Perinatal and infant mortality in rural Burkina Faso

A prospective community-based cohort study

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Dedication

To my beloved mother

For her dedication to avoid me a child death and her endless care

To my late father

For sending me at school while most of my age mates were just playing in the hot 'beach' of Dori and for raising me in strict life principles

To my son Barké Yasser

This was part of the reasons for my repeated absences during the first years of your life and I hope you will find this piece of work worthy

To Cpt. Thomas Sankara, former President of Burkina Faso

For his dedication to improve maternal and newborn heath care in rural Burkina Faso

Contributors

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Table of contents

Dedication **3**
Contributors **4**
Table of contents **5**
List of abbreviations **8**
List of figures **10**
List of tables **11**
Glossary of terms **12**
Abstract (English) **14**
Abstract (French) **16**
Original papers **19**
Acknowledgements **20**
Introduction **21**
Background information and literature review **24**
Definitions 24
Mortality outcomes 24
Course of pregnancy 25
Birth attendants 25
The global burden of perinatal deaths 26
The global burden of neonatal deaths 28
The global burden of infant deaths 29
Causes and risk factors for perinatal death 31
Factors associated with antepartum stillbirth risk 32
Factors associated with intrapartum stillbirth risk 32
Predictors of early neonatal death risk 32
Causes and risk factors for neonatal death 33
Causes and risk factors of infant death 33
Evidence-based interventions to reduce perinatal and infant mortality 36
Literature review on perinatal and infant mortality in Burkina Faso 40
Search methods 40
Actual levels of perinatal and infant mortality rates in Burkina 40
Causes and risk factors for perinatal and infant deaths in Burkina Faso 44
Evaluation of health interventions to reduce child deaths in Burkina Faso 44
Rationale for the studies **47**
Study objectives **48**
Settings **49**
Burkina Faso 49

General overview 49
The health system 50
Banfora Health District 53

Study methods 56

Study design 56
Selection and randomization of the study villages 56
Study population 57
Sample size estimation 57
Participants' selection and enrolment procedures 59
Training of field study personnel 61
Data collection and participants' follow-up 63
Ethical considerations 65
Field supervisions and prevention of bias 66
Data management 67
Data entry and cleaning 67
Statistical analysis 68

Summary of findings 71

Study profile 71
Baseline characteristics of the cohort 71
Perinatal mortality (Paper I) 74
Stillbirths 74
Early neonatal deaths 74
Risk factors for perinatal death (Paper I) 74
Early follow-up (Paper II) 75
Neonatal deaths (Paper II) 75
Predictors of neonatal death (Paper II) 76
Infant mortality (Paper III) 77
Probable causes of infant deaths during the first half of infancy (Paper III) 78
Risk factors for infant death (Paper III) 78
Association of the intervention with perinatal, neonatal and infant death risks (Paper I, II and III) 79
Estimation of overall child mortality in Burkina Faso (Paper IV) 80

Discussion 81

Methodological issues 81
Study design 81
What were the potential biases in this study and how were they controlled? 82
Confounding 87
Would these findings have been observed by chance? 89
Internal validity 90
Main findings 90
Low utilization of health services in Banfora Health District 90
The high burden of perinatal, neonatal and infant deaths in Banfora Health District 91
No difference in perinatal death risk between facility-based deliveries and home-based deliveries 92
Main risk factors for perinatal death 93
Major risk factors for infant death 93
No association of the intervention with a lower risk of perinatal and infant deaths 94
External validity of the results 95

Implications of the findings **97**
Recommendations 97
Future research 98
Conclusions **99**
References **100**
Papers I to IV **109**
Appendices **153**

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
CHR	Centre Hospitalier Régional
CI	Confidence interval
CSPS	Centre de Santé et de Promotion Sociale (Eng: primary health care facility)
DC	Data collector
DCS	Data collector supervisor
DHS	Demographic and Health Surveys
DRS	Direction Régionale de la Santé (Eng: Regional Health Directorate)
DSS	Demographic Surveillance Site
DTP	Vaccine against Diphtheria, Tetanus and Poliomyelitis
EBF	Exclusive breastfeeding
EmOC	Emergency obstetric care
END	Early neonatal death
GDP	Gross domestic product
GEE	Generalized estimating equations
GNI	Gross national income
HF	Health facility
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th revision
IMR	Infant mortality rate
INDEPTH	The International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries
IPT	Intermittent preventive treatment
IRB	Institutional Review Board
INSD	Institut National de la Statistique et de la Démographie (Eng : National institute for demography and statistics)
MICS	Multiple indicators cluster surveys
MDG	Millennium Development Goal
NMR	Neonatal mortality rate
OR	Odds ratio
PMTCT	Prevention of mother-to-child transmission of HIV
PNMR	Perinatal mortality rate
PROMISE-EBF	Promoting infant health and nutrition: safety and efficacy of the promotion of exclusive breastfeeding
PS	Peer-supporters
RCT	Randomized controlled trial
RR	Risk ratio
SBR	Stillbirth rate
SMR	Standardized mortality ratio
SOWC	State of the world's children (Annual report from UNICEF)

SP	Sulfadoxin-Pyrimethamin
SSA	Subsaharan Africa
TLHO	Télégramme lettre hebdomaire official (Eng: Weekly official telegraph)
U5MR	Under-five year mortality rate
UN	United Nations
UNDP	United Nations Development Program
UNICEF	United Nations International Children Emergency Fund
USD	United States Dollars
WHO	World Health Organization

List of figures

Figure 1: Definitions and classifications of fetal and child deaths from pregnancy until 5 years of age **26**

Figure 2: Regional variations of stillbirth rates and corresponding proportions of intra-partum stillbirths **27**

Figure 3: Distribution of the causes and risk factors for stillbirths and early neonatal deaths and associated maternal conditions in South Africa **31**

Figure 4: Regional variations of the causes of child deaths in the world in 2008 ..... **34**

Figure 5: Key stakeholders relevant for successful implementation of health-policy and effective community-interventions to reduce morbidity and mortality in a country **37**

Figure 6: Median coverage of the main interventions suggested for an effective reduction of under-5 year mortality in the 68 "Countdown to 2015" priority countries in 2008 ..... **38**

Figure 7: Geographic location of Burkina Faso in West Africa **49**

Figure 8: Administrative organization of Burkina Faso with the 13 regions in different colours and the 45 provinces outlined. **50**

Figure 9: Geographic location of the Cascades (Banfora) region in Burkina Faso **53**

Figure 10: Distribution of the 24 study villages per sub-county and study arm in Banfora Health District, Burkina Faso **57**

Figure 11: Recruitment and follow-up schedule per study paper **63**

Figure 12: Study profile **1**

Figure 13: Number of infant deaths by age at death **77**

List of tables

Table 1: Number of stillbirths by WHO regions, corresponding stillbirth birth rates (SBR) and average reduction of SBR from 1995 to 2009 ..... **28**

Table 2: Number of infant deaths and estimated infant mortality rates (IMR) in different regions of the word from 1990 to 2009 ..... **29**

Table 3: Variations in the causes and risk factors of stillbirths according to levels of stillbirths rates and time of occurrence **30**

Table 4: Number and proportion of neonatal deaths by causes for the world and for Africa in 2008 ..... **33**

Table 5: Effect of individual and combined interventions on stillbirths for different coverage levels in 2015 ..... **35**

Table 6: Number of stillbirths, neonatal and maternal deaths averted by combinations of the Life saving tools (LiST) interventions at different levels of coverage **36**

Table 7: Literature review on perinatal and neonatal mortality in Burkina Faso based on articles/reports published from 2000 to date by year of publication. **42**

Table 8: Literature review on post-neonatal and infant mortality in Burkina Faso from 2000 to 2010 sorted by year of publication. **43**

Table 9: Intervention studies (trials) which assessed potential effects on perinatal or child death risks in Burkina Faso from 2000 to 2011 by year of publication. **45**

Table 10: Background information on Burkina Faso **51**

Table 11: Administrative Units and health system organization in the Cascades region **54**

Table 12: Levels and trends of perinatal and child mortality rates, and maternal mortality ratio in Cascades region in comparison to rural areas and Burkina Faso national average from 2003 to 2010. ..... **55**

Table 13: Distribution of study villages by population, study arm, expected number of births and number of pregnant women enrolled in Banfora Health District (Burkina Faso) **58**

Table 14: Sample size estimation for the main EBF trial. **59**

Table 15: Summary of the study methods reported in this thesis by paper. **70**

Table 16: Baseline characteristics (by arm and overall) of 895 women and their newborns enrolled in the EBF-study in Banfora Health District. **73**

Table 17: Association of the study arms with pregnancy outcomes in a cohort of 895 pregnant women in rural Banfora, Burkina Faso. **80**

Table 18: Summary of the most common types of bias and methods of bias reduction **83**

Table 19: Methods for controlling potential confounders in epidemiologic studies **88**

Glossary of terms

Definitions of mortality outcomes

Mortality rate	proportion of deaths for a given period reported among the total subjects at risk
Stillbirth	Fetal death occurring from 22 completed weeks of gestation until birth. When the gestational age is not available, the birth weight of the fetal product (≥500 g) or the fetal body length (>25cm) is used for the definition.
Early neonatal death	Death of a new-born within the first 7 days of life
Perinatal deaths	Stillbirths and early neonatal deaths combined
Neonatal death	Death of a live born baby within 28 days of his/her birth
Late neonatal death	Death of a live born baby occurring after the first week of life and within 28 days of his/her birth
Post-neonatal death	Death of a live born baby occurring between 29-365.25 days of his/her birth
Infant death	Death of a live born baby before 12 months (365.25days) of age
First half of infancy death	Infant death occurring during the first 6 months of life
Second half of infancy death	Infant death occurring between 6-12 months of age
Under-five year death	Death of a live born child before his/her fifth anniversary

Definitions of epidemiological and statistical terms

Bias	A systematic distortion of the estimated effect of an exposure away from the truth
Confounder	A variable that causes a distortion in the estimated effect of an exposure variable because it is mixed with the effect of that exposure
Exposure	A variable present before the outcome and that may affect its occurrence
Measure of association	A statistical method that assesses the strength of association between one or several exposure variables and an outcome of interest. Examples include relative risk, odds ratio, hazard ratio, incidence rate ratio.
Outcome	The event of interest that is measured (i.e. here, stillbirth, neonatal and infant deaths)
Precision	The ability of a tool (device, questionnaire, etc.) or a method to obtain consistent results on repeated measurements of the same subject
Rate	A measure of frequency that provides a quantity per unit of time. It is a fraction which includes person-time at risk in the denominator and the number of events in the numerator.
Risk	A measure of frequency that is the probability to observe an outcome of interest. It is a proportion.
Validity	The ability of a tool or a method to measure exactly what it is set out to measure

Abstract (English)

Background

Recent reports estimated the annual number of stillbirths and under-five year child deaths occurring in the world to 3.2 million and 7.7 million, respectively. Over 95% of these deaths only occur in low-income countries, mainly in sub-Saharan Africa. Burkina Faso in West Africa is one of the poorest countries in the world with reported very high perinatal mortality rate (PNMR), neonatal mortality rate (NMR), infant mortality rate (IMR) and under-5 mortality rate (U5MR), but the routine statistics are of poor quality and there are few prospective cohort data. We took opportunity of the PROMISE-EBF trial that promoted exclusive breastfeeding by peer-supporters in four African countries including Burkina Faso, to conduct a study on the epidemiology of perinatal and infant mortality in a rural area in Southern Burkina Faso.

Methods

We conducted a prospective, community-based cohort study in 24 villages of Banfora Health District. During one year (2006-2007), all pregnant women were identified by community-informants. Trained data collectors contacted the women to obtain informed consent, to perform the recruitment interview and later to conduct postpartum follow-up home visits at week 1, 3, 6, 12, 24 and at 12 months. Data collection at recruitment included maternal socio-demographic baseline, medical history and antenatal use of health services. Data collection during follow-up included the pregnancy outcomes, the circumstances of delivery, and the child feeding patterns, illness episodes, and anthropometry. Verbal autopsies were conducted in case of perinatal or infant death.

Data were collected using electronic questionnaires on an early version of openXdata software, cleaned and analysed on Stata/SE 11.0. PNMR, NMR and IMR were calculated as proportions of perinatal, neonatal and infant deaths, respectively, and the 95% CIs of each outcome were calculated accounting for the cluster-design of the main EBF-study. Binomial regression was used to screen and identify risk factors for perinatal death, with a generalized-estimating equations (GEE) model to account for the cluster-design of the study. Logistic regression was used to identify predictors of neonatal death with a random-effects model to account for the cluster-design of the EBF-study. Cox regression was used to identify risk factors for infant death with a gamma-frailty model to account for the cluster-design of the main study.

Results

A total of 895 women were enrolled. The mean age was 26 (±6) years and only 17% of women were nulliparous at enrolment, and the median parity was of 3 for multiparae. Over 80% of participants had no formal education, about 95% were married and 48% lived in polygynous households. Overall, 54% of women delivered at home and 36% in a health facility. The pregnancies resulted in 915 births (of which 20 pairs of twins), 49 stillbirths, 866 live births, 40 neonatal deaths and 98 infant deaths. The stillbirth rate (SBR) and the PNMR were, 54 (95% CI 38-69), 79 (95% CI 59-99) per 1000 births, respectively. The

proportion of perinatal deaths did not differ between home deliveries (8%) and facility births (7.6%, p=0.81).

The NMR and the IMR were 46 (95% CI 22-70) and 113 (95% CI 89-143) per 1000 live births, respectively. We found that 57% of neonatal deaths occurred just during the first week of life and neonatal deaths represented 41% of all infant deaths. The proportions of neonatal deaths were higher in home deliveries (5.4%) as compared to facility births (3.2%, p=0.06). Most of infant deaths (90%) took place at home.

Multivariable analyses of the factors associated with *perinatal death risk* showed that foetuses from nulliparous and primiparae had 3 (RR=2.9, 95% CI 1.6-5.0) and 2 (RR=2.2, 95% CI 1.2-3.9) times, respectively, higher perinatal death risk compared to that from multiparous with 2-4 previous births. Babies born during the dry season had a doubling (RR=2.1, 95% CI 1.3-3.3) of the risk of perinatal death in comparison to their peers born during the rainy season and twins carried a 4-fold (RR=4.0, 95% CI 2.3-6.9) higher risk of perinatal death as compared to singletons.

Adjusted analyses on the predictors of *neonatal death risk* showed that children born in polygynous households had a doubling (OR=2.1, 95% CI 1.0-4.7) of the odds of neonatal death compared to their peers from monogamous households. Newborns from nulliparous mothers had 4 times (OR=4.3, 95% CI 1.5-12.1) increased odds of neonatal death in comparison to those of mothers with 2-4 previous births and twins were found to have over 11-fold (OR=11.5, 95% CI 4.5-29.8) higher odds of neonatal death.

Adjusted analyses on the risk factors for *infant death* found that infants from polygynous households carried over 2 times (HR=2.4, 95% CI 1.4-4.0) higher rate of death than their peers from monogamous households and children born to mothers with a previous child death were found to have 60% (HR=1.6, 95% CI 1.0-2.6) increased rate of infant death. Twins had 8-fold (HR=8.4, 95% CI 4.6-15.3) higher rate of infant death compared to singletons.

Conclusion
The burden of perinatal and infant mortality was found to be unacceptably high in Banfora Health District and this is likely the case in other rural areas of Burkina Faso. Nulliparous and primiparae, women living in polygynous households, mothers with a history of child death, a birth during the dry season and twin births were factors associated with increased risk of fetal loss, neonatal or infant death. Our findings call for urgent actions from the national health authorities in Burkina Faso as well as from local communities in rural settings.

Key-words
Epidemiology- stillbirth-perinatal-neonatal-infant- mortality-risk factors-Burkina Faso

Abstract (French)

Introduction/rationnel :
Des études récentes ont estimé le nombre annuel de mort-nés et de décès d'enfants de moins de 5 ans dans le monde à respectivement 3,2 et 7,7 millions. Plus de 95% de ces décès surviennent essentiellement dans les pays à faibles revenus, notamment en Afrique subsaharienne.

Le Burkina Faso est l'un des pays les plus pauvres du monde et enregistre des taux élevés de mortalité périnatale, néonatale, infantile et infanto-juvénile. Toutefois, les statistiques de routine sur la mortalité des enfants dans ce pays sont de piètre qualité et il y a peu de données issues d'études de cohortes prospectives.

Nous avons investigué l'épidémiologie de la mortalité périnatale et infantile dans une zone rurale située dans le Sud du Burkina Faso au cours de l'étude PROMISE-EBF qui avait été implémentée dans quatre pays Africains dont le Burkina Faso. Les objectifs de l'étude étaient de mesurer les taux de mortalité périnatale (MPN), néonatale (MN) et infantile (MI) et de décrire les facteurs de risque qui leur étaient associés.

Méthodes :
Une étude de cohorte prospective, à base communautaire a été menée dans 24 villages du District sanitaire de Banfora. Sur une période d'une année (Mai 2006- Mai 2007), toutes les femmes enceintes dans chacun des villages d'étude ont été identifiées par des informatrices résidant dans les villages concernés et un échantillon aléatoire de femmes enceintes a été tiré mensuellement pour le suivi et la collecte de données.

Des enquêteurs de l'étude ont pris contact avec les femmes sélectionnées afin d'obtenir leur consentement éclairé et effectuer un entretien d'inclusion. Ces enquêteurs ont ensuite effectué des visites de suivi à domicile lors de la $1^{ère}$, $3^{ème}$, $6^{ème}$, $12^{ème}$, $24^{ème}$ semaine et au $12^{ème}$ mois après l'accouchement. Les données collectées à l'inclusion de la femme comprenaient pour l'essentiel les données sociodémographiques de base, les antécédents médicaux et l'utilisation des services locaux de santé. Les données collectées dans le suivi portaient sur l'issue de la grossesse, les circonstances de l'accouchement, le mode d'alimentation du nouveau-né ainsi que la morbidité, et la croissance de celui-ci. En cas de décès périnatal ou infantile, une autopsie verbale était effectuée par l'enquêteur.

Les données ont été recueillies sur des questionnaires électroniques utilisant le logiciel *OpenXdata*. Elles ont ensuite été nettoyées puis analysées sur le logiciel *Stata/SE 11*. Les taux de MPN, MN et MI ont été calculés comme des proportions de décès périnataux, néonataux et infantiles correspondants. L'estimation de chaque intervalle de confiance (IC) à 95%, a tenu compte du village comme unité de randomisation dans l'étude PROMISE-EBF. Une régression binomiale, une régression logistique et une régression de Cox ont été utilisées pour mesurer l'association de potentiels facteurs avec respectivement, le risque de décès périnatal, néonatal ou infantile.

Résultats :
Les 895 femmes incluses dans l'étude avaient un âge moyen de 26(±6) ans et seules 17% d'entre elles étaient des nullipares à l'inclusion. La parité médiane chez les multipares était de 3. Plus de 80% des femmes étaient complètement analphabètes, 95% étaient mariées et 48% vivaient dans des foyers polygames.

Nous avons noté que 54% des femmes avaient accouché à domicile et 36% au centre de santé. Au total, il y a eu 915 accouchements dont l'issue a été de 49 mort-nés et 866 naissances vivantes (dont 20 paires de jumeaux). Il a été enregistré 40 décès néonataux et 98 décès infantiles lors du suivi. Le taux de mortinaissance était de 54/1000 (IC 95% :38-69) tandis que celui de la MPN était de 79/1000 (IC 95% :59-99) naissances. Il n'y avait pas de différence de risque de décès périnatal selon que l'accouchement avait lieu à domicile (80/1000) ou au centre de santé (76/1000, p=0,81).

Le taux de MN était de 46/1000 (IC 95% :22-70) et celui de la MI de 113/1000 (IC 95% :89-143) naissances vivantes. En tout, 57% des décès néonataux sont survenus juste au cours de la 1ère semaine de vie et les décès néonataux représentaient 41% des décès infantiles. Le risque de décès néonatal était plus élevé en cas d'accouchement à domicile (54/1000) qu'au CSPS (32/1000, p=0.06). La plupart des décès infantiles (90%) a eu lieu à domicile.

Les analyses multivariées portant sur le risque de décès périnatal ont montré que les fœtus des nullipares et des primipares à l'inclusion présentaient respectivement, 3 (RR=2,9 IC 95% :1,6-5,0) et 2 (RR=2,2 IC 95% :1,2-3,9) fois plus de risque de décès périnatal comparés à ceux de multipares avec 2-4 accouchements antérieurs. Les accouchements survenus durant la saison sèche présentaient aussi un risque de décès périnatal 2 fois (RR=2,1 IC 95% :1,3-3,3) plus élevé que ceux survenus durant la saison pluvieuse. De même, les grossesses gémellaires comportaient un risque de décès périnatal jusqu'à 4 fois (RR=4,0 IC 95% :2,3-6,9) plus grand que celles monozygotes.

Les analyses multivariées relatives aux facteurs associés au risque de décès néonatal ont elles, révélé que les enfants nés dans un foyer polygame avaient un risque de décès néonatal 2 fois (OR=2,1 IC 95% :1,0-4,7) plus élevé que celui des enfants nés dans des foyers monogames. De plus les enfants nés de mères nullipares à l'inclusion avaient jusqu'à 4 fois (OR=4,3 IC 95% :1,5-12,1) plus de risque de décès néonatal que ceux nés de mères multipares avec 2-4 accouchements antérieurs à l'inclusion. Enfin, les jumeaux avaient un risque de décès néonatal 11 fois (OR=11,5 IC 95% :4,5-29,8) plus élevé que celui des singletons.

Les analyses multivariées relatives aux facteurs associés au risque de décès infantile ont identifié les enfants des foyers polygames (HR=2,4 IC 95% :1,4-4,0), ceux de mères ayant eu un décès infanto-juvénile antérieur (HR=1,6 IC 95% :1,0-2,6) et les jumeaux (HR=8,4 IC 95% :4,6-15,3) comme des facteurs associés à un plus grand risque de décès infantile.

Conclusion :
Les taux de MPN et de MI sont encore inacceptablement élevés dans le District sanitaire de Banfora et ceci pourrait être aussi le cas dans d'autres zones rurales du Burkina Faso. Les nullipares et les primipares, les femmes vivant dans des foyers polygames, celles ayant des antécédents de décès infanto-juvénile, l'accouchement en saison sèche et l'accouchement de jumeaux étaient des facteurs associés à un risque accru de morti-naissance, de décès néonatal ou infantile. Nos résultats appellent à des actions urgentes de la part des autorités sanitaires nationales et des communautés locales concernées en milieu rural burkinabè.

Mots-clés :
Epidémiologie-mort-né-mortalité périnatale néonatale infantile- facteurs de risque- Burkina Faso

Original papers

The thesis is based on the following papers:

I. Diallo AH, Meda N, Zabsonré E, Sommerfelt H, Cousens S, Tylleskar T, the PROMISE-EBF study group. Perinatal mortality in rural Burkina Faso: a prospective community-based cohort study. *BMC Pregnancy and Childbirth* 2010;**10**:45

II. Diallo AH, Meda N, Ouédraogo WT, Cousens S and Tylleskar T for the PROMISE-EBF study group. A prospective study on neonatal mortality and its predictors in a rural area of Burkina Faso: Can MDG-4 be met by 2015? *J Perinatol* 2011;**31***:656-663*

III. Diallo AH, Meda N, Sommerfelt H, Traoré SG, Cousens S and Tylleskar T for the PROMISE-EBF study group. The high burden of infant deaths in rural Burkina Faso: a prospective community-based cohort study. *BMC Public Health* 2012;**12**:739

IV. Diallo AH and Meda N. Estimates of mortality in children younger than 5 years for Burkina Faso. *Lancet*. 2010;**376** (9748):1223-4

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Introduction

The Millennium Development Goals (MDGs) are one of the major global initiatives undertaken by the world's leaders to face the numerous challenges of social, economic and structural determinants of health and social inequities.[1] Although controversies remain about its strategies and the allocation of resources to the different goals, there is common agreement on MDGs' relevance.[2, 3] Goal number four (MDG-4) aims to reduce the child mortality rates by two-thirds from 1990 to 2015.[4, 5] Achieving MDG-4 is crucial not only because of its emotional nature (children are fragile human beings, who need protection, and also represent our future), but mainly because this goal is strongly linked and determined by the other MDGs, especially MDG-5, which aims to reduce maternal mortality rates by three-quarters in 1990 by 2015.[4, 5] To identify gaps in data and evidence, and also to promote the implementation of interventions known to improve maternal, newborn and child health, the Countdown to 2015 initiative was established in 2005[5] and reports every 2-3 years, mainly on MDG-4 and 5. This initiative is also very relevant in monitoring the progress of different countries towards MDG-4 and 5, and maybe in preventing the classical rhetoric of "politicians" that are not always accompanied by actions.[6]

The 2010-report of the Countdown to 2015 outlined a marked reduction of mortality rates among children under 5 years in developing countries between 1990 and 2008 (-28%), but acknowledged that, with the current average annual rate of reduction (2.3%), <30% of the 68 Countdown priority countries (which includes 43 Sub-Saharan Africa countries) were likely to reach MDG-4 by 2015.[4] Botswana, Eritrea and Malawi were the only 3 Sub-Saharan Africa countries on track for MDG-4 according to this report.[4] While data on child and maternal deaths are carefully monitored by the Countdown to 2015 experts, this group, the United Nations (UN) and the WHO agencies have overlooked the data on stillbirths and the relevant interventions to reduce the high burden of perinatal deaths.[7, 8]

The estimates of deaths among children <5 years have shifted from 2008 to 2010, owing to the lack of reliable statistics in many countries where the burden is high, and also to changes in statistical methods used to provide these estimates.[9, 10, 11] Globally, it was estimated that in 2010 over 7.7 million children <5 years died of mainly preventable diseases.[9] Over 95% of these deaths occurred in low and middle-income countries, and almost half in the Sub-Saharan Africa region alone.[10, 11] While the global statistics are consistent with decreasing under-5 year mortality rates (U5MR), strong regional and intra-country variations were found, especially in the Western and Central regions of Africa.[9, 11] Another consistent finding throughout several studies on child mortality is the high burden in rural settings of Africa and Asia, the stagnation of high neonatal mortality rates (NMRs) in the same two regions, and the almost complete neglect of stillbirths, often with them just not being counted in local and international statistics.[4, 8, 9] Some authors argued that stillbirths and to some extent early neonatal deaths, the two main components of perinatal deaths, have just been forgotten about in the MDG's agenda during the 2000 summit.[7, 8, 12] Although one can disagree on the "truth" of such a statement, there is a clear lack of visible strategies designed to reduce the high burden of perinatal mortality in many African countries. The situation was the same for

neonatal deaths some years ago, but a strong advocacy started to push this agenda after the *Lancet* series for improved neonatal survival.[13] Several studies have also concluded that, without drastic reductions of the neonatal deaths, there is little chance for most of the Sub-Saharan Africa countries will achieve MDG-4 by 2015.[4, 9, 13, 14] A recent publication showed that high NMRs were strongly correlated with high stillbirth rates (SBRs).[12]

One major requirement for the design and implementation of relevant health intervention to reduce the burden of perinatal and child deaths, is the provision of recent and reliable estimates of the burden and the description of the causes of these poor outcomes.[6, 8, 9, 12, 14, 15, 16] This in turn requires that data are collected in representative populations of countries where SBR and U5MR are very high, namely those of remote rural settings in Sub-Saharan Africa. Scarcity of data and old data are two limitations repeatedly highlighted[17], leading to low visibility of poor pregnancy outcomes, such as stillbirths and neonatal deaths, to policy-makers and donors.[8, 18, 19] As a consequence, little funding is made available to programs targeting these outcomes, which together take away the lives of over 5 million people every year.[9, 20] Two recent series,[8, 15, 21, 22, 23, 24] one in *BMC Pregnancy and Childbirth* (2009) and the other in *The Lancet* (2011), have called for increased research and more funding to reduce the unacceptably high stillbirth and neonatal mortality rates in many resource-limited countries. The *Lancet series* have especially demonstrated the relevance and cost-effectiveness of a comprehensive strategy targeting maternal, fetal and neonatal deaths.[21, 25]

Burkina Faso, a francophone country located in West Africa, is one of the poorest countries in the world, with a Gross national income (GNI) of 510 USD and where 57% of the population is living below the poverty line of 1.25 USD per day.[11, 26, 27] According to the 2011-report of UNICEF, the country experiences very high neonatal, infant and overall child mortality rates, estimated at 36, 91 and 166 per 1000 live births, respectively, in 2009 and was unfortunately ranked the world's 9th highest UM5R for that year.[11] Data on stillbirths are very rare and those that exist are old, such as the 2003-Demographic and Health Surveys (DHS) that estimated the national SBR at 35 per 1000 births.[28] As for other resource-limited countries, Burkina Faso provides either very old health statistics[28] (DHS-2003) or data coming from atypical study populations such as urban settings[29], university hospital patients[30, 31], or data collected through a weak health statistics system (TLHO)[32] where the willingness to report satisfactory results, known as the "achievement disease", may be the rule.[33] Burkina Faso does not have a vital registration system as is the case in high income countries and only 64% of births are reported,[11] often several years after a child is born. Most of the births still occur at home in rural settings,[4, 11, 28] where >75% of the current 15 million of Burkinabè population lives.[34] In the absence of a functional vital registration system, the country benefited through the INDEPTH-project of the implementation of two demographic surveillance sites (DSS) in 1992 in Oubritenga[35] and Nouna Province[36], but these DSS cover a population of only 200,000.[37, 38] Unfortunately, publications of these two DSS did not record stillbirths or neonatal deaths.[35, 39] This was mainly due to the design and objectives of the studies conducted so far by these two DSS. Elsewhere in the country, a few studies[29, 40, 41] with a variety of objectives have nevertheless provided data on stillbirths and neonatal mortality, but were often facility-based, making them unsuitable for any inference about women from rural communities who do not attend health centres. If current and reliable data on stillbirths, neonatal and overall infant mortality in Burkina Faso were to be provided, it is

important that they are collected in rural communities where the burden is expected to be the highest, and that a prospective design is used to reduce the recall bias associated with surveys.[42]

We took advantage of the PROMISE-EBF study, a cluster-randomized trial that assessed the effect of the promotion of exclusive breastfeeding (EBF) through individual peer counselling on EBF-rates in 4 African countries, including Burkina Faso,[43] to conduct a cohort study on perinatal and infant mortality in Banfora Health District, South-west of Burkina Faso. The study, the basis for this thesis, explores 3 epidemiological features of perinatal and infant deaths: a) measurement of their burden; b) description of their distribution according to maternal and infant baseline characteristics; c) identification of potential risk factors for both outcomes.

