable reduction in child mortality, with a halving of the risk of death before the age of 5 years. The majority of this reduction, however, has been due to lives saved after the first four weeks of life, with relatively little reduction in the risk of death in the neonatal period. Neonatal deaths, estimated at 3.95 million annually, accounted for 38% of the world's under-five deaths in the year 2000. The Millennium Development Goals (MDGs) represent the widest commitment in history to addressing global poverty and ill-health.[14] MDG 4, for child survival aims for a two-thirds reduction in under-five mortality by the year 2015 compared to the baseline of 1990 (Figure 1.1). This results in a target under five mortality rate of 31 per 1000.[15] However, the global neonatal mortality rate is estimated to be 31 per 1000 live births – hence the entire target for under five mortality is currently taken up by neonatal deaths.[8] If MDG 4 is to be achieved, then reducing neonatal deaths must become a major public health priority.

Figure 1.1 Meeting the Millennium Development Goal 4 for child survival: Trends in mortality for children under 5 years of age and in the first month of life (neonatal period), 1965 to 2015



Sources: Under-5 mortality estimates from Ahmad OB, Lopez AD & Inoue M. Bull WHO, 2000, 70(10). Trend fitted assuming constant proportional reduction each year. Neonatal mortality data based on WHO estimates 1980, 1995, 2000.
Figure from Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-90

1.1.2 Four million newborn deaths – do they count?

The mismatch of a low policy imperative for newborn deaths (despite huge numbers of deaths) and close linkages to other issues which do have policy momentum such as child survival and maternal health, raises a question. Do the data gaps, the lack of coherence for programme priorities, and the lack of champions explain the attention gap? Or are there specific policy conflicts that keep newborns off the agenda? Shiffman's classic article on the political imperative for safe motherhood questioned *"Why do some global health initiatives receive priority from international and national political leaders whereas others receive little attention?"* [16] Table 1.1 examines some of the factors shaping political priority for neonates, adapting from Shiffman's work.[16] Since 2005 there has been a paradigm shift with global policy beginning to recognise and address neonatal mortality.[17] In order to understand this shift from relative invisibility to increasing attention for neonatal deaths, a brief review of the visibility of newborn deaths on the global policy agenda is useful.

1. Framing the problem

The majority of neonatal mortality occurs without record of birth or death.[18] While in rich countries birth is accompanied by a fanfare, in many poorer countries, childbirth is accompanied by apprehension for the mother and baby who may remain hidden at home with limited access to care. Often the baby is unnamed until one or even six weeks have passed, reflecting a sense of fatalism and cultural acceptance of high mortality.[19]

Most babies who die in the neonatal period have neither birth nor death certificates. Thus the numbers of neonatal deaths are dependent on estimates. To date, these estimates have been generated by WHO and released every 10 years (1986, 1996[3], 2006[10]). The 2006 release provided estimates for the year 2000 and did not include clear methods or provide uncertainty ranges. This contrasts with HIV/AIDS estimates which are released every two years at a large international meeting and are generated using methods that are widely debated[20] and involve a country-level clearance process. Yet the numbers of deaths are similar – 3 million for HIV/AIDS and 4 million for neonatal deaths. Improving the process, frequency and visibility of neonatal mortality rate estimates is fundamental to keeping this large number of deaths on the agenda. The major global report for maternal, newborn and child health data, UNICEF's State of the World's Children, has included national level NMR estimates since 2007.[9] The source has been data from the WHO estimates for 2000, but it is anticipated that the United Nations Child Mortality Group, which oversees child mortality estimates, will include the NMR estimates. Global attention for the annual release of the number of child deaths has increased in recent years. The announcement in 2007 of child deaths falling below the 10 million threshold for the first time ever received wide coverage, as did the 2008 announcement of further progress

to 9.2 million child deaths. Linking the annual estimates and release of child and neonatal mortality numbers would increase visibility and link the deaths clearly with progress towards MDG-4.

Another important factor in framing the issue is the need for cause-of-death estimates that are credible and country based. Four million deaths are an overwhelming number and splitting these in to causal categories is the first step to public health solutions. This is the main theme of this thesis and will be introduced in section 1.3.

2. Prioritising and communicating solutions

One barrier to action is the perceived impossibility of reducing neonatal deaths. In industrialised countries newborn care is associated with intensive technological approaches. In Northern European countries it was not the introduction of neonatal intensive care in the early 1980s that produced the greatest mortality reduction. The current average neonatal mortality rate globally is around 31 per 1000 births. In England the neonatal mortality rate fell from a similar level in 1940 to 10 per 1000 in 1979.[9] This mortality reduction coincided with the introduction of free antenatal care, improved care in childbirth and the availability of antibiotics. Importantly, some developing countries such as Sri Lanka have also been able to improve neonatal health by investing in similar strategies.[10,21]

Interventions to reduce neonatal deaths belong in two health system programmes: in maternal health programmes covering pregnancy, childbirth and early neonatal care; and in child health programmes, which extend through infancy into childhood. Addressing neonatal mortality requires continuity between these elements of care which is lacking in many settings. Care for the neonate often receives little attention in either maternal or child health programmes. The greatest gap in coverage of care falls during the critical first week of life, when the majority of neonatal and also maternal deaths occur, often at home and with no contact with the formal health care system. In addition, behaviours such as breastfeeding, which influence survival after the neonatal period, are initiated in the first days of life. Functioning health systems, caring for the dyad of mother and foetus/child during pregnancy, childbirth and in the early neonatal period, are essential if neonatal mortality is to be reduced, and indeed also stillbirths and maternal deaths.[22]

Recent influential community-based newborn care studies have focused attention on this gap and highlighted potential solutions that work even in weak health system contexts,[23] reporting reductions in neonatal mortality by around a third with community mobilisation through women's groups[24] and up to two-thirds with a comprehensive community-based package including curative care at home.[25] These studies have demonstrated proof of concept. *The*

Lancet Neonatal series helped progress towards consensus for priority actions in varying health system contexts, and emphasising the message that in weak health system contexts up to one third of neonatal deaths could be prevented with community-based preventive care.[26] However, in contrast with malaria, for example, and the easily understood solution of bednets, there is no single solution for reducing NMR - newborn care involves many interventions and apparently complex packages. Different solutions may be the priority in differing contexts even within one country.[27-29] This apparent complexity and variability may diffuse the clear call to action and result in dichotomies similar to the 30 year conflict between "vertical" and "horizontal" approaches that followed the Declaration of Alma Ata.[30] In addition, consensus for community solutions is affected by maternal health policy conflicts regarding skilled attendants and training traditional birth attendants.[27;31]

3. The strength of organisations and individuals concerned with the issue

Issues that have gained major traction on the global agenda usually have a wide network of agencies, civil society involvement in rich and poor countries and visible champions – for example HIV/AIDS and malaria (table 1.1). For child survival, UNICEF has been a champion in the past[32] and is returning to this as a core vision. From the first child survival revolution, the focus of child survival has been primarily on deaths in the postneonatal period due to causes such as malaria, diarrhoea, and pneumonia, and to malnutrition as a major risk factor.[30] Newborn survival is gradually being added to this, as reflected in their 2008 Child Survival report.[9] Overall there is more coalescence of United Nations agencies with the formation of the so-called Health 8, linking the main health agencies to present a united voice at G8 meetings.[33] However, there remains a lack of clarity as to which agency or even which professional body carries responsibility for newborn health or how the roles and accountability would be most effectively shared. National champions from within low income countries are a crucial part of moving to greater attention and action. There are a number of high profile champions for newborn health in Asia,[21;34] but as yet few in Africa.

4. Political and investment opportunities, or conflicts

Attention and investment for global health has increased dramatically in recent years.[35] Funding for maternal, newborn and child survival rose by more than 60 percent over the last 2 years, although a large proportion of this is earmarked for immunisation.[36] The paradigm shift from Maternal and Child Health (MCH), to Maternal Newborn and Child Health (MNCH) with increasing focus on health systems provides an opportunity for integration and strengthening of newborn care. However not all policymaker within MNCH have fully embraced a joint approach. For example, some maternal advocates continue to see the child and newborn issues as a competition. Specifically some policymakers for maternal health perceive a conflict with

investment in community-based care, being concerned that this may reduce progress towards skilled care at facility level (Table 1.1).

In summary, during the lifespan of this thesis the subject of newborn survival shifted from virtual invisibility to increasing global visibility assisted by the publication of *The Lancet* Neonatal series.[17] There is some consensus on intervention priorities and some increase in investment. However in order to address the four million annual neonatal deaths, two-thirds of which could be prevented with existing, low tech interventions,[9] we need better information on - newborns are dying how many, where and when? To prioritise programmatic actions we particularly need to know *why* these deaths occur and we need this data at country and regional level not just at global level.[4]

Table 1.1 Newborns counting in policy and programme priorities

Determinant	Description	Factors favouring prioritisation of newborns	Factors diminishing prioritisation of newborns
Issues	Framing the problem	Large numbers of deaths – around 4 million Closely linked to maternal and child deaths, which have political priority and momentum in MDGs Public attention for parental grief following newborn deaths. Civil society involvement with information regarding newborn deaths and outcomes	Poor visibility of the NMR estimates released every 10 years by WHO; no clear description of methods. Previously no cause-of-death estimates so all 4 million grouped without sub-categories to guide public health priorities No direct mention of neonatal survival in MDGs or Global Burden of Disease Neonatal outcomes are often discounted in summary statistics e.g. in DALYs. Perception of newborns as not "fully human", or being disposable in poor countries "Mothers in Africa have too many babies anyway". Less importance than for example adult deaths due to HIV.
Ideas	Prioritising and communicating solutions	Close linkages with child survival programmes and maternal health programmes. Integrating newborn health has helped to advance concept of integrated packages of service delivery within continuum of care and promote paradigm shift from MCH to MNCH Influential community-based newborn care studies and Lancet Neonatal series have provided call and actions required to scale up newborn care with wide technical agreement on actions and priorities	Perceived impossibility still particularly for some health care professionals and policy makers – newborn care associated with intensive neonatal care units No single solution in contrast for example with malaria and bednets, newborn care involves many interventions and apparently complex packages. Different solutions may be the priority in differing contexts even within one country Community solutions required in weak health system settings are affected by maternal health policymakers conflicts about skilled attendance and training traditional birth attendants
Power of the actors	The strength of organisations and individuals concerned with the issue	More coalescence of UN and partner messages with respect to MNCH, and some stronger agency and advocacy voices Some more attention from professional organisations e.g. obstetricians and midwives Gates Foundation investments in newborn health, e.g. through Save the Children/Saving Newborn Lives	Newborns in low income countries have no professional body that "owns" them – e.g. obstetricians and midwives primary allegiance is for mothers, paediatricians for the child. High income countries have a new cadre (neonatalogists) which is absent in many African countries and few in many Asian countries Focus is on mothers, and children, some attention to newborns and few mentions of stillbirths, and no clear voice from agencies or individuals Parent lobby groups have limited power, except in high income countries
Political context	Political and investment opportunities, conflicts	Increasing investment in MNCH although the majority remains linked to "vertical" issues such as immunisation, malaria and HIV	Newborns rarely mentioned in maternal health priorities and advocacy and seem to still be perceived as a competition by maternal health community.

Source: adapted from Shiffman et al framework for assessing political prioritisation for maternal health[16]

1.2. Counting neonatal deaths – Where? When?

1.2.1 Where?

Only 1% of neonatal deaths occur in the 39 high-income countries where the neonatal mortality rate (NMR) is an average of 4 per 1000 live births. The remaining 99% of neonatal deaths occur in low and middle income countries where the average NMR is 33 per 1000 (Table 1.2). The rates are highest in Africa which has 12% of the world's population but over 25% of the world's newborn deaths (Figure 1.2). Of the 20 countries with the highest NMRs, 15 are African nations, many with recent conflict. South Asia accounts for a third of the world's neonatal deaths, with over a million a year in India alone. Ten highly populous countries account for 67% of the global total of neonatal deaths (Table 1.3)

There is regional variation in the proportion of under five deaths that are in neonatal period, ranging from 63% in high income countries to 24% in Africa, but it is clear that no region or country can afford to ignore these deaths. As postneonatal mortality falls the proportion of deaths in the neonatal period increases.

Between 1960 and 1990, the risk of dying in the first five years of life was halved—a major achievement. Since 1990, child mortality after the first month of life (i.e., from 1 month to 5 years of age) has declined by one-third, while the NMR has declined by only about one-quarter, mainly reflecting progress in the world's richest countries and in transitional countries in South East Asia and Latin America.[8] The survival gap between rich and poor countries is such that a newborn in West Africa is over 15 times more likely to die in the neonatal period than a newborn in Western Europe (NMRs of 46 and 3 per 1000 live births respectively).[10] Since 1990, Latin America has made the fastest progress. South East Asia has made steady progress, although faster in some countries than others.[37] South Asia and North Africa/Middle East have shown an average annual decline of 2.4% and 2.6% per year, but would need 6.2 and 5.9% per year to reach MDG 4 (Table 1.1). This is challenging but achievable. For the South Asian regional target – if not the global target – much rests on India, where 2.2 million children die every year, half of them being neonatal deaths. Africa needs to increase its annual rate of mortality reduction from 0.7% to over 8% per year –a ten-fold increase in the rate of progress. The regional average for Africa is strongly influenced by progress in Nigeria[38] which has an estimated 247,000 newborn deaths each year (Table 1.3).

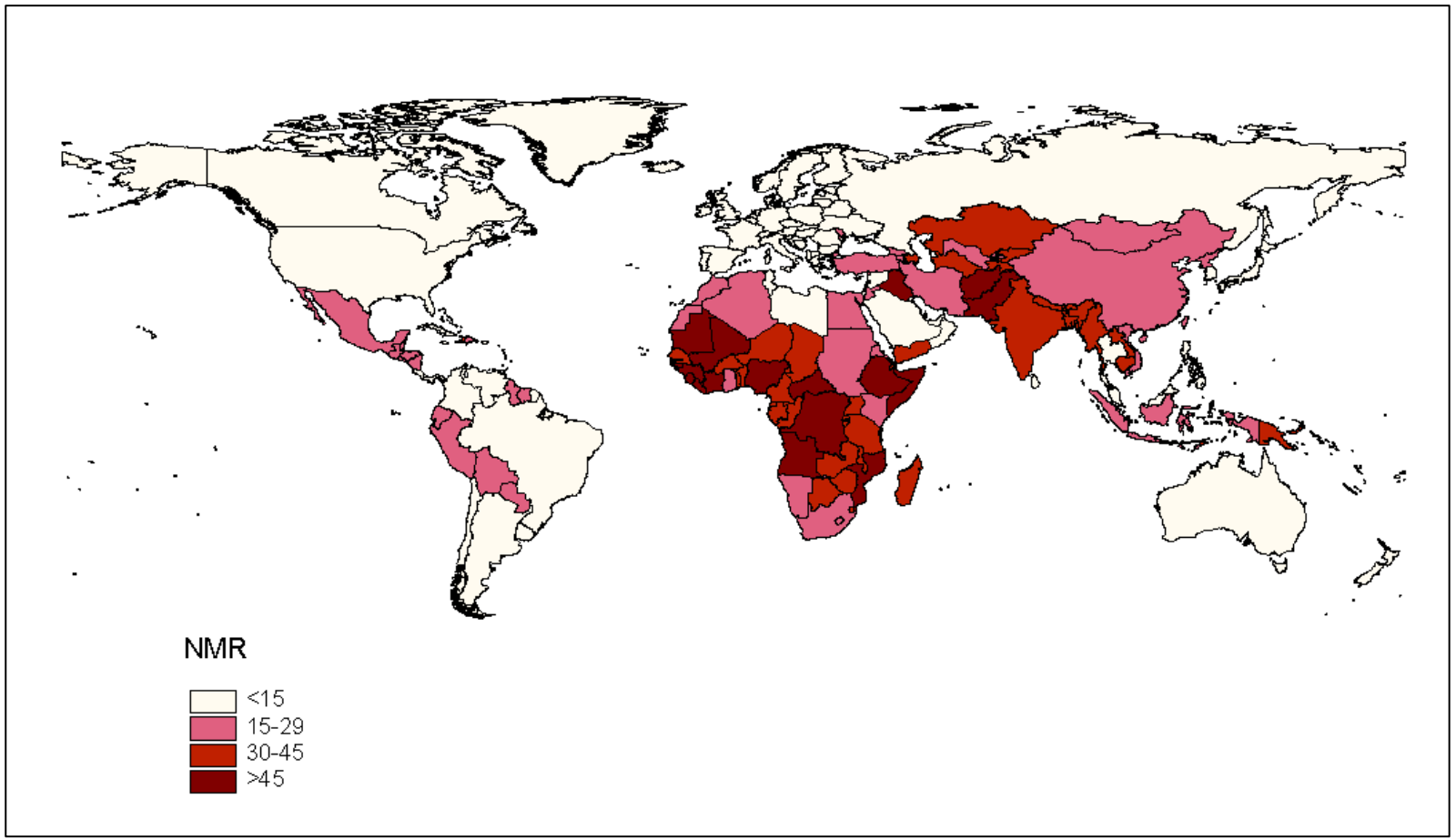
Table 1.2 Regional variations in neonatal mortality rates and numbers of neonatal deaths, showing the percentage of under-5 deaths that are neonatal, and the regional trends for the year 2000

Region or country categorization	NMR per 1000 livebirths (range across countries)	Number of neonatal deaths (1000s)	Percentage of all neonatal deaths in a given region	Percentage of under-5 deaths in the neonatal period	Percentage change in NMR between 1996 and 2005 estimates*
Total	30 (1-70)	3,998	100%	38%	-16%
Income groups					
High-income countries	4 (1-11)	42	1%	63%	-29%
Low- and middle-income countries	33 (2-70)	3,956	99%	38%	-8%
WHO Regions					
Africa	44 (9-70)	1,128	28%	24%	+5%
Americas	12 (4-34)	195	5%	48%	-40%
Eastern Mediterranean	40 (4-63)	603	15%	40%	-9%
Europe	11 (2-38)	116	3%	49%	-18%
South East Asia	38 (11-43)	1,443	36%	50%	-21%
Western Pacific	19 (1-40)	512	13%	56%	-39%

NMR: neonatal mortality rate. Sources: Neonatal mortality from WHO estimates. (around 1995 and 2005). Under-5 deaths from UNICEF 2005 (data around the year 2000)
The data inputs cover at least a 5 year period before each set of estimates. Regions according to WHO. Countries listed Appendix Table B.1
High-income countries comprise 39 countries with NMR data out of the 54 countries with GNI per capita of >US$9,386 as listed
http://www.worldbank.org/data/countryclass/classgroups.htm#High_income

Table adapted from Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; **365**: 891-900.

Figure 1.2 Variation between countries for neonatal mortality rates per 1000 live births for the year 2000



NMR=neonatal mortality rate Source: Neonatal mortality from WHO 2000 estimates. 2005[10]
Map from Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-90.

Table 1.3 The ten countries with largest numbers of neonatal deaths in the year 2000

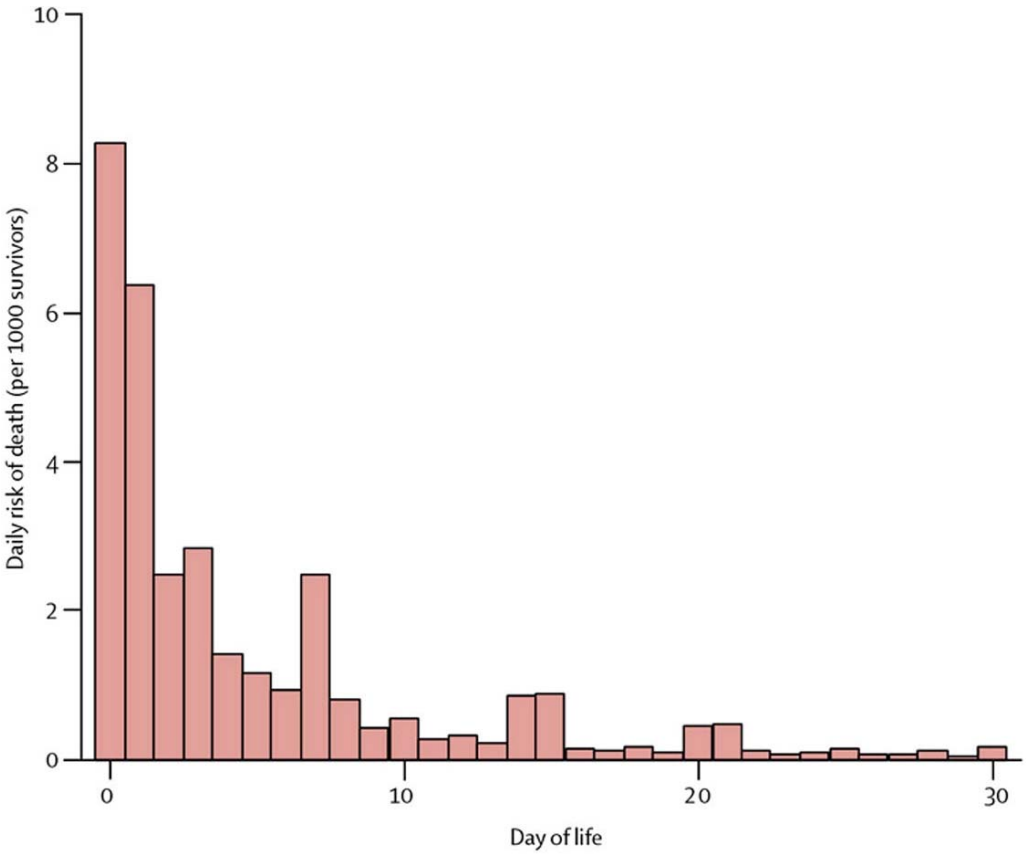
	Rank for number of neonatal deaths	Number neonatal deaths (1000s)	Percentage of global neonatal deaths	Neonatal mortality rate (per 1000 live births)
India	1	1098	27%	43
China	2	416	10%	21
Pakistan	3	298	7%	57
Nigeria	4	247	6%	53
Bangladesh	5	153	4%	36
Ethiopia	6	147	4%	51
Dem. Rep. of Congo	7	116	3%	47
Indonesia	8	82	2%	18
Afghanistan	9	63	2%	60
United Republic of Tanzania	10	62	2%	43
Total		2,681	67%	

Source: Neonatal mortality from WHO 2000 estimates. 2005.[1]
Table from Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-900

1.2.2. When?

The neonatal period is only 28 days and yet accounts for 38% of all under-5 child deaths. The remaining 62% of under-5 deaths occur over a period of almost 1800 days. Thus the average daily mortality rate during the neonatal period is close to 30-fold higher than during the post-neonatal period. Even within the neonatal period there is considerable variation in the daily risk of death (figure 1.3). Mortality is extremely high in the first 24 hours after birth (25-45% of all neonatal deaths in this analysis) and globally some three-quarters of neonatal deaths (75%) occur in the first week after birth. [4]

Figure 1.3 Daily risk of death during the first month of life



Based on analysis of 47 Demographic Health Survey (DHS) datasets (1995 – 2003) with 10,048 neonatal deaths. Source Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-900.

Data quality can effect on the analysis and interpretation of timing of death on day zero. In retrospective surveys such as Demographic Health Surveys (DHS), day zero deaths are affected by misclassification between stillbirths and neonatal deaths, but also compounded deaths by miscoding from day zero into day one. These surveys involve asking a woman about her births usually over her whole reproductive history with one separate question about stillbirths. Most survey tools concentrate on asking about live births with a subsequent question about child death and age at death. Although in perinatal epidemiology terms the day of birth is officially considered to be day zero, and this is how the data in DHS is analysed, not all field workers

apply this concept which differs from common use and they may enter day zero deaths for day one. In addition, respondents in societies where the 24 hour clock is not used may consider the next day to start after sunrise so deaths 12 hours after birth but after a sunrise, for example, may be described as taking place the next day. An analysis of DHS surveys in Africa revels that in some countries particularly in West Africa there are apparently more neonatal deaths on day one than day zero and day of death distribution reveals an atypical pattern that does not follow the usual steep drop in deaths by day, whereby around a third of neonatal deaths occur on day one, 50% in the 48 hours and 75% in the first week (Lawn, unpublished analysis). If all or most of the deaths are captured and simply recorded on the wrong day then the overall neonatal mortality rate would be not affected. However, it is possible that an apparent lack of day zero deaths could be due to deaths being missed entirely or to misclassification of day zero deaths with intrapartum stillbirths. To fully understand the underlying data issues further analysis is required including stillbirths and comparing DHS (retrospective data) with prospective pregnancy surveillance data.

In addition preference in reporting day of death can affect analysis of time of death. This is apparent in Figure 1.3, with obvious age heaping around days 7, 14 and 21. This preference for reporting deaths on certain days is common in DHS data, or indeed most retrospective survey data. There is also some heaping on day 30 which could result in misclassification of deaths out of the neonatal period. However, this is usually a small proportionate effect compared to the age heaping on day seven, which results in misclassification out of the early into the late neonatal period (Hill, K unpublished analysis for CHERG). It is currently being proposed to the United Nations Child Mortality Group that DHS data should be smoothed to correct for age heaping on day 7 and day 30 to overcome the effect on early neonatal mortality rates, and potential effect on neonatal mortality rates.

1.3. Four million neonatal deaths - the need for cause-of-death data

Many neonatal deaths are preventable with existing low-cost interventions,[3;4] but to make effective use of limited resources, planners and policymakers require reliable cause-of-death information.[5] Information regarding causes of neonatal death, particularly in the first week of life when three-quarters of neonatal deaths occur, is fundamental for developing and tracking public health strategies. However, most of the world's neonatal deaths occur in low- and middle-income countries of which few have high vital registration (VR) coverage. Thus, estimation is the only option currently available to meet this gap in information for the vast majority of neonatal deaths.

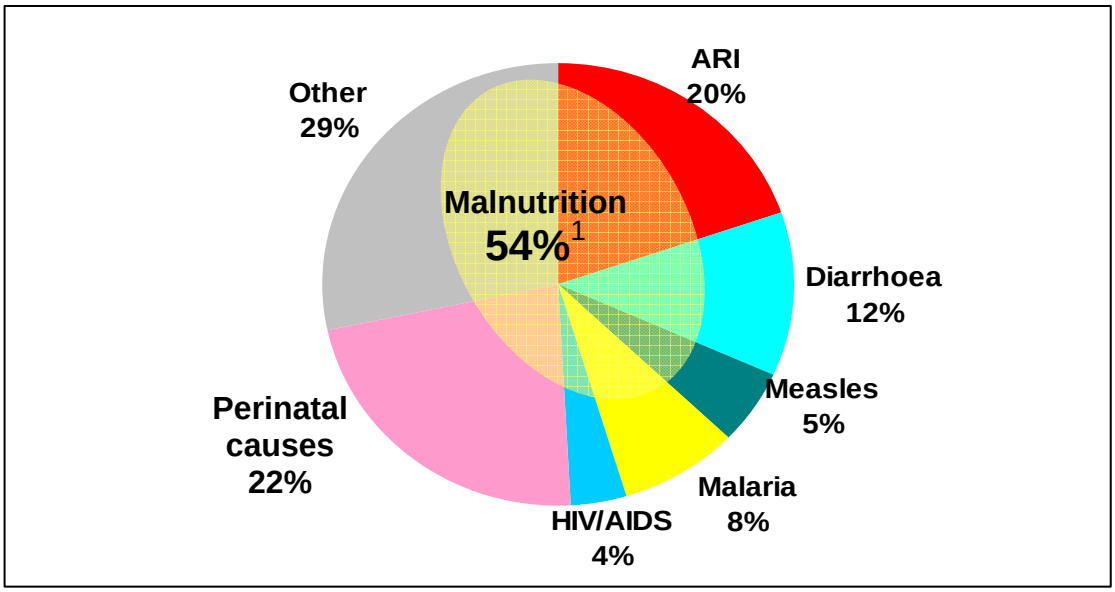
Systematic global estimates for single or multiple causes of neonatal deaths have not been published in the peer reviewed literature prior to this thesis. Prior to 2005, the World Health Organisation (WHO) which is responsible for global estimates and data, provided little detail with respect to the causes of neonatal deaths in categories that relate to programmatic decision-making.[39] In the global burden of disease tables in the annual World Health Report the biggest single category of deaths is "perinatal causes" - 2.6 million deaths grouped together.[40;41] This grouping is poorly understood by both epidemiologists and programme managers, as it is often assumed to include stillbirths. "Perinatal causes" refers to any codes for cause-of-death in the Perinatal chapter of the International Classification of Disease (ICD) volumes[2] and combines several distinct causes of death with differing programmatic solutions which together account for approximately two-thirds of neonatal deaths. However the category omits important groups such as most neonatal infections, neonatal tetanus and all congenital abnormalities. Neonatal infections, the single largest cause of neonatal deaths globally, and eminently preventable and treatable are not distinguishable in the tables despite the need for alternative prevention and treatment strategies.[39]

Furthermore, the data inputs and methods for these estimates are not in the public domain. Understanding the strengths and weaknesses of estimates is a necessary foundation before using them for programmatic decision making. In addition, the provision of such information highlights the need for more data and gives a basis to improve on methods used.

For many policymakers focused on global child survival, priorities are based on the global pie chart of estimated causes of child death. This pie chart, produced by WHO department of Child and Adolescent Health, was used by UN agencies including UNICEF in their publications and on their website, and has been well disseminated within the global child health community. In 2004 this pie chart had no programmatically meaningful components included for neonatal cause-of-death, referring only to "perinatal causes" (figure 1.4). The percentage attributed to "perinatal" was 22%, although at the time 36% of deaths were in the neonatal period. The slice called "Other" included the remaining 14% of neonatal deaths. Hence this classification masked the size of the problem for neonatal deaths, and also failed to show meaningful programmatic causes to address such as tetanus, neonatal infections, preterm birth complications and intrapartum neonatal deaths.

Finally, saving newborn lives does not occur at the global level – action is required within countries and there is substantial variation in cause-proportionate mortality between and even within countries. For more visibility and investment in countries and for more effective prioritisation and tracking of programmes, cause-of-death distributions at national or even sub-national level are required.

Figure 1.4: Estimated global causes of death for children under the age of five around the year 2004



Source WHO and UNICEF websites, February 2005

Chapter 2
Aim and Objectives

Aim

The purpose of this thesis is to review information on the causes of four million neonatal deaths, and to generate systematic, country-based estimates, advancing the estimation process for the major programmatically-relevant causes of neonatal death with a specific focus on “birth asphyxia”.

Objectives

1. Review approaches and statistical modelling methods for systematic estimation of global epidemiological parameters, distilling the implications for improving estimates for causes of death within the neonatal period. [Chapter 3]

2. Consider case definitions for causes of death within the neonatal period and propose a minimum list of programmatically relevant causal categories which are comparable in vital registration and other data sources, examining in more detail the case definitions and measurement options for intrapartum-related outcomes. [Chapter 4]

3. Undertake a systematic assessment of the coverage and quality of data for neonatal cause-of-death through vital registration systems and in published and unpublished literature in all countries. [Chapter 5]

4. Estimate intrapartum-related neonatal deaths for all countries using two different approaches (single-cause and multi-cause models), and to compare the methods and results. [Chapters 6 and 7]

5. Summarise actions to improve estimates and input data for neonatal cause-of-death, listing research priorities. [Chapter 8]

Chapter 3
Cause-of-death estimation methods
(Objective 1)

Objective 1

Review approaches and statistical modelling methods
for systematic estimation of global epidemiological parameters,
distilling the implications for improving
estimates for causes of death within the neonatal period.

3.1. Cause-of-death estimation methods

3.1.1 Overview of the new science of systematic global estimates

Given that most neonatal deaths are unrecorded,[6] estimation is the only option currently available for global level information on neonatal deaths.[42] The science of systematic reviews of interventions is advanced, with guidelines for search strategies and inclusion criteria such as used in the standards for Cochrane reviews (http://www.cochrane.org/resources/ handbook/). In contrast, however, the science of disease burden estimation is less advanced and at times controversial.[43] Nevertheless, there has been a gradual shift from "back of the envelope" estimates to a new science of global estimates requiring application of quality standards to the input data, transparency regarding assumptions and modelling and a peer review process.

3.1.2. Improving the quality of cause-of-death estimates

Most of the recent guidelines on improving global estimates have set out generic principles, but as yet specific guidelines have not been published regarding recommendations for cause-of-death estimates.[44] However, based on recently published papers providing cause-of-death estimates particularly from the Child Health Epidemiology Reference Group (CHERG),[5] and from guidelines for the GBD (2005)[45] a number of principles can be summarised regarding the inputs and the estimation process (table 3.1).

1. *Case definitions for cause-of-death:* One of the greatest challenges in estimation of disease burden is to establish if the reported variability in a parameter is true epidemiological variation or if it is affected by variability in application of case definitions. Case definitions are most likely to be variably applied if there is a lack of consensus around the case definition and especially if there are co-existing morbidities and a hierarchy has to be applied in attributing cause-of-death. The reality is that for many deaths several conditions contribute, but ICD rules stipulate enforce a "one death, one cause" approach. For a condition such as a road traffic accident or neonatal tetanus which is easy to define and widely accepted to take precedence over other causes, there may be more consistent cause-of-death attribution. However, for conditions with less consensus or even confusion around case definitions and especially for conditions which commonly co-exist with others, then the reproducibility of cause-of-death attribution may be affected. A notable example is "birth asphyxia" where terminology is confused, case definitions vary and a hierarchy is required with other co-morbidities such as preterm birth or infection. This is a recurrent theme for neonatal cause-of death estimation. While the ICD 10 instruction manual provides general guidelines on selection of the underlying cause-of-death (the primary or direct cause), and several pages of notes on perinatal causes, ambiguity remains.[7]

Estimation exercises should be explicit regarding case definitions used, as well as any hierarchy of causes of death. Standardised data extraction and additional information from authors may be required to combine data from varying sources.

2. *Input data:* Comprehensive, systematic searches for data should be the norm, and the application of explicit inclusion and exclusion criteria is to be encouraged.[5;46] The use of a standard data extraction form and examination of quality of study have been used in several recent data extraction exercises. In some cases double data extraction has been applied with a supervisor to resolve differences.[46] In the interests of transparency the input data should be detailed and be publicly available, in an online database for example.[47] Single cause-of-death estimates may be susceptible to systematic upward bias since many single cause studies are designed by groups aiming to undertake intervention trials and likely to select populations with high prevalence of the condition of interest. Consideration should be given to excluding studies with just one cause-of-death reported.

3. *Methods and modelling:* Varying the assumptions applied to data inputs and modelling can alter results markedly. Methods, assumptions and models should be described in full, and ideally sensitivity analysis performed to assess the effect on the results of any major assumptions. Global estimates often attempt to combine VR data and other sources at the end of the process, and the quality assurance criteria may be unspecified and the choices of varying inputs may be subjective. An alternative approach is to have transparent inclusion/exclusion criteria to apply to all data sources and then combine data and estimates using a defined set of rules. If all the input data are from low mortality settings, the model will not be appropriate to use for estimation in high mortality settings.

4. *Single proportionate cause-of-death modelling versus multiple:* Methodological approaches simultaneously estimating multiple causes of death in a given age band are more attractive than attempting to combine several single cause estimates generated through varying methods, the sum of which often exceeds the total number of deaths.[48;49] Previously, most cause-of-death modelling has focused on single cause models, for example for pneumonia, or diarrhoea. Once several sets of estimates are available, the numbers of several causes of child death have to be combined by country to fit within the envelope of child deaths. This has been referred to as the “smoke filled room” approach and has been criticised as non-repeatable and non-transparent. Recommendations are to move towards simultaneously estimating multiple causes of death as proportions within an envelope constrained to 1.0. This is attractive in theory but raises major data, methodological and statistical challenges. [50] Firstly, given that input data are lacking for cause-of-death in high mortality settings, multi-cause approaches restrict the input data further to only those sources with several

comparable causes of death in a given time period. The lack of high quality data covering several causes of death may mean that the very process of selection results in other biases and reduces external validity. The second challenge is the complexity of the modelling methods required.

The first published use of multi-cause modelling for child mortality estimates was developed within CHERG by Morris and Black[48] and applied using a modelling method entitled Seemingly Unrelated Regression. The Morris model aimed to include neonatal as one causal group, but was unable to find enough datasets that included it as well as pneumonia, diarrhoea, malaria and measles. Hence, neonatal causes were combined with "Other" in the residual category. For the multi-cause modelling a "corner cause" is selected, which must be a cause that is available in every dataset. Then a ratio of each of the other causes of death against this corner cause is converted to a log ratio (see definitions page 17 for more detail). Regression modelling is applied to develop estimation equations for the log of the ratio of each cause to the selected corner cause. Then all the equations are estimated simultaneously and the output constrained to a total of 1.0 eliminating the subjective step of combining single cause so they add up to 100% of the deaths. The corner cause is estimated as the remainder after all the other proportions have been predicted. This pioneering work of Morris at el advanced the use of multi-cause modelling but highlighted two key methodological problems.[48] Firstly any dataset with a missing value for any cell had to be excluded from the Seemingly Unrelated Regression model, and hence the data available were highly restricted and risked systematic bias. Secondly, smaller proportionate causes (e.g. measles) appeared to be systematically underestimated. Any future attempts to undertake multi-cause modelling would have to attempt to address these problems.

5. *Uncertainty ranges:* Given the inherent uncertainty surrounding the process of using a small minority of deaths to predict global point estimates, the provision of uncertainty estimates should be considered standard practice. Policymakers often prefer a point estimate, but presenting the point estimate with an uncertainty range would promote more understanding of the limitations of such estimates, and the need to invest in improving the information. Global estimation processes have often been produced by advocacy groups and discussion of data limitations was considered a risk to diluting the message for action to address the condition.

6. *Review process:* Given the complexity of the process and how certain assumptions in inclusion or exclusion criteria or in the modelling process may have a major effect on the estimate results, it is crucial to build expert external review into the process, similar to the quality of peer review in a high level journal.

3.2. Implications for estimation of neonatal cause-of-death

This chapter of the thesis set out to answer the first objective of the thesis, reviewing approaches and statistical modelling methods for systematic estimation of global epidemiological parameters and distil the implications for improving estimates for causes of death within the neonatal period. The need for systematic and credible neonatal cause-of-death estimates is apparent, as are the challenges. Transparency in the estimation process is to be promoted, since this helps to create a demand for further advances in the estimation methods and improved data collection. While improved estimation methods are increasingly being advocated, as yet few global estimates, particularly for cause-of-death, have applied any let alone all of these principles. The main implications for improving neonatal cause-of-death estimates are summarised in Table 3.1. A further advance that has not yet been seen in practice would be to test the model predictions against real study data to assess model performance. [51]

Table 3.1: **Improving cause-of-death estimates, and specific implications for neonatal cause-of-death estimation**

Step in estimation process	General principle	Implication for neonatal cause-of-death estimation in this thesis
1. Case definitions for cause-of-death	Programmatically relevant case definitions	Shift from "perinatal causes" to programmatically relevant categories of cause-of-death
	Clear case definitions, comparable in high and low income settings, linking to ICD coding	Agreement on a minimum list of cause-of-death categories that are comparable with more complex specific causes in high income countries New analysis of ICD 9 and ICD10 codes in the neonatal period to map multiple ICD codes to the agreed minimum neonatal cause-of-death categories
2. Input data	Combining multiple data sources; for example vital registration, published studies, unpublished datasets	All data sources must be examined including a new analysis of VR data from countries with high coverage of registration, systematic searches of published literature and attempts to identify unpublished literature
	Explicit inclusion criteria to ensure minimisation of selection bias and maximisation of comparability	Inclusion criteria for data regarding population representativeness and regarding comparability for causes of death
3. Methods and modelling	Models based on low mortality data only (e.g. vital registration) should not be applied to high mortality regions	VR data to be used for the country of origin or for modelling for countries with similar NMR, or as an input to a model with other data covering high NMR countries. VR data from low NMR countries should not be used as the sole data to predict proportionate mortality in high NMR countries
	Models should be fully explained and equation(s) published	Explain the models, and assumptions and publish equation(s)
4. Single or multiple proportionate cause-of-death modelling	If estimating one cause-of-death, single cause model may be appropriate, but for estimation of proportionate cause within a given period a multi-cause model is preferable to avoid non-repeatable expert opinion fitting multiple single cause estimates together	Compare the single and multi-cause modelling approaches in order to better understand the advantages and disadvantages
5. Uncertainty ranges	Uncertainty estimates should be provided and should not be based on 95% CI, but should take account of as many sources of uncertainty in the inputs as possible	Provide uncertainty estimates that show more realistically the level of uncertainty around estimation outputs
6. Review process	External expert group process should review the inputs, methods and results	External expert group process should review the inputs, methods and results

ICD, International Classification of Disease

Chapter 4
Case definitions for neonatal deaths
(Objective 2)

Objective 2

Consider case definitions for causes of death
within the neonatal period and propose
a minimum list of programmatically relevant causal categories
which are comparable in vital registration and other data sources,
examining in more detail the case definitions
and measurement options for intrapartum-related outcomes.

