Verbal Autopsy for Stillbirth and Neonatal Deaths – Comparing Population Cause Specific Mortality Fraction Using Two Methods

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I, Stefania Vergnano, 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.

To Michael, Miriam and Sara

Abstract

Background: Every year 3.2 million infants are stillborn and 3.6 million die within the first month. Up to 98% of these deaths occur in countries with inadequate or non-existent vital registration systems, where cause of death data are sparse and mostly derived from verbal autopsies (VA). It has been advocated that VA are included in routine national statistics. This thesis proposes and compares the strengths and limitations of methodologies to collect and interpret VA data for stillbirths and neonatal deaths.

Methods: Data were derived from three research areas in Malawi, Nepal and Mumbai. The development of classifications, diagnostic algorithms and questionnaires for VA, suitable for physician review interpretation is described. A probabilistic method to analyse all age deaths (InterVA) was adapted for stillbirths and neonatal deaths. Cause specific mortality fractions were compared using physicians' review and InterVA.

Results: Neonatal mortality rate in Malawi was 25/1000 livebirths (LB), in Nepal 31/1000 LB and in Mumbai 16/1000 LB. A total of 922 VA including both live and stillbirths were analysed to establish causes of death. Stillbirths accounted for 44-54% of deaths. Of neonatal deaths, in Malawi the majority were attributed to severe infections according to physician review (55%) and InterVA (46%); in Nepal (43%) and Mumbai (61%) perinatal asphyxia was most common according to InterVA. In Nepal however, physician review ascribed the majority of neonatal deaths to severe infections (50%). Kappa statistics for individual agreement comparing both methods was 0.60 (CI 0.567-0.702) in Malawi, 0.62(CI 0.59-0.65) in Nepal and 0.48(0.40 - 0.50) in Mumbai.

Discussion: Different VA interpretation methods exist, however standardised procedures are necessary for international comparison. The role of physician review in interpreting VA is changing while computerised methods are becoming more widespread. The modified InterVA model provides a rapid and consistent method to establish causes of stillbirths and neonatal deaths, however it requires further refinements and ultimately a validation study using a comparison other than physician review.

Acknowledgements

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I would like to thank Dr David Osrin who first introduced me to the concept of verbal autopsy, instilling in me the interest and curiosity in the subject and has since been following my progress with interest and provided me with helpful and constructive guidance.

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A huge recognition goes to my kind colleagues and friends Drs Helene Payne and Adam Irwin who spent time reading and interpreting a large number of questionnaires from Malawi to help me finish this project.

Glossary

Live Birth: Infant born at any gestational age that after delivery shows signs of life (e.g. breathing, heart beat, voluntary movements).

Stillbirth or Foetal Death: Death of a foetus after 28 completed weeks gestation (or 6 completed months gestation, when no information about weeks of gestation are available.

Antepartum or Macerated Stillbirths: Foetal death occurring prior the onset of labour (recognisable by macerated skin).

Intrapartum or Fresh Stillbirths: Foetal death occurring during labour or at delivery (recognisable by intact skin). Death is considered to have happened less than 12 hours before birth.

Neonatal Death: Death of a liveborn infant within the first 28 days.

Early Neonatal Death: Death of a liveborn within the first 7 days from birth.

Late Neonatal Death: Death of a liveborn occurring between day 8 and 28 after delivery.

Perinatal Death: Stillbirth or early neonatal death.

Maternal Death: Death of a woman after conception and within 42 days after delivery from a cause related to the pregnancy. It excludes deaths due to causes of death unrelated to the pregnancy itself (e.g. accidents).

Neonatal Mortality Rate: Number of deaths/ All livebirths/ 1000 per year.

Early Neonatal Mortality Rate: Early neonatal deaths/live births per 1000 per year.

Late Neonatal Mortality Rate: Late neonatal deaths/live births per 1000 per year.

Stillbirth Rate: Number of stillbirths/Total births (live and still) per 1000 per year

Perinatal Mortality Rate: Number of stillbirths and early neonatal deaths/ all births (live and still) per 1000 per year.

Post-neonatal Mortality: Number of infant dying after 28 days and before their first birthday/ livebirth per 1000 per year.

Infant Mortality Rate: Number of children dying within a year of birth/livebirth per 1000 per year.

Under Five Mortality Rate: Number of children dying before their fifth birthday/ livebirth per 1000 per year.

Maternal Mortality Ratio: Number of maternal deaths/ livebirths per 100,000 per year

DALY: Total number of productive life years lost to disability or premature death

Gross Domestic Product (GDP): Sum of all final products (goods and services) of a country in a given period, including taxes. Expressed in current US $

GDP Growth: Percentage Growth rate of the GDP per year

Gross National Income (GNI): sum of goods and services produced by a country, including taxes and income from abroad.

Per capita: per person calculated on the basis of the mid year population

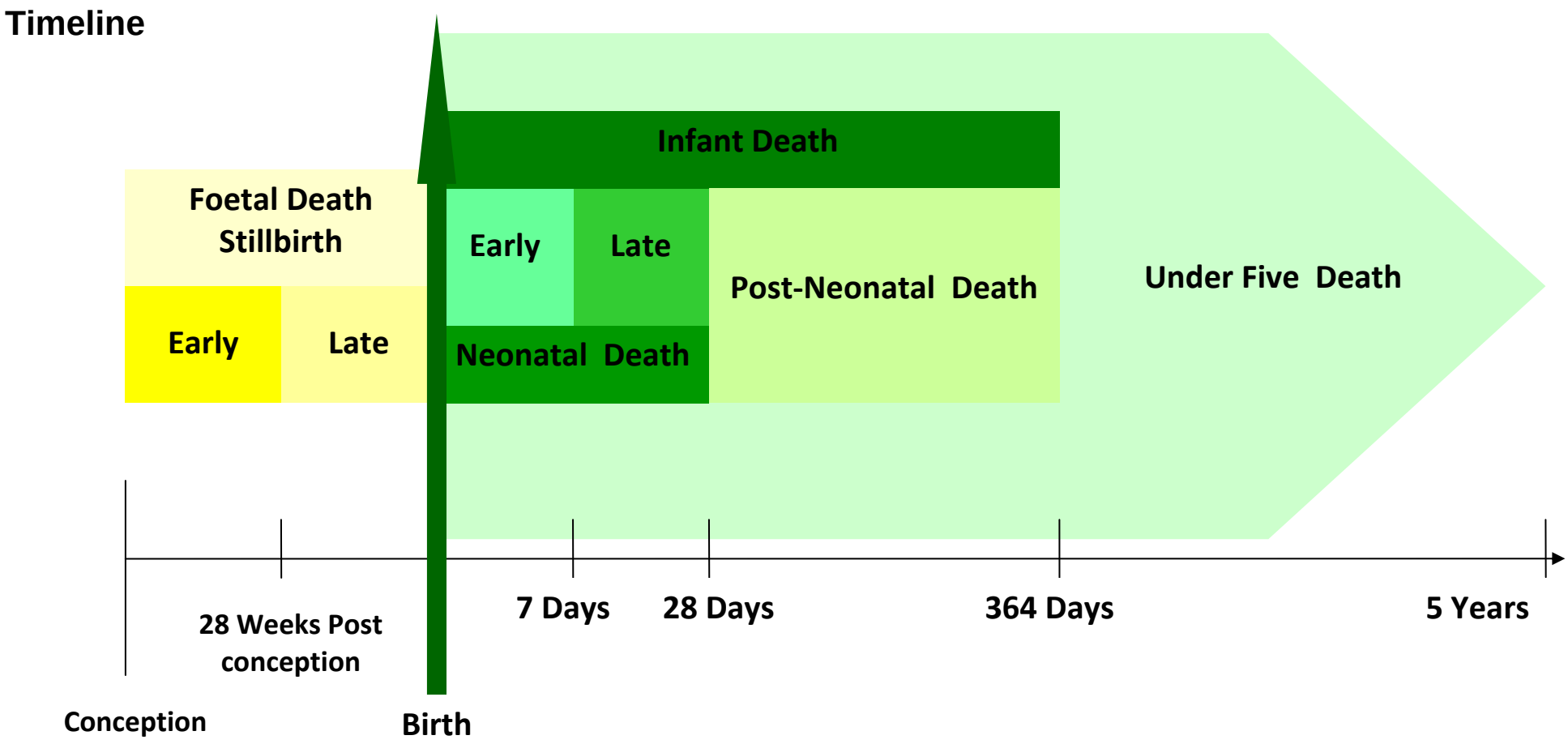
Purchasing Power Parity (PPP): a conversion factor. It is used to convert the amount of local currency necessary to purchase a product locally compared to the amount of U.S. dollars necessary to buy the same product in the United States.

Gross National Income *per capita* Purchasing Power Parity (GNI PPP): It is the GNI calculated using the purchasing power parity rates for an international dollar.

International Dollar: It is a currency with the same purchasing power as a US $ in the US at a given time.

Human Development Index (HDI): It is a composite indicator set by the United Nation Development Programme measuring health, education and well being using 4 indicators: the life expectancy at birth, mean and expected years of schooling, and the GNI per capita PPP.

InterVA: Computer software based on Bayesian probability for the interpretation of verbal autopsy data


Timeline
Infant Death
Foetal Death
Stillbirth
Early
Late
Post-Neonatal Death
Under Five Death
Early
Late
Neonatal Death
28 Weeks Post conception
7 Days
28 Days
364 Days
5 Years
Conception
Birth

Abbreviations

ANC: Ante Natal Care

CHERG: Child Health Epidemiology Research Group

CSMF: Cause Specific Mortality Fraction

DALY: Disability Adjusted Live Years

DHS: Demographic and Health Surveillance

GA: Gestational Age

GBD: Global Burden of Diseases

GBS: *Group B streptococcus*

ICD: International Classification of Disease

ICH: Institute of Child Health

LB: Live Births

MDG: Millennium Development Goals

OH: Open History

PHM: Population Health Metrics

PVA: Perinatal Verbal Autopsy

SAVVY: Sample Vital Registration with Verbal Autopsy

SD: Standard Deviation

UCL: University College London

U5MR: Under Five Mortality Rate

UN: United Nations

UNDP: United Nations Population Division

UNICEF: United Nations Children Fund

SP: Symptom Pattern

VA: Verbal Autopsy

WCBA: Women of Child Bearing Age (Between 14 and 59 years old)

WHO: World Health Organisation

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Introduction

I Aim and objectives of the thesis

The thesis was developed between 2004 and 2011. During this time the importance of establishing causes of death became a priority in the global health agenda, with the time left to meet the Millennium Development Goals looming closer and closer[1-12]. As under five mortality reduced, the consistent number of neonatal deaths contributed an ever increasing proportion of death, attention to the number of stillbirths also increased[13-22]. This thesis describes the burden of stillbirths and neonatal deaths in three developing countries: Malawi, Nepal and Mumbai and develops a verbal autopsy methodology to establish the causes of death attribution process in these populations. The verbal autopsy process is conceptualised and analysed in light of the experience obtained in Malawi and it is extrapolated and generalised to other countries.

The aims of this thesis are to:

- Conceptualise the verbal autopsy process, splitting it in its different components of data capture and analysis.
- Propose strategies to analyse verbal autopsy data for countries with non-existent or incomplete vital registration systems in a standardised and universally relevant fashion.
- Describe the epidemiology of stillbirths and neonatal deaths in three developing countries using verbal autopsy data

More specifically this thesis will discuss the following questions:

1. Is it necessary and feasible to propose a single standardised classification and diagnostic algorithm for stillbirth and neonatal deaths to interpret verbal autopsy data?
2. Can a single questionnaire to investigate stillbirths and neonatal death using verbal autopsy serve all purposes?
3. How do crude mortality fractions for stillbirths and neonatal deaths in our three studies compare with the available literature?
4. Is InterVA suitable to provide cause-specific mortality fractions in the perinatal and neonatal period in comparison with physician review in our three study settings?
5. How do cause-specific mortality fractions from three different countries compare when a standardised method is used?

II Thesis outline

Chapter 1 is a literature review of the available knowledge of the burden of stillbirths and neonatal deaths. The role of verbal autopsies is described in the context of defining causes of death in countries lacking adequate vital registration systems. The current thinking about the verbal autopsy process is discussed in broad terms and with specific focus on the perinatal and neonatal period.

An introduction to the three countries from which the data analysed in this thesis are derived is given in **Chapter 2,** with a description of the respective research projects.

Chapter 3 describes the VA tools for physician review interpretation: presenting the questionnaires, classifications and algorithms development. The adaptation of InterVA to include stillbirths and neonatal deaths is then explained.

Chapters 4, 5 and 6 report the results of the crude mortality data from Malawi, Nepal and Mumbai and the cause specific mortality obtained with two methods: physician review and InterVA.

Chapter 7 compares the cause specific mortality data in the three studies using the InterVA method, and presents different possible outcomes using alternative interpretation of InterVA data.

Chapter 8 and 9 Develop a discussion centred on the five questions set as the objectives of this thesis.

Chapter 10 Summarises the research finding and lists a series of recommendations derived from this research.

III Role of the Investigator

The original idea of the analysis presented in this study follows my participation as a clinical research fellow to the Maimwana project, originated by Professor Anthony Costello from the Centre for International Health and Development University College London, Professor Marie-Louise Newell from the Africa Centre for Health and Population Studies, University of KwaZulu Natal, South Africa (and ICH,UCL), Dr Charles Mwansambo and Dr Peter Kazembe from Kamuzu Central Hospital, Lilongwe, Malawi. When I joined the project a grant proposal had been written and funds approved. As most large international trials, Maimwana was the result of the contributions of several people with different skills and abilities. I contributed to the setting up of "Maimwana Project" in the role of technical advisor with the main task of offering technical assistance in the development of the peer-infant feeding intervention and health strengthening programme, including the setting up and development of a PMTCT programme. In my capacity as a paediatrician I was able to contribute to the development of the questionnaires used in this study. I lived in Mchinji District, Malawi from June 2003 to April 2006.

To clarify my role in this thesis I will try to spell out my original contributions:

- When this study began there were a number of different perinatal and neonatal mortality classifications mostly used in high income countries to describe causes of death from a clinical perspective. I was responsible for defining and then refining a stillbirth and neonatal death classification in collaboration with Dr. David Osrin for physician review use. This classification has since been used in other CIHD projects in Nepal, India and Bangladesh.
- I contributed to the design of quantitative data collection instruments, particularly the Perinatal/Neonatal Verbal Autopsy questionnaire used in Maimwana. I then further refined the questionnaire in collaboration with

Dr David Osrin and the final version is now in use in the Centre for International Health and Development projects.

- I devised the interpretative algorithm for physician review used in the Maimwana study and contributed to its refinement that led to the algorithms used for Nepal and Mumbai.
- To analyse the results from the VA interviews available from Maimwana project in a standardised manner I contacted the research group that devised a probabilistic approach to interpret VA data (InterVA) and proposed to trial it on perinatal data. I adapted InterVA by modifying the original probability estimates and adding new indicators and causes of death to the original model, as it was previously not possible to analyse stillbirths.
- I proposed and supported the addition of stillbirths as part of the causes of death in the modified InterVA.
- I was the third paediatrician establishing diagnoses for a part of the Malawi VA questionnaires.
- To ensure that the model was adequate to other study settings and cultural contexts I approached researchers within the Centre for International Health and Development to obtain VA from stillbirth and neonatal death and corresponding physician reviews to test the modified InterVA tool.
- I finally analysed the different data sets and compared the results.

Chapter 1

Measuring Causes of Stillbirths and Neonatal Mortality in Resource Poor Countries

"Making the best the enemy of the good is a sure way of hinder any statistical progress. The scientific purist who will wait for medical statistics until they are nosologically exact, is no wiser than Horace's rustic waiting for the river to flow away" (Major Greenwood)

In the year 2000 the Millennium Declaration was endorsed by 192 states in the United Nations General Assembly and from it the Millennium Development Goals (MDG) were drawn[23].

Principles and aims already spelled out in the Alma Ata declaration in 1978 became objectives to be achieved by all signatories in a clearly set time line[23].

MDG 4 mandates a reduction of under-five mortality by 2/3 by the year 2015 compared with 1990 figures[23].

Given the tight time limits, precise estimates on mortality rates by age and sex over time have became essential to monitor progress[24-29]. Moreover a detailed breakdown of mortality by cause became necessary to inform policy on selecting appropriate interventions to achieve MDG 4[30;31].

As vital registration is currently available in only a limited number of low mortality countries, in the short term improving verbal autopsy (VA) methods to collect causes of death in high mortality countries will increase data availability[30;32-34].

The focus of this thesis is on improving the verbal autopsy process to establish causes of deaths for stillbirths and newborns.

1.1 - Why Newborns are Central to Millennium Development Goal 4?

Published figures from the 1950s to 1999 have shown a consistently decreasing trend in under-five mortality globally. Ahmad *et al.* reported the global number of under-five deaths to be 10.5 million in 1999, with a mean mortality rate of 70.4/1000 (SD 69), much reduced from 159/1000 (SD 102), in the 1950s[28]. An extensive review of under-five mortality for the year 2000 was undertaken by CHERG, a group of technical experts established by the World Health Organisation (WHO) in 2001 with the purpose of developing and improving epidemiological tools to define the burden of mortality and disease in children under 5. From this review, it became apparent that an increasing proportion of under-five mortality was due to neonatal deaths, representing about 4 millions deaths in the year 2000[35-38].

Murray *et al.* modelled break down of mortality by age from 1970 and projected it to 2015 clearly showing the relative increase in proportion of neonatal deaths (from 31% in the 70s to 37% in 2005) within a reducing under-five mortality trend due to the stable number of neonatal deaths. Childhood mortality decreased from 13.5 million (13.4-13.6) in the 1980s to 9.7 million (9.5-10) in 2005[39]. More recent estimates continued to show a trend of decreasing under-five mortality. In 2008, when the total under-five mortality was calculated at 8.795 million an even higher proportion of neonatal deaths was calculated, by then constituting 41% of all under five deaths[40].

Counting neonatal deaths and addressing the problem of high neonatal mortality with appropriate action has consequently become necessary for the achievement of MDG 4[41;42]. A number of initiatives to improve neonatal health and raise their profile within the international political agenda took place in the last 10 years. The Lancet series on newborn health in 2003 was part of this process and contributed to bring newborns to the centre of the political agenda[43-46].

The Demographic and Health Surveillance (DHS) reports published since 2000 for 36 out of 52 African countries included neonatal mortality. The neonatal mortality rate ranged from 15/1000 in South Africa to 47/1000 in Lesotho. Perinatal mortality data were available for only 17 countries and ranged from 25/1000 in Zimbabwe to 54/1000 in Lesotho. Excluding India, China and high income countries with complete vital registration systems or sample vital registration systems, all DHS from 12 Asian countries published since 2000 included neonatal and perinatal mortality figures and indicated a NMR ranging from 12/1000 livebirths in Vietnam to 54/1000 in Pakistan and perinatal mortality from 21 in Vietnam and 159 in Pakistan (http://www.measuredhs.com/pubs/accessed Mar 2011).

Stillbirths, defined in this thesis according to the WHO criteria as the death of a foetus of more than 1000g birth-weight or born after 28 weeks gestational age without any sign of life[47], are not included in the MDGs. The interest for rate and causes of stillbirths emerged more recently compared with neonatal deaths. The "*Global Burden of Diseases*", published in 2006 included stillbirth in global mortality statistics and in the calculation of DALYs for the first time [48]. Recent estimates, calculated using data up to the year 2000, determined that stillbirths added 2.64 million deaths per year (2.14-3.82 millions) to the under-five burden[49]. Previous estimates calculated on the same datasets estimated the total stillbirth toll to be about 3.2-3.5 million deaths[47;50;51]. These differences are due to the different estimation methods used, given the same data sources. Large uncertainty margins reflect the lack of data from countries with high burden of stillbirths with lacking or incomplete vital registration systems[47;52]. The crude separation between antepartum and intrapartum stillbirths offered important programmatic information, as interventions to reduce their number are different. Estimates of the burden of intrapartum stillbirths has been modelled to amount to about 1 million deaths per year[53].

1.1.1 Uncertainties in Measuring Stillbirths and Neonatal Mortality

The interest in measuring trends of under-five mortality, assessing progress over time and testing the efficacy or otherwise of development programmes began long before the MDGs. UNICEF, the World Bank, the United Nations have been monitoring under-five mortality since at least the 1980s[54] (http://data.worldbank.org/indicator/SH.DYN.MORT). However the MDG made measuring progress paramount in a climate of scarce resources and increased interest in evidence based programming and policy[55;56].

Ideally, to describe global mortality, vital registration systems in which all births and deaths are recorded with their causes established by a skilled health professional are necessary from all countries. However, whereas vital registration systems are mostly adequate in developed countries[57]; in developing countries, where the burden of mortality lies, most deaths occur outside clinical setting[58-61], and vital registration systems are non-existent or at best inadequate[62-64], with less than 90% coverage[65].

As for any other age groups, data on crude neonatal mortality are therefore mostly available through alternative sources such as censuses, demographic health surveillances, fertility surveys, sentinel surveillance sites, multiple indicators cluster surveys and sample vital registration systems[28;66-68].

All these data sources, apart from sample vital registrations, are collected periodically though questionnaires asking the respondent to report births and deaths over a variable period of time. It is well known that neonatal deaths and particularly stillbirths are more likely to be omitted and therefore under-reported[69-71].

The available data are therefore far from being perfect and require modelling and complex analysis to produce estimates that can then be acted upon by policy makers[72;73]. UN agencies, such as WHO, UNICEF, the World Bank have been reporting annual estimates that were not consistent with each others'.

Different models to produce these estimates have been used and proposed[74-76]. Academic and UN agencies, mostly WHO and UNICEF, continue to produce better and more sophisticated analysis methods[77]. Estimates are reported with margins of error reflecting the uncertainties of the models and can differ quite substantially. The estimate of stillbirths recently calculated for the data up to the year 2000 was 560,000 per year, lower than previously calculated[78]. An animated debate regarding who should be in charge of proposing new models and analyse data surrounds the world of estimates[55;72]. It has been questioned whether attention and energy would be better dedicated to improving data collection rather than on modelling as this would make data more usable not only by academics and the international community but also by the national governments which most need it[79]. Tension also exist between the needs for data at national and global level as useful indicators may differ in the two contexts[80].

1.2 - Causes of Death for Stillbirths and Neonates: a Short History

The availability of cause of death data is progressing at a slower pace than for crude, age and sex related mortality data in all age groups[81]. For example in 2006, only 7 African countries were able to report cause specific mortality data to WHO (Figure 1.1).

Figure 1.1 - Availability of Causes of Death to WHO in 2006

Source: Health Metrics network WHO

For the neonatal period, causes of deaths were listed in the World Health Report as a single category of "perinatal deaths" without any attempt to separate them in detail until the 2005 report[38]. Congenital malformations were classified separately as causing death in any age group. Perinatal deaths formed a single but heterogeneous category of deaths and grew to include just under 40% of all under-five deaths in the year 2000[82]. As part of the review of under five-mortality CHERG, analysing the year 2000 figures, resolved to separate perinatal deaths into 7 categories[83-85]. The result of this work was published by WHO in the World Health Report 2005: "Make every mother and every child

count"[38] (Table 1.1). The following year the global burden of diseases (GBDs) 2001 was published and presented neonatal deaths and stillbirths separately (Table 1.1). The classification of perinatal deaths used by these two groups were very similar, however CHERG used prematurity as one of the causes of death for both the neonatal and post-neonatal period, and included "small for gestational age" with "other causes of neonatal death", arguing that only a small minority of infants' deaths were due to birth-weight[86]. The GBD classification however used "low birth weight" as a category of death including both premature and low birth weight infants[87]. The proportion of deaths estimated using the two methods was similar still, with the exception of neonatal tetanus, representing 7% of all neonatal deaths according to the CHERG estimates and 4% in the GBD (Table 1.1). The GDB also estimated a higher proportion of "other" causes of death and severe infections compared with CHERG (11 vs 3 and 34 vs 26 respectively) (Table 1.1). The estimates for 2004 for the GBD and 2008 for the WHO did not show major changes in the proportion of causes of neonatal deaths except from the reduction of deaths due to neonatal tetanus[30;88].

Table 1.1 - Comparison of Causes of Neonatal Mortality - CHERG and GBD

	CHERG / WHO				Global Burden of Diseases			
	Estimate for the year 2000[89]		Estimate for the year 2008[90]		Estimate for the year 2001[91]		Estimate for the year 2004[30]	
Neonatal deaths by causes	**Number** in millions	**%**	**Number** in millions	**%**	**Number** in millions	**%**	**Number** in millions	**%**
Preterm birth	1.091	28	1.033	29	1.098 ~	26	1.17	31
Birth asphyxia	0.896	23	0.814	23	0. 729	17	0.87	23
Severe infections	1.013	26	0.521	15	1.446	34	0.98	26
Pneumonia	-	-	0.386	11	-	-	-	-
Neonatal tetanus	0.273	7	0.059	2	0.168	4	0.13	3.4
Diarrhoeal diseases	0.117	3	0.079	2	0.116	3	0.10	2.6
Congenital abnormalities	0.312	8	0.272	8	0.32	8	0.26	6.8
Others	0.194	7	0.409	11	0.471*	11	0.26	7
Total	**3.91**	**100**	**3.573**	**100**	**4.195**	**100**	**3.77**	**99.8**
Stillbirths								
Antepartum					2.192		-	
Intrapartum					1.082		-	
Total					**3.274**		**-**	

Note: *not assigned ~ Low birthweight

1.3 - Limitations in Measuring Cause Specific Mortality for Stillbirth and Neonatal Deaths

Cause of death data are obtained through vital registration systems, other sources are scanty: hospital records, research studies, sentinel surveillance sites, single diseases surveys, sample vital registration systems, and some DHS, leaving large information gaps[92-97]. Apart from vital registration systems and hospital deaths, where contemporary diagnoses are made by a health professional, all other methods rely on information collected through verbal autopsies[98-100].

1.3.1 Vital Registration Systems

Vital registration systems covered only about 3% of neonatal deaths for the CHERG group estimation of the year 2000 and 4% for 2008[101;102].
Information about causes of death in death certificates is standardised across countries, and includes an underlying or direct cause of death, defined as the disease or injuries leading to death and, if appropriate, the antecedent cause of death and other associated conditions[103]. The diagnoses are coded according to the International Classification of Diseases, version 10 (ICD-10), an internationally recognised system of classification of diseases developed in collaboration with the WHO. The present version was compiled in 1989, comprises 21 chapters and cites over 2000 causes of deaths[103]. The ICD-10 coding system allows comparisons of causes of death in populations over time and between countries[103]. However variations to the ICD-10 have been developed in different countries[104].
Attribution of causes of death by the medical profession can be problematic however, as there is often lack of physician training in compiling death

certification forms and there may also be bias due to the perception of the local epidemiology[105-109]. Physicians poorly trained in ICD coding may choose information-poor codes such as “respiratory failure” or “cardiac arrest” which classify only the final process leading of death but do not record the antecedent diagnoses necessary for public health use (ICD-10). It has been shown in countries where a vital registration system, however incomplete, exists, for example in Thailand, that up to 20-30% of death certification contains such poorly informative ICD-10 coding that these cannot be utilised[12;110-112].

1.3.2 Hospital Records

Deaths occurring in hospital are documented in the health records, however in developing countries only a minority of deaths occur in hospitals[60;113;114]. It is questionable whether such deaths are representative of deaths occurring in the community for a number of reasons[58;115]. Care seeking behaviour may be different according to several factors, such as the travel time to hospital, maternal education and economic situation of the users, thus under-representing causes of death that are more common in poorer rural populations[116;117]. Moreover, deaths occurring in hospital are more likely to be due to severe diseases that occur over a period of time long enough to reach the health facility[118]. In Malawi for example maternal deaths occurring in health facilities are reported to be due mostly to post partum haemorrhage and puerperal sepsis[119;120]. Community studies found that haemorrhages are the most common cause of maternal death, when the course of disease is too rapid to reach a health facility[121;122]. Access to hospital treatment modifies the natural history of disease. For example it is well known that use of antibiotics to treat neonatal sepsis is an effective strategy to reduce neonatal deaths and WHO recommends

the use of intravenous antibiotics[123], which is possible in health facilities, therefore access to treatment can change the course of this otherwise deadly disease. However admission of low birth-weight infants in neonatal units exposes them to resistant organisms, again modifying the epidemiology of sepsis[124;125]. For all these reasons hospital records cannot be simply used unmodified to infer population CSMF. Nevertheless, hospital diagnoses remain an important resource and can be used in selected epidemiological circumstances for estimation purposes[126].

1.3.3 Other Data Sources

Data can also be extracted from research studies and longitudinal surveillance sites. Nonetheless these data cover areas chosen for reasons other than their representativeness[127]. Moreover interventions in such areas may change the mortality pattern compared to other regions in the same country.

Data for single diseases, such as malaria or HIV, have also been used to model mortality, however they may over-represent deaths due to the disease in focus[128].

All data collected through these sources use verbal autopsy methods to ascertain causes of death. Given that implementing complete and good quality vital registration systems worldwide will not be achievable in the short or medium term[129;130], the international community focused attention on the VA process as the only currently available mean to establish population CSMF in developing countries without vital registration systems[131-133].

1.4 - The Role of Verbal Autopsies in Establishing Causes of Death

Verbal autopsies consist of two stages. Firstly information is collected from a standardised questionnaire administered to a close caregiver of the deceased: for the neonate and the child this is generally the mother. Data are then interpreted to establish diagnoses. Traditionally physicians have been interpreting VA using their clinical knowledge with or without classifications or algorithms to facilitate and standardise their opinion[134-138]. Alternatively data obtained from VA questionnaires have been elaborated using computer software to produce diagnoses[139;140].

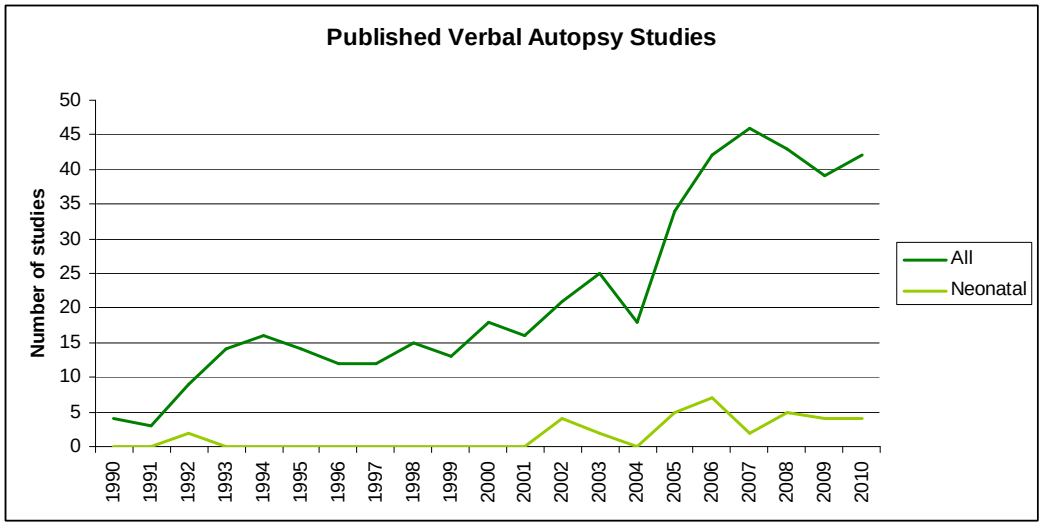
Verbal autopsies have been used in developing countries to collect information about causes of death since the 1950s. Originally, on the model of the 16th century Bills of Mortality, they were open interviews between a next of kin of the deceased and an interviewer who established the cause of death. Generally the interviewer was a physician. This method had the obvious limitation of requiring large amounts of physician time[141]. The introduction of detailed questionnaires made the method more widely available as it could be administered not only by physicians but also by other health professionals or trained lay people[142]. The technique became more widely used when the WHO published a document legitimising the use of lay interviewers[143].

Currently a renewed interest in VA methodology is reflected by a number of initiatives attempting to standardise the whole process. In 2007 WHO published standardised questionnaires for different age groups and adapted the ICD-10 coding for VA use[144]. In 2011 the first global congress on verbal autopsy was held with the aim of promoting debate on the subject, improving quality and advocating for VA to be used as a means to collect data in routine national statistics. Funds have been invested by USAID to set up "sample vital registration with verbal autopsy" (SAVVY) a system to increase the data collection using verbal autopsy within routine national statistics: sample vital

registration or DHS (http://www.cpc.unc.edu/measure/tools/monitoring-evaluation-systems/savvy accessed March 2011). The Institute of Health Metrics has been granted funds from the Bill and Melinda Gates Foundation to develop methodologies to improve data collection and transmission using new technologies, interpret verbal autopsy data, and validate them with a large hospital dataset as part of the Population Health Metrics Consortium project. (http://www.healthmetricsandevaluation.org/research/project/population-health-metrics-research-consortium-project).

A combined search using Pubmed and Medline engines with a single key word "verbal autopsy", with no limits reflects this wave of recent interest. This simple search yielded 385 articles in Pubmed and 319 in Medline. On reading the abstracts and excluding unrelated research or duplicates 319 articles were considered relevant either as original research on methodology or as studies that used VA to establish causes of death or as review articles. Interest in the neonatal period emerged in the last 10 years only (Figure 1.2).

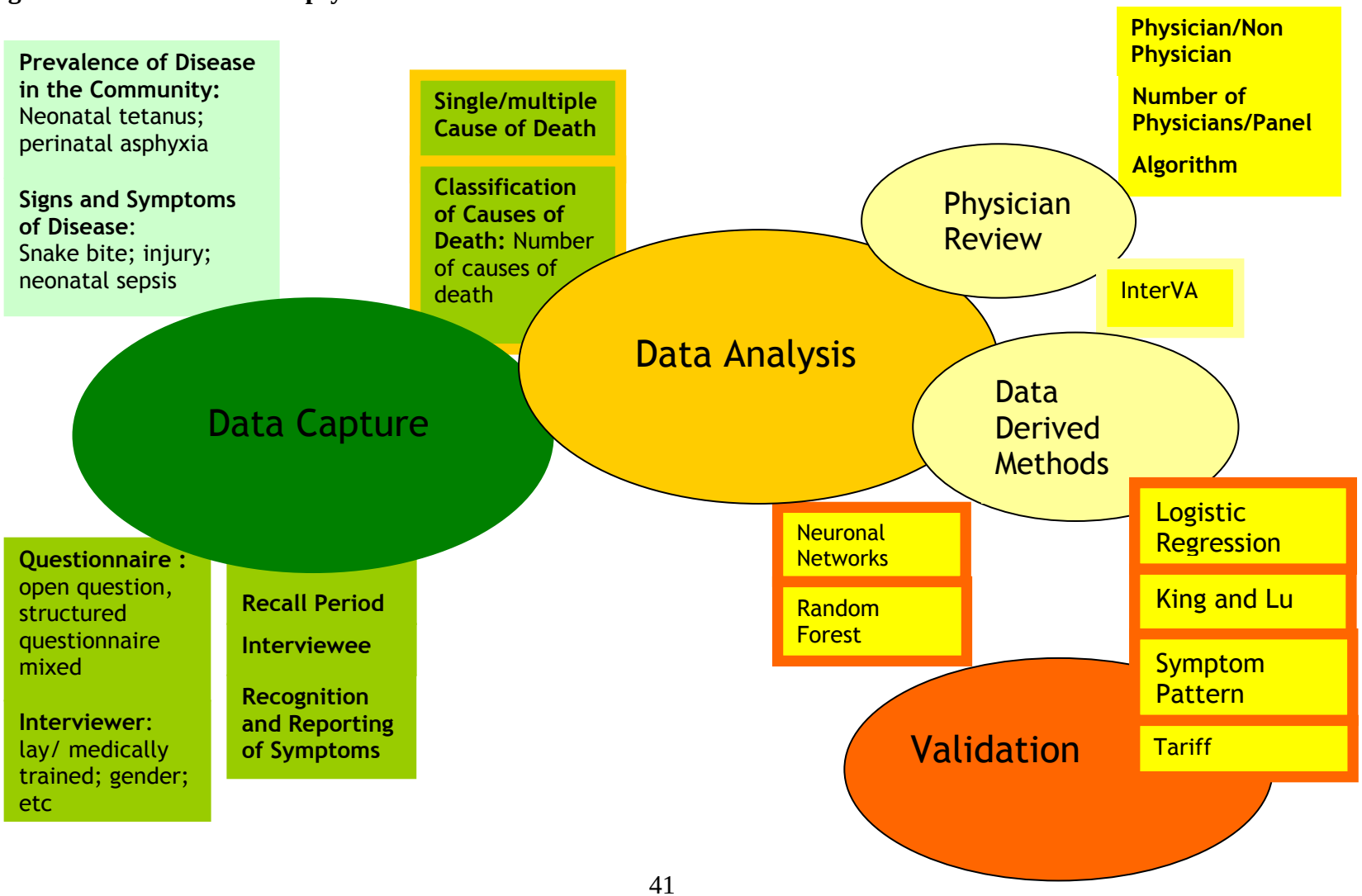
Figure 1.2 - Published Studies using Verbal Autopsies



I describe the current state of development of VAs and their limitations, as they are pertinent to the content of this thesis. Specific development issues related to

perinatal verbal autopsies are discussed in more detail. Figure 1.3 illustrates three phases of the VA process: data capture, analysis and validation as described in the following sections of this chapter.

Figure 1.3- The Verbal Autopsy Process



1.5 - Data Capture

1.5.1 Questionnaires

Questionnaires can include an open-ended question asking the carer an account of the events that led to death or a series of closed questions to establish the presence of specific signs and symptoms or a combination of the two[145]. Detailed questions can be grouped in clusters of symptoms preceded by a filter question[146;147]. Negative answers to a filter question allow moving to the next section reducing the interview length. Selection of appropriate filter questions prevents submitting long questionnaires with irrelevant questions, but requires a careful choice of filters to ensure the complete picture is captured[148]. It has been observed that clinicians mostly make their diagnoses by reading the narrative and refer to closed questions when the history section is unclear or ambiguous[149;150]. Computer algorithms, data derived and probabilistic models, however, rely mostly on closed questions that fit into a binary code[151], even though narratives can be coded and entered into computer software[152;153]. Marsh showed that mixed questionnaires increased the sensitivity of neonatal diagnoses compared with open ended or closed questions models alone when physicians are used for data interpretation[154].

Verbal autopsy questionnaires, formulated by the INDEPTH network[1] or WHO with the contribution of field experts, have been available for about a decade and are easily accessible on the web[156;157](http://indepth-network.org/). The most recent is the WHO Verbal Autopsy Standards, published in 2007[158].

[1] INDEPTH is network of over 30 longitudinal independent surveillance systems, mostly in African and Asian countries, each collecting health and demographic data from household surveys in well-defined areas at regular intervals.. The network was established to facilitate communication between sites, offer support, standardize methods and technologies suitable for surveillance systems, facilitate multisite interventional studies and build capacity within the site countries [155].

1.5.2 The Interviewer

In different studies interviewers have been either health professionals or lay people[159]. The advantage of health workers conducting interviews is their understanding of the medical signs and symptoms, their ability to probe appropriately[160]. On the other hand they can introduce bias during the interview, over-interpreting statements to reach a diagnosis rather than simply recording facts[161;162]. Finally health workers have the logistical disadvantage of being costly and scarcely available in the countries where VAs are necessary. Lay interviewers of different levels of education have been proposed by the WHO in 1970[143] and since used in various studies after training periods of variable length[163-169].

There is little research on the impact of gender, ethnicity, educational level of interviewers on the quality of responses to VA questionnaires[170]. It has been observed that interviewees may respond in different ways to very young investigators or more mature ones, but this has also not been formally assessed[171].

1.5.3 Recognition, Recollection and Reporting of Signs and Symptoms

Few studies evaluating the ability to recognise, recollect and report clinical signs and symptoms have been undertaken[172]. They are mostly based on recognition and recollection of symptoms compared with clinical records in health facilities, therefore the accuracy of recall may be higher than in communities where there has not been exposure to the hospital environment and vocabulary[173-176]. Alonso in 1987, showed that mothers accurately recognise and describe most clinical signs of serious diseases in childhood[177].

However better defined symptom clusters such as trauma or convulsions were more easily identified than common and less catastrophic ones, such as fever or cough[58;178]. In children under 2 years of age, Kalter observed that diarrhoea was reported accurately in 78-84% of mothers interviewed. Measles was also recognised and reported accurately[179]. A South African study showed good recognition of respiratory signs in children by their mothers. However the signs were not necessarily reported to health professionals during consultations[180]. In the context of verbal autopsy studies, signs of neonatal tetanus were recognised in 100% of cases, low birth weight, and prematurity had sensitivity and specificity above 75% when compared with hospital diagnoses, while symptoms associated with pneumonia, and asphyxia were more difficult to elicit, with lower sensitivity and specificities[181]. Marsh analysed causes of death in 137 newborns from Pakistan and found that mothers were accurate in their recollection of signs of neonatal tetanus (84-94% depending on the signs elicited), prematurity "pregnancy<8 months" (82%) and "baby smaller than usual" (70%), compared with hospital records[182]. A diagnostic algorithm combining "born too early and too small" was 90% sensitive and 67% specific in the same study, while prematurity alone had a sensitivity of 71% and specificity of 84%. Birth asphyxia and neonatal infections had lower sensitivities (<60%)[183]. Recall of the time of death in relation to birth is a very important discriminator to ascribe diagnosis[184]. Marsh observed that mothers were able to discriminate early and late neonatal deaths, irrespective of the cause of death, but could not remember accurately the day of death[185]. Freeman reported the respondent's ability to recall birth weight and gestational age at the time of verbal autopsy without using hospital records. Respondents were part of a study where women of reproductive age were visited every 5 weeks and had a pregnancy test if they missed their menses in the previous month, therefore gestational age could be recorded. The birth-weight of the infant was measured mostly within 72 hours of birth

allowing contemporaneous records of the small for gestational age infants. The responses to VA questionnaires could be compared with survey records. Using this method of comparison maternal reporting of size at birth was 100% specific and 45% sensitive and gestational age (<9 months) was 94% sensitive and 62% specific[186].

A number of studies in developed countries looked at the ability to recall events occurring at the time of labour by comparing hospital records and phone interviews after different time intervals[187-190]. Sou in a study in Taiwan reported that birth weight and gestational age were reported correctly 3-9 years after delivery compared with hospital records in over 80% and 90% of mothers respectively[191]. Serious events such as caesarean sections and maternal hypertension were reported accurately, while other obstetric complications such as pre-eclampsia or antepartum bleeding were more often not described. Similarly in Boston women, contacted up to 22 years after delivery, had perfect recall of having caesarean sections, breech deliveries, or multiple births (*kappa*=1); however the recall of stillbirths and preterm deliveries was low (*kappa* 0.37 and 0.5 respectively). Ability to recall changed with years in education[192]. It is unclear how these data from populations of wealthier countries, where delivery occurred in hospital could be extrapolated for developing countries settings with no access to hospitals, different educational backgrounds, socio-economic status and parity. However no studies in developing countries addressing recall of delivery events was found.

Recollection and reporting of stillbirths and neonatal deaths in a population census in Egypt showed accurate recollection and reporting of neonatal and child deaths within 1-3%, with underreporting of 4% of stillbirths compared with a prospective data collection[193].

1.5.4 Interval between Death and Interview

Before approaching a relative after the death of a child a period of mourning is observed. This period varies according to cultural norms and studies have used a range of different time-points. Research looking at recollection of symptoms after death showed that between 1 month[194], six months[195], and up to about 1 year after the event had occurred[196] recall could be considered accurate. A survey in Vietnam showed, by cross-validating different data sources, that visits after a 4 months interval were optimal to capture mortality data, including infant and newborn deaths[69].

Ideally it is recommended that VA interviews are delivered as soon as deemed appropriate and there is lack of data on the accuracy of recall above 12 months[158]. There are no studies that attempt to establish an optimal time interval to conduct verbal autopsy interviews according to age of death, for example perinatal compared with late neonatal deaths, or according to cause of death[197].

1.6 - Method for Causes of Death Assignment

Verbal autopsy questionnaires need to be read and interpreted to assign causes of death. In the clinical tradition often more than one cause of death is ascribed, as death is the end point of a number of patho-physiological processes, expressed as a hierarchy of underlying and contributing causes of death. In the public health context listing all the contributory factors leading to death is important as interventions to reduce mortality may have a greater impact than expected when contributing causes are also addressed. One of the classical examples is malnutrition which does not directly cause death but is one of the most important contributory causes of death in the under fives[198] and it is often under-estimated in VA studies[199]. Similarly in the perinatal period prematurity is the most important co-morbid event contributing to all causes of perinatal and neonatal mortality[200-203].

Traditionally verbal autopsies have been interpreted by physicians reading questionnaires and establishing a diagnosis with or without the use of expert algorithms[204-208]. Alternative methods have been used to increase the speed and the reproducibility of the process with variable outcomes[209-217] (Table 1.2).

Table1.2 - Interpretative Methods for Verbal Autopsies

Verbal Autopsy Interpretation Methods	
Physician review	
Expert algorithms	
Other health professionals	
Lay people	
Data-derived methods	Logistic regression
	Decision tree
	Neural network
	Random Forest
	Tariff
	Probability density
Probabilistic methods	InterVA
	King and Lu
	Symptom pattern method

1.6.1 Physician Review

Physician review has been the first method of interpreting VA and proved adequate in estimating causes of death in population studies, comparing diagnoses obtained using physician review with hospital records[218-221]. The method involved two or more physicians reading the VA questionnaire separately and attributing one or more causes of death to each questionnaire. When agreement between physicians was reached a cause of death was established. If there were differences of opinion either a third physician was called, the same physicians reconsidered and discussed the discordant diagnoses, or a panel of physicians reviewed the questionnaire[58;222]. When agreement was reached the diagnosis was established: otherwise the cause of death was considered undetermined[223]. Open history information was included in the diagnostic process as a diagnostic aid[219].

Recent studies demonstrated that agreement between physicians assigning causes of death justifies the use of a single coder as *kappa* statistics between two coders have been as high as 0.94 for all age groups, 0.69 for

stillbirths and 0.74 for neonatal deaths[224;225]. Using a single physician to establish diagnoses could simplify the process further, however it may lose some of the subtlety, particularly given the uncertainties of the diagnostic process[226]. Other trained health professionals less qualified than physicians have also been used in interpreting questionnaires with similar results as physicians[227;228]. Lay personnel have been compared with physicians to diagnose causes of death from adult VA in one study in India. Here the authors showed a good agreement between lay personnel, trained for one week in the use of a standardised algorithm, and physicians. They performed better for broad categories of causes of death such as communicable, non communicable diseases and injuries. Agreement remained good to moderate for injuries, diarrhoea and fever but was worse for less well defined diseases such as meningitis, HIV, pneumonia, acute abdomen, cardiovascular diseases and obstructive airways diseases[229]

The disadvantages of physician review rest on the difficulty in ensuring repeatability[230]over time and in different settings[231], particularly when diagnostic criteria are not standardised[232]. In some situations disagreement between physicians' opinions may be high[233] with a large percentage of indeterminate causes of death[211;234]. Physician review often attributes a single rather than multiple causes of death to each individual[235]. Most importantly it requires time and expertise of health professionals[236] not always achievable or cost-effective, particularly when large surveys are necessary[237].

1.6.2 Hierarchical Algorithms

Physician review can be standardised, improving repeatability with the use of hierarchical algorithms[238], where a number of criteria are established by an expert panel of physicians to determine causes of death. The Delphi method has been used to reach agreement between a panel of physicians[208]. The Delphi method consists of consulting a group of experts on a pre-defined subject. The panel receives relevant literature and a questionnaire to answer anonymously and does not necessarily meet. The analysis of the responses is fed back to the participants until consensus is reached[239].

Hierarchical algorithms need clear definitions and a fixed order of priority[240], mostly resulting in hierarchical algorithms with a single diagnosis[198]. The main criticism is that they are influenced by their hierarchical order, with causes of death appearing first more commonly reported than causes of death lower down in the hierarchy. Therefore prevalence of diseases can change substantially with alteration of the order used[241-244].

1.6.3 Data-Derived Methods

To overcome some of the limitations of physician review, such as poor repeatability, cost, time-scale, and physicians' time, data derived methods have been explored. They involve the use of different computational approaches to interpret VA questionnaires and ensure consistency of diagnosis, facilitate comparison between sites[245;246], process large datasets quickly and cheaply. They are also easy to apply[247]. Data obtained from close questioning are

entered into a computer programme. Information collected in the open history can be coded and entered[248] or is not included[249;250].

Several types of data-derived approaches have been assessed: computerised algorithms using logistic regression, decision trees and rule-based methods[251], all trying to emulate physician decision making. They require high specificity of symptom combinations for each cause of death to be accurate and a validation population (hospital based) on which to base their "learning"[252]. Computerised data derived methods perform better with clear and well defined diagnoses such as snake bites or injuries than for some less well defined diagnoses with overlapping symptoms such as malaria or meningitis[219;253], that are epidemiologically much more significant.

1.6.3.1 Logistic Regression

Most diagnostic criteria are categorical and logistic regression is familiar to epidemiologists, moreover adequate software has been easily available for a long time, so logistic regression has been one of the first computerised methods applied to VA interpretation[219;254]. To build the model of best fit, data extracted from VA questionnaires were divided into a train and a test dataset. The train dataset was used to fit the model. The test dataset was then interpreted using the model. Different logistic regression expressions have been applied to different causes of death, each applied to all subjects, allowing more than one cause of death[255].

Quigley and Chandramohan tested logistic regression models in children and adult populations[219;256]. In the test dataset for a paediatric population their logistic regression method had sensitivity and specificity above 80% for measles, accidents and malnutrition, and specificity was above 77% for all causes of death, including malaria, respiratory infections and meningitis.

It performed better than physician diagnosis and expert algorithms when validated against hospital diagnosis[219]. A logistic regression model tested for 16 causes of adult deaths in the test dataset from three African populations also had specificity above 79% but a lower sensitivity compared with physician review[257]. When they tested the model on different populations for only 4 causes of death they found that logistic regression was comparable to physician review in assigning cause specific mortality fraction (CSMF)[258]. More defined diagnoses, such as injuries and measles, with characteristic signs and symptoms had better sensitivity and specificity then less clear cut diagnoses such as malaria[198;259;260]. The use of logistic regression had the main limitation of relying on a test dataset and therefore its repeatability in different datasets was difficult to evaluate, but it allowed the use of multiple diagnoses[261;262].

1.6.3.2 Artificial Intelligence

Instruments of artificial intelligence have been used to deal with complex problems and simulate medical diagnoses and are proposed for the interpretation of verbal autopsy questionnaires[263]. The first approach was the use of neuronal networks. The network learns to recognise patterns from a training dataset: it then learns to classify new patterns and solve problems on the basis of the training on the test dataset[264]. The method was applied in a single study where 796 adult deaths were compared with physician review and logistic regression and obtained comparable results[265]. Decision trees and probability density have been used in diagnostic medicine[266] and suggested as possible methods for interpreting VA but they have never come to practice. More recently the availability of a large validation dataset by the Population Health Metrics Consortium has made it possible to refine and test new methods. They performed better than physician review for neonatal, childhood

and adult deaths when compared with hospital diagnoses. These methods also need to be modelled on medical records. They require “training” using datasets where the “true” CSMF is known. They are therefore necessarily linked to the validation datasets used. They include the tariff and random forests methods[213;215].

1.7 - Probabilistic Methods

Probabilistic methods are based on Bayes' theorem of conditional probability[267], using the following formula:

$$p(\theta|data) = \frac{p(\theta) * p(data|\theta)}{p(data)}$$

Where p(θ|data) is the *a posteriori probability*, p(θ) is the *a priori probability*. P (data|θ) is the probability based on the available data and p(data) also called "likelihood", and it is the likelihood of θ given the data [P(data ⎪ θ) x P(θ)] +[P(data ⎪ !θ) x P(!θ)][268].

The Bayesian approach is clearly distinct from the frequentist or classical approach where an iteration process is used to estimate θ. The frequentists assumption is that population and sample have the same distribution: mostly a normal distribution. The value of interest is inferred from repeated experiments on random samples considered to be representative of the population studied. The experiments assume that there is no relationship between the values measured (*null hypothesis*) and only if this statement is falsified the null hypothesis can be rejected. The p value is a measure of the probability for the null hypothesis to be rejected. Generally a value of $p<0.05$ is considered acceptable to refute the null hypothesis. The null hypothesis, however, cannot ever be accepted in line with the nature of the iteration process at the basis of the frequentist approach. In other words, if an experiment is repeated a large number of times using random samples, assuming the choice of the distribution is appropriate, the frequentists define a numerical interval where the value of interest is likely to lie. This is the confidence interval. The results of the frequentist analysis express the degree of confidence that the same results would

be obtained in subsequent experiments or that the null hypothesis would be rejected in repeated experiments.

The Bayesian approach measures directly the probability of an event: p(θ|data), it combines the knowledge of the researcher: p(θ) (*a priori probability*) with the data from the experiment under study p(data| θ) to obtain the value of interest. The a priori assumptions in Bayesian statistics derive from either previous available knowledge such as literature, previous experiments or, when this is not available, a non informative distribution, generally a uniform distribution is used, minimising the influence of p(θ). A well-known example of the use of Bayes' theory is the experience of a newborn who sees the sun rising the first day of his life. At this point the probability of the event repeating itself is 50%-50% but on the second morning of his life when the sun rises again the initial probability of the event repeating itself will be 75% and if the event keep repeating itself every day the probability of it happening again will approximate 100%. This knowledge is based on the previous knowledge of the observer and the results of the repeated experiment. The Bayesian statistical model allows the refinement of the probabilities based on current data and information acquired with previous experiments.

1.7.1 InterVA

The first application of the probabilistic theory to VA was by Peter Byass and his group in 2003 and resulted into the development of "InterVA". The causes of death and indicators used were originally derived from available questionnaires and classifications. The list of causes of death was restricted to diagnoses that could be realistically derived using VA data. The *"a priori"* probabilities were assigned according to the personal experience of a single

researcher. The method was tested on 189 VA from Vietnam and compared with physicians' review (2 physicians) and reached consensus with physician diagnoses in 70% of cases[237]. Subsequently probabilities and indicators were refined by a panel of five physicians from different disciplines with experience in working in a number of developing countries and familiar with VA interpretation[269]. The original data were re-run in the modified model and agreement with physician diagnoses was reached in 90% of cases (170)[269].

The model was subsequently used to interpret VA from Ethiopia and South Africa, including all age groups and was compared with physician review[270;271]. In the Ethiopian study the first 4-5 causes of death for children and adults accounted for over 50% of causes in each age group[272], in South Africa the 10 most common causes of death included over 80% of deaths[271]. The ranking of causes of death in both studies was comparable using physician review and InterVA. The latter had the advantage of being internally consistent, cheap and rapid to use. The method proved to be comparable with physician review when used in different settings such as Vietnam, with an older population affected by chronic degenerative conditions (http://www.who.int/whosis/en/ accessed Aug 2007) and Ethiopia, where deaths are still caused mostly by infectious diseases http://www.who.int/whosis/en/ accessed Aug 2007)[273]. In Ethiopia the model was also able to give different CSMF in rural and urban populations showing flexibility[274]. InterVA was compared with hospital diagnoses in an Ethiopian population with regard to HIV diagnosis. The sensitivity and specificity for the diagnosis of AIDS was 82% and 76% respectively and, for the combined diagnosis of AIDS and tuberculosis was 91% and 78% respectively [275]. This is to date the only study that compares the method directly to hospital records. The model has been applied to monitor the impact of an intervention introducing artemether and lumefantrine in Ethiopian rural communities on malaria deaths. The CSMF due to malaria was derived by VA using InterVA

and showed a statistically significant difference in the intervention and control groups. The same difference was confirmed by the lower prevalence of malaria and lower mortality attributed to malaria amongst inpatients in health facilities from the control and intervention areas[276].

To establish causes of maternal mortality a different tool (InterVA-M) was developed using data from Burkina Faso, Bangladesh, Ghana and Ethiopia (358 cases) and tested using 258 VA from Burkina Faso[211].

The original InterVA tool had not been tested on neonatal deaths and stillbirths had not been included.

InterVA applies the Bayesian formula:

$$P(C|I)_n = \frac{(P(I|C)_n \times P(C|I)_{n-1})}{[(P(I|C)_n \times P(C|I)_{n-1}) + (P(I|!C)_n \times P(!C)_{n-1})]}$$

where $P(\vartheta \mid \text{data})$ is $P(C|I)_n$, the probability of a death to be due to cause C given the presence of the indicator (I), n is the number of predefined independent causes of death.

$p(\theta)$ is: $(P(I|C)_n$, the probability of a given indicator I to be reported in who died of cause C, for each independent cause n.

$p(\text{data}|\ \theta)$ is $P(C|I)_{n-1}$ the probability of cause C to be associated with the indicator I.

$P(\text{data} \mid !\theta)$ is $P(I|!C)_n$ the probability of a given indicator I being present in those who died of any cause other than C

$P(!\theta)$ is $P(!C)_{n-1}$ being the probability of any cause of death other than C.

InterVA compares each cause of death with all other and treats them as independent entities.

The matrix of probabilities $P(I|C)_n$ is obtained by expert opinion[237;269].

The problem in the application of the theorem is defining $P(I|!C)_n$, in other words the probability of an indicator I to be reported in an infant dying for a cause other than C. InterVA sums all the probabilities over all n causes of death in the denominator, rather than separating each cause of death from all others to solve $P(I|!C)_n$:

$$P(C|I)_n = (P(I|C)_n \times P(C|I)_{n-1}) / \Sigma[(P(I|C)_n \times P(C|I)_{n-1})]$$

As an example a table with three causes of death, Cause 1, 2 and 3 can be created. $P(C)_0$, $P(I|C)_1$, $P(I|C)_2$, $P(I|C)_3$ are obtained by consensus. $P(C|I)_1$ for Cause 1 is calculated as A: (axd)/ [(axd)+(bxe)+(cxf)]; for cause 2 is B: (bxe)/ [(axd)+(bxe)+(cxf)] and so on; $P(C|I)_2$ for Cause 1 is calculated as (Axg)/ [(Axg)+(Bxh)+(Cxi)]. The sum of all probabilities $\sum(P(C|I)_n)$, in our example the sum of A+B+C is always 1 by definition.

Table 1.3 Application of the Bayes Theorem -

	Cause 1	Cause 2	Cause 3
$P(C)_0$ - Probability of dying in the newborn period for each cause	a	b	c
$P(I|C)_1$ Probability of dying in the newborn period if indicator I_1 is present	d	e	f
$P(C|I)_1$	**A**	**B**	**C**
$P(I|C)_2$ Probability of dying in the newborn period if indicator I_2 is present	g	h	i
$P(C|I)_2$	**D**	**E**	**F**
$P(I|C)_3$ Probability of dying in the newborn period if indicator I_3 is present	l	m	n
$P(C|I)_3$	**G**	**H**	**I**

1.7.2 King and Lu Method

King and Lu developed a method to interpret verbal autopsy questionnaires based on a matrix representation, to infer the CSMF, without estimating the causes of death at the individual level[216]. They reversed the classical approach considering the symptoms rather than causes of death as dichotomous variables resulting from the cause of death D. Their assumption is that the fraction of the hospital population with a defined symptom profile for each cause of death is the same as the fraction of the community population: P(S|D)=Ph(S|D), where P is the distribution of symptoms (S) in the community and Ph is the distribution (S) in the hospital and D is the cause of death. This assumption is independent from the prevalence of the cause of death or the symptom in the hospital or the community, but requires that the association between symptoms and causes of death is universal.

From this model King and Lu also developed a software available on the web (http://gking.harvard.edu/va/docs/va.pdf.). In non-mathematical terms it operates like a tabulation of the distribution of symptoms for each cause of death observed in a sample population (the hospital): a symptom profile corresponds to each cause of death.

For their model to be accurate, the symptoms chosen should not change whether an individual is hospitalised or dies in the community. Sensitivity and specificity of symptoms are not important and they do not have to be in the physiological cause pathway of disease but have to be associated with the cause of death[216;217].

They applied their method to 2822 deaths from China from which hospital diagnosis was available and randomly separated half of the deaths to be their "hospital population" and half of the deaths to be their "community population"

and used 13 categories of causes of death and over 50 different symptoms. They were then able to compare their "population deaths" with the true cause of death available from hospital diagnoses and demonstrated that their model almost perfectly predicted the causes of death. They also tested the model on 282 deaths occurring in the community in Tanzania where cause of death was available and similarly demonstrated almost perfect correspondence between "true" diagnoses and model diagnoses[216]. King and Lu's method needs to be validated in different settings and contexts and has never been applied specifically to the neonatal population. Stillbirths were not included[277].

1.7.3 Symptom Pattern Method

The symptom pattern method also uses Bayes' theorem. However the *"a priori"* probabilities, rather than being derived from a panel of "experts" as for InterVA, are extracted from an iterative process of a large number of combinations of symptoms profiles modelled on hospital populations using the formula proposed by King and Lu: P(S|D). From this process the programme selected 16 symptom patterns all deriving from combinations of symptoms with equal probability. These symptoms were then entered in the Bayes' formula to derive the individual level probability of dying given the presence or absence of the symptoms selected[278]. This process, repeated several times resulted in a mean of all calculated probabilities. The symptoms pattern method was tested on over 2000 deaths from China for which "true" hospital diagnosis was available. The number of causes of deaths was 23 and a simulation dataset was used to mimic a hypothetical community population. The CSMF obtained using the SP method and physician review were compared with the "true" CSMF and showed that SP method had an average relative error of 16% while physician review had a relative error of 27%[279].