Background information and literature review

This section gives definitions of the main study outcomes, as well as global information about the burden and causes of perinatal, neonatal and infant deaths in the world, and the recommended evidence-based interventions to reduce the burden associated with these poor fetal and child outcomes. We will also provide an overview of the recent literature review on these 3 outcomes for Burkina Faso.

Definitions

Mortality outcomes

Perinatal mortality is defined as the sum of stillbirths and early neonatal deaths reported among the total number of births occurring during the same period, usually one year. Therefore perinatal mortality is calculated as the perinatal mortality rate (PNMR). However, the correct statistical wording of this method should be perinatal mortality *risk*.

Stillbirth is defined by ICD-10 as any "fetal death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles". [44]

The definition of perinatal mortality and its methods of estimation are not consensual.[45, 46, 47]The ICD-10 assumes that the perinatal period commences at 22 completed weeks of gestation and ends 2 completed days after birth. However, for international comparisons, WHO proposed the use of the old definition, a period from 28 completed weeks of gestation to 7 days after birth. This latter is commonly used, especially in low-income countries.[48, 49]

Thus, ICD-10 distinguishes early stillbirths based on gestational age (22-28 weeks), or if missing on birth weight (≥ 500g), or if missing on fetal body length (≥ 25cm) (Figure 1). In contrast, WHO focuses on what is called late stillbirths or third-trimester stillbirths (Figure 1) defined as fetal loss with a birth weight ≥ 1000g, or if missing a gestational age ≥ 28 weeks, or if missing a fetal body length ≥ 35cm.

A common clinical practice is to distinguish the fresh stillbirth (for which death has occurred within 12-24 hours of delivery without symptoms of skin disintegration) from the macerated stillbirth (for which death is beyond 12-24 hours prior to delivery and with pulpy peeling skin).

From a public health perspective, a tendency is also to differentiate the antepartum stillbirths (where the intrauterine fetal death occurs before onset of labour) from the intrapartum stillbirths (in which fetal death occurs during labour) for etiological and programmatic purposes.

In contrast to stillbirth, live birth is defined as "the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta remains attached; each product of such a birth is considered live born".[44]

Live births are the denominator used to calculate neonatal mortality rate (NMR), defined as the number of newborn deaths occurring between birth and 28 completed days relative to the total number of live births during the same period.

Infant mortality rate (IMR) is the total number of child deaths before 12 months of age relative to the total number of live births during the same period.

Under-five year mortality rate (U5MR) refers to the total number of child deaths before the age of 5 years relative to the total number of live births in the cohort.
PNMR is expressed per 1000 births, whereas NMR, IMR and U5MR are expressed per 1000 live births.

Course of pregnancy

Once a woman is pregnant, gestational age as defined as the time from the first day of the woman's last menstruation to the actual date, is regularly estimated by the health personnel. Gestational age is usually expressed in completed weeks (Figure 1) and will determine preterm, "normal" or post-term birth. The gestational maturity rating is measured by the Ballard scale or Dubowitz exam.

A pregnancy of "normal" gestation is ~40 weeks, with a range from 37 to 42 completed weeks. A birth prior to 37 completed weeks of gestation is considered as a preterm birth (often called premature newborns), and a birth occurring after 42 completed weeks of gestation is defined as a post-term birth.

A neonate weighing <2500g at birth is defined as having a low birth weight, irrespective of gestational age.

Birth attendants

A birth attendant is the person assisting a woman at birth from the start of labour until complete expulsion of the placenta and initiation of the newborn feeding. In Burkina Faso, the formal health system distinguishes the following personnel:

- Skilled birth attendants: physicians (doctors), midwives, registered nurses and auxiliary-midwives.
- Unskilled birth attendants: auxiliary-nurses, and traditional birth attendants (TBA). A TBA is a woman in the village providing help to her peers during childbirth and who acquired her skill either by self-learning or after a brief training[47].

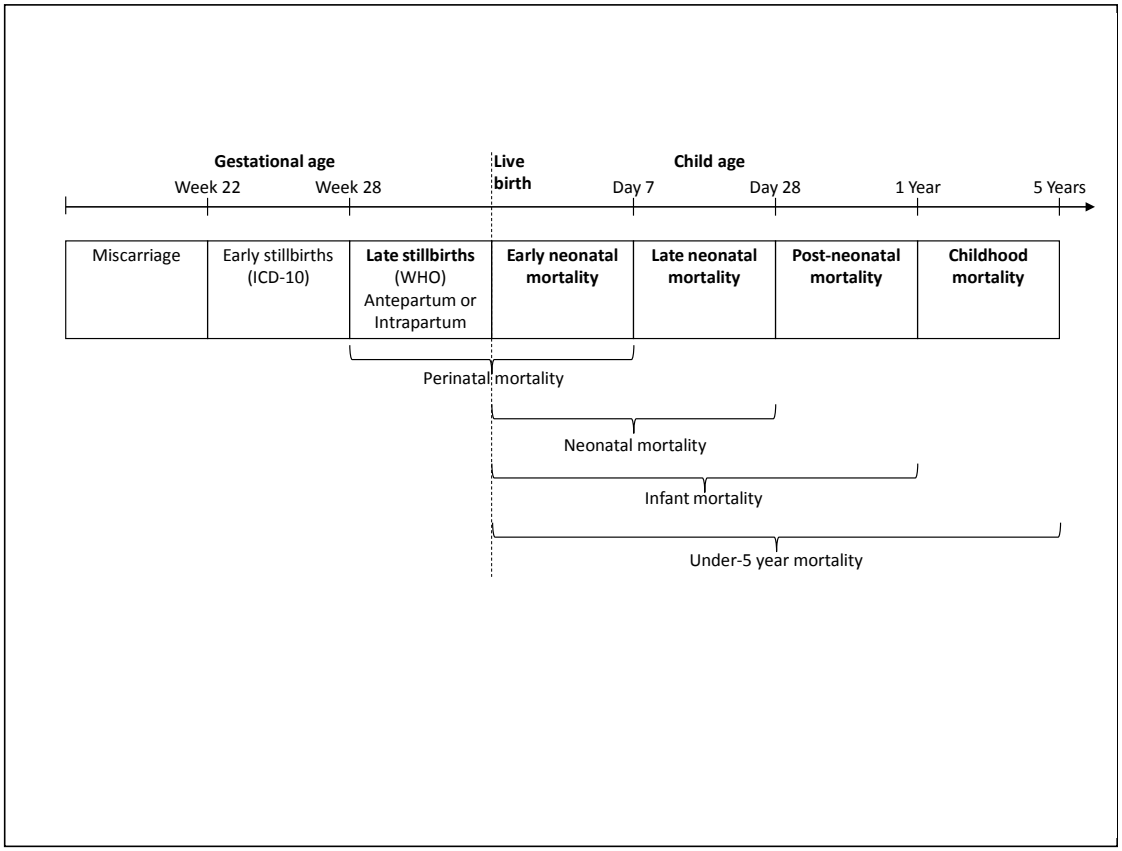

Figure 1: ***Definitions and classifications of fetal and child deaths from pregnancy until 5 years of age (adapted from Lawn et al., 2011 [8])***

The global burden of perinatal deaths

The most recent data on perinatal deaths published by WHO at country and regional levels are for 2004, which estimated the global burden to be 6 million deaths, with 3 million stillbirths and 3 million early neonatal deaths, respectively.[49] Recent trends reported in the literature have been to distinguish the two components of perinatal deaths both for academic and programmatic purposes.[8, 45] Thus, the most recent estimates of the global burden of stillbirths provided by Cousens and colleagues estimated that 2.6 million third-trimester stillbirths occurred in 2009 in the world.[12] Overall, 98% of these fetal deaths from 28 weeks of gestation until birth occurred in low and middle-income countries, and over 70% in rural areas of Africa and Asia[8]. Recent data also highlighted a higher proportion of intra-partum stillbirths (45%) than previously reported,[49] and which could now reach close to half of the stillbirths in sub-Saharan Africa[8] (Figure 2).

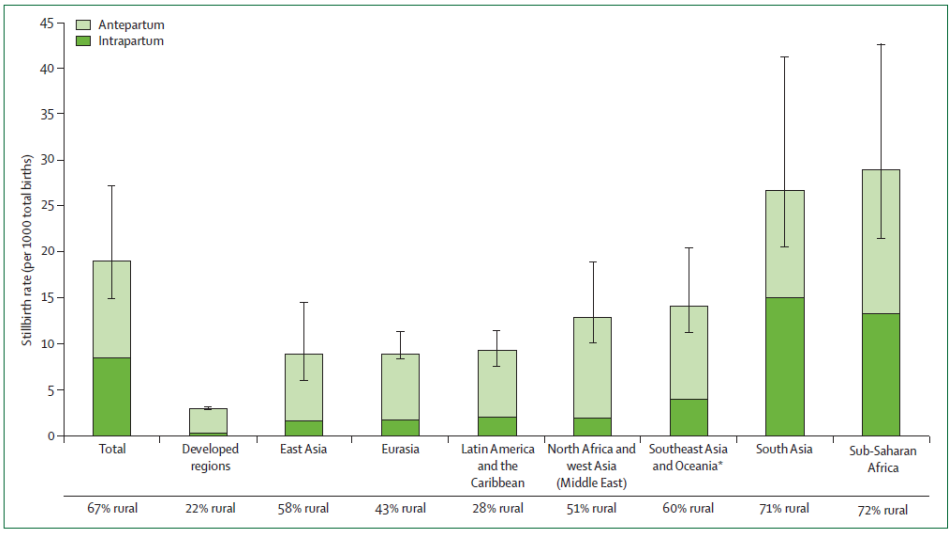

***Figure 2*: Regional variations of stillbirth rates and corresponding proportions of intra-partum stillbirths (Lawn et al. 2011, [8])**

In 2009, the worldwide SBR estimated at 18.9 per 1000 births showed a reduction by 14.5% since 1995, but the average rate of reduction (1.1% per annum) is much lower than that reported for child mortality (2.3%).[12] However, these figures mask huge regional variations of the burden of stillbirths. Indeed, in 2009, the SBRs were of 28.3 and 26.7 per 1000 births for Sub-Saharan Africa and South Asia, respectively, standing at 10 points over the world average SBR[12]. From 1995 to 2009, the percentage decline in SBRs was 47% for Asia versus <10% for Sub-Saharan Africa[12] (Table 1).

In 2009, UNICEF reported 3.3 million neonatal deaths, with an estimated 2.5 million early neonatal deaths, representing ~75% of all neonatal deaths.[11] Merging data from the current international health statistics indicates that ~5.1 million perinatal deaths (2.6 stillbirths and 2.5 million ENDs) continue to occur every year mainly in low income countries.[11, 12]

The two recent series on stillbirths in 2009[15, 16, 20, 22, 23, 50] and 2011[7, 8, 21, 25, 51] have been a serious attempt to fill the gap of unfairness and lack of recognition for both those babies who were stillborn and their parents who have been suffering in silence for so long.[7] Among the reasons given to justify the neglect of stillbirths and the limited data on this issue, are the inconsistencies across definitions and classifications of causes for stillbirths,[8] the high likelihood of stillbirths' misclassifications in countries with low proportion of health-facility deliveries,[52] and the social and cultural taboos associated with stillbirths in many communities.[7, 8] Due to the small number of studies using stillbirths as outcome for the measurement of efficacy, there is limited knowledge on the efficaciousness of interventions to reduce its burden.[16, 21, 24]

Table 1: **Number of stillbirths by WHO regions, corresponding stillbirth birth rates (SBR) and average reduction of SBR from 1995 to 2009 (Cousens et al. 2011, [12])**

	1995			2009			Reduction in stillbirth rate from 1995 to 2009
	Number of births (millions)	Number of stillbirths (1000s; uncertainty range)	Stillbirth rate per 1000 total births (relative uncertainty range [%])	Number of births (millions)	Number of stillbirths (1000s; uncertainty range)	Stillbirth rate per 1000 total births (relative uncertainty range [%])	
High-income region	11·7	45·8 (45·1 to 48·7)	3·9 (−1·6 to 6·3)	11·7	36·4 (35·7 to 38·0)	3·1 (−2·0 to 4·5)	20·3%
Eurasia (CIS in Asia)	1·7	17·9 (15·8 to 24·9)	10·5 (−11·8 to 39·0)	1·6	13·8 (12·3 to 19·0)	8·8 (−11·0 to 37·5)	16·0%
Eurasia (CIS in Europe)	2·1	22·8 (21·0 to 31·6)	10·9 (−8·1 to 38·2)	2·2	19·7 (17·5 to 24·7)	9·0 (−11·1 to 25·3)	17·6%
East Asia	22·4	414·3 (280·0 to 636·7)	18·5 (−32·4 to 53·7)	19·4	188·5 (131·1 to 294·4)	9·7 (−30·4 to 56·2)	47·5%
Latin America and the Caribbean	11·7	141·9 (119·8 to 178·1)	12·1 (−15·6 to 25·5)	11·2	97·1 (82·6 to 122·7)	8·7 (−14·9 to 26·4)	28·0%
North Africa	3·5	61·8 (46·0 to 93·5)	17·7 (−25·5 to 51·4)	3·8	51·3 (40·2 to 77·6)	13·6 (−21·8 to 51·1)	22·92%
Oceania	0·2	3·7 (2·7 to 7·3)	15·8 (−27·1 to 96·9)	0·3	3·9 (2·8 to 7·6)	14·5 (−28·6 to 96·1)	8·0%
South Asia	41·3	1248·4 (920·7 to 1912·2)	30·2 (−26·2 to 53·2)	40·5	1080·3 (855·8 to 1651·2)	26·7 (−20·8 to 52·9)	11·7%
Southeast Asia	11·8	198·5 (154·3 to 278·6)	16·8 (−22·3 to 40·3)	11·2	156·1 (123·9 to 219·6)	13·9 (−20·6 to 40·7)	17·1%
Sub-Saharan Africa	26·0	807·6 (593·2 to 1169·6)	31·0 (−26·5 to 44·8)	33·0	934·6 (706·9 to 1406·8)	28·3 (−24·4 to 50·5)	8·7%
West Asia	4·6	68·5 (50·7 to 99·8)	14·9 (−26·0 to 45·8)	5·0	60·2 (47·3 to 88·3)	12·0 (−21·4 to 46·7)	19·2%
Total (all countries)	137·0	3031·3 (2369·3 to 4189·6)	22·1 (−21·8 to 38·2)	139·7	2642·0 (2135·0 to 3818·9)	18·9 (−19·2 to 44·5)	14·5%

Numbers are rounded to one decimal place; rates were calculated with raw, unrounded data. CIS=Commonwealth of Independent States.

The global burden of neonatal deaths

Neonatal mortality constitutes the second major component of perinatal deaths[53] and followed the same history as experienced today with stillbirths[7] and of the overall child mortality before the Bellagio Group call for action in 2003.[54] Limited data and invisible policies were in place until 2005, when Lawn and colleagues[13] issued a call for improved neonatal survival in the world and stressed their concern that MDG-4 could not be reached in 2015 without a steady reduction of current NMRs.[13, 19]

In 2000, WHO estimated the total number of neonatal deaths to be 4 million, 98% occurring in developing countries.[48] The worldwide NMR was estimated at 30 per 1000 live births in 2000, but was much higher – 42 per 1000 live births – for the least developed countries, Western and Central regions of Africa recording the highest NMRs of the world, at 49 and 46 per 1000 live births,[48] respectively. Since 2000, the global figures seem to have changed, although the progress in reduction of NMRs appears very slow and almost non-existent in Africa.[4, 6] Indeed, the most recent estimates of neonatal mortality models provided by UNICEF reported a total of 3.3 million neonatal deaths[11] and a world NMR of 24 per 1000 live births in 2009. In this report, Sub-Saharan Africa continued to record the highest NMRs in the world at 37 per 1000 live births, with the NMRs in West and Central Africa being a serious concern, both being as high as 40 per 1000 live births.[11] Another lesson learnt from the most recent estimates of neonatal mortality is the increasing share of this outcome in the total number of children deaths from 2000 to 2010, moving from a 38% in 2000[48] to 41% in 2010.[10] However, this proportional change did not occur in Africa, where the overall child mortality remains high and neonatal deaths represent only 29% of all under-5 deaths.[4, 10]The increasing proportion of neonatal deaths in the global share of childhood deaths is analysed as a natural consequence of the declining trends in overall U5MR.

Data on neonatal mortality showed that >75% of deaths occur during just the first week of life (the so-called early neonatal deaths),[13] and their causes are intimately linked to the conditions of childbirth and therefore to that of intra-partum stillbirths.[8, 24] The risk of death is particularly high within 24 hours of birth.[24] Despite increased advocacy and improving statistical modelling, NMRs remain alarmingly high in Sub-Saharan Africa, especially in rural settings.[4, 9, 11]

The global burden of infant deaths

Infant mortality, which includes neonatal deaths, has been estimated at 5.7 million deaths in 2009, which represented 70% of the 8.1 million under-5 deaths that occurred in the world in that year.[11] UNICEF estimated the world IMR to be 42 per 1000 live births in 2009, but once again, the variations across regions are large, with unfortunately sub-Saharan Africa holding the first position with the highest IMR at 81 per 1000 live births.[55] As for all other components of fetal and child deaths, the Western and Central parts of Africa have the highest IMR at 92 per 1000 live births, followed by the Eastern and Southern region of Africa at 69 per 1000 live births.[55] Using a different modelling approach, Rajaratnam and colleagues estimated the burden of infant deaths to be 5.4 million in 2010 in an analysis that included 187 countries.[10] These authors reported an annual rate of decline (from 1970 to 2010) similar for all the 3 components of under-5 mortality, with 2.1% for neonatal mortality, 2.3% for post-neonatal mortality and 2.2% for childhood mortality.[10] Due to the continuing high U5MR in Africa, the total number of infant deaths represents ~60% of the global burden of child deaths in this region[55] (Table 2). The pattern of infant mortality in Africa has been affected by both the HIV-epidemics[56] and increasing resistance in *Plasmodium falciparum* infections to antimalarial drugs still used as mono-therapy in several countries in West and East Africa.[4, 57]

Table 2: **Number of infant deaths and estimated infant mortality rates (IMR) in different regions of the word from 1990 to 2009 (UNICEF/SOWC, 2011 [11;55])**

	No of infant deaths (in 1000)		IMR (per 1000)	
	1990	2009	1990	2009
World	8688	5751	62	42
Sub-Saharan Africa	2401	2503	109	81
- West and Central Africa	1270	1440	118	92
- Eastern and Southern Africa	1047	972	103	69
Asia	4932	2658	63	39
- South Asia	3280	2015	89	55
- East Asia and Pacific	1652	643	40	21

Table 3: **Variations in the causes and risk factors of stillbirths according to levels of stillbirths rates and time of occurrence (Lawn et al., 2011 [8])**

	SBR <5 per 1000 total births (six high-income country datasets*)	SBR 15–24 per 1000 total births (South Africa national data)	SBR ≥25 per 1000 total births (Bangladesh rural hospital data)
Dataset details			
SBR of input data	2–4	19	39
Year of input data	2008–09	2008–09	2007–09
Antepartum stillbirths (%)	316 (91%)	11085 (61%)	138 (34%)
Stillbirth category			
Congenital	11%	2%	1%
Infection	6%	6%	5%
Fetal growth restriction or placental insufficiency	32%	3%	28%
Other specific fetal condition	8%	1%	13%
No stillbirth condition identified (maternal event identified)	43%	88% (18%)	54% (17%)
Associated maternal condition			
Abnormal labour or uterine rupture	0%	0%	9%
Maternal hypertension	11%	20%	9%
Maternal infection (eg, syphilis)	0%	4%	1%
Chorioamnionitis	5%	2%	3%
Maternal diabetes	8%	2%	0%
Antepartum haemorrhage (abruptio placenta or placenta praevia)	15%	6%	9%
Maternal pre-existing condition (eg, cardiac)	0%	2%	2%
Spontaneous preterm labour	..	..	1%
Other maternal specific	9%	1%	1%
No maternal condition identified	62%	62%	65%

Variation in the distribution of antepartum stillbirth causation and associated maternal conditions

	SBR <5 per 1000 total births (six high-income country datasets)	SBR 15–24 per 1000 total births (South Africa national data)	SBR ≥25 per 1000 total births (Bangladesh rural hospital data)
Database details			
SBR of input data	2–4	19	39
Year of input data	2008–09	2008–09	2007–09
Intrapartum stillbirths (%)	30 (9%)	7083 (39%)	264 (66%)
Stillbirth category			
Congenital	10%	4%	4%
Infection	17%	5%	2%
Fetal growth restriction or placental insufficiency	26%	1%	6%
Other specific fetal condition	4%	1%	17%
No stillbirth condition identified (maternal event identified)	43%	88% (59%)	71% (58%)
Associated maternal condition			
Abnormal labour or uterine rupture	10%	29%	44%
Maternal hypertension	0%	19%	14%
Maternal infection (eg, syphilis)	0%	3%	0%
Chorioamnionitis	17%	2%	2%
Maternal diabetes	0%	1%	0%
Antepartum haemorrhage (abruptio placenta or placenta praevia)	10%	17%	15%
Maternal pre-existing disorder (eg, cardiac)	0%	1%	2%
Spontaneous preterm labour	7%	5%	0%
Other maternal specific condition	0%	1%	4%
No maternal condition identified	56%	22%	19%

Variation in the distribution of intrapartum stillbirth causation and associated maternal conditions

Causes and risk factors for perinatal death

Globally, there is limited knowledge of the cause and risk factors associated with perinatal deaths, with a major gap for ante-partum stillbirths.[8, 24] Most of the data on the causes of ante-partum stillbirths are mainly provided by high-income countries studies, where the SBRs are 10-14 times lower than recorded in most of the sub-Saharan Africa countries, and where the patterns of stillbirths may be different.[15, 16] The data suggest that the determinants of stillbirths may vary with the levels of SBRs.[12]

A literature review of the risk factors for perinatal death and stillbirth, in particular, found the same challenges as those associated with the definition of these outcomes. Several classifications of the cause and risk factors of stillbirths co-exist,[58, 59, 60] and ICD-10 does not provide any clear input to solving this problem.[8] Some classifications rely on fetal causes,[61] others on maternal conditions[62] and a combination of both.[58, 63, 64] The distribution of the cause and risk factors of stillbirths and early neonatal deaths varies accordingly to SBR and NMR in the region. This justifies the classification recently proposed by Lawn and colleagues[8] that focuses on the type of risk factors for 3 levels of SBRs as outlined in Table3.

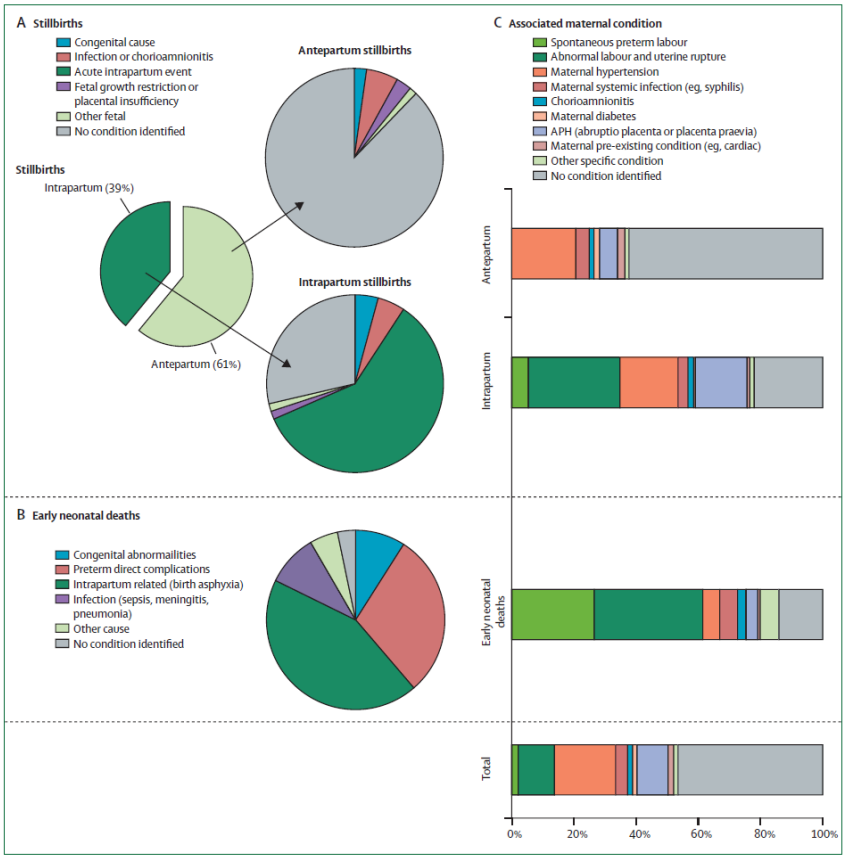

Figure 3: ***Distribution of the causes and risk factors for stillbirths and early neonatal deaths and associated maternal conditions in South Africa (Lawn et al. 2011, [8])***

The reasons for limited data on the risk factors and determinants of perinatal deaths in resource-poor settings relate to the low priority given to stillbirths in countries already facing a multitude of health challenges, lack of resources to conduct such studies, the omnipresent risk of misclassifications of stillbirths and the lack of lab equipment and facilities needed for relevant investigations of some of the causes (congenital and haematological factors). Based on the few studies conducted in Sub-Saharan Africa[58] and the consistency of their findings with similar studies from high-income countries,[63] cause and risk factors for perinatal death are classified according to the period when fetal or newborn death occurred (Figure 3).

