Evaluation of Strategies and Outcomes in Maternal and Child Health

EVALUATION OF STRATEGIES AND OUTCOMES IN MATERNAL AND CHILD HEALTH

CORRINA MOUCHERAUD

A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Science

in the Department of Global Health and Population

Harvard University

Boston, Massachusetts.

May, 2015

Dissertation Advisor: Dr. Joshua Salomon Corrina Moucheraud

Evaluation of strategies and outcomes in maternal and child health

Abstract

Maternal and child mortality, particularly during the neonatal period, are among the most challenging global health issues of this era. This burden disproportionately affects the poorest populations, across and within countries. And although many of these deaths would be avertable, improvements in most countries have been slow. This dissertation explores three main research questions: (1) what is the effect of maternal health on infant outcomes?; (2) what survival gains could be attained through improved interventions, across the continuum of care?; and (3) how do health system characteristics affect the potential impact and cost-effectiveness of such interventions? The first paper uses decision modeling to evaluate how increased use of family planning and of improved intrapartum care could reduce maternal deaths in Nepal—as well as the cost-effectiveness of doing so, and of accompanying interventions to achieve these targets. The second paper estimates the potential impact of administering interventions from the Safe Childbirth Checklist at health facilities in India, and how "real world" implementation might see different results due to health system characteristics. Lastly, the third paper examines child survival outcomes following a maternal death in Ethiopia, using a long-term household-level longitudinal dataset. Together, these papers aim to provide new insights on approaches to reducing the high level of mortality among women and children.

Table of Contents

List of Figures

List of Tables

Acknowledgments

I would like to thank my research committee for their guidance and instrumental contributions to my dissertation. In particular, I thank Josh Salomon, my academic advisor, for his advice and mentorship throughout my time at HSPH, which helped me become a better researcher. I would also like to thank Stephen Resch for his guidance and support, both for my dissertation and my academic career as a whole; and Ana Langer, for sharing her extensive expertise and many thoughtful insights, which greatly improved my papers. I also thank Vinod Paul for serving as an outside reader for this dissertation, and for his comments and suggestions for its improvement. Many thanks also to Barbara Heil, who provided critical assistance throughout this process.

For Chapter 2, I would like to thank colleagues from the Center for Health Decision Science—especially Steve Sweet, Zach Ward and Daniel Erim; and I am deeply indebted to the hospitality and valuable insights of those at the Nepal Health Sector Support Programme, especially Maureen Dariang, Suresh Mehata and Ganga Shakya. For Chapter 3, I thank Natalie Carvalho and Grace Chan for their very useful inputs into its development, as well as helpful discussions with researchers at Ariadne Labs, including Lisa Hirschhorn, Jon Gass, Grace Galvin and Katherine Semrau. For Chapter 4, I thank all my coauthors, especially Jocelyn Finlay, Alicia Ely Yamin and Alemayehu Worku, for introducing me to this project, and all their instrumental guidance and support.

I am very appreciative of the funding sources that enabled me to participate in this doctoral program and conduct my research, including from the Leopold Schepp Foundation, PEO International, the Department of Global Health and Population, the Harvard T.H. Chan School of Public Health, the Harvard Institute for Quantitative Social Sciences, the Harvard South Asia Institute, and the Maternal Health Task Force.

I also want to deeply thank my family for their support, encouragement and patience throughout my doctoral program. I also thank members of my cohort and department, and my friends, for their help and friendship over the years. Additionally, I would also like to express deep gratitude to Michael Reich and Marc Roberts, both of whom mentored me and played a significant role in shaping my development as a researcher.

Corrina Moucheraud

1 Introduction

Maternal and child mortality are intractable challenges in global health. These deaths disproportionately afflict the poorest populations, and most would have been avertable with proper high-quality medical care. But progress remains insufficient in reducing maternal and child, especially infant, mortality. This dissertation explores questions about maternal and child mortality, including the degree to which these outcomes are related, and how to address this burden in specific contexts, particularly from a health systems perspective.