1.7 - Validation

Apart from physician review and interVA all other interpretative methods illustrated have been constructed using hospital dataset as models, bringing the issue of validation to the forefront of the VA debate.

The validation of verbal autopsies consists of comparing diagnoses derived from hospital records, considered as the "gold standard", with those obtained by interpreting VA. The next of kin of patients who died in hospital are traced in the community and given a verbal autopsy questionnaire that is interpreted by physician review or data derived methods. Diagnoses are then compared, and sensitivity, specificity, positive predictive value, average error are calculated[280-285].

The validation process is however highly controversial as it assumes that the CSMF of hospitalised populations is similar to CSMF of communities without access to hospital, that hospital diagnoses are accurate, and the response to VA questionnaires is similar between relatives of people that were hospitalised and those who were not[286]. Here we will analyse these three statements.

Concern has been expressed about the assumption that the CSMF in communities with and without access to hospitals are similar. People accessing hospitals are different from people dying at home for a number of reasons: travelling distance to the hospital is a barrier to access, education and socio-economic status influence access to hospital and these factors may be associated with different patterns of disease[287]. Deaths due to sudden causes may be underrepresented in hospital as they leave little time to the patient to reach the health facility[288].

The second assumption is that hospital diagnoses are accurate. Rural hospitals and health centres in developing countries in particular lack sufficient qualified staff, basic diagnostic facilities and detailed hospital records, therefore do not allow a high level of accuracy in recording causes of death making it a

problematic “gold standard”[289;290]. Referral centres in urban areas with better diagnostic capabilities have different catchment populations from the rural areas where most deaths occur at home. The Population Health Metric Research Consortium recently used considerable resources to overcome the problem of inadequate representativeness and inaccurate diagnoses offered by the available validation datasets by recruiting large hospital populations across six countries and fixing clear diagnostic criteria for a number of causes of death[291]. This validation dataset however still presents the drawback of using tertiary referral hospitals located in urban areas in the attempt to provide better diagnostic accuracy and consistency: therefore it requires the CSMF of these urban hospital populations to be similar to any other population in need of verbal autopsy data.

The third assumption is that respondents who have been exposed to a hospital environment would respond in the same way as respondents who have not had any contact with a clinical setting. However it has been suggested that people in contact with the health system may be more accurate in their description and recognition of signs and symptoms or may know the diagnosis in comparison to communities that did not have any contact with medical personnel[292;293]. To try and overcome this issue the Population Health Metric Consortium analysed their data with and without diagnostic indicators only available to patients admitted to health facilities, to simulate the situation of populations with no contact with health services[294]. This does not, however, consider the knowledge that people derive from staying in a clinical environment during the terminal illness of a close relative, neither can account for the different socio-economic profile of populations living in urban and rural areas.

Because of the fallacies of the assumptions above, validation studies in populations with a particular epidemiological structure may not be universally applicable, as their sensitivity, specificity and positive predictive value depend on their CSMF[295]. Knowing the true CSMF in a population allows correction of

misclassification errors, defined as the failure of the VA instrument to correctly estimate the proportion of death due to a specific cause[296]. This happens when the VA instrument attributes a specific cause of death when this is not true (sensitivity) or when it fails to attribute it when this is present (specificity). Specificity increases the accuracy of a VA tool[297]. Misclassification errors are dependent on the prevalence of a specific cause of death in the population and can be corrected if the true CSMF is known, therefore through validation studies[298]. However hospital diagnoses are not necessarily an accurate substitute of the "true population CSMF" leading to a cyclical argument[58;216;299].

In populations with good access to health care a high proportion of deaths occurs in hospitals. With no, incomplete, or inaccurate vital registration systems, hospital diagnoses may play an important role to improve cause of death data. VA have a role in improving data derived from poor ICD-10 coding[300]. The King and Lu and the SP methods may be best applied in population where most deaths occur in hospitals. They could contribute information to incomplete vital registrations systems by allowing deaths occurring at home to be diagnosed with use of VA.

A number of validation studies have been conducted for VA in all age groups[301], including newborns, on the basis that even though the process may not be entirely satisfactory it is nevertheless the only way to check whether diagnoses obtained through the VA process are accurate, at least when compared with the hospital setting.

Both physician review[302] and data derived methods have been validated using hospital diagnoses. In the perinatal/neonatal period, different diagnostic algorithms have been used and therefore their comparability is poor. This is true both for the order in which diagnoses are hierarchically listed[303] and for the

specific definitions chosen[304-307] (Table 1.3). The use of algorithms has proven helpful, particularly for certain well defined diagnoses such as neonatal tetanus with distinctive signs and symptoms, but sensitivity and specificity remain low for common diagnoses such as perinatal asphyxia and infections with huge overlapping of symptoms and signs[308;309]. This constitutes a significant limitation for computerised algorithms: for example prematurity and low birth weight had high sensitivity and specificity in some studies[310] but not in others[311]. Death due to sepsis was often underestimated[312].

To optimise hospital record performance as validation tools, the use of adequate and internationally agreed standard definitions is paramount. Currently, available databases are not necessarily representative of the populations most in need for verbal autopsy data interpretation: establishing international databanks joining existing databases with standard definitions of signs and symptoms and of causes of death could potentially improve representativeness and serve as a better tool to validate new or improve existing computerised approaches to interpreting verbal autopsy questionnaires.

Physician review has been used to validate verbal autopsy tools in absence of hospital validation data, however this approach presents a large number limitations. As discussed above the cause of death in this context is driven by the physicians' opinion, which in turn depends on the single physician experience and knowledge of the local epidemiology and the use of predetermined algorithms. In studies where physicians' opinion is compared with hospital diagnoses the agreement between physicians is very variable[211;313]. Sensitivity and specificity compared with hospital diagnosis in neonatal populations varied between 64-74% in a recent study[314] and concerns about inter- and intra-rater reliability are well-described [315].

Computerised methods are becoming more and more promising as mathematical modelling and machine power improve. However the limitation in their development will always be linked to the quality of the validation data on which these programmes are modelled. The focus of future research should be centred on exploring better validation models.

In developed countries the most common cause of death un-witnessed by a health professional in the paediatric population is “Sudden Unexplained Infant Death” (SUID) or “Sudden Infant Death Syndrome” (SIDS). In these circumstances infants reach the health facilities post mortem. To investigate such cases complex inquires are undertaken including interviews with carers, visits to the place of death and finally post-mortem investigations. Only this comprehensive approach has lead to improvement in understanding and therefore effective preventive strategies to be developed[316]. Even though such thorough investigations would be difficult to apply in developing country settings an open mind to alternatives or adjuncts to hospital records should be kept to improve the quality and reliability of computerised methods which are likely to inform us on causes of death for the majority of the population of the world in the near future.

Table 1.4- Definition of Causes of Neonatal Deaths

	Congenital malformation	Prematurity/ SGA	Asphyxia	Neonatal tetanus	Neonatal sepsis	ALRI	Birth injury	Diarrhoea
Kalter[317]		Pregnancy ended early and baby very small or smaller than usual at birth	Not able to cry after birth and either convulsions or spasms or not able to breathe after birth or not able to suckle normally after birth	Age 3-27 days and convulsions or spasms and able to suckle or cry normally after birth and stopped suckling or crying		Fast breathing and chest indrawing		
Marsh[318]	Visible anomaly	Prematurity: Pregnancy <8 full months SGA: Baby smaller than usual baby <2500 at birth	Death <7 days of age, convulsions in first 2 days, breech, Labour>24 hours, continuous poor suck or, extreme irritability or weak cry or sleepiness for 1st 2 days	Death 4-28 days, baby sucks or drinks well for 2 days after birth, stops sucking any time after 2nd day jaw continually locked, arching of back or rigidity, convulsions after day 2	Death after day1 + 2 of the following: jaundice, fever or hypothermia, convulsions, vomiting	Cough, difficulty breathing, rapid breathing, chest indrawing >24hrs, nasal flaring >24 hrs, grunting >24 hrs, blue lips/tongue		3 or more loose liquid stools/day, dry mouth, sunken fontanel, extreme thirst, sunken eyes, loose stools >14 days
Baqui[319]	Physical malformation or gross malformation present at birth	Baby very small or smaller than usual at birth	Age at death ≤ 7 days AND not be able to cry after birth or not able to breathe after birth or not able to suckle normally after birth	Age at death 3-27 days AND EITHER local word for tetanus OR convulsions/spasms and able to suckle or cry normally after birth and stopped suckling or crying	At least 2 of the following: stopped suckling, fever OR cold to touch, unresponsive or unconscious OR lethargic, bulging fontanel, convulsions, vomiting (redness OR drainage from the umbilical stump), OR skin bumps containing pus or blisters or single large area of pus with swelling, chest in-drawing, fast breathing OR local term for pneumonia		Age at death ≤ 7 days AND signs of injury at birth	Local term for diarrhoea or frequent/ watery/loose stools

***Cont.* Table 1.4- Definition of Causes of Neonatal Deaths**

	Congenital malformation	Prematurity/ SGA	Asphyxia	Neonatal tetanus	Neonatal sepsis	ALRI	Birth injury	
Freeman[3] [20]	Abnormality of head, eyes, ears, nose, mouth, jaw, arms, hands, back, legs, feet or genitalia at birth	Birth at GA < 9 months and small size at birth	Death within 1st 7 days of life and failure to breathe/cry after birth; and either convulsions and died within 2 days of birth or not able to breathe/cry for 2 or more minutes or not able to suckle normally after birth	Death between 5 and 28 days and any stiffening of the body, arching of the back, fits or convulsions in 2 days prior to death	Any 2 of the following: poor suck soon after birth or prior to death, weak cry or cessation of crying, purulent rash anywhere on the body, high fever	Death between 3 and 28 days and difficulty breathing and either fast breathing or chest indrawing in the 2 days prior to death		Loose watery stools in the 2 days prior to death
Edmond[3] [21]	1 or more of: major lethal congenital abnormalities unspecified; specific abnormality e.g. neural tube defect	1 or more of: severe immaturity (<33 weeks), Bwt <1.8 Kg where GA is unknown, specific severe complications of prematurity such as surfactant deficiency or NEC	Infant ≥33 weeks GA due to 1 or more of: Obstetric complications, maternal haemorrhage, or clinical diagnosis of birth asphyxia (no cry soon after birth + either convulsions/spasms or not able to suckle normally after birth)		Infant ≥33 weeks GA due to 1 or more of: Tetanus, meningitis, pneumonia, diarrhoea, septicaemia, other infections			

1. 9 - Social Autopsies

It is well recognised that environmental and social factors have a central role in perinatal and neonatal health and disease in developed and developing countries[322-327]. In countries where vital registration is incomplete or not existing, the identification of social causes of death may be as relevant from a public health perspective, as the clinico-pathological processes investigated using verbal autopsies[328]. The systematic use of death enquires and audits has proven useful to improve health services performance in developed countries as each death is analysed in context, therefore both clinical and non clinical component are analysed and modified as required (CEMACH http://www.dur.ac.uk/ne.pho/index.php?c=473)[329]. Suboptimal care and system shortfalls are taken into consideration, changes can be implemented and reviewed for example as part of the audit cycle, to ensure mechanisms are in place to avoid death where possible (http://www.hqip.org.uk/). New concepts such as the "human factor" have acquired an increasing importance in health care in the most recent years as a result of analysis derived from deaths or critical incidents[330]. The human factor definition within the UK National Health Service consists of all features that influence people's behaviour, such as their own personality, the environment where they operate, the organisation where they work and their job requirements (http://www.patientsafetyfirst.nhs.uk). It has been recognised that factors well beyond clinical competence can impinge in the quality of care delivered when, for example, team work is not effective, therefore effort has been placed to understand and manipulate those factors. Equally in developing countries the process of establishing causes of death needs not to be limited to establishing clinical diagnoses. Audits of health facilities have been used and showed some effect in reducing perinatal mortality in several countries[331-335]. However the majority of deaths occur

outside the health facilities and there is need to explore at community level what are the circumstances leading to deaths and what changes can be introduced to avert deaths. Community audits have been used[336], and as part of them social and verbal autopsy tools have been used to gather information. Social autopsy interviews explore the context in which each death occurs and add essential information to the verbal autopsy interview for public health decision making[337-339]. Social autopsies explore death through the whole pathway from well-being to disease and death. Their framework investigates in detail the steps from the recognition of illness to the actions taken (or otherwise) to re-establish health. The analysis includes home care procedures; traditional beliefs associated with health and illnesses; and the use of health providers whether traditional or allopathic. It takes into account the actions of the health providers within the health system. If referral is required it looks at how this is (or is not) followed up. The outcome is complex but helps to establish not just the type of intervention but also the timing and the location where this could be most effective[337].

Although not originally called social autopsy, the concept has been developed initially within the maternal health groups. “Beyond the Numbers”, a WHO document aimed at understanding “the underlying factors that lead to [maternal] deaths”, calls verbal autopsy an instrument that involves a much broader remit than the term generally implies: much closer to the social autopsy framework. Concepts well described in this document could helpfully be transferred to the perinatal and neonatal context[340]. An example of information captured using the social autopsy approach is exploring the three causes of delay in receiving treatment. Understanding the reasons beyond failure to reach a health facility, for example lack of transport to access to health facilities is essential[328;341]. If the health facility is not reachable, even if health provision is optimal, death would not be averted. This information is crucial to policy makers to allocate resources.

This thesis will not analyse the social causes of neonatal deaths as its focus is the interpretation of causes of death in the clinical sense. Social autopsy data exploring care seeking behaviour were not collected with the aim of developing social autopsy tools. Definitions for social causes of death need to be developed for the perinatal and neonatal period using available frameworks. Computerised systems for the interpretation of social autopsy questionnaires could also be adapted making data more easily available to policy makers. The issue of validation is challenging as it is difficult to think about an objective gold standard comparison. As for verbal autopsies, the lack of appropriate validation is problematic if resources are allocated on the basis of results obtained by analysing questionnaires whether through computerised systems or use of health personnel.

1.10 - Perinatal/Neonatal Verbal Autopsies

As neonatal medicine progresses and infants are cared for at an ever decreasing gestational age, the definition of stillbirths has been evolving[342]. Capturing stillbirths and separating them from early neonatal deaths is difficult with VA. The accuracy of recollection and/or believes around early deaths may alter the perception and the narrative of the families involved with over or underreporting of stillbirths[343]. Therefore stillbirths are excluded in many studies describing neonatal mortality (Table 1.4)[198;344-346]. Finally, data on stillbirths are not consistently collected as they are not part of national or global mortality statistics. There are no validated algorithms to classify them accurately[347]. Nevertheless they represent a large mortality burden, almost equal to neonatal mortality and deserve attention if stillbirths are to be reduced[348-350]. Moreover interventions targeting the perinatal period are likely to affect their number and proportion, making it even more important to follow up trends over time, particularly in the context of a reduction in under-five mortality.

Table 1.5 – Methodology Studies on Stillbirth and Neonatal Verbal Autopsies

Author and year	Country	VA Stillbirths number	Purpose of the study	VA questionnaire	Classification of causes of death	Interviewers	Causes of death	Interpretative method	Recall period	Hospital "validation"
Engmann 2011[351]	Guatemala, Congo, Zambia and Pakistan	252 134	Exploring coding strategies	Open and closed questions	ICD-10	Lay	Three	2 physicians	n/a	no
Edmond 2008[352;353]	Ghana	502 314	Validation of physician review compared with hospital diagnoses	Open and closed questions WHO questionnaire	Purposefully written	Lay	One	3 physicians		Yes
Lee 2008 [354]	Nepal	759 0	Different algorithms to diagnose perinatal asphyxia	Modelled on WHO open and closed ended questions	5 diagnoses (Congenital malformations, NNT, sepsis, birth asphyxia, prematurity)	Lay – 10 years VA experience	Multiple	2 Physicians and different computer algorithms	n/a	No
Setel 2006[355]	Tanzania	582 (SB & NND)	Validation of all ages VA with hospital diagnoses	Open and closed questions	ICD-10	Lay	Three	2 physicians	n/a	Yes
Setel 2006[356]	China and Tanzania	SB & NND -	Production of core forms for VA studies	Open and closed questions	ICD- 10	Lay	Three		n/a	No
Freeman 2005[357]	Nepal	167 0	Validation of an algorithm to diagnose neonatal VA	Open and closed questions	7 diagnoses: prematurity, NNT, asphyxia, ALRI, congenital malformations, sepsis, diarrhoea	Lay	Multiple	2 physicians	n/a	No

***Cont.* Table 1.5 – Methodology Studies on Stillbirth and Neonatal Verbal Autopsies**

Author and year	Country	VA number	Stillbirths	Purpose of the study	VA questionnaire	Classification of causes of death	Interviewers	Causes of death	Interpretative method	Recall period	Hospital "validation"
Marsh 2003[358]	Pakistan	137	0	Validation of an algorithm to diagnose neonatal VA	Open and close questions	9 diagnoses (Sepsis, prematurity, SGA,LBW, birth asphyxia, NNT, congenital malformations, diarrhoea and pneumonia)	Lay: 1 woman interviewer. Education: MA in Economics	Two	2 physicians	3-230 days	Yes
Bang 1992[208]	India	-	-	Suggested perinatal VA criteria	-	List of 16 causes of death	-	-	-	-	-

For accurate reporting of causes of stillbirths and neonatal deaths there needs to be a classification of causes of death with clear and unambiguous definitions for use in verbal autopsy studies.

In the UK a succession of classifications for clinical purposes have been used, as the needs of clinicians evolved. In the 1950s in Scotland perinatal mortality rates was as high as 50 deaths per 1000 births per year and clinicians' interests were mostly focused on obstetric causes of perinatal deaths. Classifications were therefore centred on obstetric underlying causes of death and required details provided only by post mortem examinations[359-361]. As neonatal health improved, clinicians interest on newborns increased and classifications used more clinical information, moving away from the requirement of post mortems[362].

In 1980 Wigglesworth proposed a perinatal death classification listing 5 causes of perinatal death, based exclusively on clinical information: such as birth weight and time of death[363] (Table 1.5). In 1986 Hey proposed an extended Wigglesworth classification integrating Wigglesworth criteria with the original Aberdeen classification. He refined clinical definitions and suggested a flow chart to guide the correct use of the classification and suggested using the International Classification of Disease coding for each of the factors contributing to the death for comparability[364].

The debate about the most appropriate classification has been lively in the UK[365]. Several other perinatal death classifications have been proposed in different countries and at different times[366], mostly modelled on these two.

In 1998 the NICE classification was proposed in Sweden to analyse causes of perinatal death from 4 national registers using a computer based method. The NICE classification is a hierarchical etiological classification aiming at describing the events leading to death, similarly to the Aberdeen classification[367;368]. It includes 13 causes of death: 7 of which describe physio-pathological causes of death. The causes of death unexplained by etiological

criteria were divided into categories, in the attempt to store most of the available information. The approach of this classification was of interest to the international health community as it was proposed as an epidemiological tool rather than as a clinical instrument (Table 1.5).

Table 1.6- Perinatal Classifications of Causes of Death

ABERDEEN[369]	**WIGGLESWORTH**[370]	**NICE**[371]
Congenital anomaly	Lethal malformation	Congenital anomalies
		Multiple births
Maternal disorder		Maternal disease
Pre-eclampsia		
Iso-immunisation	Specific conditions	Specific foetal conditions
Miscellaneous		
		Unexplained Small for Date
Ante-partum haemorrhage		Placental abruption
Mechanical		Obstetrical complications
Unexplained <2500	Death before onset of labour	Unexplained ante partum stillbirth <37 weeks
Unexplained >= 2500		Unexplained antepartum stillbirth >=37 weeks
		Specific infant condition
	Asphyxia condition developing in labour	Unexplained asphyxia
	Condition associated with immaturity	Unexplained immaturity
Unclassifiable	Unclassifiable	Unclassifiable cases

1.11 - Classifications of Causes of Stillbirth and Neonatal Death in Developing Countries

Developed countries rely on information extrapolated from a wealth of clinical information such as clinical records, imaging, laboratory tests, and in some instances post-mortem examinations. Few studies evaluate existing neonatal death classifications in developing countries, and mostly provide data from a hospital perspective. Amar used the Wigglesworth classification for institutional deaths in Malaysia and found that nurses could classify all stillbirths and neonatal deaths in the study and only 2.9% of 482 deaths had to be reclassified by doctors[372]. Similarly in Bangladesh the same classification was used by nurses, midwives and doctors to classify 1069 perinatal deaths and only 9% were ascribed to a miscellaneous or "other" causes of death[373].

However, when data from verbal autopsy were used, the existing classifications left many deaths undetermined[374;375]. Elamin et al compared the Wigglesworth, Aberdeen and North Baltic classifications[2] in Sudan using VA data. The authors used three criteria to judge them: simplicity, validity and usefulness in improving quality of care. They valued the Nordic-Baltic classification over the others; however they found that all available classifications used very detailed categories resulting in large numbers of unclassifiable data, with information loss. They concluded that existing classifications have limited value in guiding clinical care and policies in developing countries[376]. In 1992 Bang proposed the first neonatal death classification for the analysis of neonatal verbal autopsy data[208].

In collecting and reporting the main causes of neonatal mortality CHERG proposed a very simple classification with only 8 categories: accidental deaths, congenital abnormalities, prematurity, birth asphyxia, severe infections, tetanus, diarrhoea, other specific conditions[377]. The CHERG

[2] Based on 6 criteria for diagnosis (lethal malformation, gestational age, birth-weight, Apgar score, multiple births time of death) [366]

classification is simple, with mutually exclusive categories, and discriminates between groups of diseases relevant from a public health perspective.

Given the nature of verbal autopsy data and the need to compare them across countries and over time, classifications require strict definitions, standardised for international use[378;379]. The CHERG hierarchical classification modifies and simplifies the definitions used by the NICE group, offering an accepted international standard, however it does not include stillbirths.
An adaptation of the NICE and CHERG classifications was subsequently used successfully in Kintampo, Ghana in a study to establish causes of perinatal and neonatal deaths, only 1.4% of causes of neonatal death were left undiagnosed and about 68.5% of the fresh stillbirth and 43% of macerated stillbirths were further classified[380;381] (Table 1.6).

Table 1.7 - Kintampo Classification

Antepartum stillbirths*	Intrapartum stillbirths**	Neonatal deaths***
Congenital abnormality (Major or lethal congenital abnormalities unspecified; specific abnormality: neurological, neural tube defect)	Congenital abnormality	Congenital abnormality
Maternal disease (one or more of: eclampsia, pre-eclampsia, renal disease, hepatosis, severe anaemia, severe infections (Syphilis, HIV, malaria, other)	Obstetric complications (one or more of malpresentation, cord prolapse, precipitate labour, prolonged or obstructed labour, uterine rupture, other specific obstetric complications sufficient to cause death	Prematurity (one or more of: GA < 33 weeks, Bwt< 1.8 Kg with unknown gestation, specific severe complications of prematurity: surfactant deficiency, NEC)
Maternal haemorrhage (one or more of placental abruption, other haemorrhage)	Maternal haemorrhage	Birth asphyxia (GA >33 weeks and one or more of obstetric complications, maternal haemorrhage, clinical diagnosis of birth asphyxia: no cry soon after birth plus either convulsions/spasms/not able to suckle normally after birth)
Other (cause not included in the first causes, including, accident, injury, foetal infection, hydrops foetalis	Other	Infection (GA>33 weeks and one or more of tetanus, meningitis, pneumonia, diarrhoea, septicaemia, other infection)
Unexplained: unknown cause	Unexplained	Other: GA >33 weeks and cause not included in the first causes, including, accident, injury, infant haemorrhage, RDS, severe neonatal jaundice) Unexplained

Note: *Antepartum stillbirth any foetus >28 weeks gestation dying before onset of labour when mothers reported loss of foetal movements before birth or macerated at birth; ** intrapartum stillbirths: foetal deaths above 28 weeks gestation when mothers reported baby movements in labour or delivery and normal skin at birth; ***neonatal death infant born alive and cried, moved or breathed after birth and then died within the first 28 days of life

1.11.1 International Classification of Disease

While a number of different perinatal death classifications are in use in developed and developing countries, the International Code of Diseases, Version 10 (ICD-10) has been universally accepted to code all causes of deaths. Diagnoses from death certificates and verbal autopsies therefore are best reported using the ICD-10 system[382]. Chapter 15 and 16 of the ICD-10, dedicated to "Certain conditions originating in the perinatal period (P00-P96)" and to "Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)" respectively, count over 100 causes of death[383]. This complexity is not suitable for data derived from verbal autopsies, and as a consequence, simplified versions of the ICD-10 are in use. The INDEPTH network and WHO compiled simplified lists of causes of death for VA (Simplified ICD-10 for VA) in use in many studies[158;384]. The simplified version of the ICD-10 coding for use in verbal autopsy data[158] still contains a number of diagnoses not easily distinguishable by VA such as prematurity versus low birth weight infants, neonatal pneumonia versus congenital viral diseases and bacterial sepsis to mention a few[158].

Coding the causes of death using the ICD-10 requires training as the coders needs to express multiple causes of death according to a pre-established hierarchy[103]. The ICD-10 has been conceived to classify clinical diagnoses and may not be the most appropriate mean of classifying VA data for public health use[385].

1.12 Research Gaps

In summary the knowledge gaps identified from the literature review were the following.

1. Questionnaires: the WHO proposed a standardised questionnaire for research purposes. However, it remains to explore whether much shorter versions could be devised for large surveys.

2. The most appropriate interviewers' characteristics in term of age and gender, and the ideal time interval between death and interview are still to be established.

3. A classification of causes of deaths for the perinatal period has not been universally agreed. The inclusion or exclusion of stillbirths from such classification is of relevance and is still being debated.

4. The diagnostic coding commonly used refers to the ICD 10 system of classification that is far too detailed for VA purposes and does not include stillbirths. This needs to be adapted to the VA context.

5. The main research dilemma on VA remains the interpretation of the VA questionnaires to achieve consistent and accurate diagnoses. While consistency can be achieved with computational method, establishing the accuracy of the VA interpretation is extremely difficult.

6. Closely linked with the previous point is the establishment of the most appropriate validation method to which comparing computerised methods to interpret VA questionnaires. Hospital diagnoses and physician review have been

used to compare the performance of new VA interpretation methods. Better means of comparison such as use of post-mortems[386;387] or full confidential enquiries as they occur in developed countries, (http://www.cdc.gov/sids/TrainingMaterial.htm)[316] or use of information collected from community surveys particularly for specific causes of death, such as prematurity for the newborns, need to be explored.

This thesis explores the differences in the completeness of questionnaires and availability of open histories as a proxy for quality of questionnaires at different time intervals between death and interview. It proposes a classification of perinatal causes of death, including stillbirths and a shortened questionnaire for use with a computerised interpretative methods. It highlights some of the limitations of using physician review to interpret VA questionnaires, while proposing standardised algorithms to improve consistency of data interpretation using this method.
Finally it described the adaptation of InterVA to the neonatal period, and proves its internal consistency, however it cannot provide data on its accuracy as it compares it with physician review with its limitations.

1.13 - Conclusions:

- Targeting interventions appropriately in developing countries to reduce childhood mortality requires causes of death data.
- As vital registration systems are not widespread, particularly in the poorest countries where the majority of deaths occur, different strategies to collect mortality data are necessary. They mostly rely on the use of VA to establish causes of death.
- Stillbirths are often neglected and not included in VA studies.
- Several classifications with associated definitions of causes of death are used to classify stillbirths and neonatal deaths, and international coding is not aimed to information collected through verbal autopsies.
- Verbal autopsies have been used for over fifty years, but there is no consensus on a methodology to collect (questionnaires, interviewers characteristics, time etc) and interpret data.
- Data interpretation is obtained either by physician review or by an ever increasing number of data derived methods.
- Validation methods to assess the accuracy of VA results have limitations, but no studies into the use of different validation models are available.

Chapter 2:

Study Settings

2.1 - Malawi

2.1.1 Geography and Climate

Malawi is part of East Africa and borders with Tanzania to the north and northeast; Mozambique to the south, south west and east; and Zambia to the west and northwest. The country total surface is 118,484 km^2 and is divided politically in three regions the northern, the central and the southern. About one fifth of its surface is occupied by Lake Malawi, which is part of the Rift Valley, crossing the country from north to south. South and west of the lake are high plans culminating in the south to Mt Mulanje, the highest peak in the country: 3,002m above the sea level (Figure 2.1).

The climate alternates between two seasons: dry and colder from April to October, wet and hot from November to March. The temperature reaches about 30°C on the lakeshore and can be as low as 0°C in the higher areas of the Mulanje plain.

Figure 2.1 - Map of Malawi

Note: Adapted from United Nations 2004

2.1.2 Population

Malawi has a population of just over 13 million, one of the most densely populated countries in the region[388]. The majority of the population lives in rural areas[389], and urbanisation is increasing slowly. The main ethnic groups are Chewa, Yao and Ngoni, each with their own language. The Chewa group predominates. The official languages are Chichewa and English (Table 2.1).

Table 2.1 - Malawi Demographic Indicators

	1998	2008
Total Population	9,933,868	13,077,160
Population density (per Km^2)	105	139
Northern region (per Km^2)	46	63
Central region (per Km^2)	114	155
Southern region (per Km^2)	146	184
Annual growth rate	(87-98) 2	(98-08) 2.8
Rural (%)	86	85
Urban (%)	14	15
Total fertility rate(%)	4.8	5.2
Literacy rate (%)	57	64
Women literacy rate (%)	51	59
Orphans (%)	10 (under 20 years)	12 (under 18 years)

Note: data derived from Malawi Census[388;388]

2.1.3 Economy

The country is rated amongst the low income countries by the World Bank, with about 68% of the population living under the poverty line[390]. It ranks 198th out of 210 for Gross National Income (GNI) per capita (http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf). The economy is almost exclusively agricultural with a large part of the agricultural land dedicated to subsistence farming. About 90% of the exports are from agricultural products: tobacco and, to a lesser extent, coffee, tea and sugar[391] (Table 2.2).

Table 2.2 - Malawi Economic Indicators

Malawi	1987	1998	2008
GDP (million current US$)*	1,183	1,750	4,269
GDP growth (annual %)*	2	4	10
GNI per capita, PPP (current international $)*	400	600	830
Official development assistance & official aid million (current US$)	275	434	735 (2007)
Human Development Index*	0.379 (1985)		0.493 (2007)

*Note: For the definitions please refer to the Glossary Source: http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20399244~menuPK:1504474~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html

2.1.4 Health Sector: Obstetric and Neonatal Indicators

Malawi maternal mortality ratio is one of the highest in the world[392]: 984 per 100,000 according to the 2004 DHS[393]. These data were measured using the sisterhood method, by which women were asked about whether any of their female relatives died in childbirth. Although retrospective, this remains the most accurate method available and it is indicative of the general trend[393].
In 2004, 95% of Malawian pregnant women attended antenatal care (ANC) at least once during their pregnancies, 92% in a health facility. The majority presented for the first time in the second or third trimester of pregnancy and only about 57% attended all the four recommended visits[393]. The number of deliveries assisted by a trained health attendant defined as a medical doctor or a nurse midwife was 56.1% in 2004[393]. Emergency obstetric care was of poor quality and underutilised. The highest percentage of deliveries attended by trained personnel was in cities, amongst the richest quintile and the better educated. Postnatal care uptake was still very limited, with 69% of women never receiving a postnatal check.

The 2004 MDHS reported a neonatal mortality rate of 27 per 1000 live births[394], a considerable drop from 42 per 1000, in 2000. The apparent 36% reduction of neonatal mortality was explained in the MDHS 2004 by artefacts in data collection rather than being considered as a real decrease. It was observed that the total number of births during the first year of the MDHS survey was inexplicably low compared with the preceding and following years of the survey. This seemed to occur because of a systematic error in reporting dates of birth of deceased children born in the first year of the survey as occurring in the year preceding the survey[394]. Since the last MDHS there had been no change in skilled birth attendance at delivery, rate of attendance to ANC, or coverage of TTV in

ANC, factors that are mostly related with neonatal rates. Moreover the percentage of neonatal deaths compared with under five mortality was low (20%) in the 2004 MDHS, compared with most developing countries where neonatal mortality accounts for about 40% of under five deaths[394] (Table 2.3). Between the Malawi DHS 1992 and 2004 maternal mortality ratio estimated through the sisterhood method (each woman interviewed is asked for the number of her sisters who died, their age, cause of death and whether they died in pregnancy or within two months of a pregnancy) went from 620 to 1120 to 948 per 100,000[395]. It is likely that this discrepancy is due to the inaccuracies of the sisterhood method rather than real changes over a short period of time[396].

Table 2.3 - Malawi - Maternal and Neonatal Health Indicators

	1992	2000	2004
Maternal mortality ratio (per 100,000)	620	1120	984
Neonatal mortality rate (per 1000)	42	49	27
Infant mortality rate (per 1000)	134	112	76
Under five mortality rate (per 1000)	234	187	133
Perinatal mortality rate (per 1000)	n/a	n/a	34

Note: data from[393;394]

2.1.5 Health Service Structure

Health care in Malawi is delivered free of charge. Antenatal, basic obstetric services, (defined as the availability of parenteral antibiotics, parenteral oxytocic drugs, parenteral sedatives for eclampsia, manual removal of placenta and manual removal of retained products[397]), and neonatal care are offered in the majority of health facilities. District hospitals offer comprehensive essential obstetric care defined as the availability of basic care and surgery, anaesthesia, and blood transfusion[397]. Shortage of personnel, disposables and drugs is not uncommon. A

parallel fee paying system is the Christian Health Association of Malawi (CHAM) that offers mostly a primary care service in rural areas. The private sector is limited to towns and larger centres and generally does not offer assisted deliveries.

2.2 - Mchinji District and Mai Mwana Project

Mchinji District (Figure 2.3) is one of the districts of the Central Region. Its population was just under 460,000 people in 2008[388]. The district lies in a plain. Its main road crosses the south of the district through its main centre (Mchinji Boma) and connects Lilongwe to Lusaka in Zambia. Another tarmac road crosses the district north to south and connects Mchinji to Kasungu district. Over 90% of the population depends on agriculture as the main economic activity, organised as smallholders or estate workers, but generally productivity is low resulting in food insecurity and malnutrition. Safe water is accessible to 95% of the population and latrines to 77%[388].

HIV prevalence measured amongst pregnant women aged 15-49 was 14.8 (77/522) in 2005 and decreased to 8.8 (44/500) in 2007[398;399].

The health service consists of a District Hospital located in the main market town. With about 2000 deliveries per year, it is the only facility in the district offering caesarean sections. A small nursery for neonatal emergencies is also available where oxygen and phototherapy can be delivered. Another 7 health centres, one rural hospital and 3 health facilities run by the Christian Health Association of Malawi (CHAM) are scattered in the more rural parts of the district (Figure 2.2).

Source: Centre for International Health and Development

Figure 2.2 -Map of Mchinji District Health Facilities

Source: adapted from Malawi DHS and Mai Mwana GPS map

2.2.1 Maimwana

The Maimwana (mother and child) Project is a cluster randomised controlled study set up to test the effectiveness of two community participation interventions. One intervention was based on a community action cycle delivered through women's groups on the model of the MIRA Makwampur study, Nepal [400-403]. The second intervention used peer counsellors to increase the rate of early and exclusive breastfeeding[404-406].

The study population consisted of 48 clusters (zones) each with a population of about 8,000, obtained from the 1998 census Enumeration Areas. Of each cluster about 3000 population was selected from the centre of each zone to constitute the study population.

All women of childbearing age (WCBA), who consented to the study, were visited by women enumerators (one per zone) every month with a brief questionnaire to establish whether the WCBA missed her period, when the same WCBA misses 3 consecutive periods she was considered pregnant[407] and notified to a field interviewer (FI). If the pregnancy carried on, a field interviewer (one per one to two zones) visited the WCBA at 1 and 6 months after the birth of the infant with a questionnaire about the pregnancy, delivery and postnatal care. If the pregnancy ended with a stillbirth or a neonatal or a maternal death the Monitoring and Evaluation Officer (M&EO) was notified and visited the family with a verbal autopsy questionnaire[408].

As part of the study a health strengthening strategy was set up across the district to improve maternal and newborn services within the existing health services. As part of the health strengthening activities a Prevention of Mother To Child Transmission of HIV (PMTCT) programme in the district was also established[408].

PMTCT Awareness Campaign – Mchinji District 2005

2.3 - Nepal

2.3.1 Geography and Climate

Nepal borders with Tibet to the north and India to the south, east and west. It is a landlocked country of 147,181 Km^2 with a great diversity of geographic and climatic zones. The Himalayas (4000 to 8000 m above sea level) lie on the north, bordering with China. They are the least densely populated areas of the country, with an arctic, hostile climate and extremely difficult communications. The "Hills" ranging from 800 and 4000m above sea level have a temperate climate, and are more densely populated, hosting about 42% of the population. Kathmandu, the capital city is in the Himalaya valley at 1350m above sea level. The Gangetic plains, at sea level have a tropical and subtropical climate and mostly occupy the south of Nepal (Figure 2.3). They are the most fertile, densely populated area and enjoy better communications. Nepal has a wet warm monsoon season between June and September and a dry season for the rest of the year. The rainfall varies widely across the different climatic zones.

Source: Centre for International Health and Development

Source: Adapted from http://www.venturenepal.com/nepal-resources.aspx

2.3.2 Population

Nepal's population was just over 23 million in the 2001 census and it is projected to be about 28 million in 2011[409]. The average population density was 157 per Km^2 according to the 2001 census (Table 2.4). There are 103 different ethnic groups each with a different language. Nepali is the official language and the majority of the population can understand it.

Table 2. 4 - Nepal Demographic Indicators

	1991	2001
Total Population (million)	18.5	23.2
Annual growth rate	2.1	2.2
Male – life expectancy	55	60.1
Female – life expectancy	53.5	60.7
Population density per Km^2	126	157
Urban Population per Km^2	9.2	13.9
Total fertility rate	4.6	4.1

Source: http://www.digitalhimalaya.com/collections/nepalcensus/

2.3.3 Economy

Between 1996 and 2006 a civil war between the Maoists and the government tore down Nepal's constitutional monarchy who had been in power since 1990. Nepal is now one of the poorest countries of the world with about 1/3 of its population living below the poverty line[410]. It ranks 193rd out of 210 for Gross National Income (GNI) per capita, 5 places above Malawi (Table 2.5). (http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf). The majority of the population lives in rural areas and agriculture is the main economic activity employing 80% of the population involved, but contributing to

only 39% of the national GDP. The greatest economic entry is offered by remittance from abroad.

Table 2.5 - Nepal Economic Indicators

Nepal	1988	1998	2008
GDP (million current US$)*	3,487	4,856	12,615
GDP growth (annual %)*	8	3	5
GNI per capita, PPP (current international $)*	460	730	1120
Official development assistance & official aid million(current US$)	408	401	598**
Human development index*	0.309 (1980)		0.553 (2009)

* For the definitions please consult the Glossary ** data from 2007 . Source: http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20399244~menuPK:1504474~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html

2.3.4 Health Sector: Obstetric and Neonatal Services

Health policy for Nepal, as for most countries has been dominated in the last decade by the Millennium Development Goals and improvement of maternal and under five mortality has been high on the political agenda. A number of initiatives to increase antenatal care attendance, deliveries assisted by qualified personnel and promote post natal care have been introduced. According to the 2006 demographic and health survey, the percentage of women who attended ANC at least once during her last pregnancy was 84%, however only 43% of women saw a doctor or a midwife. These figures doubled from 1996. Only 28% of women delivered in a health facility and 19% of deliveries were attended by a doctor or a midwife. About 33% of women received postnatal care. Better educated women and women living in the “hill” areas were more likely to receive antenatal care (ANC) by a

doctor or a midwife, to deliver with a health professional and to have received postnatal care (Table 2.6)[411].

Table 2.6 - Nepal: Maternal and Neonatal Health Indicators

Nepal	1996	2006
Maternal mortality ratio(per 100,000)	539	281
Neonatal mortality rate (per 1000)	50	33
Infant mortality (per 1000)	79	48
Under five mortality rate (per 1000)	118	61
Perinatal mortality rate (per 1000)	-	45

Source[412-415]

Source: Centre for International Health and Development

2.4 - Makwampur District and Mother and Infant Research Activities (MIRA)

"Mother and Infant Research Activities" (MIRA) was established in 1992 as a non-governmental organisation to improve maternal and newborn health (http://www.mira.org.np). The group is a collaboration between Nepalese health and development professionals and the Centre for International Health and Development at UCL. MIRA researches the main causes of stillbirths and neonatal morbidity and mortality such as perinatal asphyxia and neonatal sepsis, and the effects of cost effective interventions on maternal and neonatal outcomes and runs a number of projects. The VA analysed in this study are based on data collected as part of randomised controlled studies coordinated by MIRA, to test the effect of women's groups on maternal and neonatal mortality in Makwampur[416].

Makwampur district (2426 km^2) is situated in the Narayani zone, Central region and borders with Kathmandu to the north east, less than 50 km from the capital, but separated from it by the Himalayas. The total population was 392,604 in 2001 census, the main ethnic group are the Tamang, Brahmin and Chetri (http://www.digitalhimalaya.com/collections/nepalcensus/ last accessed Mar 2011). Hetauda is its main administrative town. Topographically the district is a mix of hills and plains. Two tarmac roads cross it, but communications are difficult and villages far apart. Agriculture is the main economic activity, occupying about 80% of the population. The human development index is 0.471, ranking 31 over the 75 districts of Nepal[417].

A district hospital with 24 in-patient beds is located in Hetauda. The hospital had antenatal and essential delivery facilities, without capability for operative deliveries when the study was developed. Four primary health centres, 10 health posts, 30 sub-health posts and 3 ayurvedic health facilities were scattered in the district. Sub-health posts offer mostly primary health care. All act as referral

points for TBAs and female community health volunteers. Quality of service is patchy and often staff nurses and doctors' posts are vacant in the primary health facilities[418].
From the data collected by MIRA in 2001 90% of mothers delivered at home. Only 6% of deliveries were attended by a health worker and 8% by a TBA[419;420].

The Makwampur study has been described in details before[421-424]. Briefly, it involved a cohort of 28,031 women between 15 and 49 years of age chosen from 24 Village Development Committees (an official administrative division, each with a representative) randomly selected from a total of 42. Each village development committee represented a cluster with a population of about 7000 people and was randomised to receive either the Women's groups intervention (where women's groups were formed and met regularly with the help of a facilitator to discuss problems and strategies about pregnancy, delivery and newborn care) or to be one of the controls.
In a similar way to the Maimwana study, WCBA recruited were visited every month by women enumerators who recorded their menstrual history. When the same woman misses 3 consecutive periods she was considered pregnant[425] and notified to a cluster interviewer. Women were then visited at 7 months gestation and one month after delivery by cluster interviewers who administered a questionnaire focusing on pregnancy, delivery and newborn health. If the pregnancy ended on a stillbirth, neonatal or maternal death one of nine senior field coordinators visited the family with a verbal autopsy questionnaire.
All the facilities in the district benefited from a health strengthening exercise to improve maternal and newborn care services.

2.5 - Mumbai; India

2.5.1 Geography and Climate

Mumbai is the capital city of Maharashtra district and it is situated on the West coast of the Indian peninsula, facing the Arabian Sea. The ever expanding city is structured into the City district or old Mumbai in the south and Mumbai suburban. The City district now hosts the headquarters of major business companies and has become the economic heart of the city. Mumbai suburban is a hilly area expanding toward the northern outer zone to the island of Salsette. These two administratively separate entities constitute Greater Mumbai (Figure 2.4)[426;427]. The climate is tropical with a dry season lasting for about 7 months from November to June. The South-West monsoon season extends from June to October, and pre monsoon rains start in May. (http://mdmu.maharashtra.gov.in/pages/Mumbai/mumbaiplanShow.php last accessed Mar 2011).

Figure 2.4 - Map of Mumbai

Source: Adapted from http://geology.com/world/india-map.gif

2.5.2 Population

According to the 2001 census the population of Greater Mumbai was over 16 million, being the most populous city of India with a density of 16,461 per km^2.{ref: http://www.censusindia.gov.in/towns/mah_towns.pdf }

To accommodate an ever-growing population of immigrants in search of employment the city grew and continues to expand. The original city district extends over a surface of 67.79 km^2 and lies at sea level. Greater Mumbai covers

about 430 km^2 in hilly areas reaching up to 450m above the sea and is divided in 24 wards[426;427].The population growth, however, exceeds the housing capacity of the city and a larger proportion of the population than any other Indian city lives in slums (54%) (http://www.censusindia.gov.in/2011-common/CensusDataSummary.html and http://www.regionalplan-mmrda.org/N-3.pdf last accessed Mar 2011)

Mumbai is a polyglot, multicultural large city with 16 major languages spoken. The official language is Marathi. There are at least 8 major religions represented, Hindus are the majority (67%) followed by the Muslims (19%), Buddhists, Jains, Christians, Sikhs, Parsis and Jews.

2.5.3 Economy

India is listed by the World Bank as one of the "medium human development" countries ranking 134 of 182 countries (http://hdr.undp.org/en/statistics/ last accessed Mar 2011), its Human development index is 0.612. Per Gross National Income (GNI) per capita India ranks 162nd out of 210 (Table 2.7) (http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf). Mumbai is a major port with a flourishing diversified manufacturing and commercial industry, and a developing financial sector. Its per-capita income is about 3 times higher than the national average making Mumbai the richest city in India.

Table 2.7 - Mumbai Economic Indicators

	2009
GDP (million current US$)*	1,296,085
GDP growth (annual %)*	6.1
GNI per capita, PPP (current international $)*	1040
Human development index*	0.612

*For the definitions please consult the Glossary. Source: http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20399244~menuPK:1504474~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html

2.5.4 Slums

Slums in Mumbai host about 9 million people (Census 2001) and resulted from scarcity of land and unaffordable housing prices forcing people to settle in informal accommodations, with little access to basic facilities such as clean water and sanitation facilities[427].

The definition of slums varies in the literature however the 2001 Indian census defined them as "any area notified as slum by the state, local government, administration, housing or boards. Or areas of at least 300 population (about 60-70 households) of poorly built congested tenements, in unhygienic environment usually with inadequate infrastructure and lacking in proper sanitary and drinking water facilities." (http://www.censusindia.gov.in/2011-common/CensusDataSummary.html last accessed Mar 2011).

The land where slums develop is not owned by their dwellers, and therefore the slum inhabitants are at continuous risk of land expropriation and loss of housing[428].

2.5.5 Health Service Structure

Health care is delivered free of charge in Greater Mumbai through health posts, dispensaries, maternity homes, peripheral general hospitals and tertiary medical colleges. About a quarter of hospital beds are provided by corporation hospitals. The private sector provides the rest of the available hospital beds and deliver care through general practitioners, small and larger hospitals (Table 2.8)[429]. Private practitioners, often without qualifications are often consulted partly because state services are few and partly because they are perceived to be of better quality and more friendly[430;431]

Table 2.8 - Mumbai Demographic Indicators

	1981	1991	2001
Total Population	9,902,100	13,378,249	16,400,000
Population density (per Km^2)	13,391	18,489	22,262
Annual growth rate	3.28	1.87	1,84
Literacy rate (%)	68	71	77
Women literacy rate (%)	61	65	72

Source: (http://www.censusindia.gov.in/2011-common/CensusDataSummary.html last accessed Mar 2011).

2.5.6 Health Sector: Obstetric Services

More *et al.* describe the flux of obstetric and neonatal care in the same slum areas described in this thesis[432]. As in Malawi the majority of women attended antenatal care at least once (93%) however here the majority (95%) attended all three recommended visits. About half of these women opted for private health facilities for their ANC. Of the women delivering in Mumbai 90% delivered in an institution, a much higher percentage than in both rural Malawi and Nepal, of those women 60% chose a state facility and 40% a private institution[433]. Of the women who went back to their home village to deliver 38% delivered at home[434].

Source: Centre for International Health and Development

2.6 - Slums and Sneha Project

Figure 2.5 - Map of City Initiative for Newborn Health - Slum Areas

Adapted from Centre for International Health and Development

The data for this study derive from a prospective surveillance within a cluster randomised controlled trial with the aim of improving maternal and neonatal health in 6 slum communities in Mumbai through community mobilisation, in a similar fashion to the model of the Warmi project, MIRA and Maimwana studies (Figure 2.5)[435].

Six wards of the municipality of Mumbai were involved in this project (F North, G North, H West, K west, M East and P North), 48 clusters of about 1000-1500 population were selected (Figure 2.5). These areas were served by 24 health posts. Similarly to the previous studies described, pregnancies were identified by local women enumerators and followed up with an interview 6 weeks after delivery by interviewers. If maternal, stillbirth or neonatal death occurred, a senior interviewer followed it up with a verbal autopsy questionaire[435].

Table 2.9 summarise the characteristics of the three countries and districts presented in this thesis.

Source: Centre for International Health and Development

Table 2.9 - Three Countries Comparison

	Malawi	Nepal	Mumbai
Country surface in km^2	118,484	147,181	430
Population density per Km^2	139	157	22,262
HDI~	0.493	0.553	0.612 (India)
Total Fertility rate (per woman)	6.0	3.1	1.68
HIV prevalence	12%	-**	0.62% (Maharashtra)
Maternal mortality rate (per 100,000)	984	281	183 (Maharashtra)+
Perinatal mortality rate (per 1000)	34	45	36 (Maharashtra)
Neonatal mortality rate (per 1000)	27	33	25 (Mumbai)
ANC attendance	95% (1 visit)	84%* (1 visit)	90% (3 visits)
Skilled personnel at delivery	56%	28%	82%
Post natal care	69%	33%	63%
	Mchinji District	**Makwampur**	**6 Mumbai Wards**
Population	460,000	400,000	350,000
HIV prevalence	8.8	-	-
Agriculture	90%	-	-
	Maimwana study	**MIRA**	**City Initiative**
Population	~ 150,000	~168,000	~192,000
Detection of births	Women enumerators	Women enumerators	Women enumerators
Detection of deaths	Women enumerators then verified by field interviewers	Women enumerators then verified by field interviewers	Women enumerators then verified by field interviewers
VA questionnaires	5 Senior monitoring and evaluation officers	9 Field coordinators	Supervisors

Note: ~ Human Development Index; * only 43% had ANC form a doctor or midwife. ** Data not collected as part of the DHS.+ Data collected using the snowballing methodology (only 10 deaths in the sample)[436]

2.7 - Ethics

The three projects described in the thesis underwent separate ethic approval processes involving Great Ormond Street Hospital for Children and local ethics commissions.

The MaiMwana study was approved by the Malawi National Health Sciences Research Committee and the ethics committee at Great Ormond Street Hospital for Children.

The MIRA- Makwampur study was approved by the Nepal Health Research Council and the ethics committee at Great Ormond Street Hospital for Children.

The City Initiative for Newborn Health study (Sneha) was approved by the Municipal Corporation of Greater Mumbai, the Independent Ethics Committee for Research in Human Subjects and the ethics committee at the Institute of Child Health and Great Ormond Street Hospital for Children.

Consent for the studies was sought from the hosting communities initially through a participatory process. Subsequently individual consent was obtained at enrolment and at each subsequent encounter prior to the administration of the questionnaires for each woman of childbearing age.

2.8 - Summary

This chapter described

- The countries where the studies were set up, with an emphasis on their health sector and in particular the organisation of the obstetric and newborn services and
- The three studies from which the data for this thesis were extracted

Chapter 3:

Methods

This chapter describes and compares the tools and methods used for verbal autopsy data collection in three studies. It describes two strategies to analyse and interpret VA data: physician review and a computerised method based on probabilistic theory. The data analysis plan for this thesis concludes the chapter.

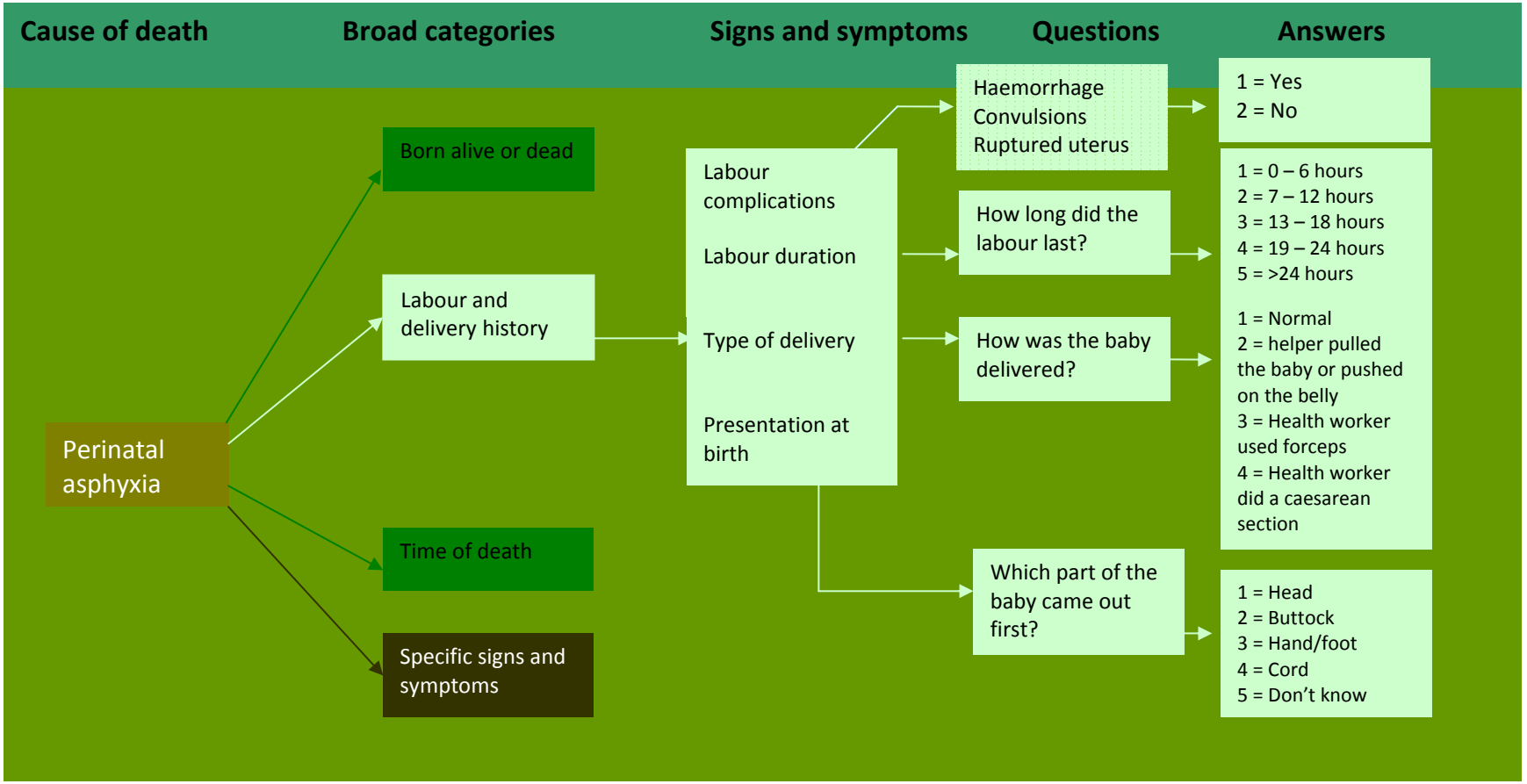
3.1 - Verbal Autopsy Tool Development

Classically, a verbal autopsy package includes a classification of perinatal and neonatal deaths, a verbal autopsy questionnaire, and an interpretative algorithm for physicians to establish diagnoses. For the studies presented in this thesis these separate instruments were developed across a period of about 8 years from the initial version developed in Nepal to the subsequent refinements in Malawi and Mumbai. The different tools were prepared expressly for physicians to scrutinise and analyse the data. During this period of time external research and development of verbal autopsy classifications and questionnaires contributed to the final shaping of the VA tools in this thesis.

VA differ from other forms of data collection as the information obtained from questionnaires need to be interpreted and converted into diagnoses or diagnostic categories before being analysed. The first step was therefore to formulate a working classification of causes of death for stillbirths and neonatal deaths. Only with a perinatal death classification a list of signs and symptoms of disease could then be derived and appropriate questions put together for VA questionnaires

(Figure 3.1). The list of questions derived from this process was subsequently enriched by questions available from the literature[208;437;438]

Figure 3.1 – Framework for the development of VA questionnaires



3.2 - Classifications

3.2.1 Stages in the Development of Stillbirth and Neonatal Classifications for Verbal Autopsies

In 2001, when MIRA Makwampur was set up, a number of classifications of perinatal deaths were available in developed countries for clinical use[366;439-441] (Table 3.1). Only Bang had proposed a classification of neonatal and child causes of deaths for VA use[208]. The classification of neonatal deaths devised originally for Nepal followed the categories proposed by Bang for neonatal deaths. It included 16 categories for neonatal death and 9 for stillbirths on the model of the NICE classification. This original classification was never used for data analysis.

Table 3.1-Classification of Causes of Perinatal Deaths

Bang 1992	NICE 1998	Nepal
Neonatal deaths	**Perinatal deaths**	**Neonatal deaths**
1. Prematurity	1. Congenital lethal anomalies (still or liveborn)	1. Congenital malformation
2. Low birth weight	2. Multiple births	2. Asphyxia or birth injury
3. Congenital malformation	3. Maternal disease	3. Complications of preterm (Apart from hyaline membrane disease alone)
4. Birth asphyxia	4. Specific foetal conditions	4. Low birth weight
5. Neonatal tetanus	5. Unexplained SGA infant	5. Respiratory distress syndrome (Includes hyaline membrane disease, congenital pneumonia or meconium aspiration)
6. Neonatal pneumonia	6. Placental abruption	6. Neonatal tetanus
7. Post natal aspiration	7. Obstetric complications	7. Neonatal pneumonia
8. Respiratory distress syndrome	8. Unexplained antepartum stillbirth < 37 weeks	8. Neonatal sepsis (includes septicaemia and meningitis)
9. Diarrhoea	9. Unexplained antepartum stillbirth > 36 weeks	9. Hypothermia
10. Dysentery	10. Specific infant conditions including infants >32 weeks gestation with sepsis/meningitis, SIDS, RDS, accidents	10. Feeding problem
11. Hypothermia	11. Unexplained asphyxia	11. Postnatal aspiration
12. Neonatal sepsis	12. Unexplained immaturity	12. Diarrhoeal disease
13. Sudden death	13. Unidentifiable cases	13. Dysentery
14. Feeding problem		14. Sudden death
15. Other		15. Other
16. Cause not known		16. Cause not known
		Stillbirths -Fresh or Macerated
		1. With low birth weight
		2. Unknown, with normal birth weight
		3. Antepartum haemorrhage
		4. Foetal malformation
		5. Maternal disease
		6. Pre-eclampsia/eclampsia
		7. Mechanical/trauma
		8. Infection
		9. Isoimmunisation

When the Maimwana project in Malawi developed in 2003, it was chronologically the second study (Figure 3.1). In 2002 the CHERG classification was formulated to describe global neonatal mortality and profoundly influenced the development of the classification used for the MaiMwana project[442;443].

The classification used in Malawi reflected a move toward simplification: pathophysiological distinctions more relevant in clinical practice than for epidemiological purposes were lost. Verbal autopsies could describe a term newborn with signs of respiratory distress but could not help in determining whether he had suffered from pneumonia, meningitis, or septicaemia. The classification reflected this and grouped causes of death in 7 main categories. A sub-classification was kept to ensure more detailed information would not be lost, when available, and to avoid the physicians classifying too many infants as "other" causes of death because of the lack of sufficient diagnostic choice (Table 3.2 and 3.3).

The classification was aimed at physicians that could choose more than one cause of death for each infant, modelled on the death certification process[158].

Table 3.2 - Maimwana Stillbirth and Neonatal Death Classification

CHERG	Malawi Maimwana (2004)
Neonatal deaths	**Neonatal death**
1. Congenital malformation	**1. Congenital anomalies and inherited disorders**
2. Prematurity	**2. External conditions**
3. Asphyxia	**3. Asphyxia**
	3a. Associated with obstetric complications including placental abruption or severe haemorrhage
4. Pneumonia	**2. Immaturity/SGA**
5. Neonatal tetanus	**4. Severe infection**
	4a. Neonatal tetanus
	4b. Neonatal sepsis/meningitis
	4c. Pneumonia/respiratory conditions
	4d. Diarrhoea/dysentery
	4e. Local infections
6. Diarrhoea	**6. Other**
7. Other	**7. Unexplained**
	Antepartum stillbirth
	1. Congenital anomalies and inherited disorders
	2. Prematurity/ small for gestational age (SGA)
	3. External condition
	4. Other
	5. Unexplained
	Intrapartum/fresh stillbirth
	1. Congenital anomalies and inherited disorders
	2. Associated with obstetric complications including placental abruption/haemorrhage
	3. Multiple births
	4. Immaturity
	5. External conditions
	6. Other
	7. Unexplained

The definitions used were derived from the literature, including CHERG and NICE[38;208;437;444-449].