Factors associated with antepartum stillbirth risk

Although there is limited knowledge on this group, studies have mainly reported maternal factors,[8, 13, 24] such as poor nutritional status prior to pregnancy, early childbearing, parity (primiparae or high multiparae), poor maternal health status (diabetes, hypertensive disease and disorders, etc.), infections (syphilis, malaria, HIV), anaemia (vaginal bleedings during the third trimester of pregnancy) and other factors, including short stature (<150 cm), to be associated with a higher risk of antepartum stillbirth. Some studies suggest other socio-economic factors, such as maternal education and income, to be predictors of ante-partum stillbirths.[47, 65, 66]

Factors associated with intrapartum stillbirth risk

More data are available for this group of factors, on which there is general agreement that the risk relates directly to the place of delivery, birth attendants, hygiene and environment at birth.[8, 24] They include obstetric complications (obstructed labour, preterm rupture of membranes, chorioamnionitis, malpresentation, maternal haemorrhage, and misuse of oxytocin), maternal infections (including malaria), and congenital abnormalities. A Ghanaian prospective study showed that 59% of mothers who experienced a stillbirth had obstetric complications at delivery.[65] Some cultural factors, such as female genital mutilation, have been suggested in a WHO-study as contributing to intra-partum stillbirths.[67]

Predictors of early neonatal death risk

This group is much better described, although controversies remain over the factors involved, such as low birth weight.[13, 47, 48] The main factors increasing the risk of early neonatal death include preterm birth complications, birth asphyxia, and maternal (HIV, malaria) and new-born infections (tetanus, sepsis). The gender of the new-born has been reported to be a potential determinant of early neonatal deaths, from which the theory of "natural resistance" of girls to neonatal deaths was developed.[13, 68] However, this finding is inconsistent and may be reversed by some preferences for boys in some societies.[69]

The numerous classifications of the causes of stillbirths result in low comparability of studies, making meta-analysis risky,[8] and none of the risk factors so far identified meets, strictly speaking, all the criteria for causation given by Bradford Hill.[70]

Causes and risk factors for neonatal death

There is more data about the causes and risk factors for neonatal deaths.[13] Recently, Black and colleagues[9] provided a global overview of the causes of neonatal deaths in the world (Table 4). Overall, the 3 main causes of neonatal deaths in Sub-Saharan Africa are preterm birth complications (28%), birth asphyxia (28%) and infections (sepsis, pneumonia, diarrhoea, tetanus, totalling 34%).[9] Unlike stillbirths, there is a better definition and classification of the causes of neonatal deaths in the ICD-10,[44] and a hierarchical model for assignment of the causes of neonatal death has been provided by the international reference group on child health for international comparisons.[71] This facilitates meta-analyses and provides modelled estimates of the causes of neonatal deaths, as in the above study.[9] Despite a better understanding of the causes of neonatal deaths, however, NMRs remain very high in Africa, which raises concern about the gap between knowledge and implementation of efficacious interventions in communities that most need it.[4, 18, 19]

Table 4: **Number and proportions of neonatal deaths by causes for the world and for Africa in 2008 (adapted from Black et al., 2010; [9])**

	World			Africa[a]	
	Deaths (Millions)	Uncertainty range	%	Deaths (Millions)	%
Preterm birth complications	1.033	0.717-1.216	29	0.336	28
Birth asphyxia	0.814	0.563-0.997	23	0.336	28
Sepsis	0.521	0.356-0.735	14	0.209	17
Pneumonia	0.386	0.264-0.545	11	0.126	10
Diarrhoea	0.079	0.057-0.211	2	0.042	3
Tetanus	0.059	0.032-0.083	2	0.042	3
Congenital abnormalities	0.272	0.205-0.384	8	0.084	7
Other	0.409	0.318-0.883	11	0.042	4
Total neonatal deaths	3.6	-	100	1.2	100

[a]Uncertainty range not provided for the African region

Causes and risk factors of infant death

Recent publications have also provided an update on the causes of infant deaths across different regions of the world.[9, 10, 11, 72] Because causes of child death after the age of one month remain broadly the same as up to the age of 5 years in developing countries,[9] few large studies from these regions investigated causes of deaths specific to infant deaths (<12 months) in comparison to deaths occurring between 1 and 5 years. Therefore, mentioning the causes of infant deaths, we will often refer to causes of postneonatal deaths.[10] A recent meta-analysis showed that infections remain the prime cause of infant and overall childhood

mortality in the world.[9] Pneumonia (14%), diarrhoea (14%) and malaria (8%) are the main infectious causes of postneonatal deaths in the world. There is notable variation worldwide in the pattern of the causes of postneonatal deaths (Figure 4) and the proportion of congenital abnormalities as causes of child deaths seems very low in Africa (2%) compared to the rest of the world (5-11%), but this may simply reflect the abundance of other causes of child death in Africa.

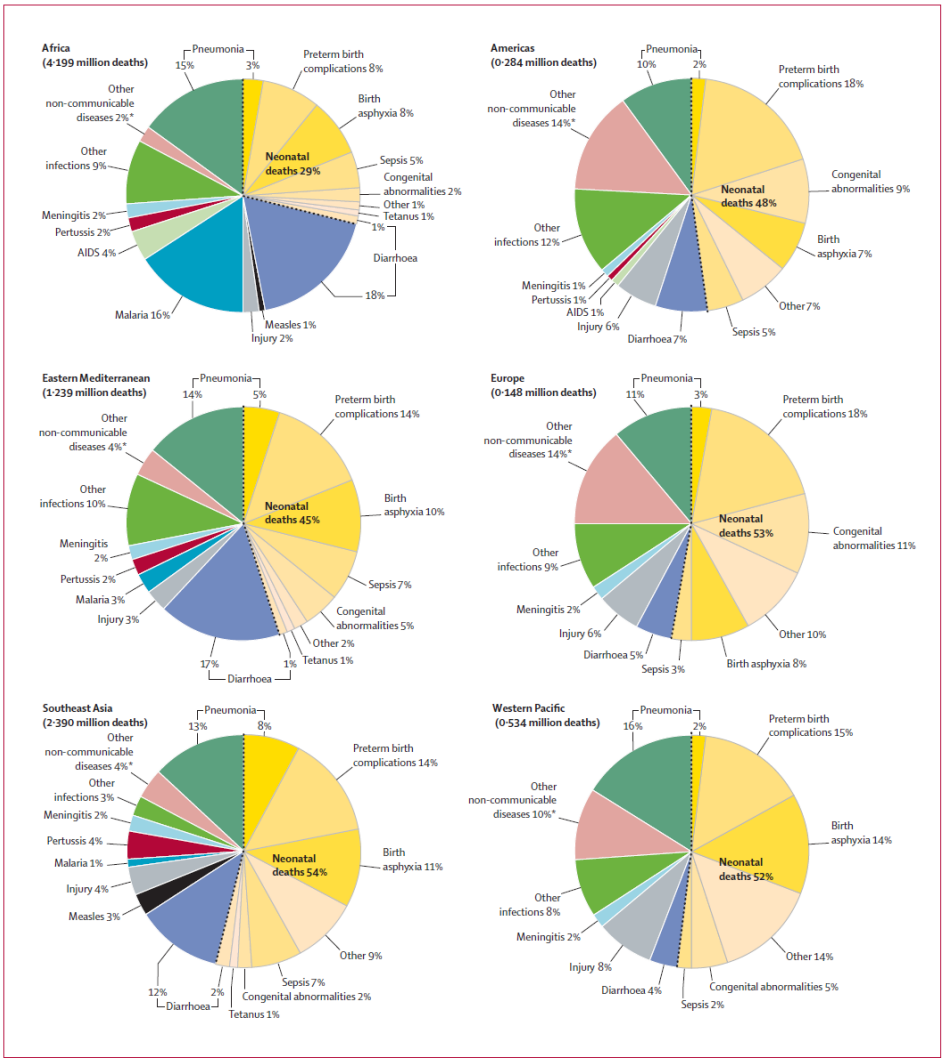

Figure 4: ***Regional variations of the causes of under-5 year deaths in the world in 2008 (Black et al., 2010 [9])***

In Sub-Saharan Africa, diarrhoea (18%), malaria (16%) and pneumonia (15%) are the leading causes of child deaths after one month of age.[9] In comparison, diarrhoea, malaria and pneumonia represented 12, 1 and 13%, respectively, of all causes of postneonatal deaths in

South-East Asia.[9] Furthermore, HIV/AIDS remains an important cause of infant deaths in Africa, estimated to account for 4% of all child deaths after one month of age, killing more children than outbreaks of meningitis (2%) and measles (1%).[9] Large efforts are still needed to control infectious diseases in Africa for a significant decrease of the under-5 year mortality.[4]

Table 5: **Effect of individual and combined interventions on stillbirths for different coverage levels in 2015 (Bhutta et al., 2011 [21])**

	60% coverage		90% coverage		99% coverage	
	Number of stillbirths	Reduction in stillbirths	Number of stillbirths	Reduction in stillbirths	Number of stillbirths	Reduction in stillbirths
Baseline estimate for 2015	2 499 000	..	2 499 000	..	2 499 000	..
Periconceptional folic acid fortification	2 481 000	0·7%	2 472 000	1·1%	2 470 000	1·2%
Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy	2 457 000	1·7%	2 433 000	2·7%	2 425 000	3·0%
Syphilis detection and treatment	2 425 000	3·0%	2 396 000	4·1%	2 350 000	6·0%
Detection and management of hypertensive disease of pregnancy	2 463 000	1·5%	2 472 000	1·1%	2 430 000	2·8%
Detection and management of diabetes of pregnancy	2 484 000	0·6%	2 475 000	1·0%	2 473 000	1·1%
Detection and management of fetal growth restriction	2 430 000	2·8%	2 391 000	4·3%	2 380 000	4·8%
Identification and induction of mothers with ≥41 weeks of gestation	2 467 000	1·3%	2 448 000	2·1%	2 442 000	2·3%
Skilled care at birth and immediate care for neonates	2 443 000	2·3%	2 355 000	5·8%	2 326 000	7·0%
Basic emergency obstetric care	2 313 000	7·4%	2 147 000	14·1%	2 088 000	16·5%
Comprehensive emergency obstetric care	2 146 000	14·1%	1 824 000	27·0%	1 723 000	31·1%

Numbers of stillbirths have been rounded to the nearest thousand, but percentages of stillbirths averted were based on actual numbers.

Estimated effects of individual interventions on stillbirths according to coverage level in 2015

	60% coverage		90% coverage		99% coverage	
	Number of stillbirths averted*	Reduction in stillbirths	Number of stillbirths averted*	Reduction in stillbirths	Number of stillbirths averted*	Reduction in stillbirths
Periconceptional folic acid fortification	17 000	0·7%	25 000	1·0%	27 000	1·1%
Insecticide-treated bednets or intermittent preventive treatment for malaria prevention during pregnancy	20 000	0·8%	32 000	1·3%	35 000	1·4%
Syphilis detection and treatment	72 000	2·9%	121 000	4·8%	136 000	5·4%
Detection and management of hypertensive disease of pregnancy	34 000	1·4%	50 000	2·0%	57 000	2·3%
Detection and management of diabetes of pregnancy	15 000	0·6%	22 000	0·9%	24 000	1·0%
Detection and management of fetal growth restriction	65 000	2·6%	98 000	3·9%	107 000	4·3%
Identification and induction of mothers with ≥41 weeks of gestation	31 000	1·2%	47 000	1·9%	52 000	2·1%
Comprehensive emergency obstetric care	361 000	14·5%	622 000	24·9%	696 000	27·9%
Total stillbirths averted	615 000	24·6%	1 017 000	40·7%	1 134 000	45·4%

Numbers of stillbirths averted have been rounded to the nearest thousand, but percentages were based on actual numbers. *Calculated on the basis of a baseline estimate of 2 499 000 stillbirths in 2015.

Estimated effects of intervention combinations on stillbirths according to coverage level in 2015

Evidence-based interventions to reduce perinatal and infant mortality

With the increasing advocacy and awareness of the burden of stillbirths, a step forward is to assess the evidence-based interventions that can effectively reduce this scourge in settings where the burden is high. The overall perinatal mortality could be reduced by cost-effective interventions targeting stillbirths, because, as previously stated, causes of intra-partum stillbirths are strongly related to that of early neonatal deaths. A modelled estimate found NMRs as strong predictors of the SBRs.[12] Bhutta and colleagues[21] assessed the effects and costs of interventions expected to significantly reduce the high number of stillbirths and the overall perinatal mortality in low-income countries, based on the periods before and during pregnancy, as well as at the time of birth. Overall, the authors found that, in high mortality settings, basic and comprehensive emergency obstetric care (EmOC) have the greatest effect on stillbirths[21] and could reduce by 16 and 31%, respectively, the actual number of stillbirths at a coverage of 99%. When combined with other suggested interventions, such as peri-conceptional folic acid supplementation, prevention of malaria, detection and treatment of syphilis during pregnancy, as well as advanced antenatal care management, up to 45% of all stillbirths could be averted at a coverage of 99% (Table 5).[21]

Scaling-up of the most cost-effective interventions to reduce stillbirths could also result in a significant decrease of maternal (-54%) and neonatal (-43%) deaths (Table 6).[25] The cost of reaching a coverage of 99% of the key interventions in the 68 countdown priority countries in Africa and Asia has been estimated at 10.9 billion USD, which corresponds to an average cost of 2.3 USD per head per year, an amount below the WHO accepted threshold of cost-effective interventions and therefore worthy of implementation.[25]

Table 6: **Number of stillbirths, neonatal and maternal deaths averted by combinations of the Life saving tools (LiST) interventions at different levels of coverage (Pattinson et al.,2011 [25])**

	Stillbirths (2 499 000 at baseline*)		Maternal deaths (371 000 at baseline*)		Neonatal deaths (3 333 000 at baseline*)		Total deaths (6 203 000 at baseline*)	
	Deaths averted	Reduction in deaths	Deaths averted	Reduction in deaths	Deaths averted	Reduction in deaths	Deaths averted	Reduction in deaths
60% coverage†	615 000	25%	106 000	29%	388 000	12%	1 109 000	18%
90% coverage†	1 017 000	41%	175 000	47%	712 000	21%	1 903 000	31%
99% coverage†	1 134 000	45%	198 000	53%	828 000	25%	2 161 000	35%
99% coverage plus maternal and neonatal interventions‡	1 134 000	45%	201 000	54%	1 447 000	43%	2 782 000	45%

Numbers of deaths averted have been rounded to nearest thousand, but percentages were based on actual numbers. Each death (maternal death, neonatal death, and stillbirth) has equal weight. *Projected number of deaths in 2015, assuming no change in coverage levels from those in 2011. †Coverage of ten stillbirth-specific interventions. ‡Coverage of ten stillbirth-specfic interventions plus five interventions specifically for mothers and neonates and with no estimated effect on stillbirths.

A framework to reduce morbidity and mortality (Figure 5) was provided by Pattinson and colleagues[25] that is applicable to all components of child deaths. It illustrates perfectly the complexity and the number of stakeholders involved in the process, if relevant and acceptable interventions are to be implemented and scaled-up. Increasing community

awareness and demand for the existing interventions, and ensuring their participation during the implementation of the interventions, is as important as the decision to convey health policy.[25, 73, 74, 75]

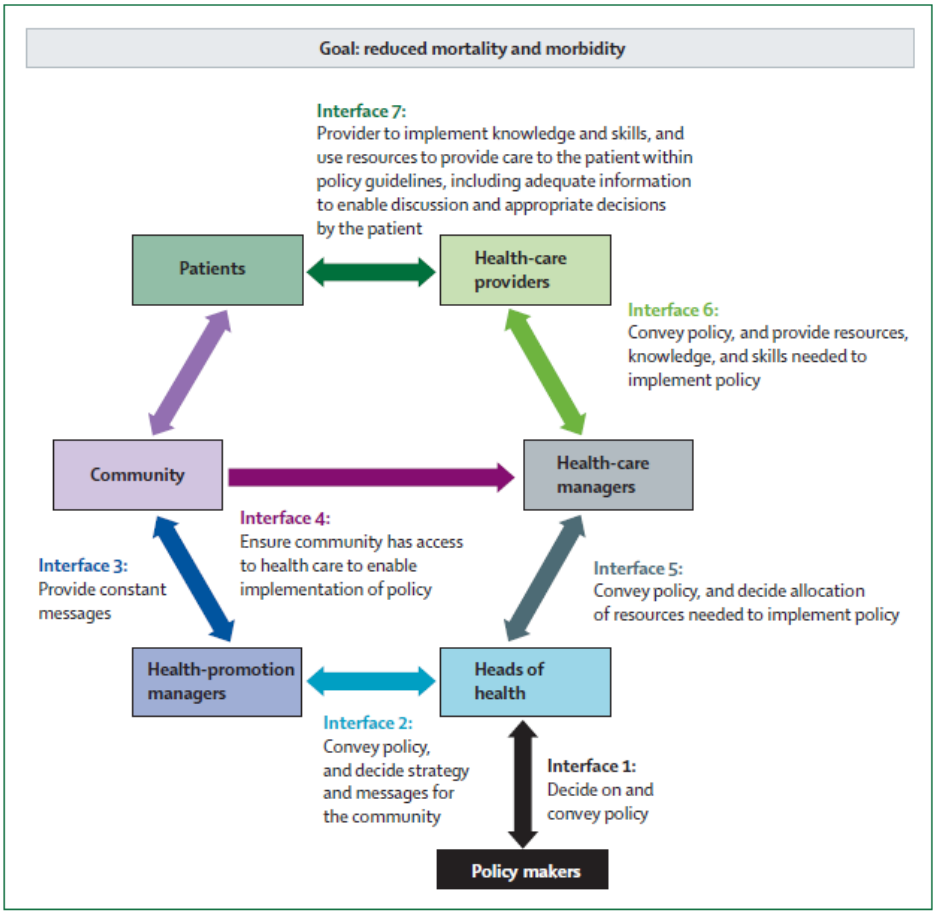

Figure 5: ***Key stakeholders relevant for successful implementation of health-policy and effective community-interventions to reduce morbidity and mortality in a country (Pattinson et al., 2011, [25])***

The most effective interventions to reduce the burden of infant and overall child deaths in the world were identified both from the Bellagio Group study and subsequent studies.[4, 76, 77, 78] Of these, promotion of exclusive breastfeeding up to 6 months was identified as the most cost-effective, potentially saving up to 1.3 million children's lives every year.[78] Other key interventions include treatment of pneumonia and diarrhoea, as well as immunization against measles, meningitis and supplementation of vitamin A (although, some controversies exist about the latter).[4, 76] Recent data on the causes of child deaths[9] did not show large differences with that provided in 2003[79], except in the reduction of HIV/AIDS-related deaths in Africa.

Therefore, the same interventions remain relevant in reducing the overall burden of child deaths. Malaria control should be a major target in countries from Sub-Saharan Africa, where this disease is responsible of >0.7 million child deaths per year;[9] this control will be reached by increasing coverage of intermittent preventive treatment for malaria (IPT) among pregnant women and infants, use of insecticide-treated bed nets, and curative measures (use of artemisin-based combinations therapy to treat clinical malaria). Countdown to 2015 has included 26 of the major interventions in its tracking package, and showed the trends in their reported coverage.[4] Overall, some improvements have been achieved in areas, such as immunization (antenatal tetanus, measles, DTP), vitamin A supplementation and improved drinking water (Figure 6).[4]

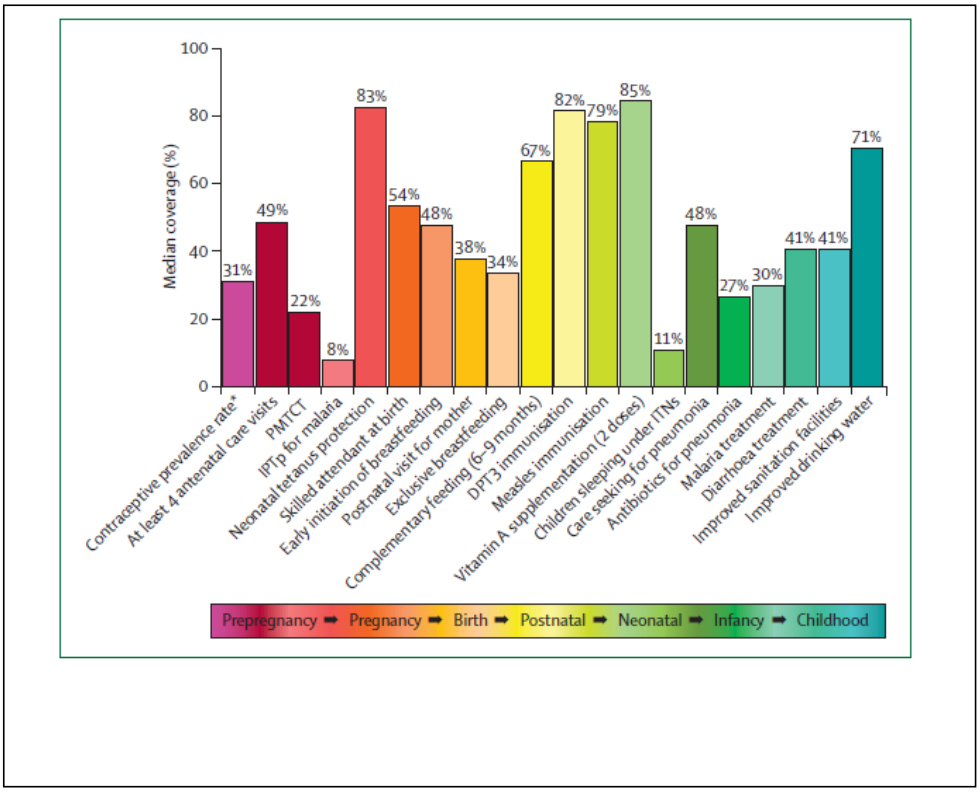

Figure 6: ***Median coverage of the main interventions suggested for an effective reduction of under-5 year mortality in the 68 "Countdown to 2015" priority countries in 2008 (Bhutta at al., 2010 [4])***

However, there is still poor coverage of interventions, such as the use of contraceptives, skilled attendants at birth, malaria prevention and treatment, PMTCT, exclusive breastfeeding rates, postnatal visits for mothers, care seeking and treatments for pneumonia and diarrhoea episodes. The trends in coverage of effective maternal, new-born and child interventions in the 68 priority countries also showed enormous disparities between urban and rural settings, within the regions, and between wealth indexes.[4] While encouraging progress has been reported from Asia (Bangladesh, China) and Latin America (Brazil)[4], the pace is very slow for most of the Sub-Saharan Africa countries.[4] The effect of external funds

provided by the overseas development aid (ODA) on the scaling-up of interventions (sometimes qualified as a "continuous infusion of an ill-patient") has often resulted in lower proportions of domestic budgets been allocated for health, and is a possible explanation of the insufficient progresses that have been observed.[2, 4] Inadequate health-policies at the local level may be another reason for poor progress.

Literature review on perinatal and infant mortality in Burkina Faso

Search methods

Data production relies on available resources, as well as on the health policy in place in the country. In a very poor country, such as Burkina Faso, where the health system is weak, especially in rural settings, data on child mortality rates will be scarce. We conducted a literature search on perinatal and overall infant mortality in Burkina Faso. For this purpose, an online search used 4 major databases:
Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/),
Cochrane library (http://www.thecochranelibrary.com/view/0/index.html),
WHO/UNICEF (http://www.who.int/publications/en/), and
INSD (http://www.insd.bf/fr/) the national institute for statistics and demography in Burkina Faso (the governmental institution providing health and demographic statistics).

In each of the websites we entered in 3 different searches using the following keywords:

- Perinatal, stillbirths, neonatal, deaths, mortality, Burkina Faso
- Infant, child, deaths, mortality, Burkina Faso
- Child health, morbidity, mortality, Burkina Faso

No limitations of year, language or type of publications were set, and the search was conducted on 21st January 2012. In all, 142 publications (articles, reports, comments, seminars, etc.) were retrieved that were carefully examined by checking their summaries. Only 40 reports clearly fitted the topics of our search, which were carefully read for this thesis. We decided to restrict the presentation to publications from 2000 to date to make it comparable with information in the previous chapter on an international literature review on the same topics.

Actual levels of perinatal and infant mortality rates in Burkina

Globally, few studies specifically focusing on perinatal and child mortality were found. Nationally representative data were mainly surveys, such as demographic and health surveys (DHS), national censuses, multiple indicators cluster surveys (MICS), and annual reports from the Ministry of Health in Burkina Faso.[28, 32, 34, 80] The prospective cohort studies with the largest sample size were reports from the 2 first DSS in Oubritenga[37] and Nouna Province, respectively.[38, 81] Other prospective studies of a relatively small size reporting on perinatal or child deaths are dominated by studies on malaria.[36, 39, 82, 83] Some studies targeting nutritional[84, 85, 86] or infectious disease outcomes measured infant mortality, but only as a secondary objective. The largest cohort study that targeted perinatal mortality was conducted in 1996 in a university hospital in Ouagadougou,[29, 87] making the data outdated and unrepresentative of rural settings. This was also the case for data on neonatal mortality, where the only available data were either from urban settings or facility-based.[30, 31, 88] As expected, relatively more data on infant and under-5 mortality was available than on perinatal deaths, but again these findings were mainly from DHS, national censuses and reports from the 2 DSS. Studies on the causes of child deaths focused mainly on malaria[36, 85,

[89, 90] and, to a limited extent, on pneumonia and meningitis that are major causes of child deaths in Burkina Faso.

Based on data collected *in situ* in Burkina Faso, we found that SBRs ranged from 50 in 1977 in the Bobo-Dioulasso area[91] to 16 per 1000 births in 2003 in the 2003-DHS.[28] Data on early neonatal mortality showed rates from 25 in the 1999-DHS[80] to 10.3 per 1000 live births in a health-facility based study in the Houndé region[41] in 2006.