Recent years have seen an overall decline in the estimated number of maternal deaths, which now number approximately 289,000 per year (this represents a 45% decrease since 1990) [1]. But there is substantial regional heterogeneity: the maternal mortality ratio (MMR) in developing countries is 14 times greater than that in developed countries (230 versus 16 maternal deaths per 100,000 live births); and the lifetime risk of maternal death is 1 in 160 in developing countries, but only 1 in 3700 in developed countries [1]. There also exist disparities in maternal mortality within countries, including by geographic area (urban versus rural, for example) and there is increasing evidence of a clear income/wealth gradient whereby poorer groups see much higher MMR values than their richer counterparts, in developed and developing countries [2].

Improvements in maternal mortality have been slow and uneven. Of all the Millennium Development Goals (MDGs), number 5 (to reduce maternal mortality) has seen the least progress [3]. Many countries will fail to meet the MDG to reduce their MMR by three-quarters by 2015: only 25 were estimated as on-track to achieve this MDG as of 2011, and no countries in sub-Saharan Africa nor south Asia (the two regions with the largest shares of maternal deaths) are likely to do so [4].

Childhood mortality has seen more worldwide progress: many countries (49) were estimated to be on-track to meet MDG number 4, to reduce deaths among children under age 5 by two-thirds—but again, most countries in sub-Saharan Africa and south Asia are unlikely to achieve this [4]. Four out of every five child (under-5) deaths occur in these two regions [5]. Although the global child (under-5) mortality rate has approximately halved since 1990 (from 90 to 48 deaths, per 1000 live births) [5], challenges remain. First, there is a gulf of difference in outcomes for children in richer versus poorer countries: in sub-Saharan Africa, one in ten children die before their fifth birthday—and this risk is over 15 times larger than that faced by children in developed countries [6]. Additionally, the mortality burden is increasingly concentrated during infancy. Neonatal survival (during the first 28 days of life) has improved at a slower pace than post-neonatal survival, so a larger share of child deaths now occur during the neonatal period: from 37% in 1990 to 44% in 2012 [6]. Stillbirths are not counted within the MDGs, but almost half of the estimated 2.6 million annual stillbirths occur during the intrapartum period (1.2 million), due to many of the same causes as early neonatal deaths, and almost all occur in poor countries [7, 8]. And similar to maternal mortality, intrapartum stillbirths and deaths among neonates are largely avoidable—mainly by improving birth conditions and providing high-quality obstetric care.

Reducing maternal and neonatal deaths are thus related global priorities: both represent truly excess burden and disproportionately affect the poorest populations; progress towards improvements for both has been slow and uneven; and both could be addressed with better medical care during the intrapartum period [7, 9]. Despite claims that "we know what works" to address this burden, much remains unclear [9]—including robust evidence on the interrelated nature of these outcomes, and the crucial aspects of health systems in delivering interventions—and that is the focus of this dissertation. I use different quantitative approaches to answer the following questions:

1. What is the effect of maternal health (morbidity and mortality) on infant outcomes? (Chapters 3 and 4)

2. What survival gains could be attained through improved interventions, across the continuum of care (Chapters 2 and 3)?
3. How do health system characteristics affect potential impact (Chapter 3) and cost-effectiveness (Chapter 2)?

In Chapter 2, I explore how achieving different degrees of contraceptive use, safe abortion care and quality intrapartum care may affect maternal mortality metrics in Nepal. Nepal has recently made substantial improvements in maternal health, as well as many recent policy changes (e.g., abortion legalization and expanded access to obstetric care), but it must make further reductions to contribute to the Sustainable Development Goals' target global MMR of 70 maternal deaths per 100,000 live births. By using a computer-based decision model that incorporates Nepal-specific information on demographics, childbearing-related behaviors, epidemiology of birth complications, health system characteristics, and costs of delivering the continuum of reproductive care to women, I analyze the potential impact and cost-effectiveness of achieving improvements in family planning, abortion safety, and intrapartum care. Additionally, I investigate how changing health system input costs could affect these outcomes; and, calculate threshold strategy prices: what is the "price tag" at which an accompanying intervention to achieve the aforementioned improvements (family planning, abortion safety, intrapartum care) would render the results non-cost-effective?