4.1 Challenges in the estimation of neonatal cause-of-death

4.1.1 Sources of cause-of-death data

There are a variety of data sources for causes of neonatal death, but good quality, nationally representative data for low-income countries are rare (Table 4.1). While around one-quarter of births occur in countries with nationally representative vital registration data, few countries (46) have vital registration systems with both high coverage and high quality of cause-of-death classification. In analyses undertaken during 2004, less than 3% of the world's neonatal deaths had certificate data meeting inclusion criteria for quality and comparability.[18] Household surveys such as DHS and MICS do not routinely investigate cause-of-death, although in some countries follow-up studies have used verbal autopsy to investigate perinatal[19,20] or child deaths.[14] In most countries without high coverage of vital registration the only sources of cause-of-death data are health facility audits, or special studies. National studies have been undertaken in some countries, the example of Jamaica being well-known.[21]

4.1.2 Verbal autopsy tools

Community-based studies frequently utilise verbal autopsy (VA) approaches, whereby an interviewer administers a questionnaire interview to surviving family members after a death and based on this information a single cause is assigned.[52] Verbal autopsy methods vary from a non-structured interview, to detailed post-mortem questionnaires with computer algorithms, or several experts assigning a cause-of-death.[53] The numbers of causes of neonatal death also vary between tools, from four simple groupings to multiple specific diagnoses. A few countries have undertaken national VA studies as a follow-up to DHS surveys – for example, investigating child deaths in Bangladesh,[54] and perinatal deaths in Egypt.[55]

Verbal autopsy methods have progressed in recent years and there have been several attempts to develop structured standard questionnaires, including a neonatal VA questionnaire developed by WHO and Saving Newborn Lives.[56] The network of around 37 Demographic Surveillance sites mainly in Africa also identified the need for a neonatal VA and a number of INDEPTH sites have developed tools, including two in Ghana.[57] (see Definitions section, page 15 for more details on INDEPTH). Some investigators have developed tools that map onto ICD codes. [58;59]

The VA definitions for neonatal tetanus have higher sensitivity and specificity that for other neonatal causes of death.[52;60] Congenital abnormalities, especially cardiac defects, are often missed, and are especially hard to capture in VA studies where family reports of poor feeding and fast breathing are likely to result in misclassification into pneumonia or severe infections.

More important than variation in the data collection forms, the proportionate mortality results are highly dependent on the cause-of-death categories chosen, the case definitions and hierarchy applied for coding cause-of-death, bearing in mind that several causes often co-exist. For example, if a moderately preterm baby dies of an infection, the ICD would attribute the death to infection, with preterm as a contributing factor;[22] but if an extremely preterm baby dies of hyaline membrane disease, prematurity is the underlying or main cause. The proportion of intrapartum-related neonatal deaths is especially open to variation with different case definitions. If the traditional clinical case definition of "not breathing at birth" is applied, then any baby not breathing at birth would be included (for example preterm infants) falsely inflating the intrapartum-related proportion. This is not an academic nicety since it has implications for the public health strategy required. Improved tools with explicit hierarchies, linking VA and VR data and with known performance characteristics are required.[61] Chapter 4 (specifically 4.3) details the specific issues regarding "birth asphyxia" case definitions and measurement.

4.2. Case definitions for multi-cause neonatal death analysis

4.2.1 Shifting from "perinatal causes" to programmatic categories

Cause-of-death classification should be meaningful for programmatic action. The classification used for neonatal deaths is enmeshed in history. In ICD terminology 'perinatal cause' refers to any code in the perinatal chapter of the ICD.[22] In the WHO's World Health Report and the GBD summary tables the largest single number of deaths falls under the heading of "perinatal causes", a total of 2.6 million deaths in one row.[23] This contrasts with single rows for some other very specific categories; for example Trachoma has a single row but no deaths in the row. Otitis media lies just two rows above "Perinatal causes" and includes 4,000 deaths. The GBD webtables provide a breakdown of "perinatal causes" into just three sub groups – "birth asphyxia", "low birth weight" and "perinatal other".

The "perinatal causes" category has a number of disadvantages in terms of the use of data for policy and programmes:

1. ***Misunderstanding of the category:*** The term is not well understood by epidemiologists or programme managers, and is frequently assumed to refer to perinatal mortality and the perinatal period and to include stillbirths.

2. ***Programmatic relevance:*** This is the largest number in the burden of disease tables but not directly correlated to specific programmatic solutions such as improved intrapartum care, or case management of neonatal infections, or improved care of preterm neonates.

3. ***Excludes several major and closely linked causes of mortality and morbidity:*** Conditions which are not in the Perinatal chapter of ICD are excluded from the "perinatal causes" group, notably neonatal infections, neonatal tetanus, and congenital abnormalities, which has a separate ICD chapter. Neonatal tetanus has a separate row within the section related to immunisable conditions. However, neonatal infections are not possible to distinguish in this tabulation, despite being the single largest cause of neonatal deaths and the most feasible to prevent in low income settings.[24]

4. ***The time period is not restricted:*** Thus a death at any age can be ascribed a perinatal code if a cause within the perinatal chapter was considered to be the underlying cause. In some countries adults dying of cerebral palsy are coded to "birth asphyxia" codes. The application of perinatal chapter codes for deaths late in adult life is practised differently in different countries, with some countries registering significant numbers of adult deaths to perinatal cause categories (personal communication Kenji Shibuya, WHO).

These factors have contributed to the invisibility of neonatal deaths on the global agenda as exhibited in the global pie chart for causes of child death (Fig 1. 4). Around half of neonatal deaths are in the 22% slice for "perinatal causes" and the remaining 14% of neonatal deaths are in the "Other child deaths" category. Adopting easily understood and programmatically relevant categories for cause-of-death is an important first step in using data to reduce neonatal mortality. Increasing the availability of useful, comparable cause-of-death data to inform public health decision-making will require wide application of a standard set of programmatically relevant cause-of-death categories, with standard case definitions that can be applied in both vital registration and verbal autopsy data.

4.2.2 Consensus process to agree on causal categories

The Child Health Epidemiology Reference Group, (CHERG) and external group of experts working with WHO and UNICEF, undertook an expert consensus process to select a minimum set of categories for cause-of-death within the neonatal period. The process involved the following steps: (1) background work reviewing categories used to date and hierarchical approaches (undertaken by the investigator); (2) Preliminary discussion at a CHERG meeting to agree on criteria and likely categories (3) a one day face-to-face meeting of most members of the CHERG neonatal group in Geneva (April 2004). This one day meeting was requested and coordinated by the investigator with participation by CHERG neonatal group members including Jose Martines, Kenji Shibuya, Martin Weber, and Jelka Zupan (all WHO, Geneva) as well as Simon Cousens and Robert Black. The purpose of the meeting was to finalise the list of causal categories and agree on case definitions and a hierarchy to apply.

Step 1: Finalising the list of causal categories

It was agreed by the expert group in advance of the meeting that the selection of the causal categories should be based on three key considerations:

1. Causal categories with public health significance and differing programmatic implications;
2. Clinically distinguishable categories in low income settings and particularly in VA; and
3. Data availability in existing multi-cause datasets.

Background work was presented by the investigator regarding causal categories in current use. The list of causes for ICD tabulation only included "Low birth weight", "Birth Asphyxia" and "Perinatal other" and was considered inadequate to guide policy and programmes. For the majority of countries the only data sources is VA and the cause of death categories for neonatal in VA tools often gave only two or three of the following categories - tetanus, infections, diarrhoea, "birth asphyxia" and preterm birth or even "low birth weight". While congenital was often omitted in VA data, this was considered a very important cause to include in estimates.

Six categories had been proposed during a previous CHERG meeting based on the agreed criteria for causal categories and including (1) preterm birth complications; (2) "birth asphyxia"; (3) severe neonatal infections (sepsis, pneumonia and meningitis); (4) neonatal tetanus, (5) diarrhoea; and (6) congenital abnormalities, and (7) residual "other neonatal" category comprising specific causes of neonatal death such as jaundice and haemorrhagic disease of the newborn (table 4.1).[18] There was strong group consensus around these causal categories as being of distinct programmatic relevance and being possible to define separately so during the one day meeting most of the discussion focused around the case definitions and the hierarchy.

Step 2: Agree on case definitions

Based on the background review, group discussion focused on two issues for case definitions identified as priorities for group consensus. Firstly around the desire to further delineate the neonatal infections group ideally into specific clinical infections syndromes; secondly how to deal with preterm as a direct cause of death versus preterm as a risk factor for death. These questions were driven by the need to be able to distinguish causes in VA data that could be comparable to more detailed information in VR systems, and consistent with ICD rules.

Neonatal infections: Since pneumonia in a neonate cannot be distinguished on clinical examination alone from septicaemia or meningitis, and because case management is similar for all three conditions, one category, subsequently referred to as "sepsis/pneumonia", was used for all three infection syndromes. Some VA tools attempt to distinguish neonatal pneumonia from sepsis/meningitis and as VA tools increase in sophistication, it is possible that more data with a reliable split will allow this causal category to be divided into more detailed subgroups. From a public health and clinical perspective the prevention and management priorities are the same for neonatal sepsis, pneumonia, and meningitis, but for ICD and GBD categories there is a desire to split these to be consistent with the tabulation used for adult infection deaths.

Preterm birth as a direct cause of death versus as a risk factor and dealing with small for gestational age (SGA) as a direct cause of death: Preterm birth may be either the main cause-of-death through specific complications of immaturity, or a risk factor for other specific causes, notably infections.[75] For a moderately preterm baby who dies of a community-acquired infection, infection is the category to highlight for intervention. ICD recommends that preterm birth alone should not be coded as the main condition on a death certificate, but rather the specific complication for example respiratory distress syndrome, or intraventricular haemorrhage.[7] In compliance with ICD, the category preterm was defined to include only deaths directly attributed to specific complications of preterm birth such as surfactant deficiency, but not all deaths in preterm infants.[7] However it should be noted that investigators do not always

specify such case definitions clearly in publications, so in secondary data analysis the quality of case definitions and application of these cannot always be controlled. For tabulation purposes the relevant specific codes for preterm direct complications can then be grouped as one category related to preterm birth which is the root cause for public health prevention and intervention.

The category of full term infant, SGA was considered important to try to distinguish from the preterm direct cause-of-death category. Analysis of VR data and the study data in the CHERG neonatal database showed that term SGA was attributed as the main cause for less than 1% of neonatal deaths, although some studies did not specify this as a cause-of-death so some misclassification into preterm birth is possible. The expert group recommended that neonatal deaths directly attributed to SGA be included in the "Other" causes of neonatal death. An additional benefit of this approach is consistency with the cause-of-death groupings for the older child deaths where deaths attributed to severe malnutrition may be undercounted or inconsistently counted and are included in the child "Other" category.

Step 3: ***Define a hierarchy for attributing neonatal cause of death categories***

Attributing each death to a single cause is an oversimplification. While this is necessary to maintain a "one death one cause" approach, this presents challenges in attributing the "correct cause." The "correct cause" should link to public health solutions to prevent that death and follow consistent, transparent rules. Misclassification between causes of neonatal death is not well studied, [62] and may especially affect the infection and preterm categories.[63] Some conditions may be synergistic, for example infection and asphyxia and not fit well into the "one death one cause" approach.[76]

To minimise inconsistency, explicit case definitions and hierarchical coding rules are required. ICD 10 includes a companion volume which gives guidelines on mortality and morbidity coding.[7] There is a section entitled "Perinatal mortality: guidelines for certification and rules for coding" which includes an example perinatal death certificate with maternal details, and a few details on the baby. However gestational age is not mentioned since birth weight was considered higher priority than gestational age in ICD 10. These rules do not give an explicit hierarchy and the implicit hierarchy may not always be applied in practice. An analysis of 2378 neonatal deaths in Sweden (1987 - 1992) looked at death certificate cause-of-death reporting, allocating the deaths to causal categories in Wigglesworth[13] and ICE (Intrauterine death Classification according to Etiology) classifications. There was very poor agreement particularly for attribution to the preterm and "birth asphyxia" categories. Among 328 infants dying from "asphyxia" according to computerised Wigglesworth classification, ICE classified 59% as "asphyxia" and 22% were labelled immaturity. For deaths classified in ICE as being due to "asphyxia", the Wiggleworth classification matched in only 50% of cases. Among 792 infants

dying from immaturity according to the computerised Wigglesworth classification, 64% were classified as such by ICE.[63] The authors argue the need for an explicit hierarchy and also for computerised allocation to combined categories.[64]

The CHERG neonatal expert group reviewed hierarchal approaches for neonatal cause-of death attribution. Wigglesworth or adapted Wigglesworth categories were close to the categories selected by CHERG but there is not an explicit hierarchy and Wigglesworth is recognised to overestimate "asphyxia"[64] and implies a preference for "asphyxia" above immaturity by the order the cause are listed in. [13] For the CHERG work, the desired case definition for "asphyxia" will shift to intrapartum-related and will exclude preterm births, or at least severely preterm births, from the intrapartum-related category. Therefore a hierarchy must put the preterm birth direct complications above intrapartum-related deaths.

The group agreed that the NICE hierarchical classification (adapted from ICE) by the same Swedish group[65] was useful and had several important principles that all the CHERG consensus group agreed on such as placing congenital causes at the top of the hierarchy. However adaptation was required as NICE included stillbirths and also was much more focused on high income countries. For example, NICE does not mention tetanus and combines neonatal infections with preterm respiratory distress syndrome in a category called "specific infant conditions".

The conditions at the top of the hierarchy (congenital and neonatal tetanus) and also at the bottom ("Other neonatal", diarrhoea and sepsis/pneumonia) were straightforward to agree the order for. The main discussion centred on how to clarify the split for intrapartum-related neonatal deaths and deaths directly due to preterm. Given agreement on the case definition for "birth asphyxia" shifting to intrapartum-related neonatal deaths and excluding preterm births it was agreed that at least some of the preterm deaths should come before the intrapartum-related neonatal deaths. At one stage the case definition for direct complications of preterm births was proposed as 32 weeks completed gestational age but later changed to preterm was agreed as less than 34 weeks (approximately 2000 gms) based on the rapid increase in the incidence of respiratory distress or hyaline membrane disease under 34 weeks completed gestation in the absence of antenatal steroids and the relatively widespread use of 2000 gms as a standard cut off in the absence of gestational age data. Hence this case definition for preterm birth direct complications was put in the hierarchy above intrapartum related deaths. The resulting consensus for case definitions and hierarchy is shown in Table 4.1.

Table 4.1: Case definitions applied for neonatal cause-of-death in vital registration and study data, given in order of hierarchy to be applied

Cause-of-death group	Case definition used in VR and sought for study data	Case definition accepted in study data
Congenital abnormalities	Neonatal death due to major or lethal congenital abnormalities Specific abnormality listed E.g. neural tube defect, cardiac defect	Congenital abnormality or Malformation
Neonatal tetanus	Neonatal death due to tetanus	Spasms and poor feeding after age of 3 days
Preterm birth as a direct cause of death	Neonatal death due to one or more of the following: - Specific complications of preterm birth such as surfactant deficiency (Respiratory Distress Syndrome), intraventricular haemorrhage, necrotizing enterocolitis etc. - Immaturity (less than 34 weeks) at which level preterm specific complications occur for the majority of babies - Neonatal death with birth weight < 2,000 g where gestational age is unknown	'Prematurity' 'Very low birth weight'
Intrapartum-related ("birth asphyxia")	Neonatal death due to: - Neonatal encephalopathy with criteria suggestive of intrapartum events - Early neonatal death in a term baby with no congenital malformations and a specific history of acute intrapartum insult or obstructed labour	"Birth asphyxia" with Apgar-based definition but excluding preterm infants Fits and/or coma in the first two days of life in a term baby Acute intrapartum complications
Sepsis/ pneumonia	Neonatal death due to one or more of the following: - Sepsis/septicaemia - Meningitis - Pneumonia/ acute respiratory tract infection - Neonatal infection	'Neonatal infection'
Diarrhoea	Neonatal death due to diarrhoea	-
Other	Specific cause of neonatal death not included in first six selected causes, including: -Neonatal jaundice -Haemorrhagic disease of the newborn -Term baby dying due to in-utero growth restriction -Injury	Authors' grouping of "other" (as distinct from unknown)

Adapted from Wigglesworth[13] and NICE[14] using a hierarchical classification approach developed by expert group consensus with each of the conditions being sought in the order listed.
Note that for study input data the investigators may have applied their own hierarchy which may not be consistent with the one shown.

4.3 Case definitions and specific challenges in the estimation of intrapartum-related outcomes

4.3.1 Overview

"Birth asphyxia" is reported to be a major cause of global mortality and morbidity. Previous numbers from WHO range from 691,000 to 1.16 million neonatal deaths worldwide and are primarily based on a definition of "not breathing at birth".[41;66] In previous GBD estimates, linking severe neurological disability to these deaths produces one of the highest Disability Adjusted Life Years (DALYs) for any single cause in the GBD.[66] Accurate measurement of this burden is hindered by general factors, particularly the overwhelming lack of information for most of the world's stillbirths and immediate neonatal deaths, but also by factors specific to "birth asphyxia" including:

- Lack of consensus on case definition(s) and terminology for "birth asphyxia" and differences in use of terminology and criteria between high and low income countries;
- Complexity of attributing cause-of-death, particularly when multiple causation is common (e.g., 'asphyxia' and infection) and also multiple classification systems are in use which may have varying perspectives (obstetric, paediatric, pathophysiological);
- Difficulties with data collection for high income country case definitions in low income settings, e.g., the feasibility of identification and skilled examination of babies with neonatal encephalopathy (NE);
- Difficulty measuring impairment/disability, particularly in young children and complexity in attribution for causation of impairment/disability.

Before assessing strategies to address the burden of disease, it is necessary to clarify what we are trying to measure.

4.3.2 What do we want to measure?

Visibility of the problem and programmatic tracking are hampered by inconsistent terminology, the lack of an agreed definition, and the lack of standard measurement. The situation of a baby in poor condition at birth has been recognised from earliest times, and the terms and definitions have evolved over time, driven both by a greater understanding of the pathophysiology and clinical manifestations, but also by increasing litigation in high-income countries. The need for a more sensitive and specific diagnosis of very soon after birth has recently gained importance because of the possibility of intervention using therapeutic hypothermia.

The word "asphyxia" is based on a Greek word meaning "pulseless" and is applied to a combined hypoxia (low levels of oxygen) and metabolic acidosis. However, the term "birth asphyxia" has no agreed scientific definition, partly because there is no direct, simple measure

of “asphyxia” for the fetus *in utero* or the baby at birth.[67] Asphyxia has been commonly assumed to imply hypoxia in the fetus due to inadequate care during labour and/or delivery, but the term is most frequently applied as a clinical description of an infant who does not breathe spontaneously at birth. This assumption confuses the clinical state with an assumed causation and with subsequent outcomes. The newborn baby may not be breathing for many reasons. The range of possible outcomes is equally wide, including death, irreversible brain injury and normal survival.

Case definitions differ depending on the purpose. At the *individual level* of clinical care, the delivery attendant and other health care providers require a sensitive case definition to identify individuals who may be at risk, in order to manage the pregnancy, birth, or clinical care and follow-up as safely as possible. At the *population level*, public health decision makers, epidemiologists and researchers require a specific case definition to ensure comparability of the selected outcome over time or place, and in controlled trials. Case definitions should take into account the purpose of identification and be appropriate to the capacity of the caregivers. For example, if clinical care at birth in the community is the purpose, then the “non-breathing baby”, or “not crying at birth” may be the most appropriate definition.

For some conditions, using a sensitive clinical case definition as a surrogate instead of a specific public health definition is possible, particularly if the clinical case definition is also fairly specific. For example, neonatal tetanus has distinctive clinical symptoms and the clinical case definition works well for tracking at population level. In contrast, for the condition colloquially referred to as “birth asphyxia”, the clinical definition of not breathing at birth must be sensitive as the consequences for missing a case could rapidly be fatal, yet these symptoms are not specific for a given causation. The baby who is not breathing at birth has not necessarily experienced a major intrapartum insult – the baby may well be preterm, or could have a major congenital abnormality. Hence interchangeable use of the sensitive clinical case definition (e.g. Apgar score) with a specific epidemiological one results in major differences in attribution and potentially misleading programmatic implications.

Three consensus statements addressing terminology and diagnosis of “birth asphyxia” have been released since 1996. All three statements have recommended that terms such as “birth asphyxia”, “perinatal asphyxia”, “fetal distress”, “hypoxic-ischaemic encephalopathy” or “post-asphyxial encephalopathy” should not be used unless some evidence specific to acute intrapartum events is available.[68-70] In view of this we use inverted commas for these terms. Table 4.2 summarises these consensus statements.

Table 4.2 Summary of consensus statements regarding the diagnosis of "birth asphyxia"

	American Academy of Pediatrics with American College of Obstetrics & Gynecology[68] (1996)	International Cerebral Palsy Task Force[69] (1999)	American College of Obstetrics & Gynecology[70] (2002)
Essential criteria	- Neonatal encephalopathy - Multi-organ dysfunction - Apgar score $\leq$ 3 after 5 mins - Metabolic acidosis (pH<7.0)	- Neonatal encephalopathy (moderate or severe) - Metabolic acidosis (pH<7.0 and base deficit $\geq$ 12 mmol/L) - Cerebral palsy of spastic quadriplegia or dyskinetic type	- Neonatal encephalopathy (moderate or severe) - Metabolic acidosis (pH<7.0 and base deficit $\geq$ 12 mmol/L) - Cerebral palsy of spastic quadriplegia or dyskinetic type - Exclusion of other pathological causes of cerebral palsy
Criteria suggestive of intrapartum timing	- Criteria suggestive of intrapartum timing	- Sentinel event - Abrupt change in fetal heart rate - Apgar score $\leq$ 6 after 5 mins - Multi-system involvement - Imaging evidence	- Sentinel event - Abrupt change in fetal heart rate - Apgar score $\leq$ 6 after 5 mins - Multi-system failure in first 72 hours after birth - Imaging evidence

The recommendations remain broadly the same across the three statements but in each case the criteria have become more restrictive (Table 4.2). The emphasis is to diagnose in a syndromic fashion with essential criteria primarily based on evidence of NE (i.e. abnormal neurological behaviour such as convulsions, coma) instead of low Apgar or perinatal depression at birth. Other causes of NE should be excluded such as central nervous system malformations or metabolic abnormalities. Additional criteria are required to assess the likelihood of intrapartum timing such as history of a sentinel event (e.g. antepartum haemorrhage), prolonged low Apgar score, multi-system involvement and imaging evidence. In the intervening years since the 2002 statement the published studies place increasing emphasis on complex imaging or electrographic techniques.[71;72]

Neurological damage in the preterm infant has a different pattern and may be particularly related to injury after delivery.[73;74]All these consensus statements refer to term infants although there is not yet a clear consensus if all preterm infants (<37 weeks gestation) or very preterm infants (<34 weeks) or some intermediate cut off (e.g. 36 weeks) should be applied.

These consensus statements are primarily designed to clarify difficult medico-legal issues when determining cause and liability for cases of perinatal brain injury in North America and other settings where inadequate obstetric care or resuscitation is a dwindling cause of NE. Even in these settings where extensive investigation is available, the origin of the presumed hypoxic event is often unresolved.[72] There is little doubt that the approach in the 19th and early 20th century over attributed deaths and cerebral palsy to “birth asphyxia”. Little implied that most cerebral palsy cases could be attributed to “birth asphyxia” brain damage whereas more recent work particularly from Nelson et al in the US and Stanley and Blair et al in Australia suggest that perhaps less than 20% of children with spastic cerebral palsy had evidence of asphyxia and in less than half of these was the perinatal insult judged to be causative.[75-78]

Currently there is a dichotomy whereby the low mortality countries have moved to a more restrictive syndromic diagnosis based on NE, yet most low income, high mortality countries and indeed researchers and UN policymakers and even the Burden of Disease continue to use the term “birth asphyxia” and in many cases use this term interchangeably for the baby not breathing at birth and the epidemiological causation of intrapartum injury. The more specific approach presents many challenges in application in the settings where the vast majority of deaths related to acute intrapartum events occur. For most of the world’s 130 million births, emergency obstetric care and neonatal resuscitation are the exception and the major outcomes related to intrapartum emergencies hence intrapartum stillbirths and neonatal deaths *before* the onset of NE are a large proportion of the burden. For those babies who do survive to develop NE, the consensus statement would require evidence of NE (necessitating a high level of

clinical skill), fetal acidaemia (necessitating blood gas analysis and all that this entails) and exclusion of other causes of NE (requiring metabolic assessment). This case definition would be hard to apply even in teaching hospitals in much of South Asia and Sub Saharan Africa.

The rest of this chapter presents a brief discussion of the underlying causal pathways in intrapartum insults and then provides a conceptual framework and case definitions for defining and measuring outcomes related to acute intrapartum events, particularly focusing on how to advance to more specific and yet feasible measurement in low or middle income countries. The chapter concludes with a recommended case definition for use in mortality estimation.

4.3.3 When and what causes the insult?

The successful transition of the newborn baby from life in-utero to life at birth is based on a complex balance of the health of the mother, the course of the pregnancy, and the process of delivery. During normal labour, the fetus will experience hypoxia but is able to tolerate this remarkably well. Problems occur if there is severe or sustained lack of oxygen to the fetus, which may occur before, during or after labour. Studies in industrialised settings give varying estimates for the proportion of NE in term infants which occurs during intrapartum ranging from very low levels in some studies[79;80] to much higher levels in other more recent studies using MRI scanning. For example one large study in the UK found that 197 of 351 term babies with NE had MRI evidence of an acute intrapartum insult.[72] Reviews suggest perhaps 10% of cases the injury may occur postnatally.[74;77] However, even in high income countries many questions remain unanswered. The proposal of causal web analysis to take into account co-existing antenatal and intrapartum factors has been an important advance in understanding.[81;82] Studies assessing the timing of insult are not available from low income country settings, but it is likely that intrapartum causes account for a larger proportion, given the higher incidence of serious complications in labour and reduced availability of skilled care during delivery.[83]

The initial hypoxic injury precipitates a derangement of cellular energy metabolism, which may initially be reversible. If hypoxia continues or if the initial insult was very severe and acute, however, then acidosis and depletion of cellular energy precipitate an irreversible cascade of cellular damage, resulting either in death or in typical patterns of brain injury such as parasagittal necrosis in the term infant.[74] Delayed cell death is linked to increasing cerebral oedema, which explains the clinical picture of the baby who appears stable after resuscitation and then after 4-6 hours begins to convulse, showing the typical features of NE. Although all the major systems may be injured, the brain is more susceptible to injury, and is less likely to recover. Thus, the most significant effect of severe hypoxia is on the fetal/neonatal brain. The degree of injury to the baby varies with the nature of the insult (severity and length), and the vulnerability of the baby. For example, preterm babies are more susceptible than term babies to

severe injury and death following hypoxia. In addition, the growth restricted fetus who has experienced chronic hypoxia related to placental insufficiency during pregnancy is at greater risk of further damage from superimposed acute hypoxia at the time of birth. Maternal infection is apparently synergistic with a hypoxic insult.[84]

Insult may result from a variety of factors and which may be acute, or chronic or acute-on-chronic as follows:[85]

1. Interruption of the umbilical circulation (e.g., cord compression, cord prolapse, knot in the cord);
2. Altered placental gas exchange (placenta praevia, placental abruption or insufficiency, abnormal/prolonged uterine contractions);
3. Inadequate maternal perfusion of the placenta (maternal hypertension or hypotension);
4. Failure of newborn respiration during transit from fetal to neonatal life (e.g., the effect of maternal anaesthesia).

Causation can be considered in terms of causal pathways, an approach which has been applied to the aetiology of cerebral palsy.[81;82] Each pathway consists of a network of factors, and prevention of a necessary factor high up the network may prevent the condition. However, given the possible combinations of timing of multiple insults, it is clear that there is much we do not yet understand, especially given the high level of antepartum factors such as maternal malnutrition and maternal infections in the settings where acute intrapartum events are also common.[84] The important programmatic message from a causal pathway approach is that prevention is more effective if the major initiating factors are addressed. For example a larger impact would be expected from improved maternal health and healthcare, rather than from neonatal resuscitation or care of the neonate with encephalopathy.

Birth trauma as a direct cause-of-death is rare compared to the direct effect of hypoxia on the brain, but is included in the same group of death for programmatic reasons. The analysis in this thesis of vital registration data for 45 countries suggests that hypoxic brain injury is about 100 times more common than birth trauma as a cause-of-death. While injuries such as fractures and nerve palsies are not uncommon, fatal trauma such as organ rupture is rare. It may be argued that birth trauma is expected to be a larger problem in countries without vital registration where obstetric care is limited. However, a number of studies from less developed countries also suggest that birth trauma is an infrequent primary cause-of-death, and the death is more often due to associated hypoxic injury to the brain.[86-89]

4.3.4 Defining intrapartum-related fetal and neonatal outcomes

There are 3 clusters of terms for intrapartum-related measurement including:

- Measures of abnormal obstetric process, such as 'fetal distress';
- Measures of the clinical condition of the neonate at birth, such as the Apgar score; and
- Outcomes for the fetus or neonate, such as death, acute morbidity (NE) or disability.

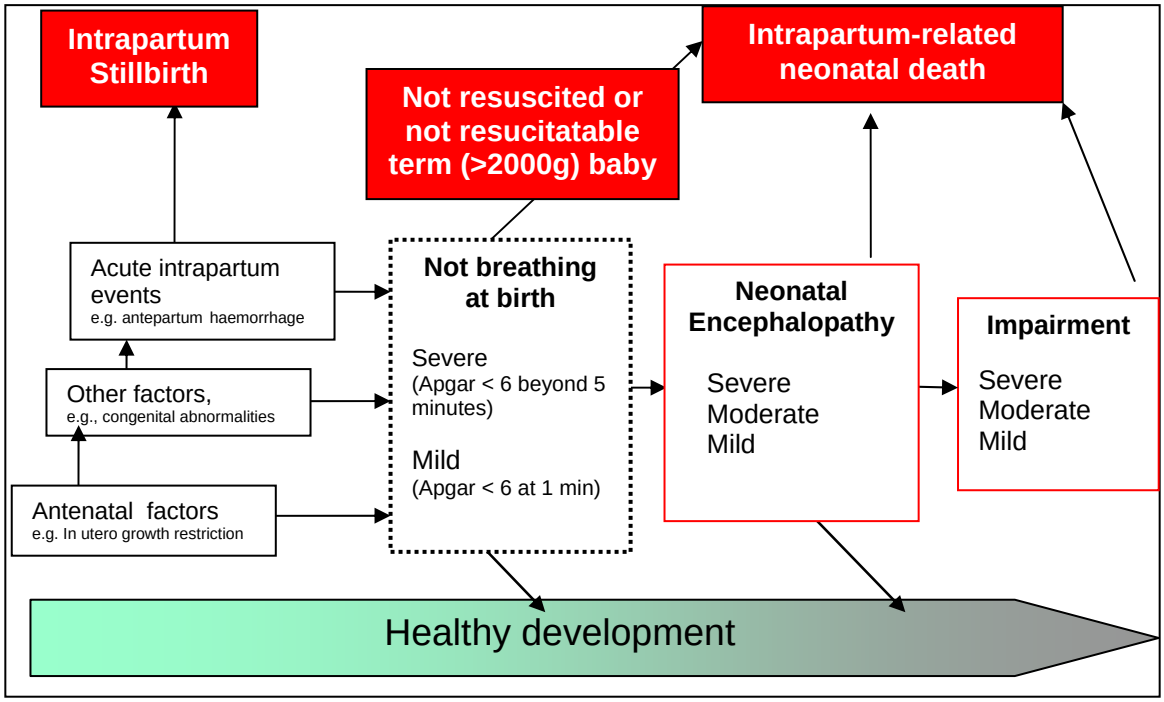
Unfortunately there is no sensitive and specific measure of the obstetric process. The surrogate measures applied in high-income countries, such as fetal heart monitoring or fetal blood gases, are not specific[90] and are not likely to be applicable to most of the world's deliveries in the near future. Similarly, measures of the clinical condition of the neonate at birth such as the Apgar score were intended to identify the infant requiring resuscitation, not to measure the burden of disease due to a specific cause. Hence, of several hundred articles examining the Apgar score, there is no clear conclusion regarding long term prognostic value.

Given the complexity and limitations of measuring an abnormal intrapartum process involving hypoxia a more feasible approach is to focus on specific morbidity, mortality or disability outcomes with standard case definitions. Furthermore, these outcomes will be directly relevant to programmes involving improved intrapartum care, and so there will be more motivation to collect the data. Figure 4.1 is a simplified disease model depicting the major conditions and outcomes for the fetus and neonate that are associated with the intrapartum period and contribute to the disease burden. These include:

1. Intrapartum stillbirths;
2. Neonatal encephalopathy
3. Neonatal deaths including:
    - the newly born live infant who cannot be resuscitated/no resuscitation is available (excluding lethal congenital malformations and preterm birth (less than 28 weeks or 1000 g));
    - neonatal death as a sequela of NE;
4. Neurological disability as a sequela of NE.

The case definitions for these conditions are detailed in Table 4.3, along with the relevant ICD 10 codes, and the next section of this chapter then covers the measurement for each.

Figure 4.1. Adverse intrapartum-related outcomes for the fetus and neonate



The case definitions for these conditions are detailed in Table 4.3, along with the relevant International Classification of Diseases version 10 (ICD-10, 1992) codes

Table 4.3 Case definitions for intrapartum-related outcomes for the fetus and neonate

Outcome	Case definition	ICD-10 codes (4 digit)
Intrapartum stillbirth	Fresh stillbirth The birth of a fetus after 28 weeks of gestation/weighing >1000 g and showing no signs of life, and which has intact skin, and is assumed to have died less than 12 hours prior to delivery	P017 to P019 , P030 to 039 (specific obstetric complications) P95 covers fetal death unspecified
Severe respiratory depression at birth	A newly born infant that does not breathe at birth, and has an Apgar at 5 minute of 6 or less Note that the causes are broader than intrapartum factors	P210 to P219
Not resuscitatable at time of birth	A newly born infant who shows signs of life (such as heart beat) and cannot be successfully resuscitated or no resuscitation is available, but excluding severe congenital abnormalities and gestational age <34 weeks (or birth weight < 2000g)	P200 to P209 P210 to P219 P030 to 039, P017 to P019 (specific obstetric complications)
Neonatal encephalopathy	Neonatal encephalopathy is "a disturbance of neurological function in the earliest days of life in the term infant manifested by...abnormal level of consciousness and often by seizures"[91] Classified as mild, moderate and severe. For a diagnosis of intrapartum-related NE, other causes (e.g. metabolic) should be excluded Exclusion of preterm birth is recommended but there is no clear consensus on the cut off with a range of 34 to 37 weeks gestation applied.	P210 to P219 P910 to P919
Death following neonatal encephalopathy or birth injury or meconium aspiration	A live born infant who dies following neonatal encephalopathy related to acute intrapartum events	P210 to P219: Hypoxic ischaemic encephalopathy P100 to P150: Birth injury P240: Meconium aspiration
Neurological disability following neonatal encephalopathy	Severe disability: presence of major impairment (such as cerebral palsy, hemiplegia, diplegia) with or without blindness, deafness and/or moderate/severe mental impairment (IQ < 70) Mild disability: learning disability, vision or hearing impairment	International Classification of Functioning, 1999

References: ICD-9 and ICD-10, ICF 1999
Fenichel et al [91]

4.3.5 Measuring intrapartum-related outcomes

The key intrapartum-related measurements for the fetus and baby can be considered by time period (before birth, at birth, after birth and after death), and are summarised in Table 4.4, and then discussed in more detail in each case considering the definition, its usefulness and feasibility in low income settings especially at community level. Recognition of fetal distress is clearly crucial for obstetric intervention but detailing the possible measurement options is not within the remit of this thesis, and the focus will be on mortality and major morbidity outcomes that have implications of relevance for measurement intrapartum related neonatal deaths.

Table 4.4 Methods to recognise and measure intrapartum-related outcomes for fetus and neonate

Timing of identification	Method to define or measure
1. Before birth	▪ "Fetal distress" ▪ Meconium staining of the liquor
2. At birth	▪ Stillbirth (specifically fresh stillbirth)* ▪ Recognition of one or more simple clinical characteristics (e.g., not crying or not breathing)* # ▪ Apgar score
3. After birth	▪ Neonatal encephalopathy score#
4. After death in community	▪ Verbal autopsy#
5. After hospital discharge or death	▪ ICD codes in Vital Registration data ▪ Post mortem
6. During infancy/childhood	▪ Identification of asphyxia-related disability#

*Methods likely to be useful and feasible for regular use at community level
Methods likely to be useful for research studies, possible scope to simplify more for routine use

At birth

Intrapartum or 'fresh' stillbirth

Definition: A stillbirth is a baby who shows no signs of life at delivery and weighs more than 1000 g or is greater than 28 weeks gestation. A fresh stillbirth is a stillborn baby that has intact skin and is assumed to have died less than 12 hours prior to delivery. The single most likely cause of fresh stillbirth is intrapartum hypoxia.

Usefulness: Intrapartum stillbirths are more frequent than intrapartum-related neonatal deaths, especially in settings with limited emergency obstetric care. Intrapartum stillbirths and

intrapartum neonatal deaths are closely linked in terms of measurement through misclassification, but also in terms of programmatic solutions.[51] A mature fetus dying during childbirth is usually considered to be a preventable death.[12;92-95] Hospital-based studies suggest that 25–62% of intrapartum stillbirths are avoidable with better obstetric care and more rapid responses to intrapartum complications, including reducing delays at home and in transportation. The fresh stillbirth rate for babies weighing ≥2000 g has been proposed as a surrogate indicator for intrapartum stillbirths.[89;96] In high mortality settings the fresh stillbirth rate probably underestimates the true rate of intrapartum stillbirths since with poor access to obstetric care, labour lasting more than 24 hours is not infrequent and the labour in excess of 12 hours usually results in a macerated stillbirth.[89] Conversely, a small proportion of fresh stillbirths may be due to non-hypoxic causes (undetected congenital abnormalities or severe infection). Studies have identified few fresh stillbirths due to causes other than asphyxia.[97-99] The extent of such misclassification biases, or of the misclassification between fresh stillbirths and intrapartum-related early neonatal deaths cannot be quantified without further study.

Feasibility: In an institution providing childbirth services recording all intrapartum stillbirths is a feasible measure[100] and indeed a basic outcome to include on the labour ward register and to compile regularly. In practice, however, there are a number of barriers to feasibility that are magnified at community level. One issue for accuracy is that of distinguishing a stillbirth from an early neonatal death. According to the definition of stillbirth, if the baby has any sign of life (such as a heart beat) at the time of delivery, and then dies even within a few minutes, the death should be classified as an early neonatal death.[2] In reality, especially in low resource settings, a subtle sign of life may be missed even in hospital settings and an early death may be considered as a stillbirth, or socio-cultural factors and possibility of blame may lead to systematic misclassification. An important influence on the recognition and counting of stillbirths are the multiple taboos that surround the subject, particularly in traditional cultures. The mother may be given little if any information by health care workers or traditional birth attendant (TBA), who may fear blame. Sometimes the health workers believe that the mother will handle the loss better if she is told the baby was already dead at birth. For example, TBAs in Bangladesh report that they prefer to tell the mother the baby died inside her in cases of failed resuscitation even if the infant showed signs of life at birth (Ellis M, personal communication). The relatives and the mother may also deny the occurrence of a stillbirth for fear the admission may evoke spiritual forces that will eventuate in a recurrence. Especially where health information is based on retrospective surveys of mothers, this could lead to significant under-estimation, although this has not been well studied. In addition, those late fetal deaths where the mother was a maternal death will be invisible in surveys of surviving women.