Table 3.3 - Definitions Used in Maimwana Study

Maimwana definitions
Congenital anomalies. Infants with lethal malformations or potentially lethal malformations that markedly increase mortality risk
Immaturity/SGA: Infants< 33 completed gestational weeks (or <8 months or wt <1500 gr, baby very early or small) or small for gestational age (SGA) <2.5 sd of birth weight for gestational age reference range
Asphyxia: not cried or breathe immediately after birth + either convulsions/spasms or poor suck, irritability or poor cry
Asphyxia + obstetric complications: as above and uterine rupture, malpresentation, cord prolapse, placenta praevia, precipitate labour, prolonged labour, obstructed labour, including placental abruption or severe haemorrhage
Severe infection: any of neonatal tetanus, meningitis, pneumonia, septicaemia, local infection, diarrhoea or other serious infection
Tetanus: Convulsions or spasms in a baby who was able to suckle normally for the first few days of life but becomes unable to suckle or cry normally *or* had lock jaw or back arching
Sepsis and meningitis Two or more signs of sepsis: fever, cold to touch, lethargy, reduced feeding, weak or absent cry *plus* no focal signs of pneumonia, diarrhoea, tetanus, skin infection or other infection *or* signs of meningitis: convulsions or bulging fontanelle
Pneumonia/respiratory conditions Cough or difficult breathing *plus* fast breathing, chest indrawing, nasal flaring, or grunting for > 1 day.
Diarrhoea/Dysentery : Abnormally frequent loose / liquid stools +/-blood *or* local term for diarrhoea for > 1 day
Local infections: Skin rash with areas containing pus or blisters containing fluid *or* any part of the skin becoming inflamed, red and hot, Pus discharging or draining from umbilical stump
External condition: Accident or injury
Other: Tumours, haemorrhagic disease of the newborn, sudden infant death syndrome, severe jaundice
Unexplained / unknown: none of the above

3.2.3 City Initiative for Newborn Health- Mumbai Classification

The Mumbai study was developed in 2004. Stillbirths and neonatal death definitions and classifications went through a new stage of refinement modelled on previous experience, new literature and the collaboration with the research group in Kintampo, Ghana[450] (Figure 3.2). The Kintampo classification was based on the NICE model, and reintroduced a number of causes of death such as specific foetal and antepartum conditions, sudden infant death and placental abruption as distinct categories from obstetric complications (Table 3.4). Physicians were allowed a single diagnosis, therefore there was a need to make the classification strictly hierarchical. Perinatal asphyxia and infection reintroduced the concept of age. Here a cut off of 33 weeks was used, rather than 34 weeks used by CHERG. The definition of prematurity and small for gestational age were joined as a single category. The Kintampo classification and questionnaires were validated using hospital diagnoses[451].

The final classification for physician diagnoses in Nepal and Mumbai is illustrated in Table 3.4 and 3.5.

Figure 3.2 - Development of Study Classifications

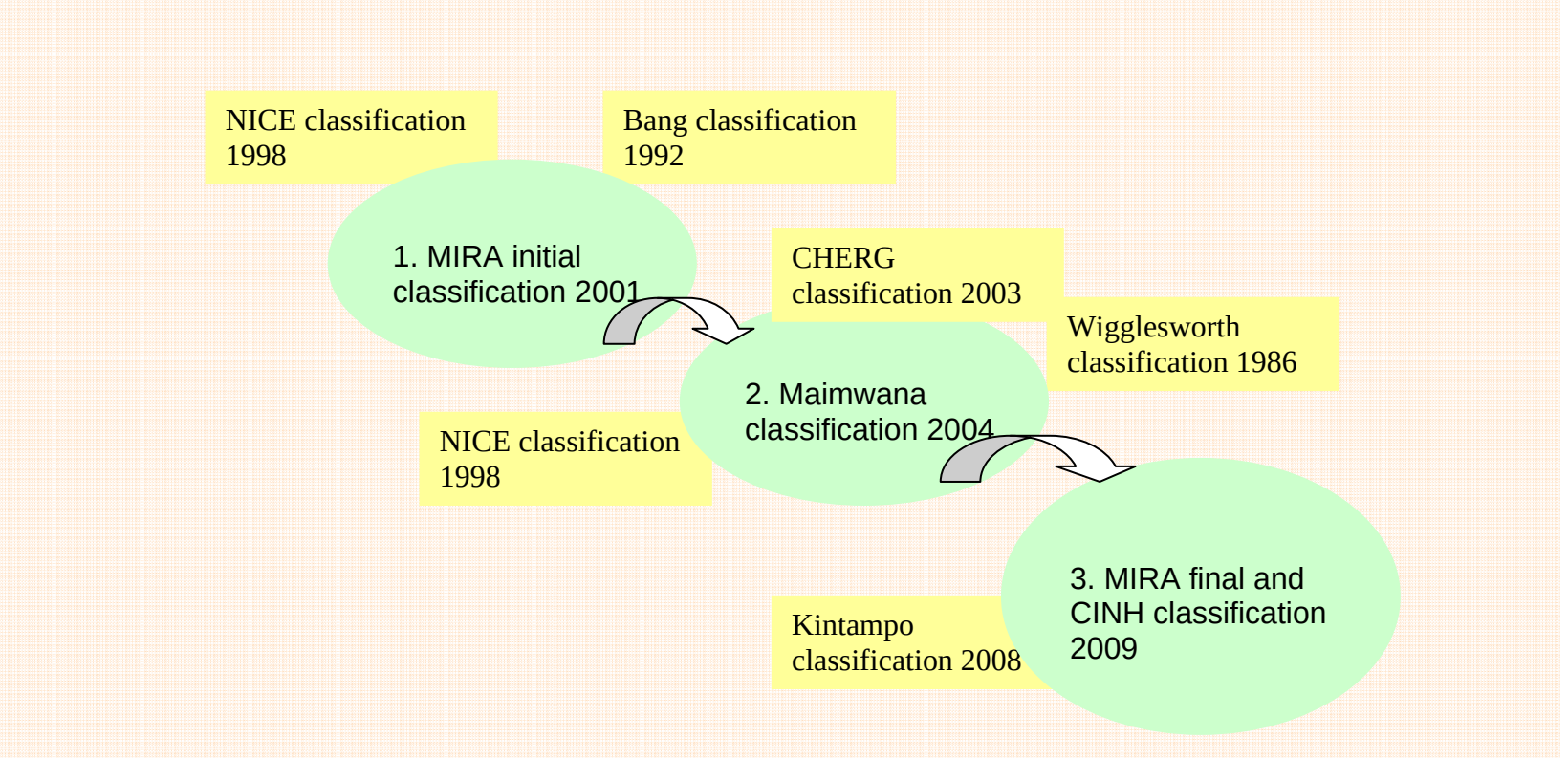


Table 3.4 - Comparative Hierarchical Classifications

Kintampo (2006)	Nepal MIRA and India SNEHA (2007)	Kintampo (2006)	Nepal MIRA and India SNEHA (2007)
Neonatal death	**Neonatal death**	**Stillbirth**	**Stillbirth**
1. Congenital anomalies	**1. Congenital anomalies and inherited disorders**	**Antepartum stillbirth**	**Antepartum stillbirth**
2. Immaturity (*<33 weeks gestation*)	**2. Immaturity/small for gestational age**	**1. Congenital abnormality**	**1. Congenital anomalies and inherited disorders**
2a. with multiple births	2a. with multiple births	**2. Maternal disease**	**2. Associated with maternal disease**
2b. with maternal disease	2b. with maternal disease	**3. Haemorrhage**	**3. Placental abruption/haemorrhage**
2c. with placental abruption	2c. with placental abruption/ severe haemorrhage		**4. Specific foetal/antepartum conditions**
2d. unexplained immaturity	2d. unexplained immaturity		**5. External conditions**
3. Asphyxia	**3. Asphyxia**	**4. Other**	**6. Other**
3a. with placental abruption	3a with placental abruption/ severe haemorrhage	4a. External conditions/ accidents/injuries	
3b. with obstetric complications	3b. with obstetric complications	4b. Specific foetal conditions	
3c. unexplained asphyxia	3c. with maternal disease	4c. Placental abruption	
	3d. unexplained asphyxia	4d. Other. Unspecified	
4. Severe infection	**4. Severe infection**	**5. Unexplained**	**7. Unexplained**
4a. Neonatal tetanus	4a. Neonatal tetanus	**Intrapartum/fresh stillbirth**	**Intrapartum/fresh stillbirth**
4b. Meningitis	4b. Neonatal sepsis/meningitis	**1. Congenital abnormality**	**1. Congenital anomalies and inherited disorders**
4c. Pneumonia	4c. Pneumonia/respiratory conditions	**2. Obstetric complications**	**2. Associated with maternal disease**
4d. Diarrhoea	4d. Diarrhoea/dysentery	**3. Haemorrhage**	**3. Associated with obstetric complications**
4e. Neonatal sepsis	4e. Local infections	**4. Other**	**5. Specific foetal/antepartum conditions**
5. Other	**5. External conditions**	4a. External conditions (accidents/injuries)	**6. Multiple births**
5a. External conditions (accidents/injuries)	**6. Specific foetal/ antepartum conditions**	4b. Specific foetal conditions	**7. Immaturity**
5b. Specific foetal/antepartum conditions		4c. Placental abruption	**8. External conditions**
5c. Other placental abruption		4d. Immaturity	**6. Other**
5d. Other. Specify		4e. Unexplained	**10. Unexplained**
6. Unexplained	**7. Placental abruption/haemorrhage**	**5. Unexplained**	
6a.Other unknown	**8. Other**		
6b. Sudden infant death syndrome			
	9. Unexplained		

Adapted from NICE, Wigglesworth and CHERG[452-454]

Table 3.5 - Definitions Nepal/MIRA

Definitions	
Early neonatal death	Death within the first week of life (0-7 days)
Late neonatal death	Death after day 7 and before day 28.
Lethal malformation/ Congenital anomaly	Stillbirth (SB) or livebirth with lethal or potentially lethal malformation (e.g. anencephaly, large meningomyelocoele, duodenal atresia, major cardiac malformation)
Macerated SB	Death before onset of labour of a normally formed infant. Mother may report loss of foetal movements before labour or the baby may be born macerated (skin and underlying tissue pulpy and disintegrating).
Fresh SB	Death during labour or delivery. Mother may report baby moving up until the time labour commences.
Asphyxia	Fresh SB with no other specific conditions OR livebirth AND gestational age ≥ 33 weeks No cry or breathing immediately after birth *plus* either convulsions or spasms or poor suck, irritability or poor cry (Supportive criteria: history of prolonged labour, malpresentation, twin, very large baby)
Obstetric complications	Obstructed labour, haemorrhage (APH, PPH), cord prolapse, eclampsia, ruptured uterus, emergency C section, malpresentation, precipitate labour, prolonged labour, placenta praevia, placental abruption**
Prematurity/ *Small for gestational age* (SGA)	***Prematurity:*** < 33 completed gestational weeks or < 8 months gestation. If gestation unknown, birthweight < 1500g, or baby born very early or very small ***Small for gestational age:*** birth weight < -2.5 SD for gestational age reference standard
Severe infections	≥ 33 weeks gestation with tetanus, meningitis, pneumonia, septicaemia, skin infection, diarrhoea or other serious infection. **Neonatal tetanus** Normal for the first 2 days of life then develops convulsions or spasms, unable to suckle or cry normally *or* lock jaw or arching back. **Severe sepsis or meningitis** ≥ 33 weeks gestation. Convulsions or bulging fontanelle *plus* either fever or one or more signs of sepsis (cold to touch, lethargy, reduced feeding, weak or absent cry). Two or more signs of sepsis - fever, cold to touch, lethargy, reduced feeding, weak or absent cry *plus* no focal signs of pneumonia, meningitis, diarrhoea, tetanus, skin infection or other infection. **Pneumonia or respiratory condition** ≥ 33 weeks gestation. Cough or difficulty in breathing *plus* fast breathing, chest indrawing, nasal flaring, or grunting for > 1 day. **Diarrhoea or dysentery** ≥ 33 weeks gestation. Abnormally frequent loose or liquid stools *or* local term for diarrhoea for > 1 day. **Local infection** Pus discharging or draining from umbilical stump, a skin rash with areas containing pus or blisters containing fluid *or* any part of the skin becoming inflamed, red and hot.
Multiple births	Multiple births other than duplex, or duplex and immaturity (< 33 completed weeks of gestation). Twin to twin transfusion syndrome
Maternal disease	Includes eclampsia, pre-eclampsia, renal disease, hepatosis, severe anaemia, severe

	malaria or other severe infection (e.g. HIV) when combined with immaturity or small for gestational age or maternal diabetes mellitus if the infant is large for gestational age*
Specific foetal conditions	***Hydrops foetalis:*** Severe generalised oedema (anasarca) at birth or on antenatal ultrasound. ***Foetal tumour*** Foetal tumour by ultrasound diagnosed by a health worker. ***Specific foetal infections*** Toxoplasmosis, rubella, cytomegalovirus, herpes simplex or other specific infection diagnosed by a health worker
Placental abruption or haemorrhage	Placental abruption if combined with asphyxia or immaturity (< 33 completed gestational weeks) or intrauterine death.
Other	Other specific infant condition. Infants ≥ 33 weeks gestation. Includes tumour, haemorrhagic disease of the newborn, sudden infant death syndrome, kernicterus
Unclassified	Other causes not included above

Note: *Definition of maternal conditions used in all algorithms: Maternal diabetes mellitus: Diabetes mellitus diagnosed by a health worker prior to the onset of pregnancy. Gestational diabetes excluded. Maternal renal disease: Renal insufficiency or failure diagnosed by a health worker. Maternal hepatosis: Liver dysfunction with jaundice and pale stools or dark urine diagnosed by a health worker. Maternal eclampsia: Convulsions plus diastolic blood pressure ≥ 90 mmHg after 20 weeks gestation *plus* proteinuria (2+) and seizures during pregnancy. Severe maternal pre-eclampsia: Diastolic blood pressure ≥110 mmHg after 20 weeks gestation *plus* proteinuria (3+) diagnosed by a health worker.
Severe maternal anaemia: Anaemia with haemoglobin less than 7g/dl, or haematocrit < 20% or clinical symptoms/signs (difficulty breathing or pallor) diagnosed by a health worker. Severe maternal malaria: Malaria with coma, anaemia, jaundice, convulsions or circulatory compromise diagnosed by a health worker. Maternal HIV infection. Mother was told she had HIV/AIDS by a health worker or had a positive HIV/AIDS test.
**Definition of obstetric complications used in all algorithms: Placental abruption: Diagnosis by a health worker of the detachment of a normally located placenta from the uterus before the foetus is delivered. The uterus is usually tense or tender and if bleeding occurs it is usually associated with abdominal pain. Placenta praevia: Diagnosis by a health worker of implantation of the placenta at or near the cervix by ultrasonography. Antepartum haemorrhage: Vaginal bleeding > 22 completed gestational weeks. If gestation in weeks is not known then use > 6 months gestation. Uterine rupture: Disruption of the wall of the uterus. Is associated with severe abdominal pain, usually associated with a tender abdomen, loss of uterine contour and easily palpable foetal parts. Bleeding may be intra-abdominal or vaginal. Malpresentation: All presentations of the foetus other than vertex (e.g. breech, face, foot). Cord prolapse: The umbilical cord lies in the birth canal below the foetal presenting part or the umbilical cord is visible at the vagina following rupture of the membranes. Precipitate labour: Labour lasting < 4 hours. Prolonged labour: Labour lasting ≥ 24 hours. Obstructed labour: Prolonged labour ended with a Caesarean section, undelivered baby and/or ruptured uterus.

3.3 - Questionnaires

The Nepal VA questionnaire was adapted from the WHO standard VA questionnaire for infants and children (WHO/CDS/CSR/ISR/99.4)[437] and its updated version from 2003 (WHO/JHU/AKU/SNL 11/05/2003). Questionnaires for all the studies were initially formulated in English then translated into the local language and piloted.

The Maimwana questionnaire was developed from the Maimwana classification of causes of death, using as a model the Nepal questionnaire and an updated WHO questionnaire version: WHO/JHU/AKU/SNL 11/05/2003. The main substantial change to this version was the use of open questions to explore signs and symptoms of maternal health in the antenatal period, labour and delivery and signs of illness in the newborn.

Finally the Mumbai questionnaire was a synopsis of the two previous questionnaires, the differences concerned the specific study questions rather than to the structure or substance of the previous versions. The "WHO standard questionnaire for stillbirths and neonatal deaths"[158] was finalised subsequently in 2007.

All the questionnaires in this thesis have an open question about circumstances surrounding death at the beginning of the interview and a series of closed questions to help define the diagnoses (Table 3.2) (Appendix I, II, III). The details regarding labour and delivery were part of the maternal questionnaire and, for all the studies in this thesis, were separate from the verbal autopsy questionnaire and delivered to all study participants giving birth in the study areas irrespective of the newborn outcome (Table 3.6).

Table 3.6 Questions from the Maternal Questionnaire

Questions	Answers
How long did the labour last?	1 = 0 – 6 hours 2 = 7 – 12 hours 3 = 13 – 18 hours 4 = 19 – 24 hours 5 = >24 hours
How many hours before the baby was born did the waters break?	1 = <24 hours 2 = >24 hours 3 = Don't know
How did the waters smell and look?	1 = No odour/normal odour and clear 2 = Foul smell and green 3 = Don't know
How long after the baby's birth did the placenta come out? IF THE BABY WAS BORN BY C-SECTION, CIRCLE "<1 hour"	1 = <1 hour 2 = >1 hour
Did you drink a traditional oxytocic medicine to assist labour?	1 = Yes 2 = No →
How many spoonfuls did you drink?	|__| spoonfuls

3.3.1 Comparison of Questions

The number of questions varied from 147 for Maimwana, 118 for MIRA-Makwampur and 274 for Sneha- Mumbai.

The questions concerning demographic information, details of the interviewee and interviewer, open account of the facts leading to death were all very similar. Consent was requested in the first section of all questionnaires. At the end of the open history account, the WHO questionnaires included a checklist of conditions to guide the interviewer during the open account of events. At the end of the open history, the 2007 WHO questionnaire specifically asked the interviewee's opinion about what caused the death, these questions were not available in any of our studies' questionnaires.

Questions to establish the conditions at birth (weight, size, gestational age and gender), presence of congenital malformations and whether the infant was a still

or livebirth and whether a stillbirth was fresh and macerated were very similar. Clinical signs were investigated in all questionnaires using closed questions and although the order of the questions varied, the information gathered was very similar (Table 3.7).

The questions about care practices such as hand washing, use of gloves, umbilical cord care, resuscitation given at birth and risk factors not strictly related to establishing signs and symptoms leading to death, and were more variable between the sites reflecting the different interests of the investigators conducting the studies.
Breastfeeding was explored in detail in the Maimwana study as it was one of the outcomes. Postnatal care and use of health services after birth were explored in Maimwana questionnaire and the last version of the WHO questionnaires.

The WHO questionnaires had a final section collecting information from death certification which had been omitted in the Nepal and Malawi questionnaires as very rarely available, but was introduced in the Mumbai questionnaire, as this information were accessible given the higher use of health facilities in this population. Finally the WHO questionnaire had a detailed section about accident and external injuries that was not present in any of the questionnaires presented in this thesis.

Table 3.7 - Comparison of Stillbirth and Neonatal Death Questionnaires –Signs of Illnesses

WHO/CDS/CSR/ISR/99.4 The WHO infant VA: the origin of the modified neonatal version	WHO/JHU/AKU/SNL 11/03/2003	MIRA	Maimwana	WHO 2007
Crying at birth	Crying at birth and onset (within 5 min/ between 5-30 min, after 30 min , never)	Crying after birth	Crying at birth and onset (within 5 min/ between 5-30 min, after 30 min , never)	
Stopped crying (<1d before death, >1d before death)	Stopped crying (<1d before death, >1d before death)	-	-	-
Able to breath after birth?	Able to breath immediately after birth	-	-	-
-	Anything done to help the baby breathe at birth? (what) repeated for still and live births	-	Anything done to help the baby breathe at birth? (what) repeated for still and live births	-
-	-	Alertness just after birth	-	-
	-	Floppiness just after birth	Floppiness just after birth	-
Suckle normally after birth	Able to suckle in the first day	-	-	-
	Ever suckle normally?	-	Ever suckle normally?	Ever able to suckle? How soon after birth did the baby suckle
		-	Did the baby always suckle normally?	-
Stopped feeding (<1d, 1-2d, 3-7d, 8-14d, 15-30d)	Stopped suckling (<1d, 1-2d, 3-7d, 8-14d, 15-30d)	Feeding difficulty (<3d old, >3d old)	Stopped suckling (at birth/between 2 and 3 d / after 3 d)	Did the baby stop suckling (in days?)
When did the infant stop suckling?		Feeding difficulty duration	Feeding difficulty duration	-
		Feeding difficulty until death	Feeding difficulty until death	-
-	-	-	Could baby open the mouth	-
-	-	Feeding (less, normal, more)	-	-
-	-	Choking on feed	-	-
Spasms or convulsions	Spasms or convulsions	Fits and on which day	Convulsions in the first day or after first day	Fits and on which day
-	-	Back arching and spasms	Back arching and spasms	Became stiff and back arching
Local term for tetanus?	Local term for tetanus?	Local term for tetanus?	Local term for tetanus?	-

Cont. **Table 3.7 - Comparison of Stillbirth and Neonatal Death Questionnaires –Signs of Illnesses**

WHO/CDS/CSR/ISR/99.4 The WHO infant VA: the origin of the modified neonatal version	WHO/JHU/AKU/SNL 11/03/2003	MIRA	Maimwana	WHO 2007
	-	Mouth opening	Mouth opening	-
Bulging fontanelle	Bulging fontanelle	Sunken fontanelle	Bulging or sunken fontanelle	Bulging fontanelle and what day
Became unresponsive/unconscious	Lethargic after a period of normal activity	Drowsy after 3 d of life	Lethargic after a period of normal activity	Become unconscious and which day
-	-	Sunken eyes	-	-
Fever and duration	Fever, onset and duration Cold to touch, onset and duration	Fever and duration	Fever, onset and duration Cold to touch, onset and duration	Fever & onset Cold to touch, onset
Cough & duration	-	Cough	-	Cough and onset
Fast breathing & duration	Fast breathing onset and duration in days	Fast breathing or intermittent breathing	Fast breathing or intermittent breathing	Fast breathing and onset
Stop breathing for long time and start again				
Difficulty breathing & duration	Difficulty breathing, onset and duration	Difficulty breathing onset (immediately, <6h, >6h) and duration Difficulty breathing until death	Difficulty breathing, onset (immediately, <6h, >6h) and duration Difficulty breathing until death	Difficulty breathing & onset -
Chest indrawing	Chest indrawing	Chest indrawing	Chest indrawing	Chest indrawing
Grunting (demonstrate)	Grunting (demonstrate)	Grunting (demonstrate)	Grunting (demonstrate)	Grunting (demonstrate)
	-	Blue colouration Cyanosis	-	-
Stridor (demonstrate)				
Wheezing (demonstrate)				
Nostril flaring	Nostril flaring		Nostril flaring (demonstrate)	Nostril flaring
Pneumonia	**Pneumonia**		Pneumonia	-
			Difficulty breathing until death	-
Local term for diarrhoea	Local term for diarrhoea	Diarrhoea >3 times a day	Local term for diarrhoea	-
	More frequent loose or liquid stools than usual	-	More frequent loose or liquid stools than usual & duration	Did the baby have diarrhoea and onset
More loose or frequent stools than usual	How many stools on the day that the diarrhoea was most frequent	-	-	How many stools per day when diarrhoea was most severe

***Cont.* Table 3.7 - Comparison of Stillbirth and Neonatal Death Questionnaires –Signs of Illnesses**

WHO/CDS/CSR/ISR/99.4 The WHO infant VA: the origin of the modified neonatal version	WHO/JHU/AKU/SNL 11/03/2003	MIRA	Maimwana	WHO 2007
Diarrhoea duration	-	-	-	-
Infant drunk oral rehydratation solution				
Blood in stool	-	Blood or mucus in stool	Blood in stool	Blood in stools?
	Vomit everything	Repeated vomiting	Vomit everything	Vomit and onset
	-	Urine colour	-	How many vomits per day when vomiting was most severe
		Urine quantity (less, normal, more)		
	-	Abdominal distension	-	Abdominal distension and onset
Red or draining umbilical stump	Red ring around umbilicus	Red ring around umbilicus	Red ring around umbilicus	Umbilical redness or discharge
Red and hot areas of skin				
Skin pustules		Skin pustules	Skin pustules	Skin pustules
Yellow eyes	Jaundice (yellow skin)	Yellower than other babies	Skin and eyes yellow	Yellow palms and soles, onset and duration
	-		Ear discharge	-
			Redness of and drainage of pus from the eyes	-
			Bleed from anywhere	-
			Where?	
			Duration of illness (in days)?	-
		Sudden death	Sudden death	-
		Head, chest and abdomen felt cold >2 h before death	-	-
			Any other illness (describe)	-

3.4 - Algorithms

Maimwana's algorithm to guide clinicians in assigning causes of death was the first to be produced. It allowed physicians to choose up to three causes for each death, similar to death certification[158], using the ICD-10 rules. This gave more flexibility in the interpretation of the questionnaires, but potentially made the process less repeatable and reproducible[455;456] (Table 3.8).

For Nepal and Mumbai a single hierarchical algorithm was subsequently developed guiding physicians to a single diagnosis. To ensure consistency in the diagnostic process the algorithm did not allow the coexistence of two diagnoses, for example a death due to prematurity could not be caused by perinatal asphyxia or severe infection, given the age restriction in the definition of asphyxia and infection. Physicians were allowed to use diagnoses not listed in the classification if deemed necessary, however a single cause of death had to be established. The hierarchical order of the algorithm was different from the one used for Malawi: congenital malformation remained the first in the hierarchical order, however prematurity was given priority over asphyxia and was followed by infection and external conditions in Nepal and Mumbai, while in Malawi external conditions preceded asphyxia, followed by prematurity and severe infections (Table 3.8 and 3.9).

Table 3.8 - Algorithm for Primary or Underlying Causes of Stillbirths and Neonatal Deaths for Verbal Autopsy Studies – Malawi

Neonatal Death Algorithm			
Choose up to 3 causes of death following the classification below, if possible use the subclassification			
		Subclassify:	
Congenital anomaly	**1**		
Accident or injury and external conditions	**2**		
Asphyxia	**3**	Associated with obstetric complications	3a
		Unspecified	3b
Immaturity or small for gestational age	**4**		
Infection	**5**	Neonatal tetanus	5a
		Severe sepsis or meningitis	5b
		Pneumonia or respiratory condition	5c
		Diarrhoea or dysentery	5d
		Local infection	5e
Other	**6**		
Unexplained	**7**		

Stillbirth algorithm			
		Subclassify…	
Antepartum or macerated stillbirth	**1**	Congenital anomaly	**1a**
		Accident or injury	**1b**
		Other	**1c**
		Unexplained	**1d**
Intrapartum or fresh stillbirth	**2**	Congenital anomaly	**2a**
		Accident or injury or external conditions	**2b**
		Obstetric complications	**2c**
		Immaturity	**2d**
		Multiple births	**2e**
		Other	**2f**
		Unexplained	**7**

Table 3.9 - Algorithm to Establish the Causes of Stillbirths or Neonatal Deaths from Verbal Autopsy Studies: Nepal and Mumbai

Neonatal Death Algorithm			
Exclude in order…	**Code**	***Subclassify…***	**Code**
Congenital anomaly	**1**		
Immaturity or small for gestational age	**2**	Multiple birth	2a
		Maternal disease	2b
		Obstetric complications	2c
		Unexplained	2d
Asphyxia	**3**	Maternal disease	3a
		Obstetric complications	3b
		Unexplained	3c
Infection	**4**	Neonatal tetanus	4a
		Severe sepsis or meningitis	4b
		Pneumonia or respiratory condition	4c
		Diarrhoea or dysentery	4d
		Local infection	4e
Accident or injury	**5**		
Specific foetal conditions	**6**		
Placental abruption or haemorrhage	**7**		
Other	**8**		
Unexplained	**9**		
Stillbirth algorithm			
Exclude in order…		***Subclassify…***	**Code**
Antepartum or macerated stillbirth		Congenital anomaly	**1**
		Maternal disease	**2**
		Obstetric complications	**3**
		Specific foetal conditions	**4**
		Accident or injury	**5**
		Other	**6**
		Unexplained	**7**
Intrapartum or fresh stillbirth		Congenital anomaly	**1**
		Maternal disease	**2**
		Obstetric complications	**3**
		Specific foetal conditions	**4**
		Multiple births	**5**
		Immaturity	**6**
		Accident or injury	**7**
		Other	**8**
		Unexplained	**9**

3.5 - Data Collection Storage and Management

In the Maimwana study, neonatal deaths were reported by the field interviewers to five monitor and evaluation officers, who were Malawians with secondary school education, experienced in working with local communities. They were trained initially for two weeks on epidemiological surveillance and interviewing techniques. Over the course of the study they received further refresher courses. After completion, the VA questionnaires were checked by a researcher and inconsistencies were clarified with the interviewers. Given the nature of the interviews, interviewers were not asked to return to the families for clarification.

Data were entered by data-entry clerks in a bespoke multi-relational Microsoft Office Access 2003 database. The database contained all the indicators derived from the stillbirth and neonatal VA, the maternal questionnaires, or maternal VA in case of maternal death: therefore it was possible to access data from all possible sources. Data were extracted using an Access query and transferred into Stata 9 for analysis[457].

The open narrative from Malawi were translated from Chichewa to English by a nurse fluent in both languages and entered into a word file. They were all read by the author and coded using a pre-defined list of clinical signs derived from the cause of death classification and definitions. Every time a clinically recognisable sign or symptom was reported it would be added to the coding list[458-460] (Table 3.10). The open histories were used in the probabilistic analysis of the Malawi questionnaires.

Table 3.10 - Open Histories Coding

Maternal conditions	Newborn
Anaemia	Fresh stillbirth
Sexually transmitted diseases, including syphilis	Macerated stillbirth
Fever	Congenital malformation
HIV	Cord around neck
Malaria	Malpresentation
Epilepsy	Resuscitation at birth
Diabetes	Large infant
Malnutrition	Twin
Tuberculosis	Difficulty breathing at birth
Other severe acute infections	Difficulty feeding at birth
Jaundice	Not crying at birth
Dysuria in pregnancy	Convulsions or spasms
Previous miscarriages/abortions	Prematurity/small infant
Accidents	Difficulty breathing occurring after birth
	Cough
	Respiratory distress
Labour and Delivery	Grunting/nasal flaring
Absence of foetal movements	Chest indrawing
Prolonged labour	Gasping
Obstructed labour	Difficulty feeding occurring after birth
Prolonged rupture of membranes	Poor/weak sucking
Green/smelly liquor	Fever/ hypothermia
Malpresentation/ cord prolapse	Jaundice
Assisted delivery (C section/ instrumental delivery, pulling on baby or pushing on abdomen)	Inconsolable crying
Antepartum or postpartum haemorrhage	Becoming unconscious/drowsy
High blood pressure/blurred vision	Umbilical redness/discharge
Swollen ankles	Diarrhoea
Maternal convulsions	Vomiting
Retained placenta	Distended abdomen
Ruptured uterus	Bleeding
	Not passing stools/urine

Similar to the data collection in Malawi, in Nepal stillbirths and neonatal deaths were reported by field interviewers to 9 senior field coordinators, who were all Nepali, recruited from the local communities and had been trained in verbal autopsy techniques.

Data were checked locally by the coordinators and centrally by the data entry team and entered into a relational database (Microsoft SQL server 7.0). Relevant data were subsequently extracted into Stata 9 for analysis by one of the principal investigators of the study[457].

VA data from the City initiative for Newborn Health in Mumbai were also collected by experienced supervisors, all from Mumbai and trained in VA techniques. Data collected were checked and entered into a Microsoft Access 2003 database, extracted into Stata 9 [457] and elaborated locally into a format suitable for the present study.

Open histories from Makwampur and Mumbai were available only to the physicians to establish diagnoses. They were not available in English for coding and therefore were not included in the probabilistic modelling (Table 3.11).

Table 3.11 - Summary of Data Collection Procedures in the Different Studies

Surveillance system	Identification of pregnant women	Questionnaires	
		Maternal & infant Questionnaires	Verbal autopsies
Maimwana	Local women enumerators visited each WCBA every month and followed up women with 3 consecutive missed periods	Field interviewers delivered the questionnaires: -1 month after birth -6 months after birth or alerted the Monitor and Evaluation Officers in case of infant or maternal death	5 Monitor and Evaluation Officers delivered the maternal questionnaire and VA interview
Makwampur	As above	Cluster interviewers delivered the pre delivery and the post delivery questionnaires: 7 months gestation 1 month after birth or alerted the field coordinators in case of infant or maternal death	9 field coordinators delivered the maternal questionnaire and VA interview
Mumbai	As above	Field interviewers delivered questionnaire 6 weeks after birth or alerted the supervisors in case of infant or maternal death	Supervisors delivered the maternal questionnaire and VA interview

3.6 - Data Interpretation and Physician Review

Questionnaires, classifications and algorithms used in this thesis were written with the plan of using physicians' review for analysis.

3.6.1 Maimwana - Malawi

The original verbal autopsy questionnaires were photocopied and two local experienced paediatricians and principal investigators to the project read 161 of 337 VA used in this thesis in the order that they received them from the project data coordinator. They read them separately and used the stillbirth and neonatal death classification and algorithm above to ascribe the causes of death on a standard proforma. Where discordance in diagnoses emerged between the physicians, they met and discussed the cases. If they reached an agreement the diagnosis was established otherwise the cause of death was considered indeterminate[461]. They could ascribe up to 3 causes of death, an immediate (direct or primary), an underlying and an associated cause of death according to the rules of the ICD-10. The agreement between physicians was tested using *Kappa (κ)* statistic in STATA version 9[457].

Data collected from physician review were added to the main Microsoft Access database for analysis. The remaining 157 VA, not yet reviewed by the Malawian physicians were interpreted by two British paediatricians with experience of working in Africa (Dr Helen Payne and Dr Adam Irwin). This choice was made to expedite the diagnostic process. The physicians were briefed in the use of the stillbirth and neonatal death classification and were given the algorithm and explained the process of interpreting the questionnaires. They also had available the open history translated into English. As with the Malawian paediatricians they could give up to 3 causes of death for each questionnaire and were encouraged to

do so. If the diagnoses amongst the 2 physicians were discordant, a third paediatrician (the investigator) read the questionnaires and established the diagnoses. Kappa statistic was used to measure agreement between the two British physicians.

3.6.2 MIRA – Nepal and Sneha - Mumbai

In Nepal all the VA were read separately by two local paediatricians and ascribed a single cause of death for each infant using the hierarchical algorithm (Table 3.8). Where there was a difference in the final diagnosis, a third paediatrician, principal investigator to both projects, experienced in interpreting verbal autopsies established the final diagnosis. In Mumbai, five local paediatricians separately interpreted a set number of verbal autopsy questionnaires. They were able to express a single diagnosis for each infant according to the algorithm used in Nepal. A larger number of doctors was chosen to expedite the process of data interpretation. The questionnaires were distributed in such a way that each was given to at least two different paediatricians. As for the Nepal data, if there was discordance in the interpretation of the VA data, the same experienced paediatrician decided on the final diagnosis. Kappa statistic was used to calculate agreement between physicians interpreting the VA data.

3.7 - Bayesian Probability

Comparing diagnoses obtained by physician's review in these three studies presented some challenges given the different data collection tools and algorithmic rules used. It was therefore difficult to establish whether differences in outcome between sites were due to the VA interpretation or linked to real diversity in these populations.

This thesis adapted a computerised model based on Bayesian probability theory (InterVA) to interpret stillbirths and neonatal deaths.

3.8 - Bayesian Theory Applied to Verbal Autopsy Interpretation: the InterVA Model

InterVA is an application of Bayesian theory to interpret verbal autopsy (VA) data for all age groups. The aim of the InterVA model is to provide a simple method of interpreting VA questionnaires for all ages in a standardised way[237].

Version 3 of the InterVA model discriminates between 34 causes of death (Table 3.12). It uses a series of matrix-probabilities p(θ) set *a priori* and a number of indicator-probabilities p(data/θ). The matrix probability for a set number of causes of death corresponds to the CSMF in the population for that cause of death established according to a semi-quantitative scale from 0 (virtually never associated to a specific cause of death) to 100% (almost always to the same cause of death) (Table 3.13)[462]. The probabilities are set by an expert panel of physicians. For example tetanus is likely to be associated with a recent injury (probability 20%), is almost always associated with rigidity and locked jaw (probability 100%) but is unlikely to be associated with an abdominal mass (probability 0.5%).

Matrix probabilities are fixed for all causes of death with the exception of deaths due to malaria and HIV. For malaria and HIV it is necessary to specify whether the prevalence of the disease is high or low before entering data into the programme. This is because the model has been developed to suit all age groups

in different geographical settings, therefore the possibility of changing the a priori probability of malaria and HIV for older infants, children and adults improved the performance[269].

Table 3.12 - InterVA List of Possible Causes of Death

1	Transport Accidents	13	Tetanus	25	Acute respiratory diseases (not pneumonia)
2	Homicide	14	Tuberculosis	26	Chronic respiratory diseases
3	Poison	15	Other acute infections	27	Malignancy
4	Suicide	16	Other chronic infections	28	Kwashiorkor
5	Drowning	17	Pneumonia	29	Diabetes
6	Other fatal accidents	18	Diseases of the nervous system	30	Sickle cell disease
7	HIV/AIDS	19	Stroke	31	Maternal cause
8	Malaria	20	Disease of the digestive tract	32	Congenital malformation
9	Meningitis	21	Liver diseases	33	Perinatal causes
10	Measles	22	Diseases of the kidneys and urinary tract	34	Prematurity
11	Diarrhoea	23	Acute cardiac diseases		
12	Bloody diarrhoea	24	Chronic cardiac diseases		

The presence of an indicator (Table 3.14) modifies the matrix probability making a diagnosis more or less likely for each case, according to the Bayes' formula.

In the InterVA model the first nine indicators refer to the age of death and establish whether the deceased was pregnant. The subsequent five questions refer to the length of the illness that led to death and the season in which death occurred. Then a series of indicators (91) lists signs and symptoms surrounding death. Once age of the deceased is specified, the relevant indicators for the different age groups are selected, making the data entry process quicker (Figure 3.3).

Table 3.13 - Probability Table

Description	Probability
Almost never	0
Uncommon	0.002
	0.005
	0.01
Moderately often	0.02
	0.05
	0.1
Frequently	0.2
	0.5
Almost always	1

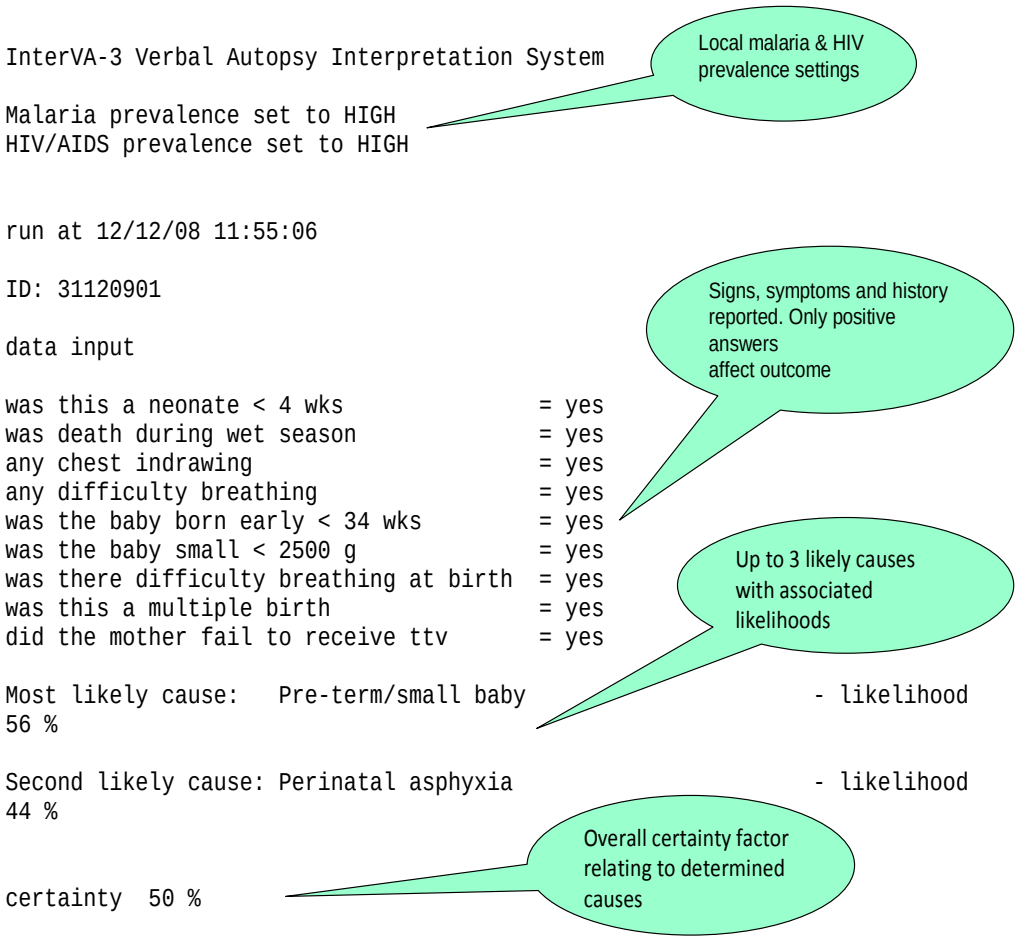
Adapted from [237]

A programme written for Fox Pro (Microsoft Visual Fox Pro 9.0 2004) allows entering data from a single VA or from batches of data for a large number of VA, providing the order of the indicators is compatible. The output is available within a few minutes; with a rate of approximately 1 case every 2 seconds and consists of a list of a maximum of three causes of death with respective probabilities and a certainty factor calculated as the sum of the probabilities for the first three causes divided by the number of causes. The model was programmed in such a way that only the cause of death with a probability higher than the square route of the baseline probability was listed in the outcome. More than one cause of death was reported if there was a difference of less than 50% between the causes of death with highest probability and the subsequent one. For example, if the first cause of death had probability 90% and the second 50% they were both shown by the model, however if the first had a probability of 90% and the second of 30% only the first one only was available for analysis. The model also had a series of conditions to be met for each cause of death to be selected. If the model had insufficient information to assign a cause of death the cause of death remained indeterminate. The InterVA tool is available at http://www.interva.net

Table 3.14 - InterVA: List of Indicators

was this an elder 65+ years	was this an adult 50-64 years	was this a female 15-49 years	was this a male 15-49 years	was this a child 5-14 years
was this a child 1-4 years	was this an infant 4 wks-1 yr	was this a neonate < 4 wks	was she pregnant at death	did pregnancy end within 6 wks
did final illness last at least 3 wks	did final illness last < 3 weeks	was death sudden or unexpected	was death during wet season	was death during dry season
was s/he in a transport accident	did s/he drown	had s/he fallen recently	any poisoning, bite, sting	was s/he a known smoker
any obvious recent injury	was s/he known to drink alcohol	any suggestion of homicide	any convulsions or fits	any diagnosis of epilepsy
was the fontanel raised	was the fontanelle /eyeball sunken	any headache	was there paralysis on both sides	any paralysis/weakness on 1 side
any stiff neck	any oral candidiasis	any rigidity/lockjaw	abnormal hair colouring	any coughing with blood
any chest pain	was there a cough for > 3 wks	was there a cough for up to 3 wks	any productive cough	any rapid breathing
any breathlessness on exertion	any breathlessness lying flat	any chest indrawing	any difficulty breathing	any breast lump or lesion
any wheezing	any cyanosis	any abdominal mass	any abdominal pain	any diarrhoea with blood
any vomiting with blood	any acute diarrhoea (< 2wks)	any persistent diarrhoea (2-4 wks)	any chronic/recurrent diarrhoea (4+w)	any abdominal swelling
any vomiting	any yellowness/jaundice	any abnormality of urine	any urinary retention	any haematuria
any swelling of ankles/legs	no bilateral swelling of ankle	any skin lesions/ulcers	any rash (non-measles)	any herpes zoster
any measles rash	any excessive night sweats	any excessive water intake	any excessive urination	any excessive food intake
any acute fever	any persistent fever (> 2 wk)	any enlarged/swollen glands	any facial swelling	was there a coma > 24hrs
any anaemia/paleness	any drowsiness	any delayed/regressed development	any diagnosis of asthma	any diagnosis of diabetes
any diagnosis of heart disease	any diagnosis of HIV/AIDS	been discharged from hospital very ill	any suggestion of suicide	any surgery just before death
any diagnosis of TB	was s/he adequately vaccinated	any diagnosis of liver disease	any diagnosis of cancer	any diagnosis of kidney disease
any weight loss	any diagnosis of stroke	any diagnosis of measles	any diagnosis of haemoglobinopathy	any diagnosis of malaria
any delivery complications	Heavy bleeding before/after delivery	was there prolonged labour > 24 hrs	were there convulsions at delivery	was the baby born early < 34 wks
was the baby small < 2500g	was there difficulty breathing at birth	any congenital malformations	was this a multiple birth	any umbilical infection

Figure 3.3 - Example of InterVA Output



3.9 - Adaptation of InterVA to Perinatal and Neonatal Deaths

The original InterVA model did not include stillbirth amongst the causes of death. To establish whether the original InterVA model was adequate to assign causes of neonatal death, the 46 live births from the Malawian dataset with available physician diagnoses were compared with InterVA results. Data were extracted both from the questionnaires and the open histories and entered into the InterVA version 3 model.

There was poor agreement between CSMF using the two methods. InterVA attributed 26% of diagnoses to prematurity, compared with 17% according to physician review, 56% to asphyxia compared with 30% and 8% to severe infections compared with 46% (Table 3.15). At individual level *Kappa* was 13 (CI 0.023-0.3).

Physician review was used for comparison as it is a widely accepted method of establishing diagnosis using verbal autopsy in the literature[463-465].

Table 3.15 - Causes of Death for Livebirths using the Original InterVA Model

CSMF	Physician diagnoses (%)	InterVA (%)	Difference in proportions (95%CI)
Congenital anomalies and inherited disorders	3	0	0.03 (-0.02-0.08)
Immaturity/small for gestational age	17	26	**-0.09 (-0.3-0.08)**
Asphyxia	30	56	**-0.3 (-0.46- -0.06)**
Severe infection	46	8	**0.4 (0.2-0.5)**
External conditions	0	0	0
Other	0	0	0
Unexplained	4	10	-0.06 (-0.2-0.04)
Total	100	100	

Causes of death:

The exclusion of stillbirths was an important limitation of InterVA version 3 when the model was applied to the perinatal period for three main reasons. Firstly the number of stillbirths globally is close to the number of neonatal deaths[466-468] and it is an important contributor to perinatal mortality. Secondly preventative interventions to reduce the number of stillbirths exist, and if VAs are needed to provide data to monitor

interventions and guide policy, it is important to include stillbirths. Ideally it is necessary to separate fresh and macerated stillbirths as different interventions are required to tackle the two problems. Finally, if the VA had to be sorted in advance to separate stillbirths from neonatal deaths, interpretation biases could be introduced making the tool less comparable between sites and over time. Manually reading, sorting and interpreting questionnaires requires time and skill and limits the use of verbal autopsies in surveys. To overcome these limitations it was decided, after some debate, to adapt the InterVA model to include stillbirths.

The main differences between InterVA version 3 and the modified version presented in this thesis were the addition of 2 causes of death: fresh and macerated stillbirths with their respective *a priori* probabilities and the adjunct of 8 new indicators.

Eight New Indicators:

New indicators were added to allow accurate cause of death ascription for the perinatal and newborn period, particularly with regard to fresh stillbirth and macerated stillbirths, neonatal tetanus and perinatal asphyxia. The indicators added were: “was there no cry/move/breath at birth?”, “Was infant's skin puffy/mushy at birth?”, “did infant have arched back after 2 days?”, “did the infant stop sucking after day 3?”, “did the mother fail to receive tetanus toxoid vaccination?”, “did the infant die on day 1?”, “did convulsions happen on day 1?”, and “did the infant fail to cry at birth?”. As the model uses only affirmative data (“yes” answers to the indicators) therefore some of the indicators are formulated using a double negation.

The indicators were added by the author on the basis of clinical experience and data on the sensitivity and specificity of algorithms published in the perinatal VA literature[208;469-471].

More in detail, the question distinguishing between livebirths and stillbirths “was there no cry/move/breath at birth?” was chosen as it is widely used in the verbal autopsy literature and it is included in the most recent Verbal Autopsy Standards[158]. Similarly the distinction between fresh and macerated stillbirths: “Was infant's skin puffy/mushy

at birth?" was also derived from the literature: Edmond defines macerated stillbirth as "skin and tissues pulpy or disintegrating" and fresh stillbirths as "skin and tissue intact"[472].

Three indicators were added to ensure the diagnosis of neonatal tetanus was possible: "did infant have arched back after 2 days?", "did the infant stop sucking after day 3?", "did the mother fail to receive tetanus toxoid vaccination?". A combination of these 3 questions plus convulsions or spasms after day 2 of birth have been used in previous studies[158;208;473-476].

The cut off of 2 days for the diagnosis of neonatal tetanus was chosen as it had been used by Marsh in Pakistan, Edmond and the WHO neonatal VA questionnaires both in 2003 and in the most recent 2007 version[158;477-480], Bang however used a cut off of 4 days[208]. The WHO included the inability to open the mouth as one of the diagnostic criteria for neonatal tetanus[158]: this was not included to keep the questionnaire short and because in the Malawi dataset most infants not feeding were described by the mothers as unable to open their mouth even in a context where neonatal tetanus had been eradicated. Finally Kalter using only the criteria of age, convulsions, back arching and difficulties sucking from day 2 and obtained a specificity for this algorithm of 89%[481].

Time to symptoms' occurrence or death ("did convulsions happen on day 1?" and "did the infant die on day 1?") were included to separate birth asphyxia from neonatal infections as suggested by the literature: Bang used a cut off of 3 days for the appearance of convulsions and drowsiness to diagnose sepsis[208]. Marsh and the WHO Verbal Autopsy Standard use death after day one in the algorithm of neonatal sepsis[158;482]. Edmond for neonatal asphyxia included the criterion of time (within the first day) for two symptoms: convulsions and not being able to suck or breathe[483]. In the context of InterVA the question "Did the infant stop sucking after day 3?" also discriminates asphyxia/prematurity from sepsis.

"Did the infant fail to cry at birth?" was added as it is used in previous algorithms for perinatal asphyxia[484;485]. No questions about the ability to suck at birth were added in the interest of keeping the questionnaire short.

The tool was trialled with the first 100 VA available from the Malawi dataset and compared with physician review. Physician review was used as a model to adapt InterVA for the perinatal and newborn period, as no death certificates were available and only 4 infants died in a health facility. Therefore validating the probabilities with hospital records was not possible. The probabilities chosen for the new indicators were ascribed using the semi-quantitative scale in Table 3.13. Indicators were associated with a specific diagnosis "frequently" (probability between 0.1-0.5) if they were part of algorithms for that diagnosis and rarely (probability between 0.002-0.01) if they were not part of existing algorithms but could co-exist by chance. For example, fever is a relatively common symptom and could be associated by chance with death due to accident, and this was assigned a probability of 0.002. Probabilities of 1 or 0 were used very rarely. For example the probability of being a stillbirth was 1 if the answer to the question "was not able to move, breathe, cry at birth" was yes, and 0 if any of the questions referring to signs of live had a positive answer.
The first change to InterVA to reach the modified version presented in this thesis was to add the new causes of death and the 8 indicators with their probabilities. The CSMF of this first version are shown in Table 3.17.

Subsequently the probabilities of 15 existing indicators were changed in correspondence with causes of death pertinent to the neonatal period (perinatal asphyxia, prematurity and pneumonia). The changes were introduced stepwise and compared with the existing CSMF obtained by physician review. The final probability used are shown in table 3.17. The indicators' probabilities in correspondence with perinatal asphyxia were reduced. The probabilities of indicators related to sepsis and meningitis were increased. The occurrence of complications during delivery was increased given the frequency of complicated deliveries amongst the neonatal deaths encountered.

After these first modifications the CSMF obtained with the new indicators was compared with the CSMF obtained by physician review: the proportion of prematurity was unrealistically low at 2% of causes of death (Table 3.16 and 3.17). This was also very low when compared with the available data from VA studies. Studies from African, Asian, Southern Pacific and Latin American countries were reviewed and considered if they reported the incidence of neonatal sepsis, perinatal asphyxia, prematurity, congenital malformations, neonatal tetanus and stillbirths (fresh and macerated)[198;486-507]. The percentages of deaths attributed to the different causes of death varied widely. Neonatal sepsis was on average 24% of deaths (range 4-63%), perinatal asphyxia 24% (range 3-54%), prematurity 24% (range 7-50%), congenital malformation 6% (range 0-22%), diarrhoea 4% (range 0-6%) and neonatal tetanus 7% (0-18%) the remaining were either attributed to other causes or were left indeterminate. The wide ranges reflected probably the different study populations: for example a study in Gaza of 68 neonatal deaths had the highest rate of congenital abnormalities (22%)[508], while one in Pakistan of 689 newborns had the highest rate of neonatal tetanus[60]. The CHERG projected figures for causes of death in the perinatal and neonatal period were: Prematurity 28%, neonatal sepsis 26%, neonatal tetanus 7%, Diarrhoea 3%, asphyxia 23% congenital malformation 7%[509]. Stillbirths represented about 50% of all perinatal deaths in several studies[510-514].

CSMF obtained using InterVA are dependant on indicator probabilities, but more so on matrix probabilities which are set for the entire population and change by age groups. The next modification for the new version of InterVA involved changing the matrix probabilities for newborns. These changes were done stepwise using the probability scale in Table 3.13 and compared with the first 100 VA interpretation using physician review and available literature. The matrix probabilities were changed keeping into account the probabilities already fixed for the whole population (Table 3.16 Baseline Population). For acute infections and pneumonia the probability was increased by one log, while for asphyxia it was decreased by one. The diagnosis of diarrhoea was reduced by 3 logs as diarrhoea was considered an extremely rare cause of neonatal death, as

indicated in the literature and in the VA interpreted by physician review. In the original version diarrhoea in the newborn had the same a matrix probability than the population as a whole. When the ranking of causes of death was the same between physician review and InterVA and the proportion of the causes of death were within the ranges described in the literature, the model was considered satisfactory.

Table 3.16 – A Priori probabilities in the different versions of the Modified InterVA model

	Occurrence	Accident	Acute infections	Prematurity	Tetanus	Diarrhoea	Meningitis	Pneumonia	Asphyxia	Congenital Malformation
Baseline population		0.002	0.005	0.002	0.002	0.05	0.005	0.05	0.002	0.002
Original	0.02	0.005	0.2	0.5	0.05	0.05	0.2	0.2	0.5	0.5
1st	0.02	0.005	0.2	0.5	**0.02**	**0.02**	0.2	0.2	**0.2**	0.5
2nd	0.02	0.005	0.2	0.5	**0.02**	**0.01**	0.2	**0.5**	**0.2**	0.5
3rd	0.02	0.005	**0.5**	0.5	**0.02**	**0.005**	0.2	**0.5**	**0.2**	0.5
4th	0.02	0.005	**0.5**	0.5	**0.02**	**0.005**	0.2	**0.5**	**0.2**	0.5
Current	0.02	0.005	**0.5**	0.5	**0.01**	**0.005**	0.2	**0.5**	**0.2**	0.5

Table 3.17 – Comparison of CSMF between different version of the modified InterVA

CSMF	Physician Diagnoses	InterVA Adding New Indicators	InterVA Changing Existing Indicator Probabilities	Modified Version Changing Matrix Probabilities
Congenital anomalies and inherited disorders	3	1	1	1
Immaturity/small for gestational age	10	2	2	6
Asphyxia	16	29	13	14
Severe infection	19	11	23	26
Tetanus	0	2	1	0
Fresh Stillbirth	40	40	44	40
Macerated Stillbirths	8	16	15	8

Ultimately the computer programme used 35 indicators including the age of death, excluding the ones stating the season of death and assuming all neonatal deaths were acute and sudden. As for the causes of death the principle was to keep the InterVA tool as close as possible to the original version to avoid altering the performance of the model for other age groups previously tested[237;269;515;516].

Table 3.18 - Comparison between "A Priori" Probabilities from the Original and Modified InterVA Model

	Occurrence		Accident		Infection		Prematurity		Tetanus		Diarrhoea		Meningitis		Pneumonia		Perinatal asphyxia		Congenital		Fresh Stillbirth	Macerated Stillbirth
	New	Original	New	Original	New	Original	New	Original	New	Original	New	Original	New	Original	New	Original	New	Original	New	Original	New	**New**
Expected			0.002	0.002	0.005	0.005	0.002	0.002	0.002	0.002	0.05	0.05	0.005	0.005	0.05	0.05	0.002	0.002	0.002	0.002	0.002	**0.002**
Was the a newborn	0.02	0.02	0.005	0.005	**0.5**	**0.2**	0.5	0.5	**0.01**	**0.05**	**0.005**	**0.05**	0.2	0.2	**0.5**	**0.2**	**0.2**	**0.5**	0.5	0.5	**0.5**	**0.02**
was there a cough for up to 3 wks	0.1	0.1	0.1	0.1	0.1	0.1	**0.002**	**0.1**	0.1	0.1	0.1	0.1	0.1	0.1	0.5	0.5	**0.002**	**0.1**	0.1	0.1	**0**	**0**
any rapid breathing	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.2	0.1	0.1	0.5	0.5	**0.1**	**0.005**	0.1	0.1	**0**	**0**
any chest indrawing	0.002	0.002	0.002	0.002	0.002	0.002	**0.05**	**0.002**	0.002	0.002	0.002	0.002	0.002	0.002	**0.5**	**0.02**	**0.005**	**0.002**	0.002	0.002	**0**	**0**
any cyanosis	0.002	0.002	0.002	0.002	0.002	0.002	0.005	0.005	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	**0.05**	**0.5**	0.002	0.002	**0**	**0**
any diarrhoea with blood	0.005	0.005	0.005	0.005	**0.02**	**0.005**	0.005	0.005	0.005	0.005	0	0	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	**0**	**0**
any yellowness/jaundice	0.005	0.005	0.005	0.005	**0.01**	**0.005**	0.01	0.01	0.005	0.005	0.005	0.005	0.005	0.005	**0.05**	**0.005**	**0.002**	**0.005**	0.005	0.005	**0**	**0**
any acute fever	0.2	0.2	0.2	0.2	0.5	0.5	0.2	0.2	0.2	0.2	0.5	0.5	0.5	0.5	0.5	**0.5**	**0.05**	**0.2**	**0.005**	**0.2**	**0**	**0**
any drowsiness	0.1	0.1	0.1	0.1	0.1	0.1	**0.005**	**0.1**	0.2	0.2	0.1	0.1	0.5	0.5	**0.2**	**0.1**	0.1	0.1	0.1	0.1	**0**	**0**
any delivery complications	**0.005**	**0.002**	0.002	0.002	0.01	0.01	0.002	0.002	**0.002**	**0.005**	0.002	0.002	0.002	0.002	0.002	0.002	**0.2**	**0.5**	0.002	0.002	**0.2**	**0.005**
Heavy bleeding before/after delivery	0.002	0.002	0.002	0.002	0.05	0.05	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	**0.2**	**0.5**	0.002	0.002	**0.2**	**0.002**
was there prolonged labour > 24 hrs	0.002	0.002	0.002	0.002	0.01	0.01	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	**0.2**	**0.5**	0.002	0.002	**0.5**	**0.002**
was the baby born early < 34 wks	0.002	0.002	0.002	0.002	0.02	0.02	1	1	0.002	0.002	0.002	0.002	**0.05**	**0.002**	**0.05**	**0.01**	**0.05**	**0.5**	**0.01**	**0.002**	**0.002**	**0.005**
was the baby small < 2500 g	0.002	0.002	0.002	0.002	0.02	0.02	**0.5**	**1**	0.002	0.002	0.002	0.002	**0.05**	**0.002**	**0.05**	**0.01**	**0.05**	**0.5**	**0.01**	**0.002**	**0.002**	**0.005**

Cont. ***Table 3.17 - Comparison between "A Priori" Probabilities from the Original and Modified InterVA Model***

	Occurrence		Accident		Infection		Prematurity		Tetanus		Diarrhoea		Meningitis		Pneumonia		Perinatal asphyxia		Congenital		Fresh Stillbirth	Macerated Stillbirth
was there difficulty breathing at birth	0.002	0.002	0.002	0.002	0.002	0.002	**0.1**	**0.5**	0.002	0.002	0.002	0.002	0	0	**0.002**	**0**	**0.5**	**1**	0.002	0.002	**0**	**0**
any congenital malformations	0.002	0.002	0.002	0.002	0.002	0.002	0.05	0.05	0.002	0.002	0.002	0.002	0.002	0.002	**0.002**	**0.005**	0.002	0.002	1	1	**0.05**	**0.02**
was this a multiple birth	0.005	0.005	0.002	0.002	**0.005**	**0.002**	0.2	0.2	0.002	0.002	0.002	0.002	**0.005**	**0.002**	**0.01**	**0.005**	**0.005**	**0.05**	0.002	0.002	**0.005**	**0.02**
was there no Cry/move/breath at birth	**0.002**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**1**	**1**
Was infant's skin puffy/mushy at birth	**0.002**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**0**		**0**	**1**
did infant have arched back after 2 days	**0.01**		**0.002**		**0.002**		**0.002**		**0.5**		**0.002**		**0.05**		**0.002**		**0.002**		**0.002**		**0**	**0**
did the infant stop sucking after day 3	**0.002**		**0.002**		**0.2**		**0.002**		**0.2**		**0.002**		**0.5**		**0.5**		**0.002**		**0.002**		**0**	**0**
did the mother fail to receive TTV	**0.005**		**0.002**		**0.002**		**0.002**		**0.05**		**0.002**		**0.002**		**0.002**		**0.002**		**0.002**		**0.002**	**0.002**
did the infant die on day 1	**0.005**		**0.002**		**0.05**		**0.02**		**0**		**0.002**		**0.02**		**0.02**		**0.5**		**0.2**		**0.5**	**0.5**
did convulsions happen on day 1	**0.002**		**0.002**		**0.05**		**0.002**		**0**		**0**		**0.05**		**0.002**		**0.5**		**0.002**		**0**	**0**
did the infant fail to cry at birth	**0.005**		**0.002**		**0.05**		**0.1**		**0.002**		**0.002**		**0.05**		**0.05**		**0.5**		**0.002**		**0**	**0**

3.9.1 Adaptation to the InterVA Format

Not all the information collected from the study questionnaires was used in the probabilistic analysis, as InterVA used a restricted number of indicators. Therefore the data extracted from the different studies in STATA spreadsheets were transferred manually to the InterVA format. For some indicators this process involved simply a change in the order of the indicator to suit the format of InterVA; for others it involved a process of interpretation of the information derived from the questionnaires and condensing data from several questions to a smaller number of indicators (Table 3.18). The fact that the InterVA programme allowed only affirmative answers to change the matrix probability required interpretation of questions with multiple answers. Strict standardised criteria were established by the author, to systematise this process. Data entry into Fox Pro was done using Stat Transfer 9 (2009 Circle Systems, Inc). Missing data, like negative answers, were not included in the model.