Chapter 3 likewise explores how to achieve improved outcomes, with an emphasis on the role of the health system. This paper assesses the readiness of the health system in India to provide quality routine obstetric care, and estimates the potential impact of a Safe Childbirth Checklist intervention given this degree of readiness in the health system. India sees more intrapartum deaths (maternal, stillbirths, early neonatal) than any other country—so success in achieving the Millennium Development Goals at a global level is largely tied to whether improvements occur in India, and these are dependent on whether the health system can provide high-quality obstetric care. The Safe Childbirth Checklist (SCC) is a tool to

guide clinicians in the provision of routine (non-emergency) intrapartum services, and many countries are implementing the SCC in health facilities, although its potential effect on health outcomes has not yet been measured. The SCC also requires certain health system inputs, in terms of infrastructure and equipment (including medicines), and it is unclear whether facilities in India could actually administer the full set of SCC activities—and, correspondingly, how the impact of the SCC might change. This study aimed to estimate the possible maximum impact of items on the SCC if all health facilities in India could implement all items, and how this would attenuate given health system capacity.

Lastly, Chapter 4 utilizes a longitudinal dataset from Ethiopia to analyze the impact of a mother's death during childbirth, or up to 42 days postpartum, on her children's survival. There is widespread belief, but only recently-emerging robust empirical evidence [10], that a mother's death has a profound effect on a child's outcomes, whether health-related morbidity, mortality, developmental (cognitive, psychological), educational, and/or social (household structure, marriage behavior, labor participation). The analysis benefits from a unique large longitudinal dataset (from a Health and Demographic Surveillance Site [HDSS] in Butajira Ethiopia), with data collected frequently from all household members in the study site over many decades. The findings point to the interconnected nature of outcomes for women and children: in this setting, a maternal death was tantamount to the death of her infant. This underscores the importance of improving access to and quality of intrapartum and postpartum care.

This dissertation aims to provide new insights on approaches to improving maternal and infant health. These are global priorities: the excess mortality burden, particularly among the poorest and most underserved populations in the world, has been slow to reduce. The topics addressed here—including the interconnected nature of these outcomes, and the role of a health system in effectively reducing these deaths—are the subject of much global discussion, particularly as we move toward a post-2015 development agenda. These papers offer several different perspectives on how datasets and methodologies may be considered in novel ways to better understand and quantify the burden, as well as

to inform the assessment of approaches to reducing this unacceptably high level of mortality among women and children.

References for Chapter 1

1. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2013*. 2014.
2. Ronsmans, C. and W.J. Graham, *Maternal mortality: who, when, where, and why.* The Lancet, 2006. **368**(9542): p. 1189-1200.
3. World Bank. *Millennium Development Goals: Improve Maternal Health by 2015*. 2014.
4. Center for Global Development. *MDG Progress Index: Gauging Country-Level Achievements*. 2011.
5. United Nations, *The Millennium Development Goals Report 2013*. 2014: New York.
6. United Nations, *The Millennium Development Goals Report: Addendum, Goal 4, Reduce child mortality*. 2014.
7. Lawn, J.E., et al., *Every Newborn: progress, priorities, and potential beyond survival.* The Lancet, 2014. **384**(9938): p. 189-205.
8. Lawn, J.E., et al., *Stillbirths: Where? When? Why? How to make the data count?* The Lancet, 2011. **377**(9775): p. 1448-1463.
9. Campbell, O.M.R. and W.J. Graham, *Strategies for reducing maternal mortality: getting on with what works.* The Lancet, 2006. **368**(9543): p. 1284-1299.
10. Grepin, K.A. and J. Klugman, *Closing the deadly gap between what we know and what we do: Investing in women's reproductive health*, ed. The World Bank. 2013, Washington, D.C.

2 Reducing maternal mortality in Nepal: The impact and cost-effectiveness of increasing use of family planning and of improved intrapartum care

Abstract

Background: Over the past decade, Nepal has undertaken policy changes such as legalization of abortion, and expanded access to antenatal and obstetric care—and has made substantial improvements in maternal health. Its maternal mortality ratio (MMR) has declined accordingly, but there is remaining room for improvement. This analysis uses a decision model to analyze the potential impact and cost-effectiveness of achieving improvements in family planning, abortion safety, and intrapartum care in Nepal.