Recommendation: Efforts must be made to count stillbirths, particularly intrapartum stillbirths.[89] These deaths constitute the largest burden of mortality due to acute intrapartum events in low income countries – an estimated 1.02 (0.66-1.48) million a year.[51] As care during delivery improves, historical data have shown that the babies who no longer die as stillbirths may then present as early neonatal deaths, before care improves enough for them to survive. If the stillbirths are not recorded then programmes will first record a rise in early neonatal deaths and miss the reducing stillbirths.[8] Stillbirths should be included in mortality surveys, and verbal autopsy tools covering neonatal deaths should include stillbirths, further evaluate causal categories and particularly develop strategies to minimise misclassification between intrapartum stillbirths and neonatal deaths.

Recognition of one or more simple markers of "poor condition at birth", such as no cry or not breathing.

Definition: The definition would depend on the chosen characteristic(s). The simplest and most frequently used are "not breathing at birth" and "no cry at birth".

Usefulness: The simplicity of this approach results in a sensitive rather than specific assessment, which is appropriate for the decision to resuscitate but less so for epidemiological measurement. While there are descriptions of this approach at community level using village health workers and TBAs,[101;102] no literature was identified which formally assessed the positive predictive value of these simple markers for the need for resuscitation. Certain characteristics, such as no cry at birth have been evaluated in validation studies of neonatal verbal autopsy for assigning causes of death in the community are summarised in Table 4.5.[52;103;104]

Feasibility: These methods are the simplest approach and may be the most likely to work for a community health worker (CHW) or TBA. However, this has not been formally assessed. Table 4.5 summarises the studies that have applied these simple methods of identification. In low resource settings, simple methods of recognition of the individual baby requiring resuscitation (e.g., not breathing, no cry, floppy) generally are more likely to be effective and result in early action than more complex scores. More research is required to assess which clinical markers are sensitive and yet feasible to recognise.[102]

Recommendation: Simple clinical identification is appropriate for clinical care, although it is possible that if every baby who did not cry at birth was resuscitated, significant harm may come to some unnecessarily resuscitated, so evaluation is required. These simple indicators alone are not helpful for epidemiological definition of cause-of-death, although they have may be useful in programmatic action or a place as part of an algorithm in a verbal autopsy tool. Indeed these are the only criteria used in some VA studies.

Table 4.5 **Identification at community level of "birth asphyxia" for the purpose of resuscitation**

Method of identification	Place	User	Number of cases	Usefulness of method
No cry	Rural Gambia (Leach A et al 1999) [104]	Mothers, TBAs, nurses, doctors	1254 neonatal deaths	Good predictor of neonatal death but not specific for "birth asphyxia" Sensitivity= 36% Specificity= 99% PVV =60%
Assessment based on one or more of: - Delayed/absent cry - Delayed absent breathing - Irregular/shallow breathing - Limp/less active - Blue/pale/white	Community-based project in Haryana State, India (Kumar R 1995)[102]	TBAs	53 of 1977 births	Sensitivity/specificity not formally assessed Apparently feasible to apply although has as many components as the Apgar score
Assessment based on one or more of: - Cry - Breathing - Colour - Activity - Reflex response - Cord pulsation - (each scored 0, 1, or 2 by pre-set criteria similar to Apgar)	Validated in a hospital setting (Ghosh D et al 1997)[105]	Researchers. Score validated against Apgar and cord pH.	62 newborns with 1 min Apgar < 6.	A combination of cry, colour and activity was the best predictor of metabolic acidosis (r = 0.38, P< 0.1, Correlation coefficient = 0.71) Complex to apply - at least as complicated as the Apgar scoring and requires skills e.g. to assess cord pulsation

TBA: Traditional birth attendant

Note: No studies were found which assessed 'not beathing' or 'floppy' as single identifiers**.**

Apgar score

Definition: The physical condition of the baby is traditionally recorded as the Apgar score. Virginia Apgar, an American anaesthesiologist, described this score in 1953, providing a standard record of the condition of the infant at birth, including breathing, heart rate, colour, muscle tone and response to insertion of a suction catheter (Table 4.6). Each of these 5 characteristics is given a score of between 0 and 2 by a trained observer, giving a maximum score of 10. In reality the maximum at 1 minute is 9 as virtually all babies will still have blue extremities at this point. The score recorded is a total for the baby's condition at 1 minute and at 5 minutes, and was intended to improve comparability of condition at birth, and speed the commencement of resuscitation when required. In addition, Professor Apgar hoped that the score would reduce unnecessary manipulation of the healthy newly born infant.[106;107] The most commonly applied categories are as follows:

- severe or "white asphyxia" with a 1 minute Apgar of 0-3;
- mild/moderate "asphyxia" with a 1 minute Apgar of 4-7;
- severe respiratory depression at birth with an Apgar still less than 6 after 5 mins

Table 4.6 **The Apgar Score**

Characteristic	Score 0	Score 1	Score 3
Heart rate	0	$\leq$ 100	> 100
Respiration	No respiration	Gasping or irregular	Regular or clear cry
Muscle tone	Limp	Reduced tone/normal tone but reduced movement	Normal with active movements
Response to pharyngeal catheter	No response	Grimace	Cough
Colour of trunk	White or blue	Pink with blue extremities	Pink

Reference: Apgar V 1957[88;]

Usefulness: The Apgar score is widely used, and also widely abused, both in terms of inaccurate assessment (simply giving a number out of 10 rather than scoring by each characteristic) and in terms of over-interpretation of results.[68] There are other causes of a low Apgar score apart from acute intrapartum events, including preterm birth and influence of maternal drugs, especially opiates and anaesthesia. The score was not designed as a predictor of outcome, and even if applied correctly, the correlation with outcome is limited apart from extreme cases such as a baby who has a score of zero at birth[108] or a very low score at 20 minutes of life.[109;110] Neither is

the 1–minute Apgar score a good predictor of later disability; in one study, only 12% of 99 children with a 1 minute Apgar <3 developed cerebral palsy.[111] On the other hand, a recent assessment of 151,891 births found that a 5-minute Apgar of < 3 in term infants was strongly predictive of death (RR 1460, 95% CI 835 - 2555). [112] The best use of a low 1-minute Apgar score (< 3) may be as a screening test for development of early complications, notably NE, with a negative predictive value of 99.9%, despite a sensitivity of only 14%.[113]

Feasibility: Even with highly trained staff in teaching hospitals, the Apgar score is often scored incorrectly. The score is unlikely to be realistic or useful for CHWs.

Recommendation: Apgars may be applicable at peripheral health centre level as a criterion for transfer to a higher level of care, where this is feasible. [105] For example urgent transfer of all babies with a one or five minute Apgar of < 3 once they are stable enough for transfer. [113] Apgar scoring may well have a role at institutional level as a marker of condition at birth, but quality assurance in application of the score is required.[114] Early Apgar scores (<10 mins) do not have a high positive predictive value for the later onset of developmental disability. Late Apgar scores are useful (20 mins +) but should be augmented with systematic assessment of NE in survivors. [113]

After birth

Neonatal encephalopathy (NE)

Definition: "A clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often by seizures", which may follow an intrapartum hypoxic insult or be due to another cause.[115] The principle is of an "abnormal neurobehavioral state" starting in a term infant within 24 hours of birth. [91] In the 1970s, the term Hypoxic Ischaemic Encephalopathy achieved wide usage, referring specifically to NE due to perinatal asphyxia although it is frequently used as if Hypoxic Ischaemic Encephalopathy were directly equivalent to NE. NE is preferred now, in view of the possibility of other causes of NE and the difficulties in establishing definitive causation.[116] NE may have several causes, including infection, jaundice and hypoglycaemia, so perinatal hypoxia is not the exclusive cause.[117]

There are several systems for categorising NE. Three categories of mild, moderate and severe were delineated by Sarnat and Sarnat[118] and developed into clinical criteria by Fenichel. [91] Table 4.7 outlines a grading system for NE, and adapting from Sarnat,[118] Fenichel,[91] Badawi[119] and Ellis.[120] The Apgar score and the clinical scoring systems for NE do not apply to preterm infant

as their neurological immaturity affects the scoring so this scoring system assumes exclusion of preterm infants although there is no clear consensus if all preterm infants (<37 weeks gestation) or very preterm infants (<34 weeks) or some other interim gestational age level should be excluded.

To assign the grade, the infant is assessed daily during the first week of life, or until death or recovery if this is sooner. The grade assigned is the highest reached. An alternative approach developed in Cape Town by Thompson et al scores the infant according to a set of criteria derived from Fenichel.[70] A comparison of the grading and scoring systems suggests both have similar predictive qualities and the key aspect is the careful daily examination of infant's neurobehavioural state.[120]

Table 4.7 Clinical staging system for neonatal encephalopathy

Clinical finding	Mild (Stage 1)	Moderate (Stage 2)	Severe (Stage 3)
Conscious level	Irritable / hyper-alert	Lethargic	Comatose
Tone	Mildly abnormal (Hypo- or hyper- tonic)	Moderately abnormal (hypotonic or dissociated)	Severely abnormal (hypotonic, flaccid)
Suck	Reduced	Poor	Absent
Seizures (EEG)	Absent (normal)	Present (periodic or paroxysmal)	Frequent (periodic or isoelectric)
Respiration	Rapid (< 60 /minute)	Occasional apnoeas	Severe apnoea
Primitive reflexes	Exaggerated	Depressed	Absent
Brainstem reflexes	Normal	Normal	Impaired
Duration	< 24 hours	2 – 14 days	Days to weeks
Severe adverse outcome following post-asphyxial NE (%)	0 (5 studies, 52 cases)	24 to 67% (6 studies, 118 cases)	94 – 100% (5 studies, 72 cases)

Notes: Primitive reflexes refer to moro and grasp. Brainstem reflexes refer to gag and corneal reflex
Adapted from Sarnat[118] Fenichel [91], Badawi[119] and Ellis.[120]
Severe adverse outcome defined as death, cerebral palsy or cognitive impairment 2SD below norm, from Pin et al [121]

Usefulness: There is a wide literature assessing various scores for Hypoxic Ischaemic Encephalopathy, and a growing number of studies for NE. A recent review of screened 3152 publications regarding NE but was only able to included 13 studies in a systematic analysis to examine outcomes in term infants with post asphyxial NE. All these studies are from

industrialised countries. All the infants with Stage 3 (mild) NE survived intact, whereas 94 to 100% of neonates with Stage 3 (severe) NE died or were severely impaired.[121] NE is more prevalent and more severe in low income than in high income countries.[120;122] There are limited data on survival by NE grade for low income countries. While NE scores have been shown to be the most accurate predictor of long term outcome, particularly death and disability,[121] they are not performed for the first time until later on the first day of life, or on subsequent days, and so are not useful to guide initial resuscitation or early management. A new incentive to improve early detection of injury is the possibility of instituting therapeutic hypothermia,[123;124] an intervention which also has the potential for a for use in low income settings.[125]

Feasibility: The advantage of NE scoring is that no technical investigations are required, but a degree of skill is necessary that is likely to be found only in hospitals, possibly even only in referral hospitals in low income settings. The only literature regarding the use of scoring systems for NE in low income countries is from teaching hospitals in Nepal[126] and South Africa.[122] While this may be the most accurate method, the current scoring systems are too complex for routine use by CHWs. A skilled attendant should be able to apply this score if trained to do so, as it is potentially less complex than the partogram (which is considered a norm for use by all midwives) and definitely more predictive of outcome than the Apgar score.

Recommendation: More research is required, both for feasibility for accurate scoring, but also re usefulness in management decisions. Scores for NE are unlikely to be feasible for use by TBAs and CHWs in most settings, and it may also be argued that babies with recognizable NE and convulsions should be cared for in an institution, so such a score is not relevant at community level. Further research is required to validate simpler NE scoring systems, particularly without primitive reflexes. In addition further research is required to incorporate some of the more specific symptoms and signs used for NE scoring into VA tools to see if specificity of verbal autopsy diagnosis of intrapartum neonatal deaths could be improved.

Additional high technology methods

There are technological approaches, such as MRI scans, that have been shown to be sensitive in detecting early neurological damage.[71;72] However, these are unlikely to be of relevance to most neonates in low income countries and will not be covered here.

After death in the community

Verbal autopsy

Definition: A verbal autopsy (VA) is an assessment tool used to assign cause-of-death after the event, using information collected from the family, community and, possibly from the health care system.[127] VA relies on recognizable clinical features which can if necessary be reported by family or lay workers.[128;128] VA tools vary from very simple to long, complex questionnaires. Several neonatal cause-of-death VA tools have been developed, mainly since the mid 1990s.

Usefulness: Due to overlapping signs with neonatal tetanus, pneumonia and septicaemia, sensitivity and specificity remain only moderately high when compared to hospital diagnosis (Table 4.8). To date most VA studies to date have used a non-specific definition for "birth asphyxia" such as "not breathing at birth" and very few such studies have added convulsions to the case definition or specify the hierarchy used with some recent exceptions published after the input data used in this thesis was finalised.[56;99] Recent analytical work comparing varying hierarchies, particularly between "birth asphyxia" and preterm birth highlights the potential overlap or co-morbidity issues and the large effect on proportionate mortality from changes in the hierarchy.[129;130]

Feasibility: In many settings where the majority of fetal and neonatal deaths occur at home, this approach is the only feasible manner to collect information on cause-of-death. However, the assessment is costly and time consuming and is usually restricted to research studies or Demographic Surveillance Sites. In addition, some familiarity with the VA tool and with the underlying clinical problems of the fetus and neonate is required, although well-trained and supervised CHWs may be capable of administering the questionnaire. There are a variety of tools in use and under development and there is a need for a standard tool[131;132] with algorithms that follow ICD rules to apportion underlying cause-of-death and so are as comparable as possible with VR data, given the limitations of both.

Table 4.8 Performance of neonatal verbal autopsy for assigning "birth asphyxia" as a cause-of-death

Condition	Sensitivity (%)	Specificity (%)	Number of cases (hospital reference)	Country/ reference
"Birth asphyxia"	58	78	52	Pakistan Marsh et al
	87	69 (72) [a]	19	Bangladesh Kalter et al

[a] Exclusion of neonatal tetanus added to algorithm/hierarchy

After hospital discharge/death

ICD codes for "birth asphyxia"

Definition: ICD codes for "birth asphyxia" have changed with time, as summarised in table 4.9. There are over 5000 codes in detailed ICD10 coding that can be applied to neonatal deaths, and 139 of relevance to 'birth asphyxia.' The tendency has been to add more codes, or more detail to existing codes for example using the fourth digit. The last revision was published in 1993 and did not reflect as shift towards a syndromic diagnosis – neither HIE nor NE are listed. Indeed "birth asphyxia" categorised as severe, mild/moderate or unspecified which is not the approach recommended in recent consensus statements. Coding to the intrapartum sentinel event or even to maternal risk factors such as pre-eclampsia is also catered for. Birth trauma also has a long list of codes, although in reality this is a rarer direct cause-of-death (Chapter 5).

Table 4.9 **Changes in ICD codes of relevance for "birth asphyxia"**

ICD version	Code
ICD-8	**776 Anoxic and hypoxic conditions not elsewhere classified** 776.3 Foetal distress 776.4 Intra-uterine asphyxia 776.9 Asphyxia of newborn unspecified
ICD-9 (1975)	**768 Intrauterine hypoxia and birth asphyxia** 768.0 Fetal death from asphyxia/ anoxia before labour or unspecified time 768.1 Fetal death from asphyxia or anoxia during labour 768.2 Fetal distress before onset of labour, in liveborn infant 768.3 Fetal distress first noted during labour, in liveborn infant 768.4 Fetal distress unspecified as to time of onset, in liveborn infant 768.5 Severe birth asphyxia 768.6 Mild or moderate birth asphyxia 768.9 Unspecified birth asphyxia in liveborn infant
ICD-10 (1993)	**P00.0- P05.0** P00.0 – P04.9 Maternal antenatal conditions e.g. pre-eclampsia P05.0 – P05.9 Maternal intrapartum events e.g. obstructed labour, haemorrhage **P10.0- 15.9 Birth injury** P10.0-1.09 Sudurals and other interracial head injuries P11.0 – 159 Specific bone and nerve injuries **P20.0 – 20.9 Intrauterine asphyxia** P20.0 Intrauterine hypoxia before the onset of labour P20.1 Intrauterine hypoxia first noted during labour and delivery P20.9 Intrauterine hypoxia unspecified **P21.0- 2.20 Birth asphyxia** P21.0 Severe birth asphyxia P21.1 Mild or moderate birth asphyxia P21.9 Birth asphyxia unspecified P240 Neonatal meconium aspiration syndrome **P90.0 – 91.9 Acquired neonatal cerebral ischemia** P91.0 Neonatal cerebral ischaemia P91.9 Neonatal coma unspecified

References: ICD8, ICD-9 and ICD-10

Usefulness: Accuracy of cause-of-death in VR requires an unbroken chain from correct diagnosis at death, accurate filing of the death certificate particularly the line regarding underlying or main cause-of-death, correct coding of the information, and accurate categorization of this detailed cause into a group cause of relevance to programmes. The usefulness will depend on consistency and appropriate coding, avoiding the more nebulous codes some of which are symptoms an could be considered "garbage codes".[133]

Feasibility: ICD codes are most feasible in countries with high coverage of VR, currently only 46 countries, covering less than 3% of neonatal deaths. Even in transitional countries with higher rates of VR, perinatal death certificates around the year 2000 were more likely to be coded using ICD-9 than ICD-10 although a number of large countries have recently increased coverage and transited to ICD 10 – e.g. Brazil. To increase use of ICD-10 in lower resource settings, a simplified short list of ICD codes is required for use in hospitals. VA diagnosis can then use the same ICD codes. A large scale project in Tanzania used 3-digit ICD-10 cause of neonatal death codes for verbal autopsy coding using a computer algorithm[134 59]

Recommendation: Although ICD-10 is looked to as the highest standard for classification of cause-of death, the intrapartum-related codes do not reflect global consensus statements over the last decade. "Birth asphyxia" is the major coding option offered and symptom based and maternal risk factors can also be coded. Revisions for ICD 11 could take the opportunity to reduce or clarify these nebulous codes and update the terminology to reflect shifts in epidemiological case definitions, notably NE.

Post-mortem

Definition: A post-mortem examination involves assessment and dissection of the body of the fetus/baby after death, and includes expert histopathological examinations, often with microbiological and metabolic investigations.

Usefulness: This method is considered the definitive approach to assigning cause-of-death.[96;135;136] However, even with the highest skills and investigations available, around 10 – 30% of stillbirths and 10% of neonatal deaths may remain of undetermined cause even in high quality data such as the UK CEMACH reports.[98;137]

Feasibility: Even in high-income settings, many babies do not undergo post-mortem examination because of the sensitivity of the issue for parents. Indeed, in the UK neonatal postmorterm rates are falling.[138] In some cultures, particularly of Islamic faith, postmortem examinations are prohibited. In addition, expert perinatal pathologists are uncommon, and the procedure is expensive.

4.4 Summary and case definition for intrapartum-related neonatal deaths used in this thesis

The second objective of the thesis was to propose a minimum list of programmatically relevant causal categories which are comparable in vital registration and other data sources, and examine in more detail the case definitions and measurement options for birth asphyxia related outcomes. Six programmatic categories of neonatal cause-of-death have been defined, plus a residual "other neonatal" category which will be used for multi-cause analysis for the remainder of the thesis. These are a minimum list of causal categories but more detailed cause-of-death information can be mapped onto these seven groups – for example dividing the "other neonatal" category to specify neonatal jaundice or haemorrhagic disease of the newborn as causes of death.

The selection of a focus on "birth asphyxia" in the thesis is deliberate since this issue is of public health relevance, yet major shifts in terminology and case definitions in high income countries have not been reflected in the language and case definitions used in many low income countries or indeed by UN and GBD. Previous estimates refer to the more nebulous condition of "birth asphyxia" usually referring to "not breathing at birth" which has multiple causes, including preterm birth, though historically the term "birth asphyxia" implies a causal link with intrapartum hypoxia. Epidemiological measurement of intrapartum injury has moved from *process-based* (e.g., long labour) and *symptom-based* (e.g., Apgar score) definitions to multiple indicator *outcomes* particularly NE which is a good predictor of outcome.[91;118] If preterm babies or those with congenital malformations continue to be misclassified into the intrapartum-related category, programmatic solutions may be misinformed as different interventions are required to prevent deaths due to these other causes. More specific diagnosis has also been driven by litigation issues in high income countries. However some aspects of measurement specified in increasingly complex consensus statements[68-70] such as blood gas analysis are unlikely to be possible even in most hospitals in low income countries, let alone for the world's 50 million home births a year. Simpler surrogate definitions are required and to test in verbal autopsy tools (Chapter 8). These simpler definitions may also be valuable for population-level programme tracking even in high income countries.

The case definition used in this thesis for intrapartum-related neonatal deaths is as follows:

> ***Intrapartum-related neonatal deaths***, including neonatal deaths with NE or term neonates who cannot be resuscitated (or for whom resuscitation is not available) or specific birth trauma. Where possible other causes should be excluded such as lethal congenital malformations and preterm birth complications (less than 34 completed weeks' gestation or birthweight <2000 g).

Chapter 5
Cause of neonatal death data: quantity and quality (Objective 3)

Objective 3:
Undertake a systematic assessment of the coverage and quality of data for neonatal cause-of-death through vital registration systems and in published and unpublished literature in all countries.

5.1 Sources and data for neonatal mortality rate and numbers of neonatal deaths

5.1.1 Overview

Timely data on births and deaths is a cornerstone for rational planning in the health sector and beyond. Yet "most people in Africa and Asia are born and die without leaving a trace in any legal record or official statistic" – a so-called "scandal of invisibility".[6] Data for counting neonatal deaths, and the necessary denominator of live births are available from a variety of sources predominantly from VR or household surveys (Table 5.1). For a smaller group of countries (33) accounting for about 5% of births, there are no nationally representative data on neonatal deaths. These are mainly conflict or post-conflict settings, or small nations such as Pacific islands. For these countries, under five mortality is estimated annually by the United Nations Child Mortality Group[11] and, intermittently, WHO has used these estimates to predict neonatal mortality rates.[3,12] The uncertainty around these may be considerable although formal uncertainty bounds around estimates of child or neonatal mortality are not usually provided. While it is not been customary to present detailed descriptions of inputs, methods and uncertainty estimates, these are becoming the norm to which global health estimates aspire.[13,14]

Table 5.1 Sources of data for numbers and rates of neonatal deaths around the year 2005

	Countries	Percent of world's births
Vital registration	81	27%
Population-based survey		
since 2003	41	39%
before 2003	48	29%
No available data (estimates based on regression on under five mortality)	33	5%
Nationally representative sample surveillance sites	2 (India and China in process)	-
Demographic surveillance sites E.g. INDEPTH network in Africa	Subnational and currently not suitable for national estimates	-

Data from: [4;10]
For details on Demographic surveillance sites and INDEPTH network please see Definitions section, page 16

5.1.2. Vital registration (VR) data for neonatal mortality

There have been recent improvements in VR coverage and quality in some transitional countries and 81 countries now have high coverage VR systems, although these countries only account for 27% of the world's births (Table 5.1). In high income countries VR data are taken for granted, but in most low income countries and even many transitional countries the coverage and quality of VR data makes it unreliable for population-based data. Even in transitional

societies, early neonatal deaths are often under-registered and stillbirths rarely registered.[139] Functional VR systems provide countries with data on numbers of births and deaths, reasonably quickly: the time lag is usually one or two years.[10] In addition, timeliness or availability may further reduce usefulness for decision makers.[133]

Stillbirths are important to record, for programmatic reasons but also as part of effective tracking of pregnancy outcomes. In countries where VR is the source for stillbirth data, there is marked variation in stillbirth definitions. National definitions reflect various combinations of gestational age, weight and documentation regarding signs of life. For example, gestational age cut-offs range from 12 to 28 weeks, and weight cut-offs are as low as 400 g. In a survey on stillbirths sent to vital registration offices, responses from 25 developed countries and 5 middle-income countries showed 17 different definitions of stillbirth.[8]

5.1.3. Household survey data for neonatal mortality

Without household surveys we would have little information globally for child or neonatal mortality, or for coverage of priority interventions. There are two major systems for such surveys: Demographic and Health Surveys (DHS), funded largely by USA government aid but usually in partnership with national statistics offices; and Multiple Indicator Cluster Surveys (MICS), run by UNICEF. Such surveys use a questionnaire to ask women about previous births, child deaths and coverage of care. They tend to be repeated every five years. DHS report under-five mortality, neonatal mortality and stillbirth rates for over 80 countries which account for two-thirds of the world's births. However, only approximately 50 countries have data within the last five years. The data and results are open access (www.measure.dhs.com). MICS report under-five mortality and coverage of interventions in many of the same countries, but do not routinely analyse or report on stillbirths or neonatal deaths. Indeed MICS do not directly measure under-five deaths through a birth history, but use indirect methods. Summary results are available (www.childinfo.org), but not the datasets. Availability of neonatal mortality data would be increased if this outcome was estimated from MICS survey results, also giving uncertainty bounds as MICS are not usually powered for neonatal mortality estimation. The Malawi MICS did increase sample size specifically to estimate the national NMR.

The importance of surveys as data sources makes recognition of their limitations essential. One limitation is their frequency. The expense and challenge of data collection and analysis in low resource settings - using a survey tool with over 700 questions in the case of DHS - means that in most countries they are only conducted every five years. Their ability to detect rapid changes in mortality or to disentangle contributory factors is therefore limited.[140] With increasing investment in maternal, newborn and child health there is a desire on the part of governments and donors for data to detect short-term trends, particularly in the years up to 2015, the target

for the MDGs. To change from a five year birth retrospective to a one year retrospective would require huge increases in sample size. For example, in Nigeria it would mean a five-fold expansion from the sample of 7,225 households that already constitutes a major feat of organisation.

Surveys have particular limitations with respect to neonatal deaths and stillbirths, of which the most important is the potential for under-ascertainment of deaths compared with prospective surveillance. There are limited systematic analyses of the extent of this problem, but one study from rural India suggests that under-reporting, especially in traditional societies, may halve the numbers of deaths captured.[16] Ghana's Kintampo study took advantage of intensive monthly household surveillance established for a trial of vitamin A supplementation during pregnancy to obtain high quality data in a country where vital registration remains low, although in this particular population over half of the births were in facilities.[141] There are no retrospective survey data with which to compare the findings, although interestingly the NMR of 32 per 1000 in this study site is lower than the Ghana national NMR of 43 reported by the DHS.

Misclassification between stillbirths and early neonatal deaths is another important issue, and was one of the arguments in favour of a combined measure of perinatal mortality, although expert opinion now favours separate reporting of stillbirths and neonatal deaths.[17] Most DHS surveys use birth histories and so the stillbirth data may rely on other sections of the questionnaire such as analysis of contraceptive calendar data, which results in much wider uncertainty and in many surveys the reported stillbirth rates are around half the expected value when compared with prospective surveillance in the same countries.[8] The use of pregnancy history in all DHS would be a major step forward in increasing the quantity and quality of stillbirth rate data, and this might also reduce under-ascertainment of early neonatal deaths although there is a dearth of systematic comparison of birth history and pregnancy history data.[8] Other issues of data quality in DHS include age-heaping on certain days, notably days 7, 14 and 30, and miscoding between day zero and day one.[4] More systematic analytical work is required to develop objective scores of survey data quality for example a composite of a age heaping index and a measure of stillbirth/neonatal death misclassification. Such an analysis could provide a basis for adjusting estimates to correct for biases in survey data.

There are a number of epidemiological and programmatic arguments for the measurement of stillbirths, and for routinely collecting stillbirth data in household surveys. Firstly, counting all births – dead or alive – increases the likelihood of correctly recording stillbirths, neonatal deaths and improving the denominator of all births. Babies who die very soon after birth are less likely to be registered than babies dying after a few days of life, and stillbirths are even less likely to be recorded than live births who then die.[139;142] Promoting the measurement of all birth

outcomes - live births, stillbirths, and early neonatal deaths is likely to capture events that might otherwise go unreported. If both stillbirths and early neonatal deaths are counted, then early neonatal deaths misclassified as stillbirths are at least recorded, even if misclassified. Live babies may be misclassified as stillbirths and vice versa for a number of reasons: lack of knowledge; lack of careful assessment for signs of life; less blame or review for the birth attendant or reasons of perceived gain or loss to the family. For example, the registration of a live birth may encumber the family with funeral arrangements and costs, whereas a stillbirth usually does not require burial. On the other hand the mother may be entitled to social benefits only with a live birth.

Secondly, not counting stillbirths better will underestimate programme impact, and possibly mislead programmatic decision making since when intrapartum care improves historical data suggest that stillbirth rates may be reduced first, and early neonatal deaths may rise.[143;144]

Finally, stillbirths are important to prevent in their own right. The death of a baby during the last trimester is a source of pain to mothers and to fathers, and indeed is reported to be associated with grief reactions more protracted than for early neonatal deaths, partly because of the social taboos associated with open grieving for a stillbirth.[145;146]

To improve the quantity and quality of data the solution is clearly to improve routine registration systems to achieve high coverage of vital statistics including births, stillbirths, and deaths for mothers or children.[15] DSS are another valuable source of data on trends, especially if they are selected to be nationally representative. Such sample registration systems are being tried in China and India, with the support of the Health Metrics Network and similar initiatives. In other countries, demographic surveillance sites which are not nationally representative may nevertheless provide useful data on mortality trends.[57] For example the INDEPTH network has multiple DSS mainly in Africa (http://www.indepth-network.org/. See Definitions section, page 16 for more details on INDEPTH). In the interim, household surveys could include pregnancy history modules instead of birth modules, increasing capture of early neonatal deaths and allowing measurement of stillbirths. There is a move to increase the frequency of UNICEF's MICS, using fewer questions and focusing on coverage of selected interventions, to provide more responsive data on programme if not on mortality outcomes.

5.2 Sources of neonatal cause-of-death data

5.2.1 Overview

The objective of this chapter, and the third objective of the thesis, was to identify, screen for inclusion and analyse all available data which may include the selected neonatal cause-of-death categories as described in Chapter 4 (Table 4.1). There are two major sources for such data: vital registration (VR) data and published and unpublished reports of research studies (study data) many of which rely on verbal autopsy. A number of large countries without full coverage VR data (notably China and India) are in the process of setting up large-scale sample registration sites. However neonatal cause-of-death data are not yet available from these surveillance systems. For both data sources a two-step screening process was applied (Table 5.2). The first filter was to exclude data that was not considered to be population-based and the second filter was to maximise data quality and comparability of cause-of-death attribution. The process for the VR data will be described first and then the details of the study data searches and screening.

Table 5.2 Systematic search strategy and inclusion criteria filters applied to screen the data identified

Filter	Vital Registration	Study Data
Search strategy	All data in WHO mortality database as of January 2004 (in the case of the asphyxia single cause estimates, VR data up until May 2004 were available)	Searches in multiple databases as follows: PubMed, Popline, LILACS, WHO regional databases (Emro, African Index Medicus, PAHO), Search terms: All cause mortality (neonatal mortality, perinatal mortality) Cause-specific terms covering multiple terms for each of the 7 selected groups of cause of neonatal death. For example tetanus, neonatal tetanus, tetanus neonatorum. Search limits: Publication after 1980 Human
Filter 1: Population-based	Countries with high (>90%) coverage of VR of adult deaths	Study set in one of 9 (of a total of 14) subregions with no or few countries with >90% VR coverage Community-based study or hospital based in populations with over 90% hospital delivery and defined catchment population. Case ascertainment: follow up of newly born infants from birth to at least 7 or 28 days
Filter 2: Comparable cause-of-death attribution	Countries with detailed ICD data for ICD9 or ICD10 within the last 5 years, and averaged for 3 years if < 500 neonatal deaths per year	Studies with all of the following: – Study duration ≥ 12 months, – Number of deaths with known cause >20, – Included 4 or more of the 6 selected programme relevant causes of neonatal death (preterm, intrapartum-related, infections, tetanus, congenital, diarrhoea, other), – ≤25% deaths of unknown cause, cause attribution based on skilled clinical investigation, post mortem or verbal autopsy, – Case definitions specified and comparable

5.2.2 Vital registration data screening and analysis

The World Health Organization (WHO) supplied a database of VR data since 1990 covering 83 countries with two different ICD coding systems (ICD9 and ICD10)[15]. Data were screened using the inclusion criteria (Table 5.2). WHO consider VR to be a reliable source of population-based data when 90% of adult deaths are captured.[133] However, even at 90% coverage, one tenth of adult deaths are missed and systematic bias in cause-of-death is probable since the unregistered deaths are more likely to be among the poorest families who experience different health risks from the richest families. Child death registration is lower than that for adults and neonatal is lower still.

For countries with more than 500 neonatal deaths a year, the data from the closest year to the year 2000 were analysed. If the annual number of neonatal deaths in the country was less than 500, in order to minimise chance variability in proportionate mortality the three years closest to the year 2000 were used.

There are a large range of detailed codes in ICD 9 and 10 that can be applied to neonatal deaths, therefore new analysis was required to allocate these multiple codes to the seven selected cause-of death categories, being as comparable as possible to the study data. The majority of the ICD codes used in the neonatal period were from the Perinatal causes (approximately 60% of the deaths), and Congenital chapters but codes from almost every chapter of ICD are also used including infections, trauma and most of the systems chapters (e.g., cardiac, renal). Excel spreadsheets (Microsoft XP, 2000) and Stata version 8 programmes (Stata Corporation, College Station, Texas, USA) were written to categorise the > 5,000 possible codes in ICD10 into the seven neonatal cause-of-death categories selected. The initial analysis was undertaken with ICD 10 datasets and several cycles of analysis and rewriting of codes were required as many unexpected codes were used for deaths in the neonatal period. Some of the codes are those considered "garbage codes" by ICD experts – for example symptom based codes such as heart failure. WHO has a process to either allocate these codes to a "garbage code" category (assume they can be redistributed equally over all causes of death), or else to review the codes and reallocate to a specific cause which is considered the most likely cause related to that symptom.[133] Once the ICD 10 analysis was finalised and able to account for all codes used for deaths in the neonatal period for countries with ICD 10 data, then an ICD9- to-10 translation guide was used to generate the equivalent ICD 9 codes to maximise consistency between the two classification systems for the analysis. An analysis of countries with ICD 9 and ICD 10 data within a few years of each other was undertaken to examine any big changes in proportionate mortality that may be due to coding errors, but there was remarkable consistency in the proportionate mortality between the ICD 9 and ICD 10 analysis in these countries. In addition the proportionate mortality output from these new analysis were compared to national high-

quality audit data (e.g. Confidential Enquiries into Maternal and Child Health (CEMACH) in the United Kingdom) and found to be very similar (Table 7.5c). The ICD code categorisation used for this new analysis is now the standard grouping used by WHO and the GBD.

5.2.3. Study data screening and abstraction

Systematic searches of the published literature were carried out in all the major electronic databases in addition to the WHO regional databases (Table 5.2). These are the databases considered essential by WHO for systematic searches on international health. A very wide range of search terms were used based on mesh terms in PubMed and then adapted for use in other databases. Searches were undertaken in all languages and extensive attempts made to identify non-English language publications by searching in regional databases and writing to neonatal experts and WHO Collaborating centres especially in China. In addition international neonatal researchers were contacted to request access to unpublished datasets of relevance.

Initial screening was undertaken on abstracts and titles. Then full text versions of possible relevance were located and screened. Any studies that met the criteria as population-based, were abstracted and then evaluated for the quality criteria set (Table 5.2, filter 2). These quality criteria were based on adaptation by the CHERG neonatal group of criteria set by the other CHERG groups and then some specific criteria for this multi-cause analysis. For example other CHERG groups, especially those dealing with malaria, pneumonia and diarrhoea, were concerned about seasonality. For neonatal cause-of-death, seasonality is not thought to be a major factor for most causes of death, with the exception of diarrhoea which is a very small proportionate cause. However there is annual variation in the birth cohort in many cultures (for example a peak in birth 9 months after major holiday seasons) and therefore to be conservative study duration of at least 12 months was sought. Other quality criteria applied were specific to the neonatal multi-cause of death work and necessary as minimum standards for the consistency and comparability of the data including the following:

- Number of deaths with known cause more than 20,
- Included 4 or more of the 6 selected programme relevant causes of neonatal death (preterm, intrapartum-related, infections, tetanus, congenital, diarrhoea, other),
- $\leq$25% deaths of unknown cause, cause attribution based on skilled clinical investigation, post mortem or verbal autopsy,
- Case definitions specified and comparable

The possible studies were abstracted by two independent abstractors using a standard form (Appendix C) and entered into an Excel database. Abstractors who were students at London School of Hygiene and Tropical Medicine assisted with the abstraction of the 112 identified studies meeting criteria as population based. An abstraction guide was developed and both abstractors were trained and closely supervised by the investigator. The abstractors worked

independently and then met to review dually abstracted studies and resolve any differences. Any unresolved differences or key questions were brought to the supervisor. Some differences were simple to resolve – for example those found to be related to errors in re-calculating proportions when combining non standard causes reported to the standard causes desired. Other differences related to different interpretations of case definitions or hierarchies but agreement was possible after discussion. If agreement had not been reached the investigator would have taken the final decision.

All the unpublished datasets were analysed and abstracted by the investigator and one of the two abstractors. The abstraction form is shown in Appendix C. Translation from six languages was required for abstraction and data entry (French, Spanish, Portuguese, Polish, Bahasi Indonesian and Chinese) and students at the London School of Hygiene of Tropical Medicine (LSHTM) who spoke these languages were recruited using the LSHTM student listserve. Each translator was briefed by the investigator and then linked to one of the abstractors to transcribe the necessary information, which was then double checked by the supervisor (JL). Deaths were allocated among the standard seven cause-of-death categories using the author's cause-of-death attribution. If authors gave more than one cause-of-death per neonate then a fixed hierarchy was applied, following ICD rules where possible (Table 4.1). For example, a death in a neonate with a neural tube defect and infection was classified as due to congenital abnormality.

Fifty five principal investigators were contacted to obtain additional information on causes of death and local explanatory variables. Initial contacts were by email or by fax by the investigator working alongside a research assistant. A 59% response rate was achieved, although in some cases this necessitated four letters. For a few of the authors phone calls or meetings were required to further discuss the data and in all these cases such personal follow up was undertaken by the investigator. In three cases the databases were re-analysed by the CHERG neonatal investigators to increase consistency of causal attribution, or to combine non-standard categories. For example neonatal tetanus may not be recorded in the paper and further information from the investigators was sought to clarify if the omission reflected zero tetanus cases or if no attempt had been made to attribute deaths to tetanus as a specific category. Some studies included unclear or non-standard causes. For example, if a neonatal death was attributed to "feeding difficulties" the authors were asked to supply additional information regarding the death to allow allocation to a standard category. Deaths from unknown causes were excluded from subsequent analysis, but if more than 25% of deaths were unknown the study was excluded (Table 5.2). The abstraction form included data for a range of variables which might explain the proportional distribution of causes in a study and in many cases this was poorly recorded in the original publications, but additional data was supplied by authors. This predictor information and its uses will be discussed in more detail in Chapter 6.