All deaths were considered for the purpose of InterVA data entry as having occurred suddenly within the first 28 days of life. The question about presence of bruising at birth was not interpreted as “recent injury”. The InterVA indicator for rigidity and locked jaw was not used as a large number of infants were considered unable to open their mouth if they had a generic feeding difficulty, while in the InterVA model rigidity and locked jaw referred specifically to spasms associated with tetanus. Any sign of respiratory distress such as grunting or nasal flare was entered as difficulty in breathing. Difficulties breathing started at birth (specified in the questionnaire as difficulties breathing immediately at birth for the Malawi and Nepal questionnaire and in the first day for the Mumbai database) were entered as “born not breathing” while difficulties in breathing that arose after birth (not immediately after birth and after the first day in Mumbai) were entered as “difficulty in breathing”. Both hyper or hypothermia were entered as “fever”. “Drowsiness” was interpreted as drowsiness developing in a previously well

infant. Delivery complications included: any abnormality during delivery, duration of labour over 24 hours, a presenting part other than the head, any type of delivery different from spontaneous vaginal delivery and moderate or severe vaginal bleeding. Infants "born early" included all infants with a gestational age <33 weeks or ≤8 months or simply born early according to the questionnaire. Infants "born small" included all infants with birth weight <2500g or, if weight was not available, infant small or very small at birth according to their mother's opinion. All congenital malformations were entered irrespective of their description. Failure to receive tetanus toxoid vaccine was defined as having fewer than two injections in the current pregnancy or fewer than 5 injections in the mother's lifetime. Convulsions occurring on day 1 were all convulsions occurring within the first 24 hours from birth. The indicator of failure to cry at birth referred to infants that were able to breathe or move at birth but failed to cry.

In MIRA, stillbirths were derived from the question about whether the infant was a stillbirth, as the question asking whether the "infant was able to breathe or move or cry even a little at birth" were not an available in the dataset. There were no questions in the database directly assessing the presence of a macerated stillbirth, such as any reference to macerated skin or any attempt to establish whether the infant was dead before labour, therefore macerated stillbirths were not evaluated.

Table 3.19 – Conversion of categorical to binary data from Questionnaires to InterVA Indicators

InterVA question	Malawi	Nepal	Mumbai	InterVA
did final illness last < 3 weeks?	The answer to this question was yes for all neonatal deaths			
was death very sudden or unexpected?	The answer to this question was yes for all neonatal deaths			
was death during wet season?	Not used			
was death during dry season?	Not used			
Was s/he in a transport accident	From Open History	Not used	Did the baby have any injury or accident? **Motor vehicle**	Yes
Did s/he drown	From Open History	Not used	Did the baby have any injury or accident? **Drowning**	Yes
Had s/he fallen	From Open History	Not used	Did the baby have any injury or accident? **Fall**	Yes
Any poisoning, bite, sting	From Open History	Not used	Did the baby have any injury or accident? **Poisoning OR Bite/sting from venomous animal**	Yes
any convulsions or fits?	Did the baby have any convulsions/fits? **Yes**			Yes
was the fontanel raised?	How did the baby's fontanel look like? **Bulging up**		Did the baby have a bulging fontanel? **Yes**	Yes
was the fontanel or eyeball sunken?	What did the baby's fontanel looked like? **Sunken**		Not used	Yes
any rigidity/lockjaw?	Not used in the Malawi dataset, as babies with feeding difficulties were said not to be able to open their mouth	Could the baby open his mouth? **No**		Yes
was there a cough for up to 3 wks?	From open history data	Not used		Yes
any rapid breathing?	What difficulty in breathing? **Fast breathing**		Did the baby have fast breathing? **Yes**	Yes
any chest indrawing?	Was there chest indrawing? **Yes**			Yes

Cont Table 3.18 – Conversion of categorical to binary data from Questionnaires to InterVA Indicators

InterVA question	Malawi	Nepal	Mumbai	InterVA
any difficulty breathing?	Did the baby ever had difficulty in breathing? **Yes AND** when did the difficulty start? **"Not immediately but within 6 hours OR more than 6 hours after birth"** **OR** What was the difficulty? **Intermittent breathing** **OR** was there grunting? **Yes** **OR** was there nostril flare? **Yes** **OR** did the baby have pneumonia? **Yes**		During the illness did the baby have difficulties in breathing? **Yes AND** when did the difficulty start? A**fter >1 day** **OR** did the baby have grunting? **Yes** **OR** did the baby's nostril flare with breathing? **Yes** **OR** did the baby ever stop breathing for a long time and start again? **Yes** **OR** did the baby have pneumonia? **Yes**	Yes
any cyanosis?	From open history	Not used	During the illness did the baby turn blue? **Yes**	Yes
any abdominal mass?	From open history	Not used		Yes
any diarrhoea with blood?	Was there blood (or mucous) in the (loose or liquid) stool? **Yes**			Yes
any acute diarrhoea (< 2wks)?	Did the baby have diarrhoea? **Yes**		Did the baby have more frequent liquid stools than usual? **Yes** **OR** did the baby have diarrhoea? **Yes** **OR** Did the baby have frequent loose or liquid stools? **Yes**	Yes
any abdominal swelling?	From open history	Not used	Did the baby have any abdominal distension? **Yes**	Yes
any vomiting?	Did the baby vomit everything? **Yes**			Yes
any yellowness/jaundice?	Were the baby's skin and eyes very yellow? **Yes**			Yes
any skin lesions/ulcers?	Did the baby have any pustules on the skin? **Yes**		During the illness, were there any of the following on the baby's skin? Any of: **Boils,** **Blisters** **Single large area of pus** **Redness with swelling**	Yes
any rash (non-measles)?	Not used			
any acute fever?	Did the baby have fever? **Yes** **OR** Did the baby feel cold? **Yes**			Yes
any anaemia/paleness?	Not used			Yes
any drowsiness?	Did the baby became drowsy or unconscious when had been normal before ? **Yes**		During the illness did the baby became unresponsive or unconscious or very sleepy? **Yes** **OR** did the baby became very lethargic after a period of normal activity? **Yes**	Yes

Cont Table 3.18 – Conversion of categorical to binary data from Questionnaires to InterVA Indicators

InterVA question	Malawi	Nepal	Mumbai	InterVA
any delivery complications?	How was the baby delivered? **Any answers >1 (TBA/Relative/friend pulled the baby or pushed on the tummy, health worker used forceps, caesarean section)** **OR** How long did the labour last? **Answer 5 (>24 hours)** **OR** Which part of the baby came out first? **Any answer >1 (buttock, hand/foot/cord)**	How was the baby delivered? **Any of:** **Manually** **Forceps** **Operatively** **OR** Which part came out first? **Any of:** **Buttock** **Hands/foot/cord**	Which part of the baby came out? **Any of:** **Bottom,** **Feet,** **Hand or arm,** **Caesarean** **OR** Did any of these problems occur during delivery? **Any of:** **High blood pressure measured by health worker** **Convulsions,** **Fever during labour,** **Umbilical cord came before the baby,** **Cord around the baby's neck,** **Heavy bleeding** **OR** How was the baby delivered? **Any of** **Baby was pulled out by manipulation by hand,** **baby was pulled out with an instrument** **C section**	Yes
Heavy bleeding before/after delivery?	From open history	Not available	Did any of these problems occur during delivery? **Heavy bleeding**	Yes
was there prolonged labour > 24 hrs?	How long was the labour? **answer 5 (>24 hours)**	How long was the labour? **>24 hours**	How long did the regular strong labour pains start before the baby was born? **>24 hours**	Yes
were there convulsions at delivery?	From open history	Not used[3]	Did any of these problems occur during delivery? **Convulsions**	Yes
was the baby born early < 34 wks?	Was the baby born at the expected time? **Early** **OR** After how many completed months of pregnancy was the baby born? **< 8 months**			Yes

[3] 27% of mothers reported having had convulsions in labour. The Nepali research team considered this indicator spurious as during the interviews there was difficulty in explaining differences between fainting and convulsions.

Cont Table 3.18 – Conversion of categorical to binary data from Questionnaires to InterVA Indicators

InterVA question	Malawi	Nepal	Mumbai	InterVA
was the baby small < 2500 g?	How big was the baby? **Very small or tiny or smaller than usual** **OR** do you know the birth weight of the baby? **<2500g**			Yes
was there difficulty breathing at birth?	Did the baby ever had difficulty in breathing? **Yes** **AND** when did the difficulty start? **Immediately at birth**		During the illness did the baby had difficulty breathing? **Yes** **AND** How long after birth did the difficulty start? **On the first day**	Yes
any congenital malformations?	Did the baby have any obvious deformity/congenital malformations? **Yes** **OR** did the baby have a very small head? **Yes** **OR** did the baby have a mass or defect at the back of the head (or spine)? **Yes** **OR** did the baby have cleft lip/palate? **Yes**		[How did the baby look at birth? **Abnormal**]	Yes
was this a multiple birth?	Was the baby one of twins? **Yes**		Was the baby a singleton or multiple birth? **Multiple**	Yes
any umbilical infection?	Did the baby had a bright red ring on the skin around (or drainage from) the umbilical stump? Yes			Yes
did the mother fail to receive TTV?	During this pregnancy how many times did you get the TTV injection in the arm? <2 injections AND have you received all 4 injections? No	Not used	Not used	
did the infant stop sucking after day 3?	Did the baby always suckle normally? No AND When did the problem start? 3 (after 3 days)			Yes
did infant have arched back after 2 days?	Did the baby arch his back or had spasms? Yes			Yes
did convulsions happen on day 1?	Convulsions: In which day of life:? After first day		Not available	
did the infant die on day 1?	Date of death – date of birth >1 day		How old was the baby at the time of death? > 24 hours old	Yes

Cont Table 3.18 – Conversion of categorical to binary data from Questionnaires to InterVA Indicators

InterVA question	Malawi	Nepal	Mumbai	InterVA
was there no cry/move/breath at birth?	Did you think the baby was born dead or alive? Dead AND Did the baby cry even a little? No AND did the did the baby ever move even a little? No AND did the baby breathe even a little? No			Yes
Was infant's skin puffy/mushy at birth?[4]	Was the baby still moving when the labour started? No OR when did you last feel the baby moving? >24 hours previous to delivery / Days before labour started OR did you think the baby was dead before delivery/ before you went into labour? Yes		Had he baby's body changed so that the skin was soft and pulpy or discoloured? Yes OR was the baby still moving when labour started? No OR When did you last feel the baby moving? Days before labour started	Yes
did the infant fail to cry at birth?	Did the baby cry at birth? No		How long after birth did the baby first cry? Never cried	Yes
Do you think the infant suffered from tetanus?	Not used in Maimwana[5]		Not used	

[4] Ambiguous question in maiMwana and Nepal's questionnaires. Therefore data from open history were used and either mum last feel baby movements >24 hours previous to delivery OR mum thought the baby was dead before delivery OR the baby was no longer moving before labour

[5] The common names for tetanus: *Kufumbata* or *kalongolongo* were used to describe a number of illnesses including the prominence of the veins around the umbilicus and umbilical flare. "Tetanus" therefore was reported commonly (6% of 156 neonatal deaths), even if it had been eliminated according to the WHO criteria (< 1 case per 1000 births) since March 2002 [517].

Table 3.18 describes in detail the criteria for interpretation of data from the questionnaires used in the 3 studies and the InterVA indicators. For the Mumbai database the data received were compatible with the InterVA format.

3.9.2 Comparison between InterVA and Physician Review Outcomes

To compare CSMFs between physician review and InterVA an "infectious diseases" category was created grouping together the probabilities calculated by InterVA for sepsis, pneumonia, diarrhoea, other infections and meningitis, because from a public health perspective they did require similar preventative interventions. Moreover, the aim of using InterVA was to classify consistently the causes of death into 6 categories for neonatal deaths and two for stillbirths. These categories were common to all perinatal death classifications while the sub-classifications varied among studies. Moreover InterVA output had to be maintained as it is written for all age groups. Neonatal tetanus was an exception. It was the only sub-classification to be maintained and compared with the two methods as its detection has important public health implications.
Kappa (κ) statistic was used to compare the causes of death obtained using InterVA and physician review. The analysis was performed in STATA9 using the "kap" and "kapci" commands[457;518]. *Kappa* was used as comparison method assuming that both InterVA and physician review are equally valid methods to interpret verbal autopsy data. *Kappa* (κ) statistic is expressed with the formula:

$$\kappa = \frac{D(obs) - D(exp)}{1 - D(exp)}$$

where D(obs) is the proportion of agreement observed between diagnoses by different physicians and D(exp) is the percentage of agreement observed between two physicians by chance alone. Kappa was used rather than sensitivity and specificity formulas as physician review cannot be considered a true gold standard for the interpretation of verbal autopsy data, given the poor repeatability of its results[519]. Agreement between methods was considered "substantial" if κ was between 0.61 and 0.8, "moderate" if κ was between 0.41 and 0.6, "fair" if κ was between 0.21 and 0.4, "slight" if it was between 0 and 0.2 and "poor" if equal 0[520].

3.10 - Analysis Plan

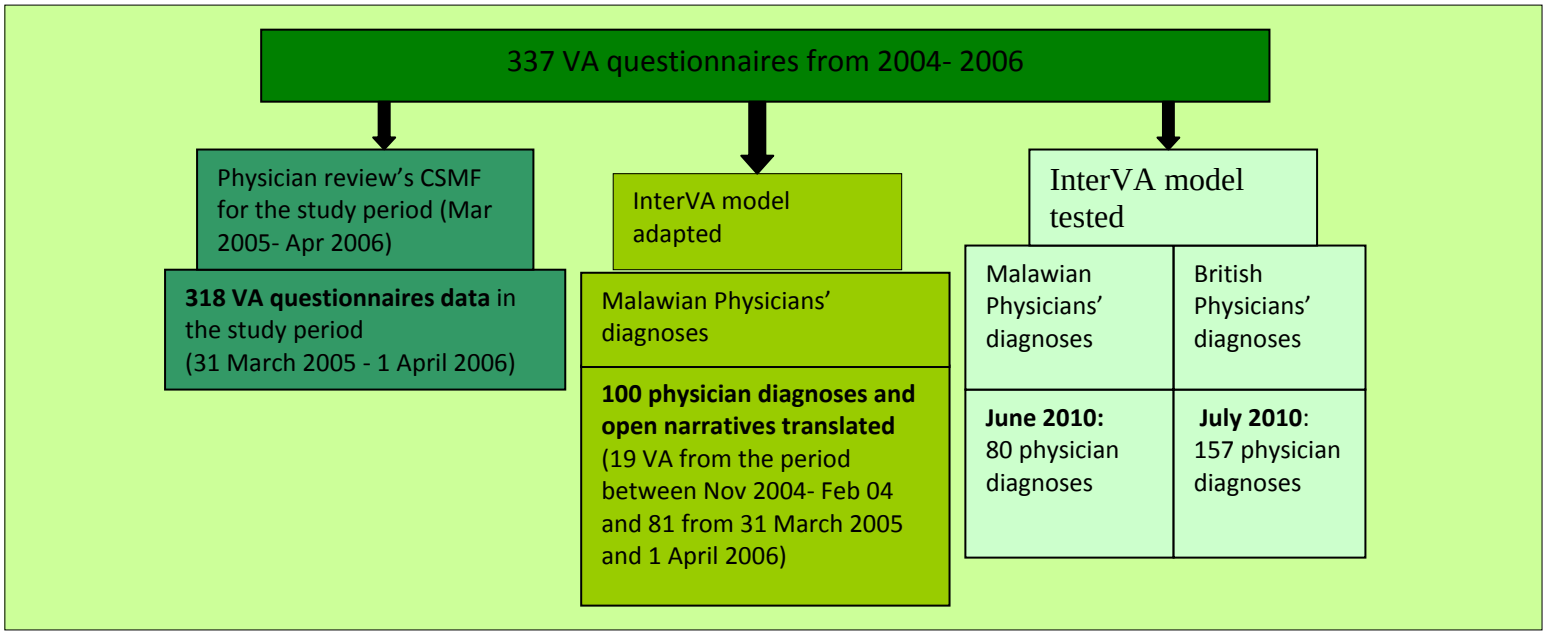
The 337 VA from Malawi collected between 2004 and 2006 were divided into 5 datasets for analysis. Two datasets included the first 100 verbal autopsies chronologically available that were used for the original adaptation of the InterVA model to include stillbirths and improve separation of causes of neonatal deaths. Those were compared with physician review to establish the performance of the adapted model. The database with the information derived from the open history coded and integrated with the closed questions was used for initial comparison. A second database with the same 100 VA data did not include the open history information and was subsequently run to compare the model performance with and without open history data to establish whether it changed the performance of InterVA.

The remaining 237 untouched VA from Malawi were separated to test the modified InterVA model in comparison with physician review when the new data were submitted. Again two databases, with and without open history information, were created to establish how essential open histories data were in the interpretation of the VA data using InterVA (Figure 3.4).

Finally only that VA data collected between 1st March 2005 and 31st April 2006 (318 deaths) were analysed using physicians' review and InterVA to present the CSMF for the study period to answer the epidemiological question of the causes of perinatal and late neonatal mortality in Mchinji District.

Causes of death by time of death were also analysed.

Figure 3.4 Analysis Plan for Malawi Data



The burden of stillbirths and neonatal deaths in Makwampur, Nepal and in the City Initiative for Newborn Health slum area in Mumbai is described using the CSMF according to physicians' review and InterVA and compares the two outcomes. Causes of death were separated by time of death of the infants. For the data from Mumbai it was also possible to assess the accuracy of maternal perception of infant's size to validate the use of the parameter in this thesis.

A comparison of the mortality figures and CSMF in the three studies using InterVA is shown, also comparing causes of death by day of death. Similarities and differences in the technical characteristics of the VA interviews such as the time lapse between death and interview, the characteristics of the respondent, the demographics and some of the health care practices are compared and discussed.

Different outputs derived from InterVA are presented using different analytical methods.

1. Calculating the model uncertainties:

InterVA expresses between one and three diagnoses for each individual death, each with an associated likelihood. The total of the likelihoods for each death does not necessarily add up to 100 as there were not always sufficient signs and symptoms to allow the model to express this degree of certainty. The original model used in the analyses of this thesis does not take account of this percentage of uncertainty. In this analysis each death was considered to have a total likelihood of 100, therefore if the sum of the likelihoods did not add up to 100, the difference was added to the indeterminate category.

2. Excluding all model uncertainties:

In this analysis the model outputs was calculated in the same manner as physician review outputs are interpreted: if a single cause of death was expressed, this was

given a value of 100 and if two were considered, they were given the value of 50 each and so on. In this way all model uncertainties were excluded.

3. Single cause of death:

Here only the cause of death with the highest likelihood was included and it was given the value of 1 in the same way as single diagnosis by physician review is calculated.

Outcomes obtained by consensus through physician review were compared to outcomes when all physicians' opinions were given the same weights without taking into consideration the consensus.

Finally, to understand on which indicators InterVA is mostly basing its cause of death attribution, indicators from InterVA and three causes of death (perinatal asphyxia, sepsis and prematurity) were tabulated. As only a small number of indicators were consistently used by the model, InterVA was re-run using a reduced number of indicators to establish whether a reduced number of questions would still provide comparable CSMF.

3.11 - Conclusions

- This chapter describes the stages of development of a verbal autopsy tool consisting of a classification of stillbirths and neonatal deaths, an interpretative algorithm and a questionnaire for physicians' review interpretation.
- The data collection tools, procedures, storage and maintenance were similar in the three studies as they evolved from one another over a period of about 8 years. The interpretation using physician review varied in the number of physicians involved, the number of causes of death allowed for each questionnaire and the interpretative algorithm used.
- The adaptation of a computerised programme based on probabilistic theory to interpret VA data in a consistent, repeatable and rapid manner was explained.
- The analysis plan of the thesis was described.

Chapter 4:

Results

Refinement and Testing of the InterVA Model Using Stillbirth and Neonatal Verbal Autopsy data from Maimwana - Malawi

4.1 - Burden and Causes of Perinatal and Neonatal Mortality in Mchinji District, Malawi

Over a period of a year between 1st April 2005 and 31st March 2006 birth and death data were collected as part of the epidemiological surveillance of a large cluster randomised trial evaluating two community participation interventions to reduce neonatal and maternal mortality in Mchinji, the westernmost district of the central region of Malawi. During this period 6574 births were followed up, of those 6,414 resulted in live-births and 160 in stillbirths. Of the live-births, 161 died in the neonatal period. Of these neonatal deaths 108 (67%) occurred within the first week of life and 53 (33%) between 8 and 28 days after birth. The overall neonatal mortality rate (NMR) was 25 per 1000 livebirths, the stillbirth rate (SBR) was 24 per 1000 total births, and the perinatal mortality rate (PNMR) was 41 per 1000 births.

During this period 318 verbal autopsy (VA) questionnaires were collected and subsequently interpreted by physician review and an adapted version of interVA. After physician interpretation of the VA questionnaires, considering that only 3 VA were missing, the NMR and SBR could be corrected to 26.6 per 1000

(171/6414) and 22.4 per 1000 (147/6574) respectively. Using the InterVA model NMR was 25.7 per 1000 (165/6414) and SBR was 23.3 per 1000 (153/6574).

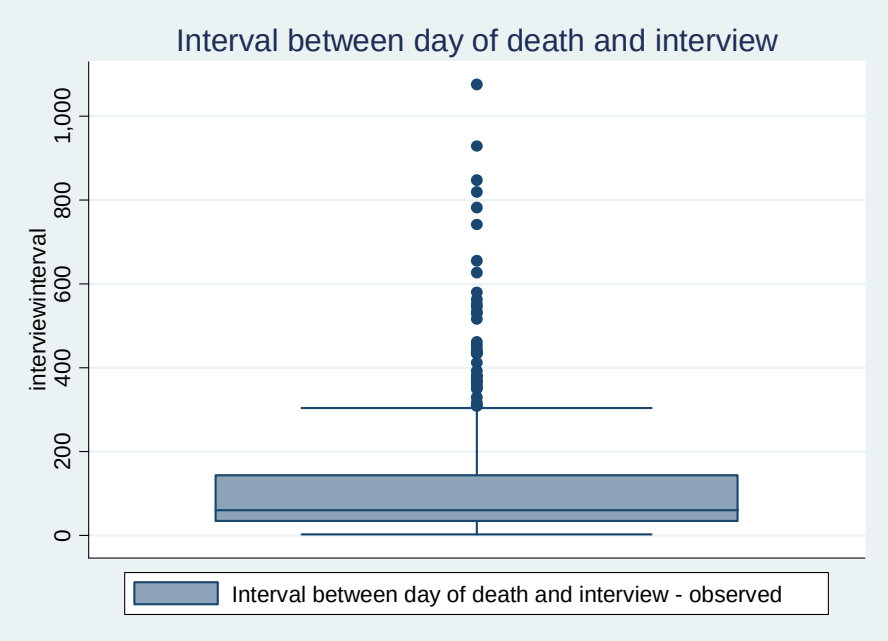
4.2 - Causes of Stillbirths and Neonatal Death – Physician Review

Mothers were the respondents for the majority of the questionnaires (n=306, 96%). In three cases of maternal death a paternal or maternal relative responded. None of the 12 VA where respondent was not the mother had indeterminate as a cause of death.

4.2.1 Quality of Verbal Autopsy Data

The VA were collected between 3 and 1076 days after the infant death with median of 62 days (inter quartile range = 109, Figure 4.1), 252 interviews (79%) were collected within 6 months and 280 (88%) within a year of the death. The date of interview was not available in 3 instances.

Figure 4.1 - Interval between Death and Verbal Autopsy Interview Dates



The open history narrative was available for 207/283 (73%) of the VA obtained within 1 year and from 20/33 (60%) of the VA over a year after the infant's death

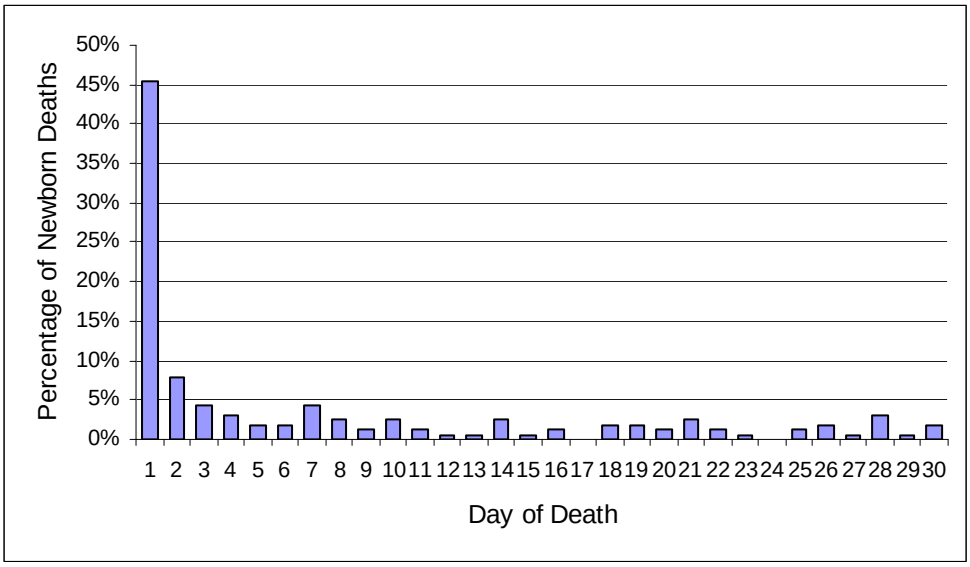
(p=0.1), in two cases the date of the interview was unknown. None of the causes of death from the VA taken a year after death were left undetermined by physician review or the InterVA model. The overall causes of death ranking did not change whether they were included or excluded.

Considering the 318 VA collected during the year from March 2005 and April 206, the agreement between Malawian physicians reading 161 questionnaires, calculated using *kappa* statistics was 76%: very good agreement[521]. The main discordance of opinion was in establishing whether a stillbirth was fresh or macerated, and whether a death was due to perinatal asphyxia or was a fresh stillbirth.

Agreement between the second pair of paediatricians after reading 157 questionnaires was 78% (*kappa* 0.7273 CI: 0.643 - 0.803).
The main disagreement was over birth asphyxia and fresh stillbirths, fresh and macerated stillbirths, neonatal sepsis and tetanus.

Of the 318 deaths, 145 (46%) were classified as stillbirths and 173 (54%) as neonatal deaths. Amongst the stillbirths there were 50 ante-partum and 95 intra-partum deaths.
About 2/3 of the 173 neonatal deaths occurred in the first week from birth and 1/3 in the late neonatal period: 83 infants (48%) died within the first 24 hours from birth, 120 (69%), in the first week, while only 53, (31%) were late neonatal deaths (between 8 and 28 days from birth, Figure 4.2).

Figure 4.2 – Distribution of Neonatal Deaths by Time



Of the neonatal deaths 96 infants (55%) were boys and 77 (45%) girls. Of the stillbirths 63 (43%) were girls and 81 (55%) were boys, for one the sex was missing. The results of physician review diagnoses are reported in Table 4.1.

Table 4.1 – Causes of Stillbirth and Neonatal Death According to Consensus Physician Review

Stillbirths						
	Fresh stillbirths		Macerated stillbirths		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Prematurity	11	11	1	2	12	8
Obstetric Complications	44	45	1	2	45	29
Accidents	0		0	0	0	0
Congenital malformation	3	3	5	10	8	5
Multiple births	5	3	-	-	5	3
Other	4	4	5	10	9	6
Indeterminate	36	35	38	76	74	48
Total diagnoses	103	100	50	100	153	100

Neonatal deaths						
	Early		Late		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Congenital malformations	6	3	1	1	7	3
Perinatal Asphyxia	36	19	-		36	14
Asphyxia with Obstetric Complications	19	10	-		19	7
Severe Infections	35		47		82	
Pneumonia	9	19	13	70	22	32
Meningitis	6		18		24	
Local Infections	3		-		3	
Diarrhoea	1		-		1	
Other	28	15	5	7	33	13
Indeterminate	14	7	5	7	19	7
Total diagnoses	189	100	67	100	256	100

Note: more then one cause of death for each questionnaire.

4.3 - Use of Multiple Diagnosis and Standardisation between Physician Opinions

The use of multiple diagnoses by physician review introduced a large variability in data interpretation and possibly some inconsistencies (Table 4.2). Overall British were as likely as Malawian paediatricians to report multiple causes of death 52% (82/157) of cases and 47% (86/181) respectively. Only 59% of infants born at a gestational age of 8 months or earlier according to the questionnaire, had prematurity listed as one of the causes of death. There were 28 infants reported to have a congenital malformation, but only 14 had this as a diagnosis. Physicians also reported a number of diagnoses as "other": such as obstetric complications, jaundice, intestinal obstruction, multiple pregnancy, macrosomia, haemorrhagic disease of the newborn and maternal infections. However in the raw data extracted from the questionnaires, those symptoms were reported for a larger number of infants than acknowledged in the diagnoses (Table 4.2).

Table 4.2 - Comparison between Questionnaire Data and Physician Diagnoses

Neonatal death	Questionnaires	Physician diagnosis			
		Final cause of death	Underlying cause of death	Associated cause of death	Total (%)
Congenital Malformation	28	3	11	0	14 (50)
Obstetric Complications*	156	0	8	56	64 (41)
Prematurity	115	18	43	7	68 (59)
Multiple Births	51	0	5	9	14 (27)
Jaundice	35	0	2		4 (11)
Large Infant (macrosomia)*	97	0	0	2	2 (2)
Bleeding	9	0	1	0	1 (10)

* Obstetric complications: Labour duration over 24 hours, infant presentation different from vertex, delivery type different from spontaneous vaginal delivery and any delivery problem

4.4 - Refinement of the InterVA Model on 100 Perinatal Verbal Autopsies

A method of estimating the CSMF using a computerised algorithm was refined and tested on the first batch of VA completed with physician diagnosis available from Malawi: 81 of these questionnaires belonged to the period under study (April 2005 to March 2006) and 19 were collected between November 2004 and the end of February 2005. Those earlier VA were collected by the same interviewers and interpreted by the same physicians, this period was excluded from this final study as the surveillance system was being piloted and not all deaths were captured, however there was no reason to assume that the VA collected in that period would differ in any way from the ones in the year considered by the study.

4.4.1. Description of the Dataset

The initial 100 questionnaires were collected between 11 and 338 days after the infant's death with a median of 65 days. Mothers were the respondents to all the questionnaires but one, where the mother also died and a maternal relative was interviewed.

4.4.2. Physician Review

All questionnaires were interpreted by the same two Malawian paediatricians who reached the same diagnosis for the underlying cause of death in 71 cases, while 29 required a discussion. Agreement was reached in 96 cases. Four deaths were considered undetermined, either there was no agreement reached (3 cases) or both physicians considered that there was not enough information to reach a diagnosis (1 case). A single diagnosis was expressed in 45 cases, two diagnoses in 47 cases

and three or more in eight cases. There were 52 stillbirths and 48 neonatal deaths of which 32 (67%) were early death (0-7 days).

For the calculation of CSMFs using physician review, if more than one cause of death was assigned by the physicians, each was considered as a proportion of the total. Therefore, if a single cause of death was assigned by all physicians, this cause counted as 100% of the death. If more than one cause of death was attributed, each contributed an equal proportion to a total of 100% of the deaths. For example, if both reviewing physicians assigned a cause of prematurity to a case and one of the physicians also assigned sepsis as a contributory cause, then prematurity contributed 75% to the death and sepsis contributed 25% (Table 4.1). This system was used to avoid loss of information and bias that can be introduced when consensus is used.

4.4.3. InterVA Model

The data from the same 100 VA questionnaires were batched and entered in the modified InterVA model. To ensure all the information available from the data were incorporated into the model, the open histories were also all read and coded. The codes were then extracted and added to the InterVA model where appropriate. The same data were analysed omitting the open histories information.

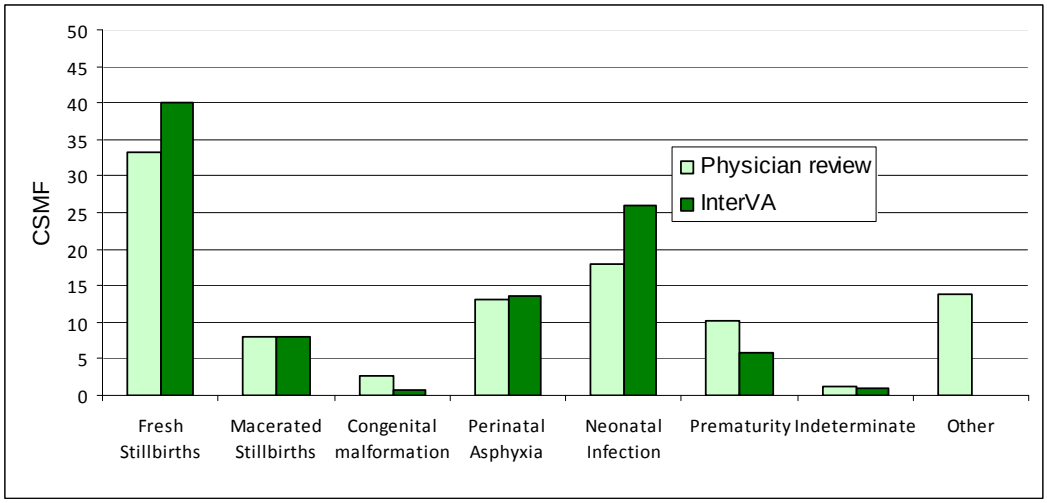
The CSMFs were calculated from the InterVA output by adding the sum of the likelihoods computed by the programme for each cause of death category divided by the sum of the likelihoods for all causes (Table 4.3).

CSMFs and individual agreement between the InterVA results and physician review were compared. Figure 4.3 shows comparability between the causes of death obtained by physician review and the InterVA model.

Table 4.3 - CSMF using Physician Review and InterVA Including and Excluding Open History Codes

	InterVA + Open History	Physician Review	Difference in proportion (CI)	InterVA No Open History
Fresh Stillbirths	40.0	33.1	0.07 (-0.005-0.14)	43.8
Macerated Stillbirths	8.0	7.9	0.001 (-0.04-0.04)	11.3
Congenital Malformation	0.8	2.5	-0.012 (-0.03-0.006)	0.8
Perinatal Asphyxia	13.7	13.2	0.01 (-0.04-0.06)	15.5
Neonatal Infection	**26**	**17.9**	**0.08 (0.02-0.14)**	**19.5**
Prematurity	5.9	10.3	-0.04 (-0.08-0.002)	9.1
Other	**0.0**	**13.9**	**-0.14 (-0.2- -0.1)**	**0.0**
Indeterminate	1.1	1.1	0 (-0.01-0.01)	1.2

Figure 4.3 - CSMF using Physician Review and InterVA – Including Open History Codes

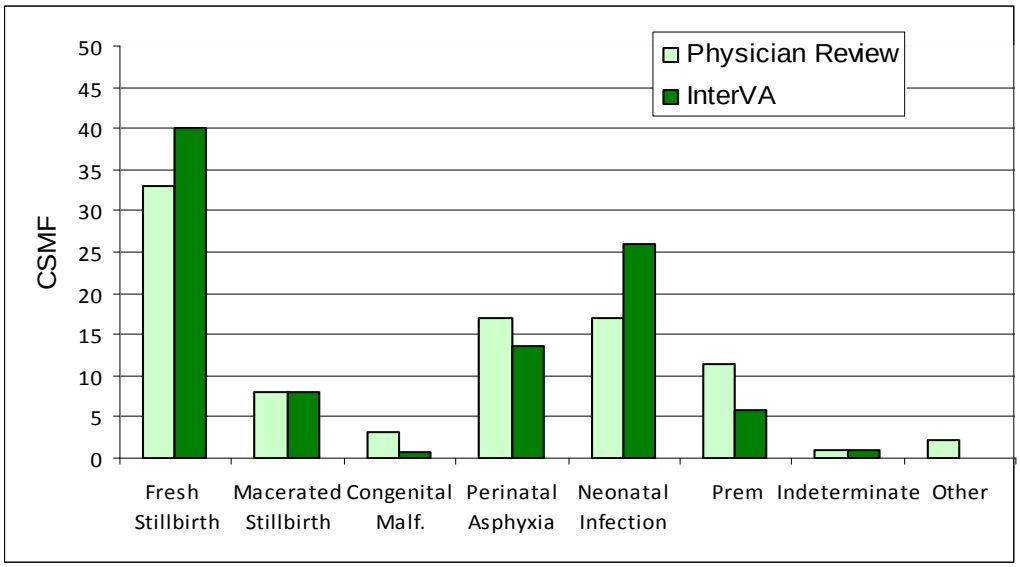


Other causes include "obstetric complications", "jaundice", "multiple pregnancies", "maternal causes", "hypothermia", "hypoglycaemia"

The hierarchy of causes of death was equivalent between the two models. InterVA had a higher proportion of fresh stillbirths and neonatal sepsis and a lower proportion of prematurity, compared with physician diagnoses. In the physician review model about 14% of causes of death were classified as "other".

The majority of the "other" diagnoses (n= 30, 85%) were obstetric complications associated mostly with fresh stillbirths and perinatal asphyxia. The remaining causes were jaundice, multiple pregnancies, maternal causes, hypothermia and hypoglycaemia and accounted for 8 cases (15%). If obstetric complications were included in the diagnoses of perinatal asphyxia and fresh stillbirth the "other" causes of death decreased to 2.4% and the two datasets remained comparable (Figure 4.4)

Figure 4.4 - CSMF using Physician Review and InterVA Considering Obstetric Complications as Part of the Diagnoses of Fresh Stillbirth and Perinatal Asphyxia

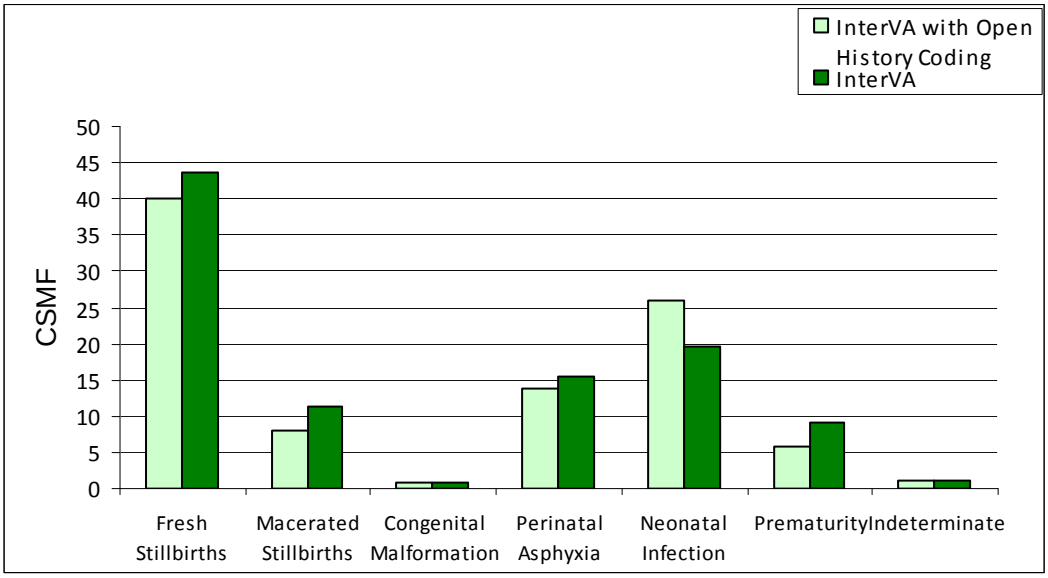


Individual agreement was calculated by comparing all the diagnoses expressed by physician review with all diagnoses obtained through InterVA. In 73% of individual cases at least one of the InterVA diagnoses agreed with at least one of the physician diagnoses (*Kappa*=0.60, 95% CI 0.567-0.702).

4.4.4. Comparison between InterVA Model and Physicians' Review – Without Open History Codes

If the open history information was included or omitted in the InterVA batched data, the ranking of CSMF remained substantially unchanged. However when the open history information was not included the proportions of stillbirths was higher by about 6%, of perinatal asphyxia by 2% and of prematurity by 35. Neonatal sepsis was lower by 6% (Table 4.1 and Figure 4.5).
Individual agreement using *kappa* statistics between all physician review diagnoses and the InterVA model without open history data was 70.59% (Kappa 0.56), comparable to the previous model.

Figure 4.5 - CSMF using InterVA Including and Excluding Open History Codes



4.5 - Comparison of CSMF using the Remaining Perinatal Verbal Autopsy from Malawi

Given the same ranking obtained by comparing physician review with the modified InterVA model and the moderate agreement for individual diagnoses obtained by using *kappa* statistics with the first 100 VA, the modified InterVA was tested on the remaining VA obtained from Malawi. The absolute standardisation of the analysis of questionnaires, internal consistency, speed and ease of analysis constituted huge advantages over the physician review method.

A further 237 stillbirth and neonatal verbal autopsies were available for the period between the 1st March 2005 and 31st April 2005.

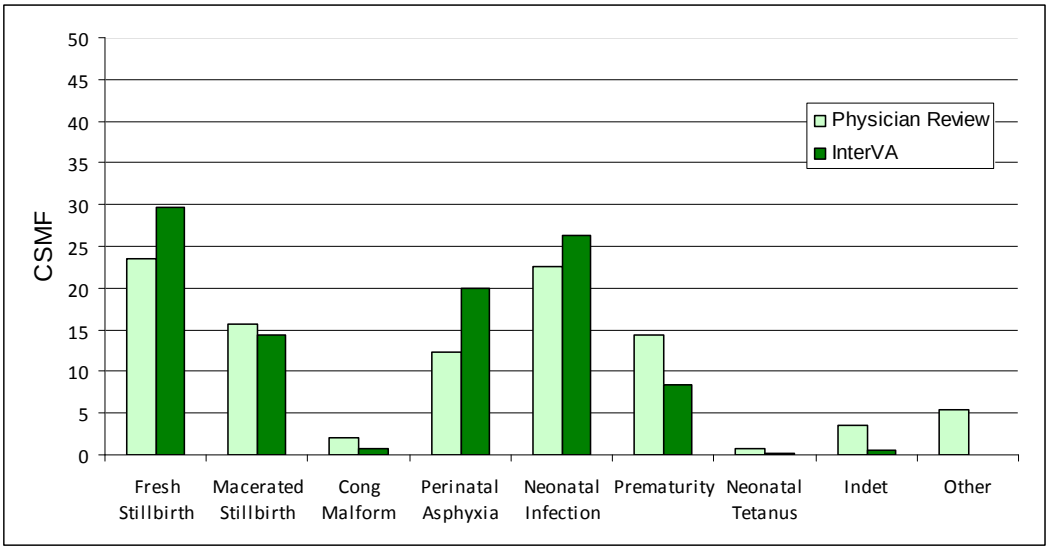
The Malawian physicians analysed 81 VA and listed one cause of death in 51 cases (63%), 2 in 17 cases (33%), and 3 in 3 (4%) cases. The British paediatricians analysed 157 VA and were more likely to give 2 diagnoses for each questionnaire (n=82, 53%) than their Malawian counterparts ($p<0.0001$, CI 0.201- 0.438).

Other causes of death included obstetric complications (malpresentation, obstructed or prolonged labour, and pregnancy induced hypertension), post-maturity, multiple pregnancy, intestinal obstruction, jaundice, haemolytic disease of the newborn and maternal infections. All the diagnoses of neonatal tetanus were made by the same British physician. The results of the comparison are reported in Table 4.4 and Figure 4.6.

Table 4.4 - Comparison between Consensus Physician Review Diagnoses and InterVA Model for 237 Remaining Verbal Autopsies

	InterVA 236	Physician Review 236	InterVA (+OH) 236	Difference in Proportions using InterVA +OH (CI)
Fresh Stillbirths	29.7	23.5	30.9	0.074 (-0.006-0.15)
Macerated Stillbirths	14.3	15.6	13.5	-0.02 (-0.08 -0.04)
Congenital Malformation	0.7	2	0.7	-0.01 (-0.03-0.008)
Perinatal Asphyxia	**20.0**	**12.3**	**20.3**	**0.08 (0.01- 0.14)**
Neonatal Infection	26.2	22.5	26.8	0.04 (-0.03-0.12)
Prematurity	**8.3**	**14.4**	**6.7**	**-0.08(-0.13--0.02)**
Other	0	5.4	0	-0.05 (-0.08--0.03)
Indeterminate	0.5	3.5	0.9	-0.03 (-0.05- -0.004)
Neonatal Tetanus	0.2	0.7	0.2	-0.005 (-0.02- 0.007)

Figure 4.6 - Graphical Comparison between Physician Review Diagnoses and InterVA Model for 236 Remaining VA



In both instances (physician review and InterVA) the most common diagnoses were fresh stillbirths and neonatal sepsis; however the proportion of deaths attributed to perinatal asphyxia by the InterVA model was 8% higher than

according to physician review, while that given to prematurity was 8% lower, the difference between those proportions was statistically significant. This discrepancy explains the different ranking of birth asphyxia and prematurity using the two methods.

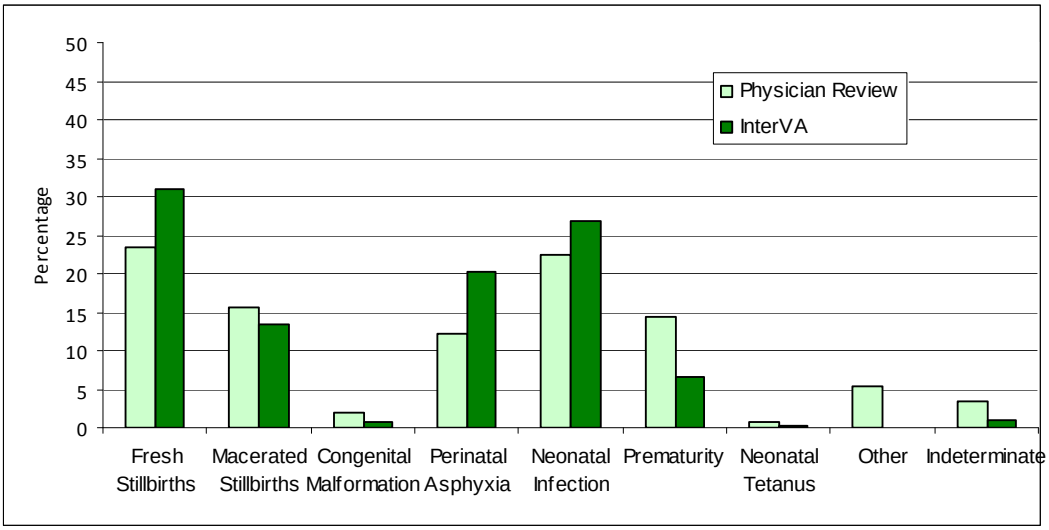
A diagnosis of neonatal tetanus by InterVA was calculated with a likelihood of 46% with an associated diagnosis of severe infections (likelihood of 36%).

The diagnoses of neonatal tetanus are unlikely to represent true cases. For the physician diagnosing it, this is likely to be due to lack of familiarity with the local epidemiology and demonstrates the difficulty of interpreting signs derived from VA questionnaires outside the local context. It also exemplifies how subjective the interpretation of signs can be when presented to different physicians highlighting one of the main limitations of a method that lacks internal consistency. Using InterVA there was still detection of neonatal tetanus in one case. This was the same as one of the cases interpreted as neonatal tetanus by physician diagnosis. InterVA likelihood was less than 50%. In this instance the infant signs included abdominal swelling, skin lesions, fever, umbilical infection, stopped sucking 3 days after birth and the mother did not receive tetanus toxoid vaccine. Neonatal sepsis and tetanus share most symptoms but it is important to separate the two. To improve InterVA performance it may be necessary to input prior to data entry whether neonatal tetanus has been eradicated, in a similar fashion for HIV and malaria prevalence.

4.5.1 Comparison between InterVA Model and Physicians' Review – Using Open History Codes

Open histories were available for 138 of the 236 questionnaires, 98 (41%) open histories were missing. The open histories available were coded and the data obtained were analysed using the InterVA model and compared with physician review. The majority, 76%, were from the dataset interpreted by the British paediatricians.

Figure 4.7 - Comparison between Physician Diagnoses and InterVA with Open History Coding



The same questionnaires were run on InterVA with and without the open history data and this did not substantially change the performance of the model, except that the proportion of prematurity according to InterVA modelling was now only 50% of that of physician review.

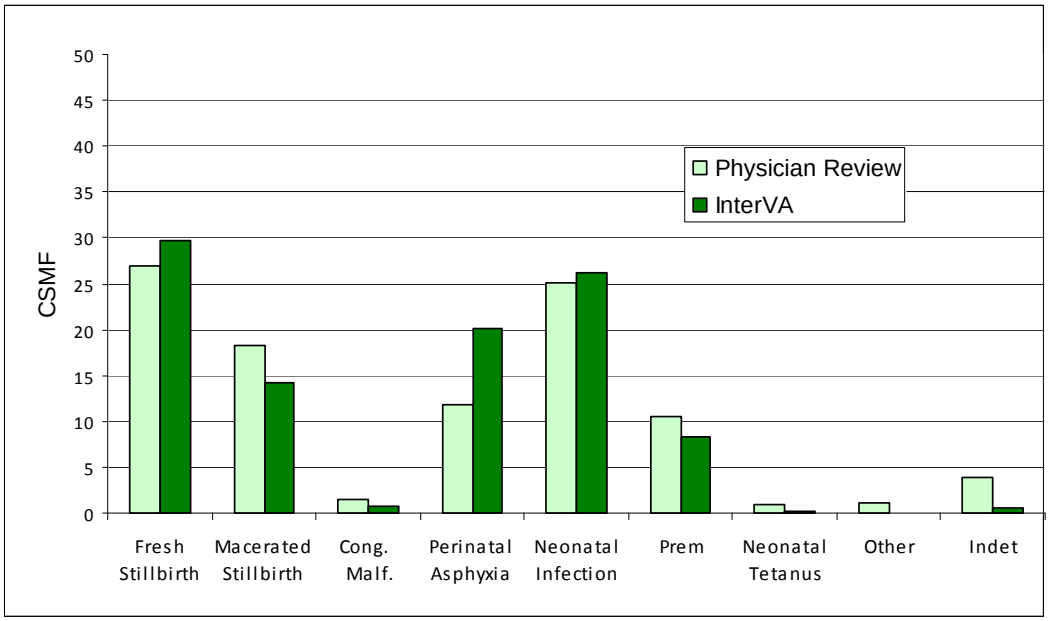
4.5.2 Comparison between Physician Review and InterVA using Single Diagnosis by Physician review

Given that several studies use single diagnosis interpretation of VA questionnaires, InterVA was compared with physician review when only the first diagnosis made by physicians was considered. The results are reported in Table 4.5 and Figure 4.8. The proportion of prematurity and neonatal sepsis between InterVA and physician review were more similar than when all causes of death were taken into account, and the ranking of neonatal deaths' causes became the same with the two methods.

Table 4.5 - Comparison between Single Physician Diagnosis and InterVA for 236 Verbal Autopsies

	Physician Review	InterVA	Difference in proportion (CI)
Fresh Stillbirth	26.9	29.7	0.03 (-0.04-0.1)
Macerated Stillbirth	18.3	14.3	-0.04 (-0.1-0.02)
Congenital Malformation	1.6	0.7	-0.009 (-0.03-0.008)
Perinatal Asphyxia	**11.9**	**20.0**	**0.08 (0.02-0.14)**
Neonatal Infection	25.0	26.2	0.01 (-0.05-0.08)
Prematurity	10.6	8.3	-0.02 (-0.07-0.02)
Neonatal Tetanus	0.9	0.2	-0.007 (-0.02-0.004)
Other	1.1	0.0	-0.01 (-0.02- 0.0005)
Indeterminate	**3.8**	**0.5**	**-0.03 (-0.05- -0.01)**

Figure 4.8 - Comparison between Single Physician Diagnosis and InterVA for 236 Verbal Autopsies



Finally all Malawi VA for the year between April 2005 and May 2006 were used and the results using Physician review with multiple causes of death and InterVA are shown in Table 4.6.

Table 4.6 - Comparison between Multiple Physician Diagnosis and InterVA for 337 Malawi Verbal Autopsies

		Malawi InterVA	**PR multiple causes**	Difference in proportion (CI)	**PR single cause**	Difference in proportion (CI)
Stillbirths	Fresh	34.2	23.3	**-0.1 (-0.2--0.05)**	30.7	-0.03 (-0.1-0.04)
	Macerated	14.0	13.7	-0.003 (-0.06-0.05)	15.2	0.01 (-0.04-0.07)
	Total	**48.3**	**37.0**	**0.1 (-0.2- -0.03)**	45.8	**-0.02 (-0.1-0.06)**
Congenital Malformation		0.8	1.8	0.01 (-0.008-0.03)	1.3	0.005 (-0.01-0.02)
Perinatal Asphyxia		19	12.5	**-0.065 (-0.1- -0.009)**	12	**-0.07 (-0.1 --0.01)**
Neonatal Infection		24.1	22.2	-0.02 (-0.08- 0.05)	25. 4	0.01 (-0.05-0.08)
Prematurity		7.7	13.0	**0.05 (0.006-0.1)**	10. 4	0.027 (-0.02 -0.07)
Neonatal Tetanus		0.2	0.6	**0.4 (0.4-0.5)**	1.1	0.9 (0.9-0.96)
Indeterminate		0	2.6	0.004 (-0.006-0.01)	3.0	**0.03 (0.009- 0.04)**
Other		0	10.2	**0.1 (0.07-0.1)**	1	0.01 (-0.0009 -0.02)
Total		**100**	**100**		**100**	

4.6 - Conclusions

- Perinatal, neonatal and maternal mortality rates in Mchinji district were respectively 42.8 per 1000 births, 25.6 per 1000 livebirths and 451 per 100,000 live births
- VA were available for 318 stillbirths and neonatal deaths. According to the raw data stillbirths represented 50% of all deaths, when physician diagnosis was considered stillbirths were 46% and when the InterVA model was used they were 48%. The majority of neonatal deaths occurred in the first day of life (45.4%) and the first week of life (68.7%).
- The median time to VA interviews was 62 days, interquartile range 104.
- The agreement between physicians reading and assessing the causes of deaths from the VA questionnaires was assessed using *kappa* statistics and was 76% amongst two Malawian paediatrician and 78% amongst two British paediatricians, classed “very good” according to the criteria set out by Landis and Koch[522].
- The causes of death were assessed according to physician review, and showed that:
    - The most common causes of death were severe infections, followed by prematurity, perinatal asphyxia, other, unclassifiable and congenital malformations.
- The InterVA model performed better with the first 100 VA tested when compared with physician review. For the subsequent 237 VA it ranked the causes of death similarly to physician review however between 7 and 8% of deaths were ascribed to prematurity compared with 14% according to physician opinion and 20% of deaths were due to perinatal asphyxia compared with 12% according to physician review. When only the final cause of death diagnosed by physician review was compared with the InterVA model, the ranking order was the same.

- Adding the open narrative coding to the InterVA data did not alter the ranking of the causes of death for the first 100 and the remaining 237 VA.
- Before submitting InterVA to a panel of experts to refine the indicators and a priori probabilities of the indicators, the model was tested using different datasets from different socio-cultural contexts to see whether the under- and over-reporting of specific diagnoses (nominally asphyxia and prematurity) remained a consistent problem or whether it was specifically linked to the Malawi data. The next two chapters discuss how the process was extended to data from two other countries.

Chapter 5

Results

Burden and Causes of Perinatal and Neonatal Mortality in Makwampur District, Nepal

5.1 - Burden of Stillbirths and Neonatal Mortality in Makwampur District

Data from Makwampur were collected over a period of 4 years from September 2001 to September 2004, as part of a large cluster randomised trial to evaluate the effect of a community participatory intervention on maternal and neonatal health[523]. During this period a total of 8,184 births were recorded, of which 439 were either neonatal deaths (248) or stillbirths (191). The majority of neonatal deaths occurred within the first 7 days from birth: 61% (n=151/248), while 97 deaths occurred between day 8 and 28 (39%). The perinatal mortality rate was 41.7 per 1000 total births (n=342/8184), the stillbirth rate was 23 per 1000 and the neonatal mortality rate was 31 per 1000 livebirths (n=248/7993).

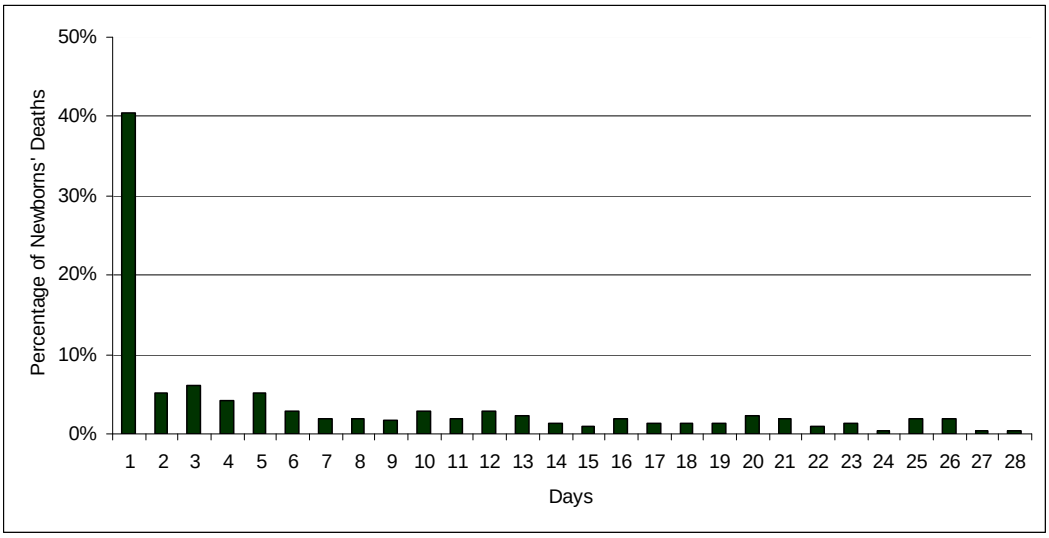
Of the 439 perinatal and neonatal deaths in the district, verbal autopsies were obtained for 385 (88%); 169 were classified as stillbirth and 216 as live birth. The majority of neonatal deaths occurred on the first 24 hours from birth (n=87/216, 40%), 54 occurred on day 2-7 (25%), 30 on day 8-13 (14%) and 45 on day 14-31 (21%), therefore (141) 65% of all neonatal deaths occurred in the first week (early neonatal deaths) and 75 were late neonatal deaths occurring between day 8 and 28 days post delivery (Figure 5.1).

Amongst all the stillbirths and neonatal deaths 44% (n=168) were female and 56% (n=217) were male infants.

For the majority of interviews the respondents were mothers (n=372, 96%). Fathers were the respondents on 8 occasions, paternal family in 3 interviews and "other" on another 3 occasions.

Two thirds of infants were born at home (n= 258, 67%), 4% (n=15) in a dedicated shed, 15% (n=58) just outside the house or in transit. 11% (n=44) were born in hospital or private clinic. For 10 the place of birth was missing.

Figure 5.1 - Percentage of Neonatal Deaths by Day of Life



5.2 - Causes of Stillbirths and Neonatal Death – Physician Review

The agreement between the two reviewing physicians was very good (96%) with *kappa* 0.95 (CI: 0.953-0.955). In only 10/385 cases did the two physicians disagree and the third physician had to review the diagnoses. The disagreement between physicians was about birth asphyxia and prematurity in 5 cases, prematurity and "others" in 2 cases, "others" and "unclassifiable" in 2 cases, and macerated stillbirth and "other" in the last case. The causes of death in these ten cases were established to be prematurity (4), unclassifiable (1), asphyxia (1), other (3) and macerated stillbirth (1).