Overall, the review showed PNMRs ranging from 219.6 in a biased group of women with severe obstetric complications in Houndé area[92] in 2006 to 31.7 per 1000 births in the same area for a group of women with health-facility deliveries[41] (Table 7).

Data on NMRs showed rates ranging from 153 in a group of hospitalized newborns[31] to a lower NMR of 14.6 per 1000 live births (Table 7) in a semi-urban setting[41].

Estimates of IMRs and overall U5MR were mainly either modelled estimates[10, 11, 55] or data from surveys.[28, 34, 80] IMRs varied from 105 in the 1999-DHS[80] to 92 per 1000 live births in the 2006-census[34] (Table 8).

There were also few cohort data that in general showed IMRs much lower than that of the surveys, ranging from 90 in 1996 in Kaya (North-central part)[93] to 57 per 1000 live births in 2003 in Nouna (North-western part of the country).[81]

U5MRs were also extremely high, ranging from 219 in the 1999-DHS to 142 per 1000 live births in the 2006-national census. Cohort data on U5MR followed similar patterns to IMR, with data from DSS providing a much lower U5MR than that of surveys. For example, one of the studies in Nouna's DSS reported an U5MR of just 31.9 per 1000 person-years in 2003.[39]

The provisional data of the 2010-DHS reported an IMR of 65 per 1000 live births (Table 8) and an U5MR of 129 for the national average.[94] Regional analyses had not been performed at the time of the submission of this thesis.

Table 7: Literature review on perinatal and neonatal mortality in Burkina Faso based on articles/reports published from 2000 to 2012 sorted by year of publication.

First author	Study Year	Type of study	Mortality per 1000					
			SBR[a]	ENMR[b]	PNMR[c]	NMR[d]	Year of publication	Source
Burkina Faso, INSD	1998-1999	DHS	30.0	25.0	54.0	41	2000	[80]
Chalumeau M.	1994-1996	Hospital-based study	20.9	-	32.5	-	2002	[29]
Burkina Faso, INSD	2003	DHS	16.0	21.0	36.0	31.0	2004	[28]
Hammer GP	1999-2003	Retrospective analysis of DSS cohort data	-	-	-	93.6	2006	[81]
Bank E (WHO)	2001-2003	Health facility-based survey	41.7	7.9[e]	50.0	-	2006	[67]
Koueta F	2002-2006	Retrospective hospital-based survey	-	-	-	153.0	2007	[31]
Fillipi V	2004-2006	Prospective health facility-based cohort study			219.6	-	2007	[92]
Bell JS	2001-2006	Community-based surveys	33	-	-	-	2008	[40]
Roberfroid D	2004-2006	RCT, Community-based study	20.6	10.3	31.7	14.6	2008	[41]
Gies S	2004-2006	Health facility-based RCT	49[f]	-	-	-	2008	[122]
Huybregts L	2006-2008	RCT, open-trial	22.5	6.8	29.1	16.2	2009	[i]
Rajaratnam JK	2010	Modelled estimates	-	-	-	32	2010	[10]
Burkina Faso, INSD	2010	DHS	-	-	-	28	2011	[94]
Cousens S	2009	Modelled estimates	26.2	-	-	-	2011	[12]
Lozano R	2011	Modelled estimates	-	25	-	39	2011	[123]
UNICEF /SOWC	2010	Modelled estimates	-	-	-	38	2012	[ii]

[a] Stillbirth rate, [b] Early neonatal mortality rate, [c] Perinatal mortality rate, [d] Neonatal mortality rate, [e]Computed only for the first 2 days of life, [f]Data of the control arm as miscarriage/ stillbirths, DHS=Demographic and health surveys, RCT=Randomized controlled trials

i- Huybregts et al. (2009). Am J Clin Nutr **90**(6): 1593-1600.

ii- UNICEF, State of the world's children 2012 report. Accessible at www.unicef.org

Table 8: Literature review on post-neonatal and infant mortality in Burkina Faso from 2000 to 2012 sorted by year of publication.

1st author	Study year	Study design	Mortality per 1000				
			Sample size	Post-NMR	IMR	Year of publication	Source
Burkina Faso, INSD	1998-99	DHS	5953	65	105	2000	[80]
Diallo DA	1993-2000	RCT and nested-cohort study in a DSS	27577	-	102	2004	[37]
Kabore P	2001-2002	Retrospective cohort study	435	-	53	2004	[95]
Vaugelade	1985-96	Prospective community cohort study	9085	-	90	2004	[93]
Burkina Faso, INSD	2003	DHS	10645	50	81	2004	[28]
Kynast-Wolf G	1993-2001	Community-based cohort study from DSS	35549	-	51.3	2006	[90]
Hammer PG	1999-2003	Community-based cohort study	22979	-	57	2006	[89]
Abdullah S	2002-2003	Multi-site, multicentre study from 7 DSS in SSA	50536	-	92	2007	[i]
Ramroth H	1999-2004	Meta-analysis of DSS studies (RCT & cohorts)	6387	-	49.6	2009	[ii]
Rajaratnam JK	2010	Modelled estimates	-	39	70	2010	[10]
Burkina Faso, INSD	2006	Population census (RGPH)	14017262	-	92	2009	[34]
Burkina Faso, INSD	2010	DHS	14424	37	65	2011	[94]
Lozano R	2011	Modelled estimates	-	48	87	2011	[123]
UNICEF (SOWC)	2010	Modelled estimates	-	-	93	2012	[iii]

Post-NMR=Post neonatal mortality rate IMR=Infant mortality rate
DHS=Demographic and health surveys DSS=Demographic surveillance sites
RCT=Randomized-control trial SSA=Sub-Saharan Africa
MICS=Multiple indicators cluster survey INSD=Institut national de la statistique et de la démographie

i- Abdullah et al. (2007). Am J Trop Med Hyg **77**(6 Suppl): 99-105.
ii- Ramroth et al. (2009). Glob Health Action **2**.
iii- UNICEF, State of the world's children 2012 report. Accessible at www.unicef.org

In all DHS and national censuses data, child mortality rates were always higher in rural settings compared to urban areas, and always higher in boys than girls. Thus, in the 2006-national census, IMR was 98 per 1000 in rural settings versus 64 per 1000 live births in urban areas[34]; IMR was 98 per 1000 among boys versus 86 per 1000 live births for girls in 2006. The same trends were observed in 2006 for the U5MR, which were 153 per 1000 in rural areas versus 91 per 1000 for urban settings, and 144 per 1000 among boys versus 140 per 1000 live births for girls.[34]

Causes and risk factors for perinatal and infant deaths in Burkina Faso

The only prospective study that focused on risk factors for perinatal death was by Chalumeau and colleagues[29] in 1996. This study found vaginal bleeding in the third trimester of pregnancy or at delivery, intrapartum hypertension, and birth complications (dystocia, infections) as the main risk factors.[29, 87] Two studies have also suggested that severe obstetric complications at birth[92] and female genital mutilations[67] might be risk factors for stillbirths in Burkina Faso.

The review on the factors associated with neonatal death risk noted that in the Pissila region (Northern part of the country) a low birth weight increased the risk of neonatal and infant death[95] (RR=4.5, p=0.005), while another study conducted at a university hospital in Ouagadougou found neonatal infections (17%), congenital abnormalities (13%) and acute incidental intoxication (13%) were factors of high lethality among the hospitalized newborns.[31]

Vaugelade and colleagues, in a community-based prospective cohort study in Kaya and Yako regions,[93] found lower mortality rates among children aged 6-24 months who had been immunized with BCG alone (RR=0.37, 95% CI: 0.29-0.48) or BCG and diphtheria, tetanus, and pertussis (RR=0.34, 95% CI: 0.29-0.40) compared to unvaccinated children of the same age. In this study, the presence of a dispensary in the village, children without malnutrition, and the rainy season (March-Oct) were associated with a lower child death risk.[93]

Evaluation of health interventions to reduce child deaths in Burkina Faso

We identified only a few trials conducted in Burkina Faso that had child death as an outcome. This was even more the case when we looked at trials targeting perinatal deaths. The findings of the 6 main trials are presented in Table 9.

Table 9: **Intervention studies (trials) which assessed potential effects on perinatal or child death risks in Burkina Faso from 2000 to 2011 by year of publication.**

First author	Year of publ.	Study sites and sample	Study year	Study design and interventions tested	Effect on perinatal death risk	Effect on infant and child death risks
Müller O [86]	2001	Nouna n=709	1999	Subject randomized, double-blind, placebo-controlled efficacy trial. Intervention arm received zinc.	NA	HR=0.41 (95% CI: 0.15-1.19) and the authors found no difference of child death risk, although the death risk was lower in the intervention arm.
Diallo DA [37]	2004	Oubritenga n=48,000	1994 to 2000	Cluster randomized-trial of 16 villages (8 vs. 8). Intervention consisted of insecticide- treated curtains (ITC)	NA	IRR=0.76 (95% CI: 0.66-0.87) for children aged 6-59 months. When considering only children <2 years, IRR=0.80 (95% CI: 0.69-0.94). The effect of ITC was not found to decrease with time (LR test, p=0.92) and the authors concluded that there was no evidence of a delayed child mortality to older ages after an early introduction of ITC.
Yé A [i]	2007	Nouna N=867	2003 to 2004	A comparative study of 2 parallel groups: A cohort of children < 5 years was recruited and followed-up for one year in 4 villages. Home visits were performed by community-members to seek and treat febrile kids with 3 days-course of chloroquine. Another group of children of the same age was recruited in 15 other villages of the area through Nouna's DSS that served as the control group. Using indirect standardization, the authors calculated SMRs to compare mortality rates in the 2 groups.	NA	The intervention had no effect on childhood mortality (SMR=0.92, 95% CI: 0.5-1.55), but the drug used (chloroquine) was also ineffective.

Roberfroid D [41]	2008	Houndé n=1426	2004 to 2006	Randomized, double-blind controlled trial. The intervention group received a daily UNICEF/WHO recommended multiple micronutrients (UNIMMAP) supplementation from pregnancy until 3 months postpartum. The control group received daily supplementation of iron and folic acid for the same duration.	Higher risk of stillbirth in the intervention arm (OR=2.23, 95% CI: 0.97-5.22) and also higher perinatal death risk in the intervention arm (OR=2.08, 95%CI: 1.07-4.07).	NMR was higher in the intervention arm (OR=2.11, 95% CI: 0.78-5.67) though this could be due to chance.
Gies S [122]	2008	Boromo n=2288	2004 to 2006	Health facility-based randomized trial with 3 arms: A vs. B vs. C with 4 facilities in each arm. Intervention A consisted of IPT_p with Sulfadoxine-pyrimethamin (SP) in health facilities, and also a community-based promotion of early and regular ANC attendance by pregnant women. Intervention B consisted only of IPT_p with SP in target health facilities. Intervention C was made of pregnancy malaria prevention with only weekly chloroquine. Although facilities were the randomization units, study villages were the intervention units.	Miscarriage/stillbirth rates were of 55, 41 and 49 per 1000 births in arms A, B and C, respectively. There was a higher OR of miscarriage/stillbirth rate in the arm A when compared to B (OR=1.36, 95% CI: 0.88-2.12) and also when compared to arm C (OR=1.15, 95%CI: 0.89-1.48), though not statistically significant.	NA
Huybregts L [ii]	2009	Houndé n=1296	2006 to 2008	Randomized, controlled, open trial of fortified food supplementation (FFS) versus multiple micronutrients (MMN) supplementation on pregnancy outcomes.	There was no difference neither on stillbirth rate (OR=0.78, 95% CI: 0.36-1.68) nor on perinatal death risk (OR=0.82, 95% CI: 0.42-1.60) between the two study arms.	No difference was found in the neonatal death risk between the two study arms (OR=0.88, 95%CI: 0.35-2.17).

HR=Hazard ratios OR=Odds ratios CI=Confidence interval SMR=Standardized mortality ratio DSS=Demographic surveillance site NA=Not available

[i] - Ye et al. (2007). J Trop Pediatr **53**(4): 292-293.

[ii]- Huybregts et al. (2009). Am J Clin Nutr **90**(6): 1593-1600.

Rationale for the studies

Several studies have underlined the limited data on perinatal[8] and infant mortality[6, 9, 13] in resource-poor settings. Sub-Saharan Africa was particularly indexed as one of the regions with scarce and unreliable statistics for these two outcomes.[4, 16, 20, 24] The design and implementation of relevant health programmes rely on data, which is also a first step where country specific interventions are to be designed.

Burkina Faso, one of the poorest countries in the world, is facing several challenges including hunger, poverty and very high child mortality rates.[11, 26] Unfortunately, the limited data available on child mortality come either from biased surveys, such as hospital-based or out-dated prospective studies from particular urban or semi-urban settings. Previous data from DHS[28] and other publications on the trends of child mortality in Burkina[36, 39, 89] suggest that the burden is much higher in rural areas of the country.

The PROMISE-EBF study was a cluster-randomized trial implemented in 24 villages in rural areas of Banfora Health District, South of Burkina Faso.[43] So far, the study has provided an opportunity to follow children born in this cohort until they had reached 12 months of age.

Study objectives

The overall aim of this thesis was to study the epidemiology of fetal and infant deaths from 7th month of gestation and onwards in rural settings in the region of Banfora. It was specifically focused on the burden of perinatal and infant deaths and their distribution through baseline characteristics of mothers and newborns, and on the possible predictors of these poor outcomes.

The specific aims were as follows:

1- To measure the perinatal mortality rate (PNMR) in the PROMISE-EBF cohort and describe its distribution according to the baseline characteristics of mothers and newborns (Paper I).
2- To assess the burden of neonatal deaths in this cohort and identify its potential predictors (Paper II).
3- To measure the overall infant mortality rate (IMR) in this cohort and identify risk factors for infant death (Paper III).
4- To compare the data on child mortality rates from a rural and relatively speaking less poor area of Burkina Faso, to suggested levels and trends in modelled estimates on child mortality rates provided for Burkina Faso (Paper IV).

Settings

Burkina Faso

General overview

Burkina Faso means land (or country) of "upright people" as literally translated from two of the local languages (*Mooré* and *Dioula*) and its citizens are named *Burkinabè* derived from the third national language (*Fulfuldé)*. It is a landlocked, francophone country situated in the middle of West Africa and that got its formal independence from France in 1960. The country is surrounded by Cote d'Ivoire, Ghana, Benin and Togo in the South, by Mali in the North-west and by Niger in the North-eastern part (Figure 7).

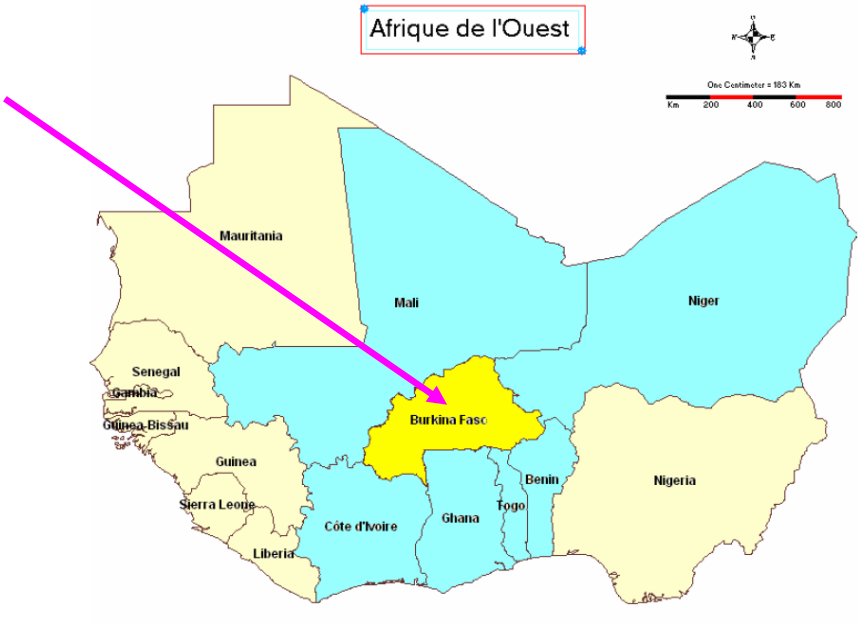

Figure 7: ***Geographic location of Burkina Faso in West Africa***

Burkina Faso covers an area of 274,000 km^2, with a Sudanese savannah climate in the South-western part (annual rainfalls >900 mm) and an almost desert-like climate in the Sahelian northern part (annual rainfalls <200 mm). The population was 14.7 million[34] based on the 2006-national census and was estimated to be over 15 million in 2010[94]. This population resides mainly in rural areas (77%), with a higher proportion of females (52%) and is very young (46% are below 15 years)[34].
From an administrative perspective, Burkina Faso is organized into 13 administrative regions (Figure 8), 45 provinces, 350 administrative counties and 8228 villages.[34] Ouagadougou

(pronounced Wagadugu), the capital city is located in the central part, and Bobo-Dioulasso, the country's second largest city is 365 km South-west of Ouagadougou.

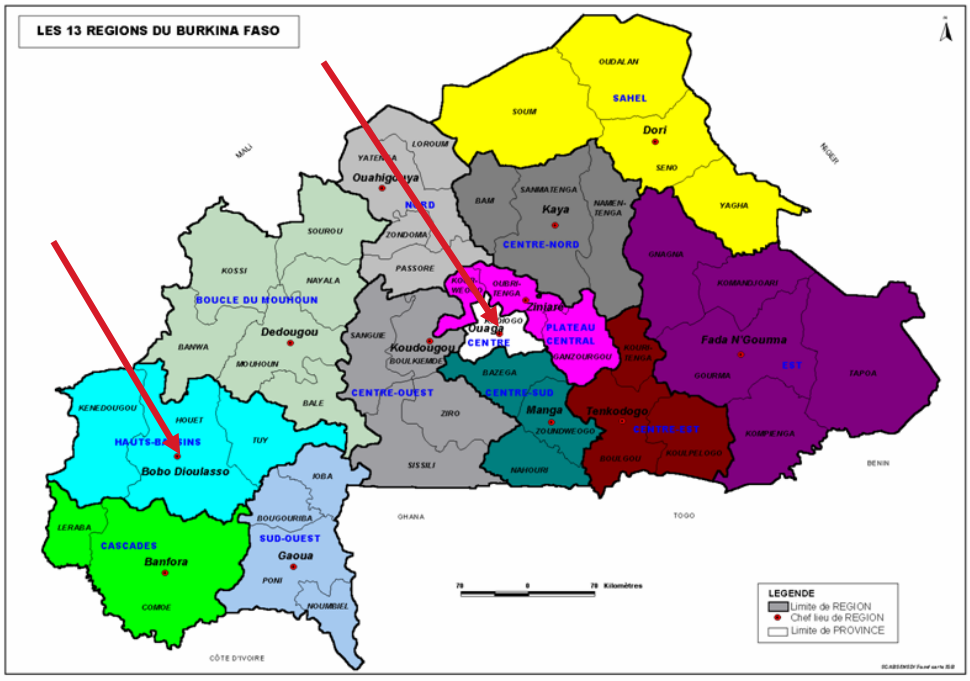

Figure 8: ***Administrative organization of Burkina Faso with the 13 regions in different colours and the 45 provinces outlined.***

Burkina Faso belongs to the group of the least developed countries and is in no doubt, one of the poorest countries in the world[96]. The GNI per capita was of 510 USD in 2009 with 57% of people living below the international poverty line of 1.25 USD per day[26]. Farming (cotton, fruits, maize, millet), animal husbandry and mining activities (gold) are the main sources for subsistence and GDP[96]. The main sociodemographic statistics of Burkina Faso are presented in Table 10.

The health system

Burkina Faso, as most of resource-poor countries has a weak health system characterized by low availability and poor access to health facilities, and a poor quality of care where these facilities exist. The country's health system rests on a three-level pyramidal system that comprises from the top to the bottom:

- The national and central health directorates, all located in Ouagadougou, the capital city. These are the national directorates of the Ministry of Health such as vertical and integrated diseases control programs (malaria, HIV/AIDS, tuberculosis, soil-transmitted helminths, etc.) and also include the cabinet of the Ministry of Health in Burkina Faso. The role of this top level is to draw the national health policy in Burkina Faso and to take appropriate

measures for funding and implementation of the health policy. Centre MURAZ, our research institute based in Bobo-Dioulasso also belongs to that national level for health policy. This Centre created since 1939 is the pioneer and the largest institute for biomedical research in Burkina Faso.

- The regional structures at the intermediate level consist of 13 regional health directorates that are in charge of health policy implementation in each of the 13 administrative regions of the country.
- The district level at the bottom is made of 63 health districts and 1373 primary health facilities which are named CSPS in French. This level is in charge of health policy implementation and also provides data and reports needed for changes or new recommendations about the national health policy.

Table 10**: Background information on Burkina Faso (INSD, UNICEF [11, 34, 94])**

	Situation in 2009/2010
Official language	French
Main local languages	*Mooré, Dioula, Fulfuldé*
Capital city (population)	Ouagadougou (1.5 million inhabitants)
Population in 2010	15 million
Annual population growth rate	3.1%
Proportion of female in the population	52%
Proportion of rural population	77%
Total fertility rate	6
Total adults literacy rate	29%
Percent primary school net enrolment	46%
Life expectancy at birth	53 years
Crude birth rate	41 per 1000
Crude death rate	11.8 per 1000
GDP per capita	563 USD
GNI per capita	510 USD
Percent share of household income (40% lowest versus 20% highest)	18% versus 47% (20% richest earns 47% and 40% poorest earns 18%)

Alongside this administrative organisation, the health care system comprises from the top to bottom:

- Three university hospitals, two in Ouagadougou and one in Bobo-Dioulasso. These facilities are expected to provide the highest available quality of care in Burkina Faso. Medical care is provided by medical experts (specialists) and clinical research should be conducted in these settings.
- Nine regional hospitals (named CHR in French) scattered through the 13 regions of Burkina Faso. These facilities are referral hospitals for a given region and the staff include specialists at least in gynaecology-obstetrics and in general surgery.
- Seventy-three district hospitals of which 42 can provide comprehensive emergency obstetric care (i.e. caesarean section and transfusion) and 1373 primary health facilities that provide basic health care.

Overall, Burkina Faso's health statistics are not satisfactory. Morbidity is common both in children and adults with malaria (45%), acute respiratory infections (14%) and diarrhoea (5%) being the main reasons for visiting local health facilities.[97] The crude death rate (12 per 1000) and the U5MR (168 per 1000 live births) were among the highest in the world in 2010.[11] The maternal mortality ratio also remains very high at 310 per 100 000 live births.[98] The main causes of child deaths are severe malaria (51%), complications of anaemia (7%) and meningitis (5%) showing the role of infectious diseases in the global burden of child mortality in Burkina Faso.[97] Almost every year, the country experiences outbreaks of meningitis and measles whose outcome is worsened by the high prevalence (31%) of malnutrition among children younger than five years.[97] The HIV prevalence is low and was estimated at 1% among the 15-49 years old subjects[94] in 2010 and was much lower in rural areas (0.6%).[94] The actual number of people living with HIV/AIDS was estimated by UNICEF at 110 000 in 2010, of whom 17 000 were below 15 years.[11]

Burkina Faso, despite its limited resources, seems to have relatively good immunization coverage (almost 100% for all EPI vaccines among infants) based on official statistics.[32]

In contrast, the proportion of health-facility deliveries and the coverage of basic EmOC are very low, being of 66% and 44%, respectively.[94, 99, 100] The Caesarean section rate is below 1% in rural areas and can only be performed at the district hospital which is commonly difficult to access due to distance.[99, 101]

Furthermore, the level of contraceptive use is somewhat low (16%)[4, 94] and contributes with other factors such as early childbearing, high multiparity and home-deliveries to maintain unacceptably high maternal and perinatal mortality rates.

Banfora Health District

Banfora is the capital city of the Cascades region (Figure 9) and is situated 85 km South of Bobo-Dioulasso. The Cascades region is made up of 2 Provinces (Comoé and Léraba). The study took place in the Province of Comoé.

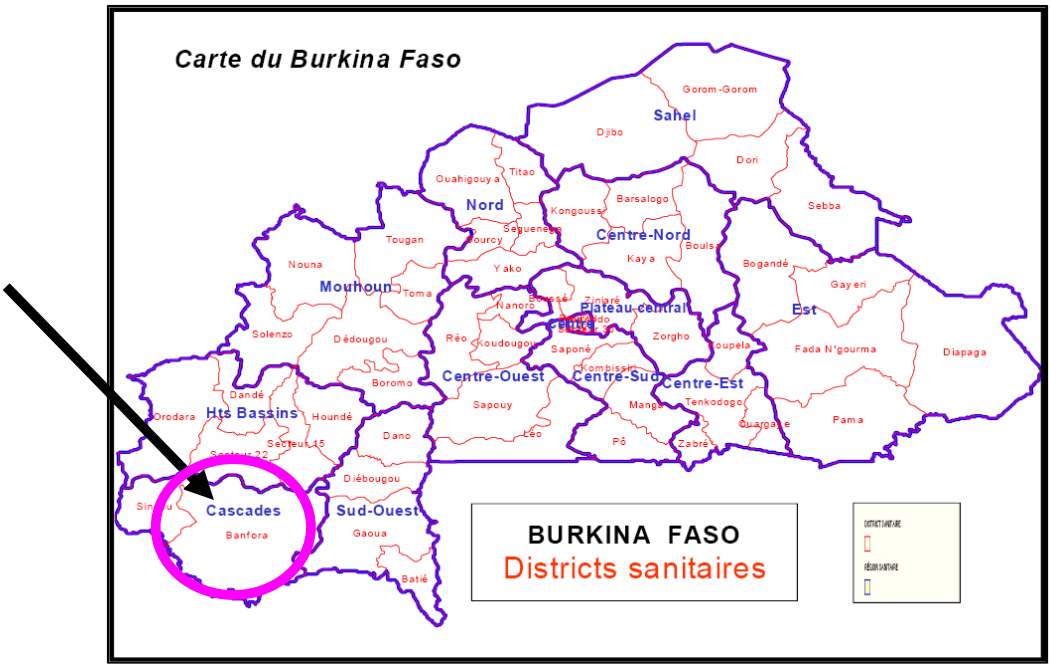

Figure 9: ***Geographic location of the Cascades (Banfora) region in Burkina Faso.***

This area is the most watered of the country with an average annual rainfall of 1300 mm and deserves definitely its nick name of the "Farmer's city". The crops are among the best in the country and over 80% of the region's economy stems from agriculture (cotton, maize, millet, rice, groundnuts, sesame, beans, fruits, potatoes, and sugar cane). Animal husbandry and fishing are other sources of income in the region, mainly in the sub-county of Sidéradougou where a large community of cattle keepers is settled since the 1970s.

From a health perspective, Banfora houses the regional health directorate (DRS in French) of the Cascades that comprises 3 health Districts (Banfora, Mangodara and Sindou) and one regional hospital (Banfora Regional Referral Hospital). The number and type of administrative Units and health facilities in the Cascades' region is presented in Table 11.

The PROMISE/EBF study was implemented in Banfora Health District which included Mangodara district in 2006, at the beginning of the study. This district covers a total area of 15000 km^2, had a total population of 385 000 in 2006, with 75 000 for the town of Banfora.[34, 102] The district has now 2 district hospitals (Niangoloko and Banfora, respectively) and 35 primary health care facilities.