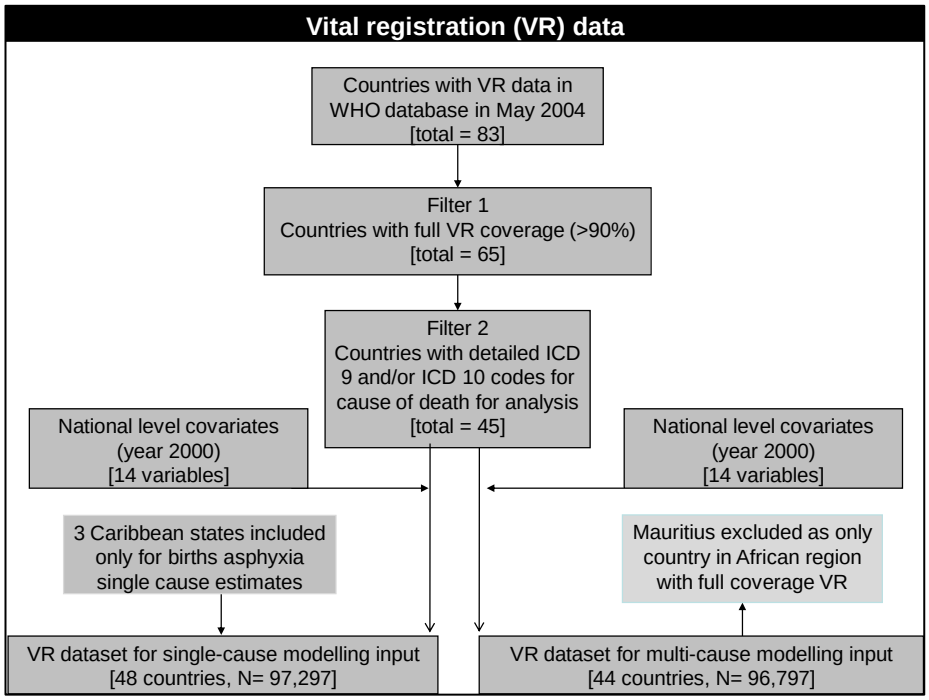
5.3 Quantity of neonatal cause-of-death data after screening and analysis

5.3.1 Vital registration data inputs

A total of 45 countries had VR data which met the initial inclusion criteria (Figure 5.1). A further 3 countries (small Caribbean islands) were available for input for the single cause asphyxia estimates as data could be used from ICD summary tables but detailed codes were not available for the multiple cause of death analysis for these island states.[51] An almost equal number of countries were excluded based on their VR coverage (18 countries) and lack of useable ICD data for analysis (19). Several large countries such as Brazil were excluded on the basis of VR coverage, but their coverage was close to 90%. Mauritius was excluded from the multi-cause estimation input dataset as it was the only African country with high coverage VR data and Mauritius is not representative of other African countries given that the NMR is 12 per 1000 live births compared to a regional average of 44 (table 1).[4] Hence for Mauritius the VR data was used as reported for neonatal cause-of-death proportions for their national estimates based on the novel analysis undertaken as for the other 44 high coverage countries but was not an input of the VR based model.

Thus, the VR dataset comprised 96,797 deaths from 44 countries which together account for about 2% of the estimated global total of neonatal deaths. NMRs ranged from 2 to 18 per 1000 live births. The annual number of deaths per country ranged from 12 (Iceland) to 23 603 (Mexico).

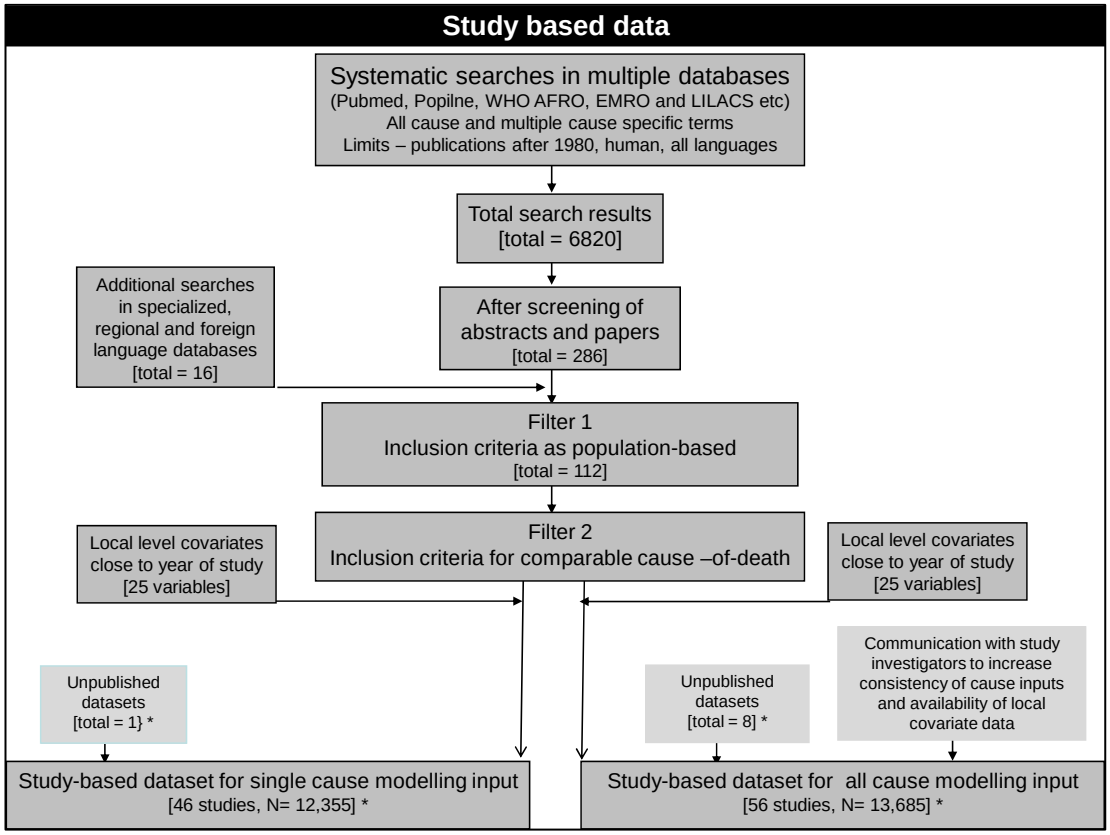
Figure 5.1 Identification of data, and inclusion criteria applied for vital registration data



5.3.2 Study data inputs

After applying inclusion criteria, 48 studies and 8 unpublished databases were identified reporting a total of 13,685 deaths with known cause (Figure 6.2 and supplementary table B.2 in appendix D).[25;58;59;86;104;147-195] The number of deaths per study with known cause ranged from 21 to 3638 (median = 102.5). NMRs ranged from 8 to 89 per 1000 live births. Any facility-based studies from populations where less than 90% of the births were in a facility were excluded as not being population based, and this was the most common reason for exclusion. Although 286 studies met criteria to be considered population-based 240 were excluded on the basis of the quality criteria such as less than 20 neonatal deaths, or data collection for less than one year (Table 5.2). The proportion of deaths with unknown cause ranged from 0 to 23%, with a median of 2%. The multi-cause approach further restricts the already limited input data since at least 5 of the 7 comparable causal categories have to be reported for a dataset to be included. Communication with authors was important in increasing the number of studies with data for 5 or more of the 7 causal categories particularly neonatal tetanus and diarrhoea. Even after communication with authors, 19 studies lacked data on one of our selected causes of death nd two studies lacked information on two causes.

Figure 5.2 Identification of data, and inclusion criteria applied for study based data



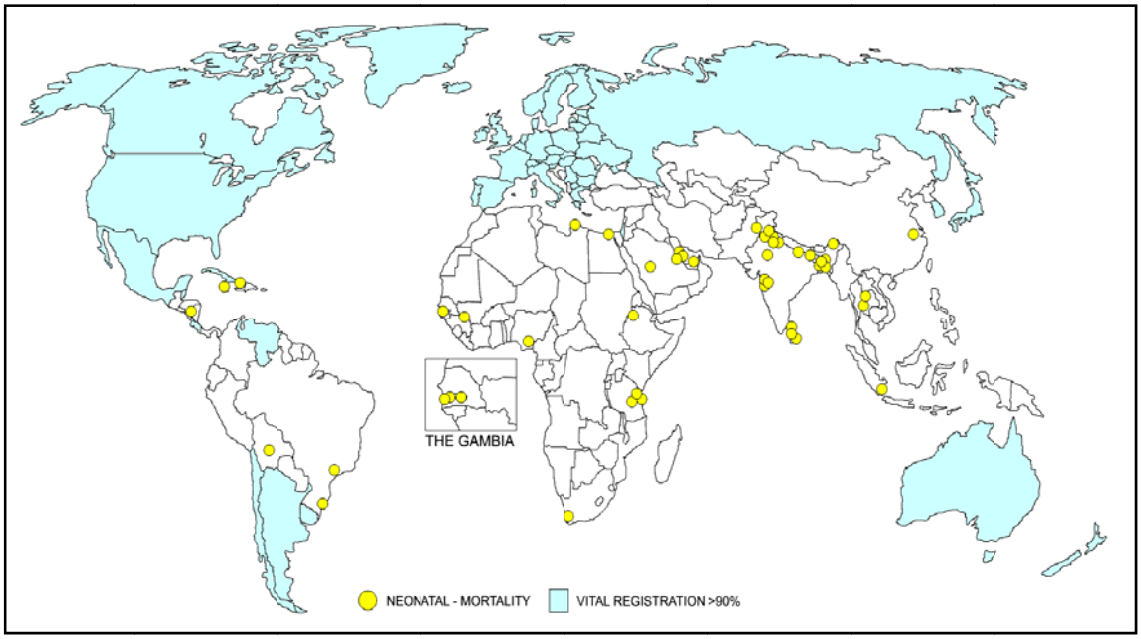
* Additional unpublished datasets were available for inclusion in the multi-cause modelling but were not available at the time of the single cause modelling

5.3.3 Geographical distribution of the input data

As shown clearly in the map in Figure 3, there are large areas with no useable information identified – notably central and north western Africa, central Asia and much of China.[25] Approximately one third of the studies included are from India, which accounts for 28% of the world's neonatal deaths. No reliable information was identified from many of the world's poorest countries which account for about one third of neonatal deaths. It is possible that some publications or unpublished data were missed due to language barriers, despite the fact that searches were carried out in several languages, and extensive attempts were made to contact researchers in China, Latin America and Francophone West Africa. From China the only two studies included in the neonatal dataset were a publication from a group of urban hospitals and a study of a rural ethnic minority group, neither of which reflect the national situation.

In contrast there are some "hot spots" of data collection – centres of international research such as the Gambia, International Centre for Diarrhoeal Disease Research, Bangladesh (ICCDR,B) in Bangladesh and Tanzania. These sites are also responsible for a disproportionate contribution to useful information for other causes of child death.[46]

Figure 5.3 The distribution of studies meeting inclusion criteria for population-based, comparable neonatal cause-of-death data in countries without full coverage vital registration data (56 studies, Number of neonatal deaths = 13,685)



Data from [18,46]

Geographic gaps are also evident for data regarding other causes of child mortality. In addition to the systematic searches presented here for neonatal cause-of-death data, CHERG undertook parallel exercises regarding cause-of-death data for pneumonia, malaria and diarrhoea. Systematic searches were carried out and data were abstracted by two separate extractors and

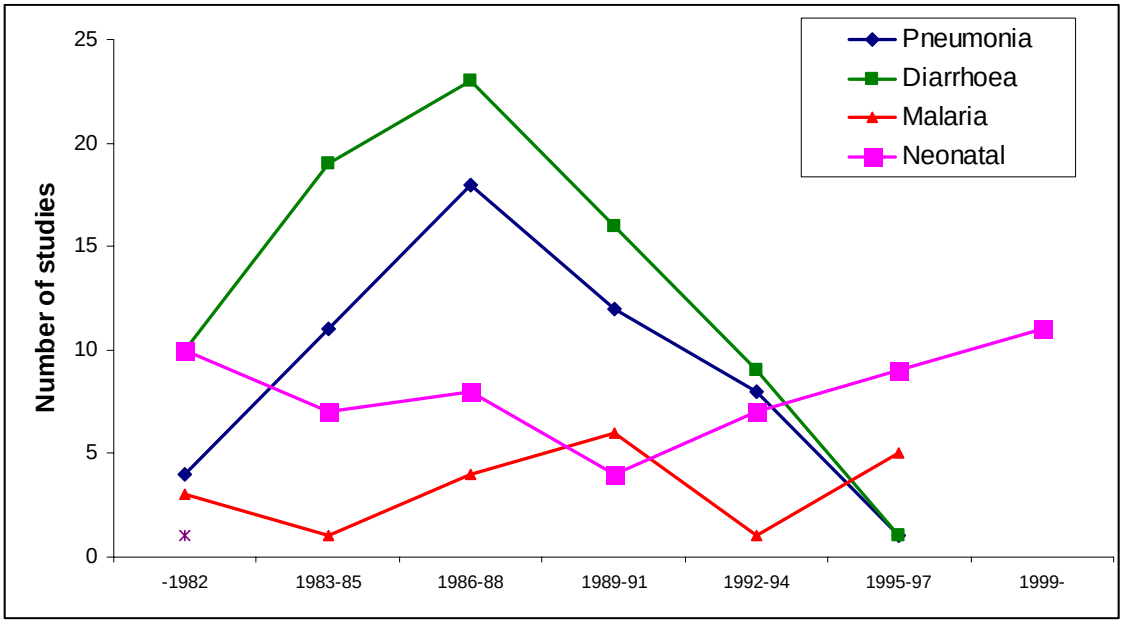
entered into databases applying similar inclusion and exclusion criteria. A joint analysis revealed a major lack of useable data for all causes of child death. - a total of around 17,000 documents were screened including the 6820 from the neonatal exercise, yet only 232 useable datasets were identified.[196] Only two groups identified any data at all from China. No useable information was identified in nine of the 25 countries with the highest numbers of deaths in children younger than five years. [46]

5.3.4 Age of the data and time trends in publication of neonatal cause-of-death data

For the VR data the median year of data included was 1999, close to the target of the year 2000. However the study data were considerably older - the median year of data collection was 1991. The average time lag between data collection and publication was four years, although this tended to be shorter at the end of the 1990s compared to the early 1990s. The time lag was longer in South Asia – a median of five years and a range up to nine years.

Although there is general dearth of data there have been changes over time in the number of studies undertaken and published, and this is more marked for some causes of child death than for others (Figure 5.4).

Figure 5.4 Time trends in the availability of useable data for cause-of-death amongst children under the age of five for major causes of child death (1982 – 1997, 2000 for neonatal)



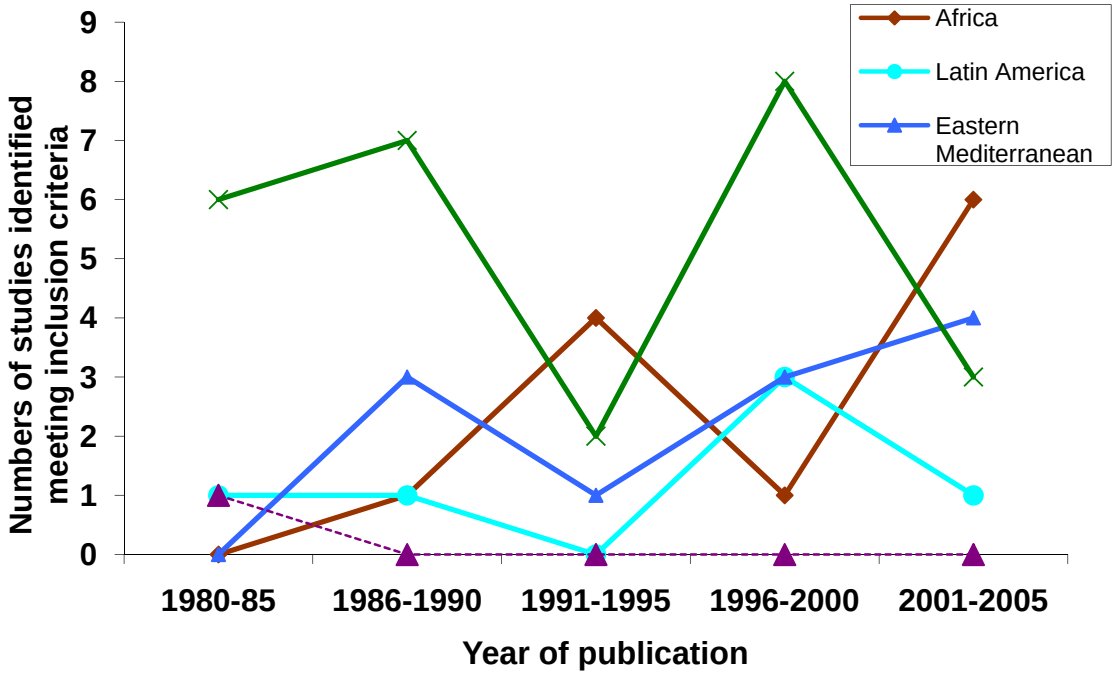
Source: Data from [18,46]

There was no obvious trend for malaria visible up to the year 2000, although with recent major investment in malaria this may have since increased. For pneumonia and diarrhoea there was a marked peak in studies around the year 1990, with over 20 studies in that year for diarrhoea

mortality incidence. 1990 was the year of the World Summit for Children and marked major interest in child survival, particularly diarrhoea and management of pneumonia (previously referred to as acute respiratory infection or ARI). However, by the end of the 1990s, the number of studies per year had dropped to almost zero. Studies on neonatal cause-of-death were few, with a median of five per year until the late 1990s when a gradual increase in studies was observed. In fact this cross–group analysis within CHERG did not include several of the unpublished datasets identified for neonatal cause-of-death data and hence the increase in information availability for neonatal is even more pronounced than the graph suggests. However, to keep this in perspective, even at a peak of 12 information units per year, and even assuming the geographic distribution addressed the gap areas, this is a ratio of one information unit per one third of a million neonatal deaths. Hence it is clear that relying on intermittent studies is unlikely to ever be an adequate source of information and more systematic building of information systems is required.

Within the neonatal datasets, there is regional variation in time trends for data collection (figure 5.5). During the 1980s and 1990s there were remarkably few studies identified which met the inclusion criteria, but there appears to be a slight upward trend in the numbers of publications, particularly in Africa. South East Asia was the only region with significant input data in the 1980s. This reflects a number of community-based studies in India and a few in Sri Lanka and Thailand, several of which were part of a WHO initiative to improve community-based surveillance for maternal and neonatal health, related to risk screening.[186] India also has strong national champions for newborn health linked to the Indian Neonatal Forum which was founded in 1980, promoting improved neonatal surveillance both in facilities and the community. The higher number of publications out of the South and South East Asian regions has been sustained across the 25 year period examined, but should be interpreted in the light of the fact that this region accounts for one third of the world's neonatal deaths. This results in an average of one study per year, in most cases reporting very small numbers of deaths, which is inadequate to provide information regarding around 4 million neonatal deaths a year.

Figure 5.5 Regional time trends in the date of publication/release of datasets for neonatal cause-of-death meeting the inclusion criteria (56 studies, N = 13,685) (1980 2005)



Source: Data from [18,46]

In Latin America and the Eastern Mediterranean region there is a possible but not very convincing trend to increasing publications. The two studies identified from China do not allow trend assessment. Africa is the only region with a strong upward trend in the availability of useable neonatal cause-of-death data. This trend is strongly influenced by four study datasets from sample registration sites – three from different regions in Tanzania and one from The Gambia. Sample registration may be a promising model to increase useful information for maternal, neonatal and child health in low resource settings. Sample registration sites with verbal autopsy questionnaires are being piloted in India, and a neonatal verbal autopsy has recently been introduced in these sites. Sample registration as a strategy to increase data availability will be further discussed in Chapter 8.

5.4 Quality of available data for multi-cause analysis

5.4.1 Variation of neonatal proportionate cause-of -death in the Vital Registration input data

In the VR data only five of the selected seven causal groups could be assessed since there were no reported neonatal tetanus deaths in these countries and very few neonatal deaths due to diarrhoea (290 or 0.3%). The few diarrhoea deaths were allocated to the sepsis/pneumonia (infection) category.

In both the VR and the study data there was substantial variation in the distribution of the different causes of death across the country (Figure 5.6a) or study inputs (Figure 5.6b). Overall the variability in proportionate mortality observed in the VR data was less than that in the study data. This may be real as in the VR countries the NMR range is only up to 15 per 1000 and indeed in most cases is less than 6 per 1000, yet in the study data the NMR ranges up to 81 per 1000.

In the VR input data the widest range in proportionate mortality was seen for preterm birth and congenital anomalies. Part of this may be real, reflecting differing case fatality rates as some countries with high VR coverage still have restricted access to intensive neonatal care, or variable quality of care. In addition differences in policies and practices for termination of pregnancy for fetal abnormality may have a real effect on incidence of congenital abnormalities.

On the other hand, some of this variation may be an artefact, reflecting an increased ability to detect certain congenital conditions, notably cardiac malformations, or due to variation in case definitions and hierarchical cause-of-death. Variable application of the ICD guidelines regarding preterm birth as an underlying cause-of-death may affect the very wide range around the proportion of deaths attributed to complications of preterm birth (Figure 5.6a). It may also be that the use of detailed 4-digit codes allows more specific diagnosis; for example, there are multiple specific complications of preterm birth defined rather than a single category of prematurity.

5.4.1 Variation of neonatal proportionate cause-of-death in the study based input data

The number of deaths with known cause per study ranged from 21 to 3638 (median = 102.5). NMR ranged from 8 to 89 per 1000 live births. In the study input data, the proportion of deaths with unknown cause ranged from 0 to 23%, with a median of 2%. Communication with authors was important in increasing information regarding cause-of-death, yet despite this 19 studies lacked data on one of our selected causes of death (11 diarrhoea, 4 congenital abnormalities, 3 tetanus, 1 preterm). Two studies lacked information on two causes (congenital abnormalities and tetanus; congenital abnormalities and diarrhoea). Asphyxia was recorded in all the studies and therefore chosen as the corner cause for the multi-cause modelling.

There were a number of outliers particularly for the proportion of deaths due to tetanus and to congenital abnormalities (Figure 5.6b). Some of the variation in proportionate mortality by cause shown in the input data is likely to be due to true epidemiological variation. For example, all the results showing a high proportion of deaths due to tetanus came from study sites with weak health care systems and extremely low tetanus toxoid coverage among pregnant women (less than 5% in many cases) and low use of skilled attendants, for example North West Frontier Province in Pakistan. Many of the studies with high proportions of neonatal deaths due to congenital abnormalities were from populations with a high prevalence of consanguinity, notably in Middle Eastern countries.[197]

However, the small size of some of the datasets and inconsistencies in the attribution of cause-of-death may also play an important role. Variation in proportionate mortality by cause in the study input data was notable in the preterm and infection categories and this may reflect a lack of consistency between studies in the case definitions and hierarchical cause, rather than true variation in cause-of-death (Figure 5.6b).

Figure 5.6 Box plots showing the proportional distribution of causes of neonatal mortality for data meeting inclusion criteria

Figure 5.6a Vital Registration data (44 countries, N = 96,797)

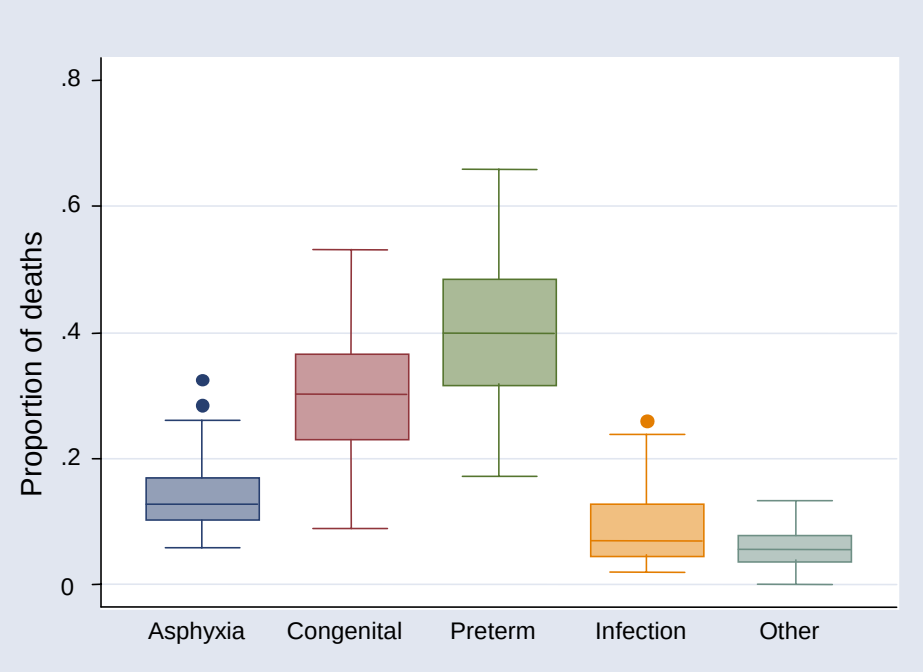
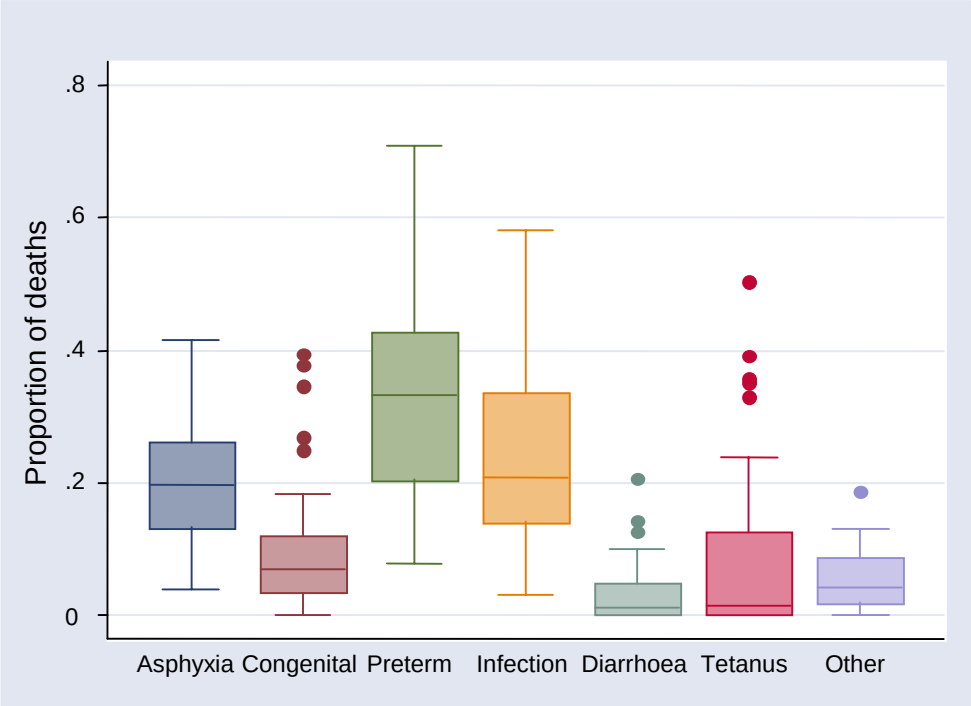


Figure 5.6 b. Study data (56 studies, N = 13,685 neonatal deaths)



5.5 Quality of the input data specifically with respect to intrapartum-related neonatal deaths

5.5.1 Overview of the intrapartum-related input data

The objective was to identify all useable data meeting specified inclusion criteria, and pertaining to the case definition outlined at the end of Chapter 4 for intrapartum-related neonatal deaths. While this was the case definition sought, it is important to note the limitation that the validity is determined by the validity of the reported cause-of-death in the input data, and that few papers give full details of case definitions and any hierarchy applied.

Vital registration data inputs: The VR data used were from WHO and the inclusion criteria and analysis have already been described for the multi-cause-of-death analysis, although for this exercise only the intrapartum-related proportion was used as an input (Figure 5.1). An additional three countries were included, giving 48 countries as opposed to the 45 in the multi-cause analysis. These were Caribbean island states that reported neonatal cause-of-death data already combined into causal groups. The intrapartum-related group was comparable with the case definition used here but the data did not provide comparable categories for the other six selected causal groups so could not be used in the multi-cause analysis. The numbers of deaths were small and had little effect on the total deaths included.

Study data inputs: Systematic searches were performed in Medline, Popline, LILACS, BioMed Central, African Index Medicus, and EMRO databases. Searches were conducted in all languages since 1985 for multiple terms, including all-cause mortality terms (e.g., neonatal/perinatal mortality, stillbirths, fetal deaths) and cause-specific terms related to acute intrapartum events (e.g., birth asphyxia, hypoxic ischaemic encephalopathy, NE, birth trauma, fresh stillbirths, intrapartum stillbirths). Extensive attempts were made to identify unpublished databases. Over 4000 documents of potential relevance were identified through these search techniques for neonatal deaths. After screening abstracts the selected publications were examined in detail for inclusion criteria using 2 screening filters (Table 5.3). For the single cause modelling database total of 46 study populations from 30 countries met the inclusion criteria, with a cumulative sample size of 12,355 neonatal deaths (Figure 5.2).

Table 5.3 Summary of the inclusion criteria applied to the input data

Method	Inclusion criteria for data inputs
Neonatal deaths: Vital registration (VR) data	• Filter 1- Population based data: Full coverage of vital registration (>90%) as defined by WHO estimates based on adult mortality coverage[1] • Filter 2- Comparable cause-of-death data available: Detailed ICD 10 or 9 codes reported to WHO as of March 2004
Neonatal deaths: Multiple regression model	• Filter 1: Population based data: Population-based study (either in the community, or in an institution if not a tertiary referral centre and over 90% of deliveries in the area were institutional); Neonatal and/or early NMR reported or could be calculated. • Filter 2 – Comparable cause-of-death data available: Cause-of-death data cover at least 12 months; At least 20 deaths with known cause-of-death were reported; method used was skilled clinical investigation, post mortem or verbal autopsy and percentage of unknown deaths was less than 30%; Comparable case definition of acute intrapartum events was possible and the cause-specific proportion of interest was specified or could be calculated from the information given; Single cause-of-death studies excluded.

1 WHO draft coverage estimates, June 2003, personal communication Doris Ma Fat

In the VR data the ICD 10 codes mapped onto the intrapartum-related category included 138 three-digit codes. As outlined in Chapter 4, there has been a transition in the ICD codes for this condition mirroring the global transition in terminology. However since ICD 10 was published in 1993 and completed in the late 1990s, some of the more recent changes may not be included – for example there is not a term for NE, only for Hypoxic Ischaemic Encephalopathy. In addition a wide range of more process-type definitions are still included e.g. low Apgar, "perinatal depression" etc. Almost half of the codes (60) refer to birth trauma, but these codes account for a small number of deaths. However, in a few countries, notably some of the Central Asian states, more neonatal deaths were classified as caused by birth trauma than the "birth asphyxia" codes, so there is local variation in application of the cause-of-death attribution and affecting specific code.

The data screening excluded studies that reported only on birth asphyxia as a single cause-of-death. Interestingly, there were no studies identified that reported on "birth asphyxia" and only one or two other causes of neonatal death. That is, apart from the studies excluded for reporting only on asphyxia, the studies that met inclusion criteria ended up being the same as the ones in the multi-cause study, although the multi-cause database was able to include 13 unpublished

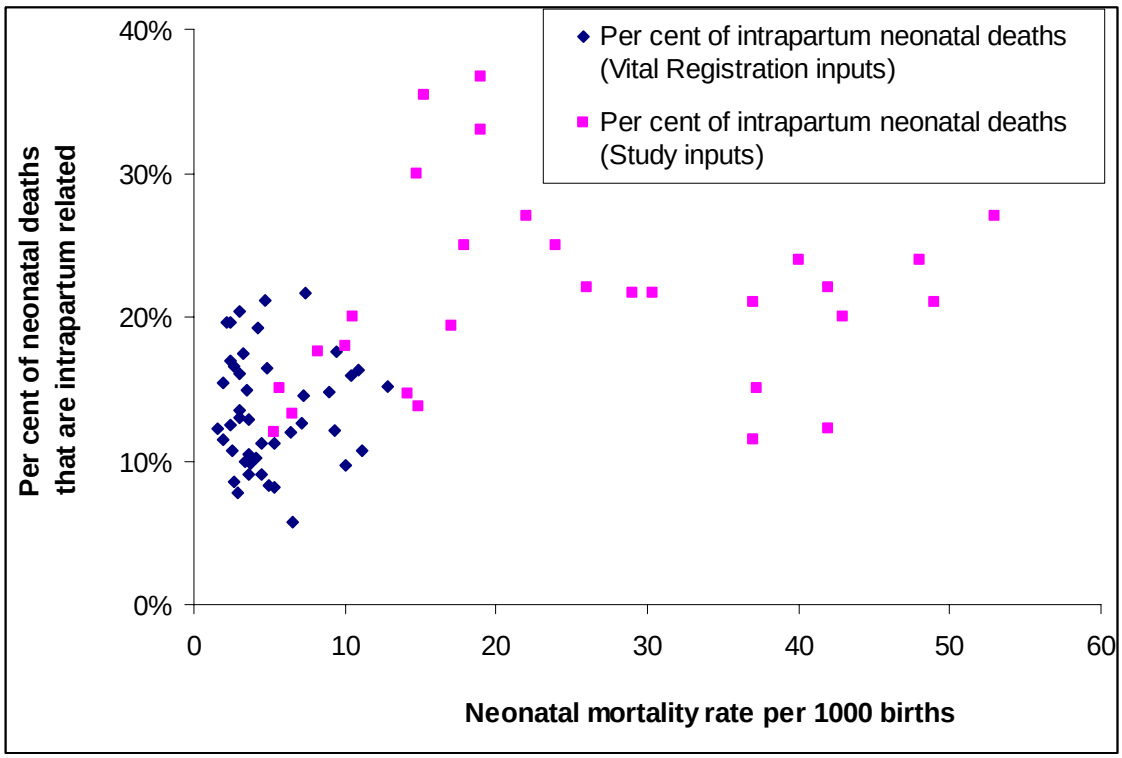
datasets and the asphyxia estimate database closed earlier for analysis and so included only 1 of these unpublished datasets. Of the single cause studies excluded the proportion of neonatal deaths attributed to “birth asphyxia” mainly using the “not breathing at birth” definition, ranged up to 70% of neonatal deaths.

The minor differences in the input data between the multi-cause database and the asphyxia estimates database do not justify separate descriptions of data quantity by time and place. The same conclusions stand – the data are limited in geographic spread, are not recent and are older in the lower income countries. The main focus of this section is on the quality of data for asphyxia proportionate mortality for intrapartum-related neonatal deaths.

5.5.2 Variation of proportion of neonatal deaths related to intrapartum events

Figure 5.7 shows all the input data by country, with the countries organised by level of NMR. The VR data are restricted to countries with NMR of 15 per 1000 births or less and the range of neonatal deaths attributed to intrapartum causes is between 5 and 20%, with a median of around 15%. Study data within the same range of NMR appeared show similar patterns. For NMRs between 15 and 30 per 1000, intrapartum events were reported to cause a higher proportion of neonatal deaths, ranging from 23% to 37%. However, at higher NMRs (above 30 per 1000 live births), the cause-specific proportion fell to 15– 25% of neonatal deaths.

Figure 5.7: Input data by country from vital registration (48 countries, N=97,297) and studies (46 populations, 30 countries, N=12,355). Countries are arranged in order of increasing NMR and the reported proportion of neonatal deaths related to intrapartum events is plotted



There are a number of possible explanations for this variation in the reported proportion of neonatal deaths related to acute intrapartum events, including:

1. Real variation with reduced or increased proportion of neonatal deaths related to intrapartum events reflecting a lower or higher risk; and
2. Measurement artefact due to bias such as misclassification bias or reporting bias which may result in over or under estimation.

These possibilities will be discussed in detail in Chapter 7.

5.6 Summary of available data for neonatal cause-of-death analysis around the year 2000

The third objective of the thesis was to undertake a systematic assessment of the coverage and quality of data for neonatal cause-of-death through vital registration systems and in published and unpublished study data in all countries. This chapter has presented a review and analysis of neonatal cause-of-death data from VR systems in 82 countries, and the available data meeting inclusion criteria from 45 countries (48 for VR inputs for intrapartum-related neonatal deaths). The searches and screening for study datasets were presented. The geographic distribution and time trends in publication were summarised, and compared with data for other major causes of child death. There is a dearth of useable data – the VR data cover less than 3% of the world's neonatal deaths but at least the median year of data available was 1999. Despite wide searches in all languages, the study data included only 56 datasets (46 for the intrapartum-related analysis) and 13,685 deaths. Thus there are many geographic gaps. The study data were much older than the VR data with a median year of data collection of 1991, compared to 1999 for the VR data. The input data showed a wide range of cause proportionate mortality, some of which is likely to be real epidemiological variation but some of which reflects inconsistencies, misclassification and biases in cause attribution.

Given the lack of national data for the vast majority of the world's four million newborn deaths, statistical modelling is the only option and Chapter 6 details the methods developed and applied.

Table 5.4 Sources of data for causes of neonatal deaths around the year 2000

	Countries	Percent of neonatal deaths
Vital registration (>90% coverage and comparable ICD 10 coding)	45	< 3% (96,797 deaths, Median year 1999)
Facility-based audit or confidential enquiry	Most northern European countries	< 1%
No available national data	148 Subnational datasets from published and unpublished studies and demographic surveillance sites. Not suitable for direct use for national estimates but possible input for modelling	56 study datasets identified (13,685 neonatal deaths, median year 1991)
Nationally representative sample surveillance sites under development	2 (India and China)	-

Data from: [18].

Chapter 6:
Modelling national-level estimates of neonatal deaths related to intrapartum events (birth asphyxia) using single cause and multi-cause methods
(Objective 4)

Objective 4

Estimate intrapartum-related neonatal deaths for all countries using two different approaches (single-cause and multi-cause models), and to compare these methods and results.

6.1 Single cause modelling to estimate the national estimation of intrapartum-related neonatal deaths

6.1.1 Overview of inputs and outputs for the estimation process

The case definition for intrapartum-related neonatal deaths sought in this analysis was given at the end of Chapter 4, aiming to maximise consistency between the stricter criteria possible to apply in higher income settings, and simpler data from VA assessments. Data inputs for neonatal cause-of-death were identified from two sources: a new analysis of vital registration (VR) data as reported to WHO as of March 2004, and published and unpublished reports of research studies (study data). The analysis, search strategy and inclusion criteria are described in Chapter 5 (figures 5.1 and 5.2), as well as a description of the input data. A random effects model was developed using this input data to predict the proportion of neonatal deaths that were related to intrapartum events. A range of independent predictor variables were tested for fit in the model.

The output national level estimates of the proportion of intrapartum-related neonatal deaths were obtained in one of two ways.

1. Vital registration data: For countries with high coverage (>90%) VR data, these data were analysed in a new analysis using specific ICD 9 and ICD 10 codes (48 countries) and this reported proportion used without adjustment.
2. Random effects model: For countries without reliable VR data, estimates were obtained by applying a regression model developed using VR and study data, and the input of national level covariate data for each country for the year 2000 (145 countries)

For all countries the proportion of neonatal deaths derived either by analysis of VR data or model output was then applied to the national number of neonatal deaths estimated to occur in that country in the year 2000, to predict the numbers of intrapartum-related deaths. Uncertainty ranges were estimated.

6.1.2 Independent predictor variables

A variety of potential independent variables, using national level data for the year 2000, were obtained from databases held by World Bank, WHO, UNICEF and UNDP. A wide range of possible predictors were tested for fit, including any that may be predictive of the proportion of neonatal deaths attributed to intrapartum-related causes. In addition to a dummy variable for type of data (VR or others), the following indicators were tested for fit in the model:

- under-5 mortality rate;
- neonatal mortality rate (NMR);
- gross domestic product (GDP);
- health expenditures;

- WHO sub-regions;
- coverage of care such as vaccination, skilled birth attendance and antenatal care; and
- measures of inequality such as Gini coefficient.