There were 170 stillbirths (45%): 56% fresh and 43% macerated. Amongst the neonatal deaths, 138 (64%) were early neonatal deaths, occurring within a week of birth, and 78 (36%) were late neonatal deaths (Figure 5.2). The results from physicians review are shown in Table 5.1. Amongst the macerated stillbirths physicians ascribed the cause of death to obstetric complications in 53% of cases

Figure 5.2 - Stillbirths and Neonatal Deaths

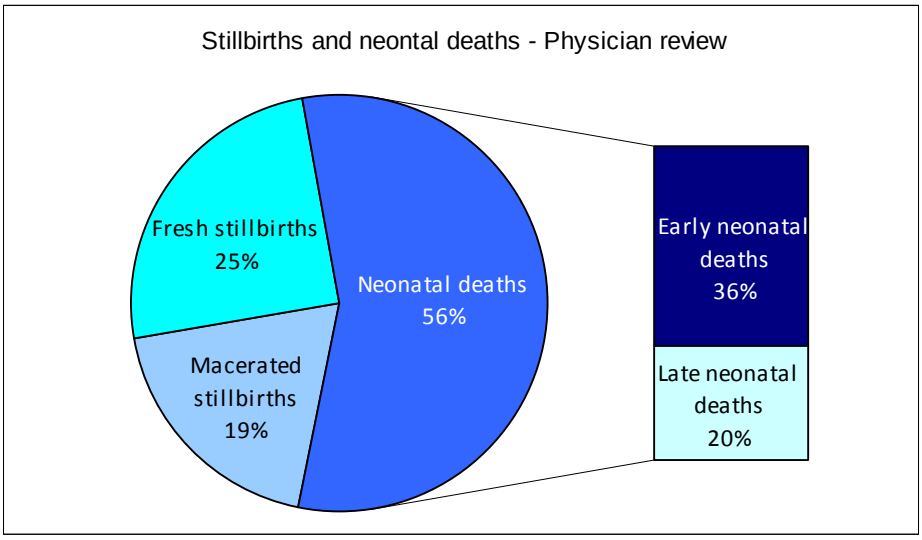


Table 5.1 – Causes of Stillbirth and Neonatal Death According to Physician Review

Stillbirths

	Fresh stillbirths		Macerated stillbirths		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Prematurity	1	1	4	5	5	3
Obstetric Complications	64	67	39	53	103	61
Accidents	3	3	1	1	4	2
Congenital malformation	1	1	7	9	8	5
Maternal conditions	13	14	12	16	25	15
Other	0		1	1	1	0.6
Indeterminate	14	15	10	14	24	14
Total	96	100	74	100	170	100

Neonatal deaths

	Early		Late		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Congenital Malformations	3	2	0	0	3	1
Perinatal Asphyxia	42	30	8	10	50	23
Asphyxia with Obstetric Complications	29	21	4	5	33	15
Severe Infections	43	31	65	83	108	50
Prematurity	12	9	0	0	12	6
Other	6	4	0	0	6	3
Indeterminate	3	2	1	1	4	2
Total	138	100	78	100	216	100

5.3. - Analysis of Stillbirths and Neonatal Mortality using the InterVA Model

5.3.1 Cause Specific Mortality Fraction using InterVA

Table 3 shows the CSMFs obtained from the InterVA model and the bar chart shows the distribution of neonatal deaths and stillbirths according to InterVA and physicians' interpretation (Table 5.2 and Figure 5.3).

Table 5.2 – Cause Specific Mortality Fraction using InterVA

InterVA data	Percentage
Stillbirth	44.0
Congenital Malformation	0.9
Perinatal Asphyxia	24.1
Meningitis	0.7
Other Infection	0.6
Pneumonia/Sepsis	21.2
All Infections	22.4
Pre-Term/Small Baby	8
Indeterminate	0.6

Perinatal asphyxia accounted for the highest proportion of neonatal deaths followed by severe infections, of which just above 1% were due to meningitis and other severe infections. There were no cases attributed to neonatal tetanus. Fewer than 1% of cases were left undiagnosed.

5.4. - Comparison between Physician Review and InterVA Model

Table 5.3 and Figure 5.3 compare physicians' with InterVA diagnoses.

Figure 5.3 – Comparison between CSMF Obtained using Physician Review and InterVA

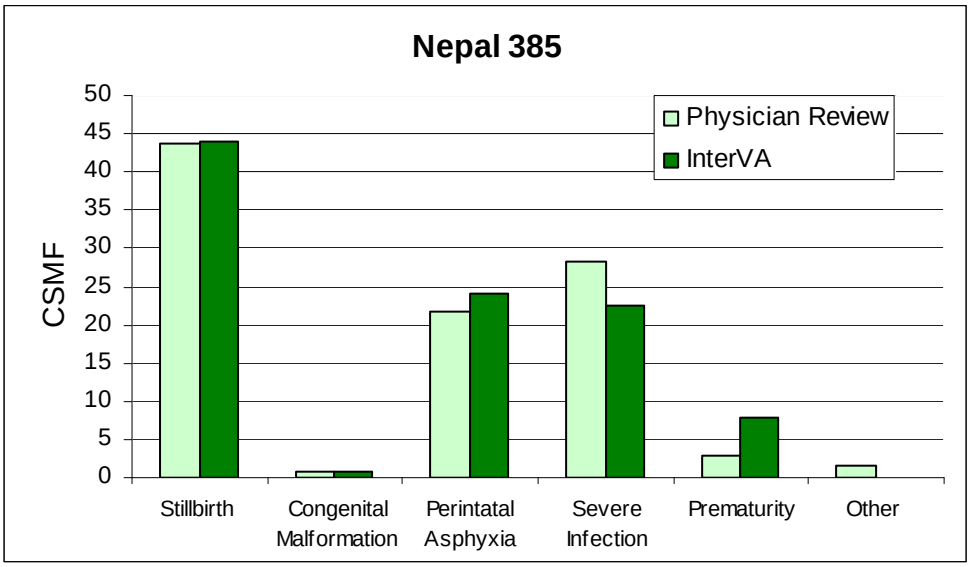


Table 5.3 – Comparison between Cause Specific Mortality Fraction using InterVA and Physician Review

	Physician review	InterVA	Difference in proportions (95% CI)
Stillbirth	43.8	44.0	0.002 (-0.07- 0.07)
Congenital Malformation	**0.8**	**0. 9**	**0.001 (-0.01-0.01)**
Perinatal Asphyxia	21.6	24.0	0.02 (-0.03-0.8)
Pre-Term/Small Baby	**2.9**	**8**	**0.051 (0.02-0.08)**
Severe Infection	28.2	22.5	-0.06 (-0.1-0.04)
Indeterminate	**1.1**	**0.6**	**-0.005 (-0.02- -0.008)**
Other causes	**1.5**	**0**	**-0.015 (-0.03- -0.003)**
Total	**100**	**100**	

At a population level, if fresh and macerated stillbirths were considered together their proportion was comparable in physician review and InterVA, representing just under 45% of all deaths. The ranking of causes of neonatal death was similar for physician review and InterVA with the exception of asphyxia and sepsis that were almost equivalent in the InterVA analysis, while neonatal infections were more common according to physician interpretation.

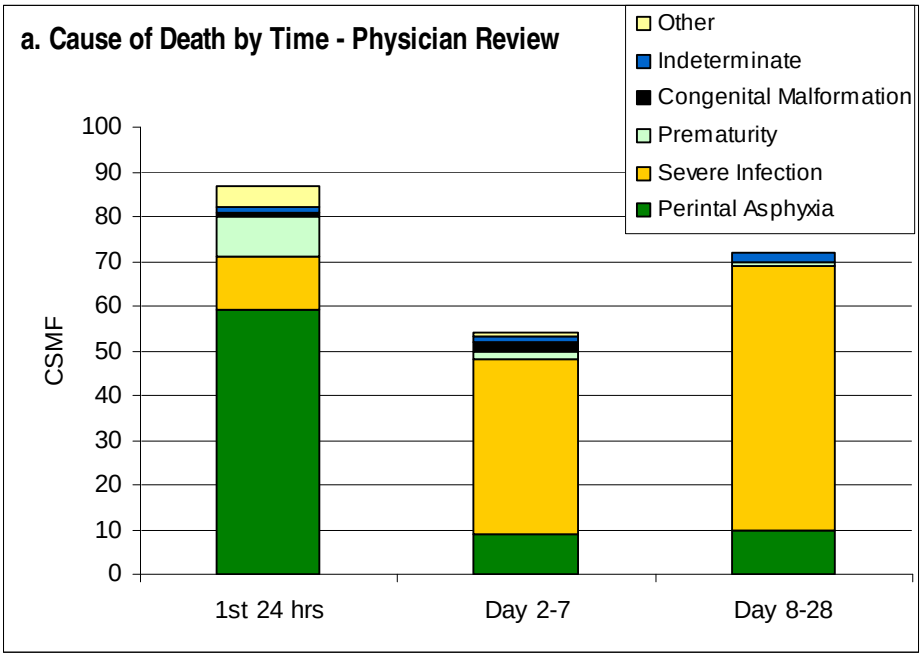
There were no reported cases of neonatal tetanus in the physician review or in InterVA.

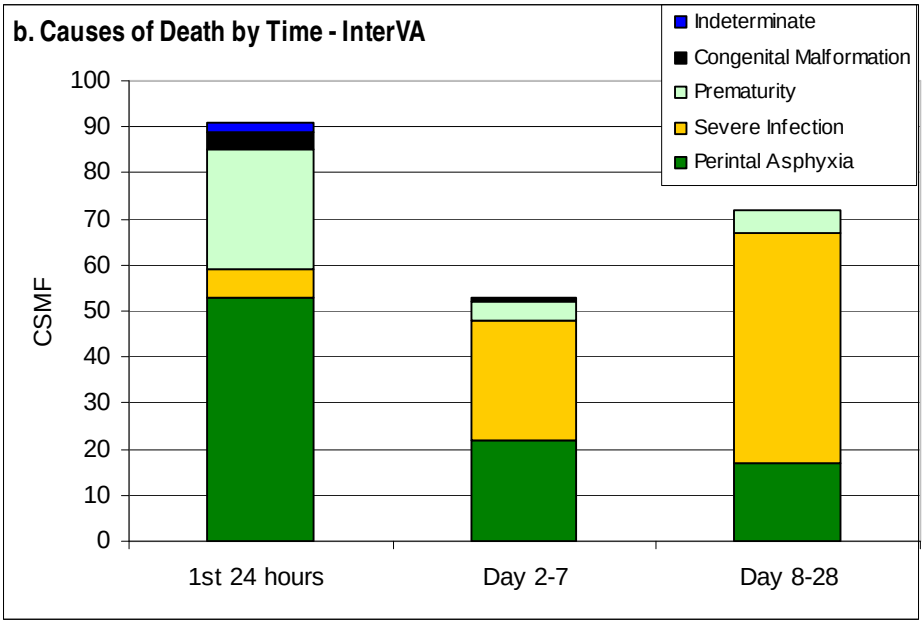
Verbal autopsies are not appropriate for individual clinical diagnoses but are essential for epidemiological monitoring of trends over time. Therefore it is most important to evaluate the comparability between CSMF using different methodologies and ideally a gold standard, however k*appa* statistics to compare physician opinion and interVA data on individual basis were calculated for completeness. The agreement was 74%, with a k*appa*=0.62 (CI 0.59-0.65), a moderate agreement according to Landis and Koch criteria[524].

5.5 - Causes of Death by Day of Death

The causes of death by age at death are shown in Figure 5.4, using both physicians' interpretation and InterVA. The most common causes of death in the first day of life were perinatal asphyxia, prematurity and severe infections. Amongst neonatal deaths, congenital malformation was the fifth cause of death and were clustered in the first week after birth. Amongst the late neonatal deaths, severe infections became the most prominent cause of death (Figure 5.4 a and b).
The profile of causes of death split by day of death is interesting as it shows some differences between physician review and InterVA. Physicians diagnosed 3 infants as having died of congenital malformation; using InterVA 6 infants deaths were ascribed to congenital malformations. All these questionnaires had congenital malformation as one of the indicators. Of those one corresponded between the two methods. Prematurity was cause of death for only 5 infants according to physicians while 37 questionnaires had prematurity ascribed as first or second cause of death by InterVA. All the infants who where considered to have died of prematurity according to physicians were amongst the 37 questionnaires that InterVA also considered as premature.
This explains the different distribution of causes of death by day of life and explains the higher proportion of death due to prematurity in the first 24 hours of life according to InterVA, as InterVA has a significantly higher proportion of deaths due to prematurity overall. The Kappa between the two methods also show that a degree of discrepancy exists, being 0.62 (CI 0.59-0.65).

Figure 5.4 - Cause of Death by Day of Death using Physician Review and InterVA





5.6 - Prematurity and “Small for Gestational Age”

Even if the inaccuracy of the verbal autopsy process does not allow it to discriminate with certainty a premature infant from a small for gestational age infant (defined as an infant with a birthweight below the 10th centile for gestational age), it is fair to assume that both prematurity and a small weight at birth coexist and overlap in the newborn period. There was a difference in the reporting of prematurity/small for gestational age in the raw questionnaire data, where the proportion of premature/small babies was higher than resulted in the diagnoses by both physician review and InterVA, even if the hierarchical algorithm listed prematurity before any other cause of neonatal death (Table 5.7).

Table 5.4 - Comparison of Infants Recorded as Small for Gestational Age or Preterm in the Questionnaires, Physician Review and InterVA Interpretation

	Questionnaire %	Physician Review %	InterVA %
Stillbirths			
Gestational Age ≤ 8 Months	26	3	n/a
Small at Birth	15		
Neonatal Deaths			
Gestational Age ≤ 8 Months	35	6	14
Small at Birth	37		
Gestational Age ≤ 8 Months & Small at Birth	20		

5.7 - Conclusions

- During the period between September 2001 and September 2004 in Makwampur district the stillbirth rate was 23 per 1000 total births and the neonatal mortality rate was 31 per 1000 livebirths
- The majority of infants died in the first day and week after birth.
- According to physician review, 44% of all deaths were stillbirths, amongst the neonatal deaths the most common cause of death was neonatal infections (28%) followed by perinatal asphyxia (22%), then by prematurity (3%). Other causes of death, indeterminate and congenital malformations accounted together for 3% of cases.
- InterVA results attributed the same percentage of deaths to stillbirths and had a very similar proportion of death caused by severe infections and perinatal asphyxia. The proportion of cases attributed to prematurity was more than double that obtained by physician review.
- None of the methods attributed any death to neonatal tetanus.
- When causes of death were separated by day of death, perinatal asphyxia was the most common cause of death in the first 24 hours after birth. After the first week neonatal infection became the most common cause of death. The biggest proportion of deaths attributed to prematurity in the InterVA model occurred in the first 24 hours.
- Results obtained with physician review and InterVA were very similar in this population and *kappa* statistics showed moderate agreement between physician review and InterVA (*kappa* = 0.62).

Chapter 6

Results

Burden and Causes of Stillbirths and Neonatal Deaths in an Urban Slum Population– Mumbai – India

6.1 - Burden of Stillbirths and Neonatal Mortality in 4 Slums - Mumbai

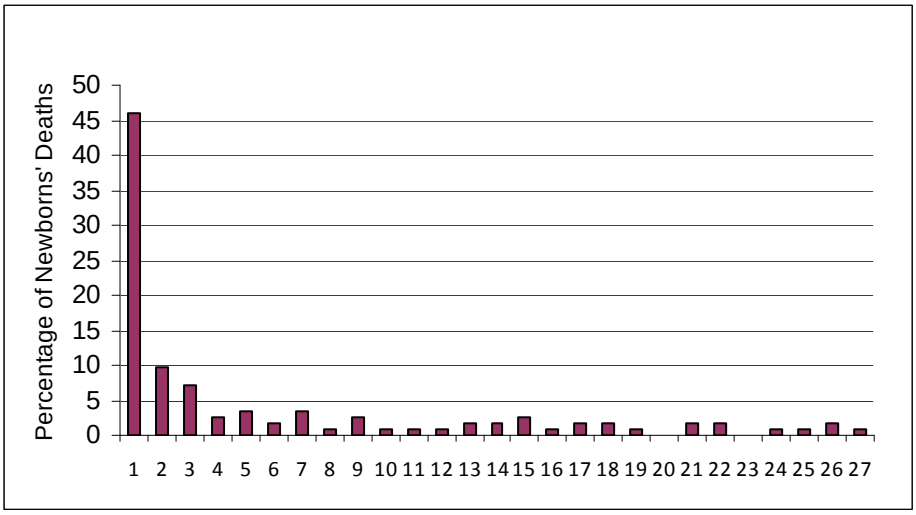
Over a 3 years period (1st October 2005 –30th September 2007) 13,467 births were recorded amongst a population of over 300,000 people living in slum areas, across 6 wards in Mumbai, as part of a large surveillance and intervention study. The data collection was part of a cluster randomised controlled trial to measure the effect of community groups lead by woman facilitators in improving maternal, perinatal and neonatal health[435;525].

During that period 369 infants died between the 28th week gestation and the first 28 days of life. Of those 159 were stillbirths and 210 died during the neonatal period. Verbal autopsies were collected by lay supervisors for 221 of those deaths. The stillbirth rate in the area was 11.8 per 1000 deliveries (n=159/13,467) and the neonatal mortality rate was 15.8 per 1000 (n=210/13,308) livebirths.

Most infants (n=185, 84%) in the study area were born in health facilities, only 15% (n=34) were born at home. Two women delivered in transit (1%).
Verbal autopsy interviews were collected at a median of 111 days after the infants' death, allowing a minimum mourning period of 7 days. The majority of interviews occurred within 200 days with a maximum of 626 days after death.

The majority of stillbirths and neonatal deaths occurred in male infants (n=125, 57%). Excluding stillbirths, most deaths (n=116) occurred on day 0 or 1 (n=53, 46%), another 27% (n=32) occurred in the first week after delivery accounting for 73% of all neonatal deaths (Figure 6.1).

Figure 6.1 – Neonatal Deaths per Day of Death



6.2 - Causes of Stillbirths and Neonatal Death – Physician Review

6.2.1 Physicians Agreement

VA questionnaires were read by five local paediatricians. The choice of dividing the workload between five doctors was pragmatic as it meant having the diagnoses from a large number of verbal autopsies in a reasonable time span. Therefore each doctor analysed a variable number of questionnaires (between 35 and 116) according to his/her availability. The majority of questionnaires (n=138, 62%) were assessed by 2 physicians. However because of duplication due to the tracking of the questionnaires, some of the questionnaires were classified by more than 2 doctors: 28 were assessed by 3 physicians, 5 by 4 physicians, and 6 were assessed by 1 physician only. A single cause of death was assigned for each infant by the reviewing physicians. Where agreement between the assessing physicians was not achieved, the questionnaires were read by a third paediatrician experienced both in verbal autopsy diagnoses and paediatrics in developing countries who established the final diagnosis. The physicians involved in the study used the same neonatal death classification and algorithm used in the Makwampur study (Chapter 5).

The overall *kappa* statistic measuring agreement between physicians was 0.69 (CI 0.66 - 0.74), when the stillbirth classification was reduced to fresh stillbirth and macerated stillbirths. All physicians involved agreed in 163 cases (74%). If only the cases where two physicians were involved were included they agreed in 135 out of 176 cases (77%). However when considering the whole stillbirths classification (7 categories), and all physicians' opinions agreement was reached on 107 out of 221 cases (48%) (*kappa* 0.47; CI 0.39-0.50). When only two physicians were involved in the process they agreed in 94 cases out of 176 (53%).

The lowest agreement was between physicians who each analysed a very small number of questionnaires (Table 6.1 and 6.2).

Table 6.1 – Number of Questionnaires Assessed by Each Physician

	Doctor 1	Doctor 2	Doctor 3	Doctor 4	Doctors 5
Neonatal Deaths	90	53	61	20	34
Stillbirths	61	42	55	15	44
Total	115	105	116	35	78

Table 6.2 - Kappa Statistic between Physicians Interpreting Verbal Autopsy Questionnaires

	Overlap	*Kappa*
Number of Questionnaires		
Doctor 1 and 2	76	0.63
Doctor 1 and 3	60	0.61
Doctor 1 and 4	12	0.66
Doctor 1 and 5	53	0.73
Doctor 2 and 3	24	0.73
Doctor 2 and 4	11	0.51
Doctor 2 and 5	5	0.46
Doctor 3 and 4	33	0.63
Doctor 3 and 5	36	0.73
Doctor 4 and 5	3	0.25

6.2.2 Physicians Classification

According to physician review there were 116 neonatal deaths (52%) and 105 stillbirths (48%). Of the stillbirths 39 (38%) were macerated and 65 (62%) were fresh. Fresh and macerated stillbirths were further classified according to the perinatal death classification used in Nepal. All of the macerated stillbirths were classified and the majority (63%) were considered to be associated with obstetric complications. Of the fresh stillbirths 63% (41) were attributed to obstetric complications (Table 6.3). Of the neonatal deaths, the majority (37%, n=81) were classified as early neonatal deaths, occurring within the first 7 days after birth, while 16% (n=35) occurred between 8 and 28 days (Figure 6.2).

Figure 6.2 – Stillbirths and Neonatal Deaths Distribution

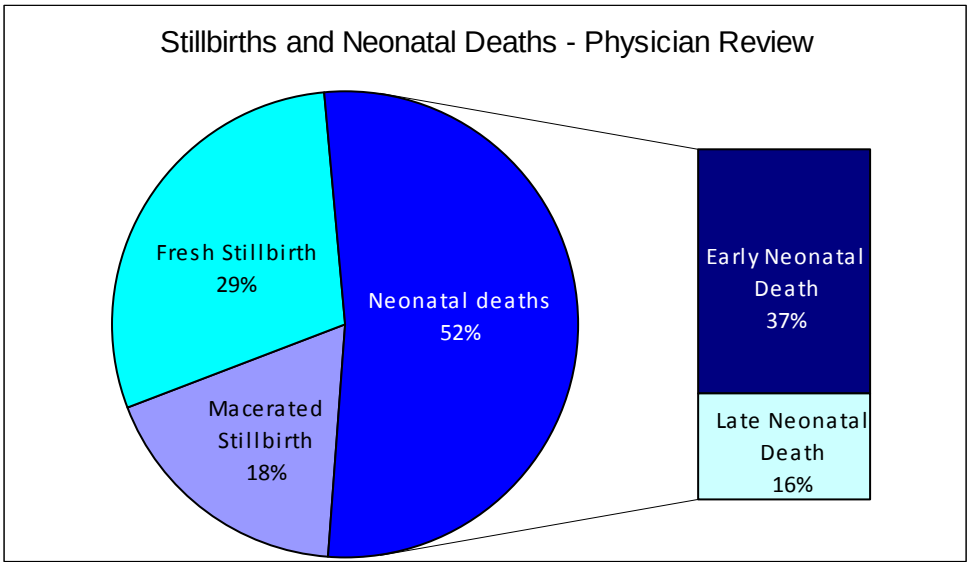


Table 6.3 – Causes of death According to Physician review

Stillbirths						
	Fresh stillbirths		Macerated stillbirths		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Prematurity	4	**6**	0	**0**	4	**4**
Obstetric Complications	41	**63**	9	**23**	50	**48**
Accidents	1	**1**	2	**5**	3	**3**
Congenital Malformation	2	**3**	1	**2**	3	**3**
Multiple Pregnancy	3	**5**	5	**13**	9*	**9**
Other	2	**3**	2	**5**	4	**4**
Unclassifiable	12	**18**	20	**51**	32	**30**
Total	65	**100**	39	**100**	105	**100**

Neonatal deaths						
	Early		Late		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Congenital Malformations	5	**6**	2	**6**	7	**6**
Asphyxia	21	**26**	0	**0**	21	**28**
Asphyxia & Obstetric Complications	10	**12**	2	**6**	12	**10**
Severe Infections	5	**6**	20	**57**	25	**21**
Prematurity	23	**28**	4	**11**	27	**23**
Other	10	**12**	0	**0**	10	**9**
Unclassifiable	7	**9**	7	**20**	14	**12**
Total	81	**100**	35	**100**	116	**100**

Note: *missing value : one of the stillbirth associated with multiple pregnancy was not classified either as fresh or macerated stillbirth

The majority of early NND were ascribed by physician review to asphyxia with or without obstetric complications (38%) or to prematurity (28%), while late neonatal deaths were mostly considered secondary to infections (21%) or unclassifiable (20%) (Table 6.3).

6.2.3 Establishing the Diagnosis of Prematurity and Small for Gestational Age

The questionnaires in the Mumbai study did not collect data on gestational age, instead data were derived from a question indicating whether the infant was born early (< 8 months gestation) or at the expected time (8-9 months gestation) or late (>9 months gestation). The diagnosis of prematurity was based on this question combined with questions about the birthweight and the size of the infant. As in Nepal there was a considerable discrepancy between the questionnaire data on prematurity and small for gestational age between both physicians and InterVA . Of 13 live born infants with a birthweight <1500 g, 9 were classified as premature while the other 4 were considered to have died of asphyxia (1), severe infections (2) and other (1), in contrast with the hierarchical algorithm rule listing prematurity above all causes of death except congenital abnormalities (Table 6.4).

Table 6.4 - Comparison of Infants Recorded as Small for Gestational Age or Preterm in the Questionnaires, Physician Review and InterVA Interpretation

	Questionnaire %	Physician Review %	InterVA %
Neonatal deaths			
Born Early	34	23	10
Small at Birth	67		

6.2.4 Maternal Perception of Size and Correlation with Recorded Birth-weight

Birthweight was available for 144 infants (66%). Amongst the stillbirths, birthweight was available for 61 infants (58%) and the median was 2100 g (430-4500g). Amongst the neonatal deaths, birthweight was available for 83 infants (71%) with a median of 2300 g (800-5000g).

The maternal perception of the infant size at birth was assessed in the interview by asking whether the infant was very small, small, average or very large. Maternal perceptions of infant size were compared with birthweight for 140 infants with complete data were available. The sensitivity of maternal judgement was 89% (CI 80-95%) and the positive predictive value 80% (CI 74-94) (Table 6.5).

Table 6.5 – Comparison between Maternal Perception of Size and Recorded Birth-weight

	Very small (%)	Average (%)	Very large (%)	Not known (%)	Total (%)
<2500g	67 (87)	6 (8)	2 (3)	2 (3)	**77**
2500-3500 g	17 (29)	11 (19)	29 (49)	2 (3)	**59**
>3600 g	0	0	8 (100)	0	**8**
Total	**84 (58)**	**17 (12)**	**39 (27)**	**4 (3)**	**144 (100)**
Mean Bwt in g(SD)	**1606 g (470 g)**	**2957g (388g)**	**4325 (384)**	-	**-**

6.3 - Analysis of Stillbirths and Neonatal Mortality using the InterVA Model

Data were adapted to the InterVA format by the Sneha researchers and checked by the author. The cause of death distribution according to the InterVA model is shown in Table 6.6.

Table 6.6 – InterVA Method Diagnoses

Diagnoses	InterVA
Fresh Stillbirth	41.6
Macerated stillbirth	8.6
Congenital Malformation	0.2
Perinatal Asphyxia	29.4
Meningitis	0.1
Other Acute Infection	0.2
Pneumonia/Sepsis	9.9
All Infections	10.3
Pre-Term/Small Baby	9.3
Indeterminate	0.5

6.4 - Comparison between Physician Review and InterVA Model

The outcome from physician review was interpreted using consensus diagnosis and considering diagnoses expressed by every physician were given equal weight. For example if 2 physicians diagnosed a death as due to perinatal asphyxia and one as prematurity. Perinatal asphyxia would have received 66% and prematurity 33% for that death. For fresh and macerated stillbirths the database only included the final classification by the reviewing physician, therefore the likelihood of stillbirths for each of the questionnaires was considered 100%.

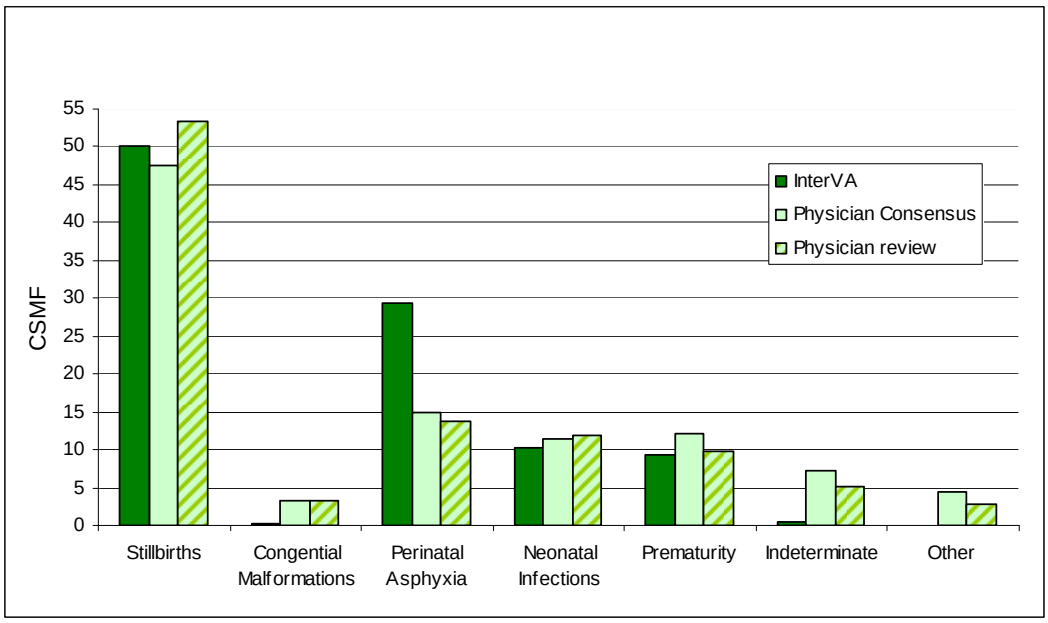
Table 6.7 and Figure 6.3 present the results obtained by comparing physician review outcomes with the two different methods and the InterVA outcome. The difference in the overall CSMF using physicians' consensus or all diagnoses varied between 1 and 4%, however it did change the ranking of the causes of death.

Table 6.7 –Causes of Death According to Physician Review (2 Methods) and InterVA

	InterVA	Consensus Physician Review	Difference in proportions (95% CI)	Physician Review (Adjusted)	Difference in proportions (95% CI)
Fresh Stillbirth	42	29	**-0.1 (-0.2- -0.04)**	33	**-0.09 (-0.2- -0.000)**
Macerated Stillbirth	9	18	**0.09 (0.03-0.1)**	20	**0.11(0.04-0.2)**
Congenital Malformation	0.25	3	**0.03 (0.004-0.05)**	3	**0.03 (0.004-0.05)**
Perinatal Asphyxia	30	15	**-0.15 (-002- -0.07)**	14	**-0.16 (-0.2- -0.08)**
Pneumonia/Sepsis	10	11	0.01 (-0.05-0.07)	12	0.02 (-0.04-0.08)
Pre-Term/Small Baby	9	12	0.03 (-0.03-0.09)	10	0.01 (-0.04-0.06)
Indeterminate	0.49	6	**0.06 (0.02-0.09)**	5	**0.05 (0.01-0.08)**
Other causes	0	5	**0.05 (0.02-0.08)**	3	**0.03 (0.008-0.05)**
Total	100	100		**100**	

Note: The physician review adjusted were calculated keeping into account all physicians' diagnoses the not adjusted are taking into consideration only the final, agreed diagnosis.

Figure 6.3 – Comparison between InterVA and Physician Review (2 Methods)



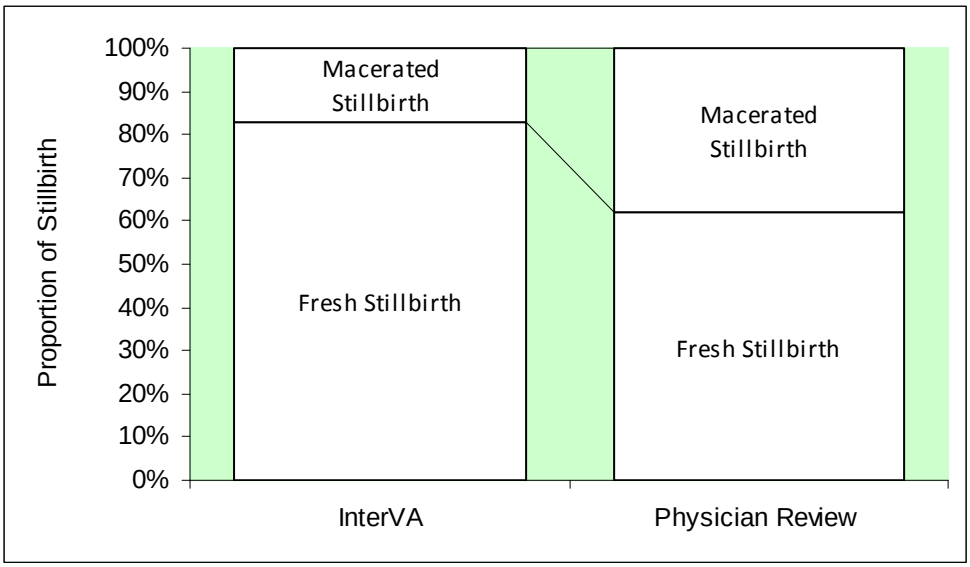
In both models the proportion of perinatal asphyxia diagnosed by InterVA was higher than recorded by physician review, while for most of the other diagnoses the proportion of InterVA and physician review was similar. Fresh and macerated stillbirths were considered together and the percentage of stillbirths was comparable, ranking first in both instances: 47% according to physician review and 50% according to InterVA.

The causes of death considered unclassifiable was higher using physician review (5-7%) than with InterVA (<1%). Physicians classified between 2% and 5% of questionnaires as “other causes of death”, while InterVA does not allow an “other causes of death” category. The agreement between the physician consensus diagnoses and InterVA for each individual questionnaire was 58% (*kappa* = 0.48; CI0.40 - 0.50) still within the category of moderate agreement[526].

6.4.1 Stillbirths

When stillbirths were split into fresh and macerated there was a higher proportion of fresh stillbirths according to InterVA (42%) compared with physician review (33%) and a lower proportion of macerated stillbirths (9%) compared with 20% respectively (Figure 6.4).

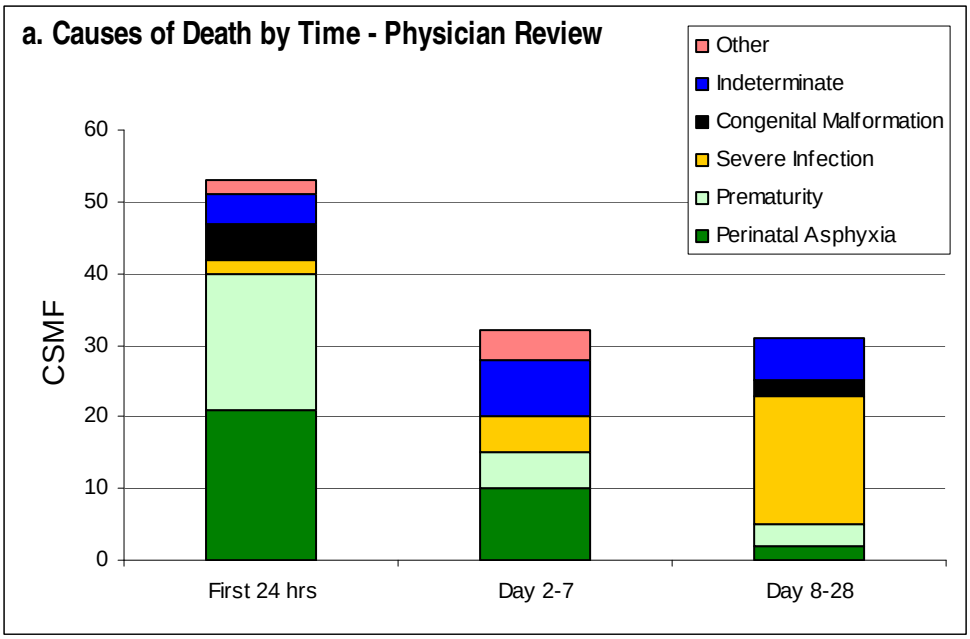
Figure 6.4 - Stillbirth Comparison between Physician Review and InterVA

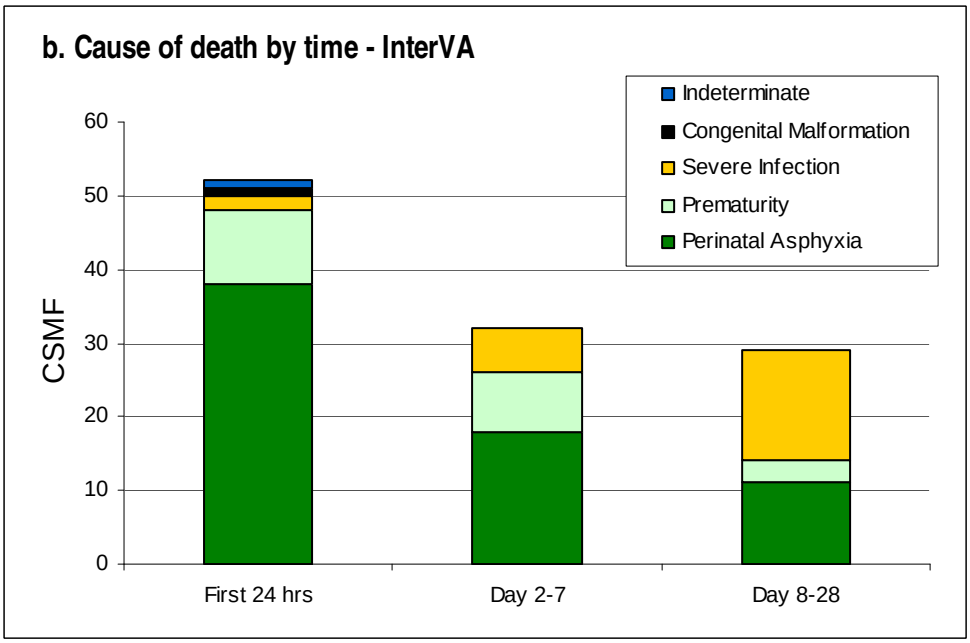


6.4.2 Causes of Death by Time

When the causes of death were plotted against the time of death, perinatal asphyxia predominated in the first 24 hours and progressively severe infections took priority in a similar way to the Nepal data (Figure 6.5). The respective proportions of asphyxia in all the three time frames were substantially higher according to InterVA than physician review, reflecting that the CSMF of InterVA attributed twice the proportion of death to asphyxia than physician review.

Figure 6.5 - Causes of Death by Day of Death





6.5 - Conclusions

- In Mumbai most infants were born in a health facility. About one half of deaths were stillbirths. Amongst the neonatal deaths the majority occurred in the first day of life (46%).
- Five physicians read and interpreted the verbal autopsies and their agreement was moderate (*kappa* =0.65).
- Birth weights were available for 66% of infants The sensitivity of maternal judgement of “small at birth” compared with birth-weight was 89%.
- As there were five interpreting physicians, InterVA results were compared with physician review in two different ways: by including all diagnoses expressed by physicians and by using only the final, agreed diagnosis. The ranking of causes of death with the two methods did change. When only the final diagnosis was considered prematurity ranked second after perinatal asphyxia while when all the physicians’ opinions were included it ranked third after neonatal infections.
- Physicians were more likely to diagnose macerated stillbirths compared with InterVA.
- Perinatal asphyxia was the most common cause of death for both physician review and InterVA. However there was a substantial disparity in the proportion of perinatal asphyxia (15% according to physicians and 30% in InterVA). This was more obvious when the data were separated by day of death. Perinatal asphyxia continued to account for a substantial proportion of deaths even in the late neonatal period using InterVA while the proportion of deaths caused by perinatal asphyxia according to physicians dropped substantially by day 2.

Chapter 7

Results:

Cause Specific Mortality Fraction for Stillbirths and Neonatal Deaths from Three Countries, using a Computerised Probabilistic Approach

7.1 - Stillbirths and Neonatal Deaths in Malawi, Nepal and Mumbai

In Malawi there were over a period of one year 160 stillbirths and 161 neonatal deaths out of 6,574 deliveries. In Nepal over three years, there were 8,184 deliveries of which 191 were stillbirths and 248 were neonatal deaths. In Mumbai over two years there were 13,467 births of which 159 were stillbirths and 210 neonatal deaths. Stillbirth rates, neonatal and perinatal mortality rates are reported in Table 7.1.

Table 7.1 - Stillbirth Rate and Neonatal Mortality Rate

	Malawi	Nepal	Mumbai
Study Period	2005-2006	2001-2004	2005-2007
Total Number of Births	6,574	8,184	13,467
Number of Stillbirths	160	191	159
Number of Neonatal Deaths	161	248	210
Total Number of Deaths	321	439	369
Stillbirth Rate (per 1000)	24	23	12
Neonatal Mortality Rate (per 1000)	25	31	16
Number of Available VA	318	385	221

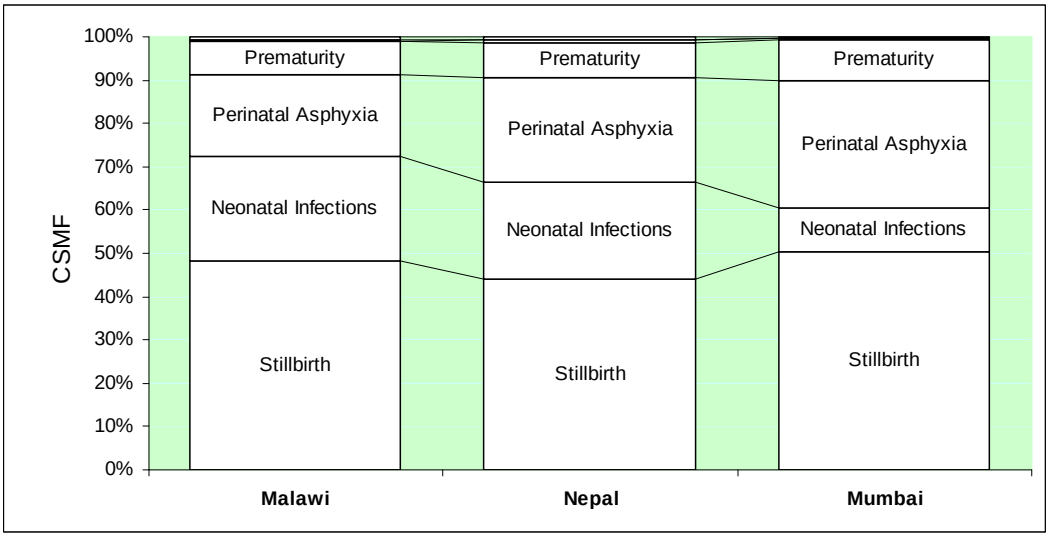
7.2 - Perinatal and Neonatal Cause Specific Mortality Fraction – Comparison between Rural Malawi, Nepal and Mumbai' Slums

The adapted InterVA model was used to compare CSMF in the three datasets described. The comparison was carried out considering that the data capture methodology in the three locations (such as the questionnaires' format and the type of interviewers) was very similar, as data were all part of related research environments. Moreover the InterVA model offered complete internal consistency and repeatability in the data interpretation. In this manner differences between the observed CSMF were likely to be due to true differences between the cause of death distribution amongst the three populations, rather than to data capturing methods or physician interpretation and perception of the local epidemiology. The data from 318 questionnaires available from Malawi, 385 from Nepal and 221 from Mumbai were batched and entered in the InterVA model. The results are shown in Table 7.2 and Figure 7.1.

Table 7.2 - Cause Specific Mortality Fraction all deaths – Multi-Country Comparison

		Malawi	Nepal	Mumbai
Stillbirths	Fresh	34.2		41.6
	Macerated	14.0		8.6
	Total	**48.3**	**44.0**	**50.2**
Congenital Malformation		0.8	0. 9	0.2
Perinatal Asphyxia		19	24.1	29.4
Neonatal Infections		24.1	22.5	10.3
Prematurity		7.7	8	9.3
Neonatal Tetanus		0.2	0	0
Indeterminate		0	0.6	0.5
Total		**100**	**100**	**100**

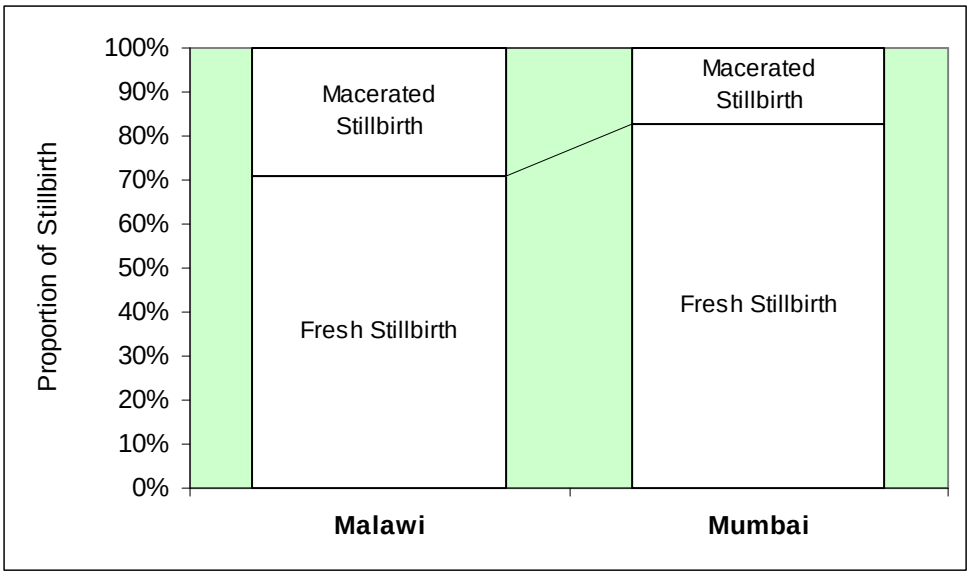
Figure 7.1 - Cause Specific Mortality Fraction – Multi-Country Comparison


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
CSMF
Prematurity
Perinatal Asphyxia
Neonatal Infections
Stillbirth
Prematurity
Perinatal Asphyxia
Neonatal Infections
Stillbirth
Prematurity
Perinatal Asphyxia
Neonatal Infections
Stillbirth
Malawi
Nepal
Mumbai

7.2.1 Stillbirths

The proportion of stillbirths in the three countries was 48% in Malawi, 44% in Nepal, and 50% in Mumbai. Intrapartum stillbirths were predominant in Mumbai (42%) compared to Malawi (34%). In Malawi a higher proportion of stillbirths occurred ante-partum (14%) compared to Mumbai (9%)(Figure 7.2).

Figure 7.2 Comparison of Causes of Stillbirths in Malawi and Mumbai -India



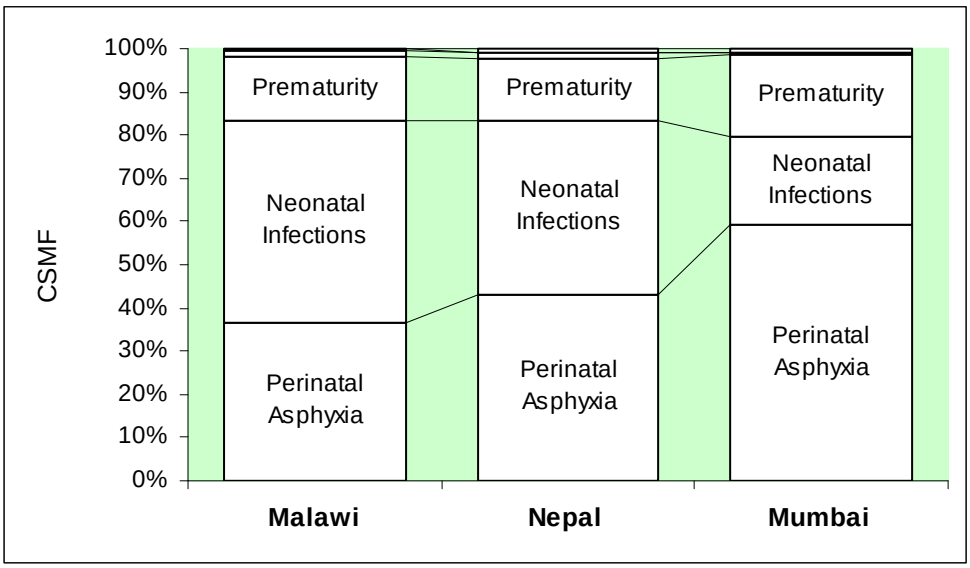
7.2.2 Neonatal Deaths

If stillbirths were excluded the respective proportions of causes of neonatal deaths is shown in Table 7.3 and Figure 7.3.

Table 7.3 - Cause Specific Mortality Fraction Neonatal deaths– Multi-Country Comparison

	Malawi	Nepal	Mumbai	Average of 3 Countries
Congenital Malformation	1. 5	1.6	0.5	1.2
Perinatal Asphyxia	36.7	43	59.1	46.2
Neonatal Infections	46. 7	40.3	20.7	35.9
Prematurity	14.9	14.2	18.7	15.9
Neonatal Tetanus	0.3	0	0	0.1
Indeterminate	0	1	1	0.7
Total	100	100	100	100

Figure 7.3 - Comparison of Causes of Neonatal Death in Malawi, Nepal and Mumbai -India

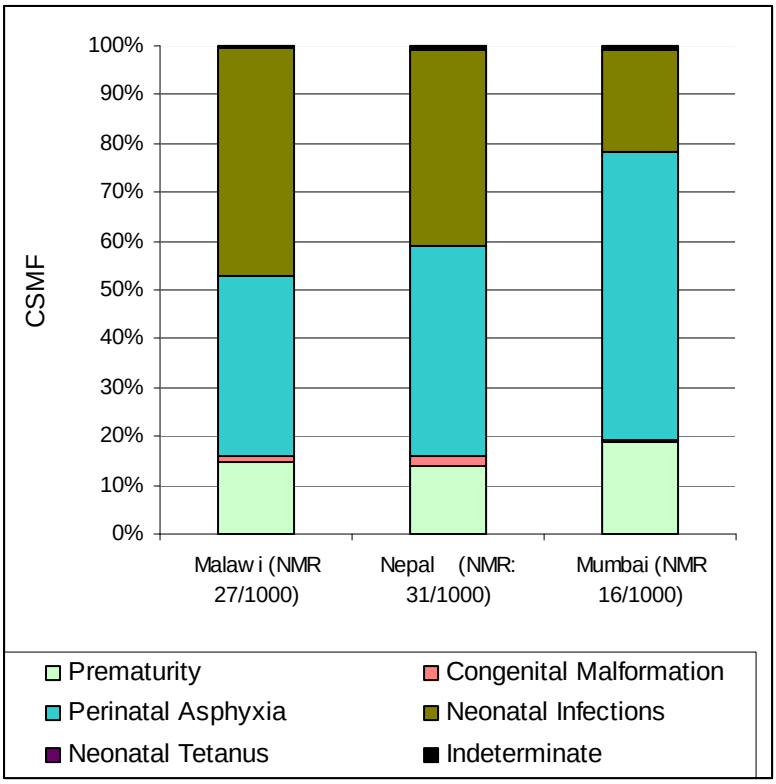


In Mumbai's slums the most common cause of neonatal death was birth asphyxia (29% of all deaths and 59% of neonatal deaths), while neonatal infections and prematurity contributed to 10% and 9% respectively, or 21% and 19% if only neonatal deaths were included.

Newborns in Malawi were more likely to die of neonatal sepsis (24% of all deaths and 47% of neonatal deaths) than their counterparts in rural Nepal (23% of all deaths and 43% of neonatal deaths) and in Mumbai's slums (10% or 21% of neonatal deaths). Prematurity (8% of all deaths and 15% of neonatal deaths) and birth asphyxia (19%, 37% of neonatal deaths) were less common than in Nepal (9% and 24% or 14% respectively and 40% when neonatal deaths were considered) and Mumbai (9% and 29% respectively or 18% or 59% when neonatal deaths were considered) (Table 7.2 and 7.3).

Figure 7.4 illustrates the different causes of neonatal death distribution in the three populations associated with the respective NMR.

Figure 7.4 - Distribution of Causes of Neonatal Death in Three Populations

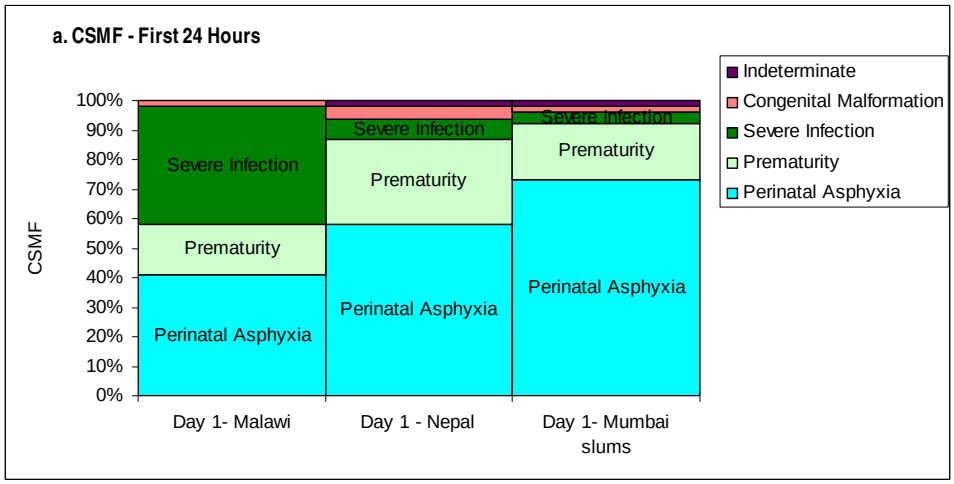


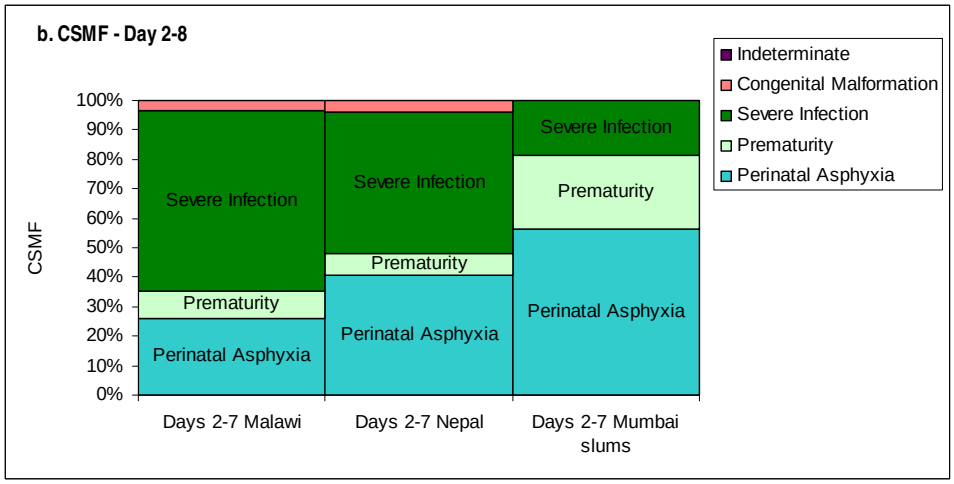
7.3 - Neonatal CSMF by Day of Death in Malawi, Nepal and Mumbai's Slums

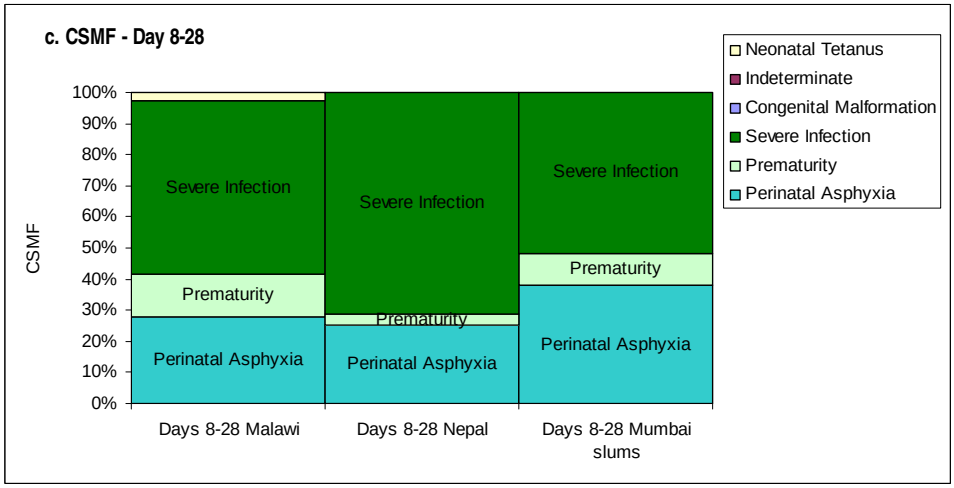
Amongst the 170 live births in Malawi, 221 in Nepal and 113 in Mumbai for which VA questionnaires were available, it was possible to separate the causes of death according to the day of death. In Malawi deaths in the first 24 hours from birth represented 61% of all neonatal deaths, in Nepal 46%, and in Mumbai 41% (Figure 7.5 a).

Perinatal asphyxia was the most common cause of death in this period in all populations (Mumbai 34%, Malawi 25%, Nepal 25%). Prematurity was the second most common cause of death in Mumbai's slums (9%) and Nepal (12%), while infection was the second cause of death in Malawi (24%).

Figure 7.5 - CSMF for Neonatal Deaths by Time







Between the second and seventh day of life the proportion of neonatal deaths was 28% in Mumbai, 24% in Nepal and 18% in Malawi. Perinatal asphyxia was the largest proportion of neonatal deaths in Mumbai (16%), followed by prematurity (7%) and severe infections (5%). Severe infections were the most common cause of death in Nepal (12%) and Malawi (11%), followed by perinatal asphyxia (Malawi 5%, Nepal 10%) and prematurity (2%). All deaths attributed to congenital malformations occurred during the first week of life. (Figure 7.5 b).

In Nepal 34% of neonatal deaths occurred after the first 7 days of life, in Mumbai 26%, and in Malawi 21%. Severe infections were the predominant cause of death in all populations (Nepal 24%, Mumbai 13%, Malawi 12%). Perinatal asphyxia was the second most common cause of death (Mumbai 10%, Nepal 8%, Malawi 6%). Prematurity represented 3% of deaths in Malawi and Mumbai and 1% in Nepal (Figure 7.5 c).

7.4 - Comparison between Baseline Characteristics of the Three Datasets

To explore whether the differences in the cause of death reported could have been due to variation in the quality of the data collected, technical differences such as the type of respondents, time elapsed between death and VA interview were analysed.

7.4.1 Respondents

Maternal recall of events around death is adequate to establish causes of death for verbal autopsy purposes[527], however recollections of events by other members of the family, particularly if not present during the death of the infant or during childbirth has not been established[528]. If substantial differences were present in the three datasets, recall biases could be introduced and sub-analysis of questionnaires with mother as respondent could have been necessary. Data on the respondents to the verbal autopsy interviews were available for Malawi and Nepal and mothers were the respondents in 96% and 98% of questionnaires respectively (p=0.3).

7.4.1.1 Comparing the Quality of Data Collection when using Mothers versus Other Respondents in the Malawi Dataset

Given the lack of data about the quality of VA interviews obtained using different types of respondents, we analysed the available data using three parameters as indicators of quality: the availability of the open history, the number of indicators missing at data entry using InterVA indicators and the number of causes of death classified as indeterminate by InterVA and physician review. The Malawi dataset was used as it was the only dataset

where the open histories were available. Given the small proportion of respondents other than the mother of the deceased, a single category of "all other respondents" was created for each database.

The open history was more likely to be available if the mother was interviewed (72% of cases) than in the seven cases when other relatives were interviewed (28%), although this did not reach statistical significance ($p=0.09$).

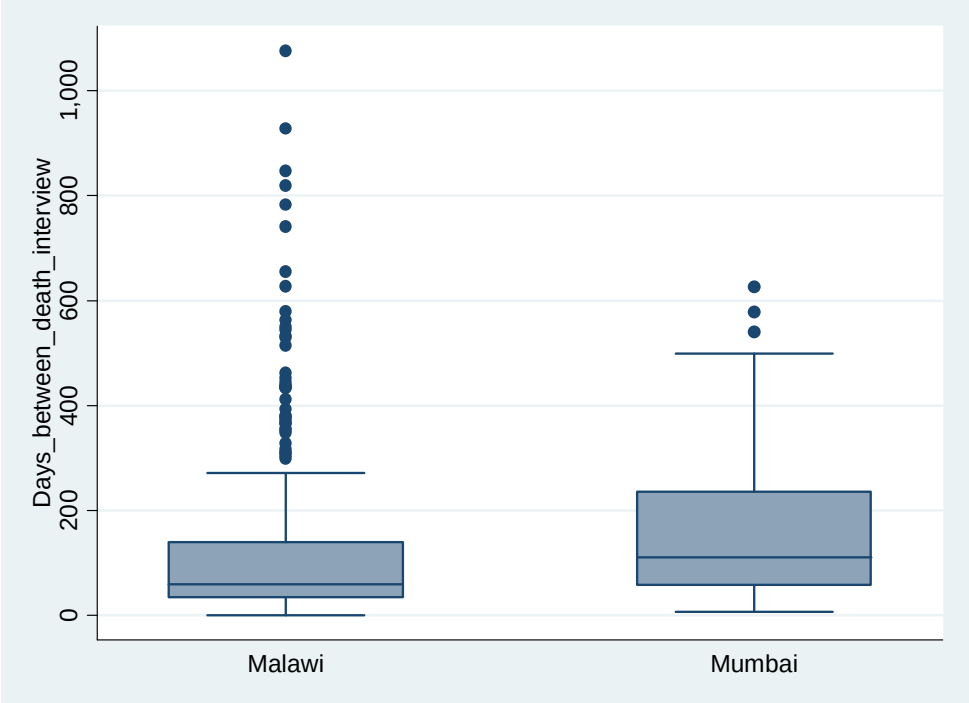
If the number of missing fields in the questionnaire were compared between interviews collected from the mothers and other respondents, the number of field left blank if the mother was not present, was significantly higher than if the mother was interviewed ($p=0.0021$).