In terms of morbidity, Banfora Health District is not very different from the rest of the country. Malaria is holoendemic, peaking during the rainy season (May to October) and remains the first cause of morbidity and mortality among the <5 years old;[32, 97] followed by acute respiratory tract infections and diarrhoea. Surprisingly, despite excellent crops, the prevalence of child malnutrition in Banfora Health District was among the highest in the country (38% for stunting, 12% for wasting and 24% for underweight) in 2010.[94] The proportion of low birth weight was estimated at 12% in 2010.[94]

Table 11: **Administrative Units and health system organization in the Cascades region (INSD 2010, [102])**

Unit/level	Administrative organization	Health system organization
Region	Cascades	Regional health directorate of Cascades (DRS) Banfora Regional Referral Hospital (CHR)
Provinces	Comoé	Banfora Health District (study site) Mangodara Health District (was part of Banfora health district in 2006)
	Léraba	Sindou Health District
Headquarters	Banfora	Banfora
	Sindou	Mangodara Sindou
Sub-counties	9 for Comoé	2 district hospitals (Banfora & Mangodara), 45 primary health facilities
	8 for Léraba	1 district hospital (Sindou), 27 primary health facilities

This health District is experiencing the annual meningitis outbreak during the harmattan (dry an dusty) season, as the rest of the country.[32] An outbreak of yellow fever has also been reported in 2006 because the region is bordering Cote-d'Ivoire, one of the main reservoirs of this disease in the West African region.

The HIV prevalence is relatively speaking high in the town of Banfora (1.2%) presumably because of the intense commercial traffic near the Ivorian border, but is much lower in rural areas of Banfora (0.6%)[94], where our study was implemented.

With regard to utilization of health services, over 90% of pregnant women were reported to attend at least one ANC visit in 2010 based on official reports from the local health system

and the 2010-DHS,[94] although only 33% did it during the first trimester of pregnancy.[32] The apparently high attendance at ANC services contrasts with the reported 77% of facility-based deliveries for the same period based on official reports.[94]

Exclusive breastfeeding rates in Banfora region were among the lowest in Burkina Faso, both for cultural and economic reasons. Indeed, previous data have reported EBF-prevalence below 20% at 3 months and below 7% at 6 months[28]. The proximity to Centre MURAZ in Bobo-Dioulasso, and the low EBF-rates were among the reasons for selecting Banfora as the study site for the PROMISE-EBF trial in Burkina Faso.

The statistics from Banfora on mortality showed the region as recording the country's third highest child mortality rates, both during neonatal and childhood periods (Table 12).[28, 34] High maternal mortality ratios were also reported for this region by previous surveys.[28, 34]

Table 12**: Levels and trends of perinatal and child mortality rates, and maternal mortality ratio in Cascades region in comparison to rural areas and Burkina Faso national average from 2003 to 2010 (DHS-2003, RGPH-2006, DHS-2010 [28, 34, 94])**

Outcomes	Banfora/Cascades			Rural areas			Burkina Faso		
	2003	2006	2010§	2003	2006	2010§	2003	2006	2010§
PNMR (/1000)	30	-	-	33	-	-	35	-	-
NMR (/1000)	50	-	44	39	-	35	51	-	28
Post-NMR (/1000)	63	-	52	56	-	46	51	-	37
IMR (/1000)	113	101	96	95	98	81	81	92	65
U5MR (/1000)	211	165	170	202	153	156	184	142	129
MMR (/100 000)	-	377	-	-	330	-	-	307	-

PNMR=Perinatal mortality rate, NMR=Neonatal mortality rate, IMR=Infant mortality rate
U5MR=Under-5 year mortality rate, MMR=Maternal mortality ratio
§No data on PNMR provided in the 2010-DHS and no regional analysis performed by the time of our thesis submission

Study methods

Study design

The main PROMISE-EBF study was a community-based, cluster-randomized trial implemented in 24 villages in Banfora Health District, Burkina Faso. The primary unit of randomization was the cluster defined as a village with an average population of 1000 and an expected number of 35 annual live births. A cohort study was nested within the main EBF-trial and included all pregnant women of both arms who were initially enrolled and is the basis for this thesis. The mother-infant pairs were followed until the children reached the age of 12 months. The cohort study outcomes were pregnancy outcomes (stillbirth or live birth) and infant death, respectively. The main exposures were maternal (socioeconomic variables, medical history, use of health services, etc.) and infant (sex, weight, season of birth, feeding patterns, etc.) baseline characteristics, and health system indicators (presence of local health facility, distance to nearest health facility, administrative area).

Selection and randomization of the study villages

A survey was conducted in the study area prior to the implementation of the EBF-trial in order to collect background information on eligible villages. Data collected included geographical information (GPS coordinates, main roads, and seasonal accessibility), names and number of villages, gathering places of the communities (wells, markets, schools, mosques, churches, mills, etc.), socio-demographic information (population, ethnicity, languages, main subsistence activities, etc.) and health statistics from the local health facilities. Criteria for village eligibility included population (1000-5000), distance to the nearest health facility (< 25 km), distance to the PROMISE headquarters in Banfora (<120 km), administrative area (belonging to one of the 3 subcounties: Soubakénédougou, Banfora and Sidéradougou) and a community consent to take part in the study.

Of the 92 villages initially visited and mapped, 38 met the cluster inclusion criteria. Corridors were thereafter created, to reduce potential contamination between clusters given the design of the main EBF-trial. Thus, 16 more villages were eliminated leaving a final list of 24 villages for randomization.

The randomization was done using Excel 97 (www.msoffice.org). Simple randomization was performed without use of blocks. A list of pseudorandom numbers was generated using the command "=rand ()"and the values were linked to the 24 selected villages that were already in alphabetical order. Thereafter, the villages were arranged in ascending order according to the generated pseudo-random numbers. The first 12 were assigned to the intervention arm and the last 12 to the control arm. The geographical distribution of the 24 study villages by sub-county and by arm is presented in Figure 10.

Although concealment of the village allocation was not relevant for the cohort study reported here, it was important for the outcomes of the main EBF-trial. Therefore, masking of the allocation was done for data collectors (DCs) by keeping the team for the intervention (peer-supporters) and that of data collection completely separated in the field and avoiding that DCs were informed of the study clusters' allocation. Strict instructions were given during the training of both DCs and peer-supporters that no interactions should occur between the two teams in field. However, we cannot rule out the possibility that DCs accidentally learnt from the mothers that they were visited by a woman talking about breastfeeding (i.e. a peer-counsellor). The success of this masking was not formally evaluated.

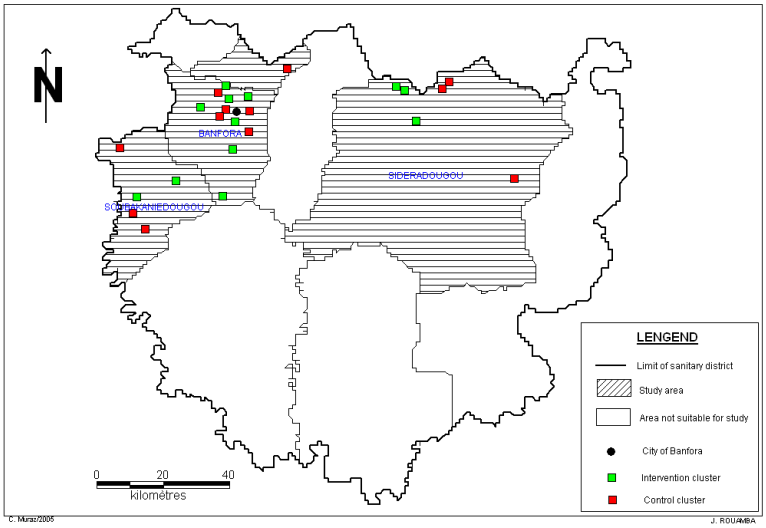

Figure 10: ***Distribution of the 24 study villages per sub-county and study arm in Banfora Health District, Burkina Faso***

Study population

The 24 villages selected and randomized for the main EBF-trial were all situated in rural areas, and covered a total population of ~35000, with a median of 1055 inhabitants per village (Table 13). The crude birth rate in 2006 was 42.6‰ in this region. The number of women of child-bearing age (15-44 years) was estimated to be 7700 in 2006[34]. There were 3 main ethnic groups in the study area (*Gouin, Karaboro, Dioula*) and the most common religion was Islam (>62%), followed by traditional African religions. Heads of households were predominantly male subsistence farmers, but women were also heavily involved in farming activities especially among the *Gouin* and *Karaboro* ethnic groups. Literacy was very low in the area and even lower among women (<20%).

Sample size estimation

The main EBF-trial aimed to measure the effect of EBF-promotion by individual peer-counselling on EBF-rates and diarrhoea prevalence among children at 12 and 24 weeks of

age. The sample size of the main study was therefore computed based on these two outcomes, for a baseline EBF-rate of 0.20 and a baseline prevalence of diarrhoea of 0.12. The intervention was anticipated to double the baseline EBF-rate (0.40) and to reduce by one third (0.04) the prevalence of diarrhoea.

Table 13: **Distribution of study villages by population, study arm, expected number of births and number of pregnant women enrolled in Banfora Health District (Burkina Faso)**

No	Village[a]	Population 2006[b]	Study arm	Expected births[c]	No of pregnant women enrolled	No of births
1	Lémouroud.Cité	600	Intervention	26	16	16
2	Gouin-Gouin	627	Control	27	40	40
3	Boborola	649	Control	28	40	41
4	Tatana	674	Control	29	30	30
5	Noumousso	692	Intervention	30	32	33
6	Sikanadjo	800	Control	34	19	19
7	Niamirandougou	818	Intervention	35	39	40
8	Kotou	824	Intervention	35	36	36
9	Tiempangora	931	Intervention	40	38	38
10	Damana	1038	Control	45	45	45
11	Karfiguéla	1045	Control	45	28	29
12	Lémouroud.village	1053	Intervention	45	29	30
13	Laferma	1058	Intervention	45	32	33
14	Tiékouna	1176	Control	51	30	30
15	Dègue-Dègue	1467	Intervention	63	37	37
16	Kouéré	1502	Control	65	49	52
17	Kossara	1547	Intervention	67	23	23
18	Kirbina	1622	Control	70	31	31
19	Gouindougouba	1772	Control	76	44	45
20	Zédougou	2422	Intervention	104	49	51
21	Létiéfesso	2442	Control	105	44	44
22	Tangora	2599	Control	112	42	43
23	Nafona1	2609	Intervention	112	34	38
24	Siniéna	4970	Intervention	214	88	91
	Total	**34937**		**1502**	**895**	**915**
	Median (IQR)	**1055 (813-1660)**		**45(35-71)**	**36(30-42)**	**37(30-43)**

[a]Villages are ranked by increasing population size
[b]Based on 2006 General population census data [INSD, 2009, [34]]
[c]Calculated from a crude birth rate of 43 per 1000 for Banfora region [INSD, 2011, [94]]

The details of the sample size calculations are provided in Table 14 and accounted for the cluster-design of the study (between-cluster coefficient of 0.30 for diarrhoea) and the usual

statistical assumptions (α=0.05, 1-β=0.80 and m=35). We found that of total of 96 clusters (48 per arm) would be needed to show the expected difference for diarrhoea and 24 clusters for the EBF-rate. Because the EBF-trial was a multicentre study (4 countries), it was estimated that 24 clusters (12 per arm) should be selected and randomized in each country. The EBF-rate was going to be obtained by country. A total of 840 newborns were expected to be included per country.

Table 14**: Sample size estimation for the main EBF-trial.**

		Increase in EBF-rate from 0.20 to 0.40	Decrease in diarrhoea prevalence from 0.12 to 0.08
Proportion in the intervention group	P1	0.4	0.08
Proportion in the control group	P2	0.2	0.12
Percentage point for α-error= 0.05	z1	1.96	1.96
Percentage point for β-error= 0.20	z2	1.28	1.28
Number of individuals in each community	m	35	35
Coefficient of variation of proportions among communities in each group	k	0.4	0.3
Average of P1 and P2	P	0.3	0.1
Number of communities needed per arm	C	12	48

In Burkina Faso and for the objectives of this thesis, additional calculations were done based on the existing cohort. Because perinatal, neonatal and infant deaths are all events that are even rarer than diarrhoea, 24 clusters are insufficient to measure the impact of the intervention on any of these outcomes. However, as we report here the findings of a cohort study, we estimated the precision that would be obtained from the expected sample of 840 newborns to be enrolled using a cluster-design, for each of the 3 cohort study outcomes. Based on previous estimates of PNMR, NMR and IMR in 2003 in Burkina Faso[28] and a confidence level of 0.95, the expected sample size (n=840) would measure the perinatal, neonatal and infant mortality rates with an absolute precision of 1%, 1.2% and 2%, respectively.

Participants' selection and enrolment procedures

All pregnant women in villages selected and randomized to the main EBF-trial were approached for study participation. A distinction was drawn between eligibility for the intervention and that for data collection. Indeed, because the EBF study was a cluster-randomized trial, all pregnant or lactating women in the intervention clusters were offered the intervention, irrespective of their participation in the study. However, a sampling frame was established for eligibility for data collection due to the following reasons:

i) Most of the villages would exceed the anticipated size of 35 annual live births per 1000 given the crude birth rate in the study area (43/1000).
ii) We sought to protect the study against any selection bias (seasonal or due to community-workers)
iii) We needed also to protect the peer-supporters and the DCs from work overload.

Thus, the rule was to include a maximum of 4 pregnant women per month per village as the recruitment would last one year. This procedure was used in 19 of the 24 villages. In one village (Siniéna) with a population of nearly 5000, we sampled 8 women per month instead of 4 (Table 13). Each month, a complete list of all eligible women to be enrolled was made available by community-workers recruited for the study. A community-meeting was scheduled with all the potential participants through community-leaders and community-workers. Eligible women or their representatives were invited to take part in the sampling procedure that was public under the supervision of the community-leader, the study team (DCs and their supervisors) and independent community-members. To make the procedure more understandable to all eligible women, we relied on a lottery method using sticks and a pot of sand. There were two types of sticks: 4 long ones (meaning the woman was included) and enough short ones to cover the number of women listed for a specific month in a specific village. All the sticks were planted in the pot of sand at the same height so that no one would know which ones were long or short. Eligible women or their representatives were then asked to come forward in random order and pick one stick each. The sampling was performed without replacement. We did not include in the sampling list women who at the first contact had declined any interaction with the study team.

Once selected for data collection, women were contacted by the DCs through the community-workers, confirm they met all eligibility criteria and thereafter, went for a formal recruitment procedure. A woman was eligible for the study if she:

a) Lived in one of the 24 study villages
b) Had a visible pregnancy ($\geq$ 7 months of gestation)
c) Had no plans to move outside the village within 1 year
d) Had given a written and informed consent to take part to the study

We excluded from the study women:

a) With a reduced ability to cooperate for psychological/mental reasons
b) With severe illness which could prevent breastfeeding
c) planning to replacement feed the baby from start
d) With a pregnancy <7 months, in which case the DC asked for permission to come back at a later point in time

In order to ensure voluntary participation and enhance the understanding of the study procedures, a detailed information sheet translated into *Dioula* (the main local language) and approved by the Centre MURAZ's IRB in Burkina Faso (see IRB approval in appendix) was used. The information was given in the language spoken by the woman and she was given a chance to ask questions and to discuss it with her family as required by the culture in this region.

Women fulfilling all the study inclusion criteria and who agreed to participate, were administered the recruitment questionnaire (see in appendix). They were also provided further information about the study methods including how to send information about her pregnancy outcomes. After her inclusion, each study participant received a yellow card where her study ID number and names were written down to help identify her at each visit. The recruitment period lasted exactly one year from 29th May 2006 to 29th May 2007.

Training of field study personnel

Apart from the study team based in Centre MURAZ (PI, study coordinator, administrative staff), the PROMISE-EBF study recruited and trained 3 types of personnel in Burkina Faso in order to ensure field data collection. This included:

- Data collectors' supervisors (DCS): four supervisors with a relatively high educational background (A-Level +3 years) and previous experience in health research were recruited and trained by the investigators. Two of the supervisors (one sociologist and a senior midwife) were in charge of the peer-supporters' supervision. The other two (one epidemiologist and a senior nurse) were in charge of formal DCs'supervision. They all spoke *Dioula*, the main dialect in the study area. The DCS worked over two months with the study coordinator on the study methods and data collection tools prior the study implementation. One of the DCS was permanently in field with the DCs and the second spent 6 months in field at the start of the study to perform supervisory field visits.
- Data collectors (DCs): seven DCs were recruited from the study area, who were fluent in at least two of main local languages (*Dioula* and *Gouin/Karaboro*) in this area and with prior experience of working with rural communities. They underwent a one-week training workshop on the objectives and overall methodology of the study and were extensively trained about each of the data collection tools (questionnaires, consent form, verbal autopsy form) to be used during the study. To improve the quality of the training and make sure the same wording would be used by all DCs in field, we relied on an experienced translator who actively participated in the training and translated each question of each questionnaire in *Dioula*. After this phase of training, DCs went for one more week of training in the field with the objective of assessing each data collection tool and validating all the questionnaires. After this second phase, the best 5 DCs were selected by the study team and the two remaining DCs were put on a reserve list. The DCs lived in the 3 administrative areas of Banfora Health District, in complete immersion in the communities throughout the study period.
- The community-workers: In order for the study team to identify all the pregnant women in each village and to monitor the pregnancy outcomes, we recruited 2-4 women in each village to participate actively in the data collection. These women were initially selected by their own communities based on their own criteria and the study team performed the final selection based on motivation and ability to write. The number of community-workers recruited was proportional to the size of the population of their village (2-4) with an average of two women per village. Two types of community-workers were recruited according to the village arm:

- In the control villages, we hired "recruiters" whose role was mainly to identify pregnant women and provide us with timely information on pregnancy outcomes.
- In intervention villages, the initial plan was to recruit both "recruiters" and peer-supporters (PS). The role of the "recruiters" was the same as in control arm. The PS had a specific role in providing individual peer-counselling to all pregnant or lactating women of the intervention villages. The intervention in the EBF-trial in Burkina Faso consisted of 7 individual counselling sessions on exclusive breastfeeding, one in the antenatal period, and the others at week 1, 2, 4, 8, 16 and 20, respectively, after birth. The counselling sessions were administered during home-visits. However, due to resource constraints and to the practical difficulty of having both PC and "recruiters" in all the intervention villages, it was agreed that the PS recruited by the study team to implement the intervention package, should also serve as "recruiters" meaning they would have to identify all pregnant women in their village and provide the study team with all relevant information on each study participant.
- Two different training workshops were organised, one for PS and another for "recruiters". While the "recruiters" workshop only focused on their role in data collection and lasted two days, the training of PS took one week with the added topics on the intervention package that focused on promotion of exclusive breastfeeding. These two trainings were provided by different teams in order to avoid any confusion about their roles. For the purpose of this thesis we will only focus on the roles in data collection of both "recruiters" (control arm) and PS (intervention arm) that were:
  a) To identify all pregnant women in the village by a weekly round of all households and approach them for initial information about the study.
  b) To send to the study team on a monthly-basis the names of all identified pregnant women.
  c) To assist the team in communication with the local population to schedule a monthly meeting for the sampling of eligible participants.
  d) To make an appointment for the DCs and assist them in identifying the houses of the women who were sampled for data collection at the first contact only.
  e) To inform study participants of the DCs'visit in the case of a missed visit and to seek a new appointment if applicable.
  f) To provide the study team (DCs) with relevant information about the study participants, especially on pregnancy outcomes (stillbirth, live birth), infant and maternal deaths, or migration of mother-infant pairs outside the study area.
  g) To note this information in a written statement (at least the date of occurrence and the ID number) and to transfer it within 2 days to the study team through the local health facility.
  h) It was clearly stated during the training that no "recruiter" or PS should attend any interview between the data collector and a study participant.

These tasks were extensively discussed during the training of the recruiters/PS and they were advised on the best ways to achieve what they were recruited for. The trainers made sure each community-worker had understood all her tasks, using her mother tongue when needed. The second day of training was used to show to the community-workers how to fill out the forms (simple data collection forms) namely, which form (different colours) to use and when (new pregnant woman in yellow, birth in rose, death in blue, migration in green). The recommended format of the date (dd/mm/yyyy) was shown and they were instructed to always write the participant names in capital letters and to write carefully her study ID number.
Although the overall educational background of eligible community-workers was low, the study team only recruited those with at least basic writing skills (names and dates) in French or *Dioula*. They were strongly advised to collaborate closely with the health personnel of the local health facility that was informed on the study procedures.

Data collection and participants' follow-up

Data collection was performed during household visits by formal DCs. In the initial main EBF-trial, each study participant was scheduled for 5 data collection visits: one at recruitment and 4 after birth, at weeks 3, 6, 12 and 24. These visits during the first half of infancy were performed at ±7 days of the scheduled exact dates. To achieve the objective of this thesis, two additional follow-up visits were conducted at day-7 and at 12 months, respectively. These additional visits aimed to collect data on perinatal deaths (day-7) and infant deaths (12 months). A summary of the study timeline is outlined in Figure 11.

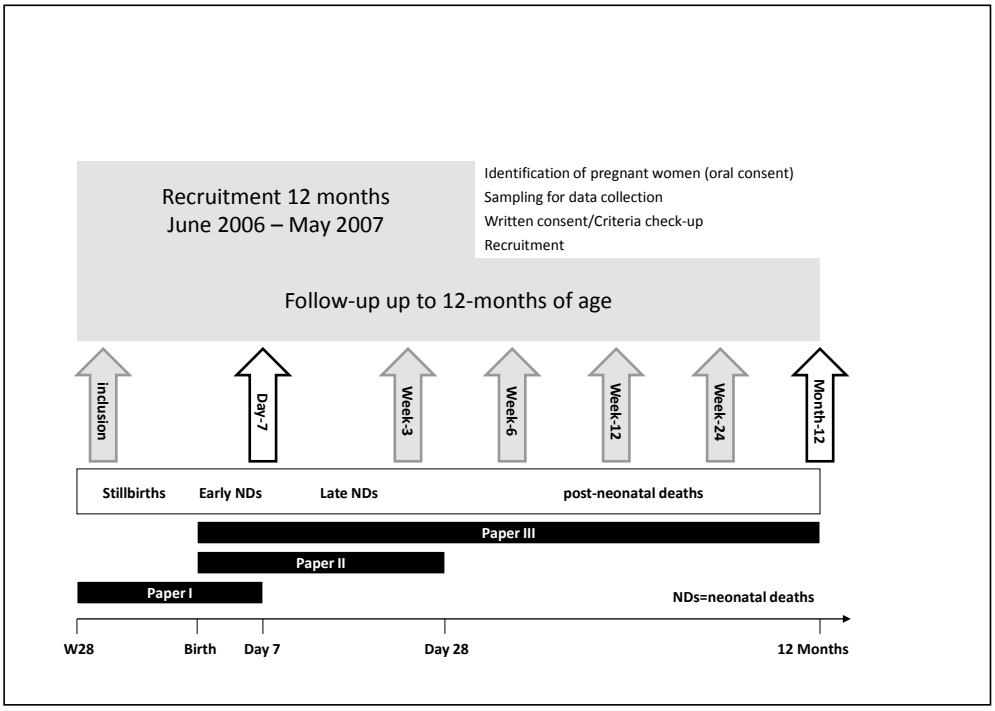

Figure 11: ***Recruitment and follow-up schedule per study paper***

The criteria for study termination were, consent withdrawal, infant or maternal deaths and loss to follow-up defined as 3 consecutive missed visits. A missed visit was defined as 3 unsuccessful attempts on different dates within one week of a scheduled visit to interview the mother.

At each visit, a questionnaire was administered to the mother and its content varied with the pregnancy outcome and the child's age. Globally the type of information collected per visit was as follows:

- During the recruitment visit, we administered the recruitment questionnaire to collect background information on the mother and her household. Data collected included geographical and personal information (GPS coordinates, village name, mother's age, parity, education, ethnicity, marital status, etc.), socioeconomic status of the household (employment, income, possession of animals, household assets, crops, etc.), medical history of the mother (previous child death including perinatal death, history of breast problems, experience of breastfeeding) and antenatal use of health services (ANC visit, use of bednet, malaria prevention, iron and folic acid supplementation, information about HIV/VCT, etc.).
- During the day-7 and the week-3 visit, the questionnaire included items about pregnancy outcomes (stillbirths, early neonatal death), the circumstances of births (date, place, birth attendants, complications at delivery, treatments received, referral to any health-facility, etc.), feeding history (time to initiation of breastfeeding, actual feeding patterns), morbidity (diarrhoea and pneumonia), immunization (BCG, oral polio) and anthropometry (weight and length).
- From week-3 until 12 months, we collected information on children's vital status, feeding patterns, morbidity and hospitalizations, immunizations and growth (weight and length). Maternal weight was measured during the week-6 postpartum visit and her height taken from the ANC card whenever available.
- In case of a perinatal or infant death, a WHO standard verbal autopsy[103] was administered to the mother/guardian. The topics covered were general information about the deceased (date of death, gender, place of death, age at death), description of the circumstances of death (disease, care seeking behaviour, treatments), probable causes of death (a narrative from the mother to be analysed later by paediatricians), feeding patterns before death (EBF, liquids, solids), immunization status at death. The time to administration of the verbal autopsy was dependant on the pregnancy outcome. Women with stillbirths were scheduled to be interviewed whenever possible within 12 weeks after their loss. Women with infant deaths were interviewed within the next 6 weeks. This difference of schedule was due to cultural considerations (mourning period) in the study area. This aspect impacted on the completeness of our verbal autopsy forms. While we managed to get detailed information on the circumstances of all infant deaths, we were only able to collect a few items of information for stillbirths (outcome and the date of occurrence mainly).

Data for the EBF-study were collected using handheld computers which are also known as personal digital assistants (PDAs). However, during the first 2 months of the study, we used both paper-based questionnaires and PDAs. Indeed it was very important for our DCs to

familiarize themselves with the PDAs and our team needed to assess under field conditions the validity, stability and user-friendliness of the PDAs before we would rely only on these electronic questionnaires. Some troubles occurred with the PDAs, mainly due to the hot climate and the initial instability of the software. So we encouraged our DCs to always have a ready-to-use paper-based questionnaire when they were going for an interview.

When using the paper-based questionnaire, the DC had to tick the mother's answers while he moved through the questionnaire. He was instructed to always cross check each questionnaire before leaving a study participant. He would then later (< 48hours) enter all the information from the paper-based questionnaire in the PDA using the electronic questionnaire and its attached electronic pen to tick the answers. In the case of direct electronic data capture using the PDA, the DC would go through the same procedure as with the paper-based questionnaire.

The GPS coordinates were taken using an Etrex® GPS and an experienced health geographer trained our DCs on its use.

Maternal weight was measured to the nearest 0.1 kg using a standard SECA® 872 scale. Infant weight was recorded with the same precision (0.1 kg) using the mother-infant function of the SECA® 872 scale. Infant length was measured to the nearest 0.5 cm with a standard SECA® 210 infantometer.

Ethical considerations

Ethical clearance was sought from the institutional review board (IRB) of Centre MURAZ in Burkina Faso (N°013/2005/CE-CM) and from the Western Regional Committee for Medical and Health Research Ethics in Norway (No 05/8197).
Prior the study implementation we sought community-consent in each selected village through the community-representatives.