The modelling could only test input predictors for which there were national data available for over 190 countries so that the data could be used as inputs for the national level modelled output. Unfortunately, many of the variables that would be likely to be most closely associated with the proportion of neonatal deaths related to intrapartum events are not available at national level in most high mortality countries. For example, coverage of caesarean section, or measure of quality of intrapartum care such as use of the partograph or use of fetal heart rate monitoring are not available at national level. Large scale surveys tend to track the overall package coverage (e.g. skilled attendance) rather than the specific content of the package in terms of high impact interventions. [198]

6.1.3 Modelling methods and final model

All analyses were performed using Stata version 8 software. A random effects model was used to predict the proportion of neonatal deaths related to intrapartum events. The dependent variable was the logit of intrapartum-related neonatal mortality proportion from VR (48 countries) and from 46 published and unpublished studies meeting the inclusion criteria (chapter 5). The random effects model was fitted using a parsimonious (forwards) approach, testing the above predictors and adding predictors if they reached significance at a level of 5%. The final model was used to predict the proportion of neonatal deaths related to intrapartum events for the 145 countries without VR data.

The final model applied to predict the proportion of intrapartum-related neonatal deaths was (standard errors in parentheses):

$$\text{logit}(\%\ \text{asphyxia deaths}) = \underset{(0.93)}{-1.53} + \underset{(0.62)}{1.83}*(\ln q5) - \underset{(0.09)}{0.28}*(\ln q5)^2 - \underset{(0.13)}{0.30}*(\ln GDP) - \underset{(0.05)}{0.13}*\text{logit}(DPT_3)$$

$$- \underset{(0.03)}{0.05}*\text{logit}(\%\text{skilled birth attendants}) + \underset{(0.07)}{0.23}*(\text{data\_type})$$

Where *lnq5* is the natural logarithm of the national risk of dying between birth and 5 years, *lnGDP* is the natural logarithm of gross domestic product in purchasing power parity, *logit (%DPT$_3$)* is the logit of national coverage of immunisation with 3 doses of Diphtheria, Pertussis and Tetanus toxoid immunisation, and *data type* is a dummy variable for data input type (VR or literature). The goodness-of-fit was satisfactory, as reflected by R-square (0.61). There was no systematic deviation among the residuals. National data for emergency obstetric care coverage were not available. Other covariates such as antenatal care were not found to be significant.

The numbers of intrapartum-related neonatal deaths were derived by applying the proportion to WHO estimates of the national number of neonatal deaths. External validity of the estimates was examined by comparing model predictions to unpublished, population-based data sets (Chapter 7).

6.1.4 Uncertainty analysis

In countries with full VR coverage, 95% uncertainty levels were derived based on the standard errors in the reported VR data. For modelled estimates, uncertainty bounds were generated using the standard error of the prediction of the logit and running 10,000 Monte Carlo simulations. These methods do not take into account uncertainty in the birth cohort or in the WHO neonatal deaths envelope by country.

6.2 Multi-cause modelling to estimate the distribution of seven causal categories of neonatal deaths including intrapartum-related neonatal deaths

6.2.1 Overview of inputs and outputs

Six neonatal cause–of-death categories, plus one residual "other neonatal" category, were selected based on the considerations outlined in detail in Chapter 4, notably public health importance with differing implications for intervention, and ability to distinguish between them in low resource settings. The cause-of-death categories and case definitions used are summarised in Table 4.1.[13;14]

Input datasets for cause of neonatal death were constructed from two sources: a new analysis of VR data and published and unpublished reports of research studies. The inclusion criteria, screening and analysis are described in Chapter 5 in addition to an overview of the input data quantity and quality.

A range of independent predictor variables were examined. Overall 25 predictors related to study design, risk factors, and health service provision were tested for fit in models to predict proportionate mortality. Sources of data were as close as possible to the population in the input data – either the country and year for vital registration, or the closest data available in place and time for study populations.

National level estimates (outputs) of proportionate cause-specific mortality within the neonatal period were obtained in one of three ways (table 6.1):

1. *Vital registration data analysis:* For countries with high coverage (>90%) VR data, a new analysis was undertaken to map the data from multiple ICD 9 and ICD 10 codes onto the five selected cause-of-death categories (45 countries). This analysis is described in Chapter 5.

2. *Vital registration based model for low mortality countries:* For countries without high coverage VR systems but with low neonatal mortality rates (less than 10 per 1000, or less than 15 per 1000 for the regions of Europe and Latin America), estimates were obtained by applying a multinomial regression model developed using VR data from high coverage VR countries, and producing estimates with the input of national level covariate data for the year 2000 (37 countries).

3. *High mortality study-based model for high mortality countries:* For countries without reliable VR data and with high NMR, (over 10 per 1000, or over 15 per 1000 for the regions of Europe and Latin America), estimates were obtained by applying a

multinomial regression model developed using the study data from studies meeting inclusion criteria and producing estimates with the input of national level covariate data for the year 2000 (111 countries).

For all countries the estimated numbers of neonatal deaths due to a given cause were obtained by applying the proportionate mortality derived by one of these three methods (Table 6.1) to the number of neonatal deaths estimated to occur in that country in the year 2000. National estimates were then added up for the 193 countries to give regional and global totals. The 193 countries here differ from the 192 countries referred to elsewhere as Timor-Leste was included as a UN member state.

Table 6.1 Overview of the source of data or modelling for the national estimates (outputs)

Country grouping	Number of countries	Method applied to derive cause specific mortality results
Full coverage VR data	45	VR data used
NMR < 10 per 1000 Or NMR 10 - 15 per 1000 and region is EUR or AMR	17 20	VR model predictions
NMR $\geq$ 10 per 1000 Or NMR > 15 per 1000 and region is EUR or AMR	111	Study based model predictions
Total	193	

6.2.2 Independent predictor variables

A wide range of potential predictor variables were required to testing the fit of the model. Some variables related to the data type or the study site and study design/methods. Other variables were selected from a long list of possible predictors for neonatal proportionate mortality for example, low birth weight rate, skilled-attendant coverage or to specific causes of neonatal deaths (e.g., tetanus-toxoid coverage or TT2+). One limitation on the selection of predictor variables to test in the model was the requirement that national covariate data would be available for all countries for when the model developed would be used for national prediction purposes. Some covariates of interest, such as coverage of emergency obstetric care, or early postnatal/newborn care, are not available at national level for enough countries to be used for prediction.

As discussed in Chapters 4 and 5, few of the input studies were nationally representative and indeed some study populations may be specifically selected to be non-representative, for example for malaria studies, or to test interventions targeting higher mortality populations. Conversely, some studies came from better than average populations where a DSS may have been present for some time. For example, the study populations in the Gambia Medical Research Council (MRC) sites had extremely high coverage of tetanus toxoid immunisation compared to the national average, and consequently had no detected cases of tetanus. Failure to link the local coverage data to the local cause proportionate mortality input data could result in systematic bias in the output estimates. In view of this possible bias, major effort was put into identifying data for potential predictor variables that were as close to the study population as possible in time and place. In some cases these data were reported in the relevant publication, but it was notable how few authors reported even obvious coverage data such as percent of births in facilities. Fifty five principal investigators were contacted to obtain additional information on causes of death and local explanatory variables. The process has detailed previously in Chapter 5. This communication was especially helpful in increasing the number of studies that reported five or more of the selected causes of death, notably tetanus.

If predictor variable data were not available from the study report or the investigator, or other publications from the same site, then data were obtained from DHS surveys giving district or regional breakdown and as close in time as possible to the study, or other local surveys. Table 6.2 summarises the independent variables collected for each study dataset, and the levels at which the data was available. Local or subregional / regional data were identified for over 90% of all 56 studies for all 12 indicators except TT2+ (83%), and those which were essentially national (GDP per capita, Gini index, Child survival inequality index). The Gini coefficient is as a measure of inequality of income distribution where zero corresponds to perfect equality (everyone having exactly the same income) and 1.0 corresponds to perfect inequality. The Child survival inequality index was a composite score used in WHO's World Health Report 2000 and calculated for each country. Gross domestic product per capita is estimated annually by the World Bank and a time series was used so that the GDP data came from the same year as well as the same country as the VR or study data.

A number of variables related to study design and causes of death attribution were also collated for each of the study inputs. These were tested for fit in the study based model, including variables related to the population (global subregion, urban/rural %, median year of data collection) or to design (research site or not, prospective or retrospective, population size, duration of study) and to cause attribution (methods for cause-of-death attribution, numbers of causes distinguished, gestational age measured, stillbirths recorded or not, early neonatal mortality only compared to all neonatal period).

Table 6.2 Independent variables tested for fit as predictors in the study based model

Predictor tested	Level of source of data used		
	Local level %	Regional level %	National level %
Related to the study population			
1. Magnitude of NMR	100	-	-
2. Magnitude of IMR	59	32	8
3. Low birth weight rate	100	-	-
4. Total fertility rate	78	20	2
5. Antenatal care coverage	77	23	-
6. Tetanus toxoid coverage (TT2+)	63	37	-
7. Skilled attendant at birth	51	42	7
8. Institutional delivery	61	39	-
9. BCG coverage	47	36	17
10. Female literacy	53	37	10
11. GDP per capita*	-	-	100
12. Gini coefficient*	-	-	100
13. World Health Report 2000 child survival inequality index*	-	-	100

* National level predictor so not available locally or regionally. GDP: gross domestic product.
Gini coefficient is as a measure of inequality of income distribution

6.2.3 Modelling methods and final models

The focus of this thesis is on the epidemiological inputs and outputs and not primarily on the modelling methods, but a description of the main steps involved in the development of multi-cause models using VR and study-based data is essential for discussion of potential strengths and limitations of the multi-cause estimation results and also for implications for future estimation methods.

All analyses were performed using Stata version 8 software. Modelling was performed separately for the two datasets (VR and study data). This was because in the countries with high coverage of VR data the NMRs did not exceed 15 per 1000 births, there were almost no neonatal deaths due to tetanus and very few attributed to diarrhoea. Hence inclusion of these data in a model to predict for countries where tetanus or diarrhoea are expected to be of public health significance would be likely to introduce systematic bias into the predictions.

As discussed in Chapter 3 of this thesis, there are theoretical advantages for estimation of multiple causes of death in one model, constraining the resultant proportions to sum to 1.0. Multi-cause modelling involves using a fixed "corner cause", which must a cause that is present in each dataset in the input data and ideally a larger proportion that is fairly stable. For example in the VR modelling preterm birth complications was used as the corner cause in the ratios with all the other causes, and in the study dataset modelling, "birth asphyxia" was used as the corner cause. A predictive equation is then established for each the log of the ratio of selected cause against the corner cause. Then all the equations are run simultaneously to estimate the proportionate causal distribution.

The only previous application of this methodology to child mortality had used Seemingly Unrelated Regression (Morris et al)[12] and a number of challenges were identified (Chapter 3). In order to address the challenges we attempted modelling initially with an adaptation of the Seemingly Unrelated Regression and also a multinomial approach which is reported to better handle missing data. Hence we tested a variety of modelling methods (as summarised in Table 6.3), including:

1. Log Ratio Seemingly Unrelated Regression, (Morris method) [12]
2. Multinomial model
3. Final multinomial model

Table 6.3: Comparison of the initial modelling strategies with the final multinomial model for prediction of cause-specific neonatal deaths in countries with neonatal mortality rate greater than 15 per 1000 births

	Log Ratio Model	Multinomial Model	Final multinomial model
Number of parameters in model excluding constants	65 backwards (18 if forwards, parsimonious)	102	16
Intrapartum-related neonatal deaths ("birth asphyxia")	21	24	23
Preterm	30	29	27
Infection	27	29	25
Congenital abnormality	7	5	7
Neonatal tetanus	10	4.4	7
Diarrhoea	2	2	2
Other	4	7	8
Performance in predicting neonatal tetanus deaths	Erratic at country level particularly for smaller portions, notably neonatal tetanus	Neonatal tetanus deaths at country level correlated with WHO estimates but lower	Specific and sensitive at country level for neonatal tetanus deaths, strongly correlated with WHO estimates (CC=0.92). 9 of top 10 countries the same and almost same rank Slightly higher % at global level (6.5 vs 5.1%)

Vaccines and Biologicals, WHO, unpublished neonatal tetanus estimates

Using the Log Ratio model two problems were noted. Firstly, more studies had to be excluded because of missing data. For example diarrhoea was missing as a cause-of-death in some studies despite correspondence with authors. The multinomial model could deal with this by assuming that any diarrhoea deaths were in the infection category, which is a reasonable assumption, but the Log Ratio Seemingly Unrelated Regression model had to exclude these studies. In addition the Log Ratio model appeared to be unstable in estimation of smaller proportionate causes of death, notably neonatal tetanus for which comparison was possible at country level with WHO single cause estimates. For example, the Log Ratio Seemingly Unrelated Regression model predicted large numbers of neonatal tetanus deaths in Morocco (700-8000), compared with a low estimate of 96 from WHO Vaccines and Biologicals department. This phenomenon appeared to be related to the strength of the relationship of tetanus mortality with institutional delivery, and in countries with low institutional delivery but high tetanus coverage the Log Ratio model showed major overestimation of the proportion of neonatal tetanus deaths.

As well as the Log Ratio Seemingly Unrelated Regression model, we applied a novel approach using multinomial modelling which was reported to be able to cope with missing data. This allowed the use of all datasets with at least 6 of the 7 cause categories. However, even with a forwards or parsimonious approach, if the model was built simply on statistical significance alone, for the high mortality model 102 variables were included (table 6.3), raising the risk of generating spurious results. This problem did not arise for the model based on the VR data, possibly because of the small range of NMR and less variability in cause proportionate mortality in the VR data. During the review process with the CHERG, the decision was taken to apply a conservative approach and use an "a priori" approach to selection of predictors to test in the study based high mortality model, in order to minimise the risk of spurious results. Therefore variables were only included in a given equation if the parameter estimate had the expected sign, explained some variability and would be expected *a priori* to be associated with that ratio. For example, we expected that the tetanus:'asphyxia' ratio would be associated with the coverage of tetanus toxoid immunisation, with the ratio decreasing as coverage increases. This then resulted in a third modelling approach, the final multinomial or "a priori" model.

For the final model Ordinary logistic regression was used to develop models for each ratio of cause to corner cause. For the VR data, we used a forward stepwise approach based on statistical significance testing, at the 5% level. For the study data high mortality model we used the *a prioiri* review of predictors and then only tested these indicators for fit in the model. Then the explanatory variables identified using the Log Ratio models as described above were fitted simultaneously in a multinomial model[16] including all causes to obtain parameter estimates for use in predictions. To allow for within-data source correlations, robust rather than model based standard errors were used.

A further difference between the log ratio and the multinomial models is in the default weights they give to observations. The log ratio approach, by default, gives equal weight to each study, regardless of size. The multinomial model, by default, gives equal weight to each death, attributing too much weight to large studies when there is within study correlation. Hence an intermediate weighting was selected in which each death in a given study carried a weight equal to $1/\sqrt{N}$ where N was the number of deaths included in that study. A sensitivity analysis using each weighting assumption in turn made little difference to the model outputs.

Vital registration – the final model

The final model developed from the VR data used inputs from 45 countries and the parameters and R-squared for the equations for the 4 causes. Preterm was the corner cause and is estimated to be the residual proportion after the remaining causes have been predicted (table 6.4.a). The model explained some of the variation between countries in the congenital abnormalities:preterm and infection:preterm ratios, but explained none of the variation in the ratio of "other neonatal" to preterm deaths, and almost none for 'asphyxia' and preterm.

Table 6.4a **Multinomial model parameter estimates for Vital Registration data (44 countries)**

Ratio	Explanatory variable	R-squared [1]	Parameter estimate	95% c.i. [2]
Infection: Preterm	GDP (1000s of US$)	0.41	-0.141	-0.170, -0.112
	GDP squared		0.0024	0.0018, 0.0030
Congenital: Preterm	Low birth weight rate (%)	0.46	-0.132	-0.224, -0.041
	Country in EMR[3]		1.678	1.296, 2.060
	Female literacy rate (%)		0.042	0.017, 0.066
Intrapartum related ("Asphyxia"): Preterm	Low birth weight rate (%)	0.09	-0.098	-0.212, 0.017
Other: Preterm	None	0	-	-

[1] R^2 value obtained when fitting the log(ratio) using linear regression with each study having equal weight
[2] Estimated using robust standard errors adjusting for within country correlations
[3] The majority of countries in the EMR region have relatively high proportions of consanguinity.

Study based data – the final model

The final model developed from the study data used inputs from 56 studies and the parameters and R-squared for the equations for the 6 causal groups are shown in table 6.4b. Asphyxia was the corner cause and is estimated to be the residual proportion after the remaining causes have been predicted (table 6.4.b) The model performed quite well in explaining variation in the infection:'asphyxia' and tetanus:'asphyxia' ratios and explained some of the variation in the congenital 'asphyxia' and diarrhoea:'asphyxia' ratios. The model explained little or none of the variation in the ratios preterm:'asphyxia' and neonatal other:'asphyxia'.

Table 6.4 b Multinomial model parameter estimates for study data (56 studies)

Ratio	Explanatory variable	R^2	Parameter estimate	95% c.i.
Infection: 'asphyxia'	BCG coverage (%)	0.57	0.011	0.004, 0.017
	Neonatal mortality rate per 1000 live births		0.010	-0.001, 0.020
	Female literacy rate (%)		-0.009	-0.016, -0.002
	Study of early neonatal deaths only		-0.716	-1.080, -0.351
Tetanus: 'asphyxia'	Neonatal mortality rate per 1000 live births	0.55	0.037	0.002, 0.072
	Female literacy rate (%)		-0.017	-0.037, 0.003
	Antenatal tetanus toxoid coverage (%)		-0.015	-0.034, 0.004
	Study of early neonatal deaths only		-1.743	-2.616, -0.870
Diarrhoea: 'asphyxia'	Neonatal mortality rate per 1000 live births	0.25	0.039	0.022, 0.057
	Study of early neonatal deaths only		-1.145	-2.573, 0.028
Congenital: 'asphyxia'	Neonatal mortality rate per 1000 live births	0.27	-0.002	-0.023, 0.018
	% of institutional deliveries		0.011	0.003, 0.018
	Country in EMRO		0.670	0.303, 1.037
Preterm: 'asphyxia'	% of skilled attendance	0.14	0.012	0.005, 0.018
	Low birth weight rate (%)		0.025	0.007, 0.044
	Study distinguished preterm and term small for gestational age infants		0.289	-0.116, 0.695
Other: 'asphyxia'	Study of early neonatal deaths only	0.05	-0.683	-1.288, -0.078

Generating national and global estimates

A database was constructed for all countries that are United Nations Members (192) including the estimated numbers of births, neonatal deaths and the predictor variables in the final models. All the data were reported to be from around 2000 and came from global databases of UNICEF, WHO and the World Bank.

For countries with high VR coverage (>90%), we used the reported distribution of causes of death (45 countries, 2.4% of neonatal deaths). The VR model was used to predict the proportional distribution of causes of death in countries without high coverage VR but with an NMR of less than 10 per 1000 (all regions) or with an NMR of less than 15 per 1000 for countries in the European (EUR) and American (AMR) regions as defined by WHO (37 countries, 2.4% of neonatal deaths). EUR and AMR regions had VR data points in the NMR range 10-15 per 1000. For all other higher mortality countries (111 countries, 95.2% of neonatal deaths), predictions were derived using the study data model. For both models, prediction of the distribution of causes of neonatal death at national level required national level covariate data.

We then applied the predicted proportions to WHO estimates of the total number of neonatal deaths occurring in each country[1] to obtain estimates of the number of deaths by cause for each country. External validity of the estimates was examined by comparing model predictions to unpublished, population-based data sets (chapter 7).

6.2.4 Uncertainty estimates for the multi-cause model

Uncertainty estimates were obtained using the jackknife approach which involves removing each study or country in turn from the multinomial model estimation step and running the predictions for that study/country obtained using the remainder of the data. [17] The distribution of the differences between the observed and estimated log ratios obtained provides an estimate of the standard error of out-of-sample predictions. We used Monte Carlo simulation (10,000 simulations) to randomly perturb country-level estimates based on these standard errors and took the 2.5^{th} and 97.5^{th} percentiles to provide an indication of the level of uncertainty in our estimates. This does not capture all the potential sources of variability and uncertainty, such as uncertainty around the number of neonatal deaths in a country, but does provide uncertainty ranges around the input data and the modelling.

Chapter 7

Results and comparison for national neonatal cause-of death estimates using single cause and multi-cause modelling

(Objective 4)

Objective 4

Estimate intrapartum-related neonatal deaths for all countries using two different approaches (single-cause and multi-cause models), and to compare these methods and results.

7.1 Results from single cause model for intrapartum-related neonatal deaths

7.1.1 Overview

An estimated 0.90 million neonatal deaths (range 0.65 to 1.17 million) are intrapartum-related, representing approximately 23% of annual global neonatal deaths (Table 7.1). The numbers are highest in South Asia, with 316,000 in the WHO South Asia region and 129,000 in the WHO region of Eastern Mediterranean which includes Pakistan. Around 245,700 neonatal deaths in Africa are estimated to be due to intrapartum events. There is regional variation in the proportion of intrapartum-related neonatal deaths, ranging from 12% in North America up to 26% in Western Pacific, which is largely reflective of China. The causes for this variation have a number of possible explanations which are discussed below.

Table 7.1 Estimated proportion and numbers of intrapartum-related neonatal deaths according to Vital registration and single cause model estimates for 192 countries summarised by 14 WHO subregions

Subregion [1] (in order of increasing NMR)	**Intrapartum-related neonatal deaths**		
	Cause-specific percent of neonatal deaths [2]	**Estimated cause-specific number of neonatal deaths (000s)** [2]	**[Uncertainty bounds]** [1]
Western Pacific region A	15	0.51	[0.4 to 0.6]
European Region A	14	2.0	[1.7 to 2.3]
Americas A	12	2.4	[2.2 to 2.5]
European Region C	15	3.2	[2.4 to 5.1]
European Region B	24	15.1	[10.7 to 19.6]
Americas B	24	31.7	[29.4 to 34.2]
Eastern Med region B	13	6.8	[4.7 to 8.8]
South East Asian region B	24	24.8	[17.5 to 32.3]
Western Pacific region B	26	128.4	[91.0 to 167.5]
Americas D	22	9.6	[6.8 to 12.5]
South East Asian region D	24	316.0	[223.0 to 410.3]
African region D	23	118.2	[83.6 to 151.0]
African region E	20	116.7	[82.1 to 151.0]
Eastern Med region D	23	129.0	[90.3 to 166.8]
Global estimated numbers of deaths [uncertainty bounds]		904,400 [646 to 1,170]	
Percent of global neonatal deaths		23 %	

Countries in the 14 subregions of the Global Burden of Disease listed in Table B1 in appendix

1. Uncertainty estimates based on 10,000 Monte Carlo simulations of the model

7.1.2 Limitations and sources of bias

Extensive efforts were made to identify the best available information. A new analysis of VR data ensured that the input data from VR and from studies were as comparable as possible. The modelling relies on variation amongst the input data. If variability is due to true epidemiological differences that are predictable then more robust estimates are likely. However if some of the variation between countries and datasets is due to measurement errors or inconsistencies, this affects the estimates. Plausible, but not necessarily mutually exclusive explanations for the variation of the proportion of intrapartum-related neonatal deaths include the following:

1. ***Real variation reflecting differing rates of intrapartum-related neonatal deaths***: For example, in the highest income countries such as New Zealand, UK, Bahrain, Oman and United Arab Emirates between 7 and 11% of neonatal deaths are reported in the VR data analysis to be intrapartum-related, with cause-specific mortality rates of less than 0.5 per 1000. In contrast around 22% of neonatal deaths in Sub Saharan Africa are categorised as intrapartum, a cause-specific rate of around 10 per 1000 births. The proportion is double, but the cause-specific rate is 20 times greater. At high NMR levels the proportion of intrapartum-related deaths may be reduced by higher rates of other causes of neonatal death, notably infections and tetanus. In addition, in very high NMR settings obstetric care may be so distant or low quality that acute intrapartum events are more likely to produce intrapartum stillbirths than in neonatal deaths.[89]

2. ***Over-estimation:*** The use of older case definitions based on clinical status at birth, for example "not breathing at birth" or low Apgar may misclassify into the intrapartum-related deaths category if these older case definitions are applied without a specific hierarchy to remove very preterm babies from the intrapartum category. In addition undetected congenital abnormalities resulting in early death may be misclassified as intrapartum related, although these are more commonly misclassified into the infection categories in VA studies. Measurement tools, particularly the simplest verbal autopsy tools, may overestimate intrapartum-related neonatal deaths because of these factors.

3. ***Under-estimation:*** For example, under-estimation could occur due to misclassification of live births as stillbirths, particularly affecting fresh stillbirth and intrapartum-related neonatal deaths. This may be genuine error or may be a means to avoid response on a VA tool or filling of death certificates. Other misclassification away from the intrapartum category may occur for example where a simple hierarchy is applied removing all preterm infants prior to the intrapartum-related category.[56;129;130] Systematic avoidance of the terms "intrapartum" or "birth asphyxia" may occur in litigious societies where there may be consequences for use of these terms on death certificates.

7.2 Results from multi-cause model for all causes of neonatal deaths including intrapartum-related neonatal deaths

7.2.1 Model results

The results of model prediction for both the VR low mortality and the study-based high mortality models are shown in Table 7.2, along with the jackknife analyses used to estimate the uncertainty range. For the VR model, the mean observed and predicted proportions were close in both absolute and relative terms (maximum absolute difference 0.7%, maximum relative difference 7%). Differences were slightly larger for the study data model (maximum absolute difference 2.1% [asphyxia], maximum relative difference 21% [diarrhoea]).

Table 7.2 Estimated proportionate cause-of-death for 4 million neonatal deaths in the year 2000 based on multi-cause Vital registration and study data models

Cause	Vital registration Mean proportion of deaths across 44 countries		Study data Mean proportion of deaths across 35 studies with all causes recorded		Estimated global number (%) of deaths (millions)	Uncertainty range around the global point estimate[1]
	Observed (Range)	Predicted	Observed	Predicted		
Preterm	40.3% (17-66%)	40.5%	32.7% (8-71%)	32.0%	1.12 (27.9%)	0.74 – 1.38
Infection	9.2% (2-26%)	9.8%	23.6% (3-58%)	22.3%	1.04 (26.0%)	0.69 – 1.24
Intrapartum-related ("birth asphyxia")	14.4% (6-33%)	13.8%	19.9% (4-42%)	22.0%	0.91 (22.8%)	0.60 – 1.08
Congenital	30.1% (9-53%)	29.8%	8.5% (0-39%)	7.8%	0.30 (7.4%)	0.22 – 0.48
Diarrhoea	-	-	2.9% (0-21%)	2.4%	0.11 (2.8%)	0.08 – 0.41
Tetanus	-	-	7.0% (0-50%)	7.9%	0.26 (6.5%)	0.20 – 0.79
Other	5.9% (0-13%)	6.1%	5.4% (0-23%)	5.6%	0.26 (6.6%)	0.19 – 0.62
Total					4.00 (100%)	

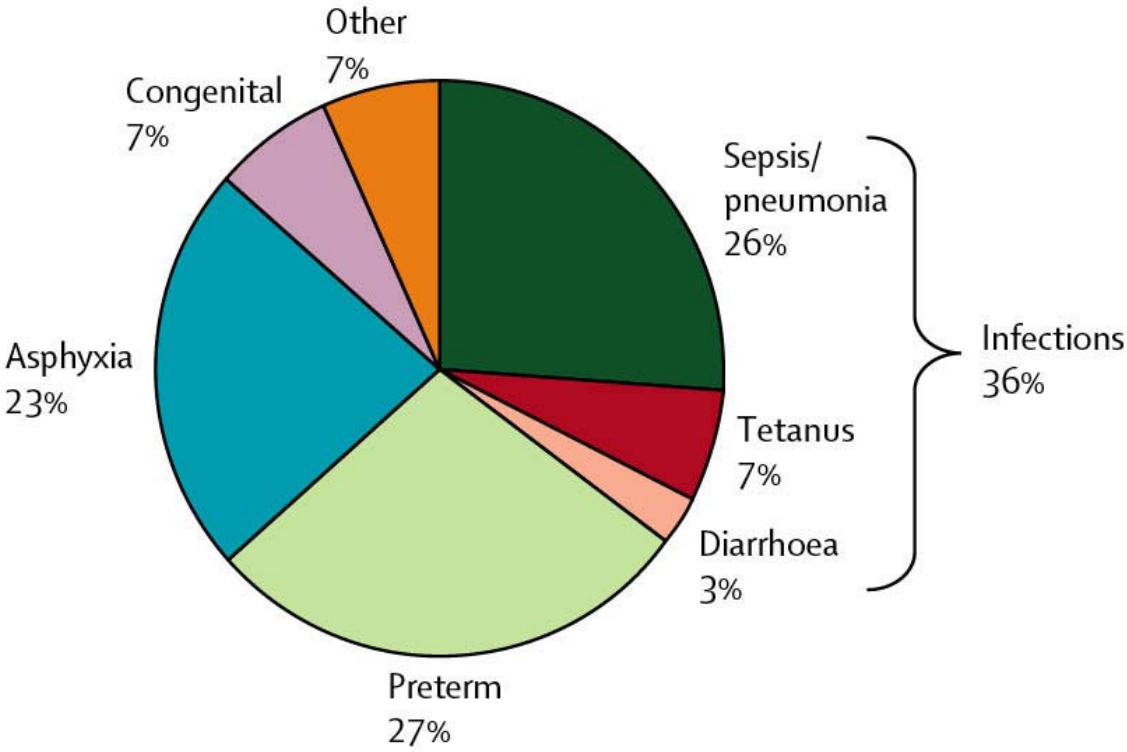
For the observed data the range is shown. For the predicted proportion, the 95% CI by parameter are shown in Table 6.4a for the VR modelled estimates and Table 6.4b for the study data modelled estimates

[1] Uncertainty estimates around the global point based on jackknife analysis and 10,000 Monte Carlo simulations whereby each input observation in turn is dropped from the database for the multinomial modelling. The distribution of the differences between the observed and predicted log ratios provides an estimate of the standard error of the out-of-sample predictions (see 6.2.4 for more detail)

7.2.2 Global and regional distribution of causes of neonatal deaths

The estimated global distribution of the causes of neonatal deaths is shown in Figure 7.1, with global point estimates and uncertainty ranges in Table 7.2. Three major cause groups predominate - preterm birth, birth asphyxia and infections (sepsis or pneumonia, diarrhoea, tetanus) – with each responsible for approximately one quarter to one third of all neonatal deaths. The remaining deaths (approximately half a million) are distributed across the remaining causes of congenital, and "other neonatal" The "other neonatal" category includes specific conditions such as haemorrhagic disease of the newborn and jaundice which were specified in too few of the input datasets to be estimated separately, although such delineation is possible in the VR data.

Figure 7. 1 Estimated distribution of direct causes of 4 million neonatal deaths for the year 2000



Source: Lawn JE, Cousens SN, Zupan J Lancet 2005 for 192 countries based on cause specific mortality data and multi cause modelled estimates.

The multi-cause estimates are broadly consistent with the available single cause estimates at global level (Table 7.3). Using different approaches, deaths in the year 2000 have been estimated at 220,000 for neonatal tetanus[7], at 904 400 for acute intrapartum events, [6] and at 1.33 million for prematurity, although the latter includes deaths attributed to preterm birth up to the age of 5 years.[7] Each of these estimates lies well within the uncertainty range in the multi-cause estimates. A comparison of these country-level estimates for neonatal tetanus deaths with those produced by WHO Vaccines and Biologicals Department shows reasonable agreement; seven of the ten countries with the highest numbers of neonatal tetanus deaths according to WHO are in agreement with these predictions.

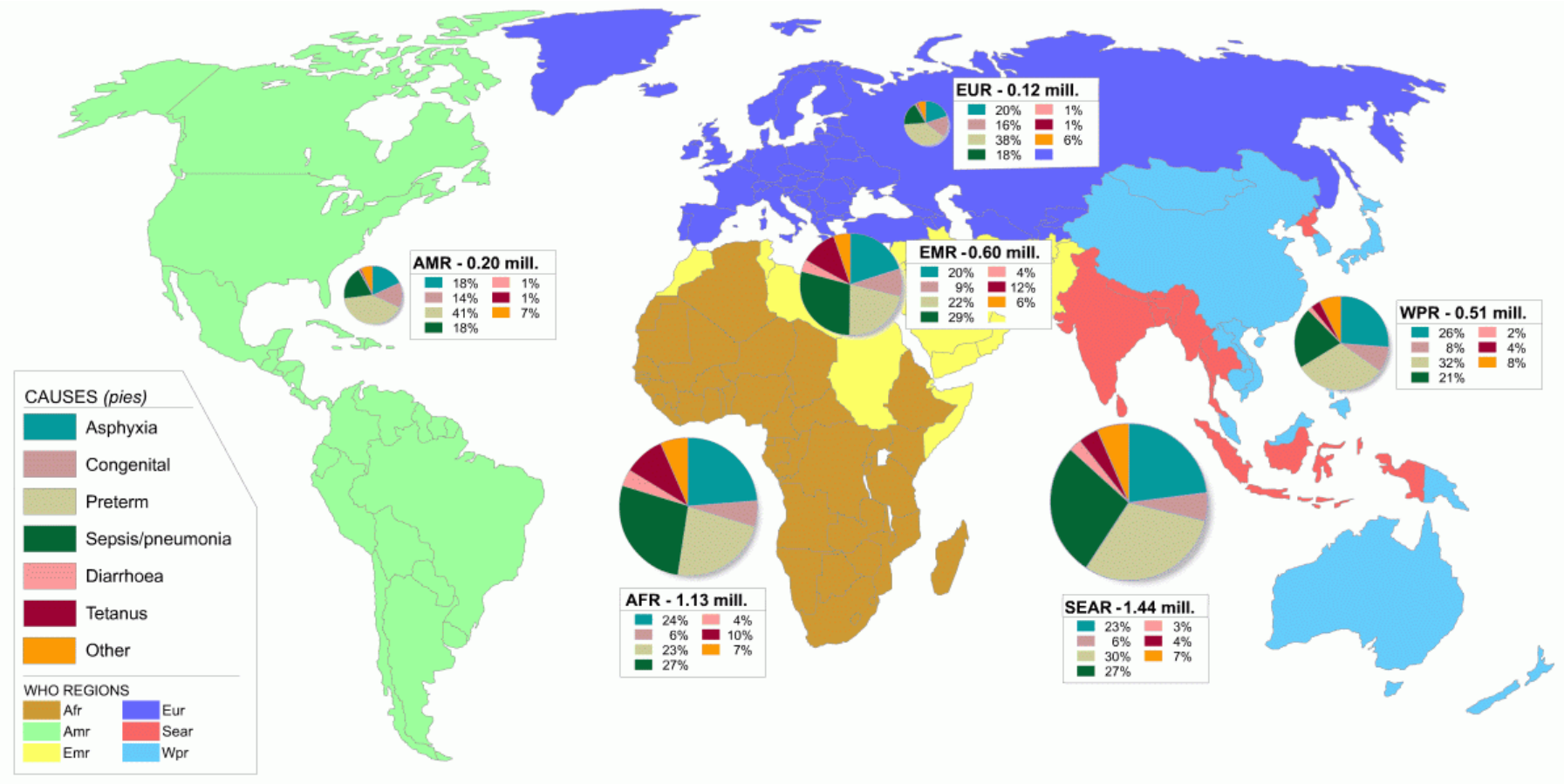
Table 7.3 Comparison of neonatal multi-cause results with existing estimates

Neonatal COD category	Neonatal multi-cause model	Global Burden of Disease version 2004	Other single cause estimates
Intrapartum events ("Birth asphyxia")	910,000 (0.69 – 1.24 million)	751,545*	904,400[51] (0.65 – 1.17 million)
Preterm ('LBW')	1,120,000 (0.74 – 1.38 million)	1,330,269*	
Congenital	300,000 (0.22 – 0.48 million)	462,574*	
Neonatal tetanus	260,000 (0.2 – 0.79 million)	214,604*	200,285 #
Infection/ARI	1,040,000 (0.69 – 1.24 million)	NA	
Diarrhoea	110,000 (0.08 – 0.41 million)	NA	
Other	260,000 (0.19 – 0.62 million)	NA	

* applies to the entire period 0 to 4.99 years, not restricted to the neonatal period
# Tetanus estimates from WHO Vaccines and Biologicals unpublished estimates

There is considerable variation in proportionate cause by region, particularly for neonatal tetanus, diarrhoea and congenital malformations (Fig 7.2) but in all cases the three main causes predominate. Neonatal tetanus is mainly confined to Africa, South Asia and the Eastern Mediterranean regions, and in these higher mortality regions infections and diarrhoea account for 30 to 33% of neonatal deaths. The proportion of deaths attributed to preterm complications in the Americas (41%) is almost double that in Africa (23%). Western Pacific is the only region where the proportion of deaths attributed to intrapartum exceeds that attributed to preterm – more analysis and better data are required to ascertain whether this is a true reflection of the lower preterm birth prevalence in the region or a measurement artefact.

Figure 7.2 The estimated distribution of causes for 4 million neonatal deaths for the six WHO regions in the year 2000



Size of circle represents number of deaths in each region. AFR=Africa. AMR=Americas. EMR=Eastern Mediterranean. EUR=Europe. SEAR=Southeast Asia. WPR=Western

Source: Lawn JE, Wilczynska-Ketende K, Cousens SN. Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol 2006; 35(3):706-718.

7.3 Comparison of model results with local data

7.3.1 Comparison of single cause model results with local data

Table 7.4 compares model predictions with unpublished population-based data from 4 high-mortality countries. These datasets met the inclusion criteria (Chapter 5), but were not included in modelling. A paired t-test did not detect a statistically significant difference between observed and predicted proportions (p=0.76). The average absolute difference between observed and predicted proportionate mortality was only 4%.

Table 7.4. Consistency of single cause estimates with unpublished data from population-based datasets

Country	Study site	Percentage of neonatal deaths related to intrapartum events	
		Unpublished population-based data (Number of neonatal deaths) [95% Confidence Interval]	National estimate predicted by model (%) [uncertainty range] #
Gambia[1]	Rural community with primary healthcare and some access to emergency obstetric care	19 % (78) [18-20]	22 [16-28]
Tanzania[2]	Urban (Dar es Salaam): Rural (Hai): Rural (Morogoro): National weighted result	18 % (91) 25 % (142) 33 % (158) 29 % [28-30]	26 [19-33]
Bangladesh[3]	Peri-urban community in Dhaka with potential access to emergency obstetric care	24 % (124) [23-25]	30 [22-38]
Pakistan[4]	Rural site with limited access to basic and emergency obstetric care	26 % (154) [25-27]	23 [18-29]

No significant difference detected between observed and predicted proportions. Paired t test 0.76

1. Walraven G, personal communication, March 2004
2. Setel P, Whiting D, Hemed Y, personal communication March 2004. National result derived from 3 sites using p-weights based on census data for 2002
3. Perry H, personal communication, March 2004
4. Bhutta Z, personal communication, April 2004

#Uncertainty range based on standard error of the logit using 10,000 Mote Carlo simulations (see 6.1.4 for more detail)

7.3.2 Comparison of multi-cause model results with local data

Comparison of the multi-cause model predictions with unpublished population-based data from 2 high-mortality countries (India and Ghana) are shown in Tables 7.5 a, b. These datasets met the inclusion criteria (Chapter 5), but were not included in modelling. The four studies used to compare the model predictions from the single cause model could not be used for comparison with multi-cause model estimations because they were included as input data in the multi-cause model. The VR data analysis categories and results (without predictive modelling) are compared with national surveillance confidential enquiry data for England, Wales and Northern Ireland (Table 7.5b). [137]

The study from India is a setting with high NMR (57 per 1000) – almost 50% higher than the national average (Table 7.5a).[56] Overall the study and model data match reasonably well, although for the small proportionate causes (diarrhoea, congenital) small absolute differences are large in percentage terms. Not surprisingly, the study data have a higher proportion of deaths attributed to tetanus and neonatal infections – this would be expected at such a high NMR. While the preterm birth proportion predicted by the model and the study are the same (35%), the study attributes a much lower proportion of neonatal deaths to birth asphyxia. The algorithm or hierarchy used in this study places all deaths in preterm neonates above asphyxia. This hierarchy may explain the low asphyxia and high preterm proportions for this level of NMR, especially as gestational age data were not available; the preterm category here is apparently dependent on maternal perception of gestational age and/or size. In this population where the LBW rate is around 30%, hence term babies who were small for gestational age (and at higher risk of intrapartum injury) or borderline preterm infants could be misclassified into preterm cause-of-death category from intrapartum–related category of neonatal deaths.