There was, however, no difference between the number of indeterminate causes of death if the mother or another person was interviewed, both if physician review or InterVA were used to interpret the data. ($p=0.6$).

7.4.2 Timing of Verbal Autopsy Interview

The interval between the time of death and the verbal autopsy interview was available for the Malawi and the Mumbai databases. The median and interquartile range for Mumbai (median 111 days range 7-626 interquartile range 178) were larger than for Malawi (63 days range 3-1076 interquartile range 110). As the interval between the death and the interview was not distributed normally, a non parametric test was applied (Mann Whitney test) and showed that the difference between the two medians is statistically significant: $z= -5.413$ $p<0.001$. Figure 7.6 illustrates graphically that the interval between death and interview was shorter in Malawi than in Mumbai.

Figure 7.6 - Interval between Death and Verbal Autopsy Interview - Malawi and Mumbai



Using the Maimwana database, the impact of the interval between death and VA interview on the quality of the data obtained through questionnaires was assessed using the same parameters as per the evaluation of the respondents. In Malawi 255 interviews occurred within 6 months from death, 285 within a year and 31 after one year of death (2 missing values).

The open histories were more likely to be missing if the interview occurred over one year after death (13/31; 42%), than if they occurred within a year (76/285; 27%), however it was not statistically significant (risk difference 0.15, CI -0.08-.38; p= 0.07).

There was no correlation between the timing of death and VA interview with the number of missing fields in the VA interview, calculated using linear regression (ttest 1.4 p=0.2 CI: -1.4-8.9).

Finally there was not a statistically significant difference in the number of missing fields using the independent t test for difference in means with a 6 months cut off (CI -0.4- 1.2; p=0.3) or a one year cut off (CI -1.7-.51 p=0.3).

A longer interval between administering a VA questionnaire and time of death did not result in a higher number of causes of death defined as "unclassifiable" both by physician review or InterVA (t test0.6,. CI -61-119 p=0.53 and t test -0.4 CI -119-76 p= 0.7)

7.4.3 Demographic Characteristics

The sex split, the proportion of stillbirths and prematurity, defined as birth before the 8th month gestation, or reported to have been "born early" according to the questionnaire, are illustrated in Table 7.4. Stillbirths represented 46% of all deaths in Malawi, 43% in Nepal and 49% in Mumbai. In Malawi 16% of stillbirths and neonatal deaths were twins, twice as many as in Mumbai (9%) or Nepal 8%. Congenital malformations were reported in 27% of the VA questionnaires collected from Nepal, 9% from Malawi and 16% from Mumbai (Table 7.4).

Table 7.4 - Comparison of the Demographic Characteristics between the Three Studies

	Malawi N (%)	Nepal N (%)	Mumbai N (%)	P value^
Male	174 (56)	217 (56)	125 (57)	0.81
Stillbirth	147 (46)	164 (43)	108 (49)	0.29
Twins	52 (16)	32 (8)	19 (9)	0.001
GA < 8 months OR Born early	70 (42)	76 (34)	39 (35)	0.003
Congenital Malformation*	28 (9)	106 (27)	36 (16)	<0.001

Note: ^p value amongst the three countries obtained using chi^2 for trend
*Congenital malformations were defined in the questionnaires as the presence of any "obvious deformity".

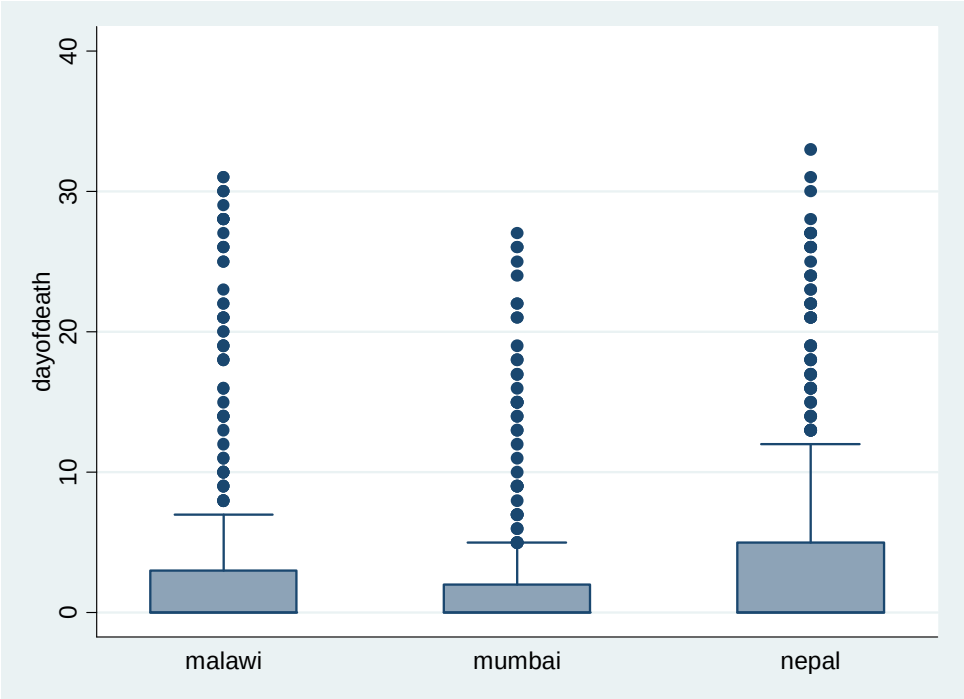
In Nepal 42% of the infants reported to have congenital abnormalities were macerated stillbirths, and of all macerated stillbirths 60% were considered to have congenital abnormalities. This does not seem plausible. It is more likely that this high rate of congenital abnormalities is to ascribe to a misinterpretation of the meaning of congenital malformation by the respondents that over-reported macerated infants, not looking "normal" as malformed infants. This view was also shared by the physicians interpreting VA in Nepal. In Mumbai 19% of the macerated SB were reported to be malformed and in Malawi 36%.

It is not clear why Malawi had a high proportion of twins. It is likely this is due to the higher rate of twinning in the African population (calculated to be 21 per 1000 in Malawi[529]. higher compared with the very low twinning proportion in all of the South and South East Asia (6-9 per 1000)[530].

7.4.3.1 Time of Death

The median age at death for livebirths was within the first 24 hours of birth in Malawi (range 28, interquartile range 5), within day 3 in Nepal (range 28, interquartile range 11) and within day 2 in Mumbai (range 27, interquartile range 8). About 2/3 of neonatal deaths occurred in the first week (p= 0.0003) (Figure 7.7).

Figure 7.7 - Age at Neonatal Death in Malawi, Nepal and Mumbai, Live Births



7.4.3.2 Obstetric Care

Amongst mothers in Malawi and Mumbai 76% received either 2 tetanus toxoid injections during the current pregnancy or at least 5 injections in their life time, in 58%.

In Mumbai 84% of infants died in a health facility, in Nepal 11%. The birth-weight was available for 66% of the Mumbai infants but for only 14% of the Malawi infants. The rate of caesarean sections, available for Malawi and Nepal was 10% and 2% respectively.

Women of infants who were stillborn or died in the neonatal period received oxytocic drugs, either as an allopathic or traditional medicine in 30% of cases in Malawi and 9% in Nepal (Table 7.5).

Table 7.5 - Comparison of Available Obstetric Care Indicators between the Three Studies

	Malawi	Nepal	Mumbai	OR	Pvalue (CI)
Neonatal Tetanus in Pregnancy	242 (76)	148 (58)	167 (76)	1.2	<0.0001 (0.91 - 0.14)
Delivery in Health Facility*	70 (23)	44 (11)	185 (84)	1.2	<0.0001 (0.97- 1.50)
C Sections	31 (10)	6 (2)	-	-2.2	<0.0001 (-2.54- 1.79)
Oxytocic	95 (30)	33 (9)	-	-0.8	<0.0001 (-1.07- 0.59)

*for Malawi it is place of death rather than delivery place.
Logistic regression is used to calculate the odds ratio and Malawi is used as baseline

7.5 - Comparing InterVA Output Using Different Analytical Methods

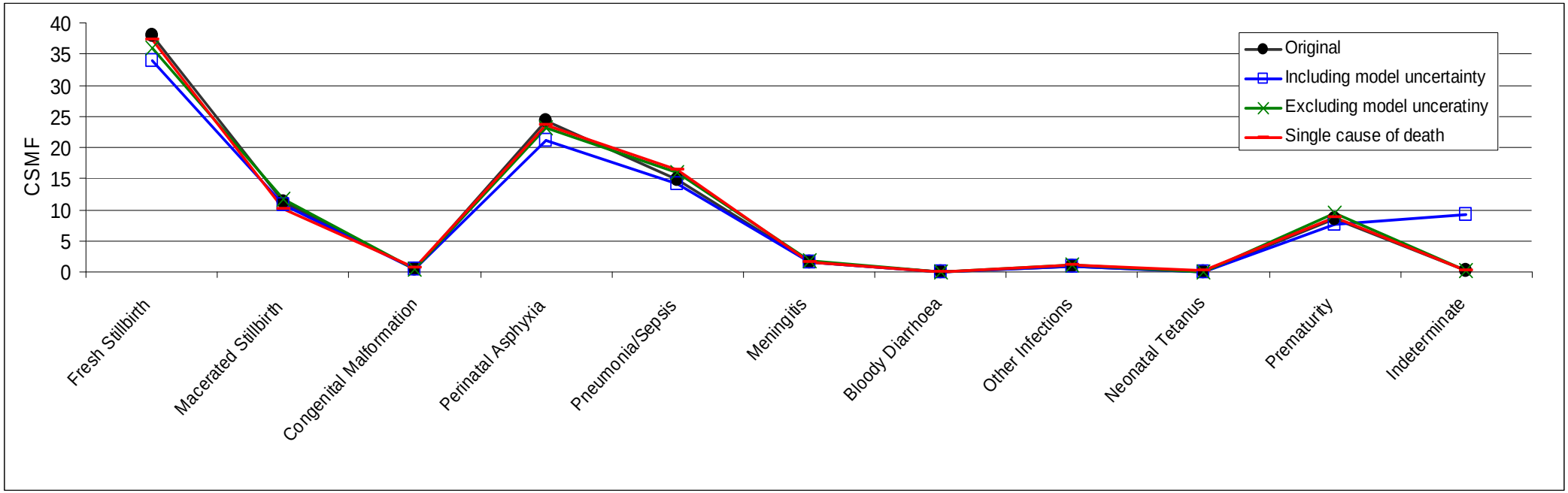
In this thesis the InterVA output (CSMF) was obtained by dividing the total likelihood for each diagnosis obtained from the model, by the total likelihood of all diagnoses, as stated in the methods (Chapter 3). However this is not the only way of interpreting the InterVA likelihoods. For this analysis only the Malawi and Mumbai databases were used, as the Nepal data did not allow the distinction between fresh and macerated stillbirths, reducing the number of diagnostic categories. Three different analysis strategies were used to obtain the overall InterVA output: the first accounted for model uncertainties, the second excluded all model uncertainties and the third considered only a single cause of death: the most likely, according to the model.

Table 7.6 and Figure 7.8 compare the results using the original model and these three different approaches. Differences over 2% are noted when including model uncertainties. In this situation perinatal asphyxia is reduced by about 3% and fresh stillbirths by about 4%, while the proportion of indeterminate is increased by almost 9%.

Table 7. 6 - Comparison between Different InterVA Outputs using All InterVA Diagnoses

	Original Model	Including model uncertainties	Excluding model uncertainties	Single cause of death
Fresh Stillbirths	38	34	35.9	37.3
Macerated Stillbirths	11.3	10.7	11.6	10.2
Congenital Malformation	0.5	0.5	0.6	0.7
Perinatal Asphyxia	24.2	21.2	23.2	23.6
Bloody Diarrhoea	0.1	0.1	0.1	0
Meningitis	1.5	1.6	1.8	1.7
Pneumonia/Sepsis	14.7	14.2	15.9	16.3
Other Infections	1	1.0	1.2	1.1
Neonatal Tetanus	0.1	0.1	0.1	0.2
Prematurity	8.4	7.5	9.5	8.7
Indeterminate	0.2	9.1	0.2	0.2

Figure 7.8 - Comparison of InterVA Output Using All Causes of Death



7.6 - Use of Different Physician Review Outputs to Interpret Verbal Autopsy Data

Similarly to the previous analysis, challenging the original approach to interpreting the VA data produced by InterVA, physician review outcomes can be interpreted in different ways. VA have been traditionally interpreted by consensus of a number of physicians, therefore if there was discordance between two physicians this was resolved either by discussion between the original physicians involved in interpreting the VA, by a third physician or by a panel of physicians[531;532]. This method has been recently criticised for the loss of information through consensus diagnosis, causing loss of the minority opinion[226].

In this thesis we used the consensus approach when we reported physician review results, apart from the Mumbai dataset. When comparing physician and InterVA we assigned a value of 100 to every death and shared it between all the diagnoses provided by each physician involved.

Here we are comparing the results for Nepal and Mumbai physician review systematically using only the consensus diagnoses or using all diagnoses given by physician review weighing them equally and ignoring the consensus.

For the Nepal database the discordance between physicians was very low. Physicians disagreed in only 19 cases and a third paediatrician had to review their diagnoses. Given that in Mumbai 5 physicians were involved in the process of VA questionnaires interpretation, the discordance between physicians was higher.

Table 7.7 show the data from all diagnoses available and from the ones used for comparison between InterVA and physician review in Nepal and Mumbai.

The main differences emerging were the proportions of prematurity and neonatal sepsis in the Mumbai dataset. Prematurity was more commonly diagnosed by consensus and neonatal sepsis by considering the multiplicity of opinions.

Table 7.7 - Physician Review Outputs using Two Different Methods

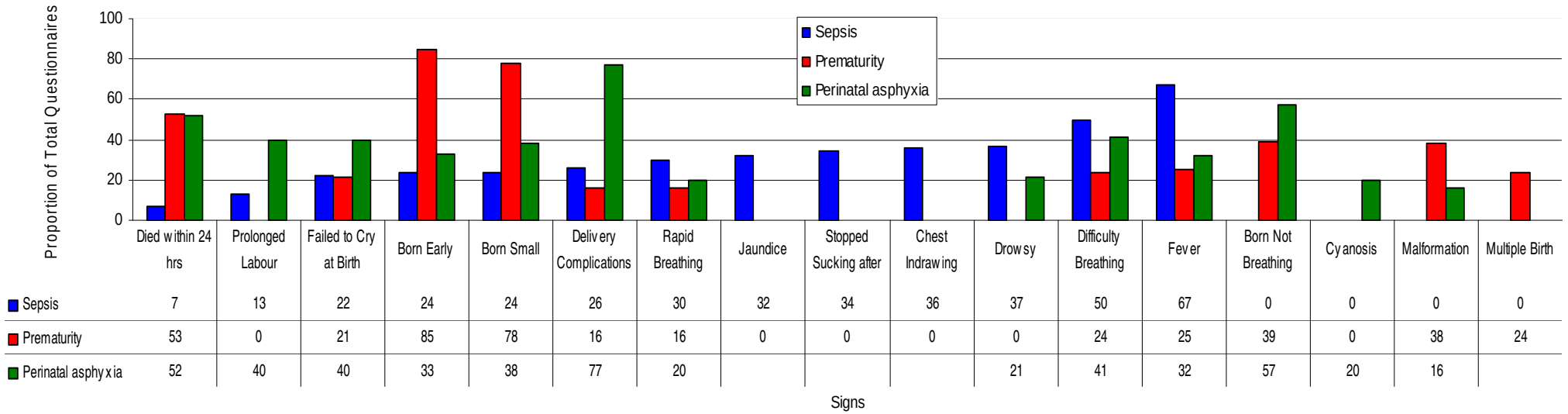
	Nepal		Mumbai	
	Consensus diagnoses	**Split diagnoses**	**Consensus diagnoses**	**Split diagnoses**
STILLBIRTHS				
Accident and External Conditions	1.0	1	1.4	1.9
Congenital Malformation	2.1	2.1	1.4	2..8
Obstetric Complication	27.0	27	23.8	21.2
Prematurity	1.3	1.2	1.9	6.9
Maternal Disease	6.2	6.7	4.3	3.0
Other	3	0.3	1.9	1.2
Unclassifiable	6.2	6.1	10.0	9.2
NEONATAL DEATHS				
Congenital Malformation	0.8	0.8	3.3	4.3
Perinatal Asphyxia	21.3	21.5	15.7	15.4
Severe Infection	28.8	29.0	11.9	15.8
Prematurity	2.9	2.8	12.9	10
Indeterminate	0.5	0.4	6. 7	5.2
Other	1.6	1.3	4.8	3.0

7.7 - Understanding the Impact of Different Indicators on InterVA Outcomes

As InterVA is the result of a combination a mathematical probabilistic model and expert opinions establishing which indicators are included in the model and their respective probabilities for each cause of death is important; the similarities and differences in the use of indicators by InterVA compared with physician review were compared for the diagnoses of sepsis, prematurity and perinatal asphyxia, as those represent over 80% of causes of neonatal death.

Using InterVA analysis, if all cases of sepsis, prematurity and perinatal asphyxia were plotted against all the InterVA indicators, only about 10-12 indicators were used in 20% or more of the cases. Of these 8 were the same in the 3 diagnoses: born early, born small, delivery complications, died within the first 24 hours, difficulty breathing, fever, rapid breathing and failed to cry at birth. However the respective proportions of these indicators was different for each cause of death. (Figure 7.9).

Figure 7.9 – Distribution of Indicators for the Three Main Neonatal Death Categories



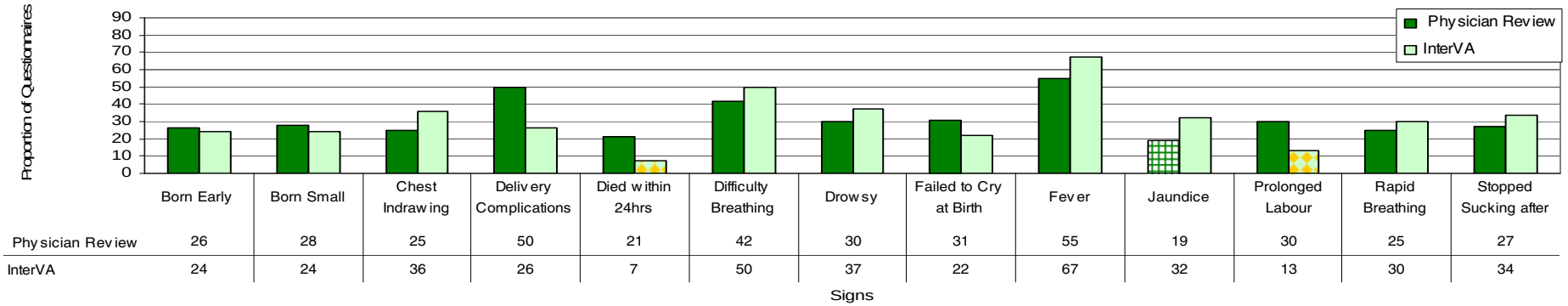
	Died within 24 hrs	Prolonged Labour	Failed to Cry at Birth	Born Early	Born Small	Delivery Complications	Rapid Breathing	Jaundice	Stopped Sucking after	Chest Indrawing	Drowsy	Difficulty Breathing	Fever	Born Not Breathing	Cyanosis	Malformation	Multiple Birth
Sepsis	7	13	22	24	24	26	30	32	34	36	37	50	67	0	0	0	0
Prematurity	53	0	21	85	78	16	16	0	0	0	0	24	25	39	0	38	24
Perinatal asphyxia	52	40	40	33	38	77	20				21	41	32	57	20	16	

Moreover, the use of indicators was similar in InterVA and physicians review. For the diagnosis of sepsis 11 signs were present in more than 20% of cases in the InterVA analysis, while 12 were present in the physician review analysis. The indicators were the same in InterVA and physician analysis with the exception of "did the baby die within the first 24 hours" and "was the labour prolonged", which were present in less than 20% of cases in the InterVA analysis; and jaundice, which was present in less than 20% in the physician's analysis (Figure 7.10).

Similarly for prematurity, 10 signs accounted for all signs present in over 20% of cases for physician review and InterVA analysis. For Perinatal asphyxia 11 signs were present in the physician review analysis at least 20% of the cases and 12 in the InterVA analysis (Figure 7.10).

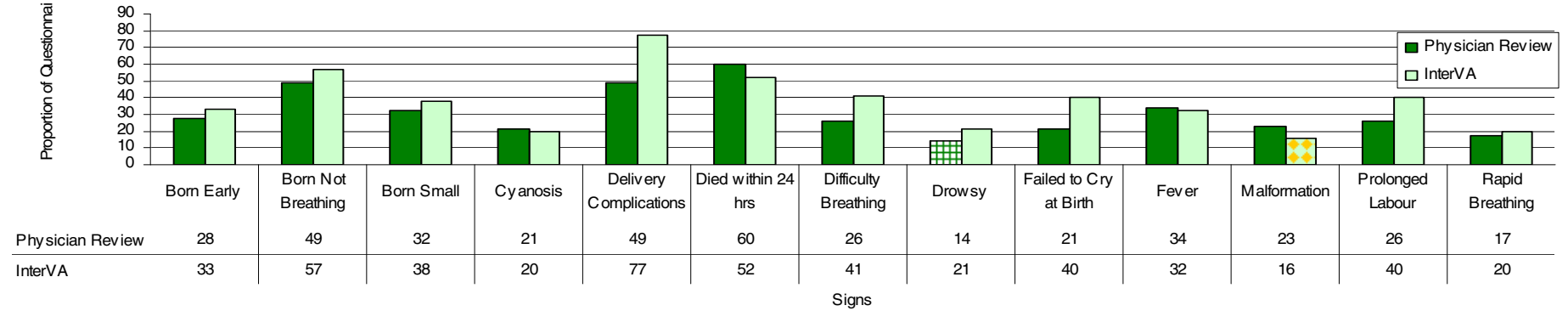
Figure 7.10 – Use of Indicators by Physicians and InterVA

a. Sepsis



	Born Early	Born Small	Chest Indrawing	Delivery Complications	Died within 24hrs	Difficulty Breathing	Drowsy	Failed to Cry at Birth	Fever	Jaundice	Prolonged Labour	Rapid Breathing	Stopped Sucking after
Physician Review	26	28	25	50	21	42	30	31	55	19	30	25	27
InterVA	24	24	36	26	7	50	37	22	67	32	13	30	34

b. Perinatal Asphyxia



	Born Early	Born Not Breathing	Born Small	Cyanosis	Delivery Complications	Died within 24 hrs	Difficulty Breathing	Drowsy	Failed to Cry at Birth	Fever	Malformation	Prolonged Labour	Rapid Breathing
Physician Review	28	49	32	21	49	60	26	14	21	34	23	26	17
InterVA	33	57	38	20	77	52	41	21	40	32	16	40	20

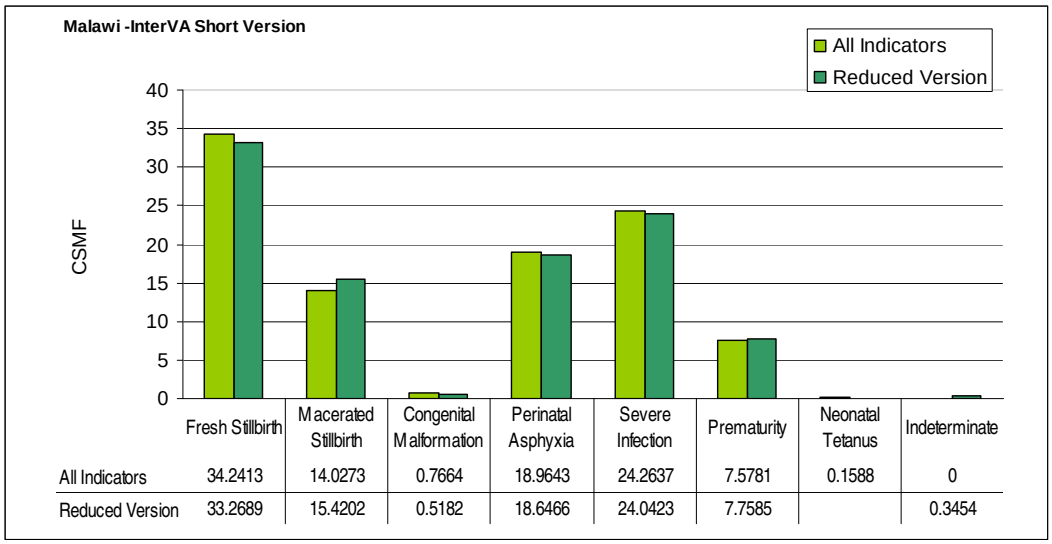
***Cont.* Figure 7.10 – Use of Indicators by Physicians and InterVA**

Given that only a small number of indicators were consistently used for diagnosis, the data from the three sites were re-run on InterVA using 27 indicators. The results were virtually unchanged Figure 7.11.

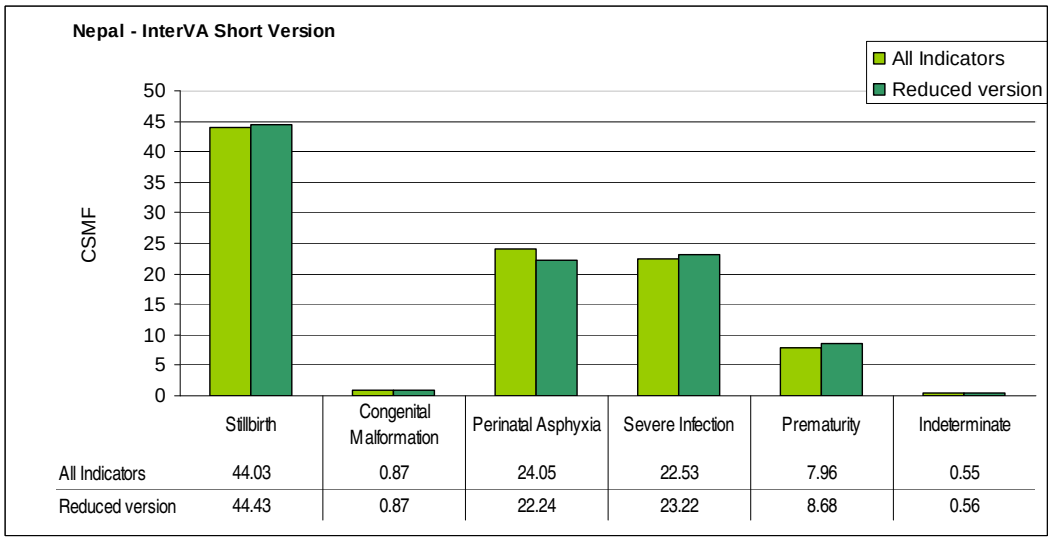
Table 7.8 –27 Indicators Used in the Reduced Version of the Questionnaire

Indicators used in the reduced version		
Was this a neonate <4 wks?	Was infant's skin puffy/mushy at birth?	Any difficulty breathing?
Did the final illness last <3 wks?	Was the baby born early (<34 wks)?	Any chest indrawing?
Was death sudden or unexpected?	Was the baby small (<2500g)?	Any rapid breathing?
Was death during the dry season?	Any congenital malformations?	Was there prolonged labour (>24 hours)?
Was death during the wet season?	Any cyanosis?	Any delivery complications?
Any obvious recent injury?	Any drowsiness?	Did the infant die within 24 hours?
Any convulsions or fits?	Any acute fever?	Did the infant fail to cry at birth?
Did the mother fail to receive Tetanus Toxoid vaccination?	Did the infant stopped sucking after day 3?	Was this a multiple birth?
Was there no cry/move/breath at birth?	Any jaundice?	Was there difficulty breathing at birth?

Figure 7. 11 – Data from Malawi, Nepal and Mumbai Using 27 Indicators

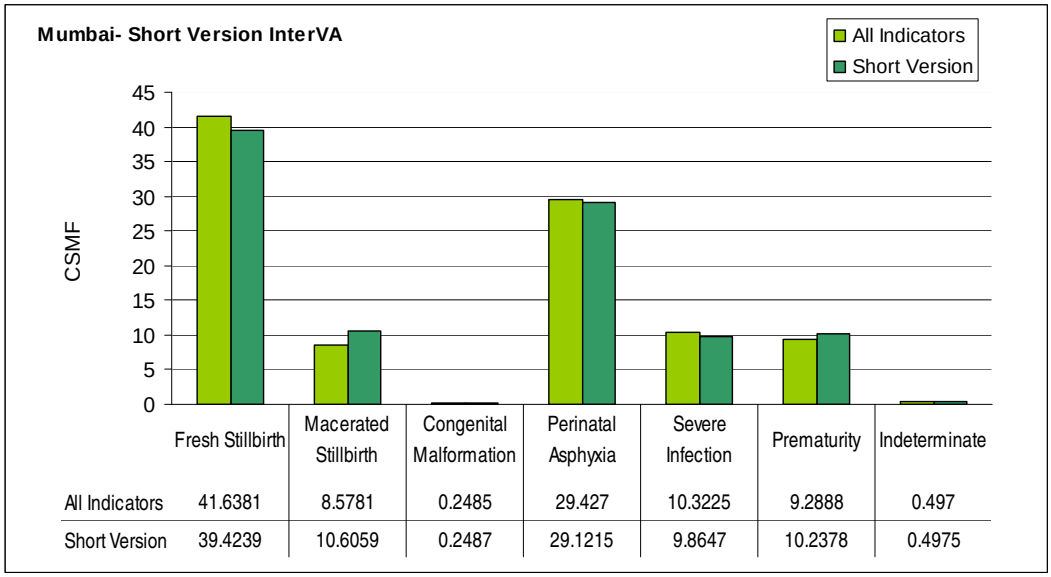


	Fresh Stillbirth	Macerated Stillbirth	Congenital Malformation	Perinatal Asphyxia	Severe Infection	Prematurity	Neonatal Tetanus	Indeterminate
All Indicators	34.2413	14.0273	0.7664	18.9643	24.2637	7.5781	0.1588	0
Reduced Version	33.2689	15.4202	0.5182	18.6466	24.0423	7.7585		0.3454



	Stillbirth	Congenital Malformation	Perinatal Asphyxia	Severe Infection	Prematurity	Indeterminate
All Indicators	44.03	0.87	24.05	22.53	7.96	0.55
Reduced version	44.43	0.87	22.24	23.22	8.68	0.56

Cont. **Figure 7. 11 – Data from Malawi, Nepal and Mumbai Using 27 Indicators**



	Fresh Stillbirth	Macerated Stillbirth	Congenital Malformation	Perinatal Asphyxia	Severe Infection	Prematurity	Indeterminate
All Indicators	41.6381	8.5781	0.2485	29.427	10.3225	9.2888	0.497
Short Version	39.4239	10.6059	0.2487	29.1215	9.8647	10.2378	0.4975

7.8 - Conclusions

- The comparison between CSMF for stillbirths and neonatal deaths in the three studies using InterVA shows differences amongst the proportion of neonatal deaths due to asphyxia, prematurity and neonatal infections. In Malawi neonatal infections were the most common cause of neonatal death followed by perinatal asphyxia and prematurity. In Mumbai's slums perinatal asphyxia was the most common cause of death followed by neonatal infections and prematurity.
- Stillbirths accounted for 44%, 50% of all deaths. The proportion of antepartum stillbirth was higher in Mumbai's slums.
- The variations observed are unlikely to be due to the VA tools used for the studies or the interpretation of the questionnaires with InterVA method, however training of interviewers and interviews techniques were not investigated or controlled for.
- Mothers represented the majority of respondents in Malawi and Nepal. When mothers were interviewed the number of missing indicators was lower compared to other respondents.
- An interval between death and interview up to a maximum of 6 months provided the lowest number of missing indicators in the InterVA questionnaire.
- InterVA outputs were analysed using different methods, the inclusion of model uncertainties reduced the proportion of deaths due to perinatal asphyxia and fresh stillbirths, increasing the proportion of deaths left indeterminate.
- When several physicians are used, considering all physicians' diagnoses rather than consensus provided higher percentage of death attributed to

severe infection, a lower percentage to deaths due to prematurity, other and indeterminate causes of death.

- The use of shortened questionnaires using InterVA showed results comparable to the original questionnaire version. A new version of InterVA could therefore have a reduced number of questions, making it more convenient for large surveys.

Chapter 8

Discussion

Objective 1 - Is it necessary and feasible to propose a single standardised classification and diagnostic algorithm for stillbirth and neonatal deaths to interpret verbal autopsy data?

8.1 - Classifications of Stillbirth and Perinatal Deaths

The three studies in this thesis from the same research group covered a period of about eight years, and resulted in three different perinatal and neonatal death classifications being used to analyse VA: two for physician review and one for InterVA.

8.1.1 Classifications for Physician Review

Researchers proposed different classifications according to their knowledge derived from internal and international work. The process of developing physician review classifications illustrates a tension between simplifying existing classifications whilst keeping essential distinctions of public health relevance and maintaining a complexity acceptable to physicians devising and using such classifications. At the public health level it is important that causes of death that can be prevented with different interventions are kept separate. For example, neonatal infections requiring use of antibiotics or clean delivery kits is separated

from perinatal asphyxia requiring skilled birth at delivery. While fresh stillbirths and perinatal asphyxia are both likely to respond to the same interventions of skilled birth attendant, improved access to health facilities, and improved referral pathways between health facilities. However, for clinicians the distinction between stillbirths and early neonatal deaths is important.

The groupings of causes of death were very similar in the version used in Malawi and the ones in Nepal and Mumbai. For neonatal deaths they were: congenital abnormalities, external conditions, asphyxia, prematurity or small for gestational age, severe infections, other, unexplained. The Nepal and Mumbai classifications also included specific foetal/antepartum conditions and placental abruption/haemorrhage. Stillbirths were separated into ante- and intra-partum, both further classified into 4-10 categories. The antepartum stillbirths were divided into congenital anomalies and inherited disorders, prematurity/small for gestational age (SGA), external conditions, other, unexplained and the intrapartum stillbirth in congenital anomalies and inherited disorders, associated with obstetric complications including placental abruption/haemorrhage, multiple births, prematurity. The Nepal/Mumbai classification included three further categories: conditions associated with maternal disease, specific foetal/antepartum conditions, both with a list of diagnostic criteria attached, and placental abruption/haemorrhage which was listed separately from other obstetric complications.

The proportion of “other” causes of death was higher for the Malawi study (10%) compared with the Nepal and Mumbai studies (1.5%) $p<0.001$. This was however more likely to be due to the option of multiple diagnoses given to the physicians in this context, rather than to the smaller number of diagnoses available to physicians. In Malawi, physicians did not list as “other” any condition that would have better been included in specific foetal/antepartum

conditions. The diagnosis of placental abruption/haemorrhage was captured in obstetric complications. None of the Nepal or Mumbai physicians classified any deaths as specific foetal/antepartum conditions or placental abruption/haemorrhage. The only sub-category used by all physicians was the presence of obstetric complications associated with asphyxia. In the Kintampo Ghana study, physicians did not ascribe any of the neonatal deaths to specific maternal conditions or foetal/antepartum conditions, however maternal disease or haemorrhage was listed as cause of antepartum stillbirth in 18% of cases and maternal haemorrhage was diagnosed in 5% of intrapartum stillbirths[533]. Very little international work has gone into defining a classification for stillbirths. Most research has been done in developed countries[203;534]. A systematic literature review of causes of stillbirths using the available literature and modelling methods is underway and the classification used will attempt to distinguish deaths into 8 categories: congenital abnormalities, maternal conditions, antepartum haemorrhage, infections, intrapartum stillbirth, preterm, other and unclassifiable[203].

There are several advantages in choosing classifications with a limited number of categories significant for public health use. Long and complicated lists of diagnoses are difficult to reach and require complicated algorithms[535], their repeatability is low and are more difficult to validate; the sensitivity and specificity of diagnostic algorithms is low if symptoms are overlapping[219;536;537]. The aim of VA is not to reach accurate individual diagnoses, but establish accurate CSMF for public health use, therefore the precise patho-physiological process is not important: for example the distinction between abruptio placentae and other obstetric complications is academic and can all be targeted using similar interventions delivered though care bundles such as increased awareness, improved access to health facilities, trained birth attendants, etc. It is therefore

important to reflect these points when classifications of causes of death are proposed.

As the world of VA historically has been dominated by physicians developing VA tools and interpreting them it is not surprising that the tendency has been toward emulating the clinical process of a post-mortem with the individual as a main focus. As VAs are becoming more and more the dominion of demographers and policy makers, VA are used to establish CSMF at population level and the clinical perspective is less and less relevant. The choice of a classification of causes of death has therefore to be based on groups of causes of death amenable to be modified by wider public health intervention packages rather than necessarily clinical means. Social and cultural causes of death, for example, amenable to behavioural change, need to be found a place in a classification of causes of death for VA use.

8.1.2 Classifications for Computerised Methods

The classification used for InterVA was not purposefully made for the neonatal period as it is part of an instrument designed for all age groups. It includes 9 broad categories pertinent to the perinatal and neonatal period: congenital abnormalities, injuries, asphyxia, prematurity or small for gestational age, severe infections (including pneumonia/sepsis, meningitis and diarrhoea), neonatal tetanus, unexplained and fresh or macerated stillbirth. The categories are very similar to the ones used by CHERG with the exception of diarrhoea that InterVA included in the sepsis group for the purpose of analysis[538]. InterVA separates stillbirths into fresh and macerated similarly to the global burden of diseases classification[28;539] .

8.1.3 ICD-10 Coding

It has been advocated that a revised version of the ICD would include a simplified stillbirth classification for VA use[203]. It would be an important step toward the standardisation of the VA process to include a separate classification of causes of death for VA use for all age categories with associated codes internationally agreed.

8.2 - Algorithms: Single and Multiple Causes of Death

When physician review is used to interpret VA data, hierarchical algorithms are believed to standardise the diagnostic process and increase repeatability[540]. We used two algorithms for physicians' use: one allowed multiple diagnoses and the other was a strict hierarchical algorithm allowing a single diagnosis.

The use of multiple causes of death may offer a more accurate picture of reality, as death is always the end point of a complex and generally multi-factorial process: a premature twin infant born cold and in poor condition may die of asphyxia, but the associated causes of death are equally important contributors. In order to describe the CSMF for planning and monitoring, interventions contributory causes of death are important[58;208;541-545]. Introducing multiple diagnoses for physician review on the model of the ICD, however makes the diagnostic process more complex. Studies using ICD-10 in developed countries demonstrate the difficulties in accurately compiling death certificates from hospital records resulting in the need for regular training to improve the accuracy of physicians' coding[546-548]. With the limited amount of information from VA interviews, the process of assigning multiple causes of death is likely to be even less rigorous and accurate. Although the ICD-10 and the Verbal Autopsy Standards documents provide guidelines for hierarchical classification of direct, underlying and contributing causes of death, not all physicians may necessarily list more than the direct cause of death as they may have a different threshold for listing underlying and concomitant causes of death[103;158]. In our previous example different physicians may choose asphyxia as the primary cause of death and prematurity as an underlying cause of death, however others may only record asphyxia. Hoj, in a study of maternal deaths, points out that listing more than a cause of death may lead to different outcomes depending of the environment where death occurs and the information available to the coder[549]. In the Malawi study, the British and Malawian paediatricians assigned different proportions of deaths to multiple causes. Different thresholds of assigning multiple causes of

death can affect the final CSMF. The CSMF for the Malawi study changed when single or multiple causes of death were considered: the proportion of stillbirths changed from 46% when a single cause of death was considered to 37% when multiple causes of death were included.

Different systems to assign multiple causes of death have been proposed with the use of probabilistic methods. InterVA, for example, lists multiple causes of death without respecting the ICD-10 definition of direct, underlying and contributing causes of death but expresses a different likelihood for each cause[211;237;550].

For physicians, seeking a consensus diagnosis by discussion or involving different physicians has been the traditional method of interpreting VA questionnaires. This probably dates back to interpreting VA by reproducing clinical scenarios. It has been pointed out that this approach does reduce the complexity of VA interpretation by excluding the minority opinion, only including the majority voice in the final CSMF[226]. As different mathematical approaches are used more and more frequently in the interpretation of VA data, the traditional clinical model of consensus may need to be challenged. In the Mumbai dataset 17% (39/221) of questionnaires were interpreted by more than two physicians and overall consensus was only reached in the first instance for 48% of cases (107/221). By using consensus and introducing a different physician to resolve discordance at least 114 different opinions were ignored. By using a different model of interpretation, however, all available diagnoses may be accounted for and assigned a probability, in a very similar way as in the InterVA model. For the Mumbai data, when all physicians' diagnoses were assigned the proportion of "indeterminate" and "other" causes of death were reduced by 1%, "severe infections" increased by about 4%, while "prematurity" decreased by about 3%. It is difficult to establish which method most approaches the true CSMF as this is not available. Different options to assign probability giving a higher weight to the consensus diagnosis may further change the final CSMF.

Further studies may help clarifying a better method of interpreting physicians' data, using multiple diagnoses in a clearly repeatable manner without incurring

the inconsistencies and needs for continuous training required by the use of the ICD-10 multiple causes of death. A number of different strategies could be studied, such as comparing simple rules such as listing a minimum of two diagnoses per questionnaire, without separating between underlying and final diagnosis could be compared with using a single diagnosis or using the criteria set by the ICD10 to see how much it would change VA interpretation and CSMF. The decision to resolve to a single cause of death and use a hierarchical algorithm has been advocated to simplify the diagnostic process and render it more homogeneous for epidemiological purposes. However the hierarchical nature of the algorithm heavily determines diagnostic choice[551]: Lee in Nepal demonstrated that different hierarchical algorithms listing perinatal asphyxia after congenital malformation and neonatal tetanus as the first or second or third cause of death, substantially changed the proportion of deaths due to perinatal asphyxia, from 30% in the first scenario to 12% in the last[552]. Improved consistency seems to be obtained at the expense of introducing an artificial rank order. Moreover, physicians adhere loosely to clinical guidelines in their everyday practice: if, in their clinical judgement, they believe that, for a given patient, a different management approach from that suggested by a clinical guideline is more appropriate they may deviate from guidelines. This is likely to be similar in applying VA algorithms. In Nepal and Mumbai physicians diagnosed prematurity in fewer cases than it would have been expected if the hierarchy of the algorithm was strictly followed. Premature or "small at birth" infants were given alternative diagnoses at physician's discretion. The same inconsistencies amongst physicians were noted by Lee in Nepal[553]. Physicians' personal experience and perception of local epidemiology is likely to influence the VA interpretation. In our dataset the only diagnosis of neonatal tetanus was made in Malawi by one of the British paediatricians. Neonatal tetanus has been declared eradicated from Malawi since 2001-2002 when a survey carried out by WHO and UNICEF in three high incidence districts failed to report any cases[554]. It is likely that the Malawian paediatricians were aware of this and would not have used this

diagnosis, but paediatricians not familiar with the local epidemiology were more likely to simply follow the algorithm to the diagnosis. It is not possible to know who is right.

8.3 - In Summary

Having a single standardised classification of causes of death for stillbirths and neonatal deaths with associated definitions is essential if data have to be compared between different studies, across time and serve for international statistics. Classifications used for physician review or computerised methods are substantially similar. The implementation of a universally recognised classification will require the support of bodies such as the WHO to be endorsed. The next ICD revision may be an appropriate forum to introduce an international classification of diseases suitable for VA interpretation, including a classification for stillbirths.

VAs serve different purposes, consequently several methods to interpret VA questionnaires exist: physician review, data derived algorithms and probabilistic approaches have all been demonstrated to be valid options, each offering advantages and disadvantages. The use of a single algorithm for the interpretation of VA questionnaires is probably not feasible. However, it would be essential to establish a standardised algorithm for physician review to at least in part improve comparability between datasets and over time. This is even more important as physician review remains widely used to compare the performance of new interpretative methods for VA, when hospital data are not available[211]. An international consensus on an algorithm for physician interpretation of VA questionnaires remains a priority.

For this purpose it remains to be established whether single or multiple causes of death are best at reflecting population CSMF reliably and accurately: in particular whether the loss of information obtained by using single causes of death and strict hierarchical algorithms is sufficiently compensated by the gain in comparability and consistency. Moreover exploring different modality of assigning multiple causes of death, learning from probabilistic approaches may constitute an acceptable and viable compromise. From both a clinical and an epidemiological

point of view multiple causes of death, although more complex to achieve, will better reflect the reality, and more consistently help predicting the impact of interventions to reduce neonatal mortality and stillbirths. Whereas restricting to a single cause of death could mislead to under- or over-estimate the value of such interventions.

Objective 2 – Should a single questionnaire to investigate stillbirths and neonatal death using verbal autopsy be proposed?

8.4 - Questionnaires for Physician Review Interpretation

The three studies in the thesis used questionnaires pre-dating the last WHO version in 2007. They were very similar in design and partly contributed to the present format of the WHO questionnaire structure.
The choice of a mixed format including an open history and closed questions derived from the assumption that this format is best[555]. Formal research is lacking. In a study of causes of neonatal death questionnaires interpreted by physician review using only closed questions or only open history were less sensitive in diagnosing low birth weight and small for gestational age compared to using a mixed questionnaire including both an open history and closed questions[556].

The result of a mixed approach has been the production of very long documents. The questionnaires for data collection in this thesis included between 118 (MIRA) and 274 (Mumbai) questions requiring over one hour for their delivery. The WHO questionnaire lists 121 questions. These documents represent an attempt to be as complete as possible including questions used in the literature to enable comparison with previous studies. The questionnaires, including the WHO version go beyond trying to establish causes of death and collect data also on care at delivery, risk factors and newborn care[158]. This makes the questionnaires long and less likely to be used in the exact form recommended.

In this thesis, when questions were maintained for completeness, even if culturally less appropriate, the answers had to be excluded from analysis. This indicates that questionnaires should not include concepts unfamiliar to the culture where they are administered. In Malawi the word “tetanus” (*kalongolongo or kufumbata*)

was used to describe engorged abdominal vessels and did not correspond to the clinical definition of tetanus, therefore had to be dropped in the analysis. Similarly in Nepal convulsions in labour were considered in the lay language as “faints” and therefore the indicator had to be excluded from analysis.

8.4.1 Are Open Histories Necessary?

Anecdotally, the open history has been considered an important part of the VA interview as it allows the respondent to emotionally grieve the loss and to create a relation with the interviewer[557]. However this has also never been formally assessed[558]. The unstructured nature of the open histories may on the contrary be damaging to the interviewer and/or the respondent if not appropriately contained. The added value of open histories on the quality of the interviewer/respondent relation and therefore the quality of data collected overall needs to be studied.

Open histories have the potential to offer rich material for qualitative analysis of care seeking behaviour or traditional beliefs around causes of death[559]. If open histories are collected to explore in a qualitative manner issues around believes, quality of care, care seeking etc. appropriate qualitative analysis should be planned at the outset rather than being a post-hoc analysis. A small number of open histories may be sufficient for this purpose. Moreover they are important in the context of social verbal autopsies[560].

Physician review is mostly based on reading the open history and scanning through the closed section to confirm some details[561]. In the Malawi dataset, for example an infant was diagnosed as having died of asphyxia with obstetric complications using data available only in the open history, as they were not reported in the closed ended section. Coding signs and symptoms of the open history and entering them into a computerised analysis did not change the output

in a study assessing neonatal[562] or maternal deaths[211]. Entering the open history coding for 90% (288/318) VA from Malawi in InterVA did not change the overall CSMF. More studies addressing the best format for VA questionnaires are underway and suggest that using computer algorithm mixed questionnaires do not offer any advantages over questionnaires using only closed questions[563]. A study in Ethiopia showed that causes of adult death can be assessed with a short questionnaire using only closed questions[564].

It seems that when physician review is the main method of VA diagnosis the open history may have a crucial role, but when computerised systems are used this may no longer be necessary. If VAs move away from the domain of physicians to the one of the demographers and computerised methods of analysis, the open history may become irrelevant to assigning causes of death. Extracting data from the history may introduce subjectivity and require trained people able to code them. The open histories add time to the interview process, the training of the interviewers and the analysis and may not improve quality in the context of computerised systems. Before considering the open history superfluous in computer data analysis, evidence is needed regarding the quality of data collected by the interviewers when the opportunity of expressing the circumstances leading to death is given or when only closed questions are delivered. In other terms, are short interviews with closed questions sufficient to collect rich data that can be interpreted to establish causes of death by a computer programme, or the open history? Even if data are not entered, is the open history essential to help the next of kin to recall, clarify and express more clearly crucial signs listed in the closed questions that would otherwise be lost?

8.4.2 InterVA Questionnaire

The questionnaire used for InterVA is about 1/3 of the WHO questionnaire, (43 questions for stillbirth and neonatal deaths), which has the advantage of being quick and easy to standardise in different cultural settings. In our study the number of indeterminate causes of death was smaller than using physician review, showing that reducing length and complexity of questionnaires still allowed adequate diagnoses. This was also a finding of other studies using InterVA and other computerised methods[211;565]. Re-running the available data using only 27 indicators did not change the overall CSMF for the main causes of neonatal deaths (severe infections, birth asphyxia and prematurity), showing that the number of questions (indicators) used in InterVA could be further reduced without impacting on the overall results (Table 7.8). This is an important finding as a new versions of InterVA could use fewer indicators to obtain similar results for the neonatal period. If VAs are to become part of routine national surveillance systems the move toward shorter and easier to administer instruments will become paramount and therefore exploring the impact of shorter questionnaires is essential.

8.5 - In Summary

Given the different uses of VA, a single questionnaire may not be the only option for VA: mixed questionnaires may be useful for physician diagnosis, while closed questionnaires seem to be more appropriate when computerised methods are used. Open histories may have a role in social autopsies and in qualitative studies looking at aspects of death different from the population CSMF and may also be essential for physicians' diagnoses. Moreover the opportunity for the next of kin to explain the facts surrounding the death of a loved one may be an important factor to improve the accuracy and the quality of the closed questionnaire. This has not yet been studied.

Studies to establish which questions are essential for different age groups are now feasible using computerised methods as the same data can be run including and excluding indicators, informing researchers and demographers designing VA tools, as shown by King[217] and demonstrated in this study.

For international comparison, agreement on the indicators to be included in mixed questionnaires for physicians' review interpretation, as proposed by the WHO[158] are of great importance, however simplified documents to explore causes of death for all age groups for the purpose of large surveys would be essential if data are to be included in international statistics for comparison.

Objective 3 – How do crude mortality fractions for stillbirths and neonatal deaths in our three studies compare with the available literature?

8.6 - Crude Mortality Rates

In our study areas perinatal and neonatal mortality rates were highest for Nepal (NMR: 31/1000 LB and PMR: 42/1000 total births) and Malawi (NMR: 25/1000 LB and PMR: 41/1000 TB) and lowest for Mumbai (NMR: 16/1000 LB). According to Malawi DHS data, neonatal mortality represented 20% and 35% of under-five and infant mortality respectively[394]. In Nepal and urban India neonatal mortality represented over 50% of under-five deaths (54% Nepal and 55% urban India) and just under 70% of infant mortality (69% in both countries) [414;566]. The figures from our studies in Malawi and Nepal were comparable with the respective DHS data (Table 8.1)[394;414].

Table 8.1 - National and Study Neonatal Mortality Rates

	Malawi MaiMwana 2005-2006	Malawi [394]	Nepal MIRA	Nepal [411;414]	DHS	Mumbai SNEHA	India DHS – urban [566]
NMR *1000LB	25	27	31	33		16	24
PMR *1000 total births	41	34	42	45			
MMR *100,000		984	238	281		150	n/a

In Malawi, a study of perinatal mortality for the late 80s from Mangochi (Southern Malawi) reported a rate of 68.3/1000 total births[567]. Data from two more recent community studies found neonatal mortality rates between 37/1000 deaths in Southern Malawi between 1995 and 1996 [568] and 22/1000 in Northern Malawi for the years 2002-2006[569].

In Nepal Freeman found a neonatal mortality rate of 42/1000 LB in a rural south eastern district in the period between 1998-2001[570]. A study from our same study area for the year 2006-2008 not surprisingly reported a very similar neonatal mortality rate of 38/1000 LB[571]. In Southern Nepal between 2002 and 2006 a cluster randomised study assessing the impact of using chlorhexidine to clean newborns' skin and umbilical cord on neonatal survival, reported a neonatal mortality rate between 32 and 34.5/1000[572;573].

In Mumbai the NMR in the study area was lower than the most recent DHS estimates for Mumbai slums (Table 8.1)[566]. The Indian sample registration system does not include slum areas given the difficulty in data collection in these very unstable populations[435]. According to the DHS data for 2005-6, the national neonatal mortality rate was 39 per 1000 livebirths (DHS), with a slightly lower rate in Maharashtra (32/1000) and an even lower rate in urban areas (19 per 1000 livebirths). In Mumbai's slum area neonatal mortality was on average 24 per 1000, lower than in non slum areas (27 per 1000)[566]. Information about births and deaths were collected prospectively, unlike the DHS who collect data for the previous four year period, therefore generally subject to underestimations due to low reporting particularly for neonatal deaths and stillbirths[574].

Morbidity is known to be higher in slum than in non-slum dwellers, however not as high as in rural areas[575;576]. Vaid in a slum population in 1995-2003 reports a NMR of 20.6 per 1000 LB, however in this study the retrospective nature of data collection may have led to underreporting of neonatal deaths[577]. It is possible that our study underestimated stillbirth and neonatal mortality although this is unlikely as the City Initiative for Newborn Health is a prospective research project[578]. Data were collected for this thesis between 2005-2007, while the DHS reports data between 2001 and 2005; it is plausible that neonatal mortality may have declined in the study areas due to the implementation of interventions targeted to reduce neonatal mortality. Moreover, data on inequality in access to health and

health outcomes on the basis of economical status show, in the same population, a range of neonatal mortality rates between 16 to 25/1000 LB reflecting the heterogeneity of slum populations[429].

Studies from different countries, collecting prospective data on neonatal deaths and stillbirths have reported lower rates (23/1000 LB) compared with DHS statistics (43/1000 LB)[579].

The rate of health facility deliveries in the study area was similar to the national statistics for Mumbai, where about 83% amongst women living in slums delivered in a health facility, compared with 91% in the non slum areas[580].
In Nepal figures were also comparable to the national statistics: about 81% of women deliver at home and only 17% of births occurring in health facilities[411].

8.7 - In Summary

Stillbirths rates and NMR reported for our three study areas in Malawi and Nepal are comparable with the respective DHS reports and published literature. Mumbai SB and NNM rates were lower compared with the available literature.

Chapter 9.

Discussion

Objective 4 – Is InterVA suitable to provide cause-specific mortality fractions in the perinatal and neonatal period in comparison with physician review in our three study settings?

9.1 - "Validation" of InterVA using Physician Review

In this thesis, physician review was used to assess the accuracy of InterVA to establish causes of death for stillbirths and newborns. This approach has limitations. Physician review, compared with hospital diagnoses was demonstrated to have 64-74% sensitivity in a study of stillbirths and neonatal deaths by Edmond[581]. In another setting, in Tanzania, sensitivity was as low as 43% for perinatal asphyxia and 48% for prematurity and low birthweight[582]. Murray similarly showed that the average relative error of physicians estimating CSMF was 27% when compared with hospital records[583]. This implies that our comparison with physicians diagnoses using *kappa* statistics and CSMF may be better or worse than we report. Sensitivity of physician review compared with hospital diagnoses depends, as discussed previously, on a number of factors including classification of causes of death, algorithms used, number of diagnoses, experience, training and beliefs of the physicians interpreting the questionnaires. Some of these factors cannot be adjusted for.

While hospital diagnoses with clear diagnostic criteria are the recognised "gold standard" for VA interpretation, physician review remains widely used both in comparing new methods of VA interpretation[211;584] and to analyse large datasets such as the million deaths study in India[585].

The main limitation of this study is the weakness of InterVA results validation, as comparing it with physician diagnosis is not robust and leaves uncertainty in data interpretation as will be discussed. This thesis did not provide an alternative and more reliable validation dataset. Hospital diagnosis data were not collected in Malawi and Nepal for two reasons: firstly there were concerns about the representativeness of hospital deaths as over half occurred at home, secondly health records and diagnostic capabilities of the health centres in the study areas were of poor quality, making health record diagnoses a suboptimal comparison. For example in Malawi none of the health facilities provided basic radiology. The laboratory facilities were limited to the district hospital offering cross matching for blood transfusion, malaria blood films and HIV rapid testing. Only CHAM hospital provided limited biochemistry and full blood counts, moreover record keeping in all facilities was of very poor quality and not always available (personal observation). The Mumbai data were collected from an urban population with 84% of deaths occurring in health facilities and may have offered a better opportunity to collect health records diagnosis. However these were not available at the time this thesis was written and analysed as the study in Mumbai was not set up to collect such data.

It has been shown in the million deaths study that there is higher disagreement in the causes of death assigned by physicians', at the extremes of age: the neonatal period, especially the early neonatal period compared with older children (*kappa* for neonatal deaths: 0.56 CI 0.55-0.57)[586]. This seems to be due to the difficulty in ascribing causes of death when signs are few and common to different diagnoses. *Kappa* statistics in our study did not support this observation demonstrating good agreement between physicians particularly for the Malawi and Nepal datasets.

9.1.1 In search of the "Philosopher's Stone"

Drawbacks of hospital validation datasets have been discussed in the first chapter of this thesis. Existing validation datasets, such as the one collected by the Population Health Metric Consortium (PHMC), are an important resource for researchers developing and improving VA models . Previous validation datasets were small and mostly limited to a single age groups[587-589]. The PHM consortium produced the largest database for VA validation ever collected, including all age groups from seven locations in four countries: Bohol in the Philippines, Andhra Pradesh and Uttar Pradesh in India, Dar el Salaam and Pemba Island in Tanzania and Morelos, Hidalgo and Mexico City in Mexico. The diagnostic criteria for each cause of death were rigorously assessed taking into consideration clinical, radiological and laboratory data, in an effort to provide a true "gold standard" for causes of death in all age groups[291]. On the other hand only tertiary urban hospitals, mostly from Asia and Latin America, were included. Only one African country, Tanzania, was selected, for pragmatic reasons. Therefore there is concern about its representativeness for rural populations, particularly in Southern Africa. Moreover, even in developed countries with the most advanced diagnostics, death certification based on health records, when compared with post mortem, shows varying degrees of inaccuracy[590;591]. The SIDS literature has shown that only pathology post-mortem examinations associated with detailed investigations of the environments where death occurred have produced sufficient information to establish accurate diagnoses and have advanced the knowledge of the pathogenesis of the disease and therefore informed about risk factors and prevention of its causes[316].

Validating new VA methods using a single, large validation dataset obtained exclusively from urban hospitals from a limited number of countries and extrapolating its accuracy to different countries and settings is at the same time exciting and problematic. It made possible the development of highly complex

computational methods, such as tariff and random forest approaches, using the database with "true" hospital CSMF as a training dataset for modelling purposes[213;215]. However, given the small number of countries represented and the inclusion of a mostly urban hospital population, raises concern about its applicability to rural African populations. InterVA, when validated with such a large database, did not perform well and this was particularly true when neonatal deaths were considered[592]. InterVA version 3 preceded the modifications to InterVA suggested in this thesis, and it will be essential to test this new version using the PHM validation dataset to explore whether InterVA performance for neonatal death improved.

Hospital diagnosis may not offer a "gold standard" for VA validation in all situations[593;594]. Ultimately "hospital validation" is likely to be better suited for urban populations, closer to the large referring hospitals, and might be a true "gold standard" for those populations only, in this context comparing the Mumbai InterVA results with hospital records would be an important and logical next step to further test the accuracy of InterVA performance.

Different comparative methods, other than hospital diagnoses need to be explored for use in rural communities. Where only a small number of infants die in health facilities, survey data collected prospectively may, at least for some diagnoses, be a useful source of information to compare with VA output. Freeman *et al.* used data on birth-weight, gestational age and recognition of congenital malformation collected by surveyors to compare diagnoses derived from VA. Surveyors visited women of reproductive age every month, to establish when they became pregnant and visited the newborns by 72 hours of birth and weekly up to the age of a month, producing reliable data to compare VA diagnoses of prematurity, low birth weight and congenital malformations[595]. The use of large community surveys with the adjunct of point of care diagnostics may be a feasible alternative gold standard comparison in future.

An alternative worth exploring further, as suggested by King and Lu[217], are completely fictitious databases with VA indicators corresponding to signs and symptoms that are recognisable, easy to remember and report, and are unchanged by local epidemiology or use of health facilities and by “true” diagnoses.

9.2 - Comparing InterVA and Physician Review

InterVA offers many of the advantages lacking in physician review, such as a consistent approach to data analysis, a fixed classification and questionnaire. It is therefore entirely reproducible and repeatable. It is rapid: each VA was processed in 2-3 seconds; easily available and cheap. The programme can be downloaded from the internet. Once downloaded, it is not dependant on internet access therefore can be easily used in remote locations with a basic processor and unreliable web access.