An individual consent form information sheet was written in French and later translated from French to *Dioula,* and then back-translated by two independent translators as requested by the IRB's guidelines. The consent was obtained in the mother's local language, since all the DCs spoke the local dialects. The information sheet emphasised the voluntary nature of participation and the possibility of withdrawing from the study at any time if a woman wished to do so and without prejudice.

Benefits of study participation were stated and were: the possibility to receive individual peer-counselling on EBF for women from intervention clusters. Furthermore, all the mother-infant pairs enrolled in the study received free medications and care throughout the study period, if they were sick and visited the local health facilities. Indeed, Centre MURAZ made available commonly used medicines such as antimalarials, antibiotics, rehydration salts and basic surgical material for treatment of breast abscesses. Mothers and infants with serious illness that could interfere with infant feeding were referred to Banfora Regional Referral Hospital and the project paid all the related-fees (hospitalization, lab tests, and medicines).

Many mothers also appreciated that their children were regularly weighed by DCs as many did not attend the regular well-baby clinics.

There was actually few risks linked to mothers' participation in the EBF study. Among the foreseen risks were the feeling of "intrusion" that might arise from frequent DCs' home visits, the discomfort related to some verbal autopsy questions and the average time needed to fill a questionnaire. To minimise these risks, we sought for a household visit permission that was signed by the head of each household and women were told about the topics that would be covered during data collection. Recruitment interviews were conducted at the mother's convenience and the average time needed at each follow-up interview (45 min) was clearly stated to each study participant.

Field supervisions and prevention of bias

We conducted weekly field supervisions during the first 3 months of data collection. The supervisions became monthly from the fourth month up to the end of the study. The DCs' supervisors took an active part in the training of the DCs. Once the study started, they performed 3 types of supervisions:
- Direct supervisions where supervisors were in the field with the DCs while they conducted interviews. Supervisors observed and listened to all the questions and the answers of the mothers. They took notes and later discussed with the DCs strengths and weaknesses observed during interviews, and ways to improve their performance.
- Assessment supervisions: supervisors re-interviewed a random sample of participants (10-30%) already seen (or sometimes to be seen during the same week by the DCs). They would then compare their data, to that collected by the DC for the same participant.
- Data cross-checking: the supervisor in collaboration with the data manager picked a random sample of questionnaires (20-50%) already completed by a DC and went through them to check for consistency between answers, missing items, typing errors or invalid answers, etc. Thereafter, they produced a set of queries that were sent back to the field during the next supervision and DCs filled query forms and sent them back to the study team. All queries and their answers were kept in a separate binder that was used during the data cleaning procedure. In case of significant discrepancies between the two questionnaires, that of the supervisor was used to validate the data on the condition that the time between the two interviews met the study procedures (±7 days).

Some preventive measures were taken at different phases of study implementation to reduce potential biases and to improve the overall data quality of the study. These included:

- The randomization of study villages by an independent researcher outside the country.
- The sampling frame for data collection which could prevent the selection bias from the community-workers recruited by the study team.
- The training of community-workers on basic forms to take note in real time of pregnancy outcomes (participants' ID, date of occurrence) and thus, provide the team with timely information on dates of birth or death even for home deliveries.
- The training and refresher training of the DCs on anthropometry (child weight and length) throughout the study (5 times) in order to enhance precision and validity of anthropometric data. Similar training was also provided for verbal autopsy.

- The DCs' ability to speak the local dialects and their complete immersion in the study villages where they lived throughout the study, should have reduced misunderstanding of maternal answers during interviews and also improved cooperation with study participants through a better knowledge of local cultures.
- The supervision team established a reliable and updated tracking log form which the study team could use to monitor in real time what was happening on the ground and remind data collectors about pending visits when the interview deadline was approaching. We also set up a phone fleet which allowed easy communication between the DCs and their supervisors.

Data management

The data management Centre at Centre MURAZ (Centre de Calcul) assured the overall management of the EBF-trial data in Burkina Faso. Synchronization between PDAs and the central server was done on a weekly basis and a back-up system was available on 3different hard drives kept physically apart. The data manager was actively involved in the data quality control and later in the exportation of datasets and the data cleaning process.

Data entry and cleaning

Standard operating procedures (SOPs) for electronic and physical (paper) data capture were written and used by DCs during the study. They specified when and how to use both PDAs and paper-based questionnaires. All data collected on paper-forms were entered on the electronic form within a maximum of 48 hours of their collection. By the end of the study, a complete electronic dataset in the Epihandy software was available and this was an advantage of using the PDAs. A limitation of early Epihandy versions was the impossibility to edit the data and make necessary corrections in case of erroneous data entry. To deal with this, we created an excel sheet and reported all the queries and their answers in real time.

By the end of the study, the Epihandy updates had improved its performance and we were able to start the data cleaning procedures based on the original datasets exported from this software to SPSS 15 using a syntax file. The entire data cleaning procedure was performed in Stata 10.1 (www.stata.com) after transferring the SPSS file (.sav) into a Stata (.dta) file using Stat transfer 8.2. In order to document all the data cleaning procedures as recommended by good clinical practice guidelines, we used two types of do-files in Stata:

- The first type (check.do) aimed at identifying the errors, gaps, inconsistencies for each of 465 variables of the recruitment questionnaire, and also that of other follow-up questionnaires (week 3 to 12 months) and the verbal autopsy forms.
- The second type (clean.do) aimed at making the required changes after further checks with source documents from Centre MURAZ that included the tracking log forms, the copy books used daily in field by each data collector, the numerous field supervision reports, the paper-based or the electronic original questionnaires but also the forms filled by the community-workers. This job required over 8 months of full time work.

The cleaned datasets were named and locked definitively in the central dataset server in Centre MURAZ.

Statistical analysis

Data were analysed with STATA 11/SE (Statcorp, College Station, Texas, USA).

We computed descriptive statistics for both continuous (means, median, inter-quartiles range) and discrete (proportions, frequencies) variables of interest. Categorical variables were analysed using Pearson chi-squared tests, correcting for the cluster-design of the EBF-trial.

We generated a relative wealth index as a proxy for socioeconomic status based on data collected during recruitment on housing material (walls, floor, window and roof) and household assets such as possession of the following items: car/truck, motorcycle/scooter, bicycle, mobile phone/telephone, plough and chart. The index was constructed using principal component analysis[104] and classes were obtained by dividing the index into quintiles.

In paper I, we calculated SBR, ENMR and PNMR and expressed them per 1000 births. Because of the potential for misclassification of stillbirths in this study and the small number of early neonatal deaths, we investigated risk factors for perinatal death including all births. Binomial regression with generalized estimating equations (GEE) to adjust for village clustering was used to calculate risk ratio (RR) estimates[105] and their 95% confidence intervals (CI). Confounding variables were screened by measuring their effects on crude RR estimates (post-estimation method) and interactions were assessed by stratified analyses for categorical variables of interest (Mantel-Haenzel method). Multivariable regressions using GEE to account for the cluster-design of the EBF-study, included covariates associated with risk of perinatal death in univariable analyses ($p<0.10$) and those reported in the literature.

In paper II, we calculated NMR as the risk of neonatal death and expressed it per 1000 live births. We assessed between-cluster variation in NMR using a likelihood ratio test with random-effects logistic regression where the cluster variable was set a random effect. The associations of maternal and infant baseline variables with odds of neonatal death were measured using logistic regression with random-effects model to account for the cluster sampling of the EBF-study.[106, 107] We thus obtained crude odds ratios (OR) and their corresponding 95% CI. In order to reduce the potential for reverse causality, the analyses of the association between feeding covariates (EBF-status) and risk of neonatal death, were restricted only to singleton births who survived the first week. Multivariable regression models were built using the Mosley and Chen framework for risk factors analysis of child survival in developing countries.[108] This framework distinguishes 3 levels of factors which are distal (maternal education and wealth index, polygyny), intermediate (parity, distance to health facility, ANC visits, place of birth, newborn sex, twinship) and proximal (infections,

feeding patterns, trauma). Only predictors associated ($p<0.05$) with the odds of neonatal death after confounders were taken into account, were retained.

In paper III, we calculated IMR both as a risk (probability of death by 12 months of age expressed per 1000 live births) and a rate (Kaplan-Meier method expressed per 1000 person-years of observation). The survival analysis set infant death as the failure event and time until death, loss to follow-up or exit time (365.25 days) as the time-dependent event. Between-cluster variation in mortality rates was assessed using a likelihood ratio test with random-effects Cox regression where the variable cluster was set as a random effect. The crude associations of maternal and infant exposures with infant death rates were measured for 3 ages ranges (first half of infancy, post-neonatal period and overall infancy) using Cox univariable regressions that fitted a Gamma shared frailty model (option *shared* in Stata) to account for the cluster-design of the EBF-study.[107] Thus, we obtained unadjusted hazard ratios (HR) and their 95% CI with robust standard errors. Only variables with a $p<0.25$ in Wald-statistic tests were included in further exploration. Confounders were screened through post-estimation methods (likelihood ratio tests) and interactions were estimated with the Mantel-Haenzel methods for Cox regression (command *stmh* in Stata). Multivariable Cox regression was built from Mosley and Chen framework of risk factors analysis for child survival in developing countries[108]. All exposures with adjusted HR > 1 at a significance level of $p<0.05$ were considered as risk factors for infant death.

In paper II and paper III, probable causes of infant deaths occurring within 6 months of age were assigned using the mothers' narrative on the verbal autopsy forms. Two independent physicians reviewed the verbal autopsies and used a hierarchical grouping adapted from the Child Health Epidemiology Reference Group Classification[71] and ICD-10[44] to assign probable causes of death. Multiple causes were allowed, although only the primary cause of death is reported here. The opinion of a senior paediatrician was sought in cases of disagreement between the two physicians.

In an additional analysis we examined the association of stillbirth, perinatal, neonatal and infant death risks with the study arm as the main exposure using two methods. The first was based on cluster-level summaries of the data (command *collapse* in Stata) using Student and Wilcoxon-Ranksum tests, respectively, as recommended by Haynes and Colleagues[106] for cluster-randomized trials with $n<15$ in each arm. The second method used logistic regression with a random-effects model to account for the cluster design of the EBF-study. To account for likely baseline imbalances between the two study arms, the multivariable model in this analysis adjusted for distance to nearest health facility and maternal use of bednet. This analysis was also repeated using Cox regression.

In Paper IV, we re-estimated the average annual rates of decline in U5MR for Burkina Faso as reported in Rajaratnam and Colleagues' paper[10] for the period 2000 to 2010 and compared it with the most recent nationally representative data available for Burkina Faso at the time of their publication.[34] We also looked at the data used by the authors for their estimation of U5MR in 2010. We calculated estimates of U5MR for the EBF-cohort.

A summary of the study methods used in each paper is presented in Table 15.

Table 15: **Summary of the study methods reported in this thesis by paper.**

Paper	Design	Sample size	Statistical methods
I	Prospective cohort study with a follow-up of enrolled pregnant women until 7 days after births. Data collection at inclusion and by day-7.	n=915	Calculation of SBR, ENMR, PNMR using robust standard errors to account for the cluster design of the main PROMISE-EBF trial. Binomial regressions with generalized estimating equations (GEE) were used to identify risk factors for perinatal death.
II	Prospective cohort study with a follow-up of live births until 6 weeks of age. Data collection at day-7, week-3 and 6.	n=864	Calculation of NMR using robust variance to account for the cluster design of the main PROMISE-EBF trial. Logistic regressions fitting random-effect models were used to assess between cluster variations of NMR and identify predictors of neonatal death.
III	Prospective cohort study with a follow-up of live births until 12 months of age. Data collection at day-7, week 3, 6, 12, 24 and at 12 months.	n=866	Calculation of IMR using robust standard errors to account for the cluster-design of the main PROMISE-EBF trial. Estimation of different cumulative risks of death (Kaplan-Meier curve) and mortality rates until 1 year using a survival analysis. Cox regressions adjusting for clustering were used to estimate the association between rate of death and several maternal and infant baseline exposures. Multivariable Cox regressions with Gamma shared frailty models were used to identify risk factors for infant death.
IV	A critical review (comment) of findings from modelled estimates, providing child mortality rates for 2010 in Burkina Faso.	NA	Analysis of the reported child mortality estimates and comparison of the origin and completeness of data used for different estimations of U5MR. Inconsistencies between the reported low estimates, the actual health interventions ongoing in Burkina and the recently observed high infant mortality in a rural area of a largely rural country

SBR=Stillbirth rate ENMR=Early neonatal mortality rate PNMR=Perinatal mortality rate NNM=Neonatal mortality rate IMR=Infant mortality rate
NA=Not applicable

Summary of findings

Study profile

Over a period of one year (May 2006 to May 2007), a total of 1162 pregnant women were identified in the 24 villages and all were approached for study participation. Overall, 895 were included in the study and the pregnancy outcomes resulted in 49 stillbirths and 866 live births (of which 846 singletons and 20 twin pairs). The study flow chart is presented in Figure 12.

Baseline characteristics of the cohort

The mean age (± SD) of women at recruitment was 26 (± 6) years with most women aged 20-35 years (73%). About 95% of women were married and 48% lived in polygynous households. Polygyny was higher among women without any formal education (51%) compared to those who have had primary or secondary education (39%, p=0.017). Only 17% of women were nulliparous and the median parity among multiparae was 3. Over three quarters (80%) had never attended school in this cohort. Medical history of mothers revealed that 12% of multiparous mothers have experienced previous perinatal death and almost 60% have had a previous child death.
At enrolment, the median gestational age as reported by mothers was of 8 months with a range from 7 to 9 months. Overall, 642 women (72%) have attended ANC at enrolment and only 18% had >2 ANC visits. The probability of having an ANC visit was decreasing with parity (chi-2 of trend, p<0.001) ranging from 82% for nulliparous to 62% among women ≥5 previous births.

The median time from enrolment to birth was 52 days. Over half of women (54%) gave birth at home. About one third (36%) delivered in a health facility while 9% delivered in a TBA's home. The proportion of health facility-delivery decreased with parity ranging from 51% for nulliparous to 29% for multiparae with ≥5 previous births (chi-2 of trend, p=0.001). The probability of a health-facility delivery also decreased with increasing distance from the village to the nearest health facility (from 54% in villages within 5 km of a facility, to 23% for villages located 6-10 km from a facility, to 21% for villages situated over 10 km from the nearest health facility, p=0.011). The proportion of women with skilled attendant at birth was higher among mothers living in monogamous households (42%) compared to their peers in polygynous households (33%, p=0.027).

In the group of women with a live birth (n=846), 17 (2%) reported a complicated labour (obstructed labour, severe haemorrhage or placental retention) and only 1% had a caesarean-section. Of the 866 live births, 51% were boys and 52% were born during the rainy season (from May to October). Only 295 babies had their birth weight recorded in the ANC card with a mean (± SD) of 2971g (±527) and 14% of newborns in this group had a low birth weight (< 2500 g).

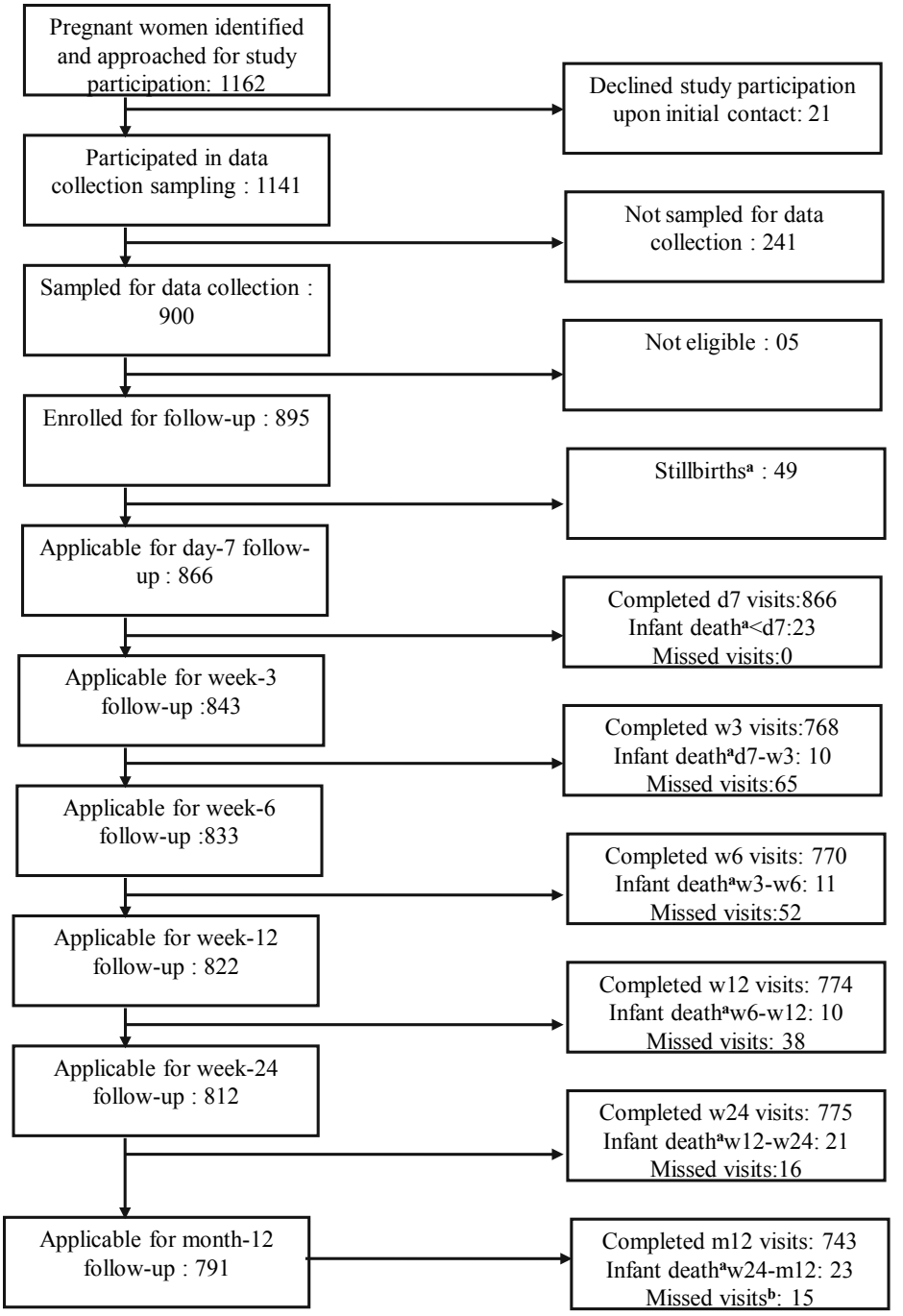

Figure 12: Study profile

Table 16: **Baseline characteristics (by arm and overall) of 895 women and their newborns enrolled in the EBF-study in Banfora Health District.**

Variables	Control N=442 (%)	Intervention N=453 (%)	Total cohort n=895 (%)
Distance from village to the nearest health facility			
- ≤5 km	252 (57.0)	177 (39.0)	429 (48)
- >5 km	190 (43.0)	276 (61.0)	466 (52)
Maternal age (years)			
- <20	75 (17.0)	73 (16.1)	148 (16.5)
- 20-35	319 (72.2)	337 (74.4)	656 (73.3)
- >35	48 (10.8)	43 (9.5)	91 (10.2)
Parity			
- 0	73 (16.5)	80 (17.7)	153 (17.1)
- 1	68 (15.4)	78 (17.2)	146 (16.3)
- 2-4	207 (46.8)	205 (45.2)	412 (46.0)
- ≥ 5	94 (21.3)	90 (19.9)	184 (20.6)
Mother lives in a polygynous household			
- Yes	216 (49.0)	217 (48.0)	433 (48.0)
- No	226 (51.0)	236 (52.0)	462 (52.0)
Maternal education			
- None	354 (80.1)	366 (80.8)	720 (80.4)
- Literacy/primary school	54 (12.2)	66 (14.6)	120 (13.4)
- Secondary school	34 (07.7)	21 (04.6)	55 (06.2)
Socioeconomic status (based on household assets)[a]			
- Quintile 1 (most poor)	89 (20.1)	102 (22.5)	191 (21.3)
- Quintile 2	76 (17.2)	92 (20.3)	168 (18.8)
- Quintile 3	85 (19.2)	103 (22.7)	188 (21.0)
- Quintile 4	97 (21.9)	83 (18.3)	180 (20.1)
- Quintile 5 (least poor)	95 (21.5)	73 (16.1)	168 (18.8)
Maternal history of child death[b]			
- Yes	220 (60.0)	216 (58.0)	436 (59.0)
- No	149 (40.0)	157 (42.0)	306 (41.0)
Maternal history of perinatal death[b]			
- Yes	47 (13.0)	41 (11.0)	88 (12.0)
- No	322 (87.0)	332 (89.0)	654 (88.0)
Mother sleeps under bednet			
- Yes	147 (33.3)	194 (42.8)	341 (38.1)
- No	295 (66.7)	259 (57.2)	554 (61.9)
Antenatal care visits			
- None	126 (28.5)	127 (28.0)	253 (28.3)
- 1-2	240 (54.3)	241 (53.2)	481 (53.7)
- > 2	76 (17.2)	85 (18.8)	161 (18.0)
Place of birth			
- Health facility	156 (35.3)	163 (36.0)	319 (35.6)
- TBA's place	52 (11.8)	25 (05.5)	77 (08.6)
- Home/other places	234 (52.9)	265 (58.5)	499 (55.8)
Newborn sex (for live births only)	N=431	N=435	N=866
- Boy	215 (49.9)	223 (51.3)	438 (50.6)
- Girl	216 (50.1)	212 (48.7)	428 (49.4)
Low birth weight (<2500g)[c]	N=135	N=160	N=295
- Yes	13 (10.0)	28 (18.0)	41 (14.0)
- No	122 (90.0)	132 (82.0)	254 (86.0)

[a]A relative wealth index as a proxy for socio-economic status was based on data collected at recruitment on housing material (walls, floor, windows, roof), and household assets such as possession of the following items: car/truck, motorcycle/scooter, bicycle, mobile phone/telephone, plough and chart. The index was constructed using principal component analysis.
[b]Restricted to multiparous mothers (N=742) [c]Data available for a subsample of 295 newborns

In order to measure the association of the study outcomes (stillbirth, neonatal and infant death risks) with one exposure not initially explored (study arm), we examined the baseline data for the two study arms (Table 16). The only variables that seemed imbalanced were the proportion of mothers sleeping under a net that was higher in the intervention group (43% versus 33%), the proportion of mothers residing >5 km from the nearest health facility, which was higher in the intervention group (61% versus 43%), and the proportion of newborns (in a subgroup of N=295) with a low birth weight that was higher in the intervention group (18% versus 10%).

Perinatal mortality (Paper I)

There were a total of 915 births and 72 perinatal deaths occurred throughout the study. This included 49 stillbirths and 23 early neonatal deaths (ENDs), a ratio of stillbirths to ENDs of 2.1:1. Overall, the PNMR was 79 (95% CI: 59-99) and the SBR was 54 (95% CI: 38-69) per 1000 births. The ENMR was 27 (95% CI: 9-44) per 1000 live births.

Stillbirths

There was no stillbirth among twin births. Observed SBR ranged from 0 to 151 per 1000 births , although analyses found no evidence that variations in observed risk of stillbirth across villages were higher than might be expected by chance (LR test, p=0.49).

The proportion of stillbirths was the same among facility births (5.5%) and home deliveries (5.3%). No data on the sex or weight of the fetal losses were recorded in the ANC cards, not even among mothers who delivered in health facilities.

Early neonatal deaths

The distribution of early neonatal deaths by village showed that two villages (Nafona1 and Karfiguéla), recorded very high ENMR (Table 2, paper I). Both village houses a health facility and the proportions of twins and facility-delivery were of 22% and 45% for Nafona1, and 7% and 52% for Karfiguéla. Eight of the deaths were among twins, a specific ENMR of 200 per 1000 live births. ENMR was 25 for boys and 28 for girls, per 1000 live births. Six of the newborns (26%) died within 24h of their births and the median age among babies who experienced an early neonatal death was 3 days. Almost all these deaths (91%) occurred at home.

Risk factors for perinatal death (Paper I)

Of variables explored in univariable analyses, young age of the mother (RR=2.7, 95% CI:1.0-6.9) , nulliparity (RR=2.2, 95% CI:1.2-3.9), a birth during the dry season (RR=2.0, 95% CI:1.3-3.2) and twin births (RR=2.8, 95% CI:1.4-5.3), were found to be associated with higher risk of perinatal death. Neither living at a short (<5 km) distance to a health facility (RR=1.2, 95% CI:0.8-2.0), nor a health facility delivery (RR=1.0, 95%CI:0.6-1.6) , provided any evidence of a lower perinatal death risk.
Multivariable analyses adjusting for potential confounders identified low parity, a birth in the dry season and twins as factors associated with an increased risk of perinatal death.

Nulliparous carried almost three times (RR=2.9, 95% CI: 1.6-5.0) higher risk of perinatal death compared to mothers with 2-4 previous births. Primiparae also showed a doubling (RR=2.2, 95% CI:1.2-3.9) in the perinatal death risk compared to the same group of multiparous mothers. Infants born during the dry season carried a two-fold (RR=2.1, 95% CI:1.3-3.3) higher risk of perinatal death as compared to their peers born during the rainy season. Twins had a particularly high risk of perinatal death, as high as 4 times (RR=4.0, 95% CI:2.3-6.9) that of singletons in this cohort. Adjusting for potential confounders did not provide any evidence of a lower risk of perinatal death for a health facility delivery as compared to deliveries in other places (RR=1.0, 95% CI:0.4-2.3).

Early follow-up (Paper II)

A total of 864 live births were included in the analysis of paper II. Data on feeding patterns were only collected among singleton births and showed that 90% of newborns who survived the first 24h received colostrum. Breastfeeding was initiated within 1 hour of birth for 32 mothers (4%) whereas a further 371 (49%) did so within 12 hours of birth. In the group of singleton births who survived up to week-3 visit (±7 days), the proportion of newborns reported by their mothers to be EBF was 54% (95% CI:38-69).

Among singleton births who had anthropometric data collected during the week-3 visit (n=715), 17% were wasted (95% CI:13-22), 11% were stunted (95% CI:9-13) and 16% were underweight (95% CI:13-20). Overall, 18 infants (2.5%) combined all these 3 poor anthropometric status.

By week-3 visit ((±7 days), 34% of singleton births had received BCG vaccine and 37% had received oral polio vaccine, based on records from mothers'ANC cards.

Neonatal deaths (Paper II)

Out of 864 live births, there were 40 neonatal deaths, yielding a NMR of 46 per 1000 live births (95% CI: 22-70). There were 23 early neonatal deaths, which is 57% of all neonatal deaths. Eleven of the neonatal deaths were among the 40 twins (28%) and the NMR was particularly high among twins at 289 (95% CI: 138-440) per 1000 compared with 35 (95% CI: 22-48) per 1000 for singleton births ($p<0.001$).

Neonatal deaths occurred in 20 out of 24 villages and two villages, Karfiguéla and Nafona1 appeared as outliers. Further analyses revealed that these two villages had a higher odds of low birth weight (in a subsample of N=295, OR=3.6, 95% CI: 2.0-6.3) and a higher odds of twin births (OR=5.1, 95% CI:2.0-12.8) as compared to other villages put together.