The study from Ghana (Table 7.5b) has a moderate NMR level (31 per 1000), but is lower than the national average NMR of 42 based on DHS.[99;141] Differences between the study data and model predictions are more than for the Indian study but have plausible explanations. Fewer tetanus deaths in the study area are to be expected as the NMR is lower than national level, although the study reports a higher proportion of infections. The multi-cause model predicts congenital to be 6% of neonatal deaths and the study reports 3%. As discussed before, VA tends to underestimate congenital cause-of-death, particularly cardiac abnormalities so these may have been undetected. The major difference is between the categories of preterm and asphyxia, where the study reported 10% higher in asphyxia and 6% lower in preterm compared to the model predictions. The case definition used in the study for birth asphyxia was “not breathing at

birth". Although the specified hierarchy put preterm above birth asphyxia, the categorisation was undertaken by three experts, not a computer algorithm. Thus it is likely the proportion in the study may be inflated compared to a stricter intrapartum-related definition.

The data from England, Wales and Northern Ireland comes from a CEMACH 2004 annual report.[137] The confidential enquiry data is drawn from a rapid reporting system in facilities, and are compiled by CEMACH offices. When the CEMACH data is cross checked with registration data for stillbirths and neonatal deaths from the Office of National Statistics[137] the CEMACH data capture is currently higher than the VR capture especially for stillbirths. The VR data are for 2000 so not are not exactly comparable with the CEMACH input data here for 2004, but the results are very close (Table 7.5c). The analysis of multiple VR codes and mapping onto the selected cause-of-death categories seems to match well the classification and the data collected through the confidential enquiry process. However the VR data does not included the richness possible in the CEMACH data where analysis by gestational age is possible, as well as multiple other variable of interest for programmatic action.[138]

Table 7. 5a Comparison of neonatal multi-cause model predictions with study neonatal cause-of-death data - India

	Study description		Comparison of study and model neonatal proportionate mortality results					
			Cause-of-death	Study result (%)	Model result (2004) (%)	Absolute diff	% diff	Comment
India	NMR (national NMR)	57 (39)	Intrapartum related ("birth asphyxia")	19	22*	3	14	Lower asphyxia % in study may be explained by hierarchy used in the study with all preterm births placed above birth asphyxia, but not accurate measure of gestational age, so term IUGR or borderline preterm infants with intrapartum –related neonatal deaths could be misclassified into preterm cause-of-death category
	Population representativeness	Poor, rural pop, higher than national NMR	Preterm	35	35	0	0	No difference
	Population size	61,591 households	Infections	31	25	-6	-24	Expect infection % to be higher in study population as higher NMR
	Health system context	Approx 30% births at home, no intensive care	Tetanus	5	4	-1	-25	Expect tetanus % to be higher in study population as higher NMR than national
	Date	Not specified - estimated to be 2002-2004	Diarrhoea	2	2	0	0	No difference
	No. neonatal deaths	1048	Congenital	8	6	-2	-33	Expect congenital % to be higher in study population as high consanguinity
	Methods	Retrospective survey and verbal autopsy, causes allocated by computer algorithm	Other	NA	6	NA	NA	138 deaths unallocated as no "specific other" category in hierarchy

Study data source for India.[56]

Model predictions using the same multi-cause model as for 2000 but revised for Countdown 2004 with latest coverage data and used here as better time period match to the study data

* The single cause model prediction for India is 21%

Table 7. 5b Comparison of neonatal multi-cause model predictions with study neonatal cause-of-death data - Ghana

	Study description		Comparison of study and model neonatal proportionate mortality results					
			Cause-of-death	Study result (%)	Model result (2004) (%)	Absolute diff	% diff	Comment
Ghana	NMR (national NMR)	31 (42)	Intrapartum related ("birth asphyxia")	33.5	23*	-10.5	-46	Higher % in asphyxia may be explained by non-specific case definition (not breathing at birth)
	Population representativeness	Rural population, lower than national NMR	Preterm	20	26	6	23	Probable misclassification from preterm to birth asphyxia
	Population size	4 districts (out of 110)	Infections	38	32	-6	-19	Not major difference
	Health system context	Approx 50% births and neonatal deaths at home, no intensive care	Tetanus	0.5	4	3.5	88	Expect tetanus % to be lower in study population as lower NMR than national
	Date	Jan 2003- June 2004	Diarrhoea	2	3	1	33	Minimal absolute difference
	No. neonatal deaths	623	Congenital	3	6	3	50	Probable under-detection of congenital using verbal autopsy (especially cardiac)
	Methods	Demographic surveillance and verbal autopsy, expert medical opinion for allocation	Other	3	6	3	50	Low % attributed to specific other may reflect tool and expert focus on major causes

Study data source for Ghana[99;141]

Model predictions using the same multi-cause model as for 2000 but revised for Countdown 2004 with latest coverage data and used here as better time period match to the study data

* The single cause model prediction for Ghana is 23%

Table 7. 5c Comparison of neonatal multi-cause VR analysis with real national neonatal cause-of-death data - England, Wales and Northern Ireland

	Study description		Comparison of study and VR analysis neonatal proportionate mortality results					
			Cause-of-death	National result (2004) (%)	VR data (2000) (%)	Absolute diff	% diff	Comment
United Kingdom	NMR (national NMR)	3.7 (same)	Intrapartum related ("birth asphyxia")	11	14	3	21	Minimal absolute difference, although percentage difference is large. Difference in year (2000, 2004) may be a factor.
	Population representativeness	All of UK	Preterm	48	45	-3	-7	Minimal absolute difference
	Population size	60.5 million	Infections	7	6	-1	-17	Minimal absolute difference
	Health system context	High income, full coverage including intensive care	Tetanus	0	0	0	0	Not estimated
	Date	2005	Diarrhoea	0	0	0	0	Not estimated
	No. neonatal deaths	2,380	Congenital	23	28	5	18	Model may not fully account for increasing termination of pregnancy
	Methods	National reporting and surveillance	Other	7	7	0	0	Specific other the same, but 2.5% allocated to SIDS, 1.3% unknown or unclassified

National data source for England, Wales and Northern Ireland, 2004[137]
VR data analysis, input data 2000

7. 4 Comparison of single cause and multi-cause results

7.4.1 Comparison of results from the two modelling approaches

Remarkably, despite the differing approaches for the multi-cause and single cause models, the global point estimates for intrapartum-related neonatal deaths are almost the same, at 0.904 and 0.91 million respectively. Indeed, the uncertainty estimates are also very close (0.65–1.17 million and 0.60-1.08 million), although also generated by different methodologies (Chapter 6).

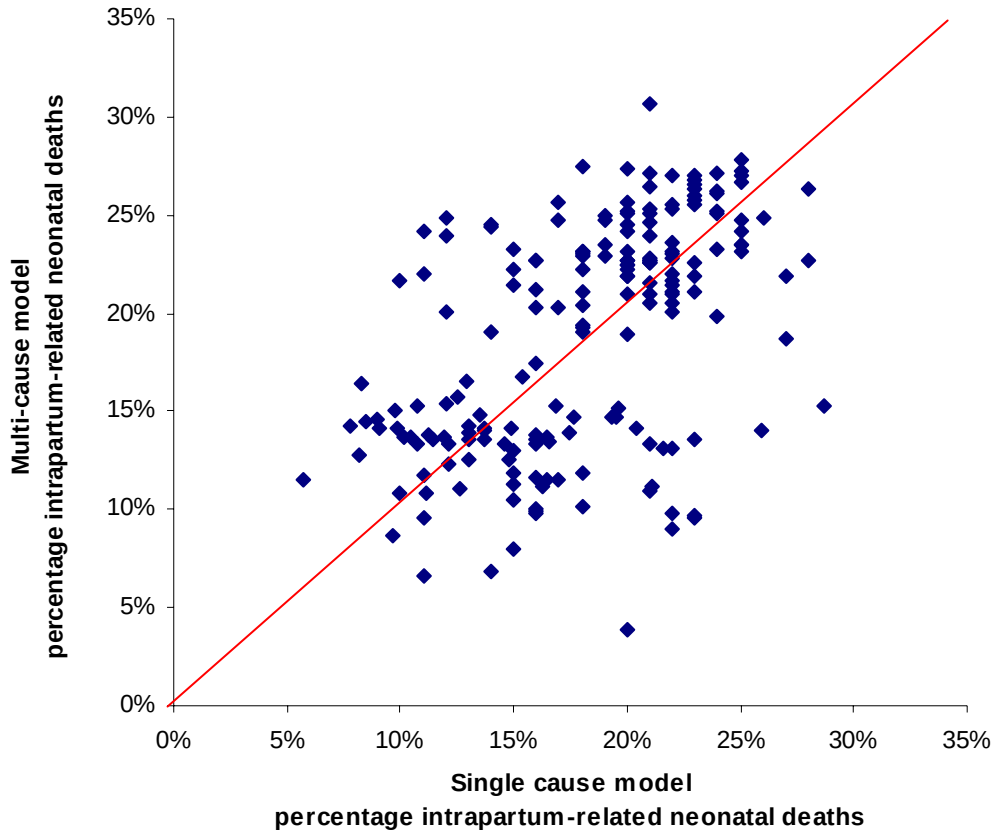
Given the close match of the input databases, apart from the additional unpublished datasets included for the multi-cause model, perhaps this is not surprising. However, it may be that the global agreement is a coincidence whilst regional or country estimates disagree. Table 7.6 shows a regional comparison of the single and multi-cause results for the proportion of neonatal deaths that are intrapartum-related. There is very little difference in absolute terms. The percent variation ranges from 4% to 22%, with the biggest difference in the Americas and Europe. However, although the difference is apparently greatest in the low mortality regions, there is not a consistent direction in this difference – the single cause model predicts a higher proportion in the Americas and a lower proportion in Europe compared to the multi-cause model.

Table 7.6 Comparison at regional level of the proportion of intrapartum-related neonatal deaths ("birth asphyxia") comparing estimates from single cause and multi-cause modelling

Region	Numbers of neonatal deaths (1000s)	Proportion of neonatal deaths estimated to be due to asphyxia	
		Single cause model results	Multi-cause model results
Africa	1128	21%	24%
Southeast Asia	1443	24%	23%
Eastern Mediterranean	603	23%	20%
Western Pacific	512	25%	26%
Europe	116	18%	20%
Americas	195	22%	18%
Global average		23%	23%
Global total (1000s)	3,997	904 (650 to 1170)	910 (600 to 1080)

A national level comparison of the two sets of estimates shows a wide scatter (figure 7.3). There appears to be a cluster of countries with lower proportions (> 15%) with some agreement and then a cloud of scatter. Then at higher proportions (20% to 30%) the multi-cause model seems to estimate a slightly higher proportion than the single cause model. Clearly the coincidence of the same point estimate at global level is just that – a coincidence based on a combination of higher and lower estimates in each set that happen to come to the same total. This emphasises the challenges involved in using estimates at national level, the need for more analytic work to advance model work and to include uncertainty limits on national estimates. The punch line remains the same - improved input data is the only real answer. Much of this uncertainty is due not just to lack of data but also to low quality or inconsistent cause attribution.

Figure 7.3 Comparison for 192 countries of the proportion of intrapartum-related neonatal deaths ("birth asphyxia") comparing estimates from single cause and multi-cause modelling



* The red line is a 45 degree line representing equality between the two sets of estimates

7. 5 Summary of the comparison of the two modelling approaches

The objective of this chapter, and Objective 5 of the thesis, includes a comparison of the single and multi-cause modelling methods. Table 7.7 summarises the similarities and differences for each step of the estimation process. In both exercises the same case definitions for intrapartum-related neonatal deaths was specified, although both remain at the mercy of the VR data death certificate certifier or the study investigators in terms of the details and application of the case definition in reality. The input data for the two exercises is very similar (Chapter 5). The results at global level are remarkably similar – both giving 23% of the global total of neonatal deaths and both falling well within each others uncertainty range. The regional results are not very different (Table 7.6) although at national level the predictions exhibit major variation (figure 7.3). The main difference lies in the modelling methods.

The limited available single comparisons of each model suggests they perform with an acceptable level of consistency compared to real local data, and that more marked variations in proportionate mortality results could be explained. However in order to make a definitive statement on which method (single or multi-cause) is performing better at national level a "gold standard" would be required to compare with national level predictions from both models. Such a reliable measure of intrapartum-related neonatal deaths in a number of countries, at national level does not currently exist. One more limited option is to compare the single cause model predictions against the two studies in high mortality settings used to validate the multi-cause model. In the Indian study (Table 7.6a) the reported intrapartum-related percentage was 19%, the multi-cause model predicted 22% and the single cause model predicted 21%. In the Ghanaian study (Table 7.6b) the reported percentage was 33.5%, the multi-cause model predicted 23% and the single cause model also predicted 23%. In these two examples the single and multi-cause model estimates were close to each other and the study comparison data for India was reasonably close but for Ghana was very different, possibly because of the use of an older case definition for "birth asphyxia". However, the possibility remains that at national level both models may be sometime overestimating and sometimes underestimating, influenced by the weaknesses in the input data variation for proportionate cause. If a considerable proportion of the variation is measurement and misclassification issues, particularly with older case definitions of "birth asphyxia", this may be more challenging to predict in a model.

Overall multi-cause modelling holds a number of the advantages compared to single cause modelling as laid out in Chapter 3. The major advantage is the consistency and transparency by

which multiple cause estimates can be produced within a given time period (for example neonatal), avoiding expert opinion in combining multiple single cause estimates which are very unlikely to add up to 100% just by chance. On this basis the multi-cause estimates are the most likely to be used widely and to receive further investment in refining, unless the single cause estimates can be convincingly demonstrated to be superior for national level predictions.

Table 7.7 Comparison of single and multi-cause models for estimation of intrapartum-related neonatal deaths

Step in estimation process	Single cause model	Multi-cause model
1. Case definitions for intrapartum neonatal deaths	Same definition sought Same limitation with input data in terms of consistent application of the case definition or detailing of case definition and hierarchy	
2. Input data for cause-of-death	VR data – 48 countries Study data – 46 studies, 12,335 deaths	VR data – 45 countries (44 as model inputs) Study data – 56 studies, 13,685 deaths
3. Methods and modelling	Single cause	Multi-cause
4. Predictors in final equation for intrapartum-related neonatal deaths	Regression model equation including: - Under five mortality rate - Gross domestic product per capita - DPT3 immunisation coverage - Skilled birth attendant coverage	Multinomial model with log ratio equations for all the causes against one corner cause: - Study-based model: Asphyxia estimated as the residual of all the other causes as asphyxia was the corner cause - VR based model for log of ratio of asphyxia/preterm ratio the only significant predictor was low birth weight rate
5. Global results	904,400 (0.65 – 1.17 million)	910,000 (0.60 – 1.08 million)
6. National results	Very poor agreement at national level and no obvious pattern	
7. Uncertainty ranges	Provided at global level, but not at regional or national level	Provided at global level by cause, but not at regional or national level
8. Review process	Expert review process at WHO and peer review	Expert review through CHERG and UN and peer review process
9. Comparison of model predictions with local data	Model predictions compared well with data from 4 studies in high mortality settings and performed well	Compared with data from 2 high mortality studies and VR data in one low mortality country. Performed well for VR data but for the studies the most variability was for the birth asphyxia category

Chapter 8
Implications for improving estimation methods and data collection (Objective 5)

Objective 5

Summarise actions to improve estimates and input data for neonatal cause-of-death, listing research priorities

8.1 Overview of neonatal cause-of-death estimates and their application

These are the first systematic global estimates of intrapartum-related neonatal deaths aiming to use a more specific case definition, shifting from previous use of "not breathing at birth" and attempting to exclude preterm infants and congenital abnormalities. However changing from the strongly held term "birth asphyxia" will take time. Using two different methods, an estimated 23% of neonatal deaths globally are associated with acute intrapartum events, over 900,000 deaths each year. Closely associated with this loss of almost one million live born infants, are an additional 1.02 (range 0.66-1.48) million intrapartum stillbirths,[51] accounting for 32% of 3.2 million stillbirths.[51] This total burden of around 2 million intrapartum-related deaths is largely invisible in both safe motherhood and child survival programme priorities. Improving health systems at the time of childbirth potentially holds a triple benefit - reducing neonatal mortality and intrapartum stillbirths as well as many of the estimated 0.5 million maternal deaths a year.

These are the first systematic, country-level estimates for multiple causes of neonatal death, detailing inputs and methods, as well as providing uncertainty estimates.[1;11] The WHO has used these estimates in the World Health Report 2005[1;11] and has now institutionalised the methodology in the United Nations process for national and global estimates. In addition, these results were incorporated in the World Bank Disease Control Priorities publication and Data volume,[199] and are used for the GBD for the year 2005 (www.globalburden.org).

Improving the estimates and data is not an end in itself, but is a means of moving to more attention, investment and action especially for the poorest countries, and indeed also the poorest families in transitional and even in rich countries. While global estimates are helpful for visibility and increasing policy and programme imperative, the most important use for cause-specific data is at national and programme level. The marked variation in cause proportionate mortality emphasises the need for local data for decision-making (Figure 8.1). At country level these estimates and an update for 2004 have been used for national data profiles for newborn health in 46 countries in Africa,[38] and an input for MDG profiles for the 68 priority countries[198] in the Countdown to 2015 reports.[33]

Although the uncertainty around modelled estimates is considerable at global level, it is wider still at country level. The major mismatch at country between the single and multi-cause model results for intrapartum-related neonatal deaths underlines the many factors affecting estimation at this more specific level. However, the data being used for programmatic priority setting in low income countries may be so misleading that national estimates are seen as a useful input

particularly where current data are utterly lacking or are misleading for programmes. For example, in Ethiopia only 6% of births occur in hospital and less than 5% of the estimated 120,000 neonatal deaths are in facilities. Yet the data for neonatal deaths in facilities was used as the basis for decision-making for the national child survival strategy in 2005. This pie chart reported very few neonatal deaths due to tetanus, a low proportion of neonatal infections and included a very high proportion of intrapartum deaths, probably because of referral bias. The multi-cause model estimates suggests that in Ethiopia tetanus accounts for 7% and sepsis/pneumonia for 36% of neonatal deaths. These are the most feasible causes to address in the local health system context. The Ethiopian Federal Ministry of Health and UN agencies are now using the new neonatal cause-of-death estimates as basis for planning.

Even in South Africa there are no nationally representative, reliable cause-of-death data for neonates. Vital registration coverage is at about 80% of adult deaths, but lower for neonatal and child deaths. Facility based audit data for the national Perinatal Problem Identification Programme (PPIP), or "Saving Babies", covers about 20% of births[200] and predominantly pre-discharge deaths, selectively missing infections in the late neonatal period. Policy dialogue around the estimates from the multi-cause model has raised awareness of the "missing" infections in the national data and highlighted the need to address these programmatically, and also to improve data collection.

Proportionate cause-of-death in the neonatal period is closely associated with the level of NMR (Figure 8.1). The higher the NMR is, the greater the proportion of deaths due to infections and tetanus. For example, at NMRs of over 45 per 1000 more than half of neonatal deaths are due to infections and tetanus, whereas at NMRs of less than 15 only 15% are due to infections and tetanus is a negligible proportion.[2] Hence if there are no useable data for neonatal cause-of-death and no local estimates, the level of NMR can be used as an approximate guide, at least for programme priority setting.[27] This variation of cause proportionate mortality by NMR level has been used in some planning and prioritisation exercises to phase neonatal care strategies.[27]

These estimates advance the science of systematic cause-of-death estimates, particularly in terms of simultaneous estimation of multiple causes of death within a given time period. The uncertainty estimates provided are wide but still do not capture all the potential sources of uncertainty. The next section of the thesis discusses in more detail the estimation process and implications for future estimation.

Figure 8.1 Estimated distribution of causes of neonatal death for 192 countries, according to the level of neonatal mortality rate

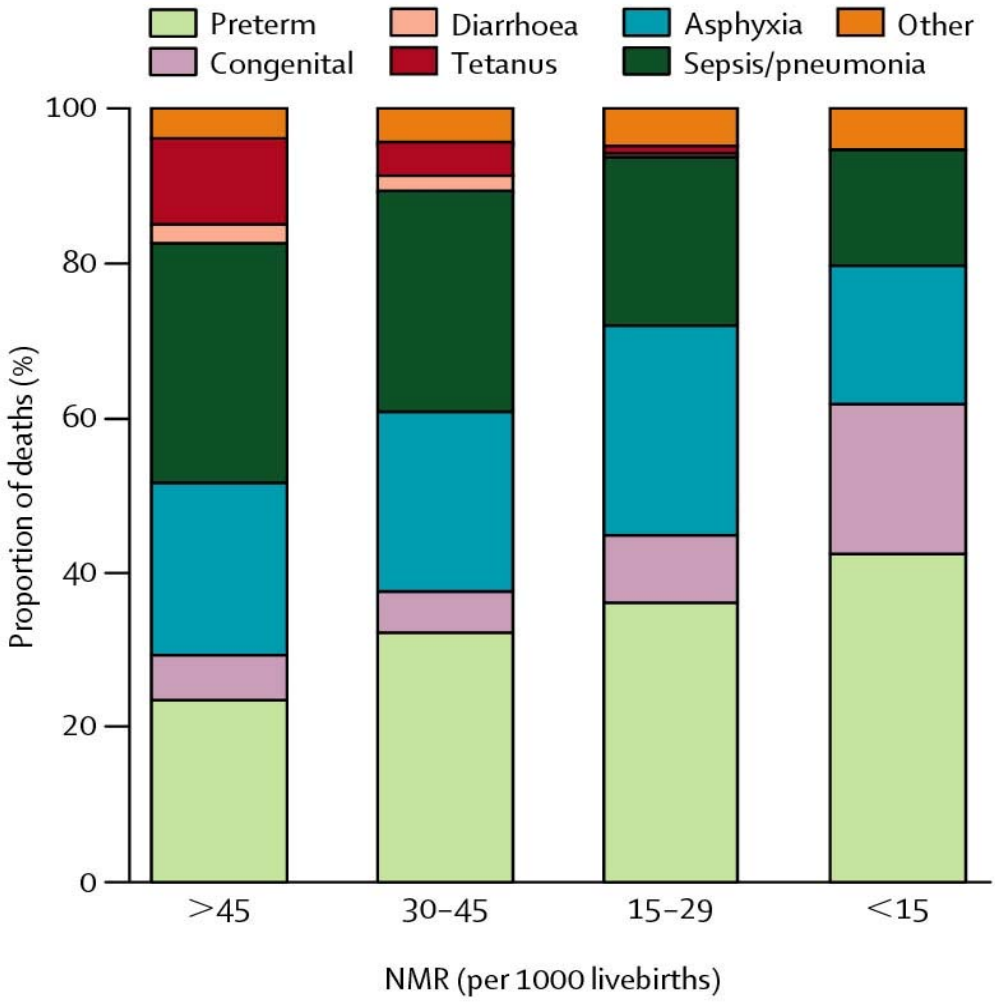


Figure from Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-900.

8.2 Improvements implemented for estimation of neonatal cause-of-death, limitations and implications for improving future estimation

In developing these neonatal cause-of-death estimates recent advances in global estimation science have been applied (Chapter 3). Further innovation introduced particularly for multi-cause estimation which has many theoretical advances but in reality is challenging to undertake, particularly given the complex statistical approaches required.[12] Despite the wide uptake of the results by the UN,[1;11] Countdown[33] other global burden groups, and national level use, major limitations remain. The estimates for 95% of neonatal deaths (111 countries, 3.8 million deaths, study data model) were based on data on fewer than 14 000 neonatal deaths from 56 studies. The substantial uncertainty around these estimates is inevitable given the limited quantity and quality of data from the settings in which the great majority of neonatal deaths occur, and improving the input data will be discussed under section 8.3. In this section the focus is on further improvement of the estimation process. In order to systematically examine the strengths and weaknesses of this work and implications for future advances, the steps in the estimation process outlined in Chapter 3 will each be examined in turn and summarised in table 8.2.

8.2.1 Case definitions for cause-of-death

The lack of consistent case definitions and rules in hierarchical assignment of causes hinders comparisons across time and between studies, and particularly between VR and verbal autopsy (VA) data. There was substantial variation in the distributions of causes between individual data sources in both the VR and the study datasets, although highest for the study data (Chapter 5). The equations within the multi-cause model explain only some of this variability, and the R-squared value is better for some causes, e.g. tetanus. Challenges in predicting ratios involving the "other neonatal" cause category are not surprising since this category is a combination of several specific causes of death such as jaundice and haemorrhagic disease of the newborn and hence hard to predict as one entity. Some of the variation in proportionate mortality by cause shown in the input data is likely to be due to true epidemiological variation. For example, in figure 2 the outlying studies with a higher proportion of tetanus deaths were from populations with extremely low (<10%) tetanus immunisation coverage.

Inconsistencies in the attribution of cause-of-death also play an important role, however. Preferences were apparent for certain codes in certain countries and also probable misclassification between causes such as between preterm and infections in both VR and VA data (Chapter 5). Addressing this issue in input data is not possible through modelling alone but

modelling advances may contribute to some extent. If datasets with significant misclassification could be identified consistently and objectively and if the direction of the effect is consistent then a dummy variable could be introduced into the cause specific equation to reflect this. Another more feasible option, at least for the study data, is the introduction of a dummy variable for quality of case definitions and hierarchy applied. We did test a number of data quality scores but none remained in the final model. Hence, the only real solution is improvement in the input data, which is discussed in Section 8.3.3.

8.2.2 Input data and inclusion criteria

There are challenges to overcome in developing estimates, not least of which is the lack of reliable data.[46] While inclusion criteria were explicit, in many cases authors' descriptions of case definitions was limited or ambiguous and few gave detailed algorithms or information on the hierarchies applied. Extensive efforts have been made to systematically identify and use the best information available. Of the almost 7,000 abstracts screened, only 48 published studies (and 8 unpublished datasets) provided population-based, comparable cause-of-death data for enough causes of neonatal death to meet the inclusion criteria for the multi-cause modelling. There are large areas of the world, representing approximately one third of neonatal deaths, with no useable input data at all. Most crucially, no useable data were identified for many of the world's poorest countries which together account for about one third of neonatal deaths.[46] It is possible that some publications or unpublished data were missed due to language barriers, despite not limiting searches by language. Attempts were made to contact researchers in China, Latin America and Francophone West Africa. Approximately one third of the studies included are from India, which accounts for 28% of the world's neonatal deaths. Data are particularly lacking from central and north western Africa, central Asia and much of China. This makes recent studies from Kintampo[6,7] and Navrongo[26] demographic surveillance sites in Ghana particularly welcome. The lack of available data from China is a wider issue than for neonatal death alone and indeed is a recurrent theme for all the expert groups in the GBD work. A sustainable and nationally used data source that can be shared outside the country is an important priority for global health estimates given the size of China population.

In the data screening process the single largest group of studies excluded were those facility-based studies that were not likely to be representative, in populations where less than 90% of women give birth in facilities. These studies were excluded because the distribution of causes of death in these studies may not reflect the distribution of causes of death in the general

population and the direction of selection bias is not predictable. For example, if obstetric referral is effective, then birth asphyxia will be over-represented in facility-based data.[73] Conversely, in isolated areas with low demand for facility-based care, facility-based data may under-estimate asphyxia as a cause-of-death.[74]

The data included in many regions are dependent on international research sites (Chapter 5 figures 5.2 and 5.3). It is possible that the populations in these long-term study sites are systematically different from the national populations of their host countries. Local data regarding immunisation coverage and other characteristics that may differ from the national level may be important to avoid introducing systematic biases into estimates. While the use of local covariate data (for example, high tetanus toxoid coverage data) may account for some of this population unrepresentativeness through modelling, there may well be other variables unaccounted for that result in biases. Some of these biases may be in the direction of worse health outcomes (e.g. study sites selecting higher mortality populations) and some may be in the direction of better health outcomes (e.g. study sites with lower mortality because they are easier to study or have already benefited from health intervention trials). It cannot be assumed that these two biases would cancel each other out. In order to avoid future heavy dependence on opportunistic data not originally collected for this purpose, investment is needed in larger scale data collection that is regular and consistent over time. Examples include a VA follow up study after national DHS, and establishing a Sample Surveillance site such as in India and China.

Other exclusions were for the specific quality criteria set. For example, studies with few deaths of known cause (<20) which were mostly small studies in rural India. Such a small number of deaths are too unstable for proportionate mortality evaluation. A number of studies were excluded due to reporting less than 5 causes of neonatal deaths. Very few studies (3) had 25% or more unknown neonatal cause-of-death and were excluded on this basis. Similarly, a few studies were excluded because they covered a period of less than a year. Most causes of neonatal death are not strongly seasonal, apart from the small proportion due to diarrhoea, and possibly pneumonia. However, in most countries birth rates show seasonality. This may result in bias if a short period of data collection coincided with a peak in deaths just because of variation in the overall birth prevalence, or for example in a peak in preterm births such as may occur 6 or 7 months after a major holiday.

These exclusions all carry lessons learned for design of future studies. Publication of a set of guidelines for study quality for cause-of-death studies in general, with specific guides for

various causes including neonatal cause-of-death, may help improve the design of future studies. In addition, it could be argued that VR data with coverage of 80% or 85% are better than one or two small studies or no national data at all, and future estimation processes should consider sensitivity analysis looking at inclusion of varying VR quality cut-offs.

8.2.3 Methods and modelling

Given the lack of population-based cause-of-death data for most of the high burden countries, modelling is the only option for cause-of-death information for the near future, not just for neonatal deaths or child deaths, but also in many countries for adult deaths. If modelled results are presented as if they are "real data" this creates a false impression that more data are adequate. Hence transparency in modelling methods is not just good practice but is important in highlighting data gaps. In both the single and multi-cause neonatal mortality models, every attempt has been made to explicitly detail inputs, modelling equations and key assumptions.

In addition to other limitations on input data and modelling methods, a further constraint is the lack of local input predictor data to account for atypical study populations. Sourcing predictor data as close as possible in time and place to the study population was very time consuming but considered worth the investment given the atypical nature of many of these populations particularly in long standing research sites such as the Gambia MRC site. Other indicators which may be more closely linked to addressing intrapartum complications such as emergency obstetric care coverage could not be tested for fit due to lack of comparable national data for coverage affecting both the input dataset for modelling and the generation the output national estimates which require recent national level data.

8.2.4 Single versus multiple proportionate cause-of-death modelling

For estimation of proportionate cause within a given period, a multi-cause model is more challenging but preferable, as discussed in Chapter 3. For estimating one cause-of-death consistently over time, for example neonatal tetanus or measles, a single cause model may be appropriate, but should follow similar steps and where possible avoid input of studies designed to measure only one cause because of the inherent biases.

The multi-cause modelling approach used here builds on that used previously for child deaths, based on Seemingly Unrelated Regression applied to log ratios of causes.[12] For this exercise

multinomial regression models were used and these offer a number of advantages. First, this approach can handle studies which do not provide information on all the causes of death being modelled by applying assumptions about the category into which unreported causes have been assigned. Using the log ratio approach, such studies were excluded.[12] Second, the log ratio approach faces a problem with rarer causes which result in zero deaths in a proportion of data sources. A non-zero value must be introduced, but the choice of which non-zero value to use may affect the results obtained from the model and this contributed to the low proportion of deaths assigned to measles in the under five child mortality multi-cause model developed by Morris et al.[4812] Using the multinomial model, zeros are modelled naturally this challenge is avoided. Further advances are possible and a range of models for first day, first week and late neonatal periods is of use for policy and programmes. A key input would be improved predictor variables that explained more of the variability between causes, which is complicated by the need for covariates that are able to predict a difference in the ratio to the corner cause. For example, the coverage of skilled attendants at birth may correlate with the proportion of neonatal deaths that are intrapartum-related, but may not be predictive for differences in the ratio of preterm birth to intrapartum-related neonatal deaths as the predictor may have a similar effect on both causes. Hence the range of predictors is restricted to those available for all countries and able to predict the relationship between changes in proportionate mortality as a ratio.

8.2.5 Uncertainty ranges

In the past, uncertainty around estimates has been portrayed as the 95% Confidence Interval of the input data. However this is a very limited part of the considerable uncertainty inherent in an estimation process where data are limited, of variable quality and multiple sequential assumptions may be multiplicative not just additive for the uncertainty. The approaches used to estimate uncertainty in these two models do take account of uncertainty in the modelling and to some extent in the input cause-proportionate mortality data, particularly the jackknife approach used for the multi-cause model. The uncertainty around neonatal death estimates is expected to be considerable but is not included as WHO did not provide this information.

For the multi-cause model it is clear that the uncertainty varies by cause and in most cases is asymmetric (Table 7.2). For example, for the category of “other neonatal” causes of neonatal deaths the uncertainty range is from 0.19 to 0.62 million, which is almost 30% below but 134% above the point estimate. This makes sense. For large causes, the upper limit is set by the total

number of deaths so expect more uncertainty below. For rare causes which have a low proportion, the minimum is zero so more uncertainty is expected above the point estimate giving an asymmetrical distribution of uncertainty.

There are no clear guidelines on estimation of uncertainty in national and global estimates and if left to individuals it may be highly misleading. The WHO World Health Report 2005 was unable to give uncertainty around the child cause-of-death estimates as the approaches used for different estimates were non-comparable. These differences probably reflect the assumptions applied in estimating uncertainty more than they reflect real differences in the uncertainty of different estimates.[44] For example, the uncertainty bounds for the CHERG estimates for child health varied from around 10% above and below the point estimate for malaria mortality[201] to the much wider uncertainty shown around the neonatal results. The malaria estimates also have major inherent uncertainty since there are limited input data, mostly from malaria study sites, and the data are based on fever symptoms reported through VA rather than screening blood for parasites. Assumptions were also applied at a number of key points in the malaria estimates process but were not reflected in the uncertainty estimates provided.[46] Standard guides and advances in the uncertainty estimation methods would help to promote a conservative and comparable approach. Presenting wide uncertainty ranges underlines the lack of input data and many other sources of uncertainty in global estimates.

8.2.6 Review process

These neonatal cause-of-death estimates, and particularly the multi-cause model, benefited from a rigorous built in peer review process though the CHERG meetings every 6 months, hosted alternately by WHO and UNICEF. Many of the challenges experienced in cause-of-death estimation are not unique to the neonatal period. Cross group dialogue, for example with the pneumonia, malaria and diarrhoea groups resulted in new insights around key assumptions. Expert review is time consuming and takes a high level of expertise. Currently this expertise is limited in most of the countries with the highest burden of newborn deaths. Capacity building in perinatal epidemiology is key both for review and revision of estimates, but also to critique and improve current data.

Table 8.1 Advances implemented in neonatal cause-of-death estimation and implications for further improvements in estimation

Step in estimation process	ADVANCES IN IMPROVING ESTIMATION	IMPLICATIONS FOR FURTHER ADVANCES
1. Case definitions for cause-of-death	- Shift from perinatal causes to programmatically relevant categories of cause-of-death - A minimum list of cause-of-death categories that can be used in low income countries, and mapped onto more complex specific causes used in high income countries i.e. VR codes from ICD 9 and ICD10 requiring examination of the ICD codes in the neonatal period to set up this mapping process	- Consensus case definitions and increased detail for causes if desired – e.g. split 'other' category to show jaundice, split infections into specific infection syndromes (pneumonia, sepsis, meningitis) - Consensus on classification and hierarchies and standard application in Verbal Autopsy use - Simplifying ICD, minimum list of ICD 10 codes that links with VA tool
2. Input data	- All data sources examined including a new analysis of VR data from countries with high coverage of registration, systematic searches of published literature and attempts to identify unpublished literature - Explicit inclusion criteria for data regarding population representativeness and regarding comparability for causes of death	- Methods to increase coverage of neonatal/child cause-of-death data through existing data collection e.g. VA after DHS, DSS, Sample SS - Explicit quality criteria to guide design of future studies e.g. data reported by year - Exploratory analysis regarding use of facility data
3. Methods and modelling	- VR data to be used for the country of origin or for modelling for countries with similar NMR, or as an input to a model with other data covering high NMR countries. VR data from low NMR countries should not be used as the sole data to predict proportionate mortality in high NMR countries - Explain the models, assumptions made and publish the equation(s)	- Potential use of historical VR data to predict proportionate mortality for countries with a similar NMR
4. Single proportionate cause-of-death modelling versus multi-cause	- For estimation of proportionate cause within a given time period a multi cause model is preferable - If estimating one cause-of-death, single cause model may be appropriate, but should follow similar steps and where possible avoid input of studies designed to measure only one cause because of the inherent biases	- Simplification of multi-cause modelling - Increased detail for causal categories if desired - Model for multi-cause neonatal deaths in first week and first day of life
5. Uncertainty ranges	- Uncertainty estimates should be provided and should not be based on 95% CI, but should take account of as many sources of uncertainty in the inputs as possible	- Better delineation of sources of uncertainty and methods to account for these in a comparable way across varying estimates
6. Review process	- External expert group process should review the inputs, methods and results	- Expert review is time consuming and takes a high level of expertise – capacity building in perinatal epidemiology and especially in the high burden countries is key
7. Compare model predictions with local data	- Both single and multi-cause model estimates compared with local data for a range of NMR levels and meeting the criteria set for inclusion in the study database	- In addition to statistical comparison, review by country level policymakers increases ownership and use of the data in country and awareness of need for better data collection

8.2.7 Validation of model predictions by comparing with real data

For both the neonatal intrapartum single cause and the neonatal multi-cause models a validation exercise was undertaken. The single cause model validation was undertaken at the time and included in the publication. For the multi-cause model all data meeting inclusion criteria had been used as inputs to the model and hence the validation awaited new high quality data for comparison. These validation exercises suggest the models are performing well with remarkably close agreement to real data. There are a few variations which are small in absolute terms and would be expected given selection biases in the study datasets used for validation key causes for the multi-cause model. For example, the India study was in a poor rural population with NMR almost 50% higher than the national average, and so would be expected to have a higher proportion of neonatal deaths due to tetanus than in the model which is predicted at national level. However, the variation between model and study data for birth asphyxia and preterm is high both for the India study and the Ghana study, and is in the opposite direction– for India where the study reports the preterm proportion as higher than the model prediction. In contrast in the Ghana study data 'birth asphyxia' is higher than the model prediction. This is a recurrent issue in data quality, with misclassification between preterm and birth asphyxia, particularly where the case definitions are the older clinical case definitions based on condition at birth and low Apgar score (Chapter 4). Section 8.3.3 discusses advancing the case definitions, tools and hierarchies to address this challenge.

Conclusions regarding advancing the modelling

The neonatal multi-cause modelling process has been established as a regular exercise every five years by the CHERG to revise input data and reconstruct the model. The 2005 estimates will also feed into the GBD. In the intervening years incremental updates are possible with a much faster exercise applying the same multi-cause model but using the latest national predictor variables and the annual estimates of neonatal deaths.

There is interest from policymakers in models for cause-of-death by time blocks within the neonatal period, notably early and late, and ideally also for the first day of life. There is a tension between the demand for increased granularity in the causal categories, which increases the complexity of the dataset construction and the modelling, and on the other hand the desire for simpler modelling processes and wariness of spurious results especially once the estimates are being published and used at country level. The only real solution is to improve the input data.

8.3 Improving the input data for neonatal deaths now and the research agenda

8.3.1 Overview of improving the data

Despite a large number of neonatal deaths, reliable information is lacking on the numbers of these deaths,[4] even more so for cause-of-death. This exercise has highlighted the paucity of reliable, representative data on the causes of neonatal death from settings in which most neonatal deaths occur (Chapter 5).[46] While improved and transparent estimation methods are important, the quantity and quality of input data must be improved. If not, then at the time of the next cause-of-death estimates in five years or even after the target of the MDGs in 2015, we will still be basing decisions on estimates with inevitably wide uncertainty due to the lack of useable data.