Methods: A computer-based decision model (the Global Maternal Health Policy Model) was used to simulate the natural history of pregnancy and childbirth. It incorporated information from Nepal-specific data sources on behaviors, e.g., use of family planning, of antenatal care and around childbirth (differentiated by birth location and attendant); as well as epidemiologic information about birth complications. Additionally, costs were estimated based on global, regional and national data sources. The main outcomes of interest were maternal deaths and incremental cost-effectiveness ratios (ICERs).

Results: Nepal could achieve large reductions in the number of maternal deaths (up to 80%) by reducing unmet need for family planning, continuing to improve abortion safety, and addressing the "three delays" of intrapartum care (recognition of complications, transportation, and care availability). This would also be highly cost-effective, and even cost-saving if achievements were attained sequentially. Attaining the most ambitious set of intrapartum targets (to eliminate all intrapartum barriers) has an estimated ICER of US$ 997/year of life saved (YLS) versus status quo, which is very far below the international standard for cost-effectiveness (triple GDP per capita, which is approximately US$ 700 in Nepal). If universal antepartum improvements were also achieved (eliminated unmet need for family planning and unsafe abortion), this would be cost-saving versus baseline. Increasing health system costs did not render this less attractive from a cost-effectiveness perspective: even with a doubling in health worker salaries or facility costs, the most intensive levels of coverage still had ICERs below US$ 1500/YLS. Lastly, we

calculate strategy thresholds: how much would an accompanying intervention strategy need to cost in order to achieve non-cost-effective results? To achieve universal improvements in family planning (eliminated unmet need), abortion safety (universal safety) and intrapartum care (full improvements), total program costs would need to exceed US$ 272 per woman for these to no longer be cost-effective (i.e., ICER versus baseline would exceed triple-GDP per capita), which would be equivalent to a national cost of US$ 405.6 million.

Conclusions: There are further gains to be made in saving women's lives in Nepal, especially if it seeks to reduce its MMR below 100. These results indicate that this will be attainable only with an approach that pairs family planning with safe abortion and improved intrapartum care. The health system improvements that may be necessary to provide this level of increased coverage would require additional investments—but, importantly, these are unlikely to negate the cost-effectiveness findings presented here.

Background

Nepal long had one of the highest maternal mortality ratios (MMR) outside of sub-Saharan Africa [11], but it has made significant recent improvements and now appears likely to meet the Millennium Development Goal to reduce its MMR by at least three-quarters by 2015 [1]. The updated interagency modeled estimates for maternal mortality in Nepal indicate a large and consistent decline, from an MMR of 580 deaths (all per 100,000 women) in 1995, to 430 in 2000 to 310 in 2005, and 190 in 2013 [1]. This overall downward trend is also supported by other sources: the 2006 Demographic and Health Survey estimated a MMR of 281 deaths per 100,000 women [12], a substantial decline from the MMR of 539 indicated a decade earlier [13].

These declines in maternal mortality may be attributable to recent initiatives by the Nepal government—including expanded access to family planning, legalization of abortion, and incentives for antenatal and childbirth services—and accompanying improvements in many indicators, such as the contraceptive prevalence rate and use of institutional deliveries [14]. This study aims to estimate the potential health impact and cost-effectiveness of achieving continued improvements in these three areas, as well as the cost implications of strategies to achieve such improvements.

Maternal health situation in Nepal

Current use of modern contraceptive methods has been steadily increasing in Nepal: the most recent DHS saw 43.2% of married women reporting use, although rates remain low among the youngest age group (only 14.4% among women aged 15-19, and rising to 60% in women above 35). The method mix also differs by age: young women more commonly report use of hormonal methods (pills and injectables) as well as condoms, while older women rely on sterilization (female and, to a lesser extent, male) for contraception. Correspondingly, unmet need is quite high, with 38% of women under 20 reporting an

unmet need for spacing and around one-quarter of women above age 25 reporting an unmet need for limiting methods. [15]

Abortion is now legal in Nepal but there remain challenges with access to and quality of care. According to the most recent DHS, for which data were collected nearly a full decade after abortion legalization in Nepal, women reported that 7.5% of pregnancies within the last five years ended in abortion; the likelihood of this termination outcome increased with maternal age and parity. Most abortions were performed by doctors and nurses. But only 58.8% of women reported having knowledge of where to access safe abortion services, and a quarter of women with recent abortions experienced complications during the procedure, plus another one-quarter of women who experienced complications afterward. [15] Abortion safety significantly affects the likelihood of adverse outcomes: in settings with safe high-quality induced abortion, these case fatality rates can be as low as 0.7 per 100,000 procedures, versus 160 per 100,000 unsafe abortions in Asia [16].