Physician review is a very time-consuming process, each questionnaire requires about 20 minutes physician's time. If diagnoses are discordant physicians have to meet and discuss or another physician has to review the data, adding further physicians' time to the process. To deal with this issue in this thesis the three studies used different approaches.

For the Malawi dataset, as two senior paediatricians were initially involved in the interpretation of the verbal autopsies, it took a number of years to collect the diagnoses. Ultimately, to ensure all the VA were interpreted, two different paediatricians shared the burden of the remaining cases. Using a different set of doctors with different training and epidemiological perspective may have introduced new inconsistencies into the process. In Nepal two more junior paediatricians were involved in reading and diagnosing verbal autopsy data, and one senior paediatrician resolved discrepant cases only. The Mumbai dataset was interpreted by 5 different physicians. This allowed the process to be quicker, but may have impacted on the internal consistency of the diagnoses. For the Mumbai dataset, when more than 2 physicians read the same questionnaire a higher discordance of physicians' opinion was observed with lower kappa statistics. This approach has been used in large studies such as the million deaths study in India[596].

Recent studies have questioned whether the use of more than one physician improves the accuracy of the diagnostic process or else only adds physicians' time without substantially changing the outcomes[597;598]. The *kappa* statistic between physicians in Malawi and Nepal showed "substantial" agreement, strengthening the observation that a single physician's diagnosis can be considered sufficiently accurate to establish CSMF for stillbirths and neonatal VA. In Nepal, where concordance was highest, only 10 causes of stillbirths and 9 of neonatal deaths were diagnosed differently by two physicians out of a total of 386 VA. In Mumbai, however, concordance between physicians was low when all neonatal and stillbirth categories were included (*Kappa* = 0.47). Even when only two physicians were considered, only 94 out of 176 VA were given the same diagnosis (53%). In this last scenario the need for a third physician to reach consensus diagnosis is substantial. The use of alternatives to consensus, such as assigning a proportion of the total CSMF to each physician and including all opinions in the final CSMF, is a viable alternative.

In the three studies presented the majority of deaths were ascribed a diagnosis by physicians, however in the literature as much as 40% of neonatal deaths were left undetermined by the use of physician diagnosis[599].

9.2.1 Individual Agreement

Kappa statistic to assess individual agreement between physician review and InterVA showed "substantial" agreement for the Malawi and Nepal datasets. *Kappa* for Mumbai data was 0.48: "moderate" according to Landis and Koch criteria[600]. The lower level of concordance for the Mumbai dataset may have been due to the use of a higher number of physicians for diagnosing the available VA questionnaires. The *Kappa* statistic for physicians' agreement was lower (0.69;

CI 0.66 - 0.74) in Mumbai, compared with the other two databases even when stillbirths were considered together as a single category (0.73; CI: 0.64 - 0.80 and 0.96; CI 0.953-0.955).

9.2.2 Cause Specific Mortality Fraction

9.2.2.1 Stillbirths

About half of all deaths in each of our three studies were stillbirths: 48% in Malawi, 44% in Nepal and 50% in Mumbai according to InterVA and 48%, 44% and 47% respectively according to physician review. These proportions are similar to the published literature: a study in Ghana attributed 56% of 1251 perinatal and neonatal deaths to stillbirths[601]. In India Baqui ascribed 41% of 1048 perinatal and neonatal deaths to stillbirth[602]. In Gaza 43% of 119 perinatal and neonatal deaths were stillbirths[603].

Global health statistics for stillbirths have large margins of errors as stillbirths are not accounted for in most low income countries where the majority of stillbirths occur[203;604]. There is therefore need for data to substantiate existing modelling. Including stillbirths in computerised programmes such as InterVA offers an opportunity to collect primary data to inform local policies and ultimately improve the quality of national and global health data.

InterVA separated fresh and macerated stillbirths. Both physician review and InterVA diagnosed a higher proportion of fresh stillbirths, however in Malawi the percentage of fresh stillbirths was lower by 11% (CI -0.2- -0.05) using physician review. In Mumbai the proportion of macerated stillbirths was double according to physicians compared with InterVA (difference in proportion 11%: CI 0.04-0.2). It is difficult to establish which method offered the most accurate split as physician review has several limitation and its accuracy is variable. From the literature, macerated stillbirth prevailed in some populations, while fresh

stillbirths were more common in others[605-609]. In the study already mentioned from Ghana the proportion of macerated stillbirths was 64% of all stillbirths[610]. In Bangladesh fresh stillbirths predominated in four out of five communities studied by Azad et al[611]. In Jamaica in a hospital population intra-partum stillbirth was the most common cause of perinatal deaths followed by antepartum stillbirths[612]. The proportion was reversed in a Malaysian hospital where 60% of stillbirths were classified as macerated[613]. Similarly in a hospital in Bangkok 47% of all perinatal deaths were attributed to antepartum events[614].
In the Makwampur dataset, 43% of stillbirths were macerated according to physician review. Physician review allowed a sub-classification of causes of fresh and macerated stillbirths and showed that the majority of intra-partum deaths were associated with obstetric complications, implying that interventions during labour and delivery may be appropriate to reduce the burden of fresh stillbirths.

Global estimates show that about 1 million deaths occur intra-partum and this proportion increases proportionally to the neonatal mortality rate[615]. It is estimated that counties with a NMR between 15 and 30/1000 LB have estimated proportion of intra-partum stillbirths ranging between 23-37%. Countries with a NMR <15/1000 LB have a lower proportion of intra-partum stillbirths ranging between 10 and 20%, while countries with a NMR>30/1000 LB have a proportion of intra-partum stillbirths between 25 and 35%[616]. In our populations with NMR between 16 and 31/1000LB intra-partum stillbirth caused between 31 and 42% of all stillbirths.

The proportion of stillbirths was highest in Mumbai. Of all stillbirths 42% were intra-partum stillbirths (29-33% according to physician review). This finding was surprising in a population where the majority of deliveries occurred in hospital. It may indicate suboptimal obstetric and neonatal services where intra-partum complications may not be dealt with appropriately[617](D. Osrin, personal communication), or else may indicate better reporting of stillbirths or

misreporting of early neonatal deaths as stillbirths[618]. Finally it may be due to misinterpretation of VA questionnaires as physician review has well described limitations and InterVA is an experimental model. Comparison with health facility records seems to be a logical next step to validate the accuracy of this finding. This is a clear example of the limitations of the methodology used in this thesis: comparing InterVA with physician review interpretation. Where different results are obtained with the two methods and in contrast with available literature, it is not possible to judge which method is more accurate in reflecting the reality and a better validation method is needed, whether using facility data, post-mortems, or surveillance data.

9.4.2.2 Neonatal Deaths

Overall the rank order of the CSMF for neonatal deaths using physician review and InterVA was unchanged in Mumbai and Malawi. In Nepal severe infections (28%) were the most common causes of death according to physician review followed by perinatal asphyxia (22%), while the order was reversed in the InterVA with perinatal asphyxia (24%) more common than neonatal infections (22%), neither of the differences in proportion were statistically significant. The difference in proportion of deaths due to perinatal asphyxia and severe infections using the two systems was 2.4% and 6% respectively in Nepal.

Apart from perinatal asphyxia, discrepancies between physicians and InterVA changed direction (in excess or in defect) for the other causes of death in each database, making it difficult to know which estimate was more accurate in the absence of a population of reference for which CSMF is known.

In Malawi the proportion of neonatal sepsis was higher according to InterVA compared to physician review using single or multiple causes of death. In Nepal and Mumbai this was the opposite. In all populations the difference in proportion was not statistically significant. The proportion of prematurity in Malawi was just

2% (not statistically significant) lower compared to physician review when a single cause of death was considered. However, it was only about 50% compared to physician review when multiple causes of death were considered (CI: 0.6-10%). In Nepal the proportion of prematurity was double according to InterVA (8%) compared to physicians (3%) (CI 2-8%). In Mumbai the proportions were comparable and statistically not significant (Physicians: 10%; InterVA 9%).

Neonatal sepsis

Considering the three populations studied, neonatal sepsis was responsible for 36% of all neonatal death, a percentage similar to global estimates (Table 9.1). It has to be considered however that global estimates are inferred from a paucity of data modified according to mathematical models and therefore may not necessarily reflect reality accurately and have wide confidence intervals.

Table 9.1 - Global Estimates of Neonatal CSMF for Africa and South East Asia according to CHERG Estimates

	CHERG 2000[619;620]			CHERG 2008[621]		
	Africa	**South East Asia**	**World**	**Africa**	**South East Asia**	**World**
Severe infections (incl diarrhoea and NNT)	41	34	36	34	37	29.24
Perinatal asphyxia	24	23	23	27	20	22.78
Prematurity	23	30	27	27	26	28.91
Congenital malformations	6	6	7	7	4	7.61
Other	7	7	7	3	17	

The difference in the proportion of deaths ascribed to neonatal sepsis between physician review and InterVA varied between 4 and 10%. In Malawi neonatal infections caused 40% of all neonatal deaths according to physician review and 47% according to InterVA. In Nepal they caused 50% of neonatal deaths according to physicians and 40% according to InterVA and in Mumbai 25% and

21% respectively, the differences in proportion did not reach statistical significance for Malawi and Mumbai but did for Nepal.

The only recent study describing population mortality in Malawi was in Karonga district (Northern region). In this population 81 neonatal deaths and 86 stillbirths were analysed using VA interpreted by clinical officers and physicians. Of the neonatal deaths 25% were due to neonatal sepsis[622], a substantially smaller proportion than in our study. In Karonga infant and under-five mortality (U5MR) were lower compared with the rest of the country and in this study the results were even lower than estimated by the DHS (IMR: 53/1000 and U5MR: 85/1000). The different cause of death split in the neonatal period may reflect a different burden of disease in Karonga district compared to Mchinji. However, insufficient details about birthing practices and the obstetric and neonatal services available in Karonga study area were available to speculate whether those may have contributed to a lower proportion of neonatal infections. In Karonga 80% of the population was reported to have access to safe water sources and 64% to live in burnt bricks houses, compared with 64% and 42% respectively in Mchinji[623]. http://www.nso.malawi.net/index.php?option=com_content&view=article&id=106&Itemid=6 accessed March 2008).

In a rural Indian population (NMR 52/1000 LB) amongst 40 neonatal deaths, sepsis accounted for 52%, followed by asphyxia (20%), prematurity (15%) defined as deaths before 32 weeks gestation, and other causes (13%)[624]. No data about neonatal causes of death from Indian urban populations were available.

In the literature the proportion of deaths attributed to neonatal sepsis varies between 63% in Ghana to 4% in Tanzania (Table 9.2).

InterVA did ascribe 0.3% of deaths in Malawi to neonatal tetanus. In Malawi and Nepal neonatal tetanus has been eradicated according to the WHO criteria[625;626]. InterVA associated the likelihood of 46% for neonatal tetanus and 36% for severe infection to one infant. It is impossible to know whether InterVA detected a genuine case of tetanus because it could not be followed up retrospectively in the

community. It would, however, been very unlikely that any of the deaths investigated were due to neonatal tetanus. VA studies have demonstrated high sensitivity and specificity for the diagnosis of neonatal tetanus[627;628]. InterVA was used in three populations where neonatal tetanus has been eradicated and it is encouraging that only 0.3% of all deaths were diagnosed as neonatal tetanus. There is nevertheless need to test InterVA in populations where neonatal tetanus is an important cause of death to establish whether the model can detect it accurately.

Table 9.2 - Causes of Death from Verbal Autopsy Studies for Stillbirths and Neonatal Deaths

Country	NMR (per 1000//LB)	Number of deaths	Total Stillbirth n (%)	Fresh n (%)	Macerated n (%)	Total Neonatal deaths (NMR)	Neonatal Sepsis n (%)	Perinatal asphyxia n (%)	Prematurity n (%)	Neonatal tetanus n (%)	Congenital malformations n (%)	Diarrhoea n (%)	Other n (%)	Indeterminate n (%)
Zambia, Congo, Pakistan, Guatemala [629] 2011		252	134	-	-	118 (only END)	52 (44)	31 (26)	20 (17)	5 (4)	4 (3)	-	2 (2)	4 (3)
Africa														
Zambia [630] 2011	n/a	88	50	36	14	38	14 (37)	6 (16)	13 (34)		1 (3)			4 (10)
Zambia[631] 2011	30.4	168	66	n/a	n/a	100	33 (33)	31 (31)	22 (22)	1 (1)	3 (3)	4 (4)	6 (6)	
Malawi[632] 2010	22.4	167	86			81	20 (24.7)	15 (18.5)	23(28.4)	-	-	-	-	-
Ghana[633] 2008	30.6	1251	661 (56)	248 (37)	413 (62)	590	236 (40)	196 (33)	118 (20)		16 (2.7)	-	16 (2.7)	8 (1.4)
Ghana [634] 2007	30.1	-	-	-	-	140	89 (63)	16 (11)	21 (15)	2(1)	6 (4)	2 (1)	4 (3)	0
Morocco[635] 2007	30	403	-	-	-	403	25 (6)	136 (34)	146 (36)	7 (2)	7 (2)	8 (2)	74 (18)	-
Ghana[636] 2006	20	1118	-	-	-	1068	419 (39)	154 (15)	278 (26)	-	-	-	150 (14)	67 (6)
Tanzania [637] 2006	n/a	605	243	-	-	362	16 (4)	196(54)**	41 (11)	-	-	-	110*** (30)	-
Kenja 2005[638]	23	-	-	-	-	75	32(42)	16 (21)	15 (20)	-	-	2 (2.7)	10 (13)	

Cont. **Table 9.2 - Causes of Death from Verbal Autopsy Studies for Stillbirths and Neonatal Deaths**

Country	NMR (per 1000//LB)	Number of deaths	Total Stillbirth	Fresh n (%)	Macerated n (%)	Total Neonatal deaths	Neonatal Sepsis n (%)	Perinatal asphyxia n (%)	Prematurity n (%)	Neonatal tetanus n (%)	Congenital malformations n (%)	Diarrhoea n (%)	Other n (%)	Indeterminate n (%)
Egypt[639] 2004 ~	26	220	93	-	-	117 ~	19 (16)	21(18)	48 (41)	3 (3)	9 (8)	1 (1)	2 (2)	14 (13)
Tanzania[640] 2003	n/a	136	60	-	-	76	28 (37)	17 (22)	18 (24)	-	5 (6)	-	10 (13)	
Egypt[641] 2000	30	41	-	-	-	41	8 (19)	14 (34)#	3 (7)	5 (12)	-	8 (19)	1 (2)	2 (5)
Asia														
India[642] 2011	n/a	225	225	93 (41)	114 (51)	-	-	-	-	-	-	-	-	-
Bangladesh [643] 2011	36.3 (SBR)	1584	1584	619 (39)	965 (61)	-	-	-	-	-	-	-	-	-
Bangladesh [644] 2010	32.2	365	-	-	-	365	65 (18)	164 (55)	55 (15)	-	3 (0.8)	-	45 (12)	33 (9)
Nepal [645] 2010	38	1292	601	504 (84)	97 (16)	671	205 (30)	250 (37)	101 (15)	-	6 (1)	-	78 (12)	31 (5)
Iraq [504]* 2009	n/a	2744	-	-	-	2744	1243 (45.3)"	99 (3.6)""	280 (10.2)	-	283 (10.3)	156 (5.7)	628 (22.9)	55 (2)
Thailand[646] 2009	ENM only	38	24	19 (79)	5 (21)	14	2 (14)	2 (14)	1 (7)	0	6 (43)	0	3 (21)	0
Gaza[647] 2008	14.7	119	51	15 (29)	32 (63)	68	10 (15)	7 (10)	16 (23)	-	15 (22)	-	14 (20)	6 (9)
Nepal[648] 2008	32	759	-	-	-	759	225 (30)	249 (33)	223 (29)	0	61 (8)	-	-	-
India[649] 2007	20.6	119	-	-	-	119	-	38 (32)	20 (17)	0	9 (7)	-	-	-
India[650]t 2006	35.1 (ENMR)	1048	430 (41)	-	-		149 (24)	87 (14)	166 (27)	25 (4)	40 (6.5)	10 (1.6)	-	141 (23)

Cont. **Table 9.2 - Causes of Death from Verbal Autopsy Studies for Stillbirths and Neonatal Deaths**

Country	NMR (per 1000//LB)	Number of deaths	Total Stillbirth	Fresh n (%)	Macerated n (%)	Total Neonatal deaths	Neonatal Sepsis n (%)	Perinatal asphyxia n (%)	Prematurity n (%)	Neonatal tetanus n (%)	Congenital malformations n (%)	Diarrhoea n (%)	Other n (%)	Indeterminate n (%)
Bangladesh [651] 2005	53.5	91	41	-	-	50	16 (32)	13 (26)	-	8 (16)	-	-	3 (6)	10 (20)
India 2005[652;653]	52.4	40	-	-	-	40	21 (52)	8 (20)	6 (15)	0	0	-	5 (12)	-
Nepal [654] 2005	n/a	167	-	-	-	167	36 (21)	5 (3)	44 (26)	1 (0.6)	6 (3)	7 (4)	9 (5)	68 (41)
India[655] 2003	n/a	50	-	-	-	50	5 (10)	9 (18)	15 (30)	-	4 (8)	-	17 (34)	-
Pakistan[656] 2003		137	-	-	-	137	16 (8)	46 (23)	99 (50)	17 (9)	-	-	19 (10)	-
Pakistan [60] 2002	47-65	649	-	-	-	649	70 (11)	78 (12)	124 (19)	119 (18)	23 (3.5)	33 (5)	50 (8)	152 (23)
India[657] 2001	-	1000	-	-	-	1000	245 (24)	233 (23)	254 (25)	18 (2)	33 (3)	11 (1)	206 (21)	
Bangladesh [198] 1998	-	311	-	-	-	311	(18.6)	(47.6)#		(15)	(0.9)	(1.7)	(1.5)	(14.8)
India[658] 1996 perinatal deaths only	59 (PNMR)	57	36	23## (64)	-	21	7 (33)	4 (19)	8 (38)	-	1 (5)	-	1 (5)	-

*v different classification made it impossible to compare the other COD **includes intrauterine disorders, complications of labour and delivery, maternal complications of pregnancy *** maternal conditions related to pregnancy ~ Used 3 different classifications obtaining different COD split

natal and early neonatal problems ##birth asphyxia and birth injury "cough/difficulty breathing, fever and infections and parasitic diseases

""disorder of pregnancy, difficult labour and perinatal conditions

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Perinatal asphyxia

In Malawi perinatal asphyxia was 8% more common using InterVA than according to physicians, using single or multiple causes of death. In Mumbai it was twice as common (InterVA: 30%; physician review: 14%). This difference was much smaller in Nepal with InterVA ascribing 2% more deaths to perinatal asphyxia compared to InterVA. The observed difference in Malawi and Mumbai might have been due to the smaller proportion of deaths left indeterminate when using InterVA (<1% in all datasets), compared with physicians who classified between 7 and 9% of death as "other causes" or "indeterminate". In Nepal the categories of "other" or "indeterminate" cause of death were ascribed to only 2.5% of cases jointly hence InterVA and physician had more similar rates of birth asphyxia.

Using InterVA, perinatal asphyxia was the most common cause of death in Nepal and Mumbai representing 43% and 61% of all neonatal deaths respectively. In Malawi it was the second most common cause of death after infections (36%). According to physicians' review perinatal asphyxia (20%) was the third most common cause of death after infections and prematurity in Malawi. It was the second most common cause after severe infections (37%) in Nepal, and it was the most common cause of death (30%) in Mumbai.

Global neonatal mortality estimates for 2008 ascribed 23% of neonatal deaths to perinatal asphyxia (27% in the Africa region and 22% in SE Asia). In Africa it was the second most common cause of death with prematurity, while in SE Asia it was in the third position after severe infections and prematurity[659]. In the literature, as with neonatal sepsis, different proportions of the CSMF are ascribed to perinatal asphyxia (from 3% in Nepal to 55% in Bangladesh; Table 9.2). In the Nepal study, physicians analysed 167 neonatal deaths and reported prematurity (26%) and lower respiratory tract infections (20%) as the most common causes of

death, while birth asphyxia in only 3% of cases, however they left 41% of deaths undiagnosed. In the same study a computer algorithm classified 52% of deaths as severe infections, 29% as birth asphyxia and 24% as prematurity[660]. In Ghana 33% of neonatal deaths were attributed to asphyxia[661], in India 13% of neonatal deaths were attributed to birth asphyxia using an algorithm ranking asphyxia after neonatal tetanus, congenital abnormalities and prematurity[662]. In Pakistan using single versus multiple diagnosis 34-38% of neonatal deaths were attributed to perinatal asphyxia. In Malawi a study conducted between 2002 and 2006 ascribed 15/81 (18%) neonatal deaths to perinatal asphyxia[663] (Table 9.2).
The difficulty in interpreting the data is the lack of an accurate comparison for the estimates produced by InterVA and physician review. Comparing the data produced with the literature it appears that InterVA and physicians have overestimated the importance of perinatal asphyxia in the population but this cannot be affirmed with certainty as the study has not triangulated the data with other sources as discussed previously.

Prematurity

Prematurity was the third most common cause of neonatal death in our three populations. It was responsible for about 13% of neonatal deaths in Malawi, 14% in Nepal and 18% in Mumbai according to InterVA and 23%, 5% and 21% respectively according to the physicians. The difference in the proportion of deaths caused by prematurity using the two methods was statistically significant for both Malawi and Nepal . The ranking of prematurity amongst the causes of neonatal death was comparable to the available literature[664;665], however the proportion of prematurity was generally lower[666], particularly for Asian countries[667].

Prematurity and small for gestational age infants have higher rates of mortality than term infants both in developed[668] and developing countries[669-671]. They are more vulnerable to other morbidities such as neonatal infections[672;673] and

hypothermia[674;675]. In a study from Nepal, premature infants were seven fold more likely to die of perinatal asphyxia than term infants[676].

The ICD-10 recommends not to use the diagnosis of "prematurity" but to classify deaths more explicitly using specific terms of broncho-pulmonary dysplasia or intra-ventricular haemorrhage for example[103]. This is difficult where data are collected through verbal autopsy, but may explain why physicians rarely reported prematurity as a single cause of death. With physician review and single diagnosis in Malawi the proportion of neonatal deaths due to prematurity was about half as common as when multiple causes were included. This reflects the argument that, although prematurity is often a contributing factor, it may not be considered as the underlying cause of death. Studies listing a single cause of death, such as in Nepal and Mumbai are likely to underestimate it.
A study in southern Malawi reported an incidence of preterm delivery of 20.3 amongst 453 mothers. Infants were 6 times more likely to die in the first 24 hours of age if they were born before 37 weeks gestation compared with term infants[677].
A recent estimate of causes of death in Northern Malawi assessing 81 neonatal deaths attributed 29% of deaths to prematurity[678]. These figures compare with physician review when multiple causes of death are considered.
InterVA assigns up to three causes to each death. In our study however a minority of questionnaires were assigned multiple causes of death: 10% (32/318) in Malawi, 3% (12/385) in Nepal and 11% in Mumbai (23/210). If the model was modified to increase the proportion of deaths ascribed multiple diagnoses, the attribution of prematurity may prove more in line with international estimates and data.

When examining the available literature, discrepancies in the classification of prematurity and low birth weight infants may partially explain higher or lower estimates. Some authors combine prematurity and low birthweight infants in a single category, as it is recognised that the distinction between prematurity and

small for gestational age using VA data is difficult[539;679;680]. This strategy was used in this thesis. The CHERG group however merged "low birth-weight" infants with "other" causes of death and kept prematurity as a separate category[86].

In Nepal, Freeman ascribed 23-26% neonatal deaths to prematurity, using an algorithm or physician review respectively[681]. In the million deaths study, in the whole of India 3631/10,892 (33%) deaths in the neonatal period were due to prematurity[682]. According to the CHERG group's estimates, the proportion of prematurity corresponded to about 30% of all neonatal deaths in populations with a NMR between 30% and 45%, and even higher in populations with a lower NMR[683]. Global estimates for 2008 reported a proportion of prematurity of 27% for Africa and 26% for South East Asia[684]. However the estimates available are based on a small number of data points[685]. The ascription of only 5% of deaths to prematurity and small for gestational age by physicians in Nepal illustrates again the important dilemma posed by comparing a new methodology to interpret VA questionnaires with physician review, which itself has limitations. The algorithm used in Nepal with the listing of prematurity as the first cause of death after congenital abnormalities should have increased the likelihood of physicians ascribing death to such a diagnosis. It is interesting to note (Table 5.4) that, amongst livebirths, although 35% of questionnaires described infants born at less than 8 months gestation, 37% small at birth and a further 20% of questionnaires reported both small at birth and born early, the physicians still only considered 5% of all deaths were due to prematurity. It is possible that multiple diagnoses would have changed the perceptions of the physicians involved, but the need for a valid term of reference is needed.

An important point needs to be made about the definition of prematurity used in this thesis as it appears to be very imprecise ranging from the InterVA definition of <33 weeks to < than 8 months. This very wide definition derived from the observations that in Malawi pregnancies are often counted in lunar months of 28

days, therefore a full pregnancy lasts 10 months, while in the western concept a 40 week pregnancy lasts 9 months. Considering that the two definitions co-existed in the Malawi data, preterm infants born at less than 8 months could be infants born between 32-35 weeks. On physiological terms there is a very large difference between newborns born at less than 32 weeks and less than 35 weeks as important embryological development occur in these weeks of gestation but realistically the accuracy of data used in this thesis were unlikely to detect these differences. Less than 34 weeks gestation is included in this interval and was therefore accepted unchanged as an established definition in InterVA.

The availability of accurate gestational ages and weights around the birthdate through data collected in longitudinal surveys could provide a more robust term of comparison to substantiate the diagnosis of prematurity.

Equally the size of the infant at birth could only be a crude measure of the infant weight. Only in Mumbai it was possible to prove a good correlation between size at birth and weight as only a minority of infants were weighted in Malawi and Nepal. This measure would however never be sufficiently precise to separate infant born small for their gestational age and growth restricted infants which is clinically a much more relevant information as it carries a very different prognostic outcome[686].

Congenital malformations

The rate of congenital malformation in the three countries is low compared with the neonatal survival series estimate for Africa and SE Asia (Table 9.2)[687;688]. It has been observed that the proportion of deaths due to congenital abnormalities is higher in developed countries, even if their absolute number is higher in developing countries[689]. Using verbal autopsy however it likely to underestimate congenital malformations not obviously evident, such as cardiac malformations and therefore lead to misclassification errors[690]. Surveillance data where infants are visited soon after birth by personnel trained in recognising physical malformation may improve information about the real burden of congenital

malformations but ultimately only post-mortem data could detect more common but less recognisable malformations such as cardiac abnormaltites.

9.3 - In Summary:

It was possible to modify InterVA to include stillbirth and neonatal causes of death as part of an all age model. Our comparison was with physician review and this approach has important limitations as it is not by itself an accurate method. The rank order of causes of death, using the two models, was the same for Malawi and Mumbai. For the Nepal data although perinatal asphyxia was the most common cause of death using InterVA and the second most common using physician review, the respective proportions were of the same order of magnitude and not statistically different (24 and 22% respectively). The proportion of neonatal sepsis and congenital malformations were similar using InterVA and physician review. Prematurity was, however, overestimated by InterVA compared to physician review but underestimated comparing InterVA with the international literature and global data. Perinatal asphyxia was more common using InterVA, in comparison with physician review and the international literature.

It is not possible at present to establish whether the "true" CSMF was closer to the InterVA or to the physicians' outcomes, however, comparing these data with the available literature InterVA may over-diagnose perinatal asphyxia, and under-report prematurity. In future comparing InterVA with a combination of surveillance data, hospital records and post-mortem examination or with enquires to neonatal (and adult or maternal deaths) combining detailed investigation and visits to the place of death with questionnaires and post-mortem data may provide a gold standard with which comparing and refining the model. An important obstacle to such a high intensity approach will be the representativeness of the sample chosen.

Objective 5 - How do cause-specific mortality fractions from three different countries compare when a standardised method is used?

9.4 - Cause Specific Mortality Fractions

The three study sites described in this thesis used similar data capture methods and data collection instruments. Whereas using physician review introduced subjectivity and therefore was difficult to interpret, InterVA offered the advantage of complete internal consistency. The differences in cause of death distributions established in this manner could therefore be considered as "true" differences. One of the main advantages of using InterVA was the consistent distinction between live and stillbirths. Several studies have shown that either mothers or attendants at delivery prefer to report stillbirths rather than neonatal deaths in some settings[691;692] or vice-versa in others[693;694]. Having a reliable method to separate stillbirths from early neonatal deaths is therefore crucial. InterVA is a useful tool for this purpose, providing the information collected at the time of the interview is accurate.

The inclusion of stillbirths in the description of the population CSMF is conceptually relevant as it represents a reconciliation between maternal and neonatal/child health[695]. Traditionally champions of maternal health concentrated their efforts on improving skilled birth attendance at delivery and facility based care[696-698], while the neonatal health advocates demonstrated and supported the effectiveness of community based programmes in reducing neonatal deaths[408;435;699-709]. The first group quantified their progress using maternal outcomes, the others neonatal survival. This separation between pregnant mothers and their children (at whichever status of maturation), health facility and community care is nevertheless artificial. Ideally all mothers and their children should receive good quality antenatal, delivery and post-natal care with or under the supervision of competent health professionals, however this target is not going

to be achieved soon[710]. In the interim there is urgent need to reach women and their newborns who are delivered with inadequate or no support[711-713]. In this context the separation between pulling resources into community care or facility care is artificial[714], as is the separation between maternal and child health. Interventions aimed at improving neonatal health showed an impact on mothers as well as on newborns[715]. It is likely that interventions aimed at improving care given around the time of delivery, whether originally conceived as "maternal" or as "neonatal" interventions will benefit both mothers and children, providing all the relevant outcomes are appropriately studied[716-719]. Reliably and consistently counting stillbirths offers an opportunity to both maternal and neonatal programmes to better quantify their impact.

The availability of cause specific mortality profiles using internally consistent methods can guide the implementation of effective policies, as changes within the most prevalent causes of death during the perinatal and neonatal period can be monitored. A large number of studies have demonstrated the effectiveness or otherwise of many low cost interventions to reduce neonatal and maternal mortality[720-742] (Table 9.3). Given that death in the neonatal period is rarely due to a single cause, but is the end result of a number of factors, the combination of interventions is likely to have a cumulative effect[743]. Similarly to the use of care bundles in infection control in developed countries combining a small number of interventions with the aim of improving health outcomes[744], the use of antenatal, delivery and post-partum care packages has been proposed in developing countries to increase the impact and reduce the cost of single interventions[745-748]. Monitoring the impact of multiple interventions requires systems than can reliably and consistently detect changes and trends. InterVA with its short questionnaire, rapid and reliable outcomes could contribute the epidemiological basis for programmatic decisions.

9.4.1 Malawi

In Mchinji district, like in the rest of Malawi, the majority of women received antenatal care, mostly in health facilities. According to national figures, about 50% of mothers delivered in health facilities while a very small proportion of women received post-natal care[393]. The prevalence of HIV and syphilis was high in Malawi and the country has one of the highest maternal mortality ratio in the world: 984 per 100,000[396].

Our study reports a high NMR (27/1000 LB). Stillbirths, neonatal sepsis, followed by perinatal asphyxia were the most important contributors to perinatal and neonatal mortality. Consequently community interventions aimed at improving hygienic conditions at delivery, use of clean delivery kits, encouraging early and exclusive breastfeeding, are likely to improve care at delivery, and reduce the early risk of neonatal sepsis. Moreover to reduce late neonatal mortality due to sepsis, interventions using oral antibiotics in the community may be effective, particularly when the use of postnatal care is low[749-751]. The high use of ANC in health facilities could be an opportunity to deliver the ANC interventions available. Further research to establish which factors would increase use of health services at delivery and in the postnatal period could help shaping a more efficient and acceptable health service[752;753].

9.4.2 Nepal

In Nepal the most common causes of death were perinatal asphyxia and neonatal infections, causing together just under 50% of all deaths. Stillbirths added a further 44% to this burden.

The poor attendance at ANC, delivery and post-natal care in this population makes working at community level both in delivering interventions and advocating the use of health facilities the most feasible approach to reach the

majority of women. In this context community interventions encouraging and facilitating women's groups to deal with problems arising in the antenatal, delivery and post-partum period have been demonstrated to be effective in reducing neonatal and maternal mortality[754]. It is likely that building on these interventions, targeting neonatal sepsis in the community, as suggested for Malawi will further improve neonatal health. A study is currently ongoing to test this hypothesis in Dhanusha, Nepal[755]. In the longer term community interventions may increase demand for health care[756]. The health services need to be prepared to receive the increase in demand and offer appropriate quality of care.

9.4.3 Mumbai

In the Mumbai slum population studied, stillbirths and perinatal asphyxia constituted up to 79% of all deaths in the perinatal and neonatal period, if InterVA conclusions are accurate in describing CSMF in this popualtion. Prematurity followed causing about 10% of neonatal deaths. Differently from Malawi and Nepal, a high proportion of women attended ANC and the majority of births occurred in health facilities. Interventions focusing on quality obstetric and newborn care in health facilities may have an important role in this context in reducing the rates of stillbirths and neonatal deaths.

The complexity of referral systems and use of health care in this population has been described[757]. Within the intricate net of public and private providers of antenatal, delivery and postnatal care, the use of maternal and newborn death audits or confidential enquiry would be likely to offer further important information on the most effective interventions to improve care[758;759]. Working with midwives and other health care professionals to improve neonatal resuscitation practices and care of the newborn may be necessary in some facilities for example, but not in all. Similarly the adoption or the use of kangaroo

mother care models may need to be explored to target the high proportion of deaths due to prematurity[760;761].

As part of the City Initiative for Maternal and Newborn care a surveillance system has been set up in these same slum areas and allowed to explore different socio-economic aspects in relation to the use of health care for pregnant women and their infants. From this surveillance system important information emerged allowing a more detailed analysis of health care use. Antenatal, delivery and postnatal care differed between the poorest and the least poor, when the slum population was divided into 5 quintiles. In the ANC setting the poorest were less likely to have attended to all the 4 recommended antenatal care visits, they received poorer quality ANC, measured as access to ultrasound scan examination and iron and folic acid supplementation. They were more likely to deliver at home, or to deliver in government health facilities, and less likely to receive postnatal care. Babies born from the poorest women were less likely to receive BCG vaccine at birth[429]. Crude neonatal mortality was higher in the poorest quintiles even if not statistically significant[429]. A study looking at catastrophic health expenditures for maternal health in these same areas, defined as pregnancy related costs reach the threshold of 41% of the total income[762]. However it failed to demonstrate a difference across economic quintiles, reflecting the high cost of maternal health care for this overall disadvantaged population[763]. In this study the better off were more likely to deliver in private facilities incurring into higher costs[763].

One of the weaknesses of our study was the inability to explore the socio-economic characteristics of our populations in relation to cause specific mortality fraction for stillbirths and neonatal mortality. However this complexity will need to be taken into account when auditing and planning interventions to improve neonatal health outcomes within health facilities. If it is true that the majority of deaths occur in the poorest quintile where most home deliveries seem to occur, interventions targeted at these poorest women that can be delivered in the community may have a higher impact in reducing stillbirths and neonatal deaths

than expected considering the overall high use of hospital facilities. This would be of course an essential information to collect if interventions are to be effectively targeted.

Table 9.3 - Interventions for Newborn and Child Survival

	Fresh Stillbirths and Perinatal Asphyxia	Infections	Prematurity	Reduction in perinatal mortality
Community Interventions			Birth spacing	Birth spacing
			Smoking cessation	Smoking cessation
	Balanced protein energy supplementation (SB)	Balanced protein energy supplementation (LBW)	Balanced protein energy supplementation (LBW)	
			Insecticide impregnated bed nets; intermittent preventive treatment	
	Birth preparedness	Birth preparedness		
			Delayed cord clamping	
		Access to diagnosis and management of STIs		
		PMTCT		
		Early exclusive breastfeeding	Early exclusive breastfeeding	
		Antisepsis at delivery (chlorhexidine?)		
		Clean delivery practices		
	Training of TBA/CHW on neonatal resuscitation		Training of TBA/CHW on neonatal resuscitation	
	Bag and mask resuscitation using room air (BA)		Bag and mask resuscitation using room air	
		Recognition and management of sepsis with oral antibiotics	Recognition and management of sepsis with oral antibiotics	
				Folate (reducing neural tube defects)
Community or facility		Kangaroo mother care	Kangaroo mother care	
			Thermal care of the newborn	
		Treatment of asymptomatic bacteriuria	Treatment of asymptomatic bacteriuria	
			Calcium supplementation to prevent preeclampsia	
			Intermittent Preventive treatment for malaria	

Cont. **Table 9.3 - Interventions for Newborn and Child Survival**

	Fresh Stillbirths and Perinatal Asphyxia	Infections	Prematurity	Reduction in perinatal mortality
			Progesterone for high risk pregnancies	
	Syphilis screening and treatment (SB)	Syphilis screening and treatment (SB)	Syphilis screening and treatment	
		Tetanus toxoid vaccine (neonatal tetanus)		
				Folate supplementation to prevent neural tube defects
Facility interventions	Emergency obstetric care	Antibiotics for premature prolonged rupture of membranes		
			Steroids for preterm labour	
	Skilled attendance at delivery			
	Training programmes for health professional in neonatal resuscitation		Training programmes for health professional in neonatal resuscitation	
			Vitamin K to the infant	
		Diagnosis and treatment of neonatal sepsis with iv antibiotics		
	Maternal Education			
	ANC packages (TTV, Iron and folate supplements, ITN and IPT for malaria, Syphilis diagnosis and treatment, PMTCT, Tx for asymptomatic bacteriuria, Calcium supplementation to prevent preeclampsia, deworming)			
	Community programmes training TBA/CHW in birth preparedness, neonatal resuscitation, etc			
	Women's groups			
	Perinatal death audits (community and health facility)			

Note [764-770]

9.5 - Causes of Death by Day of Life

Overall mortality is highest in the first day after birth than at any point thereafter[771-775]. A study in India shows that the high proportion of deaths in the first week of life has remained constant for over two decades[776]. Our three locations confirm a high mortality rate in the first day after birth. Of the Malawian newborns Malawi 61% died within the first 24 hours after birth, the percentage was 46% for Nepal and 41% for Mumbai. We were able to describe the distribution of causes of deaths over time in our three populations. In Makwampur and Mumbai, perinatal asphyxia was the most common cause of death in the first day after birth accounting for 25% and 34% of deaths respectively. Prematurity was the second most common cause of death (12% in Nepal and 9% in Mumbai). In Malawi perinatal asphyxia (25%) and neonatal infections (24%) were the two most common causes of death on day one. Perinatal asphyxia was the most common cause of early neonatal death in a number of studies that looked at causes of early neonatal death in Asia[777-779]. In a rural Indian population, Baqui reported birth asphyxia (31%) and prematurity (26%) to be the most common causes of death on day zero of life[780]. From day 1 to day 28 infections, sepsis and pneumonia were responsible for an increasing proportion of deaths[781], similar to our findings. In a study from Gadchiroli, Bang reported perinatal asphyxia as the most common cause of early neonatal death while pneumonia and sepsis predominated in the late neonatal period[782]. Chowdhury in Bangladesh reported that 53% of all deaths in the first week of life were due to perinatal asphyxia[783].

There are some differences between these studies in view of the cutoffs used: Baqui[784] separated infants dying on day zero from infants dying on day 1 to 6, this may have increased the relative proportion of deaths due to asphyxia on day 0 in his study. Bang and Chowdhury used day 3 and day 7 respectively as a cut off, but still observed the highest mortality due to asphyxia in the first days of life[785;786].

Using 24 hours as a cut off, perinatal asphyxia was the most common cause of death in Nepal and Mumbai. In Malawi the proportion of deaths due to infections was almost as high as perinatal asphyxia. A number of studies from Southern Africa showed neonatal infections to be the most common cause of neonatal deaths[787-791], however no study separated causes of death by day in this context. It is difficult to speculate why neonatal infections were more commonly identified in Malawi compared to Nepal from the first day after birth.

Most studies exploring causes of neonatal sepsis describe hospital populations of inborns and infants presenting to health facilities for treatment, therefore including almost exclusively late onset sepsis. The WHO Young Infant Study Group selected a number of peripheral health facilities in four different developing countries (The Gambia, the Philippines, Papua New Guinea and Ethiopia) and monitored pathogens causing sepsis and meningitis in infants younger than 3 months presenting at these facilities[792-795]. This multicentre study did not show large differences in organisms causing neonatal sepsis across different continents with *S. aureus, S. pneumoniae* and *Group A Streptococci* being the most common Gram-positive organisms. A larger variety of Gram-negatives were isolated most commonly *E. coli*, Klebsiella, Enterobacter, Pseudomonas and Salmonella[796]. *Group B streptococcus* (GBS) was rarely isolated in this series[797]. Data extracted from available studies in a more recent review conducted by the same group reported a higher number of Gram negative isolates in Asian compared to African countries[798]. A Malawian hospital study including inborn and outborn infants admitted to a tertiary referral hospital showed a high rate of GBS, Salmonella and *S. pneumoniae* septicaemia and meningitis. Mortality rate was very high for Salmonella infections (62% for sepsis and 64% for meningitis)[799]. Differences in risk factors for early neonatal sepsis such as maternal genital tract bacterial carriage, prolonged rupture of membranes, maternal pyrexia and preterm delivery were not available in our study. Rates of maternal bacterial colonisation have been poorly studied in developing countries with the exception of GBS, which seems to be as common as in developed countries[800]. It is also possible that

different risk factors such as placental malaria and HIV contribute to high rates of sepsis from the early neonatal period in African countries[801].

Rates of home deliveries in our Malawian and Nepali populations were high, however birth practices will need to be compared in more detail to explore whether differences in home care practices could account for the different rates of infection. It is likely that home care practices such as feeding, including the use of pre-lacteal feeds and care of the umbilical cord, affect the rates of late rather than early onset sepsis[802].

Neonatal infections are an important cause of death, however little is published about the epidemiology of early onset sepsis in developing countries[803]. Published literature is biased toward to hospital studies and particularly tertiary neonatal care centres, where often only very low birth weight or extremely low birth weight infants are included and generally only describes culture proven sepsis [804;805]. Incidence therefore varies widely[806;807]. It is well known that early onset sepsis has a higher fatality rate than late neonatal sepsis in both hospital and community studies, therefore it is expected that the proportion of death due to early onset sepsis is higher even if the overall incidence is lower than late onset sepsis[808;809]. Unfortunately this knowledge does not validate or refute the plausibility of our findings and we lack a stronger validation dataset. Unfortunately clinical definitions of neonatal sepsis are by themselves very non specific and require bacteriological confirmation which is not itself sufficiently sensitive (with positive blood cultures available in only about 25% of cases[810]). It may be possible in future to improve diagnosis by using molecular techniques usch as 16S PCR or even more powerful tools such as genomics or proteomics technologies[811;812].

9.6 - In Summary

Stillbirths represented about half of all deaths in all three locations, fresh stillbirths accounting for the majority of stillbirths. Malawi had the highest

proportion of deaths due to sepsis, with a similar proportion of sepsis and perinatal asphyxia from day one. In Mumbai perinatal asphyxia was the most common cause of death.

Taking into consideration the crude neonatal mortality, the general use of health facilities and the cause specific mortality fraction in these populations, different intervention packages need to be tailored to the highest mortality causes to obtain the maximum effect in view of the MDGs impending deadline. Malawi and Nepal have high NMR and deliveries mostly occur at home. In the short term, packages of care targeting antenatal, delivery and postnatal care through community interventions may be the most effective strategy in reducing stillbirths and neonatal mortality. In Mumbai the poorest quintiles of the populations are more likely to deliver at home and benefit from community interventions. However, given the high use of healthcare facilities and the multiplicity of the healthcare providers, further studies investigating the health sector needs, for example using audits and confidential enquiries, are necessary.

Chapter 10

Research gaps and Recommendations

VA is at present the only available method of documenting causes of death in most of the developing world, where the highest mortality burden lies. To reach workable results, a complex process of data collection, controversial stages of data interpretation and analysis are required. There is still little consensus internationally on how best to undertake this task: different classifications of causes of death are used, a universally accepted method to collect and interpret questionnaires' data is lacking. Partially this is due to the different uses of VA from local epidemiology studies to national surveys, partially, until recently, to the lack of interest on the VA process. This thesis analysed the different stages of the VA process, proposed strategies and identified research gaps.

A Single Classification of Causes of Death is Essential for International Use

To compare results and follow up trends over time across different regions it is essential that the same outcomes are measured across the boards. A single, internationally accepted classification of neonatal death and stillbirths, with associated definitions is the first step to provide comparable results.
While a neonatal death classification that is widely accepted and used has been proposed by the CHERG group, a single classification for stillbirths has yet to be produced. In the current study, stillbirth was classified as ante and intra-partum. This was the only classification provided by InterVA. Physician review allowed the distinction amongst macerated stillbirth between congenital malformation and maternal conditions, and amongst fresh stillbirths between accidents, obstetric

complications, maternal conditions and congenital malformations. Maternal conditions, while not selected by physicians in the Malawi and Nepal contexts, were used in the Mumbai dataset where more deaths occurred in hospital. It is possible that more information was provided in this setting. The distinction of multiple births as a cause of death is questionable, as it seems difficult in the VA setting to identify causality in multiple pregnancies. A proposed classification for stillbirths includes antepartum haemorrhage separated from other obstetric complications and infections[203]. It may however not be necessary to separate antepartum haemorrhages from other obstetric complications, as they are all likely to require skilled help at delivery.

Data Capture Methods Have to Take into Account the Analysis Strategy

The questionnaires used in this thesis are all very similar in content to the WHO standard[158] and were conceived for analysis by physicians. However the use of shorter questionnaires, limited to 30-40 questions, without an open history was sufficient when a probabilistic method was used. It is important to highlight however that although only a proportion of data collected were analysied using InterVA the data collection method still involved the use of a long questionnaire with an open account of the events leading to death.

As more methods for data interpretation are proposed and viable alternatives to physician review become available, it is important that data capture tools are adapted to the type of analysis that will follow. Computerised methods for data interpretation may allow shortened questionnaires without open histories, while physician review relays on open histories.

It is important to understand that until now there are no studies comparing the quality of data collected by interviewers using mixed questionnaires with open histories and close questions and short questionnaires with only closed questions. A study comparing the quality of data collected using these two methodologies

will be important to before proposing large studies using simplified questionnaires.

InterVA for Stillbirths and Neonatal Deaths is Simple and Feasible and Can Process Large Quantities of Data but needs to be better validated

The adaptation of a probabilistic method for VA to include stillbirths and newborns as part of a model to derive mortality data for all age groups offers advantages over physician review. It is completely internally consistent, rapid and cheap and could be used in large scale surveys and for international comparisons. The adjunct of stillbirths amongst the causes of death contributed to increasing awareness and monitoring progresses of the burden of late foetal deaths. Benchmarking the cause of stillbirths and neonatal deaths in three different populations by using InterVA lead to the suggestion of possible intervention strategies.

The most important limitation of the present study is the lack of an objective validation for InterVA other than physician review which itself has major drawbacks. Different possibilities could be explored with further research. Firstly the opportunity of having the Mumbai population with a high proportion of deaths occurring in health facilities provides the opportunity to test InterVA against hospital diagnoses. Secondly the increased interest in interpreting and validating verbal autopsy data provided a large hospital database established by the PHM consortium, that could be made available to the research community. Alternatively or in combination a large hospital dataset with diagnostic criteria standardised and agreed internationally could be created to provide data from different countries and become truly representative for validation and refinement of new or existing VA tools.

Finally alternative validation methods, possibly more accurate such as post-mortem investigations, death enquires, use of data collected through surveillance

systems need to be explored. New technologies such as point of care testing using molecular or genetic technology may also became available and affordable in the future opening up the possibility of community validation datasets.

The Data Capture Process Needs to be Studied in More Detail

The quality of VA outcomes is dependant on the quality of data collected, hence it remains essential to study the impact of gender, education, profession (lay versus health professionals) of the interviewers on the quality of responses to VA questionnaires. Irrespective of the analytical method used, but in particular if short questionnaires are used in large surveys, attention needs to be given to the type, content and length of training and training materials for interviewers. Assessment of the quality of data collected and rigorous and efficient systems of supervision will also need to be evaluated.

Proposed InterVA Model Refinements

Although demonstrated to be a workable model, the proposed version of InterVA will need to be modified as it seems to overestimate perinatal asphyxia and underestimate prematurity. InterVA is a combination of expert opinion and probabilistic analysis, therefore submitting the current probabilities and indicators to a panel of paediatricians, in the light of the results presented in this thesis will be the first step to improve its performance.
The crucial question is going to be which validation method would be best to test InterVA against, as without a reliable comparison the data obtained are difficult to interpret and therefore to act on with confidence at a local or global level.

A wider discussion about including the uncertainties implicit in the calculated likelihoods in the final output will need to be considered not only for the perinatal period but for all age groups.

From this study it seems that it would be important to compare the present InterVA methodology to establish multiple causes of death with a less stringent criteria which allows the inclusion of a larger number of multiple causes of death (for example comparing the model when more than one cause of death is included when the difference between the probabilities is set a lower cut offs than the current 50%: 20%,30% etc), to establish whether this improves the model performance.

An option to select stillbirths in or out according to the needs of the tool could be built in a new version of InterVA to make the tool more versatile to different analysis needs.

Finally InterVA may be modified to include a broadened rimate of social autopsy questions and analyse the socio cultural aspects of death. It is possible that the mixed nature of the model using expert opinion and probabilistic theory would be particularly suitable and will need to be explored.

Future applications of interVA

InterVA has been used to follow up the evolution of epidemics and to monitor the effect of malaria treatment in other age groups[813;814]. When the model has been refined and tested further it will have important applications in understanding the impact of complex interventions to reduce neonatal mortality such as women's groups, and possibly aid to better define the reasons why similar interventions have different success in different contexts[815;816]. InterVA model will also allows to establish causes of maternal deaths making the tool particularly relevant to understand the associations and implications of maternal health on neonatal health. Establishing the causes of death in different socio-economic groups could also reveal important dynamics and help construct effective prevention strategies.

Outcomes of studies applying specific interventions to reduce neonatal mortality such as the introduction of antibiotics for presumed neonatal sepsis could be followed up in more detail if CSMF due to sepsis for example could be determined in a reliable and repeatable way. All effects of interventions could be monitored by observing the shift amongst different causes of death.

The separation between fresh and macerated stillbirths would provide the possibility of clarifying the full contribution of perinatal asphyxia on perinatal death.

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Appendix I

MaiMwana Project – Malawi, Perinatal Verbal Autopsy

Consent

Zone ID: |__|__|	Village ID: |__|__|	Village name:	
Household ID: |__|__|__|		Name of head of household:	
WCBA ID: |__|__|-|__|__|-|__|__|__|-|__|		WCBA name: first/second/alternative	
Interviewer ID: |__|__|	Date of interview: |__|__|/|__|__|/|__|__|		Supervisor's signature:
			Date received in office: |__|__|/|__|__|/|__|__|
Is the mother still alive?			1 = Yes 2 = No
What is the relationship of the respondent to the infant?			1 = Mother 2 = Father 3 = Mother's relative 4 = Father's relative 5 = Neighbour 6 = TBA 7 = Other (specify _____)

RECORD TIME STARTED INTERVIEW: __ __ : __ __

Part A: Details of the Birth

First I would like you to tell me the details about the birth of this baby			
Details of the birth			
1.1	What date was the baby born on?	Day/ Month/ Year __ __/__ __/__ __	
1.2	What date did the baby die on?	Day/ Month/ Year __ __/__ __/__ __	
1.3	Where did your baby die?	1 = At home 2 = On the way to treatment 3 = At a health facility (specify _____) 4 = At TBA's house 5 = At sing'anga's 6 = Other (specify _____)	
1.4	Was your baby a girl or a boy?	1 = Girl 2 = Boy 3 = Don't know	
1.5	What was the name of your baby? IF NOT GIVEN WRITE 'NO NAME' AND GO TO Q1.6		

1.6	Was the baby born at the expected time?	1 = Early 2 = On time 3 = Late	
1.7	After how many completed months of pregnancy was the baby born?	|__|__| months	
1.8	Was the baby one of twins?	1 = Yes 2 = No →	Q1. 10
1.9	Was the baby the first or second born twin?	1 = First 2 = Second	
1.10	How big was the baby?	1 = Very large 2 = Average 3 = Very small 4 = Don't know	
1.11	Was the baby weighed at birth? CHECK HEALTH PASSPORT	1 = Yes 2 = No →	Q1. 13
1.12	How much did the baby weigh? CHECK HEALTH PASSPORT	|__|•|__| kg	
1.13	Where was the baby born?	1 = Mchinji District Hospital 2 = Kapiri 3 = Kaigwazanga 4 = Kochilira 5 = Mkanda 6 = Guillime 7 = Nkhwazi 8 = Chipumi 9 = Chiwosha 10 = Ludzi 11 = Mikundi 12 = Kapanga 13 = Tembwe 14 = St Gabriel's 15 = TBA 16 = At home 17 = On the way to health facility 18 = Other (specify _____)	
1.14	Was there a fire, stove or any form of heating in the room?	1 = Yes 2 = No 3 = Don't know	
1.15	Who helped with the delivery?	1 = Doctor/Nurse/Clinical Officer/Midwife 2 = Other health worker 3 = TBA 4 = Relative/friend 5 = Nobody →	Q1. 18
1.16	Did the person who helped wash his/her hands with soap before the delivery?	1 = Yes 2 = No 3 = Don't know	
1.17	Did the person who helped wear gloves during the delivery?	1 = Yes 2 = No	

		3 = Don't know	
1.18	How was the baby delivered?	1 = Normal 2 = TBA/relative/friend pulled the baby or pushed on the belly 3 = Health worker used forceps 4 = Health worker did a caesarean section	
1.19	Which part of the baby came out first?	1 = Head 2 = Buttock 3 = Hand/foot 4 = Cord 5 = Don't know	

Part B: Open History

Verbal autopsy	
2.1	We need to understand how and why your baby died. So please tell me the story of how the death came about, including all of the problems he/she had, from the beginning to the end. PROBE UNTIL THEY HAVE TOLD YOU EVERYTHING THEY CAN REMEMBER

Part C: Details of Illnesses Leading to the Death of the Baby

Congenital abnormalities			
3.1	Did the baby have any obvious deformity?	1 = Yes 2 = No →	Q3.7
3.2	Can you describe it for me?		
3.3	Did the baby have a very small head?	1 = Yes 2 = No	
3.4	Did the baby have a mass or defect on the back of the head or spine	1 = Yes 2 = No	
3.5	Did the baby have a cleft lip or palate?	1 = Yes 2 = No	
3.6	Did the baby have abnormal arms or legs	1 = Yes 2 = No	
Stillbirth or live birth			
3.7	Did the baby have bruises or signs of injury?	1 = Yes 2 = No 3 = Don't know	
3.8	Was the baby born alive or dead?	1 = Alive → 2 = Dead	Q4.1
3.9	Was the baby still moving when labour started?	1 = Yes → 2 = No 3 = Don't know	Q3.12
3.10	When did you last feel the baby moving?	|__|__| Days before labour started |__|__| Hours before labour started	
3.11	Do you think that the baby had died before you went into labour?	1 = Yes → 2 = No	Q3.15
3.12	Did the baby ever cry, even a little?	1 = Yes → 2 = No	Q4.1

3.13	Did the baby ever move, even a little?	1 = Yes → Q4.1 2 = No	
3.14	Did the baby ever breathe, even a little?	1 = Yes → Q4.1 2 = No	
3.15	Did the baby look like a normal baby, or had the skin and body changed and become pulpy/puffy/mushy/swollen?	1 = Yes 2 = No 3 = Don't know	
3.16	Was anything done to try to help the baby to breathe at birth?	1 = Yes 2 = No → STOP 3 = Don't know → STOP	
3.17	What was done to try to help the baby to breathe?	1 = Stimulation STOP 2 = Mouth to mouth STOP 3 = Mouth to tube or mask STOP 4 = Bag and mask STOP	
THIS IS THE END OF THE INTERVIEW IF THE BABY WAS A STILLBIRTH. IF YOU HAVE NOT SKIPPED TO Q4.1, STOP THE INTERVIEW HERE AND THANK THE RESPONDENT			
Now I would like to ask you some more questions about the illness of the baby before he/she died			
Breathing difficulties			
4.1	Did the baby cry at birth?	1 = Yes → Q4.3 2 = No	
4.2	How long after birth did the baby first cry?	1 = Within 5 minutes 2 = Within 5-30 minutes 3 = More than 30 minutes 4 = Never	
4.3	Was anything done to try to help the baby to breathe at birth?	1 = Yes 2 = No → Q4.5	
4.4	What was done to try to help the baby to breathe?	1 = Stimulation 2 = Mouth to mouth 3 = Mouth to tube or mask 4 = Bag and mask	
4.5	Was the baby sleepy and floppy at the time of birth?	1 = Yes 2 = No	
4.6	Did the baby ever have difficulty breathing?	1 = Yes 2 = No → Q4.15	
4.7	What was the difficulty?	1 = Intermittent breathing 2 = Fast breathing	
4.8	When did the difficulty start?	1 = Immediately at birth 2 = Not immediately but within 6 hours 3 = More than 6 hours after birth	
4.9	How long did the difficulty continue?	|__|__| days	
4.10	Did the difficulty continue until the baby died?	1 = Yes 2 = No	
4.11	Was there chest indrawing?	1 = Yes 2 = No	
4.12	Was there grunting (demonstrate)?	1 = Yes 2 = No	
4.13	Was there nostril flaring (demonstrate)?	1 = Yes 2 = No	
4.14	Did the baby have pneumonia?	1 = Yes	

		2 = No	
Difficulty feeding			
4.15	Did the baby ever suckle normally?	1 = Yes 2 = No →	Q4.20
4.16	Did the baby always suckle normally?	1 = Yes → 2 = No	Q4.20
4.17	When did the problem start?	1 = On the day he/she was born 2 = After the day of birth but in the first 3 days 3 = After the first 3 days	
4.18	How long did the problem continue?	|__|__| days	
4.19	Did the feeding problem continue until the baby died?	1 = Yes 2 = No	
Tetanus			
4.20	Could the baby open her mouth?	1 = Yes 2 = No	
4.21	Did the baby arch her back and have spasms? SHOW PHOTO	1 = Yes 2 = No	
4.22	Did the baby have tetanus?	1 = Yes 2 = No	
Diarrhoea			
4.23	Did the baby have more frequent liquid stools than usual?	1 = Yes 2 = No	
4.24	Did the baby have diarrhoea?	1 = Yes 2 = No →	Q4.27
4.25	Was there blood in the stool?	1 = Yes 2 = No	
4.26	How long did the diarrhoea continue?	|__|__| days	
4.27	Did the baby vomit everything?	1 = Yes 2 = No	
Other illness			
4.28	Did the baby have a fever?	1 = Yes 2 = No →	Q4.31
4.29	When did the fever start	|__|__| days after birth	
4.30	How long did the fever continue?	|__|__| days	
4.31	Were the baby's skin and eyes very yellow?	1 = Yes 2 = No	
4.32	Did the baby have any fits/convulsions/seizures?	1 = Yes 2 = No →	Q4.34
4.33	On which day of life?	1 = First day 2 = After first day	
4.34	Did the baby feel cold?	1 = Yes 2 = No →	Q4.37
4.35	When did the baby start feeling cold?	|__| days	
4.36	How long did the baby feel cold?	|__|__| days |__|__| hours	

4.37	Did the baby have pustules on the skin?	1 = Yes 2 = No	
4.38	Did the baby have ear discharge?	1 = Yes 2 = No	
4.39	Did the baby have red eyes with pus in them?	1 = Yes 2 = No	
4.40	Did the baby have a bright red ring on the skin around the umbilical cord stump?	1 = Yes 2 = No	
4.41	Did the baby bleed?	1 = Yes 2 = No →	Q4.43
4.42	Where did the baby bleed from?		
4.43	What did the baby's fontanelle look like?	1 = Sunken down 2 = Normal 3 = Bulging up	
4.44	Did the baby become drowsy and unconscious when he/she had been normal before?	1 = Yes 2 = No	
4.45	How long was the baby ill before he/she died?	|__|__| days	
4.46	Did the baby die suddenly without any sign of illness?	1 = Yes 2 = No	
4.47	Did the baby have some other problem that we haven't discussed?	1 = Yes 2 = No →	Q5.1
4.48	What was the problem?		