Data collection for intrapartum-related neonatal deaths, or generally for neonatal cause-of-death, cannot be separated from other streams of national data collection. Improving national data collection systems in low income countries is a global priority given the focus of the international community on tracking the MDGs and increasing investment in health and development.[46] Significant funding and several new global initiates have been launched to improve health metrics.[202] Pregnancy outcome data are crucial for MDG tracking and especially for the goals 4 (child survival) and 5 (maternal health). For many of the priority indicators for MDGs 4 and 5, the numerators depend on pregnancy outcome data and for almost all the indicators the denominator is live births.

While the biggest data gaps are in the poorest countries with the highest burdens, there are also missing data in high-income and especially transitional countries. In addition, as mortality falls, the risk of disabled survivors becomes more of a public health issue and the countries with the least data on morbidity outcomes are transitional countries where the problem is likely to be greatest, including large countries such as China.

Table 8.2 summarises actions possible now to improve the data, and research questions with a focus on low income countries. Then the following key data areas will be discussed in detail:

1. Counting neonatal deaths, all births and other pregnancy outcomes
2. Case definitions and hierarchical cause-of-death attribution
3. Neonatal morbidity and risk factors
4. Counting avoidable factors and sub optimal care

Table 8.2 Improving country level data for neonatal deaths– what can be done now and what are the key research questions?

	ACTIONS TO IMPROVE DATA		RESEARCH QUESTIONS
	High income	**Low income countries**	**(low income country focus)**
1. Counting pregnancy outcomes including all births, maternal deaths neonatal deaths stillbirths	VR and use of specific death certificates for stillbirth and neonatal deaths. Crosslink civil registration system and health system databases	Household surveys (retrospective): use of pregnancy history not birth history in DHS to better capture early neonatal deaths and stillbirths, promote inclusion of key modules in UNICEF MICS Demographic surveillance sites (prospective): Consider Sentinel Surveillance sites especially in large countries (e.g. India and China), or network or study sites (e.g. INDEPTH) Improve VR: Increase coverage and quality of births and deaths registration, crosslink civil registration system and health system databases	- Improving measurement of pregnancy outcomes in surveys – e.g. comparing pregnancy history and birth history for validity and additional time taken during survey - Developing a "quality score" to assess neonatal mortality data for representativeness, age heaping etc - Novel use of facility data – can recognised biases in facility data be adjusted for using modelling?
2. Case definitions and hierarchical cause-of-death attribution	Consensus on consistent list of programmatically relevant, comparable categories, case definitions, and explicit hierarchy Data collected through: - VR - Confidential enquiry systems - Special studies	Consensus on consistent list of programmatically relevant, comparable categories, case definitions, and explicit hierarchy Verbal autopsy studies with standard data collection tool, and hierarchical attribution Data collected through: - Follow up study after household surveys (e.g. DHS) - Demographic Surveillance Sites (e.g., sentinel sites) - Improved VR - Special studies	- Evaluation of standard verbal autopsy tool, case definitions and hierarchy, mapping more complex sub categories from ICD onto the basic list of programmatically relevant causes. - Effect of varying hierarchies on proportionate mortality - Comparison of cause-of-death allocation by experts or by computer algorithm - Inclusion of a standard social autopsy module.
3. Neonatal morbidity and risk factors	Standardise case definitions for tracking morbidity e.g. neonatal encephalopathy Crosslink existing databases (e.g. perinatal follow up and cerebral palsy registers)	Standardise case definitions for tracking morbidity e.g. neonatal encephalopathy. Data collected through: - Demographic Surveillance Sites (e.g., sentinel sites) - Special studies	- Improving gestational age data – e.g. weight as a surrogate, simplified clinical assessment - Developing disability assessment standards, simpler tools across cultures (e.g. motor, IQ) and set protocol for what to measure at what age
4. Counting avoidable factors, and sub optimal care	National audit systems with regular reports on data and trends, as well as specific themes e.g. intrapartum stillbirths Consider confidential enquiry for maternal, infant deaths and stillbirths	Audit system for maternal, neonatal deaths and stillbirths. Collate data nationally and promote sentinel sites in varying regions and health systems contexts so information can be useful for policy prioritisation whilst not representative. Consider focus on few indicators initially e.g. intrapartum stillbirths and pre-discharge neonatal deaths in babies >2000 g	- Evaluation of simplified audit tools and mechanism to maximise resultant change in policy and programmes

For more details on INDEPTH network of surveillance sites please see Definitions section of this thesis, page 16

8.3.2 Counting pregnancy outcomes

What to count?

For most of the history of global health the focus has been on measuring fertility and child deaths, particularly in large scale surveys. Maternal mortality has also become a programme priority and a measurement challenge.[203;204] Global attention on the time of birth has recently increased with recognition that almost 40% of child deaths under the age of 5 years occur in the first month of life, indeed 30% in the first week of life.[4] However, one large group of deaths yet to count or to be counted are stillbirths, here defined as babies dying during the last trimester of pregnancy. A baby who dies five minutes after birth, or indeed who has a detectable heart rate at birth, counts in the global estimates of child deaths. A baby who dies even in the process of birth does not count.[51] Stillbirths are not reported in WHO routine mortality data, or included in the MDGs or the GBD, although novel work is in progress to develop methods to achieve this.[199] The epidemiological, programmatic, and rights-based arguments for improved measurement of stillbirths have already been summarised (Chapter 5). In moving forward the key pregnancy outcomes to capture are all births, stillbirths, neonatal deaths and maternal deaths. In addition low birth weight, prematurity and NE are important intermediary outcomes to measure.

How to collect the data?

In high income countries VR provides a good source of data for most pregnancy outcomes, although stillbirths may continue to be under-reported. Currently national stillbirth data is not included in many population-based surveys or collated annually by any international organisation, in contrast to annual reporting to WHO of deaths among live born infants. The use of specific death certificates for stillbirths and neonatal deaths improves capture of specific data such as intrapartum complications and gestational age. Most European countries have specific perinatal certificates, but few low and middle income countries do.

In the short time left until 2015 it is unlikely that VR will reach the benchmark of 90% coverage of adult deaths in most South Asian and Sub Saharan African countries where fertility and mortality are highest (Chapter 5). For some countries – notably India and China – the strategy is to develop Sample Registration Sites which are spread across the country and designed to be nationally representative. However, these sites take some time to "mature" and valid assessment of pregnancy outcomes and especially reliable neonatal cause-of-death data is not expected in the next few years.[205] Hence for most low income countries the only nationally representative mechanism for pregnancy outcome data are intermittent household surveys, principally the DHS which takes place every 5 years in around 50 countries and whose core questionnaire uses a birth history module. To date UNICEF's MICS includes minimal data around the time of birth

and relies on indirect mortality estimation for child mortality outcomes, not even a basic birth history. Increased investment in MICS means these surveys are being run in more countries and more often so inclusion of a pregnancy history could result in a major increase in availability and frequency of data.[206]

Is under-reporting an inevitable failing of retrospective data collection compared to prospective, or can retrospective surveys such as DHS improve stillbirth reporting, for example by using pregnancy history instead of birth history? Use of a pregnancy history in surveys would enable collection of regular, national stillbirth data and would likely to increase capture of early neonatal deaths. During the 1960s, '70s and '80s when data collection in low and middle income countries was expanding, there was tremendous experimentation in demographic methods for the collection of fertility and mortality data. The World Fertility Surveys applied both backwards and forwards questioning for pregnancy histories. Casterline analysed pregnancy loss data in 41 of these retrospective surveys,[207] concluding that various formats of pregnancy history compared to results from prospective, clinical studies in Western countries detected 50-85 percent of all recognisable pregnancy losses, with stillbirths after 28 weeks better captured than earlier pregnancy losses.[207] There is a trade-off in terms of length of questioning, and receiving valid answers, that has not been well studied, and this is a general concern given the hundreds of questions (>700) in the current DHS core questionnaire. (www.measuredhs.com)

Advancing the tools and key research gaps

Thus, many questions remain unanswered regarding the most valid, reliable, feasible and affordable means of collecting nationally representative pregnancy and vital events data in different settings. Key questions include: comparing the validity and time taken for pregnancy history compared to birth history; comparison of complete live birth or pregnancy histories with histories truncated in time (e.g. the last 5 years). The goal of such research efforts should not be restricted to identification of the methods to achieve the highest quality, but to identify feasible ways to collect affordable, comparable data at scale – for example quantifying the loss of data quality for a truncated versus a complete live birth or pregnancy history, or a survey covering wide-ranging issues versus a highly focused questionnaire, balanced with time or cost savings. The expanded number of demographic surveillance sites in various low and middle income world regions offer opportunities for examining these questions regarding retrospective reporting of pregnancy outcomes in a site with prospective data to use as a "gold standard."

8.3.3 Cause-of-death data

What to count?

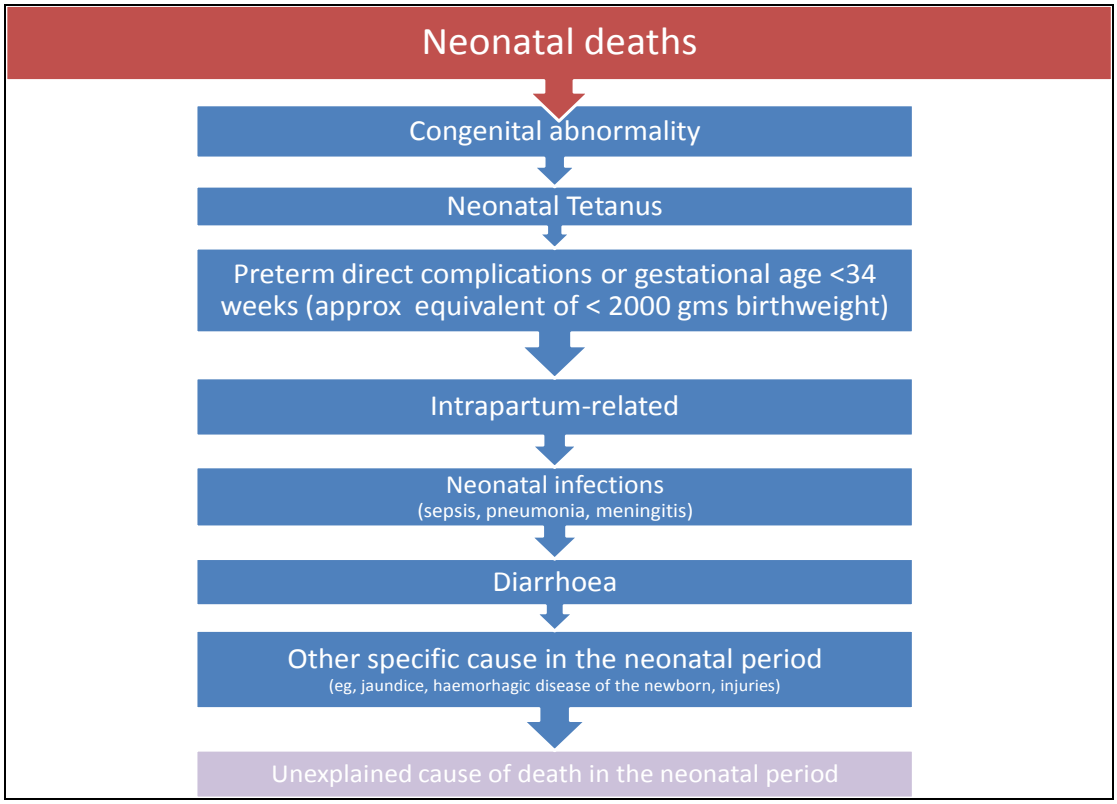
There has been a shift from the group category of "perinatal causes" based on the Perinatal chapter of ICD[2], to programmatic categories for causes of neonatal deaths (Chapter 4). Six selected categories, with a residual group of 'neonatal other' were outlined in Table 4.1 and have been used for the multi-cause modelling. While a few are single causes, such as neonatal tetanus, most are causal categories and some such as congenital include hundreds of specific diagnoses. Where the health information system capacity allows this, analysing more detail within these causal categories may be useful for programmatic planning and tracking. Table 8.3 proposes relevant sub groups possible through facility data, and VR data which can map onto the basic 7 categories which are possible in VA data. This layered approach allows comparison across different countries and levels of data capacity, but still enables high income, high data capacity settings to have more complex and detailed information.

Table 8.3 Case definitions for neonatal cause-of-death showing mapping of seven programmatic categories which are possible in Verbal Autopsy onto more detailed categories possible where complex data collection is at high coverage

Cause-of-death category (possible through VA)	More detailed cause-of-death sub-category (possible through clinical audit data or VR)	Finer level of detail (with ICD codes from VR)
Congenital abnormalities	Chromosomal abnormalities Cardiac defects Neural tube defects Other major structural abnormalities (e.g. abdominal wall, gastro-intestinal, genitor urinary) Other congenital (residual)	Specific e.g. which chromosomal abnormality, defined cardiac defect e.g. Fallot's tetralogy
Neonatal tetanus	Neonatal death due to tetanus	-
Preterm birth	Surfactant deficiency (Respiratory distress syndrome), Intraventricular haemorrhage, Necrotizing enterocolitis	Specific complications or other more detailed codes
Intrapartum (Birth asphyxia)	Neonatal encephalopathy Birth injury	More details eg type of birth injury
Sepsis/ pneumonia	Sepsis/septicaemia Meningitis Pneumonia/ acute respiratory tract infection Other neonatal infection	Specific organisms Specific complications
Diarrhoea	Neonatal death due to diarrhoea	Specific organisms
Other	Neonatal jaundice Haemorrhagic disease of the newborn Term baby dying due to in-utero growth restriction Sudden Infant Death Syndrome Injury (deliberate and accidental)	Multiple codes possible in ICD

Case definitions do have an effect on proportionate outcome, particularly for "birth asphyxia" (Chapter 4), but the major effect on proportionate mortality comes from varying the hierarchy.[130] For example the WHO and London School of Hygiene and Tropical Medicine child survival VA tool which categorised all deaths in the first 3 days of life as "early perinatal".[52] In addition, since diarrhoea was the first category in the hierarchy and congenital was far down the hierarchy, a baby with a neural tube defect and incontinence would be coded as dying from diarrhoea. The next generation of VA tools in the late 1990s followed two different approaches in attributed cause-of-death amongst preterm babies. One extreme is to assume that for all preterm babies who die, preterm is assigned as the cause. This does not follow ICD rules, and also results in the vast majority of deaths in one large category (60 to 95%) which reduces the value for public health prioritisation. At the other extreme, preterm birth is the last on the hierarchy and so it is only considered a cause if the baby did not die of anything else. It also classifies all babies not breathing at birth as being due to "birth asphyxia", which is an over-estimate for intrapartum neonatal deaths in term babies and an underestimate for preterm birth complications.[208] Adapting from NICE,[65] the CHERG expert group developed a hierarchy (Figure 8.2) which has since been used by several large VA studies, including in India[56] and Ghana.[99;141]

Figure 8.2 Hierarchical classification system for causes of neonatal death used by the Child health Epidemiology Reference Group



Note: the hierarchy is consistent with table 4.1. If congenital abnormality and neonatal tetanus are both present then expert opinion may be required to determine the primary underlying cause. Congenital abnormalities are markedly underestimated in verbal autopsy data as only obvious external abnormalities will be detected and congenital heart disease is commonly misclassified as infection.

How to collect the data?

As with counting pregnancy outcomes, the potential data mechanisms for cause-of-death will vary by country. For high income countries, VR data are high coverage but not always high quality. There are multiple codes used for causes of death in the neonatal period – in this analysis we identified around 12 000 codes across the 83 countries. WHO have proposed a marker of quality for VR based on the proportion of cause-of-death codes that are considered to be "garbage" codes.[133]

For low and middle income countries, while increasing coverage and quality of VR is important, in the short to medium term other larger scale data collection mechanisms are urgently required, not just for neonatal cause-of-death but also for child and potentially stillbirths and maternal deaths. The main options were outlined in Chapter 5 and include Sample Registration sites, networks of DSS such as the INDEPTH network (see page 16 for more detail), follow-up studies after national DHS and special research studies. Follow-up studies after nationally representative DHS are especially promising, for example in Bangladesh,[209] Egypt[168] and a recent one in Pakistan which is the first to include stillbirths and maternal, neonatal and child deaths (Prof ZA Bhutta, personal communication). If investing in these or other special studies for cause-of-death or morbidity data, it would be crucial to consider quality criteria in designing sample size, seasonality issues and use of standard tools so that the data will be comparable and useful for policy and programmes.

One recently suggested option is that of using data collected at health facilities and correcting for known biases with modelling. Facility data may differ systematically from population based data in a predictable manner - the case mix, for example, might show a higher proportion of intrapartum-related neonatal deaths in high-risk and referred infants. Such modelling could provide a useful, and inexpensive, tracking method.

Advancing the tools and key research gaps

Recently the Health Metrics Network have facilitated a process to develop standard VA data collection forms for neonatal deaths, child deaths aged 1 month to 5 years and all deaths from 5 years to old age.[131] The neonatal VA form is only 8 pages long and takes around 30 minutes to administer.[27] The variables provide enough information to categorise a stillbirth into intrapartum or antenatal as well as attribute a neonatal death to any of the 6 specific categories and also to jaundice and haemorrhagic disease of the newborn. This allows comparable cause-of-death with high income countries, mapping with ICD codes.

A standard VA questionnaire is an important step, but will not necessarily prevent questionable variation in cause-proportionate mortality patterns if subsequent steps remain unstandardised.

However there is as yet no specific algorithm or guide for attributing causes of death. More research is required to compare expert opinion as used in most VA studies, with expert option using an algorithm (as per the recent Ghana Kintampo VA study),[99] with computer algorithms. The Bill & Melinda Gates Foundation Grand Challenges VA research group based at Johns Hopkins are attempting to develop computer algorithms (Baqui, personal communication). Another important area of research for VA is to detail the implications of varying algorithms. Recent analysis by Lee and colleagues[130] using a dataset from Nepal has examined various hierarchies for birth asphyxia and shows major differences in the proportionate mortality attributed to birth asphyxia depending if it is put above or below preterm birth in the hierarchy. Through another Gates Grand Challenges grant Murray and colleagues are using probabilistic approaches to allocate cause-of-death.[30] All of these hold potential to make verbal autopsy both more standardised and also less reliant on time-intensive expert input which may extend the use of the tools beyond research teams.

8.3.3 Neonatal morbidity and risk factors

What to count?

As neonatal mortality falls, the risk of disabled survivors becomes a significant public health issue. The countries with the least data on morbidity outcomes are transitional countries where the problem is likely to be greatest, including huge countries such as China. A major discussion of neonatal morbidity outcomes is beyond the scope of this thesis, but comparable, high quality, population-based neonatal morbidity data are almost entirely lacking in low income countries.[210] Without more systematic attention now to embedding morbidity measures in studies and in health information systems in low and middle income countries, there will be little or no useable data for public health planning on major issues from multi-domain disability (cerebral palsy) to specific impairments such as retinopathy of prematurity.

Specifically for intrapartum-related outcomes, the key is to track the incidence of NE. In settings with higher coverage of skilled institutional delivery use of simplified scoring systems is feasible but at community level assessment of NE is only potentially feasible in research studies and even then proves challenging (personal communication Dr Anne CC Lee).

Preterm birth is an important morbidity outcome to track in terms of an adverse pregnancy outcome, but also to allow more useful cross tabulations of data, for example to identify what proportion of neonatal deaths attributed to infection are in preterm infants. Given the almost total lack of nationally representative data on gestational age in many low and transitional income countries, birthweight is often used as a surrogate. However, birthweight data are also missing for more than two-thirds of newborns in the least developed countries which account

for around two-thirds of the burden (Table 8.5). Other measurement options are simplified gestational age assessment and the possibility of asking maternal perception of gestational age or last menstrual period in DHS-type surveys. The "gold standard" of first trimester ultrasound gestational age assessment is increasingly the norm in transitional countries and in many urban settings in South Asia, but even when undertaken does not necessarily connect through to the neonatal records.

Advancing the tools and key research gaps

An important priority to ensure comparability is to develop feasible case definitions for tracking neonatal morbidities, especially NE, severe infection and jaundice. Increasing the national availability of gestational age data and the quality of birthweight data require innovation such as simplified gestational age assessment scores and birthweight scales or birthweight surrogate measures(e.g. chest circumference)[211] for low literacy CHWs.[212] Standardised but simpler disability assessment tools are required for use across varying cultures to assess IQ, but also motor skills. Assessment of behavioural abnormalities is a quagmire of non-standard terms. Consensus protocols for what to measure at what age are necessary to increase comparability across studies, particularly to develop summary estimates for exercises such as the GBD.

Table 8.4 Regional variation of the percentage of babies weighed at birth around the year 2000

Region	Percent of births weighed at birth
South Asia	26
Sub-Saharan Africa	35
Middle East and North Africa	40
East Asia and Pacific	70
CEE/CIS	79
Latin America and Caribbean	83
"Developing" countries	42
"Least developed" countries	32

Source: Using data from[213]

8.3.4 Counting avoidable factors and improving care

What to count?

Improving case definitions, while of relevance to estimation of burden of disease, may not directly link to the specific programme actions to reduce the burden. To reduce intrapartum-related deaths the key information required for programmes is the proportion of intrapartum stillbirths and intrapartum neonatal deaths due to avoidable factors so that health system and community delays are identified and addressed, for example through perinatal audit. There are many examples of effective audit from high income countries – for example the UK CEMACH.[93] There are fewer examples from low income countries, particularly of audit at national scale – one example is from South Africa where the maternal audit is a national confidential enquiry.[200] Stillbirth and neonatal audit are voluntary, facility-based and currently cover about 20% of the country's births. National reports are produced every 3 years, called Saving Mothers and Saving Babies. A new audit for children has started more recently. Most audits apply a common process that includes the following steps: 1) recording every death with underlying medical, administrative and social causes and discussing in a non-condemnatory way; 2) synthesis of data and identification of local priorities for action to reduce death, and implementation of these at local level; 3) Intermittent collation of national data to make national recommendations; and 4) implementation of these actions, then assessment of whether the recommendations have been undertaken. This last step in the process is the most critical and often lacking in most examples, especially at national scale.

Advancing the tools and key research gaps

Audit tools for use at scale in Sub Saharan Africa and South Asian facility settings may need to be simplified and adapted given the human resource crisis, especially in many African countries.

Selecting a few limited indicators and using these to leverage change may be more realistic than comprehensive databases. One proposed indicator of particular relevance to intrapartum care tracking is the Intrapartum Case Fatality Rate – a composite of intrapartum stillbirths and predischarge neonatal deaths in term babies. This indicator has been proposed by United Nations Population Fund (UNFPA) as an addition to United Nations core indicators for tracking Emergency Obstetric Care.[214] Evaluation of the indicator and feasibility of use is required. Implementation research into mechanisms to maximise resultant change in policy and programmes using audit process could help to maximise the effectiveness of audit. Community level death audits or community and facility partner audit have been tested in small scale projects, but may be a useful tool for increasing facility quality of care and community trust.[23]

8. 4 Summary for improving the estimates and improving the data

The fifth and final objective of the thesis was to summarise actions to improve estimates and input data for neonatal cause-of-death, particularly related to birth asphyxia, listing research priorities. Chapter 8 has detailed the steps involved in the estimation process, based on the review of methods in Chapter 3. The advances achieved, the challenges and suggestions for further improvements have been described.

However the key issue in improving the estimates remains the quantity and quality of the input data. While the focus of the thesis is on cause-of-death proportionate data, the estimates for numbers of deaths by cause are dependent on the reliability of data regarding numbers and rates of neonatal deaths. Counting pregnancy outcomes is an essential step in capturing the numerator and the denominator for NMRs. Increasing VR coverage is the most comprehensive and also estimated to be the most cost-effective approach in the long term,[215] and would also advance the available cause-of-death data. In the interim other data collection systems hold promise such as Sample Registration and DSS with linked VA, or with DHS and subsequent VA studies. Data regarding neonatal morbidity and comparable assessment of long term impairment following neonatal complications are almost entirely lacking even at facility level in low income countries. This gap will become increasing important as care improves and more babies survive.

The underlying purpose of perinatal epidemiology is not merely to improve the numbers and validity but to reduce deaths and disability - counting avoidable factors and improving care. Many research questions remain regarding improving both the process of data collection, refining the data collection tools and analysis, and the process of linking the data to action.

Chapter 9
Conclusions

Two clear messages resound. Firstly, while the data have uncertainties, there are now more than enough data to be certain that action is required to reduce around four million annual neonatal deaths, and around 910 000 intrapartum-related deaths. Secondly, while there are enough data to drive action, there are important data gaps and the poorest and highest risk families and countries have the least data and receive the least attention.

Neonatal deaths are now on policy priority lists, but investment and implementation action are still not proportionate to the size of the burden. There is more progress in reducing neonatal deaths from infections and tetanus, than for intrapartum-related and preterm birth complications. Intrapartum-related deaths are a major contributor to the global burden of disease, accounting for almost one million neonatal deaths and are closely associated with over one million intrapartum stillbirths, maternal deaths due to direct obstetric causes and an unknown burden of NE and subsequent disability (Figure 9.1). The 910 000 intrapartum-related child deaths exceed the estimated 840 000 child deaths due to malaria.[5] Attention and investment in malaria is much greater and is increasing exponentially. The UN Summit in September 2008 committed $3 billion of extra funding for malaria bednets, drugs and a vaccine – already more than the total invested in all of maternal newborn and child health in the 68 priority countries in 2006.[36] Malaria deaths justify action, but in a data-based world, neonatal deaths and intrapartum-deaths should also be linked to investment and action. Panel 9.1 summarises priority actions for reducing neonatal deaths based on current data.

Figure 9. 1 The burden of intrapartum-related neonatal deaths, intrapartum stillbirths, maternal deaths and the unknown associated burden of neonatal morbidity and disability

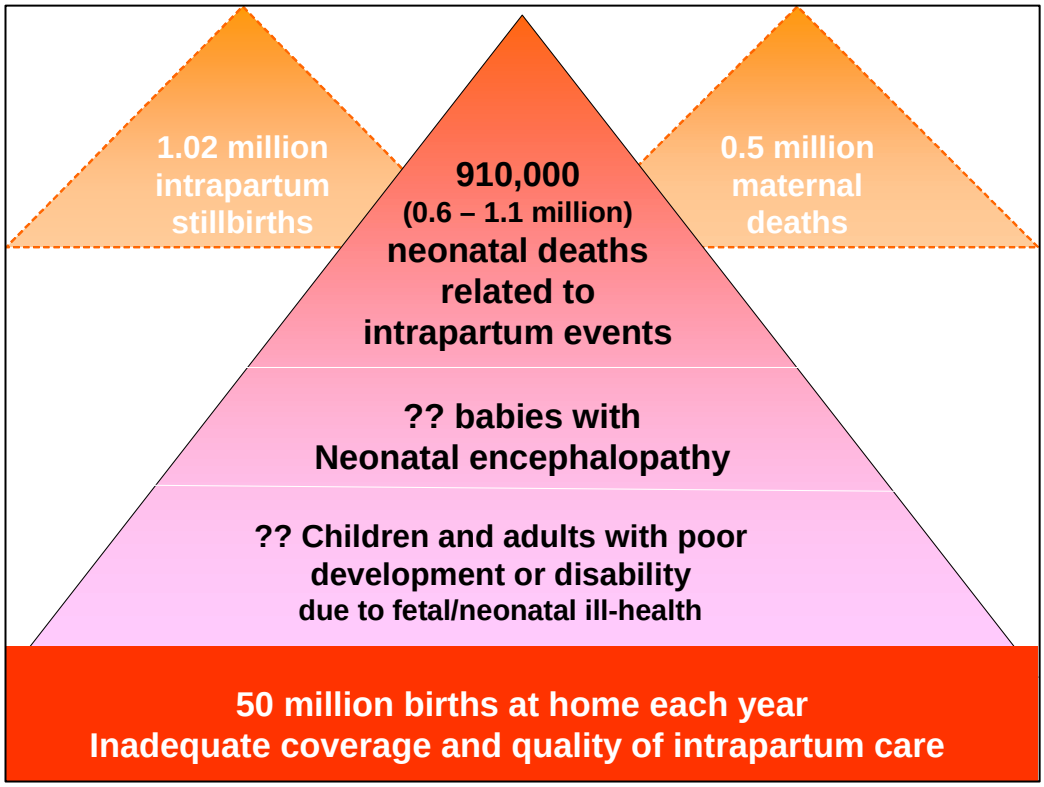


Table 9.1 Applying the information to improve neonatal survival

How many?

Reducing 4 million neonatal deaths is a moral imperative and essential for achievement of MDG-4 for child survival.

When?

42% of child deaths occur in the first month of life, up from 37% in the year 2000.

Between quarter and half of all neonatal deaths occur within 24 hours of birth—the riskiest day of life. Yet 50 million births occur at home.

Three-quarters of neonatal deaths occur in the first week of life, and yet postnatal care coverage within 2 days of birth is a median of 22% for the 14 of 68 Countdown countries with comparable data.

Where?

99% die in low- and middle-income countries, where data are limited.
< 3% die in countries with full coverage VR systems.

Three-quarters of neonatal deaths are in South Asia (2 million) and Sub Saharan Africa (1.2 million) with two-thirds dying in just 10 countries.

Approximately half of neonatal deaths occur after home births and without contact with the health system, and rural populations and families with the lowest incomes have the highest risk of neonatal death.

Why?

Intrapartum-related neonatal deaths account for an estimated 23% of neonatal deaths, the third largest cause after infections (34%) and direct complications of preterm birth (28%).

Neonatal proportionate mortality varies with the level of neonatal mortality and across regions, with infections accounting for almost half of deaths in settings with high mortality.

Maternal complications, especially during childbirth, carry a high risk of neonatal death.

Approximately 60-80% of neonatal deaths occur in low birthweight babies. Reducing case fatality rates for moderately preterm and term in-utero growth restriction infants is feasible without complex technology.

Eliminating the equity gap for neonatal mortality risk between the richest and poorest families within countries in sub-Saharan Africa and South Asia could avert almost three-quarters of a million deaths.

The second clear message is that although there is ample evidence here to show that action is required now to reduce this burden, current neonatal mortality data are far from adequate, and morbidity data are virtually totally lacking. Stillbirths, which are a closely linked outcome, remain invisible and uncounted in most low income countries.[214] Systematic, programmatically relevant estimates for neonatal cause-of-death as presented in this thesis have been a crucial short term step. These methods are now institutionalised in United Nations estimation processes for neonatal cause-of death and will become an annual estimation output. However the wide uncertainty ranges, especially at national level, could result in low prioritisation for policy and programme investment.

This exercise has highlighted the paucity of reliable, representative data on the causes of neonatal death from settings in which most neonatal deaths occur.[46] While improved and transparent estimation methods are important, these are no panacea. The quantity and quality of input data must be improved or by 2015, the target year of the MDGs, we will still be relying on inherently uncertain estimates – stumbling in the dark.[196]

Specific recommendations to improve the data quality will depend on the setting and the local capacity for information tracking, but some generic principles can be stated:

1. ***Counting pregnancy outcomes including neonatal deaths requires investment in information systems***

   The focus in all data collection systems (vital registration, surveys, sample registration) should be on capturing *all* births and *all* deaths around the time of birth in order to evaluate the effectiveness of programmatic interventions and to improve the capture of fatal and non fatal outcomes for mothers, babies and children. Neonatal outcomes are integral to the tracking system that is the foundation of any effective national health management information system. Not counting stillbirths, and especially the one million occurring at the time of labour, may result in misinterpretation of progress.[51] Registration systems are a key component of development infrastructure, but remain underfunded by governments and development partners.[6] Counting births has a human rights dimension as well as a statistical function – a birth certificate confers legal citizenship. Some low income countries have shown rapid jumps in the proportion of children with birth certificates.[9] Interim measures such as household surveys and demographic surveillance could be improved in a short period to provide more reliable pregnancy outcome data. Progress is possible and is necessary to track the increasing investments in global health and MNCH care services.

2. ***Counting neonatal cause-of–death and outcomes related to acute intrapartum events requires innovation in tools and methods for verbal autopsy and for morbidity tracking***

Outcomes related to acute intrapartum events must be actively sought and counted, or they will be easily missed. This will require innovation in both rich and poor countries. In high income countries capture of intrapartum-related mortality outcomes is generally good, although potentially subject to systematic misclassification in litigious societies. Tracking NE incidence and linking databases for long term morbidity information remains a challenge, and is urgently required in transitional/middle income countries.

In low income countries the priority is for feasible methods to enable the health system and existing survey tools to count deaths and to attribute causes for stillbirths, and neonatal deaths. Table 8.2 has summarised some immediate opportunities to improve the data, as well as research priorities. Wide consensus on a standard VA tool and use of a consistent hierarchy is an urgent need. Practical, but simple classification systems for cause of fetal and neonatal deaths can help to identify preventable deaths, prioritise interventions and facilitate the monitoring of impact of interventions. Neonatal morbidity measurement in low income settings should not be left until after mortality has been addressed. There are only three cohort studies following cases of NE from low income countries and all start from hospital populations. Well designed cohort studies are an important gap and these will require consistent case definitions and standard protocols and tools for disability assessment which are currently lacking for low income settings.

3. Counting and addressing avoidable factors requires wider scale implementation of audit systems

To reduce intrapartum-related deaths data on avoidable factors are essential so that health system and community delays are identified and addressed. [93] There are fewer examples of wide scale audit from low income countries, [200] and a systematic analysis is required of the process of how to reach wider scale in such settings and how to maximise and sustain change. In the meantime an indicator combining fresh stillbirths and predischarge neonatal deaths amongst babies weighing over 2500g and without major congenital abnormalities may be useful, and possible to collect from existing information in facility birth registers.[214]

4. Community and civil society ownership are important for sustainable change

Promoting community accountability for maternal and fetal/neonatal survival in each pregnancy will enable community ownership of the problem and joint action as well as better data collection.[137;216] Successful models of such community participation and ownership for addressing maternal and fetal/neonatal outcomes in various low and middle income countries are scarce but suggest that community power has been under-rated.[24;217] In high income countries the power of bereaved parents in gaining attention for stillbirth

and neonatal deaths and in effecting change has been crucial. As yet, the bereaved parents in low income countries are largely silent and also unsupported.

Improving estimates, data and visibility is one step but does not automatically result in investment. Another key factor is consensus on feasible solutions and communicating these effectively for both national governments and donors to see achievable solutions within their political time frames.[16] Each year 50 million women give birth at home[27] and in sub Saharan Africa the average coverage of skilled attendance has not increased significantly in a decade.[38] Moving forward to effective partnerships between obstetric and neonatal/child survival groups has potential to clarify the problem of acute intrapartum events, measure the outcomes better and reduce the huge burden of deaths and disability. The need could not be clearer - both for better counting but also for action to make neonatal and stillbirth outcomes count. Innovative approaches are required to increase information for decision-making and improve care at birth in settings where far too many babies do not cry at birth. Continued invisibility and inaction will ensure their cries remain unheard.

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Appendices

A. Publications and presentations associated with the thesis

B. Supplemental tables summarising the study datasets

C. CHERG Neonatal Data Abstraction form

Appendix A: Publications and presentations related to the thesis

Table A. 1: Publications so far of relevance to the PhD subject of neonatal cause-of-death estimates

Publication type	Title, journal and authors
Journal articles	1. Lawn JE, Shibuya K, Stein C. No cry: Global estimates of intrapartum-related stillbirths and neonatal deaths. *Bull.World Health Organ* 2005; 83: 409-17. 2. Rudan I, Lawn J, Cousens S *et al*. Gaps in policy-relevant information on burden of disease in children: a systematic review. *Lancet* 2005; 365: 2031-40. 3. Lawn JE, Wilczynska-Ketende K, Cousens SN. Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol 2006; 35(3):706-718. 4. Lawn JE, Cousens S, Bhutta ZA, Darmstadt GL, Martines J, Paul V et al. Why are 4 million newborn babies dying each year? Lancet 2004; 364:399-401. 5. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005; 365: 891-900. 6. Knippenberg R, Lawn JE, Darmstadt GL, Begkoyian G, Fogstad H, Walelign N et al. Systematic scaling up of neonatal care in countries. Lancet 2005; 365:1087-1098. 7. Lawn JE, Cousens SN, Darmstadt GL, Bhutta ZA, Martines J, Paul V et al. 1 year after The Lancet Neonatal Survival Series--was the call for action heard? Lancet 2006; 367:1541-1547. 8. Lawn JE, Osrin D, Adler A, Cousens S. Four million neonatal deaths: counting and attribution of cause-of-death. Paed Perinatal Epi. 2008 22: 410-416. 9. Lawn JE, Rudan I, Rubens C. Four million newborn deaths: Is the global research agenda evidence-based? Early Hum Dev 2008. in press 10. Lawn JE, Costello A, Mwansambo C, Osrin D. Countdown to 2015: will the Millennium Development Goal for child survival be met? Arch Dis Child 2007; 92(6):551-556. 11. Lawn JE, Manandhar A, Haws RA, Darmstadt GL. Reducing one million child deaths from birth asphyxia--a survey of health systems gaps and priorities. Health Res Policy Syst 2007; 5:4.:4. 12. Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. Lancet 2006; 367:1487-1494. 13. Darmstadt GL, Walker N, Lawn JE, Bhutta ZA, Haws RA, Cousens S. Saving newborn lives in Asia and Africa: cost and impact of phased scale-up of interventions within the continuum of care. Health Policy Plan 2008; 23(2):101-117. 14. Bryce J, Daelmans B, Dwivedi A, Fauveau V, Lawn JE, Mason E et al. Countdown to 2015 for maternal, newborn, and child survival: the 2008 report on tracking coverage of interventions. Lancet 2008; 371(9620):1247-1258. 15. Darmstadt GL, Walker N, Lawn JE, Bhutta ZA, Haws RA, Cousens S. Saving newborn lives in Asia and Africa: cost and impact of phased scale-up of interventions within the continuum of care. Health Policy Plan 2008; 23(2):101-117.