Most women in Nepal deliver their babies at home: only 35.3% of recent births as surveyed by the 2011 Nepal DHS were at a health facility, with highest numbers among young women (41% for women under 20, versus 20% for women over 35). It is becoming more likely to give birth at a health facility, however: in the 1996 and 2001 DHS, 8% of births within the prior five years occurred at a health facility, and this rose to 17% in 2006 [17-19]. There is considerable heterogeneity in facility use for childbirth; in addition to varying by maternal age, the likelihood of institutional delivery appears to be associated with parity, urban versus rural residence, education group and geographic region. For women who delivered at home, only 2.8% of these births were attended by a skilled provider (doctor, nurse, or nurse/midwife). When asked why they did not deliver at a health facility, women commonly reported lack of necessity and custom, as well as distance and transportation barriers, and cost. [15]

In 2005, the Nepal government began introducing financial incentives to promote institutional childbirth: women received a payment following a birth at a public health facility, user fees were eliminated for women living in the poorest districts, and health workers received incentives to attend deliveries (institutional or at home). In 2009, public facilities in Nepal removed all user fees for childbirth services (all types of births), and began to provide transportation incentives, a voucher for antenatal care, and referral incentives for birth attendants. An early evaluation concluded that the policies were significantly associated with an increased proportion of deliveries occurring at health facilities [20]; this was a particularly notable finding since the majority of surveyed women (nearly three-quarters) were unaware of the free childbirth services by early 2010, and such low levels of knowledge may have inhibited uptake. In the 2011 NDHS, the proportion of surveyed women of reproductive age who were aware of free delivery services was 76.2% and knowledge of the transportation incentive was 88.7%—suggesting that knowledge may have substantially increased in the recent past.

Methods

Overview

This analysis used the computer-based Global Maternal Health Policy Model [21, 22], which combines the best-available data on the epidemiology of pregnancy and its related complications, with local individual and health system characteristics, to simulate the natural history of pregnancy and childbirth in a given context. The model uses Monte Carlo and Markov simulation to estimate outcomes, including individual demographic and clinical events (pregnancies, births, maternal complications and sequelae), population-level measures (fertility rate, maternal mortality ratio, lifetime risk of maternal death, life expectancy), and costs.

We identified possible pathways to reducing burden of maternal death in Nepal, via increases in family planning, abortion safety, and obstetric care. There were 4 family planning improvement scenarios, 4

abortion safety improvement scenarios, and 4 intrapartum care improvement scenarios—each of which incrementally changed the model variables, to represent population-based improvements. These were each modeled independently, and then were analyzed as combinations.

All pathways were ranked by ascending costs and benefits, and those more-costly and less-effective than others on the list were considered inefficient. For the remaining, we calculated incremental cost-effectiveness ratios (ICERs): the additional cost of that option divided by its additional benefit, as compared to the next least-costly option. Using WHO-CHOICE criteria, ICERs were classified as cost-effective for Nepal if they were less than 3 times Nepal's GDP per capita (pcGDP) of approximately 700 USD (i.e., 2100 USD) [23]. Additionally, we analyzed whether the main results changed if different cost assumptions were used, both due to geographic heterogeneity (e.g., the higher cost to transport women in mountainous areas), and to explore uncertainty around health system cost parameters (bed-day costs, and health worker salaries). We also estimated the "price tag" at which a strategy for achieving the gains analyzed here would no longer be cost-saving in the case of family planning increases, or would render ICERs below the triple-pcGDP threshold for intrapartum improvements. Lastly, we conducted sensitivity analyses to assess how much the findings may have been influenced by parameter uncertainty.