Now I would like to ask you some details about how you looked after the baby after he/she was born

Newborn care

5.1	What was the cord cut with?		
5.2	What was the cord tied with?		
5.3	What substances were put on the cord stump after it was cut?		
5.4	How long after birth was (NAME) wrapped up?	|__|__| hours |__|__| minutes	
5.5	How long after the birth was (NAME) bathed?	|__|__| hours |__|__| minutes	
5.6	What was the first thing the baby swallowed after he/she was born?		
5.7	Did (NAME) have a BCG immunisation? CHECK HEALTH PASSPORT IF AVAILABLE	1 = Yes 2 = No	
5.8	Did (NAME) have oral polio vaccine? CHECK HEALTH PASSPORT IF AVAILABLE	1 = Yes 2 = No	

Post-natal Check-up

6.1	After the baby was born, did a health professional or a traditional birth attendant check on your or your baby's health? THIS DOES NOT INCLUDE CHECKS MADE BY HEALTH WORKERS IMMEDIATELY AFTER A DELIVERY AT A HEALTH FACILITY	1 = Yes 2 = No →	Q6.6
6.2	How many days after delivery did the first check take place?	|__|__| days	

6.3	Why did you go?	1 = Normal check-up 2 = Problem for mother 3 = Problem for baby	
6.4	Where did this first check take place? FOR OUTREACH SPECIFY WHERE THE OUTREACH WAS, NOT THE HEALTH FACILITY THAT IT CAME FROM	1 = Mchinji District Hospital 2 = Kapiri 3 = Kaigwazanga 4 = Kochilira 5 = Mkanda 6 = Guillime 7 = Nkhwazi 8 = Chipumi 9 = Chiwosha 10 = Ludzi 11 = Mikundi 12 = Kapanga 13 = Tembwe 14 = St Gabriel's 15 = TBA 16 = Outreach (specify _____) 17 = Other (specify _____)	
6.5	Since the delivery, have you received a dose of Vitamin A? SHOW VITAMIN A TABLET	1 = Yes → 2 = No →	Q7.1 Q7.1
6.6	Why was there not a check?		
Now I would like you to tell me about how you fed your baby			
Breastfeeding			
7.1	Did you ever breastfeed (NAME)?	1 = Yes 2 = No → 3 = Baby died immediately, before it could be given anything →	 Q7.3 Q9.1
7.2	How long after birth did you first breastfeed the baby/put (NAME) to the breast?	|__|__| hours |__|__| minutes	
7.3	What did you give (NAME) to drink in the first three days after delivery, before your milk began flowing regularly? PROBE 'Anything else?' RECORD ALL FOODS/DRINKS MENTIONED IF BREAST MILK ONLY, GO TO Q7.5		
7.4	Why did you give these things?		
7.5	Did (NAME) drink any pharmaceutical medicine after he/she was born? INCLUDE LIQUID MEDICINES AND LIQUID VITAMINS OR MINERALS AND COMMERCIAL GRIPE WATER	1 = Yes (specify _____) 2 = No →	Q7.8
7.6	What was the medicine for?		
7.7	How many times did (NAME) drink pharmaceutical medicine?	|__|__| times	
7.8	Did (NAME) drink any traditional medicine after he/she was born?	1 = Yes (specify	

		_____) 2 = No →	Q7.11
7.9	What was the medicine for?		
7.10	How many times did (NAME) drink traditional medicine?	|__|__| times	
7.11	Did (NAME) drink any water after he/she was born?	1 = Yes 2 = No →	Q7.13
7.12	How many times did (NAME) drink water?	1 = Only on the first day 2 = On some days 3 = Every day 4 = Other (specify) _____	
7.13	Were you still breastfeeding (NAME), until the day he/she died?	1 = Yes → 2 = No	Q7.15
7.14	Why did you stop breastfeeding?		
7.15	Did you have any problems with breastfeeding?	1 = Yes 2 = No →	Q7.20
7.16	What were they?		
7.17	Did you go, or were you referred to a health facility because of these problems?	1 = Went without referral 2 = Was referred 3 = Didn't go	
7.18	Did you change the way you fed your baby during the time you had breast problems?	1 = Yes 2 = No →	Q7.20
7.19	What did you do differently? WRITE ALL CHANGES MENTIONED		
7.20	Did you change the way you fed your baby at any time the time when you were sick after the delivery?	1 = No → 2 = Yes, when I was sick 3 = Yes, when the baby was sick 4 = Yes, for another reason (specify _____ _____)	Q7.22
7.21	What did you do differently? WRITE ALL CHANGES MENTIONED		
7.22	Did anyone else (beside yourself) ever breastfed (NAME)?	1 = Yes 2 = No → 3 = Don't know →	Q7.24 Q7.24
7.23	Why did the other person breastfeed (NAME)?		
7.24	Did you ever express your breast milk after (NAME) was born?	1 = Yes 2 = No →	Q8.1
7.25	Did you give the expressed breast milk to (NAME)?	1 = Yes 2 = No →	Q7.27
7.26	How did you give the milk to (NAME)?	1 = Cup 2 = Bottle 3 = Other (specify _____)	

7.27	Did you heat-treat your breast milk?	1 = Yes 2 = No	
7.28	Why did you express milk?		
7.29	Who explained to you how to express the milk?	1 = Health worker 2 = Sister 3 = Mother 4 = Other family member 5 = Neighbour 6 = MaiMwana IF counsellor 7 = Other (specify _____)	

Feeding recall

Now I would like you to tell me the details about how you fed (NAME)

		First I'm going to ask you about all the things (NAME) drank during the first week after birth			IF THE BABY DIED WITHIN 7 DAYS AFTER BIRTH, GO TO Q9.1 Now I want to ask you about all the things (NAME) drank in the last 7 days before he/she died	
		8.1	8.2	8.3	8.4	8.5
		Before you gave any breast milk, was (NAME) given…	On the day he/she was born, was (NAME) given…	Between day 2 and day 7 after (NAME) was born, was he/she given…	On the day before (NAME) died, was he/she given…	Apart from the day before (NAME) died, in the last week, was he/she given…
01	Breast milk?					
02	Other milks?					
03	Water/dawale?					
04	Home-made gripe water/rice water/mzuwa?					
05	Phala?					
06	Other foods or drinks (specify)?					
07	Traditional medicines					
08	Pharmaceutical medicines					
09	Unsure of other foods or drinks given					

		1= Yes 2 = No 3 = Baby died 4 = Don't know	1= Yes 2 = No 3 = Baby died 4 = Don't know	1= Yes 2 = No 3 = Baby died 4 = Don't know	1= Yes 2 = No 3 = Baby died 4 = Don't know	1= Yes 2 = No 3 = Baby died 4 = Don't know

REMEMBER: **OTHER MILKS** INCLUDE COMMERCIAL FORMULA MILK, FRESH ANIMAL MILK, TINNED OR POWDERED MILK, FERMENTED OR SOUR MILK, YOGHURT, CHEESE, AND ALL OTHER MILK FROM A COW OR OTHER ANIMAL

Part H: Problems, Healthcare-seeking and Treatment – Baby

Now I would like to ask you about any help you sought for the problems (NAME) had, that we talked about earlier									
9.1 What was the first/next problem (NAME) had? CONTINUE UNTIL YOU HAVE COVERED ALL OF THE PROBLEMS MENTIONED IN PART 4	9.2 Did you consult anybody?	9.3 If NO, why not? SKIP TO NEXT PROBLEM AT Q9.1	9.4 If YES, who was the first/next person you consulted?	9.5 What did the person you consulted do? WRITE ALL THAT APPLY	9.6 Did you have to ask permission from anyone before you could go there? If YES, who?	9.7 How long was it from the start of the illness until (NAME) received treatment?	9.8 Did you go to anyone else for help for (NAME)? If YES, were you referred or did you go of your own accord?	9.9 Did you go?	9.10 If NO, why not?
1	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
2	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
3	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
4	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
5	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
6	|__|		|__|		|__|	|__||__| days |__||__| hours	|__|	|__|	
	1 = Yes → 9.4 2 = No		1 = Sing'anga 2 = TBA 3 = HSA 4 = Health worker in Mchinji 5 = Health worker outside Mchinji 6 = Grandmother 7 = Other relative 8 = Other (specify)		1 = No 2 = Husband 3 = Mother 4 = Father 5 = Mother-in-law 6 = Other relative 7 = Other (specify)		1 = Didn't go → Q9.1 (SKIP TO NEXT PROBLEM) 2 = Went without referral → Q9.4 (START A NEW LINE) 3 = Was referred → Q9.9	1 = Yes 2 = No IF YES, START AT Q9.4 WITH A NEW LINE	

Appendix II

MIRA - Nepal Stillbirth and Neonatal Verbal Autopsy

1. Household ID No.

VDC ☐☐ WARD ☐

Tole.....

Sector ☐ HH No. ☐☐☐

MW ID ☐☐ ☐☐ ☐☐☐ ☐

Name of MW.....

Interviewer ID. ☐☐☐

Interveiw Date

day ☐☐ month ☐☐ year ☐☐

Observed ☐ Checked ☐

Mother's Status ○ A live ○ Maternal Death

2.Respondent's Name .....

3.Respondent's relationship with the baby.

○ Mother herself ○ Father ○ Father's family member ○ Mother's family member

○ Birth attendent ○ Other (who ?).....

4.Date of Birth : day ☐☐ month ☐☐ year ☐☐

5.Date of Death : day ☐☐ month ☐☐ year ☐☐

6.Baby's Name (if given) .....

7.Sex of Baby ○ Male ○ Female ○ Don't know

8.Where did the baby die ? ○ Home ○ On the way of treatment ○ Health Facility

○ Traditional healer's place ○ Other.....

9.In order to help, we need to understand how and why the baby died. So please tell me the story of the pregnancy, delivery and baby.

.....

.....

.....

10. After how many months of pregnancy was the baby born ? ☐☐ months

11. Was the baby born at the expected time ? ○ Early ○ On time ○ Late

12. Did you have long labour more than 24 hours ? ○ Yes ○ No

Newborn Care

13. Where was the baby born ?

○ At home ○ Hetauda Hospital ○ Other Hospital ○ P H C ○ H P
○ S H P ○ Private clinic ○ Medical Shop ○ Area around home ○ Field / Jungle
○ Shed ○ Others..... *(for hospital and phc delivery go to question no. 87)*

14. How was the baby delivered ?

○ Normally ○ Manually ○ Forceps ○ Operatively
(if baby was delivered at hospital or phc and operatively go to question no. 82)

15. Which part of baby came out first?

○ Head ○ Buttock ○ Hands/Foot ○ Cord
○ Don't know

16. Was there a fire, stove or other form of heating in the delivery room ?

○ Before baby was born ○ After baby was born ○ Before and after baby was born
○ No ○ Don't know

17. Who helped with the delivery ?

☐ Doctor ☐ Nurse ☐ ANM ☐ HA / AHW / CMA
☐ tTBA / UntTBA ☐ MCHW ☐ VHW ☐ FCHV
☐ Mother in law ☐ Family Member ☐ Neighbours / Friends ☐ None (Alone)
☐ Others.....

18. Did the person who helped, have washed his/her hands ?

○ Yes ○ No ○ Don't know

19. Do you know what is this ? *(Show delivery kit)* ○ Yes ○ No *(if no go to question no.83)*

20. Did you use this ? ○ Yes ○ No *(if no go to question no.83)*

21. If yes, which one did you use ? ○ MCH Product ○ Mother's Group Product

22. Was the baby twin ? ○ Yes ○ No *(if no to to 13)*

23. If yes, was the baby the first or second born twin ? ○ First ○ Second

24. How did baby look like during birth ? ○ Normal ○ Abnormal

if abnormal, describe it.....
.....
.....
.....

25. Did the baby have a very small head ? ○ Yes ○ No
(show photo of anencephaly)

26.Did the baby have a mass or defect on the back of the head or spine ?
(show photo of meningomyelocele) ○ Yes ○ No

27. Did the baby have a cleft lip or palate ? ○ Yes ○ No
(show photo ofcleft lip and palate)

28. Did the baby have abnormal arms or legs ? ○ Yes ○ No

29. How big was the baby ? ○ Very small ○ Samaller than usual ○ Normal ○ Bigger than usual

30. Did the baby have bruises or signs of injury ? ○ Yes ○ No ○ Don't know

31. Was the baby born alive or dead ? ○ Alive ○ Dead *(if alive go to 31)*

32. Was the baby still moving when labour started ? ○ Yes ○ No *(if alive go to 24)*

33. If no, when did you last feel the baby moving ? ○ Hours before labour started ○ Days before labour started

34. If no, do you think that the baby had died before you went into labour ? ○ Yes ○ No *(if yes stop interview)*

35. Did the baby ever cry, even little ? ○ Yes ○ No *(if yes go to 31)*

36. Did the baby ever move, even little ? ○ Yes ○ No *(if yes go to 31)*

37. Did the baby ever breathe, even little ? ○ Yes ○ No *(if yes go to 31)*

38. Did the baby look like a normal baby, or had the skin and body changed and become pulpy/puffy/ mushy/swollen ? ○ Yes ○ No ○ Don't know

39. Was anything done to try to help the baby to breathe at birth ? ○ Yes ○ No ○ Don't know

40. If yes, what was tried among these ? ○ Stimulation ○ Mouth to mouth ○ Mouth to tube and mask ○ Bag and mask

41. Do you know the birth weight of the baby ?*(look at health records)* ☐☐☐ grams ○ No

42. What was the cord cut with ?

○ Boild Blade ○ Unboiled Blade ○ knife / scissors ○ Sickle / woodknife ○ Bamboo ○ Don't know ○ Others.....

43. Did you tie the cord ? ○ Yes ○ No

44. What was put on the cord stump after it was cut ?

○ Oil ○ Turmeric ○ Unwashed cloth / cotton ○ Washed cloth / cotton ○ Medicin /dettole ○ Powder ○ Mud ○ Nothing ○ Don't know ○ Other.....

45. How long after birth was the baby wrapped up ? ☐☐ After minutes or ☐☐ After hour/s

46. How long after birth was the baby bathed ? ☐☐ After minutes or ☐☐ After hour/s or ☐☐ After day/s

47. What was the first food given to the baby ?

○ Mother's milk ○ Other mother's milk ○ Cow /buffalo milk ○ Furmola/ Lactozine ○ Milk food ○ Ghee/Sugar/ Honey ○ Oil ○ Don't know ○ Others.....

48. Has your baby had the BCG immunization ? ○ Yes ○ No ○ Don't know

49. Did the baby cry at birth ? ○ Yes ○ No *(if yes go to 33)*

50. If no, how long after birth did the baby first cry ? ○ Within 5 min ○ Within 5-30 min ○ More than 30 min ○ Never

51. Was anything done to try to help the baby to breathe at birth ?
○ Yes ○ No *(if yes go to 35)*

52. If yes, what was tried among these ?
○ Stimulation ○ Mouth to mouth ○ Mouth to tube and mask
○ Bag and mask

53. Was the baby sleepy and floppy at the time of birth? ○ Yes ○ No

54. Did the baby ever have difficulty breathing ? ○ Yes ○ No *(if no go to 45)*

55. What was the difficulty ? ○ Intermittent breathing ○ Fast breathing

56. When did the difficulty start ?
○ Immediately at birth ○ Not immediately but within 6 hours
○ More than 6 hours after birth

57. How long did the difficulty continue ? ☐☐ days

58. Did the difficulty continue until the baby died ? ○ Yes ○ No

59. Was there chest indrawing ? ○ Yes ○ No

60. Was there grunting (demonstrate) ? ○ Yes ○ No

61. Was there nostril flaring (demonstrate) ? ○ Yes ○ No

62. Did the baby have pneumonia ? ○ Yes ○ No

63. Did the baby always suckle normally ? ○ Yes ○ No *(if yes go to 52)*

64. If no, when did the problem start ?
○ On the first day ○ After the first day but in the first 3 days
○ After the first 3 days

65. If no, how long did the problem continue ? ☐☐ days

66. If no, did the feeding problem continue until the baby died ? ○ Yes ○ No

67. If no, could the baby open his/her mouth ? ○ Yes ○ No

68. If no, did the baby arch her back and have spasms ? *(Show photo)* ○ Yes ○ No

69. If no, did the baby have tetanus ? ○ Yes ○ No

70. Did the baby have more frequent liquid stools than usual ? ○ Yes ○ No

71. Did the baby have diarrhoea ? ○ Yes ○ No *(if no go to 56)*

72. If yes, was there mucus or blood in the stool ? ○ Yes ○ No

73. If yes, how long did the diarrhoea continue ? ☐☐ days

74. Did the baby vomit everything ? ○ Yes ○ No *(if no go to 60)*

75. Did the baby have a fever ? ○ Yes ○ No

76. If yes, when did the fever start ? ☐☐ days

77. If yes, how long did the fever continue ? ☐☐ days

78. Were the baby's skin and eyes very yellow ? ○ Yes ○ No

79. Did the baby have any fits/convulsions/seizures ? ○ Yes ○ No *(if no go to 63)*

80. If yes, on which day of life ? ○ First day ○ After first day

81. Did the baby feel cold ? ○ Yes ○ No *(if no go to 66)*

82. If yes, when did the baby start feeling cold ? ☐☐ days

83. If yes, how long did the baby feel cold ? ☐☐☐ hours ☐☐ days

84. Did the baby have pustules on the skin ? ○ Yes ○ No

85. Did the baby have ear discharge ? ○ Yes ○ No

86. Did the baby have red eyes with pus in them ? ○ Yes ○ No

87. Did the baby have a bright red ring on the skin around the umbilical cord stump ? ○ Yes ○ No

88. Did the baby bleed ? ○ Yes ○ No *(if no go to 70)*

89. if yes, from where ?.....

.....

90. what did the baby's fontanelle look like ? ○ Sunken down ○ Normal ○ Bulging up

91. Did the baby have become drowsy and unconsious when she/he had been normal before ? ○ Yes ○ No

92. How long was the baby ill before she/he died ? ☐☐ days

93. Did the baby die suddenly without any sign of illness ? ○ Yes ○ No

94. Did the baby have some other problem that we haven't discussed and which had made you worry? ○ Yes ○ No *(if no go to 76)*

95. if yes, what problem ?.....

.....

.....

.....

Breastfeeding

96. Have you breastfed your baby ? ○ yes ○ No *(If no go to question no. 92)*

97. How long after the birth did you first feed the baby ?

☐☐ After minutes or ☐☐ After hour/s or ☐☐ After day/s

98. Did you throw first milk before you feed the baby first ? ○ Yes ○ No

99. Do you feed the baby only mother's milk or you are giving some other things like : water, lactogen, cow's/buffalo milk as well ? ○ Yes ○ No

Treatment of the baby

(if baby had fever, diarrhoea, jaundice, cord infection and caughing ask the following questions)

100. Did you seek treatment when the baby was sick ? ○ Yes ○ No *(if yes go to question no. 95)*

101. if not,why did not you go ?

.....

.....

.....

102. Who did you consult with at first ? *(stop interview)*

○ Doctor ○ Staff Nurse ○ HA ○ ANM ○ AHW

○ Medical shopkeeper ○ MCHW ○ FCHV ○ TBA ○ Dhami

○ Others

103. Where did you go for treatment ?

☐ Health Institution ☐ Medical shop ☐ Shaman ☐ Call Health worker at home ☐ Other

104. How did you get there ?

☐ Walked ☐ Carried ☐ Ambulence ☐ Car / Tempo / Bus / Rickshaw

☐ Stretcher (MIRA) ☐ Stretcher (Other) ☐ Doko

105. Did they treat the baby ? ○ Yes ○ No *(if no go to question no. 100)*

106. What did they do ?

.....

.....

.....

107. How long was it from the start of the baby's illness to receive treatment ?

☐☐ After hours or ☐☐ After day or ☐☐ After week

108. Did you then consult anyone else ? ○ Yes ○ No *(If No go to 105)*

109. Who did you consult with at first ?

○ Doctor ○ Staff Nurse ○ HA ○ ANM ○ AHW
○ Medical shopkeeper ○ MCHW ○ FCHV ○ TBA ○ Dhami
○ Others

110. Where did you go for treatment ?

☐ Health Institution ☐ Medical shop ☐ Shaman ☐ Call Health worker at home ☐ Other

111. How did you get there ?

☐ Walked ☐ Carried ☐ Ambulence ☐ Car / Tempo / Bus / Rickshaw
☐ Stretcher (MIRA) ☐ Stretcher (Other) ☐ Doko

112. Were you reffered or did you just decide to go ? ○ Reffered ○ Just decided to go

113. Did they treat the baby ? ○ Yes ○ No *(if no, go to 104)*

114. What did they do ?

.....

.....

.....

115. How long was it from the start of the baby's illness to receive treatment ?

☐☐ After hours or ☐☐ After day or ☐☐ After week

116. Did you or your family member give a treatment without consulting anyone else ?

○ Yes ○ No

if Yes, describe it.....

.....

117. How much did you paid in total for transportation and treatment ? Rs.....

118. How did you get money ?

☐ Wages Rs.....

☐ Saving Rs.....

☐ Sale of Land	Rs.……
☐ Sale of Livestock	Rs.……
☐ Borrowed money from relatives	Rs.……
☐ Borrowed money from Lender	Rs.……
☐ Borrowed money from MIRA MCH Fund	Rs.……
☐ Borrowed money from Other Fund	Rs.……
☐ From Other Organisation	Rs.……
☐ From Donation	Rs.……

Appendix III

SNEHA –Mumbai, Birth Surveillance Questionnaire

City Initiative for Newborn Health

Stillbirth and neonatal death interview tool

This questionnaire should be used only if the baby has died

Survival status of mother	Alive ☐	Died ☐

Mortality category

*Place the infant in one of the following groups. Do this **after** completing the form in order to be sure that it is correct.*

Stillbirth: Born at 28 w gestation or more and born dead: child did not cry, move or breathe after birth ☐

Early neonatal death: Born alive and died in the first 7 days (ie up to 1 week) ☐

Late neonatal death: Born alive and died after 7 days and before 28 days (ie from week 2 up to week 4) ☐

If the mother has died, ask this questionnaire to family members who are best able to answer. There are some questions about the mother that other people may not be able to answer. Fill in as much of the questionnaire as possible.
Before the interview, request the mother or family members to collect all medical records, antenatal care records, delivery records and any others relating to mother and baby.

	Section A: Administrative							
A1	**Ward**	F/N ☐	G/N ☐	H/E ☐	K/W ☐	M/E ☐	P/N ☐	
A2	**Cluster number** ☐☐	**Woman number** ☐☐☐			**Baby number** ☐			
A3	**Household address**	……						
A4	**Name of mother**							
A5	**Consent section**							
A6	**Number of visits made to complete interview**	☐						
	If more than 1 visit, reason ……							
A7	Language of interview Translator (specify language)	☐ ……	Hindi ☐	Marathi ☐	Gujarati ☐	English ☐		
A8	**Date of interview**	_ _ / _ _ / _ _ _ _ *day/month/year*						
A9	**Date of delivery**	_ _ / _ _ / _ _ _ _ *day/month/year*						
A10	**Date of infant death**	_ _ / _ _ / _ _ _ _ *day/month/year*						
		Interviewer check						
A11	**Questionnaire complete**	Yes ☐	No ☐					
A12	**Reason for incompleteness**	……						
Interviewer signature ……..		Write full name ……..						
A13	**Date of receipt at office**	_ _ / _ _ / _ _ _ _ *day/month/year*						
A14	**Location of woman**	Lives in basti ☐	Just arrived in basti ☐	Moved out of basti ☐				
	Do you have the antenatal case paper?	Yes ☐	No ☐					

A15 What is the name of the main respondent? .....

A16 What is the age of the main respondent? ☐☐ *years*

A17 What is the relationship of the main respondent to the deceased baby?

- Mother ☐ — ***Go to A22***
- Father ☐
- Grandmother ☐
- Grandfather ☐
- Aunt ☐
- Uncle ☐
- Birth attendant ☐ — *Who?* .....
- Other male ☐ — *Who?* .....
- Other female ☐ — *Who?*

A18 Is the mother still alive? Yes ☐ ***Go to A21*** No ☐

A19 When did she die? During the delivery ☐ ***Go to A22*** After the delivery ☐

A20 How many days after delivery did she die? ☐☐ *days* ***Go to A22***

A21 Why is the mother not the main respondent?

- Mother does not live in household ☐
- Mother is not present at interview ☐
- Mother is not capable of answering ☐
- Mother refused interview ☐
- Other ☐
- Don't know ☐

A22 Were other people present at the interview? Yes ☐ No ☐ ***Go to B1***

A23 Who was present during the pregnancy, delivery, illness and death and is here for the interview?

	Present during pregnancy N/A	Present at delivery N/A	Present during illness	Present at death
Mother	☐	☐	☐	☐
Father	☐	☐	☐	☐
Grandmother	☐	☐	☐	☐
Grandfather	☐	☐	☐	☐
Aunt	☐	☐	☐	☐
Uncle	☐	☐	☐	☐
Birth attendant *who*	☐	☐	☐	☐
Other *who*	☐	☐	☐	☐

A24 ***How many people in total were present at the interview (excluding the interviewer)?*** ☐☐ *people*

Thank you for answering those questions. First I am going to ask you some things about you, your family and your home.

Section B: Background characteristics

B1	How old were you on your last birthday? *(Completed years)*			☐☐ *years*	Don't know ☐
B2	What is your date of birth? *Cross check with B1*			_ _ / _ _ / _ _ _ _ *day/month/year*	Don't know ☐
B3	How old were you when you first got married?	☐☐ *years*		Not married ☐	Don't know ☐
B4	How old were you when you first became pregnant?			☐☐ *years*	Don't know ☐
B5	What sort of education have you had?	No education at all ☐	Informal education ☐	School ☐ *up to class* ☐☐	College ☐
B6	Can you read?	Yes, ☐	No ☐		
B7	What is your religion?	Hindu ☐ Muslim ☐ Other ☐	Christian ☐ Sikh ☐ (specify)	Buddhist ☐ Jain ☐	Parsi ☐ No religion ☐
B8	What is your caste?	SC ☐	BC ☐	OBC ☐	Other ☐(specify) .....
B9	What is your current marital status?	Married ☐ Widowed ☐		Separated or deserted ☐ Divorced ☐	Never married ☐
B10	Do you currently live with your husband/father of your child?			Yes ☐ No ☐	
B11a	Do you live in a Nuclear, Joint or Extended family?			Nuclear ☐ Joint ☐	Extended ☐
B11b	How many household members are there?			☐☐ *members*	
B12	*Not to be asked to unmarried or widowed mother* How old was your husband on his last birthday?			☐☐ *years*	Don't know ☐
B13	*Not to be asked to unmarried or widowed mother* What sort of education has your husband had?	No education at all ☐	Informal education ☐	School ☐ College ☐	Don't know ☐
B14	How long have you been living in this basti? ***If less than 1 month, write 01 in months***	☐☐ *months* or ☐☐ *years* ***If over 1 year go to B16***			All her life ☐
B15	Did you come here just for the pregnancy/delivery?				Family moved to this basti not linked to pregnancy ☐ Came for pregnancy/delivery and intend to return home ☐ Came for pregnancy/delivery but now intend to stay ☐
B16	Do you own this house?	Other ☐ Yes ☐	(specify) ..... No ☐		
B17	Type of house *Interviewer to observe*	Pucca ☐	Semi-pucca/semi-kacha ☐		Kacha ☐
B18	Does your household have a ration card?	White ☐	Yellow ☐	Orange ☐	No card ☐ ***go to B20***
B19	Does the card have your name on it?		Yes ☐		No ☐

B20	Do you possess the following items? *Interviewer to read out slowly* Interviewer may tick more than one box	Mattress ☐ Pressure cooker ☐ Gas cylinder/chula ☐ Stove ☐ Chair ☐ Cot or bed ☐ Table ☐ Clock ☐ Electric fan ☐		Bicycle ☐ Radio ☐ Sewing machine ☐ Telephone or mobile ☐ Refrigerator ☐ Television ☐ Moped, scooter or motorcycle ☐ Car ☐
B21	Is your electricity supply legal or illegal?	Legal ☐	Illegal ☐	No supply ☐
B22	Is your water supply legal or illegal?	Legal ☐	Illegal ☐	From another basti ☐
			Bought ☐ ***go to B24***	
B23	Is your water supply private or public/shared?	Private ☐	Public/shared ☐	From another basti ☐
		Other ☐	(what)	

B24	Is your toilet facility private or public/shared?	Private ☐	Public/shared ☐	No toilet facility ☐
		Other ☐		(what) .....

Thank you for answering those questions
Now I am going to ask you about any pregnancies you might have had before this one

Section C: Maternity History

C1 **Previous pregnancies**

Pregnancies *in order from first*	Miscarriage	MTP	Birth		Boys born alive		Girls born alive	
1	☐	☐	Born alive ☐	Born dead ☐	Now alive ☐	Now dead ☐	Now alive ☐	Now dead ☐
2	☐	☐	Born alive ☐	Born dead ☐	Now alive ☐	Now dead ☐	Now alive ☐	Now dead ☐
3	☐	☐	Born alive ☐	Born dead ☐	Now alive ☐	Now dead ☐	Now alive ☐	Now dead ☐

C2 **Totals**

Pregnancies	Miscarriages	MTPs	Born alive	Born dead	Now alive	Now dead	Now alive	Now dead
☐	☐	☐	☐	☐	☐	☐	☐	☐

For the last pregnancy before the current one…

If the current one is the first pregnancy, go to C4

C3 What was the date of delivery (or end of the pregnancy if miscarriage or MTP)?
Needed to calculate the interval between the last two pregnancies
_ _ / _ _ / _ _ _ _ *day/month/year* Only had one pregnancy ☐ Don't know ☐

C4 When you became pregnant this time, did you want to become pregnant at that time, would you have preferred to delay your next pregnancy, or did you not want any more children?
Didn't think about it ☐ Wanted to become pregnant at that time ☐ Wanted to delay next pregnancy ☐ Did not want any more children ☐

C5 When you became pregnant this time, did the father of the child want you to become pregnant at that time, would he have preferred to delay your next pregnancy, or did he not want any more children?
Didn't think about it ☐ Wanted to become pregnant at that time ☐ Wanted to delay next pregnancy ☐ Did not want any more children ☐

C6 When you became pregnant this time, did you want to have a son or a daughter, or did you have no preference?
Wanted a son ☐ Wanted a daughter ☐ No preference ☐

C7 *Not to be asked to unmarried or widowed mother: go to D1*
When you became pregnant this time, did the father of your child want to have a son or a daughter, or did he have no preference?
Wanted a son ☐ Wanted a daughter ☐ No preference ☐

C8 *Not to be asked to unmarried or widowed mother: go to D1*
Have you and your husband ever used any family planning method?
Yes ☐ No ☐ ***Go to D1***

C9 Which method have you used in the last 3 years?
Do not read out options
Interviewer may tick more than one

Breastfeeding ☐
Oral contraceptive pill ☐
Norplant ☐
Depo provera ☐
Other ☐

Intrauterine device (coil, copper T, loop) ☐
Condoms ☐
Safe period ☐

Traditional medicine ☐
Tubectomy ☐
Vasectomy ☐
Emergency contraception ☐
Withdrawal ☐
(what)
……

Comment ……

Thank you for answering those questions.Now I am going to ask you about what happened to the baby.

D	Open history				
D1	Was the baby a single or multiple birth? *If two or more children are born, it is counted as a multiple birth, even if any baby is born dead. If multiple birth, fill a form for each baby who died.*		Singleton ☐ ***Go to D4***		Multiple birth ☐
D2	**Was this baby born first, second or later?**		First born ☐ ***Go to D4***		Second born ☐
			Third or later ☐		Don't know ☐
D3	How long after the first baby was this baby born?	☐☐ *minutes after*			
D4	What was the baby's gender?		Male ☐	Female ☐	Don't know ☐
D5	Was the baby given a name?		Yes ☐	No ☐ ***Go to D7***	
D6	What was the baby's name?	……..			
	We would like to understand how and why the baby died, so I am going to ask you to tell me the story. *Allow the respondent to tell you about the pregnancy, delivery and the baby's injury or illness in her own words. Write down what the respondent tells you in her own words. Do not prompt except for asking whether there was anything else after the respondent finishes. Keep prompting until the respondent says there was nothing else. While recording underline any unfamiliar terms.* *Also remember to prompt about care seeking during pregnancy, labour, delivery, after the birth of the baby and during the fatal illness. Ask what the mother did and who she sought care from during all of these times*				
D7	Could you tell me about the pregnancy for this baby?				
D8	Could you tell me about the labour and delivery for this baby?				
D9	Could you tell me what the baby was like at birth?				
D10	Could you tell me what happened to the baby immediately after delivery? *In this question we want to know what happened to the baby **immediately** after delivery: **if the baby cried after birth** or needed any treatment or special care as soon as he or she was born.*				
D11	Could you tell me about the baby's illness or accident that led to death?				
D12	Why do you think the baby died?				
D13	What do you think could have been done to save the baby?				

Thank you for answering those questions. Now I am going to ask you about antenatal care in the pregnancy you have just had.

Section E: Antenatal care

E1 Who confirmed your pregnancy? Herself ☐ Doctor ☐

E2 How was the pregnancy confirmed? Signs and symptoms ☐ Examination by provider ☐
Interviewer can tick more than one option Urine test ☐ Ultrasound ☐
Other ☐ (what) ……

E3 In which month of pregnancy did you confirm the pregnancy? ☐ *months* Don't know ☐
Write 1 if less than 1 month

E4 Did any health worker register your pregnancy? No ☐
Yes… BMC CHV ☐ ICDS AWW ☐ NGO CHV ☐
Other ☐ (who) ……

E5 Did you go for an antenatal check-up during this pregnancy? Yes ☐ ***Go to E7*** No ☐

E6 Why not?
Interviewer may tick more than one box. *Do not read out the options. Choose options depending on what respondent says.*

No problem ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐ Not customary ☐
Other ☐ (specify) ……

E7 Who or what influenced you in your decision?
Interviewer may tick more than one box. *Do not read out the options. Choose options depending on what respondent says.*

Decided herself ☐ Other family member ☐ Doctor, nurse ☐ TV, Radio, Newspaper ☐
Husband ☐ Friend or neighbour ☐ CHV/polio dawakhanawali ☐ Community group ☐
Other ☐ (specify) ……

If no antenatal care go to E15

E8 What was the reason for your First antenatal care visit? Check-up ☐ Problem ☐ (what) ……

E9 Where did you go for antenatal care? Health Post ☐ Maternity home ☐ Peripheral hospital ☐
Tertiary hospital ☐ Private facility ☐ Other ☐(what) ……

Name of institution ……..

E10 In which month of pregnancy did you go for your first antenatal check-up? ☐ *months* ***if < 7 go to E12***
Write 1 if less than 1 month

E11 What were the reasons for waiting until this stage of pregnancy?
Interviewer may tick more than one box *Do not read out the options. Choose options depending on what respondent says.*

No problem ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐ Not customary ☐
Other ☐ (specify) ……

E12 How many antenatal check-ups did you have?

In first 3 months ☐ times In middle 3 months ☐ times In last 3 months ☐ times Total ☐

E13 During antenatal care, did this check happen… *Read out options one by one*

Measured your weight ☐ Took a blood sample ☐
Measured your height ☐ Did an internal examination ☐
Examined your abdomen ☐ Did an ultrasound scan ☐
Measured your blood pressure (with a cuff) ☐ Gave you an injection in the arm to prevent tetanus (TT) ☐
Took a urine sample ☐ Gave you iron supplements ☐

E14 What was the due date for delivery (EDD)? _ _ / _ _ / _ _ _ _ *day/month/year* Don't know ☐

E15 Did you take iron tablets during the pregnancy? No ☐ Yes: 1 packet ☐ Yes: 2 packets ☐ Yes: 3 packets ☐ ***go to E17***

E16 What were your reasons for not taking the full course of iron tablets?

Had side-effects ☐ Did not see need ☐ Lost or misplaced tablets ☐ Someone else took tablets ☐
Other ☐ (why) ……

E17 While you were pregnant, did a health worker visit you at home to discuss issues about the pregnancy?
Yes ☐ No ☐ ***Go to E19***

E18 Who visited you?

BMC CHV ☐ ICDS AWW ☐ NGO CHV ☐ Other (who) ……

E19 Did you register your name for delivery at a health facility? Yes ☐ No ☐ ***go to E22***

E20 Where did you register your name for delivery?

Maternity home ☐ General hospital ☐ Very large hospital ☐
Private facility ☐ Other ☐ (what) ……

Name and location of institution ……..

E21 In which month of pregnancy did you register your name for delivery?
Write 1 if less than 1 month
☐ *months*

E22 Did you do any of the following before you were pregnant, or during pregnancy?
Read out the options one by one Interviewer may tick more than one box

	Before pregnancy	*During pregnancy*
Chew tobacco	☐	☐
Use mishri	☐	☐
Chew paan	☐	☐
Chew gutka	☐	☐
Smoke bidis or cigarettes	☐	☐
Drink alcohol	☐	☐
Take snuff (tapkir)	☐	☐

E23 Did the amount of rest you took during pregnancy change from before you were pregnant?

In first 3 months	More ☐ Same ☐ Less ☐	In middle 3 months	More ☐ Same ☐ Less ☐	In last 3 months	More ☐ Same ☐ Less ☐

E24 Did the amount of physical work you did during pregnancy change from before you were pregnant?

In first 3 months	More ☐ Same ☐ Less ☐	In middle 3 months	More ☐ Same ☐ Less ☐	In last 3 months	More ☐ Same ☐ Less ☐

E25	Did the amount of food you ate during pregnancy change from before you were pregnant?						
	In first 3 months	More ☐ Same ☐ Less ☐	In middle 3 months	More ☐ Same ☐ Less ☐	In last 3 months	More ☐ Same ☐ Less ☐	

Thank you for answering those questions
Now I am going to ask you about the birth itself

	Section F: Current delivery				
F1	On what date was your delivery?				_ _ / _ _ / _ _ _ _ *day/month/year*
	What time was your delivery?		☐☐☐☐ *time according to 24 hr clock*		
	After how many months of pregnancy was the baby born?	Months			
	Was the baby born at the expected time?	Early On time Late			
F2	Where was your delivery?		In Mumbai ☐		Outside Mumbai ☐
F3	In which place was your delivery?		Home ☐ **go to F4**	On way to facility ☐	**go to F4**
	Government Hospital ☐		Maternity home ☐	General hospital ☐	Very large hospital ☐
	Private facility ☐ Other ☐		(what) ……..		
	Name and location of institution		……		

F4 **Did the waters break before or after labour started?** ☐☐ *hours before labour* After labour started ☐ Don't know ☐

F5 What colour were the waters when they broke? Green or brown ☐ Clear or normal colour ☐ Don't know ☐ Other *what?* .....

F6 Did the waters smell foul? Yes ☐ No ☐ Don't know ☐

F7 How long did the regular, strong labour pains start before the baby was born? ☐☐ *hours* No labour ☐ Don't know ☐

F8 Which part of the baby came out first?

Head ☐
Bottom ☐
Feet ☐
Hand or arm ☐
Cord ☐
Caesarean ☐
Don't know ☐

F9 Did any of the following problems occur during labour or delivery?

Health worker measured blood pressure and said it was high ☐
Convulsions: shaking arms and legs with loss of consciousness ☐
Fever during labour ☐
Umbilical cord came out before the baby ☐
Umbilical cord around the baby's neck ☐
Heavy bleeding, that soaked the bed or the floor ☐
Placenta would not deliver ☐
Someone put hand inside womb to remove placenta ☐
Other *what?* .....

Section G: Home delivery

G1 Why did you give birth at home? .....

G2 What sort of surface did you give birth on?

Chattai ☐ Bedsheet ☐ Quilt ☐ Blanket ☐
Plastic sheet ☐ Rubber sheet ☐ Uncovered floor ☐ Uncovered bed ☐
Sacking ☐ Other ☐ (specify) .....

G3 Who was the main person who assisted you in delivering your baby?

Friend or relative ☐ Dai ☐ CHV ☐ Nobody assisted ☐ ***Go to G6***

Other ☐ (who) ……

G4 Did the person who helped wash her hands with soap before the delivery? Yes ☐ No ☐ Don't know ☐

G5 Did the person who helped wear gloves during the delivery? Yes: new gloves ☐ Yes: old gloves ☐ No ☐ Don't know ☐

G6 What was the cord cut with? Blade ☐ Knife ☐ Scissors ☐ Don't know ☐

Other ☐ (what) ……

G7 Was the cutting implement brand new, boiled or used?

Absolutely new ☐ Boiled ☐ Used ☐ Don't know ☐

Other ☐ (what) ……

G8 What was the umbilical cord tied with?

Clamp ☐ Boiled thread ☐ Unboiled thread ☐ Don't know ☐

Other ☐ (specify) ……..…

G9 What was applied on the cord stump after it was cut?

Nothing ☐ Kerosene ☐ Oil ☐ Turmeric ☐ Antiseptic cream ☐

Boric powder ☐ Other ☐ (specify) ……..…

Section H: Facility births

H1 Was medicine given to make the labour start? Yes *what?* ..... ☐ No ☐ Don't know ☐

H2 Was medicine given after labour had already started, to make the labour progress more quickly? Yes *what?* ..... ☐ No ☐ Don't know ☐

H3 How was the baby delivered?

Normally through vagina ☐
Baby was pulled out after manipulation by hand ☐
Baby was pulled out with an instrument ☐
Go to I1
C-section or operation ☐
Other *how?* .....

H4 Did you know it was going to be a C-section before the labour started? Yes ☐ No ☐ Don't know ☐

Section I: The baby

I1 What time was your delivery? ☐☐☐☐ *time according to 24 hr clock*

I2 Was the baby born alive or dead? Alive ☐ ***Go to I7*** Dead ☐

I3 Did the baby ever cry, even a little? Yes ☐ ***Go to I7*** No ☐ Don't know ☐

I4 Did the baby ever move, even a little? Yes ☐ ***Go to I7*** No ☐ Don't know ☐

I5 Did the baby ever breathe, even a little? Yes ☐ ***Go to I7*** No ☐ Don't know ☐

The baby was a stillbirth

I6 Had the baby's body changed so that the skin was soft and pulpy or discoloured? Yes ☐ No ☐ Don't know ☐

Was the baby still moving when labour started? Yes ☐ No ☐ Don't know ☐

… If no, when did you last feel the baby moving? Hours before labour started ☐ Days before labour started ☐

i7 Was anything done to try to help the baby to breathe at birth? Yes ☐ No ☐ Don't know ☐

I8 How big was the baby when he/she was born?

Tiny ☐
Smaller than usual ☐
About average ☐
Larger than most babies ☐
Don't know ☐

I9 What was the weight of the baby? ☐☐☐☐ *g*
Record birth weight in kilograms. Ask to see any medical records

I10 Were there any bruises or marks of injury on the baby's body at birth? Yes ☐ No ☐ Don't know ☐

I11 Did the baby have a very small head at the time of birth? Yes ☐ No ☐ Don't know ☐

I12 Was there a mass or defect on the back of the head or spine? Yes ☐ No ☐ Don't know ☐

I13	Was there a cleft lip or palate?	Yes ☐	No ☐	Don't know ☐
I14	Were there any other limb defects?	Yes ☐	No ☐	Don't know ☐
I15	Were there any other congenital abnormalities?	Yes *what?*	No ☐	Don't know ☐

If the baby was a stillbirth, go to Section U

Section J: Neonatal death

J1	How long after birth did the baby first cry?	Immediately ☐	*After* ☐☐ *mins*	Never cried ☐
J2	On the day of birth was the baby well?	Yes ☐	No ☐	Don't know ☐
J3	Was the baby examined by a healthcare provider after birth? *Use available papers to help answer the question*	Yes ☐	No ☐	***Go to J6***
J4	How long after birth was the baby examined?	☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*		
J5	Who examined the baby?	Doctor ☐	Nurse ☐	Dai ☐
J6	Was the baby given to you or kept in a special room?		Yes ☐	No ☐
J7	Was the baby given oxygen through a mask, tube of headbox?		Yes ☐	No ☐
J8	How old was the baby when the fatal illness started?		☐☐ *hours old*	☐☐ *days old*
J9	How old was the baby at the time of death?		☐☐ *hours old*	☐☐ *days old*

Section K: Feeding

K1 Was the baby breastfed? Yes ☐ No ☐ ***Go to K3*** Don't know ☐ ***Go to K4***

K2 **How long after the birth was the baby first put to the breast?**

Within an hour ☐ *After* ☐ *hours* ***Go to K4*** *After* ☐☐ *days* Don't know ☐

K3 Why was the baby not put to the breast on the first day?

Mother ill or weak ☐
Baby ill or weak ☐
Baby died ☐
Breast or nipple problem ☐
Not enough milk ☐
Baby would not feed ☐
Traditional practice ☐
Other *what?* .....

K4 In the first 24 hours after birth, was the baby given the following?

Breastmilk from another woman ☐
Other milk such as cow's milk, tinned milk, formula ☐ *what?* .....
Other fluids such as water, medicines ☐ *what?* .....
Other ☐ *what?* .....
Nothing was given ☐

K5	On the day of birth, was the baby able to suckle or bottle feed in a normal way?	Yes ☐		No ☐	Don't know ☐
K6	Did the baby always suckle normally?	Yes ☐	***Go to L1***	No ☐	Don't know ☐ ***Go to L1***

K7	**When did the feeding problem start?**	On the first day ☐			*After* ☐☐ *days*
K8	How long did the feeding problem continue?				☐☐ *days*
K9	Did the feeding problem continue until the baby died?	Yes ☐	No ☐	Don't know ☐	
K10	Could the baby open his/her mouth?	Yes ☐	No ☐	Don't know ☐	
K11	Did the baby arch his/her back and have spasms?	Yes ☐	No ☐	Don't know ☐	
K12	Did the baby have tetanus?	Yes ☐	No ☐	Don't know ☐	

	Section L: Breathing				
L1	During the illness, did the baby have difficult breathing?	Yes ☐	No ☐ ***Go to L4***	Don't know ☐	***Go to L4***
L2	How long after birth did the difficult breathing start?	On the first day ☐		*After* ☐☐ *days*	Don't know ☐
L3	How long did the difficult breathing last?		☐☐ *days*		Don't know ☐
L4	During the illness, did the baby have fast breathing?	Yes ☐	No ☐ ***Go to L7***	Don't know ☐	***Go to L7***
L5	How long after birth did the fast breathing start?	On the first day ☐		*After* ☐☐ *days*	Don't know ☐
L6	How long did the fast breathing last?		☐☐ *days*		Don't know ☐
L7	During the illness, did the baby have indrawing of the chest? *Demonstrate*	Yes ☐	No ☐	Don't know ☐	
L8	During the illness, did the baby have grunting? *Demonstrate*	Yes ☐	No ☐	Don't know ☐	
L9	During the illness, did the baby's nostrils flare with breathing? *Demonstrate*	Yes ☐	No ☐	Don't know ☐	
L10	During the illness, did the baby ever stop breathing for a long time and start again?	Yes ☐	No ☐	Don't know ☐	
L11	During the illness, did the baby have pneumonia?	Yes ☐	No ☐	Don't know ☐	
L12	During the illness, did the baby turn blue?	Yes ☐	No ☐	Don't know ☐	

	Section M: Neurological problems				
M1	During the illness, did the baby have fits or convulsions? *Demonstrate*	Yes ☐	No ☐ ***Go to M3***	Don't know ☐	***Go to M3***
M2	How long did the fits or convulsions last?	Less than 1 day ☐	☐☐ *hours*	☐☐ *days*	Don't know ☐
M3	During the illness, did the baby have a bulging fontanelle?	Yes ☐	No ☐	Don't know ☐	
M4	During the illness, did the baby become unresponsive or unconscious or very sleepy?	Yes ☐	No ☐	Don't know ☐	

	Section N: Skin and eyes			
N1	How long after birth did anyone dry the birth fluid from the baby's skin?	☐ *mins*	☐ *hours*	Never ☐
		Not applicable ☐		Don't know ☐
N2	How long after birth did anyone wrap the baby?	☐ *mins*	☐ *hours*	Never ☐

			Not applicable ☐	Don't know ☐
N3	During the illness, did the baby have redness of, or drainage from, the umbilical cord stump?	Yes ☐	No ☐	Don't know ☐
N4	During the illness, were there any of the following on the baby's skin?			
		Boils ☐ Blisters ☐		Single large area of pus ☐ Redness with swelling ☐
N5	During the illness that led to death, did the baby have redness of and drainage of pus from the eyes?	Yes ☐	No ☐	Don't know ☐

	Section O: Diarrhoea			
O1	During the illness, did the baby have frequent loose or liquid stools? (watery/green/foulsmelling)	Yes ☐	No ☐	Don't know ☐
O2	During the illness, did the baby have diarrhoea?	Yes ☐ No ☐ ***Go to P1***	Don't know ☐	***Go to P1***
O3	How long did the baby have loose or liquid stools or diarrhoea?	Less than 1 day ☐	☐☐ *days*	Don't know ☐
O4	How many times did the baby pass stool on the day that the loose stools or diarrhoea was most frequent		☐☐ *times*	Don't know ☐
O5	Do you feel that this represented more loose or liquid stools than usual for a baby?	Yes ☐	No ☐	Don't know ☐
O6	During the illness, was there visible blood in the loose or liquid stools?	Yes ☐	No ☐	Don't know ☐

	Section P: Problems suggesting infection			
P1	During the illness, did the baby have a fever?	Yes ☐ No ☐ ***Go to P4***	Don't know ☐	***Go to P4***
P2	How old was the baby when the fever started?	Less than 1 day ☐	☐☐ *days*	Don't know ☐
P3	How many days did the fever last?	Less than 1 day ☐	☐☐ *days*	Don't know ☐
P4	During the illness, did the baby become cold to touch?	Yes ☐ No ☐ ***Go to P7***	Don't know ☐	***Go to P7***
P5	How old was the baby when he/she became cold to touch?	Less than 1 day ☐	☐☐ *days*	Don't know ☐
P6	For how many days did the baby feel cold to touch?	Less than 1 day ☐	☐☐ *days*	Don't know ☐
P7	Did the baby have abdominal distension?	Yes ☐	No ☐	
P8	During the illness, did the baby become lethargic after a period of normal activity?	Yes ☐	No ☐	Don't know ☐

	Section Q: Other problems			
Q1	During the illness, did the baby vomit everything?	Yes ☐	No ☐	Don't know ☐
Q2	During the illness, did the baby have jaundice?	Yes ☐	No ☐	Don't know ☐
Q3	During the illness, did the baby bleed from anywhere?	Yes *where?*	No ☐	Don't know ☐
Q4	During the illness, did the baby pass urine?	Yes ☐	No ☐	Don't know ☐
Q5	During the illness, did the baby pass stool?	Yes ☐	No ☐	Don't know ☐
Q6	Did the doctor recommend that the baby have surgery?	Yes ☐	No ☐	Don't know ☐

Q7 Did the baby die from an injury or accident? Yes ☐ No ☐ ***Go to R1*** Don't know ☐ ***Go to R1***

Q8 What kind of injury or accident?

Motor vehicle accident ☐
Fall ☐
Drowning ☐
Poisoning ☐
Bite or sting from venomous animal ☐
Burn ☐
Violence ☐
Other ☐ *what?*
.....
Don't know ☐

Q9 How long did the baby survive after the injury or accident?

Died in 24 hrs ☐ Died after a day or more ☐ Don't know ☐

Section R: Newborn care seeking

R1 Did you do anything to treat the illness at home? Yes ☐ No ☐ ***go to R5***

R2 What did you do? ……..

R3 Who or what influenced you in what you did?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Decided herself ☐	Other family member ☐	Doctor, nurse ☐	TV, Radio, Newspaper ☐
Husband ☐	Friend or neighbour ☐	CHV/polio dawakhanawali ☐	Community group ☐
Other ☐	(specify) ……		

R4 How long was it from the time you recognized the baby had a problem until you first treated it at home? ☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

R5 Did you seek care from someone outside the home? Yes ☐ ***go to R7*** No ☐

R6 Why not?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐	Family did not allow ☐	Too far away ☐
Did not see need ☐	Nobody to manage children or home ☐	Cost of service ☐
No time to go ☐	Nobody to accompany ☐	
Other ☐	(specify) ……	

R7 Who or what influenced you in what to do?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Decided herself ☐	Other family member ☐	Doctor, nurse ☐	TV, Radio, Newspaper ☐
Husband ☐	Friend or neighbour ☐	CHV/polio dawakhanawali ☐	Community group ☐
Other ☐	(specify) ……		

If they did not seek care for the baby from someone outside the home go to R21

R8 Where did you seek help?

Health Post ☐ Maternity home ☐ Peripheral hospital ☐ Tertiary hospital ☐

Private facility ☐ Other ☐ (what) ……

Name and location of institution ……..

If mother and baby were already in hospital go to R10

R9 How did you go there? Walked ☐ Rickshaw ☐ Taxi ☐ Bus ☐ Train ☐ Ambulance ☐

Other ☐ (specify) ……..

R10 How long was it from the time you recognised the baby had a problem until the baby was treated? ☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

R11 What treatment did they give, and to what extent did you complete it? ……..…..

R12 Was the baby referred or transferred for further treatment? Sent from gate/OPD ☐ Transferred ☐ No ☐ ***go to R15***

R13 Did you go to the place to which they referred or transferred you? Yes ☐ ***go to R15*** No ☐

R14 Why didn't you go?

Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐
Other ☐ (specify) ……

R15 Did you seek care from someone else? Yes ☐ ***go to R17*** No ☐

R16 Why not?

Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐
Other ☐ (specify) ……

If she did not seek care from someone else go to R21

R17 Where did you seek help? Health Post ☐ Maternity home ☐ Peripheral hospital ☐ Tertiary hospital ☐

Private facility ☐ Other ☐ (what) ……

Name and location of institution ……..

R18 How did you go there? Walked ☐ Rickshaw ☐ Taxi ☐ Bus ☐ Train ☐

Ambulance ☐ Other ☐ (specify) ……..

R19 How long was it from the time you recognised the baby had a problem until the baby was treated? ☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

R20 What treatment did they give, and to what extent did you complete it? ……

R21 Where did the baby die? At home ☐ Health Post ☐ Maternity home ☐ Peripheral hospital ☐

Tertiary hospital ☐ Private facility ☐ Other ☐ (where) ……

Name of institution ……..

Section S: Records

Look at all the records available for the baby and try to fill in the following

S1 Did the baby have a BCG immunisation? Yes ☐ No ☐ Don't know ☐
Demonstrate the place at the top of the arm

S2 What medicines did the baby have?
Leave space for writing

S3 Did the baby have a blood transfusion? Yes ☐ No ☐

S4 *Transcribe all the entries before the baby died. Include all dates. Make sure you include immunisations.* What was the date of the last medical note? _._/_ _/_._
Leave space for writing

S5 Record the two most recent weights of the infant in kilograms. Do not include birth weight, which should be included in **section G**.
Date 1 _._/_ _/_._ ☐☐☐☐ *g*
Date 2 _._/_ _/_._ ☐☐☐☐ *g*

Section T: Death certificate

T1 Was a death certificate issued? Yes ☐ No ☐ ***Go to U1*** Don't know ☐ ***Go to U1***

T2 Can I see the death certificate? Yes ☐ No ☐ ***Go to U1***

T3 Record the immediate cause of death from the certificate

T4 Record the first underlying cause of death from the certificate

T5 Record the second underlying cause of death from the certificate

T6 Record the third underlying cause of death from the certificate

T7 Record the contributing cause(s) of death from the certificate

Section U: HIV test

U1 Has the child's mother ever been tested for HIV? Yes ☐ No ☐ ***Go to U4*** Don't know ☐ ***Go to U4***

U2 Was the HIV test ever positive? Yes ☐ No ☐ Don't know ☐

U3 Did the mother receive antiretroviral medicine (ARV) to prevent mother-to-child transmission of HIV? Yes ☐ No ☐ Don't know ☐

U4 Has the child's mother or father ever been told she or he had AIDS by a health worker? Yes ☐ No ☐ Don't know ☐

Thank you for answering those questions.
Now I am going to ask you about postnatal care after the birth

Section V: Postnatal care

V1 Have you gone for a postnatal check-up since the birth? Yes ☐ ***Go to V3*** No ☐

Why not?

V2 ***Do not read out the options.*** *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

No problem ☐ Family did not allow ☐ Too far away ☐

Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐ Not customary ☐
Other ☐ (specify) ……

Who or what influenced you in your decision?

V3 ***Interviewer may tick more than one box*** *Do not read out the options. Tick options depending on what respondent says*

Decided herself ☐ Other family member ☐ Doctor, nurse ☐ TV, Radio,
Husband ☐ Friend or neighbour ☐ specify) CHV/polio Newspaper ☐
Other ☐ …… dawakhanawali ☐ Community group ☐

If no postnatal care go to V7

V4 How long after the birth did you go for the postnatal check-up? ☐☐ *days* or ☐☐ *weeks*

V5 Where did you go for the postnatal check-up?

Health Post ☐ Maternity home ☐ Peripheral hospital ☐ Tertiary hospital ☐
Private facility ☐ Other ☐ (what) ……..
Name of institution ……..

V6 How many times did you go for a postnatal check-up? ☐ *times*

V7 Has a health worker visited you at home since the birth? Yes ☐ No ☐ ***go to V9***

V8 Who visited you? BMC CHV ☐ ICDS AWW ☐ NGO CHV ☐ Other (who)

V9 Have you been given a vitamin A capsule since the delivery? Yes ☐ No ☐ Don't know ☐

V10 Women have certain problems after a birth. For example, she may have problems passing urine or with breastfeeding. What sort of problems have you had since the birth?
Interviewer may tick more than one box *Do not read out the options. Choose options depending on what respondent says*

No problem at all ☐ ***go to W1***

Backache ☐
Difficulty seeing at night ☐
Convulsion, fit, seizure, loss of consciousness ☐ Breathless while doing normal household tasks ☐
Severe abdominal pain ☐ Burning when passing urine ☐
Persistent vaginal bleeding ☐ Frequent need to pass urine ☐
Leaking of urine or faeces ☐ Abnormal vaginal discharge ☐
Womb coming down or out ☐ Fever ☐
Exhausted, very tired, weak ☐ Diarrhoea ☐
Headaches, dizziness ☐ Cough ☐
Nausea, bloating, indigestion ☐ Breast problem: cracked nipple, abscess, engorgement ☐
Constipation ☐ (specify)
Cramps ☐ ……..
Other ☐

V11 Did you do anything to treat the illness at home? Yes ☐ No ☐

V12 What did you do? ……

V13 Who or what influenced you in what you did?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Decided herself ☐ Other family member ☐ Doctor, nurse ☐ TV, Radio, Newspaper ☐
Husband ☐ Friend or neighbour ☐ CHV/polio dawakhanawali ☐ Community group ☐

Other ☐ (specify) ……..

V14 How long was it from the time you recognized you had a problem until you first treated it at home?

☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

V15 Did you seek care from someone outside the home? Yes ☐ ***go to V17*** No ☐

V16 Why not?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐
Other ☐ (specify) ……

V17 Who or what influenced you in what to do?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Decided herself ☐ Other family member ☐ Doctor, nurse ☐ TV, Radio, Newspaper ☐
Husband ☐ Friend or neighbour ☐ CHV/polio dawakhanawali ☐ Community group ☐
Other ☐ (specify) ……

If she did not seek care from someone outside the home go to V31

V18 Where did you seek help?

Health Post ☐ Maternity home ☐ Peripheral hospital ☐ Tertiary hospital ☐
Private facility ☐ Other ☐ (what) ……
Name and location of institution ……

V19 How did you go there?

Walked ☐ Rickshaw ☐ Taxi ☐ Bus ☐ Train ☐ Ambulance ☐

Other ☐ (specify) ……..

V20 How long was it from the time you recognised you had a problem until you got treatment?

☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

V21 What treatment did they give, and to what extent did you complete it? ……
……

V22 Were you referred or transferred for further treatment?

Referred ☐ Transferred ☐ No ☐ ***go to V25***

V23 Did you go to the place to which they referred or transferred you? Yes ☐ ***go to V25*** No ☐

V24 Why didn't you go?
Do not read out the options. *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐
Other ☐ (specify) ……

V25 Did you seek care from someone else? Yes ☐ ***go to V27*** No ☐

Why not?

V26 ***Do not read out the options.*** *Interviewer may tick more than one box. Allow the woman to answer and tick options accordingly.*

Got better ☐ Family did not allow ☐ Too far away ☐
Did not see need ☐ Nobody to manage children or home ☐ Cost of service ☐
No time to go ☐ Nobody to accompany ☐
Other ☐ (specify) ……

If she did not seek care from someone else go to V31

V27 Where did you seek help?

Health Post ☐ Maternity home ☐ Peripheral hospital ☐ Tertiary hospital ☐
Private facility ☐ Other ☐ (what) ……

Name of institution ……..

V28 How did you go there? Walked ☐ Rickshaw ☐ Taxi ☐ Bus ☐ Train ☐

Other ☐ (specify) ……

V29 How long was it from the time you decided to seek further help until you got treatment?

☐☐ *mins* or ☐☐ *hours* or ☐☐ *days*

V30 What treatment did they give, and to what extent did you complete it? ……
……

V31 If you had the problem again, where would you go? Hospital (*which)*…… Nowhere ☐

Thank you for answering those questions.
Now I am going to ask you some final questions

Section W: Grievance and community groups

W1 Did you have any grievance when you utilised antenatal, delivery or postpartum services?

Yes ☐ No ☐ ***Go to W5*** Not applicable ☐ ***Go to W5***

W2 What grievance did you have?

Antenatal ……

Delivery ……..

Postnatal mother ……

Newborn ……

W3 Did you register your grievance at the health facility? Yes ☐ No ☐ ***Go to W5***

W4 Was there any follow-up from the facility about your grievance? Yes ☐ No ☐

W5 Are you aware that you can register any grievances at any facility? Yes ☐ No ☐

W6 Have you heard of any groups in your basti? Yes ☐ No ☐ ***Go to W8***

W7 Which groups have you heard of? ……

W8 Are you a member of any group in your basti? Yes ☐ No ☐ ***Stop here***

W9 Which group? ……

Thank you very much for taking the time to answer our questions.
Is there anything you would like to ask?

Interviewer's comments

Interview end time ☐☐☐☐

Interview duration ☐☐☐ *minutes*