Chapters and books	1. Lawn JE, Cousens SN. Newborn Survival: Background paper for the World Health Report 2005, Neonatal chapter and the statistical annex. 2. Lawn JE, Zupan J, Begkoyian G, Knippenberg R. Newborn Survival. In: Jamison D, Measham A, editors. Disease Control Priorities. 2 ed. The World Bank and the National Institutes of Health; 2006. 3. Jamison D, Shahid-Salles S, Jamison J, Lawn JE, Zupan J. Incorporating Deaths near the Time of Birth into Estimates of the Global Burden of Disease. In: Lopez AD, Mathers CD, Ezzati M, Jamison D, Murray CJ, editors. Global Burden of Disease and Risk Factors. 2 ed. The World Bank and the National Institutes of Health; 2006. 4. Joy Lawn, Pyande Mongi, Simon Cousens. Africa's newborns – counting them and making them count. In Opportunities for Africa's Newborns. Eds Lawn JE, Kerber KJ. PMNCH, Cape Town, 2006. ISBN ISBN-13: 978-0-620-37695-2. ISBN-10: 0-620-37695-3 5. Countdown working group. Countdown to 2015. Maternal Newborn and Child Survival: Tracking progress in Maternal Newborn and Child Survival. The 2008 report. UNICEF, New York 2008. 6. Situation Analysis of newborn health in Uganda. Uganda Ministry of Health, Government of Uganda, September 2008. 7. Situation analysis of newborn health in Tanzania. Tanzania Ministry of Health, Tanzania, 2009. 8. Situation analysis and action plan for newborn health in Nigeria. Nigeria Federal Ministry of Health, in preparation, publication due early 2009

Table A.2 Presentations related to the thesis

Table A. 2: Selected presentations so far of relevance to the PhD subject of neonatal cause-of-death estimates, and experience gained			
Event	**When**	**Where**	**Presentation/role or experience gained**
Child Health Epidemiology Reference Group hosted by WHO	June 2004	Geneva, Switzerland	Presentation of work in progress regarding neonatal cause-of-death estimates
United Nations Expert meeting to review child cause-of-death numbers for the World Health Report 2005	October 2004	UNICEF, New York	Presentation of work on neonatal cause-of-death estimates and discussant on incorporation of these numbers in to WHO national estimates for use in World Health Report 2005
Review meeting for *The Lancet* Neonatal Series	November 2004	Geneva, Switzerland (approximately 60 people)	Presenter for paper 1 of the series regarding "Four million neonatal deaths: When? Where? Why?"
Media launch of *The Lancet* Neonatal series	March 2005	London, England	Part of media panel
WHO High Level Meeting to review policy briefs for the World health Report 2005	March 2005	Geneva, Switzerland	Participant in high level meeting with 5 Ministers of Health
Pediatric Academic Societies of America	May 2005	Washington DC (about 400 in the audience, conference registration ~5000)	Plenary presentation "No cry at birth: Counting intrapartum stillbirths and neonatal deaths related to intrapartum complications and making them count" (Also 2 posters)
African Maternal, Newborn and Child Health Task Force	October 2005	Addis Ababa, Ethiopia (approximately 100 people)	Plenary presentation "1 million newborn deaths in Africa- when? Where? Why?" Experience in applying data regarding newborn deaths for policy/programmes in varied African settings
Tri-annual conference of the Union of African Paediatric Societies and Associations/ International Paediatric Association	November 2005	Cotonou, Benin (several hundred participants)	Keynote presentation on the State of newborn health in Africa and running a one day workshop for African Paediatricians from 27 countries on newborn health status, policy and programmes. Experience in policy and programme application of data and in running a workshop with a varied audience
WHO Inter–regional capacity building workshop for Integrating newborn care into Maternal and Child Health Programmes	December 2005	WHO South East Asian Regional Office, New Delhi (approximately 30 people)	Co-leading the technical inputs for a one week workshop for WHO staff from all 6 WHO regions to build capacity for WHO staff to use data and examine existing policy and programmes to accelerate progress to integrate newborn care into exiting programmes and to address gaps in care. Experience in simplifying the process of examining national data, evaluating this data and developing a step by guide to be followed in countries which has now been used in 2 large inter country workshops, translated into French and will be part of a guide to be published by WHO and partners.
Child Survival Countdown to 2015	December	University College of London/	Participated in the Planning team for the conference, particularly

Conference (biannual)	2005	LSHTM (several hundred participants)	working with country teams on their data regarding child survival progress. Made a plenary presentation on Costing interventions to reduce newborn impact modelling was based on *The Lancet* Neonatal Series model applied to cause specific estimates of neonatal deaths by country.
UNICEF East and Southern African region (24 countries). Annual health Network Update Meeting for Senior health personnel	February 2006	Held in a conference hall in Cape Town (approximately 50 people)	Keynote presentation and discussions regarding newborn health status in Africa and priorities to improve newborn survival and health in very different countries. Experience in applying data regarding newborn deaths for policy/programmes in varied African settings
National Stakeholder meetings for newborn health in Malawi, Ethiopia, Uganda	March, April 2006	Malawi, Ethiopia, Uganda (approximately 40 -100 people present at each meeting)	Presentations using data (including cause-of-death estimates) regarding the State of Newborn health in Malawi, Ethiopia, Uganda Experience in interpreting and evaluating data regarding newborn deaths for policy/programmes in varied African countries and discussing the implications and crucial gaps in knowledge that affect scaling up of care
Child Health and Nutrition Research Initiative, workshop in research priority setting	May 2006	Bloomberg School of Public Health, John Hopkins School of Public health, Baltimore (approximately 40 people)	Leading a Technical Working Group on Research Priority Setting for Birth Asphyxia as part of a team developing and testing a new method for systematic research priority setting. Experience in testing and refining a new systematic method for research priority setting being developed by Child Health and Nutrition Research Initiative and the Global Forum for Health Research
African Inter–country workshop for Integrating newborn care into Maternal and Child Health Programmes (7 country teams with high level Ministry of Health participation)	June 2006	Harare, Zimbabwe (approximately 60 people)	Co-organizing with WHO and partners a workshop to support Ministry of health teams from 7 countries to use data and examine existing policy and programmes to accelerate progress to integrate newborn care into exiting programmes and to address gaps in care. Experience in simplifying the process of examining national data for policy and programmes.
Africa Newborn Regional Research network meeting	October 2006	Addis Ababa, Ethiopia (approximately 50 people)	Organizing and facilitating a workshop for 5 country teams of researchers, policymakers and programme managers in to develop research study designs and protocols to test key questions related to scale up of newborn care in their countries Experience gained in assisting teams in research design, sample size calculation, data collection tools etc
International Paediatric Association global meeting linked to Nigerian Paediatric Association meeting	October 2006	Abuja, Nigeria (approximately 200 people)	Keynote presentation on Integrating newborn care into existing programmes in Africa, with a focus on Nigeria, and using Nigeria specific data and analysis
Global Forum Health Research	October 2006	Cairo, Egypt (approximately 100 people)	Presenting the preliminary findings of Technical Working Group for Birth Asphyxia for the systematic research priority setting methods for the Child Health and Nutrition Research Initiative

			This meeting and session provided an opportunity to examine research priority setting for birth asphyxia in the context of other major child health challenges
Pan African Parliament special session	November 2006	Pretoria, South Africa	Plenary overview of the publication – Opportunities for Africa's Newborns Special session of Pan African Parliament to launch the publication, plus media conference, TV and news coverage
Priorities in Perinatal Care Meeting in South Africa	March 2007	South Africa (approximately 300 people)	Invited guest plenary 1. State of Africa's newborns, with a focus on South Africa 2. No Cry at birth: counting intrapartum stillbirths and neonatal deaths related to acute intrapartum events, and making them count
World Bank Newborn Health Symposium	March 2007	World Bank, Washington DC (approximately 300 people)	Plenary opening talk: "Newborn survival – what is progressing, what is not and where are the gaps?"
PMNCH The Partners Forum	April 2007	Dar es Salaam, Tanzania (approximately 400 people)	Talk in the opening plenary "Opportunities for Africa's Newborns"
Pediatric Academic Societies Meeting - special session on Child health Priorities (DCP)	May 2007	Toronto, Canada (about 400 in the audience, conference registration ~5000)	Newborn Survival - delivering the future (Plenary), Special session organised by PGPR and Gates Foundation
Child Health Epidemiology Reference Group hosted by WHO	June 2006	Geneva, Switzerland (approximately 30people)	Presentation on neonatal cause-of-death work and next steps needed to advance this.
International Paediatric Association Congress (every 3 years)	July 2007	Athens Olympic Convention Center (about 4000 in the audience, conference registration ~8000)	Plenary talk in special session on MDGs Newborn survival and the Millennium Development Goals
Royal Society of Tropical Medicine of Hygiene, Centenary celebration	Sept 2007	Queen Elizabeth Conf Center, London (approximately 1000 people)	Plenary talk in opening session Newborn survival and Millennium Development Goal 4
Global Burden of Disease 2 – Launch meeting	Sept 2007	Seattle, USA (approximately 100 people)	Lead for the Global Burden of Disease Group for Neonatal, Stillbirths and Congenital conditions
Women Deliver	Oct 2007	Excel Conf Center, London (approximately 100 in audience)	Symposium talk Stillbirths – delivering systematic estimates
Africa Newborn Regional Research network meeting	Nov 2007	Blantyre, Malawi (60 participants)	Lead technical organiser for a workshop to assist 7 country teams (Ministry of health, Save the Children and academics) in practicalities of implementing research and ensuring comparable measurement across sites
Child Health Epidemiology Reference Group hosted by UNICEF	Dec 2007	UNICEF, New York (approximately 60 participants)	Presentation of work in progress to update neonatal cause-of-death estimates, with new analysis of Vital Registration data and updating and advancing the study-based dataset
Countdown to 2015 Core group and	February	Geneva, Switzerland	Teamwork on data and publications review regarding death, cause-of-

editorial meeting to review Lancet special edition papers and data for Countdown report	2008	(small working meeting)	death and coverage data
Countdown to 2015	April 2008	Cape Town, South Africa (approximately 400 participants including 14 Ministers of Health)	Organising committee member Plenary speaker on "Research Advance for Maternal, Newborn and Child Health"
Norway expert roundtable on MNCH evaluation	April 2008	Cape Town, South Africa Small expert meeting approximately 50 people	Presentation on Implementation research to inform the scale up of integrated newborn care
Global Alliance for Prevention of Preterm birth and Stillbirths (GAPPS)	May 2008	Seattle, USA	Presentation on Measurement gaps for stillbirths and preterm birth
Union of African Paediatric Societies and Associations (UNAPSA) 3 yearly Congress	May 2008	Sun City, South Africa, Approximately 500 people	Plenary talks 1. Saving Africa's Newborns 2. Appropriate technology for Child health Also organised a 7 country panel on Saving Newborn Lives around Africa
Global Burden of Disease Neonatal Morbidity expert group meeting	June 2008	Geneva, Switzerland, small working meeting of 27 people	Organiser of meeting, and technical support for the 7 working groups
Child Health Epidemiology Reference Group hosted by WHO	June 2008	Montreux, Switzerland Approximately 40 people	Presentation on work in progress to update and advance the neonatal cause-of-death estimates and develop stillbirth cause-of-death estimates and neonatal morbidity estimates
Annual programme Review Meeting, Saving Newborn Lives	July 2008	Bangkok, Thailand Approximately 60 people	Presentations on 1. Measuring progress, counting deaths in newborn health programmes 2. Updates on birth asphyxia interventions
Global Alliance for Prevention of Prematurity and Stillbirths (GAPPS)	August 2008	Seattle, USA	Overview of the epidemiology and research gaps for measuring preterm birth and stillbirths
David Harvey Lecture, Neonatal Update	November 2008	Imperial College, London, UK	Invited keynote (David Harvey lecture) Delivering a global research agenda for 4 million newborn deaths

Appendix B: Supplemental tables summarising study datasets

Table B.1 WHO Regions and Global Burden of Disease Subregions

GBD region	Reporting subregion	WHO Member States
AFRO	AFRO D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome And Principe, Senegal, Seychelles, Sierra Leone, Togo
	EMRO D	Djibouti, Somalia, Sudan
	AFRO E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMRO	AMRO A	Canada, United States of America
	AMRO B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
	AMRO A	Cuba
	AMRO D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EMRO	EMRO B	Bahrain, Cyprus, Iran (Islamic Republic Of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
	EMRO D	Egypt, Iraq, Morocco, Yemen
EURO	EURO A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
	EURO B	Albania, Bosnia and Herzegovina, Bulgaria, Georgia, Poland, Romania, Slovakia, the Former Yugoslav Republic of Macedonia, Turkey, Yugoslavia
	EURO B	Armenia, Azerbaijan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan
	EURO C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SEARO	SEARO B	Indonesia, Sri Lanka, Thailand
	WPRO B	Malaysia, Philippines
	WPRO A	Brunei Darussalam, Singapore
	SEARO D	Bangladesh, Bhutan, India, Maldives, Nepal
	EMRO D	Afghanistan, Pakistan
WPRO	WPRO A	Australia, Japan, New Zealand
	WPRO B	China, Mongolia, Republic Of Korea
	SEARO D	Democratic Republic of Korea
	WPRO B	Cambodia, Lao People's Democratic Republic, Viet Nam
	SEARO D	Myanmar
	WPRO B	Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States Of), Nauru, Niue, Palau, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu

AFRO, WHO African Region; AMRO, WHO Region of the Americas; EMRO, WHO Eastern Mediterranean Region; EURO, WHO European Region; SEARO, WHO South-East Asia Region; WPRO, WHO Western Pacific Region.

Table B.2 Summary of vital registration and study data inputs by WHO sub-regions

Sub-region [1]	***Number of countries***	***Regional average NMR per 1000 live births*** [2]	***Number of countries with high coverage Vital Registration data***	**Number of countries with study data (number of studies)**
Afro D	26	43	0 (1) [3]	4 (6)
Afro E	20	42	0	3 (6)
Amro A	3	5	3	NA[4]
Amro B	26	14	6	4 (4)
Amro D	6	21	0	3 (3)
Emro B	13	17	2	4 (6)
Emro D	9	46	0	2 (5)
Euro A	27	3	21	NA[4]
Euro B	16	17	5	NA[4]
Euro C	9	10	4	NA[4]
Searo B	4	17	0	3 (6)
Searo D	7	42	0	2 (19)
Wpro A	5	2	3	NA[4]
Wpro B	22	19	0	1 (1)
Total (Median yr)	193	30	44 countries, 96,797 deaths (2000)	26 countries, 56 studies, 13,685 deaths (1992)

Wpr, WHO Western Pacific Region; Euro, WHO European Region; Amr, WHO Region of the Americas; Emr, WHO Eastern Mediterranean Region; Sear, WHO South-East Asia Region; Afr, WHO African Region.
[1] Countries in the 14 subregions of the Global Burden of Disease [Supplementary table 1 on website]
[2] NMR based on WHO estimates (WHO 2004)
[3] Vital registration data were available for Mauritius but were not used as inputs in the modelling exercise
[4] NA = not applicable. Studies from these sub-regions were excluded due to high VR coverage
Details of the 56 studies included are given in Supplementary table B.2

Table B.3: Studies meeting inclusion criteria for assessment of multiple causes of neonatal cause-of-death. (56 studies, 26 countries, N=13,685)

Author or Principal investigator	Country	□□□□□□ gion	Year pub	Median year data collection	Study population NMR	Number of live births in study	No of neonatal deaths	% unknown cause-of-death	No of causes of death with available data after author communication
Greenwood [1]	Gambia	AFRO D	1987	1982	65	630	41	22	7
Leach [2]	Gambia	AFRO D	1999	1992	39	32164	1254	18	7
Walraven [3]	Gambia	AFRO D	not pub	2000	24.6	3167	78	10	6
Schumacher [4]	Guinea	AFRO D	2002	1998	50	-	97	3	7
Ekanem [5]	Nigeria	AFRO D	1994	1991	37.3	-	24	0	7
Pison [6]	Senegal	AFRO D	1993	1987	36	809	33	4	6
Fantahun [7]	Ethiopia	AFRO E	1998	1992	52.8	909	48	2	6
Dommisse [8]	South Africa	AFRO E	1991	1988	10.45	26887	281	2	7
Woods [9]	South Africa	AFRO E	2001	2001	12	27462	253	0	7
Setel (AMMP) [10] (Dar es Salaam)	Tanzania	AFRO E	not pub	2000	53.2	21,769	87	14	7
Tanzania a (AMMP) [10] (Hai district)	Tanzania	AFRO E	not pub	2000	43.5	39618	142	16	7
Tanzania (AMMP) [10] (Morogoro district)	Tanzania	AFRO E	not pub	2000	52.1	27,927	147	16	7
Barros [11]	Brazil	AMRO B	1987	1982	19.2	7270	127	11	7
De O Gomes [12]	Brazil	AMRO B	1997	1991	16.53	8348	138	0	6
Samms-vaughn [13]	Jamaica	AMRO B	1990	1986	17.9	10249	950	0	6
Mendieta [14]	Paraguay	AMRO B	1999	1996	10.7	343047	3638	0	6
Aguilar [15]	Bolivia	AMRO D	1998	1995	47	-	85	7	7
Perry [16]	Haiti	AMRO D	not pub	1997	28.5	2390	68	18	7
Aleman [17]	Nicaragua	AMRO D	1998	1993	11.59	6229	72	0	6
El-Shafei [18]	Bahrain	EMRO B	1988	1986	7.8	27644	228	0	7
Ebrahim [19]	Bahrain	EMRO B	1998	1996	6.4	9531	61	0	6
Kishan [20]	Libya	EMRO B	1988	1984	20	16277	245	0	6
El-Zibdeh [21]	Saudi Arabia	EMRO B	1988	1983	12	8111	80	3	6
Asindi [22]	Saudi Arabia	EMRO B	1998	1994	9.6	92088	184	0	6
Dawodu [23]	UAE	EMRO B	2000	1991	6.7	8083	54	2	7
Yassin [24]	Egypt	EMRO D	2000	1995	49.3	1636	41	5	7
Campbell[25]	Egypt	EMRO D	2004	2000	25.2	5406	117	12	7
Jalil[26;27]	Pakistan	EMRO D	1993	1984	54	1476	80	0	6
Fikree [28]	Pakistan	EMRO D	2002	1992	56.6	15360	649	23	7
Bhutta [29]	Pakistan	EMRO D	not pub	2001	39.3	3917	154	1	7
Djaja [30]	Indonesia	SEARO B	not pub	2001	25	-	180	2	7
Sivagnanasundrum [31]	Sri Lanka	SEARO B	1985	1982	18.5	2738	51	10	7
Fonseka [32]	Sri Lanka	SEARO B	1994	1987	23.2	-	267	5	5

Lucas [33]	Sri Lanka	SEARO B	1996	1993	14.6	407	120	0	6
Khanjanasthiti [34]	Thailand	SEARO B	1984	1984	31.28	1119	35	0	7
Horpaopan [35]	Thailand	SEARO B	1989	1985	8.02	100193	804	1	6
Islam[36]	Bangladesh	SEARO D	1982	1976	89	1351	120	13	7
Rahman [37]	Bangladesh	SEARO D	1989	1986	70.12	984	69	0	6
Bhatia [38]	Bangladesh	SEARO D	1989	1982	67	926	549	6	6
Fauveau [39]	Bangladesh	SEARO D	1990	1982	55	57837	2273	4	7
Chowdhury [40]	Bangladesh	SEARO D	1996	1983	64.9	7304	474	0	5
Perry [16]	Bangladesh	SEARO D	not pub	1997	35.2	3518	124	11	7
Gupta [41]	India	SEARO D	1981	1977	56	-	31	0	5
Damodar [42]	India	SEARO D	1983	1979	70	579	30	23	6
Shah [43]	India	SEARO D	1984	1978	39.2	3083	121	0	7
Pratinidhi [44]	India	SEARO D	1986	1982	52	2990	135	0	6
Datta [45]	India	SEARO D	1988	1988	50.5	-	168	3	7
Singhal [46]	India	SEARO D	1990	1984	54.3	920	50	0	7
Khalique [47]	India	SEARO D	1993	1990	50.5	415	21	0	7
Phukan [48]	India	SEARO D	1998	1994	46.5	2432	113	11	7
Awasthi [49]	India	SEARO D	1998	1996	86.7	-	286	0	6
Bang [50]	India	SEARO D	1999	1996	58.1	1016	52	10	6
Anand [51]	India	SEARO D	2000	1993	11.5	5703	59	0	7
Bang [52]	India	SEARO D	2001	1996	52.4	-	40	10	7
Shrivrastava [53]	India	SEARO D	2001	1995	44	-	1000	11	7
Ben-Li [54]	China	WPRO B	1985	1980	11.6	85773	991	1	6
Total	26 countries	9 subregions	Median 1994	Median 1991			17619	Range 0-23%	

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Appendix C: CHERG Neonatal Data Abstraction form

Child Health Epidemiology Reference Group (CHERG)
Data Abstraction Form 2004
Neonatal Mortality

General instructions:

1. Always feel free to ask someone if you are not sure how to answer a question
2. Please write legibly, and use a pencil so mistakes can be erased
3. When filling out the boxes during data entry please RIGHT JUSTIFY
4. For all coded questions CIRCLE the correct response
5. f information is unknown or not available - CIRCLE "9 = unknown" for coded questions, or write "N/A" for all other questions
6. If you encounter a "major flaw", record the flaw in Section F, Question 1. Examples include a lack of internal consistency (e.g., a set of percentages that should sum to 100% do not sum to 100%), or methods so incomplete or confusing that you cannot determine what was done.
7. If you think of information that would greatly improve the study's usefulness and that study investigators could provide, record the "request" in Section G, Question 2.
8. If you have additional notes or comments, record them on the last page (Section H).

SECTION A. IDENTIFIERS

A1. Paper identification number ☐☐☐

A.2 Name of data abstractor: _____

A3. Code for data abstractor ☐☐

A.4 Today's date (ddmmyy) ☐☐☐☐☐☐

SECTION B. STUDY REFERENCE

B1. Last name of the first author (or a phrase if no name, e.g., "WHO Young Infants Study"):
_____

B2. Is the study published? (circle correct response) ..... No = 1 Yes = 2 Unknown = 9

IF QUESTION A2. WAS "NO", SKIP TO SECTION C (Study design)

B3. Year of publication: ☐☐☐☐

B4. Journal name:
_____

B5. Volume number: ☐☐☐ B6. Issue number: ☐☐

B7. Issue month: ☐☐ B8. First page number: ☐☐☐☐ B9. Last page number ☐☐☐☐

B10. Language of paper (circle only one of the following

1. English 2. French 3. German 4. Italian 5. Spanish 6. Other

SECTION C. STUDY DESIGN

C1. Was neonatal mortality the central focus of the study? (circle) No = 1 Yes = 2 Unknown = 9

C2. If no then what was the central focus of the study? _____

C3. Does the study examine neonatal mortality? (circle correct response) No = 1 Yes = 2 Unknown = 9

IF QUESTION C.3. WAS "NO", END HERE

C4. What study design(s) was/were used to study neonatal mortality?

4a. Prospective cohort No = 1 Yes = 2 Unknown = 9

4b. Retrospective cohort No = 1 Yes = 2 Unknown = 9

4c. Cross-sectional No = 1 Yes = 2 Unknown = 9

C5. What mortality outcomes are documented? (circle correct responses and if definition used differs from the standard then record this here and in Section G1. e.g. if the study counts early neonatal as to the 6th day)

5a. Neonatal mortality (death in the first 28 days of life) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

5b. Early neonatal mortality (death in the first 7 days of life) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

5c. Late neonatal mortality (death between day 8 and 28 of life) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

5d. Stillbirths (late fetal death after 28 weeks gestation) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

5e. Early fetal death (death between 22-27 weeks gestation) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

5f. Perinatal mortality (stillbirths plus early neonatal deaths) No = 1 Yes = 2 Unknown = 9

Definition used if different _____

C6. Does the study examine neonatal morbidity? (circle correct response) No = 1 Yes = 2 Unknown = 9

IF QUESTION C.6. WAS "NO", SKIP TO QUESTION C9.

C7. What study design(s) was/were used to study neonatal morbidity? (check all that apply)

7a. Prospective cohort No = 1 Yes = 2 Unknown = 9

7b. Retrospective cohort No = 1 Yes = 2 Unknown = 9

7c. Cross-sectional No = 1 Yes = 2 Unknown = 9

C8. What morbidity outcomes are documented? (circle correct responses)

8a.	Neonatal tetanus	No = 1 Yes = 2 Unknown = 9
8b.	Severe infection	No = 1 Yes = 2 Unknown = 9
8c.	"Birth asphyxia"	No = 1 Yes = 2 Unknown = 9
8d.	Diarrhoea	No = 1 Yes = 2 Unknown = 9
8e.	Congenital malformations	No = 1 Yes = 2 Unknown = 9
8f.	Low birth weight	No = 1 Yes = 2 Unknown = 9
8g.	Preterm birth	No = 1 Yes = 2 Unknown = 9
8h.	Other (please list concisely)	No = 1 Yes = 2 Unknown = 9

_____

C 9. Was an intervention tested as part of the study? ..... No = 1 Yes = 2 Unknown = 9

IF QUESTION C9.. WAS "NO", SKIP TO SECTION D.

C10. Was the intervention allocation randomised? No = 1 Yes = 2 Unknown = 9

C11. Briefly describe the intervention:

_____

_____

C12. What was the coverage of the intervention in the intervention arm? (circle only one of the following):

1 0-19%

2 20-39%

3 40-59%

4 60-79%

5 80-99%

9 Unknown

C13. Briefly describe the coverage of the intervention

_____

C14. Was any gender specific data presented in the study ..... No = 1 Yes = 2 Unknown = 9

ECTION D. STUDY METHODS: POPULATION, SETTING, AND TIME

D1. Country where the study was done: _____

D2. Geographic setting of the study (e.g., "360 villages in the Upper River Division, eastern Gambia"):

_____

IF THERE WAS <u>MORE THAN ONE STUDY POPULATION</u> (e.g.. Geetha et al in Nepal with 2 urban hospitals, peri-urban community and rural community) THEN COMPLETE A SEPARATE DATA ABSTRACTION FORM FOR EACH RELEVANT COMMUNITY-BASED SUB-POPULATION.

D3. Was the study setting a research site? (circle correct response) No = 1 Yes = 2 Unknown = 9

D4. If the answer to D3. Was YES, then what was the name of the research site?

_____

D5. Was the study population selected from: (circle correct response)

5a. The whole community/population	No = 1	Yes = 2	Unknown = 9
5b. Health facility	No = 1	Yes = 2	Unknown = 9
5c. Selection not well characterised	No = 1	Yes = 2	Unknown = 9

D6. Which category or categories best describe the study population? (circle correct responses)

6a. Rural	No = 1	Yes = 2	Unknown = 9
6b. Urban	No = 1	Yes = 2	Unknown = 9
6c. Peri-urban	No = 1	Yes = 2	Unknown = 9
6d. Slum	No = 1	Yes = 2	Unknown = 9
6e. Population not well characterised	No = 1	Yes = 2	Unknown = 9

D7. Describe what the results are representative of: For example, the country (e.g., "Ghana"), the district (e.g., "Kassena-Nankana District"), or simply "the study site" (if the results only apply to the study area). Circle only <u>one</u> of the following:

1 The country

2. The district

3. The study site

9. Unknown

Background maternal and neonatal services (questions D.8 to D.9)

D8. What percentage of deliveries was with a skilled attendant (midwife, doctor or nurse with midwifery training)?

Circle only one of the following:

1. 0-19%

2. 20-39%

3. 40-59%

4. 60-79%

5. 80-97%

6. 98-100%

9. Unknown

D9. Was there availability of in-patient care for neonatal emergencies? No = 1 Yes = 2 Unknown = 9

When the study was carried out (questions D10 – D14)

D10. Date of mortality study start

10a. Month (Jan = 1, Feb = 2, March = 3 etc Unknown = 0)…… ☐☐

10b. Year (write the year fully e.g. 1971). …… ☐☐☐☐

D11. Date of mortality study finish

11a. Month (Jan = 1, Feb = 2, March = 3 etc Unknown = 0). ☐☐

11b. Year (write the year fully e.g. 1971). ☐☐☐☐

D12. Study period/duration of study (months). ☐☐☐

D13. Duration of follow-up (days) ☐☐☐

D14. Duration of follow-up (months) ☐☐☐

NOTE IF THE STUDY WAS A "BEFORE AND AFTER" THEN COUNT THE START AS THE BEGINNING OF MORTALITY DATA COLLECTION EVEN IF INTERVENTION NOT IN PLACE.

SECTION E . ASCERTAINMENT AND ASSIGNMENT OF DEATHS

E1. Were any causes of death ascertained in this study? No = 1 Yes = 2 Unknown = 9
IF NO CAUSES OF DEATH WERE ASCERTAINED THEN SKIP TO SECTION F

E2. Data source for assessing the cause-of-death (Circle all that apply)

2a. Family member's report. No = 1 Yes = 2 Unknown = 9

2b. Verbal autopsy No = 1 Yes = 2 Unknown = 9

2c. Clinical information No = 1 Yes = 2 Unknown = 9

2d. Post mortem No = 1 Yes = 2 Unknown = 9

2e. Other (specify)_____ No = 1 Yes = 2 Unknown = 9

E3. Verbal autopsy validation (circle only one of the following):

1. Verbal autopsy data were collected and a validation study was reported

2. Verbal autopsy data were collected, but no validation was reported

3. Not applicable: verbal autopsy data were not collected

9. Unknown

E4. Which of the following categories of cause of neonatal death are documented in this study?
(Circle yes for each cause that is documented)

4a. Neonatal tetanus No = 1 Yes = 2 Unknown = 9

4b. Severe infection (sepsis, meningitis, pneumonia) No = 1 Yes = 2 Unknown = 9

4c. "Birth asphyxia" No = 1 Yes = 2 Unknown = 9

4d. Diarrhoea No = 1 Yes = 2 Unknown = 9

4e. Congenital abnormalities/malformations No = 1 Yes = 2 Unknown = 9

4f. LBW including growth retarded babies and preterm babies No = 1 Yes = 2 Unknown = 9

4g. Prematurity No = 1 Yes = 2 Unknown = 9

4h. Other (please describe briefly e.g. neonatal jaundice) No = 1 Yes = 2 Unknown = 9

4hi_____

4hii_____

E5. Did at least one child have more than one cause-of-death reported No = 1 Yes = 2 Unknown = 9

E6. How were the deaths ascertained

6a. Continuous surveillance by community based workers No = 1 Yes = 2 Unknown = 9

6b Repeated visits (2 or more per year) to identify deaths (Please describe regularity) No = 1 Yes = 2 Unknown = 9

6c. Annual census No = 1 Yes = 2 Unknown = 9

6d. Retrospective recall No = 1 Yes = 2 Unknown = 9

6e. Other (specify)_____ No = 1 Yes = 2 Unknown = 9

SECTION F. MORTALITY RESULTS

No intervention' group (Questions F1-F4)

Please include all births and relevant deaths in the control group of an intervention study, the 'before' group of a before-after study, or the whole sample of a cross sectional/descriptive study (depending on the study design).

F1. Please write all the numerators and denominators for deaths in the specified time periods in the 'no intervention' group into the table below

	Time period	**Number of births (denominator)**		**Total number of deaths**	**Total no of deaths for which a cause-of-death was investigated**	**No of deaths for which a cause-of-death was assigned***	**Numbers of deaths by cause**							
		Live births	*Still births*				*Tetanus*	*Severe infection*	*Birth asphyxia*	*Diarrhoea*	*Congenital abnormality*	*LBW*	*Preterm*	*Other. Specify*
Day 1	0-24 hours of life													
Early neonatal	0-7 days													
Late neonatal	8-28 d													
Neonatal	0-28 d													
Infant	0-11 m													
Early fetal deaths	22-27 w													
Late fetal deaths	28-42w													
Perinatal deaths	28w-D7													

* i.e. exclude the no agreement and unknown categories

F2. Please write all *reported* all-cause and cause-specific mortality rates in the specified time periods for the 'no intervention' group into the table below

	Time period	**Reported all cause mortality rate per 1,000 live births*‡**	**Reported cause specific mortality rate per 1,000 live births**							
			Tetanus	*Severe infection*	*Birth asphyxia*	*Diarrhoea*	*Congenital abnormality*	*LBW*	*Preterm*	*Other. Specify.*
Day 1	0-24 hours of life									
Early neonatal	0-7 d									
Late neonatal	8-28 d									
Neonatal	0-28 d									
Infant	0-11 m									
Early fetal deaths*	22-27 w									
Late fetal deaths*	28-42 w									
Perinatal deaths*	28w- D7									
Low birth weight	LBW									
Preterm	Preterm									

* Early fetal deaths, late fetal deaths and perinatal deaths should be reported per 1000 still births and live births

Low birth weight data.

F3. Please write all *neonatal* or *early neonatal* mortality data for infants in the 'no intervention' group into the table below.

Number of live births (denominator)	**Number of live births who had birth weight recorded**	**Total number of LBW infants**	**Total number of LBW infants who had a neonatal death recorded**	**Total number of LBW infants for which a cause of neonatal death was investigated**	**Number of deaths for which a cause of neonatal death was assigned***	**Numbers of deaths by cause**					
						Tetanus	Severe infection	Birth asphyxia	Diarrhoea	Congenital abnormality	Other Specify
Neonatal (i.e. 0-28 d)											
Early neonatal (i.e. 0-7d)											

* i.e. exclude the no agreement and unknown categories

Preterm data.

F4. Please write all *neonatal* or *early neonatal* mortality data for infants in the 'no intervention' group into the table below.

Number of live births (denominator)	**Number of live births who had gestational age recorded**	**Total number of preterm infants**	**Total number of preterm infants who had a neonatal death recorded**	**Total number of preterm infants for which a cause of neonatal death was investigated**	**Number of deaths for which a cause of neonatal death was assigned***	**Numbers of deaths by cause**					
						Tetanus	Severe infection	Birth asphyxia	Diarrhoea	Congenital abnormality	Other Specify
Neonatal (i.e. 0-28 d)											
Early neonatal (i.e. 0-7d)											

* i.e. exclude the no agreement and unknown categories

Intervention' group (Questions F5-F8)

Please include all births and relevant deaths in the intervention arm of an intervention study or the 'after' group of a before-after intervention study.

F5. Please write all the numerators and denominators for deaths in the specified time periods in the 'intervention' group into the table below

	Time period	**Number of births (denominator)**		**Total number of deaths**	**Total no of deaths for which a cause-of-death was investigated**	**No of deaths for which a cause-of-death was assigned***	**Numbers of deaths by cause**							
		Live births	*Still births*				*Tetanus*	*Severe infection*	*Birth asphyxia*	*Diarrhoea*	*Congenital abnormality*	*LBW*	*Preterm*	*Other. Specify*
Day 1	0-24 hours of life													
Early neonatal	0-7 days													
Late neonatal	8-28 d													
Neonatal	0-28 d													
Infant	0-11 m													
Early fetal deaths	22-28 w													
Late fetal deaths	29-42w													
Perinatal deaths	29w-D7													

* i.e. exclude the no agreement and unknown categories

F6. Please write all *reported* all-cause and cause-specific mortality rates in the specified time periods for the 'intervention' group into the table below.

	Time period	**Reported all cause mortality rate per 1,000 live births*‡**	**Reported cause specific mortality rate per 1,000 live births**							
			Tetanus	*Severe infection*	*Birth asphyxia*	*Diarrhoea*	*Congenital abnormality*	*LBW*	*Preterm*	*Other. Specify.*
Day 1	0-24 hours of life									
Early neonatal	0-7 d									
Late neonatal	8-28 d									
Neonatal	0-28 d									
Infant	0-11 m									
Early fetal deaths*	22-28 w									
Late fetal deaths*	29-42 w									
Perinatal deaths*	28 w-D7									
Low birth weight	LBW									
Preterm	Preterm									

* Early fetal deaths, late fetal deaths and perinatal deaths should be reported per 1000 **still births and live births**

Low birth weight data.

F7. Please write all *neonatal* or *early neonatal* mortality data for infants in the 'intervention' group into the table below.

Number of live births (denominator)	**Number of live births who had birth weight recorded**	**Total number of LBW infants**	**Total number of LBW infants who had a neonatal death recorded**	**Total number of LBW infants for which a cause of neonatal death was investigated**	**Number of deaths for which a cause of neonatal death was assigned***	**Numbers of deaths by cause**					
						Tetanus	Severe infection	Birth asphyxia	Diarrhoea	Congenital abnormality	Other Specify
Neonatal (i.e. 0-28 d)											
Early neonatal (i.e. 0-7d)											

* i.e. exclude the no agreement and unknown categories

Preterm data.

F8. Please write all *neonatal* or *early neonatal* mortality data for infants in the 'intervention' group into the table below.

Number of live births (denominator)	**Number of live births who had gestational age recorded**	**Total number of preterm infants**	**Total number of preterm infants who had a neonatal death recorded**	**Total number of preterm infants for which a cause of neonatal death was investigated**	**Number of deaths for which a cause of neonatal death was assigned***	**Numbers of deaths by cause**					
						Tetanus	Severe infection	Birth asphyxia	Diarrhoea	Congenital abnormality	ther Specify
Neonatal (i.e. 0-28 d)											
Early neonatal (i.e. 0-7d)											

* i.e. exclude the no agreement and unknown categories

SECTION F. OTHER IMPORTANT RATES AND DATA

Severe infection

F9. Was severe infection assessed in this study? No = 1 Yes = 2 Unknown = 9

IF F9 WAS 'NO' SKIP TO QUESTION F11.

F10. What was the agent (e.g Staphylococcus aureus) involved in the severe neonatal bacterial infection deaths? Give the number and percentage of each, if possible.

	Agent	Number of cases	Number of deaths	Reported percentage
F10a	_____	_____	_____	
F10b	_____	_____	_____	_____
F10c	_____	_____	_____	_____
F10d	_____	_____	_____	_____

Congenital anomalies

F11. Were congenital anomalies assessed in this study? No = 1 Yes = 2 Unknown = 9

IF F11 WAS 'NO' SKIP TO QUESTION F13.

F12 What were the important congenital anomalies involved in the congenital anomaly deaths? Give the number and percentage of each, if possible.

	Malformation	Number of cases	Number of deaths	Reported percentage
F12a.	_____			
F12b	_____			

Assessment of gestational age

F13. Was gestational age assessed in this study? No = 1 Yes = 2 Unknown = 9

IF GESTATIONAL AGE WAS NOT ASSESSED SKIP TO QUESTION F15.

F14. What methods were used to assess gestation (mark all that apply)?

14a. Last menstrual period (LMP) No = 1 Yes = 2 Unknown = 9

14b.Clinical assessment of the newborn No = 1 Yes = 2 Unknown = 9

14c. If clinical assessment which method (e.g. Parkin) _____

Assessment of birth weight / birth size

F15. Was birth weight or birth size assessed in this study? No = 1 Yes = 2 Unknown = 9

IF BIRTH WEIGHT / SIZE WAS NOT ASSESSED SKIP TO QUESTION F17

F16. What methods were used to assess birth weight/ birth size? (Circle all that apply)

16a Scales	No = 1	Yes = 2	Unknown = 9
16b.Mother's impression (too small, normal etc)	No = 1	Yes = 2	Unknown = 9
16c. Health professional's impression (too small, normal etc)	No = 1	Yes = 2	Unknown = 9
16d. Other. Please specify. _____	No = 1	Yes = 2	Unknown = 9

Case definitions (be specific; use direct quotes):

F17a. Write the case definition for a case of neonatal tetanus

---

F17b. Write the case definition for a neonatal tetanus death

F18a. Write the case definition(s) for a case of severe infection (this may require several e.g. one for sepsis, one for meningitis, one for pneumonia.

_____

F18b. Write the case definition for a death due to severe infection, (this may require several e.g. one for sepsis, one for meningitis. Be specific; use direct quotes):

_____

F19a. Write the case definition(s) for a baby with "birth asphyxia" (e.g.., Neonatal encephalopathy graded into mild/moderate severe, or Apgar score less than 5 at 5 minutes. _

_____

F19b. Write the case definition(s) for a death due to "birth asphyxia:

_____

F20a. Write the case definition(s) for an infant with diarrhoea.

_____

_____

F20b. Write the case definition for a death due to diarrhoea

_____

F21a. Write the case definition(s) for a baby with congenital abnormalitie(s)/malformation(s).:
(note if the case definition is for a specific abnormality e.g. neural tube defect then record below under specific malformations) _

_____

F21b. Write the case definition for a death due to congenital abnormalitie(s)/malformation(s).:
(note if the case definition is for a specific abnormality e.g. neural tube defect then record below under specific malformations)

F22a. Write the case definitions for specific malformations listed in QF12.

F22a.
_____

_____

F22b.

_____

F22c.

_____

F23a. Write the case definition(s) for a baby with low birth weight

_____

F23b. Write the case definition for a death in a baby with low birth weight:

_____

F24a. Write the case definition(s) for a baby with preterm birth.

_____

F24b. Write the case definition for a death due to prematurity.
_____

F25. Write the case definitions for the other causes of death you recorded in QE3, QF1 and QF5

F25a

_____

F25b.

Case fatality rate

F26. Were case fatality rates assessed in this study? No = 1 Yes = 2 Unknown = 9
(no of deaths/no of episodes)

IF F26 IS NO SKIP TO QUESTION F28

F27. List the most important case fatality rates presented in the study (List the **neonatal** case fatality rate if available. List only one rate for each cause).

Cause	**Age of youngest**	**Age of oldest infant**	**Number of deaths**	**Number of episodes**	**Reported case fatality rate (%)**
27a. Tetanus					
27b. Severe infection					
27c. Birth asphyxia					
27d. Diarrhoea					
27e. Congenital abnormality					
27f. LBW e.g. neonatal deaths among LBW babies / number of LBW babies					
27g. Prematurity e.g. neonatal deaths among preterm babies / number of preterm babies					
27h. Other. Specify					

SECTION G. POTENTIAL FLAWS AND QUESTIONS FOR AUTHORS

G1. Record any potential serious flaws of the study (if none, please write "NA"): _

_____

_____

_____

G2. If you think of information (that study investigators could provide) that would greatly improve the study's usefulness, record what information should be requested. For example, a study reports outcomes for preterm and LBW babies together despite assessing gestation age, and you think the investigators could provide data by gestational age, which is what you ideally want. If no questions, please write "NA".

_____

_____

SECTION H. RECORD ANY ADDITIONAL NOTES OR COMMENTS ON THE ARTICLE IN THE SPACE BELOW.

_____

_____