The model

The Global Maternal Health Policy Model is a computer simulation that models the natural history of pregnancy and childbirth. A woman's lifetime is divided into monthly time increments within which a woman transitions between health states. Girls enter the model and, within each time period, experience some likelihood of pregnancy, depending on age, clinical background and use of contraception (by method, with associated failure rates). If a woman becomes pregnant, there is some chance that the pregnancy ends in miscarriage or in induced abortion (some fraction of which are unsafe and may lead to complications) or that it continues to term. During childbirth, a woman may experience a complication and this may cause death or other sequelae, all depending on the complication type and severity or the

woman's underlying comorbidities. All women also face some annual risk of death due to age-specific non-maternal all-cause mortality.

In the model, deliveries vary by location and care (home, with family member, traditional or skilled birth attendant [SBA]; or health facility by type, i.e. health centers with SBA, and basic or comprehensive emergency obstetric care facilities [bEmOC and cEmOC, respectively]). Interventions to manage complications during childbirth were modeled as reducing incidence or case fatality, with a degree of effectiveness and availability that varies by delivery attendant and setting. The Appendix to this chapter provides more detailed information on all aspects of the model.

Data and assumptions

Epidemiology and interventions: Selected model values and assumptions are shown in Table 2-1, and additional details are provided in the Appendix, including parameters (and ranges used for sensitivity analyses) for: incidence and case fatality rates of pregnancy- and childbirth-related complications; approaches to reduce these; and intervention coverage for contraception, antenatal care and childbirth care (including site and type of health worker present).

In the model, if a referral is required during childbirth at home or at a lower-level health facility, women face three potential barriers [24]: delay in recognizing the need for the referral (including recognition of complications and symptoms, and permission to seek care elsewhere), delay in transfer to the referral facility (including means of transportation), and delay in receiving appropriate care at the referral facility (including adequate staffing and supplies, high-quality services). Data to inform assumptions about the likelihood of these delays came from surveys of facilities and households in Nepal, as well as government reports and published studies from Nepal (more detail in the Appendix, section 2.2).

Table 2-1: Selected model parameter inputs and assumptions, epidemiologic and intervention-related

Coverage of contraception, by age group (among currently married women) [15]							
	Age 15-19	Age 20-24	Age 25-29	Age 30-34	Age 35-39	Age 40-44	Age 45-49
Family planning (any method)	17.6%	29.5%	46.3%	59.6%	67.4%	68.1%	53.7%
Modern methods	14.4%	23.8%	39.8%	52.2%	59.9%	59.9%	48.0%
Pill	20.8%	15.5%	13.6%	10.5%	7.5%	5.0%	3.5%
IUD	0%	0.5%	4.5%	2.5%	3.2%	2.0%	1.3%
TOL	0%	15.1%	29.6%	35.8%	39.7%	45.2%	47.7%
Condom	45.1%	21.8%	14.3%	8.6%	5.8%	3.8%	2.7%
Injectables	34.0%	35.7%	24.9%	21.3%	18.2%	15.9%	11.9%
Unmet need	41.5%	36.8%	30.5%	26.0%	20.7%	15.8%	13.1%
Coverage of prenatal care [15]							
Prenatal care	50.1%						
Delivery location [15]							
	Age 15-19	Age 20-34			Age 35-49		
Facility delivery	41.2%	35.2%			19.9%		
Home delivery with SBA	2.9%						
Assumptions for available transport to appropriate facility							
From home to EmOC	20%						
From sub-health post or health post or PHCC to EmOC	35%						
From bEmOC to cEmOC	50%						
Assumptions for available facility, staff/supplies, quality of care							
bEmOC	50%						
cEmOC	70%						

Abbreviations: IUD – intrauterine device; TOL – tubal ligation; SBA – skilled birth attendant; EmOC – emergency obstetric care center; PHCC – primary health care center; bEmOC – basic emergency obstetric care center; cEmOC – comprehensive emergency obstetric care center

Costs: Information about economic data included in the model is presented in Table 2-2, and more detail is provided in the Appendix (section 2.3). Costs were estimated using the United Nations Population Fund (UNFPA) Reproductive Health Costing Tools Model, which estimates direct costs (including drugs, supplies, and personnel requirements) of 45 reproductive health interventions, and investments required for scale-up [25]. It incorporated Nepal-specific information on salaries for health workers [26], and

estimates from WHO-CHOICE on facility costs in Nepal [27]. All costs were converted to 2006 US dollars.