The proportion of neonatal deaths was higher in home deliveries (5.4%) as compared to facility births (3.2%, p=0.06), but did not differ between boys (4.8%) and girls (4.5%, p=0.80). Birth weight was only available for 4 of the deceased with a median of 2810g. Overall, 36 neonatal deaths (90%) occurred at home, 3 at the local health facility and one in a local healer's home. Most of newborns who experienced a neonatal death were treated by

their parents at home (83%) and only 5 children were brought to the local facility prior to death.

Predictors of neonatal death (Paper II)

Of the factors explored in univariable analyses, twin births (OR=9.7, 95% CI:4.1-23.1) and unskilled attendant at birth (OR=2.3, 95% CI:1.1-5.1), were the two variables statistically associated with increased odds of neonatal death in this cohort. Pauciparae (parity=0 or 1), residing in a shorter distance to the nearest facility and polygyny showed all, weak evidence of increased odds of neonatal death (Table 1, paper II). Neither maternal education, nor ANC visit showed any evidence of an association with the odds of neonatal death (Table 1, paper II).

Univariable analyses focusing on feeding variables and restricted to singleton births who survived the first week, found that newborns who were not given colostrum at birth, had over 3 times higher odds of neonatal death compared to their peers who received it (OR=3.5, 95% CI:1.1-11.4). Neither a delayed initiation of breastfeeding (i.e >24h, OR=1.4, 95% CI: 0.4-5.1), nor being reported not-EBF by the mother at week-3 visit (OR=0.8, 95% CI: 0.3-2.5), showed any evidence of a higher odds of neonatal death.

Multivariable analyses adjusting for potential confounders (parity, polyginy, birth attendant, twinship) found that being a nulliparous mother, living in a polygynous household and being a twin, as factors increasing significantly the odds of neonatal death in this cohort (Table 1, paper II).

Living in a polygynous household doubled (OR=2.1, 95% CI: 1.0-4.7) the odds of neonatal death in this cohort and nulliparous mothers had 4 times (OR=4.3, 95% CI:1.5-12.1) higher odds of neonatal death when compared to women with 2-4 previous births. Twin births carried particularly high odds of neonatal death, as high as 11-fold (OR=11.5, 95% CI: 4.5-29.8) that of singletons. An unskilled attendant at birth was associated with a doubling of the odds of neonatal death after controlling for other factors, although this was not statistically significant (OR=2.1, 95% CI:0.9-4.7). However, multivariable models did not provide any further evidence of an association of a shorter (<5 km) distance to health facility with increased odds of neonatal death, especially when the two villages with the highest observed NMRs were removed (OR=1.2, 95% CI: 0.5-2.7).

After controlling for polygyny status and birth attendant, newborns not given colostrum after birth, remained associated with higher odds of neonatal death compared to their peers who got it (OR=3.1, 95% CI:0.9-10.2), albeit not statistically significant (p=0.06).

Infant mortality (Paper III)

All live births (N=866) were included in the infant mortality analysis. A total of 98 deaths occurred before the age of 12 months resulting in an IMR of 113 (95% CI:89-143) per 1000 live births. The post-neonatal mortality rate was 67 (95% CI:51-88) per 1000 live births.

There were 21 infant deaths among the 40 twins, a very high IMR of 525 (95% CI:359-685) per 1000 live births. Overall, 75 infant deaths (76%) occurred during the first 6 months of life, which equal to a mortality rate of 181 (95% CI:144-227) per 1000 person-years of observation (PYO). The risk of infant death among twins who survived the first 6 months was of 136 (95% CI:58-289) per 1000 live births, much higher than that of singletons who survived the same period, 26 (95% CI:15-44) per 1000 (p=0.006).

The distribution of infant deaths (Figure 13) revealed the neonatal period as that with the highest rate of death (41% of all infant deaths and a mortality rate of 610 per 1000 PYO) though, a Kaplan-Meier plot (Figure 2, Paper III) showed high mortality rates at all ages in this cohort until 12 months, with a cumulative mortality rate of 123 per 1000 PYO by 12 months.

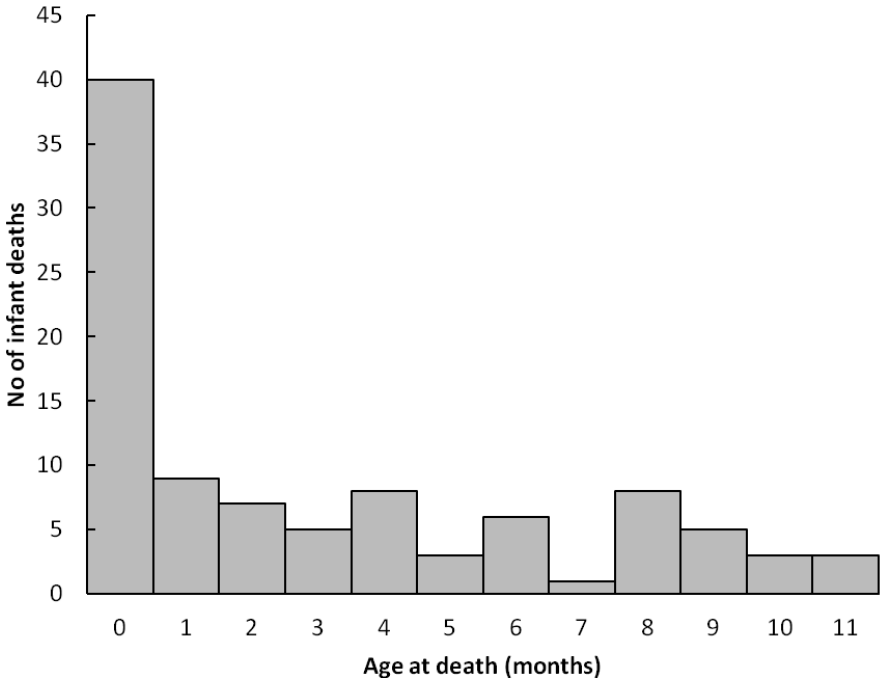

Figure 13: ***Number of infant deaths by age at death.***

The proportion of infant deaths did not differ between children living within 5 km of the nearest health facility (13%) and those living farer (9.6%, p=0.16). This proportion was the

same for boys and girls (11.3%, respectively) and it was slightly lower among infants whose mothers reported to sleep under a bednet (9.6%) compared those who did not (12.4%, p=0.32). In the group of children with anthropometric data at week-3 visit, and who died (N=48) by 12 months, 27 infants (56%) had poor z-score (<-2).

The distribution of infant deaths by village showed that 23 out of 24 villages recorded ≥ 1 death. However, we found no evidence that the variations of observed IMRs across villages were higher than might be due to chance (LR test, p=0.32).

Most of infant deaths occurred at home (90%) and during the rainy season (56%). A low proportion (21%) of infants was brought to health facility prior to death, and antimalarials (chloroquine, amodiaquine, quinine) were the most frequently prescribed drugs based on records from the child health card.

Probable causes of infant deaths during the first half of infancy (Paper III)

Probable causes of infant deaths were recorded only for children who died within the first 6 months of life. Of the 75 infant deaths that occurred in this period, infections (26 cases) and preterm births complications (17 cases) were the most common probable causes of death, but their proportions varied with age at death (Table3, Paper III) .The probable causes of death could not be identified for 26 infants, mainly due to missing narrative history of death from mothers.

Risk factors for infant death (Paper III)

Analyses were conducted for 3 age ranges (0 to 6 months, 1 to 12 months and 0 to 12 months) corresponding to the first half of infancy, the postneonatal period and the overall infancy, respectively.

During the first half of infancy, multivariable analyses found children born into polygynous households (HR=2.4, 95% CI:1.3-4.3), those born to a mother with previous child death (HR=1.5, 95% CI:1.0-2.7), boys (HR=1.8, 95% CI:1.0-3.1) and twin births (HR=10.6, 95% CI:5.4-20.8) as factors associated with higher infant death rate in this cohort (Table 5, paper III).

In the postneonatal period, multivariable analyses identified polygyny (HR=2.0, 95% CI:1.1-3.6), low anthropometric z-score at week-3 visit (HR=3.3, 95% CI:1.8-6.0) and absence of maternal use of bednet in weak evidence (HR=1.8, 95% CI:0.9-3.4) as variables associated with increased rate of infant death (Table 5, paper III).

For the entire period of infancy, three factors were associated with increased rate of infant death in adjusted analyses (Table 5, paper III). Maternal history of child death increases by 60% the rate of infant death (HR=1.6, 95% CI:1.0-2.6); children born in polygynous households had over 2 times higher rate of death compared to those from monogamous households (HR=2.4, 95% CI:1.4-4.0); twins carried 8-fold higher rate of death compared to singletons (HR=8.4, 95% CI:4.6-15.3). We did not find any evidence in multivariable

analyses that a birth in the dry season, being a boy or living closer to a health facility was associated with a significantly increased rate of infant death in this cohort (Table 5).

Association of the intervention with perinatal, neonatal and infant death risks (Paper I, II and III)

Further analyses were conducted to measure the association of the study arms with risk of stillbirth, neonatal and infant death, respectively, in this cohort. Using semi-parametric (Student) and non-parametric (Wilcoxon-rank sum) tests on cluster-levels summaries of the data, we found no evidence of a mean difference between the intervention and the control arms, both for stillbirth and neonatal death risks (Table 17). There were marginal mean differences both for perinatal and infant death risks between the two study arms, in analyses using the Wilcoxon-rank sum test (p=0.08 and p=0.07, respectively).

When we fitted random-effects logistic regression, univariable analyses accounting for the cluster design of the EBF-study, found that the intervention was associated with 70% higher odds of stillbirth, 80% higher odds of perinatal death and 60% greater odds of infant death (Table 17). There was no evidence of association of the intervention with the odds of neonatal death in this study.

Multivariable analyses adjusting for distance to the nearest health facility, mother's use of bednet (to account for baseline difference between study arms) and village clustering, confirmed the results observed with non-parametric tests on cluster-levels summaries. Although the intervention remained associated with higher odds of stillbirth and higher odds of neonatal death (Table 17), none of the models was statistically significant (Table 17, Wald chi-test, p>0.10). However, the adjusted model showed that the intervention was associated with almost a doubling (OR=1.9) of both the odds of perinatal and infant deaths (Table 17).

We also performed a multivariable analysis restricted to the group of infants who had birth weight records (N=295) and we did not find any further evidence that the intervention was associated with a higher risk of infant death (OR=1.7, 95% CI: 0.7-4.4).

We repeated the same analyses using Cox Gamma frailty model and we observed findings similar to that obtained using logistic regression for the association of the intervention with both the risk of neonatal death (HR=2.0, 95% CI:0.9-4.7) and that of infant death (HR=1.8, 95% CI:1.2-2.8).

Table 17: **Association of the study arms with pregnancy outcomes in a cohort of 895 pregnant women in rural Banfora, Burkina Faso.**

Outcomes	Control N=442	Intervention N=453	t-test[a]	Wilcoxon-Rank sum test[a]	Crude OR [95% CI][b]	Adjusted OR [95% CI][c]	Wald-test p
Stillbirths	18	31	-	-	-	-	-
perinatal deaths	26	46	-	-	-	-	-
Neonatal deaths	15	25	-	-	-		-
Infant deaths	38	60	-	-	-		-
SBR[d] (/1000)	41	63	0.17	0.24	1.7 [0.9-3.1]	1.7 [0.9-3.2]	0.30
PNMR[d] (/1000)	63	96	0.10	0.08	1.8 [1.1-2.9]	1.9 [1.1-3.2]	0.047
NMR[e] (/1000)	40	58	0.48	0.12	1.7 [0.6-4.3]	2.1 [0.8-5.2]	0.12
IMR[e] (/1000)	95	129	0.19	0.07	1.6 [1.0-2.6]	1.9 [1.2-2.9]	0.005

[a]Based on cluster-level summaries (command *collapse* in Stata) and following the Haynes's recommendations on cluster-randomized trials analysis when n<15 per arm. Only p-values are displayed.
[b]OR were adjusted for clustering using a random-effects logistic regression
[c]OR were adjusted for distance to nearest health facility, mother's use of bednet and clustering
[d]Calculated for all births including twins (n=915)
[e]Calculated only for live births including twins (n=866)

Estimation of overall child mortality in Burkina Faso (Paper IV)

A critical comment on modelled estimates of U5MR in 2010 for Burkina Faso was made. Inspection of the webappendices provided by Rajaratnam JK et al.,[10] showed that the datasets used were old and were the same as that used by UNICEF to estimate U5MR for Burkina Faso in 2008. Therefore, the U5MR of 134 per 1000 live births provided by the authors in 2010 was far away from the 168 computed by UNICEF. In our opinion, neither the time difference (+2 years), nor the statistical methods (Gaussian Process Regression model) could be valid explanations of such difference of estimates. Furthermore, recalculation of annual reduction of U5MR in Burkina Faso from 2000 to 2010 showed an average reduction rate of 2.5% per year with a sudden acceleration of up to 6% per year from 2008 to 2010. No large scale interventions were implemented in the country that could explain such a surprising "jump" in the reduction of the burden of child deaths in Burkina.

Our observation of an IMR of 113 per 1000 live births in 2008 in a rural area of a predominantly (>75% of the population) rural country, suggests that the estimates of U5MR provided by Rajaratnam JK et al. are unrealistically low. Assuming the childhood mortality rate of 61 per 1000 in rural areas of Burkina Faso as provided by the 2006-national census data,[34] we anticipated that a further 47 children still alive by 12 months of age in the EBF-cohort, would die by 5 years of age. We estimated the U5MR in the EBF-cohort in Banfora at 167 (95% CI:143-194) per 1000 live births.

Discussion

This thesis focused on the burden of fetal losses during the third trimester of pregnancy and child deaths occurring during the first year of life in Banfora Health District, a rural area in southern Burkina Faso. Our estimates of PNMR, NMR and IMR were 79, 46 and 113 per 1000, respectively. These figures illustrate the stubbornly high rate of child deaths in a rural area of Burkina Faso, which are in stark contrast with some of the recently published modelled estimates of PNMR and IMR from this country.

An overall weak health system is characterized by low availability and poor access to health facilities, poor quality care in antenatal and childbirth services and understaffed teams; these are all combined with a context of exceptionally low women's literacy and cultural challenges, such as unequal gender distribution of power may be the reasons for such high PNMR, NMR and IMR.

Of the variables explored, nulliparous or primiparae mothers, birth in the dry season and twinship were the factors associated with higher perinatal death risk. Moreover, polygyny, maternal history of child death and twinship were also associated with higher neonatal and infant death risks.

While this study was conducted in a context of EBF-promotion, this intervention did not lower the risk of perinatal and infant deaths in this cohort.

Methodological issues

Study design

The findings presented in this thesis are all drawn from a prospective community-based cohort study. Such a cohort is the best study design to measure mortality in a population or from a random sample.[109, 110] The study outcomes (perinatal, neonatal and infant deaths) had not yet occurred at the beginning of the follow-up, and as such, the exposures evaluated here preceded the outcomes, meeting, strictly speaking, a cohort study design. The community perspective of our study enhanced the ability to capture events happening in the villages where the study was carried out, unlike health facility-based studies that only reflected a "narrow view" of a selected group of women attending such facilities.

Moreover, the sample size in this study enabled us to estimate the burden of all the 3 study outcomes with an acceptable precision of 1-2% depending of the actual outcomes. The high number of fetal and infant deaths recorded actually increased our precision.

However, one limitation of the study design was its weak power to detect risk factors associated with small increases in the study outcomes. The failure of some exposure variables (household assets, maternal education, number of ANC visit) to show statistical associations may simply be due to the relatively small sample size for risk factor analysis.

Overall, the study design was suitable for the objectives of this thesis. The next steps in assessing the internal validity of our findings were to check whether they may be due to:

a) Bias
b) Confounding
c) Chance

What were the potential biases in this study and how were they controlled?

Bias is defined as a systematic distortion of the estimated effect of an exposure away from the truth, caused by inadequacies in the design, conduct, analysis of a study or in the publication of its findings.[111] Bias identification is relevant both for estimation of the burden of diseases and also in the assessment of risk factors being followed in this thesis. There are several types of bias, but two were of major interest in the framework of this study:

- Selection bias that occurs if a systematic difference is introduced in the way in which study participants were enrolled (accepted or rejected) in a study, or the way the intervention was assigned to those enrolled if the study was a trial.[112] This also includes participation bias that reflects the proportion of refusers and those lost to-follow-up during the study.
- Measurement bias is a systematic error, either in the way information about the study exposure/outcome was collected or in the way study participants recalled or provided this information.[113] Measurement bias might have been related to an instrument (scale, length board, questionnaire, etc), to the data collector (e.g. did not collect data in a standardized way), to investigators (e.g. oriented study populations or selected findings for publications), or to study participants (may choose to report some information and not other, or to improved recall of some events rather than others). Information or reporting bias is a systematic measurement error that may lead to differential misclassification (related to the value of outcome or exposure variables) or non-differential misclassification of risks. Differential misclassification is particularly hazardous as it results in a "true" bias, with a distortion of the measured associations in both directions, whereas non-differential misclassification tends rather to reduce the strength of an association.[110] Recall or memory bias is typically found in retrospective studies (case-control or retrospective cohort studies), but may also be found in prospective studies when questions are asked about medical or personal history of study participants. The accuracy of reporting, the exposure or outcome variables of interest are highly dependent on participants' memories.[114] The literature revealed that memory precision is better with recent events, but often important events are reported as being more recent than they actually were.[115]

Poorly designed studies frequently contain a combination of both selection and measurement biases. Bias, of whatever type, is a serious threat to the internal validity of any study and should be carefully addressed during the design, conduct, analysis and publication of the study.[109, 111] It is usually almost impossible to determine exactly the impact of a potential source of bias on an estimate of an effect. However, one should try to identify the likely magnitude and the direction of the bias on the estimates.[116] We present the different types of biases and the ways to deal with them in Table 18.

Table 18**: Summary of the most common types of bias and methods of bias reduction (adapted from Wang and Bakhai et al., 2006 [113])**

Type of bias	**Method to reduce bias**
Selection and participation bias	- Random sampling selection - Randomized intervention assignment (if a trial) - Concealment of intervention assignment - Schedule several visits to collect data - Careful analysis of refusers' profile and loss-to-follow-up rates
Measurement bias - Information bias (study management)	- Standardized study procedures (SOPs) - Standard equipment (scales, length boards, questionnaires,) - Training and certification of data collectors
- Reporting bias (observer ascertainment)	- Blinding or masking
- Recall bias	- Prospective studies - Short recall periods - Consistency checks across answers
Post-randomization exclusions bias	- Intention to treat analysis (for trials) - Worse-case scenario analysis (sensitivity analysis)
Publication bias	- Prospective registration of studies (www.clinicaltrials.gov) - Publication of "negative" findings

Selection bias

Selection bias in this thesis could have affected both our estimates of the burden of child deaths and factors associated with the outcomes. We anticipated most of them (as mentioned earlier in the methods section, page 66) and took adequate preventive measures. The following bottlenecks were foreseen:

- Selection bias among pregnant women to be enrolled: if the selection of study participants was the sole responsibility of local community-informants or data

collectors, the probability of a bias selection would be higher. To reduce this, women that were enrolled were drawn from a random monthly list of pregnant women in each of the study villages. The selection process was made public and active involvement of potential study participants and community-leaders was ensured. However, due to variation in villages' population, the random sampling method faced a "saturation process" in 4 of the study villages (Karfiguéla, Kossara, Lémouroudougou Cité and Sikanadjo) where we could not get >4 pregnant women monthly for the last 2 months of the recruitment period. However, this unexpected situation on the actual distribution of our cohort sample is unlikely to have had a significant effect. Moreover, the variation of population size across villages may have resulted in lower probability of women from larger or high fertility villages of being recruited. Since only one village (Siniéna) was a 'true outlier', this is unlikely to have had a significant effect on our estimates of PNMR and IMR.

- Participation bias: if a large number of pregnant women refused to take part to the study, this could also have resulted in a selection bias. Only 21 women (1.8%) in this study refused to participate upon initial contact. The high proportion of participation was due to the use of local community-informants who spoke to potential study participants in their own local languages, thus reducing misunderstanding and increasing women's confidence. For ethical reasons, we could not request the reasons for non-participation. However, the baseline data (age, parity, marital status) of this group of refusers were similar to that of women who agreed to take part (data not shown). Therefore, the very low proportion of refusers would not be expected to have had any effect on the findings.
- Lost to follow-up rate: if a significant number of mother-infant pairs were lost to follow-up during the study, this could constitute another bias. In this study, 99% of the mothers sampled for data collection completed a day-7 visit; 97% of those with live births were visited by week-24 and the vital status was known for 100% of live births by one year of the child's age (Figure 12). Fifteen mother-infant pairs (1.7%) were physically missing at the 12 months visit; but information collected from their close relatives was reliable, as death was a major social event in this area and was associated with some local mourning practices. The high follow-up rates achieved in our study were possibly due to the study design (3 attempts for any scheduled home visit), the involvement of local community-workers (daily reporting on study participants), and because our data collectors were accepted both by study participants' families and the whole local community.

Measurement (reporting) bias

The most likely significant reporting biases to occur in this study were the poor identification of pregnant women, the potential for misclassifications of perinatal deaths, information bias regarding exposures such as parity or medical history of the mother, and the potential errors in anthropometric measurements. We will explore their respective roles:

- Poor identification of the target population (pregnant women) in the study villages: because no complete census was conducted prior to the study, and because our formal DCs (although born in the study area) were not former residents of the study villages, they could have failed to identify and report properly the number of pregnant women in each village. To overcome this challenge, we relied on local community-informants

("the recruiters" and peer-supporters) who were initially selected by their own communities. They were familiar with the village borders, households and cultural practices. They targeted specific gathering places (mills, wells, mosque, etc.) and social events, such as baptism and women's meetings. They also conducted weekly household visits throughout the recruitment period (one year). The average number of pregnant women identified and enrolled in each village was proportional to the village population (Table 13). Overall, 1162 pregnant women were identified in a total population of ~35 000. This is consistent with the reported crude birth rate (42 per 1000) in the study area;[34] if under-reporting of pregnancies had occurred, it was likely to be low so as not to affect either the socio-demographic baseline (random sampling) of the cohort or the estimates of PNMR and IMR reported (i.e. the assumption is that numerator and denominator would vary in the same proportions). Moreover, we found no evidence of differential reporting of the number of pregnancies between study arms, as the number of pregnant women was proportional to the arm population (555 for the intervention versus 607 for the control with populations of 16,000 and 19,000, respectively).

- Misclassifications of pregnancy outcomes, especially during the perinatal period:
    - The first type of misclassifications that could have occurred is that some of the reported stillbirths were in fact miscarriages. Such an hypothesis would result in a SBR lower than the one actually reported. We used the WHO's definition of stillbirths in this study, i.e. fetal losses from 28 weeks of gestation and onwards.[44] The median gestational age reported by mothers at enrolment in this cohort (8 months) and the median time from enrolment to birth (7.5 weeks) do not suggest such a misclassification, assuming an average of 40 weeks for a term delivery. Ascertaining gestational age is difficult in a population where 80% of mothers have had *no* formal education and the recorded symphysis-fundal heights for mothers who attended ANC were poor quality. In similar contexts, the reliability of women's self-reported gestational age compared to ultrasonography was inconsistent across studies.[117, 118, 119, 120]
    - The second misclassification that could have occurred is that some stillbirths might have actually been reported as early neonatal deaths. Such misclassification would result in a lower SBR and a higher ENMR than those actually observed. The SBR reported here is one of the highest ever reported in Burkina Faso[12, 29, 121] and the observed ENMR is just consistent with previous data from the country.[28, 80, 122] Given the actual figures, the probability that this misclassification occurred is really low, and would not change significantly the current estimates of PNMR.
    - A third misclassification that might occur in this study is that some early neonatal deaths have been reported as stillbirths. Such an hypothesis would result in a higher SBR and a lower ENMR than the actual rate in the study population. This type of misclassification cannot be excluded from our study, given the actual ratio of stillbirths to early neonatal deaths (2.1:1) is considerably higher than that usually reported from low-income countries.[8, 12, 23, 47, 49] In this study, where almost two-thirds of the births took place at home (or in the local TBA's place), it is difficult to distinguish between stillbirths and very early neonatal deaths by verbal autopsy. If such a misclassification has

occurred, our actual findings will have overestimated the real SBR and underestimated the ENMR in this cohort. Nevertheless, such a misclassification would not affect the reported overall PNMR in this cohort.

To reduce the probability of these misclassifications, our DCs were extensively trained in the use of the standard WHO verbal autopsy (VA) tool[103] that was translated into *Dioula*, the main local language. Furthermore, regular field supervisions and re-assessment of a sample of verbal autopsies showed high accuracy of the DCs' reports with their supervisors on the main VA items. Diagnostic accuracy of VAs at the community-level in Africa was good (>80%) both for stillbirths and neonatal deaths, and its sensitivity and specificity in ascertaining the major causes of both outcomes were also acceptable (>60%).[123] We did not aim to increase health facility-delivery in the study areas; the community-VA was the best tool that could be used to collect data on pregnancy outcomes and causes of death in this community-based study.

The most important reasons for misclassifications of stillbirths during home deliveries often relate to cultural practices,[8, 23] but these misclassifications have been reported even in health-facility deliveries due to limited knowledge or insufficient training of the staff.[123, 124] In some communities, the mothers' fear of stigmatization and their feeling of guilt often lead to the reporting of early neonatal deaths as stillbirths because it is culturally more acceptable.[24, 52] This may also be the case in Banfora region, though no published data are available to confirm this. Sometimes, the mourning practices and costs associated with stillbirths or early neonatal deaths may lead to misclassifications of deaths reported by families.[52]

Another type of reporting bias that we could have expected was error in death reporting: in community-based studies, errors in reporting children still alive as being dead may occur. In this prospective study, child death was considered as one of the major study outcomes and was also a major social event. It is highly unlikely that children still alive would be erroneously reported as being dead. Community-informants visited the mother-infant pair on almost a daily basis and reported timely information to our team. Furthermore, each mother-infant pair was visited at each of the scheduled visits by a formal DC, irrespective of whether or not the child was reported as dead by the community-informant. Three attempts were made to complete any scheduled visit before it was considered as missing. An underlying question about this issue is whether there has been differential death reporting in the 2 study arms, a hypothesis that could elucidate the observed higher risk of child death in the intervention arm both during perinatal and the entire infancy periods. We do not believe this could have happened for the simple reason that the same DCs collected data in both arms, were likely to be masked about the cluster allocation, and visited mother-infants pairs irrespective of the visits paid by community-workers. Furthermore, the number of pregnancies recorded per arm strengthens our feeling that community-informants did a good job through regular weekly household check-ups. The field supervisions conducted by the study investigators reported data consistent with that of our DCs. Overall, if any death reporting bias occurred in this study, it would have been towards a non-differential misclassification resulting rather in a lower association of the study arm with risk of perinatal or infant death, contrary to our actual findings (Table 17).

Recall bias for some exposure variables in our study, such as parity and history of child death, was also anticipated. The use of clear definitions, the translation of all questionnaires in *Dioula* and the training of DCs were the methods used to reduce their potential occurrence. Thus, parity (the number of births irrespective of the pregnancy outcomes) was preferred to gravidity (the number of pregnancies where mothers could omit pregnancies that resulted in miscarriages), and DCs learnt specific wording for miscarriage, stillbirth and live birth in the local dialects. We think that these preventive measures resulted in a low proportion of reporting bias for parity and history of child death.

A last possible measurement bias in this study was measurement errors that could affect the association of anthropometric variables (stunting, wasting, and underweight) with neonatal or infant death risk. Preventive measures taken to reduce this reporting bias included field training and refresher training on anthropometry (validity and reproducibility exercises on a quarterly basis) for DCs , the use of standard equipment (SECA® 872 scales and SECA® 210 length boards), and a training on good clinical practices (GCP) for DCs so as to improve their skills in adequately completing and editing the anthropometric variables on the study questionnaires. During the field tests on anthropometry (data not reported), DCs had high validity when compared to their supervisors and reliable intra-observer measurement both for weight and length (coefficient of variability <2 times that of the supervisor)[125]. The effect of potential measurement errors on the association of anthropometric status with neonatal and infant death risks may be small, given the preventive measures and the observed validity and reproducibility coefficients during field exercises (data not shown).

Confounding

A confounder is a variable that causes a distortion in the estimated effect of an exposure of interest with a given outcome because it is mixed with the effect of that exposure.[126] A confounder therefore must have an effect and must be unbalanced between the exposure groups being compared. For a factor to be a confounder, it needs to meet the following criteria:[110, 126]

a) It must be associated with the outcome studied
b) It must be associated with the exposure of interest
c) It should not be in the causal pathway (an intermediate factor) to the outcome, i.e. not a consequence of the exposure being studied

Confounding is of particular interest in risk factors analyses and may result in an overestimation or underestimation of a 'true' association between an exposure and an outcome of interest. It can even change the direction of the observed effect.[127] Although bias is not mutually exclusive from confounding, the latter can be controlled in several ways during the design, the implementation, and particularly during analyses of the data, as shown in Table 19.

Table 19: **Methods for controlling potential confounders in epidemiologic studies (adapted from Hennekens et al. 1987, [117]).**

Study phase	Techniques for controlling potential confounders
Design	Randomization, restriction, matching
Implementation/conduct	Protocol amendment and data collection on suspected confounders
Analysis	Stratification, adjustment (multivariable analyses)

In this thesis, evaluation of confounding was particularly relevant in the identification of exposures associated with increased risk of perinatal, neonatal and infant deaths.
During the study design, confounding of the potential effect of the study intervention on risk of death was controlled through randomization. However, most of the confounders were in fact controlled for during the data analysis stage, using multivariable or stratified analyses. Thus, classical confounders, such as maternal age, parity, education, polygynous status and socio-economic status, were suitably adjusted in most of the multivariable analyses. Newborn variables that could confound the association with risk of perinatal or infant death, such as gender, season of birth, feeding status and anthropometric z-scores, were also included in multivariable analyses. We also investigated whether distance to nearest health facility modified the association between polygyny and neonatal and infant death risks. Distance to nearest health facility was considered as being on the path to place of delivery and was not considered as a potential confounder when measuring the association between that exposure and neonatal death risk (Table 1, paper II). The same line of argument was used for the exposure 'history of perinatal death', when looking at the association of parity and risk of perinatal death (Table 3, paper I).

To account for the potential confounding of the baseline imbalance between the two study arms, the association of the intervention with risk of infant death was adjusted for distance to nearest health facility and maternal use of bednet (Table 17). Despite a possible imbalance in the study arms for proportions of low birth weight (Table 16), we were unable to adjust for this potential confounder in the multivariable model due to the small number of babies whose birth weights were recorded. We cannot exclude the potential confounding effect of this variable on the higher infant death risk observed in the intervention group. Indeed, analyses restricted to that subgroup (n=295) and accounting for birth weight showed that the intervention was no longer associated with a higher infant death risk.

Of all estimates provided for risk factors of infant death in this study, that of intervention is the most likely to be confounded, as no scientific argument could back our observation of a higher risk of infant death in the intervention group. If we exclude the role of chance, then our finding of a higher risk of infant death in the intervention group may simply be the result of a confounder not being clearly identified (low birth weight?) and therefore not measured in the study.

Finally, while most of the potential confounders were accounted for during the analysis of our data, we could not control for 2 variables, gestational age at birth and birth weight. Gestational age is considered an important predictor of perinatal death[13, 47] and birth weight has been associated with higher risk of neonatal death in several studies from low-income countries, although controversies remain on the relevance of including birth weight in the pathway to child death risk.[47, 128] Gestational age was difficult to ascertain in a community-based study lacking ultrasonography, where literacy was very low, and where overall attendance at health centres was low. Thus, the high proportion of home deliveries resulted in few babies having their birth weights recorded.

Other confounding variables explored in our analyses include child anthropometric scores and immunization status (the latter not being included in the scope of this thesis).

Would these findings have been observed by chance?

Chance may always affect the results of a study because of random variations from sample to sample. Statistical inference is founded on the use of random samples of populations in studying a given public health issue.[110, 116] However, doing so leads to uncertainty about the role of chance in the actual findings. Hypothesis testing and confidence interval (CI) estimations are the 2 standard methods to evaluate the role of chance in observed results.[110, 116]

A major determinant of the degree that chance plays in a particular study is sample size, which affects the precision of the findings and therefore the size of the calculated 95% confidence intervals (CIs). Our estimates of PNMR and IMR appear rather precise because their 95% CIs had both an upper limit (UL) to lower limit (LL) ratio ≤ 2, consistent with high precision. Although the 95% CI of our estimated NMR was relatively large (ratio=3.2), our cohort sample size was sufficient to measure it with a precision of 1.2%.

With regard to risk factors identified for all the 3 study outcomes, only variables that showed a statistical association in multivariable analyses and a p value of <0.05 were retained. Therefore, the likelihood that the reported risk factors were associated to these outcomes by chance is low. Nonetheless, the observed association of higher perinatal and infant mortality risks in the intervention group may have occurred by chance. Indeed, the use of 2 different statistical analyses led to inconsistent findings and the small number of clusters per arm increased the risk of failed randomization (Table 17); we cannot exclude the possible role of chance here, especially given that we have no reasonable scientific background to assume that EBF-promotion would increase risk of death in this cohort.

In our opinion, the estimates of fetal and infant deaths reported in this thesis, as well as the identified main risk factors for perinatal and infant deaths, were unlikely (excepting the intervention) to be due to chance.

Internal validity

Internal validity is the ability of a study to measure what it sets out to measure; it is highly compromised by bias and confounding.[112] Validity is also termed as "accuracy" and is the ability of a tool (instrument, questionnaire) or a data collector to measure the true, exact value of an exposure or outcome of interest. Precision (often termed as reproducibility or repeatability) is the ability of a tool or a data collector to obtain consistent findings with repeated measurements of the same subject.[116]

We are confident that the estimates in this thesis given for PNMR, NMR and IMR are valid based on the study design, the tools used for data collection, and statistical methods used for their estimation.

The findings on risk factor analysis for perinatal and infant deaths showed relatively narrow CIs for most of the exposure variables identified as risk factors in multivariable analyses, and as such are valid findings. However, we should mention the weakness of our study to identify risk factors associated with small increases in the study outcomes.

Main findings

Low utilization of health services in Banfora Health District

Attendance at antenatal care and childbirth services are 2 major outcomes when assessing the efficiency of a local health system on maternal and newborn health. Both indicators were low in this cohort. Only 18% of the pregnant women had over 2 ANC visits and about a third gave birth in a health facility. Our findings are consistent with previous results from prospective studies in rural areas of Burkina Faso,[129, 130] but are below the proportions provided in the official health statistics from the Ministry of Health[32] or DHS.[34, 94] The reasons for this difference lie with the studies designs and the motivation of providing unreliably high numbers. Our study was prospective, the data were retrieved from the ANC cards, and therefore the information provided is probably more accurate than data collected either through recalls (surveys) or a poor quality registration system from the local health system (where over-reporting of activities, also known as 'achievement disease,' was, in our opinion, usually the rule).

The reasons for the low utilization of health services are poor access to facilities both geographically and financially, low literacy, unequal gender distribution of power in couples, and the overall poor quality of care in childbirth services.[101, 129, 130] Factors, such as distance to nearest health facility, parity, polygyny status and maternal education, were associated with ANC attendance and health facility delivery in our study (Table 2, paper II). In this respect, our findings are consistent with the literature and highlight the roles of the local health system and socio-cultural factors on levels of child mortality rates.

Although no published data was found on gender distribution of power in Banfora, our team observed some local practices during its EBF-study suggesting an imbalanced gender distribution of power in this area, as reported elsewhere in Sub-Saharan Africa.[131, 132, 133] Women in Banfora invariably tended to seek the permission of their husband or his family,

prior any visit to the local health centre. We even had to seek from the husband an authorization to visit the household before we could ask the mother's willingness to participate in the study. Moreover, factors such as polygyny and low maternal literacy, seemed to limit the women's autonomy.[134] Our data showed that polygyny was more common among women without formal education.

The high burden of perinatal, neonatal and infant deaths in Banfora Health District

The PNMR of 79 per 1000 births found in this study is the highest ever published to our knowledge in recent reports from Burkina Faso. Our data are close to those reported from rural areas in the Democratic Republic of Congo and Zimbabwe, where PNMRs were 64 and 65 per 1000 deliveries, respectively.[47, 135] In relation to other developing countries, Burkina Faso has scarce and unreliable statistics on stillbirths and early neonatal deaths. The main data found for comparison were old,[29, 87] from surveys[28, 80] or modelled estimates.[12] Our estimate of PNMR was rather precise and the prospective nature of this study increases the credibility of our data. Furthermore, the rural location of the study clusters, the involvement of local community-informants who provided our study team with timely information on fetal losses and early neonatal deaths, and the use of formally well-trained DCs for data collection on all the study tools (questionnaires, verbal autopsies), should have resulted in high quality data. In such a context, the number of events recorded is expected to be higher and more accurate than that collected by retrospective studies or surveys, and may explain the differences from previous data.

The NMR observed in this cohort was 46 per 1000 live births, which is much higher than the national average for rural areas (35 per 1000) provided in the last DHS from Burkina Faso.[94] Our results are also higher than the estimates of NMR provided from recent modelled estimates.[10, 11, 122]
However, our findings are consistent with the observed high PNMR in the same cohort and also consistent with an NMR of 44 per 1000 provided for Banfora region in 2010.[94] Our data support the results from previous reports showing that the levels of NMR are strongly correlated with those of SBR.[8, 12] Many studies have shown that throughout in sub-Saharan Africa, the causes of perinatal deaths overlap with those of neonatal deaths,[8, 12, 23] and there is evidence that the overall reduction of SBRs will result in decreased NMRs and reduced maternal deaths.[21]

We found an IMR of 113 per 1000 and a postneonatal mortality rate of 67 per 1000 live births. Although high, our results lie in the range of previous data from Burkina Faso, especially for rural areas.[28, 34] Most of the published data acknowledged the high burden of infant deaths in rural areas of Burkina compared with urban settings.[28, 34, 94] It should be noted that our IMR was almost twice that of the national average (65 per 1000) provided by the 2010-DHS in Burkina, and was higher than the average IMR provided for rural areas (81 per 1000) in the same dataset.[94] Interestingly, regional data from the 2010-DHS showed Banfora region to have the third highest regional IMR and U5MR in Burkina Faso at 96 and 170 per 1000 live births, respectively.[94] As such, these findings confirm our prospective data of high PNMR and IMR and raise questions about their exact causes.

The underlying reasons for the high burden of perinatal and infant deaths in Banfora are, in our opinion, the same as those mentioned previously for the low utilization of childbirth services, i.e. a weak health system, low maternal literacy, a high proportion of grand multiparae and cultural factors, such as polygyny (that may be a proxy for poor socio-economic status in our context), and the apparent imbalance in distribution of gender power, resulting in limited women's autonomy in rural settings.

Another factor that might explain part of the high PNMR even in health facilities is the poor quality of care they provide. Beyond the low health-facility delivery rate in this cohort, some of our findings suggest that there is generally poor quality of care provided during birth in these centres, such as the proportion of babies born in a facility, and whose birth weight was not recorded. The fact that ANC visit and health-facility delivery were higher among primigravidae may also be a reflection of the poor quality of care in childbirth services. Indeed, one probable explanation is that the women who have had prior contact with the local health system acquired personal experience of, for instance, being overlooked by the health staff, poor labour management, or even poor pregnancy outcomes (all symptomatic of poor quality care), which created good reasons for not attending it as long as possible.

Finally, other objective reasons for the high burden of child deaths in Burkina Faso relate to the country morbidity patterns, characterized by malaria holendemicity, high prevalence of child malnutrition at all ages, recurrent outbreaks of meningococcal meningitis and measles.[32, 94, 97] Malaria is the major cause of child deaths before 5 years in Burkina Faso, and it also affects pregnant women, often resulting in poor pregnancy outcomes.[32, 94, 97] Malnutrition affects both young infants (worsening the prognosis in infectious diseases) and pregnant women, often leading to intra-uterine growth retardation with potentially poor pregnancy outcomes.[32] Despite reported good coverage of meningococcal and measles vaccines , these 2 diseases continue to be responsible of ~7,000 child deaths every year in Burkina Faso.[97] Clearly, there is a need for a comprehensive policy to address the structural and medical causes of child deaths in rural areas of Burkina Faso.

No difference in perinatal death risk between facility-based deliveries and home-based deliveries

An unexpected finding in this study was the absence of difference in perinatal death risk between women delivering in a health facility and those who delivered at home. This contrasts with previous data on perinatal deaths in Sub-Saharan Africa.[124, 136] In our opinion, these results may simply reflect the poor overall quality of care in maternities in rural areas of Burkina Faso. If the care offered at birth in these facilities do not differ substantially from those provided during home births, it is unlikely that delivering in a facility will reduce the risk of perinatal death. An alternative explanation is that some of the women delivering in facilities are those who had a complicated labour that started home, and ended up at the health centre where they delivered. In this regard, our findings are consistent with a study from Democratic Republic of Congo where PNMR was also high and the authors found no difference in perinatal death risk between home- and facility-based deliveries.[47]

Our personal opinion, based on a subsequent study on the quality of obstetric and perinatal care in primary health facilities in Banfora, is that a 'cold' welcome by the health staff, poor hygiene at delivery, unskilled staff and lack of basic equipment could permanently be seen in all the facilities studied. This supports our hypothesis that a poor quality of care may be the main reason for the lack of perinatal death risk difference between home deliveries and facility deliveries in Banfora Health District.

Main risk factors for perinatal death

Pauciparae women (nulliparous or primiparae at enrolment) and being a twin were factors associated with a higher risk of perinatal death in this cohort, which is in agreement with the literature.[8, 23, 47, 66]
Primigravidae are reported to be at high risk of complicated labour[8, 29, 47] and pauciparae women are known to be at an increased risk of malaria during pregnancy compared to multiparae. Malaria complications during pregnancy lead to poor pregnancy outcomes.[137, 138] The proportion of pauciparae was more than a quarter in this study (Table 1, Paper I), which took place in an area holoendemic for malaria.

Multiple births, including twins, have been reported to be at a higher risk of perinatal death in several studies.[47, 124] Preterm birth complications and poor hygiene during home births are factors that might increase the perinatal death risk among multiple births.

The higher risk of perinatal death among children born during the dry season contrasts with previous data from Burkina Faso.[81] It may relate to the epidemiological patterns of infectious diseases, such as meningitis and pneumonia, which are common both in adults and infants from November to March in Burkina Faso.[32, 139] Moreover, this result does not preclude the potential role of malaria complications because of its delayed effect on pregnancy outcomes.

Major risk factors for infant death

Nulliparity, polygyny, maternal history of infant death and being a twin were the main factors associated with an increased risk of neonatal and infant death in this cohort.
These results are fully consistent with previous studies.[10, 122] Social variables, such as parity and polygyny, are well described distal and intermediate determinants of child deaths.[108, 140, 141]

Nulliparity was associated with higher utilization of antenatal and childbirth services in this study, which could to some extent have compensated for the inherent higher infant death risk in this group. However, as previously mentioned, if care offered in health centres is of poor quality, then attendance at such facilities is unlikely to affect the risk of infant death. Ignorance, higher vulnerability to some infections (malaria), the high probability of obstructed labour and the frequent use of poor nutritional practices for their babies (often due to the influence of elderly women) may be additional mechanisms through which primigravidae are at increased risk of infant death in this area.

Maternal history of child death has been associated with higher infant death risk in previous studies including Burkina Faso.[36, 142] Prior obstetric history is likely to be the most prominent factor through which previous child death may affect the risk of infant death.

Few studies have focused on the role of polygyny on risk of child death, and their findings have been inconsistent.[143, 144] Polygyny is often associated with poverty, low maternal literacy (as in this study) and reduced autonomy of women. Some studies have suggested that parental selection or neglect may be the mechanisms through which polygyny increases the risk of infant death.[140, 143] Polygyny was common in Banfora, a predominantly Muslim area (62%), and our observation of a heavy involvement of women in farming activities suggests that polygyny is associated with a larger number of household members (i.e. more people to feed) and therefore to poor socio-economic status.

In other societies, polygyny tends to reflect wealthy households as only rich men can afford to take two or more wives.[145] This was not the case in Banfora, where polygynous households were not the wealthiest in our cohort.

Multiple births are known to be at increased risk of death throughout the first 12 months of life, our findings being consistent with previous reports from rural Burkina Faso.[89, 146] This risk is usually high during the neonatal period,[13, 65] but even twins in our cohort who survived the first 6 months of life remained at high risk of death. The poor anthropometric scores at all ages combined with a context of endemic malaria and malnutrition may partially explain the persistent high risk of infant death for both twins and singletons (Figure 2, Paper III).

No association of the intervention with a lower risk of perinatal and infant deaths

We found that the intervention was not associated with a lower risk of child death, neither during the perinatal period nor the overall infancy period. To the contrary, there was an indication of a marginally higher perinatal death risk and a significantly increased infant death risk in the intervention group, although these findings were inconsistent from one analysis to another (Table 17).

Our results contrast with most data from the literature, in which it has been reported that breastfeeding (in general) and exclusive breastfeeding (in particular) are associated with a reduced morbidity due to diarrhoea and pneumonia, [147, 148] and also associated with lower child mortality rates compared to non-breastfed or partially breastfed children.[78, 149, 150, 151] However, our findings are similar to those of two studies from Ghana and Guinea Bissau, in which the risk of child death was higher, but not significantly, in the intervention group.[152, 153] The PROBIT trial in Belarus, the largest trial on EBF-promotion, found no difference in infant death risk between the 2 study arms.[154]

Although unexpected, our results are consistent with the observed lack of effect of the EBF-intervention on diarrhoeal morbidity in this study.[43] These findings are also consistent with the poorer child anthropometric status at 3 and 6 months in the intervention arm in the EBF-trial (unpublished data).

The overall explanation of these higher perinatal and infant death risks in the intervention group of our cohort may be due to a randomization failure. Indeed, as reported in the baseline table (Table 16), the proportion of newborns with low birth weight was higher in the intervention group, although in a subsample of only N=295 children. This factor is known to be associated with higher perinatal and neonatal death risks.[13, 47] If we assume that our subsample was representative of the whole sample, then the potential for a randomization failure in this study exists, including other unknown or non-measured confounders, which could explain our unexpected findings.

An alternative explanation of the higher risk of perinatal and infant deaths in the intervention group is the high proportion of predominantly breastfed infants in Burkina Faso.[28, 94] It is important to note that most studies that found an association of EBF-promotion (or EBF-status) with lower risk of child death had non-breastfed or partially breastfed children as the comparison group.[150, 151, 155]

Our results also suggest that, in contexts such as Banfora where breastfeeding is the 'standard' feeding mode of infants and where the proportion of predominantly breastfed infants by 3 months is high,[94] the effect of EBF-promotion on infant survival may be small or absent . This is even more the case when the intensity of the intervention was low, as in our study, in that women received only one antenatal peer-counselling session on EBF and 5 postnatal home visits.[43]

External validity of the results

External validity (also known as generalizability of the findings) refers to whether the findings from a study population are applicable to other populations.[116]

In this thesis, the 2 main questions about generalizability were whether the estimates provided for PNMR, NMR and IMR were representative of that in other rural areas of Burkina Faso, and whether the factors identified as increasing the risk of perinatal, neonatal and infant deaths in this cohort could be the same as in other cohorts from rural settings in Burkina Faso.

Recent data from Burkina Faso indicate over three-quarters of its population still lives in rural areas and that child mortality rates are higher in rural than urban settings.[34, 94] These data have also underlined common problems in rural settings, such as low literacy, low availability with poor access to health facilities, low proportion of health-facility deliveries, high total fertility rate per woman (≈7 per woman), high maternal mortality ratio (330 per 100,000 live births), and an overall higher incidence of poverty in households living in rural areas compared to those in urban settings.[32, 34, 94, 96]

Based on the above described socio-demographic and health system status, we believe that the observed PNMR, NMR and IMR in our study are representative of other rural settings in Burkina Faso. However, it should be noted that Banfora region was – relatively speaking – better off from an economic perspective compared to other rural areas in Burkina Faso[96] and,

we cannot therefore exclude the possibility that estimates of PNMR, NMR and IMR which were higher than those reported here may be observed in other rural areas of Burkina Faso poorer than the Banfora area. Poor socioeconomic status is not the only determinant of high child mortality rates, and we think persistent cultural practices, such as inadequate nutritional practices during infancy, use of hazardous traditional medicines and the limited women's autonomy in couples in rural areas of Burkina Faso, are potential predictors.

Nevertheless, our primary hypothesis is that the overall poor health system in Banfora's region, as in the other rural areas of Burkina Faso, was the key factor in the observed high PNMR and IMR. Only a quarter of the villages in this study had a local health facility and almost all the households in these areas were dependent on the public health system.

In such a situation, it is unlikely that being relatively not so poor compared to other regions would affect the risk of perinatal or infant death. Both the ratio of health personnel to population and the average distance to the nearest local health centre in Banfora were indicative of a weak health system in Banfora, a situation that also persists in other rural settings of Burkina Faso.[102] With this assumption, our data may be generalized to other rural areas of Burkina Faso.

Implications of the findings

In this thesis, we were able to assess the burden of perinatal and infant deaths in a rural area of Burkina Faso, and identify potential risk factors for these outcomes. While scrutinizing their predictors, we indirectly assessed the role of the local health system and cultural factors for the persisting high PNMR and IMR.

We concluded that our findings could probably be generalized to other rural areas of Burkina Faso, and therefore our recommendations go beyond the region of Banfora and should be relevant in any effort to address this unacceptably high burden of fetal losses and infant deaths in rural Burkina Faso. In addition, we also provide suggestions for future research on the same topic in Burkina Faso.

Recommendations

The Ministry of Health, national health authorities and policy makers in Burkina Faso needs to:

- Recognize in a clear policy and action plan that reduction of perinatal and child mortality is an urgent health priority, especially in rural areas.
- Improve the local and national health statistics on stillbirths, early neonatal deaths, and overall infant deaths, and set up a birth registry or reproductive health registry in all local health facilities of Burkina Faso. Data generation is a first step towards customized interventions.
- Increase advocacy for mobilization of funds and donors' sensitization of the 'true' levels of SBR, PNMR and IMR in rural Burkina Faso. National average data may be misleading and the consequences of the 'achievement disease' need to be avoided.
- Revise the current policy on the training of skilled birth attendants to serve in maternities of primary health facilities, both the educational requirements (> high school level) and the content (curriculum to focus on quality of obstetric care and includes a module on the ethics of care).
- Provide basic equipment (for clean deliveries, basic EmoC and basic neonatal resuscitation), and improve the number and motivation of staff in local health facilities in rural settings, including a reward policy for those willing to serve in these areas.

For health staff of local health centres in Banfora and elsewhere in rural areas:

- Improve their knowledge of the cultural practices or barriers to high attendance at local facilities where they are available.
- Remain professional and follow the ethics of care, even when working in the context of low maternal literacy and extreme poverty, as in rural areas.
- Maintain their skills and knowledge in the provision of primary health care through individual refresher training and increased demand for continuous training at the district level.

- Establish and maintain a permanent dialogue with community-leaders, as their participation is the key in the successful implementation of activities at the local health facility.

For local communities in rural areas:

- Increase their demand for health infrastructures, health care and health interventions, as stipulated since the Alma Ata conference.
- Discuss regularly with policy makers through their representatives, and make suggestions for improved utilization of antenatal and childbirth services.
- Get involved in all activities aimed at improving maternal and newborn health and care in their village through provision of local community workers.
- Uncompromising self-criticism of cultural challenges preventing high facility-delivery rates, or that leading to frequent home deliveries, or limited women's autonomy in care-seeking behaviour.

Future research

There is scope for further research on the themes below that should improve our knowledge of risk factors for perinatal and child deaths in rural areas of Burkina and also provide some insights for successful implementation of community-based and facility-based interventions considered to reduce perinatal and infant mortality rates:

- The role of the actual health system in the persistent high burden of perinatal and infant deaths in rural areas of Burkina Faso.
- Assessment of the association of EBF-promotion with perinatal and infant death risks in the context of Burkina Faso in larger cohort studies or trials.
- Field evaluation of the actual coverage and quality of obstetric and perinatal care in primary health facilities in rural Burkina Faso.
- An effectiveness study of the current subsidy policy for emergency obstetric care on utilization of antenatal and childbirth services, and on infant survival in rural settings.
- Evaluation of culturally perceived barriers to high attendance at maternities in rural areas of Burkina Faso and opportunities for improved utilization.
- Implementation and evaluation of community-based health interventions (cash transfer, phone reward, delivery subsidy, community-owned transportation means, etc.) to reduce significantly the actual levels of SBR, PNMR and IMR in rural areas of Burkina Faso.
- Implementation and evaluation of facility-based interventions (phone reward, online support, grant for training, ambulance, etc) to improve the overall quality of care at facilities, and to reduce the risk of maternal and perinatal deaths at local health centres.
- Assessment of the feasibility and the relevance of an electronic reproductive health registry in rural areas of Burkina Faso.
- Assessment of the feasibility and relevance of an electronic and self-learning programme for refresher training of local health staff and remote assistance for local staff during management of women in labour and immediate postpartum.

Conclusions

The burden of perinatal and infant deaths remains unacceptably high in rural areas of Banfora. We found the highest PNMR and IMR ever published in recent reports from Burkina Faso.

Factors associated with increased risk of perinatal, neonatal and infant deaths included mainly the socio-demographic background of the mother (pauciparity, polygygny), her medical history (previous child death) and the newborn baseline characteristics (birth at the dry season and twinship). The proportion of health-facility deliveries was low, but was not associated with risk of perinatal death. The study intervention appeared to be associated with higher risk of perinatal and infant deaths, but this needs further investigation.

Overall, the rural location of the study villages and its local environment characterized by low maternal literacy, a poor health system with low health facility deliveries and apparent poor quality care in maternities, and the presence of cultural challenges (e.g. polygyny) were all the likely reasons for this scourge. However, there are opportunities for improving the current situation both at community and facility levels.

We believe that our findings are generalizable to other rural areas in Burkina Faso, and as such this country is unlikely to meet MDG-4 by 2015. Our results call for urgent actions both at facility and community levels, for further political commitment and increased advocacy from national health authorities and local stakeholders to strengthen the actual health system, mobilize the local communities, and raise funds for improved perinatal, neonatal and infant survival in rural areas of Burkina Faso. This is a noble fight that deserves to be undertaken.

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