Table 2-2: Selected model cost inputs

Cost component	Base case (in 2006 US dollars)
Family planning	
Oral contraceptives	7.24
Injectable contraceptives	7.39
Condoms	5.87
Intrauterine device	4.63
Female sterilization	10.42
Male sterilization	5.77
Antenatal care	
Four visits	7.99
Abortion	
Incomplete abortion	6.08
Elective abortion	
Post-abortion complications	12.03
Delivery	
Home (TBA, SBA)	2.63, 3.61
Facility (birthing center, bEmOC, cEmOC)	11.52, 12.18, 15.60
Management of complications (bEmOC, cEmOC)	
Obstructed labor	16.14, 39.87
Maternal hemorrhage	17.41, 103.22
Sepsis	21.70, 48.26
Severe pre-eclampsia/eclampsia	23.57, 61.02
Postpartum care	
One visit	2.94

Analyses

Model validation: The model's performance was assessed by inputting the above information and then comparing model-generated outputs to empirical data found in the literature: life expectancy, total fertility rate, MMR, proportionate mortality ratio, and distribution of the direct causes of maternal death. Certain parameters in the model were adjusted (i.e., likelihood of severity in the case of sepsis or of pre-

eclampsia) during a calibration exercise, to better match model results to the aforementioned empirical endpoints.

Cost-effectiveness analyses: We evaluated approaches to reducing maternal mortality, by reducing unmet need for family planning, reducing unsafe abortions, and as bundled health system improvements (including SBA recognition of symptoms, transportation systems, and quality of bEmOC and cEmOC care).

First, stepwise improvements in each of these were independently explored. Unmet need for family planning was reduced in 25% increments, and unsafe abortions were likewise reduced in 25% increments; the highest attainable level of each was to eliminate unmet need, and to eliminate unsafe abortions. Intrapartum care changes were modeled as "upgrades," which combined improvements in starting delivery locations and attendance, recognition of complications by different types of birth attendants, availability of transportation between delivery site types, and availability of emergency obstetric services at different facility types. Each upgrade included improvements in all of these variables, in 25% increments, until each attained universal (or near-universal) levels in the final upgrade. Further details are available in the Appendix. After assessing the changes in outcomes and costs achieved with each of these 12 scenarios (4 for family planning, 4 for abortion safety, 4 for intrapartum care), we explored combinations of these: for example, a 25% reduction in unmet need plus a 25% increase in abortion safety; and then also with the addition of a 25% change in the intrapartum care variables. The incremental cost-effectiveness of each scenario was assessed, both compared to baseline (status quo) and compared to the adjacent next-best package. In particular, we were interested in paired stepwise reductions in unmet need and unsafe abortions (i.e., 25% reductions in both, 50% reductions in both, etc.), alone and in combination with the 4 intrapartum care scenarios.

Cost changes: We also assessed the effect of changing cost assumptions, in two different analyses. First, to reflect Nepal's extreme geographic diversity and the effect this might have on scaling intrapartum-related costs—especially transportation and referrals—we explored the possibility that such costs would increase heterogeneously via regional differences. We used 3 groupings, to roughly correspond with Nepal's eco-development zones: mountain regions (as the most difficult to reach), hill regions (with the exception of the Central hill zone, which includes Kathmandu), and Kathmandu plus the terai (mostly plains and valleys). As a verification, we assessed variability in institutional delivery rates by eco-development zone in the 2011 Nepal DHS: the highest rates were in the terai and Central hill zones, and the lowest were in the mountains and hills [15].

The most recent Nepal census reports that 6.7% of the population lives in the mountains, 28% lives in the hills, and 65.3% lives in the terai plus Central hills [28]. We used this population distribution, and applied different magnitudes of price change to each group: intrapartum care costs were estimated to be 50% higher in the hills versus the terai, and twice as high in the mountains versus the terai. We re-ran the main analyses using these three different cost levels, and weighted the results based on the population distribution to attain aggregate national values.

The second cost-related analysis focused on health system inputs. The cost estimates outlined in Table 2-2 are comprised of three main components: health workers (salaries, effort, quantity), health facilities (bed-day costs, number of days), and supplies (equipment, medicines). As described in the Appendix (section 2.3), the latter (supplies) are derived from prices quoted in the UNICEF Supply Catalogue [29] and the MSH International Drug Price Indicator Guide [30]; but health worker salaries and bed-day costs are estimated, from a recent local report [26] and from the WHO-CHOICE modeled estimates [27] (respectively). Using these data at face value introduces possible measurement error: the estimates themselves may have some degree of uncertainty, and they may not be precisely applicable to the situation in which we apply them in the model—for example, Nepal may not see the exact drug price

listed in the MSH Guide, or the prices may not be relevant under changing conditions such as greater use leading to bulk purchasing. We therefore explored the potential impact of changing these health system input costs, by doubling bed-day costs and health worker salaries.

The WHO-CHOICE project models bed-day costs as a function of occupancy rate, inpatient volume, and inpatient stay duration. The base estimated bed-day cost uses an assumption of 7.15 days for the average inpatient length of stay. Since few women remain at the hospital for so many days following childbirth in Nepal [31], we halved this assumption (which approximately doubled the bed-day cost), and analyzed the effect of doing so on our cost-effectiveness results. We also doubled health worker salaries from the baseline values (which had been collected via a survey of health workers in Nepal), and examined how this changed the main results.

Intervention threshold analyses: Cost-effectiveness analyses such as these compare different options for improving maternal outcomes—e.g., via family planning and intrapartum care at various levels of coverage—but they do not explore issues of implementation. This model analyzes different levels of reductions in unmet need for contraception, for example, but not the specific approach(es) required to achieve these. So, using the main cost-effectiveness results, we estimated a threshold "price tag" for an accompanying intervention strategy. In other words, given the incremental cost-effectiveness ratio of a 25% reduction in unmet need versus status quo, how much could be spent on an intervention that achieves this reduction, before it becomes non-cost-effective (or non-cost-saving, depending on the starting ICER). The per-woman costs were estimated from the model, and these were extrapolated to population-level values using the 2011 Nepal census [28]. The per-woman cost captures an investment that begins during a woman's adolescence and spans her reproductive life course (given the structure of the model), so population-level estimates draw from the number of women aged 15-19 in Nepal.

Sensitivity analyses: Sensitivity analyses were conducted to estimate the impact of parameter uncertainty. We decomposed improvements in family planning, safe abortion and intrapartum strategies to assess the potential impact of components of each. Full results of all sensitivity analyses can be found in the Appendix.

Around family planning, we tried other combinations of achieving increased use of family planning: for example, eliminating unmet need for spacing, and of limiting, for different age groups. We also examined the effect of shifting women's use of contraception to methods with lower failure rates. Since data on abortion prevalence and safety are generally not very robust, we conducted sensitivity analyses to examine the effect of changing these parameters (likelihood of elective abortion, and safety) on outcomes. And, to assess the sensitivity of our results to assumptions made about intrapartum care, we analyzed the separate effects of eliminating only the first and second "delays" of childbirth careseeking [24] (recognition of complications, and transportation to a facility), as well as adjusting assumptions about EmOC capacity at health facilities.

Results

Model validation

Model-generated estimates of health outcomes were similar to those found in the published literature, see Table 2-3. This includes concordance on life expectancy, total fertility rate, and MMR, which were within the confidence intervals of several recent published estimates. The distribution of maternal deaths by cause was very close to that from a recent regional estimate.

Table 2-3: Model outputs and published values (model calibration results)

Model output compared to literature estimates of maternal health indicators		
	Published	**Model**
Total fertility rate (TFR)	2.6 [15]	3.13
Life expectancy (at ages 15-19 years)	58.1 [32]	59.0
Maternal mortality ratio (MMR) (range)	190 (110-340) [1]	257
Lifetime risk of maternal death	1 in 200 [1]	1 in 124
Attributable mortality [33]		
Hemorrhage	43.0%	43.0%
Obstructed labor	16.9%	17.0%
Hypertensive disorders	16.7%	16.7%
Sepsis	15.8%	15.7%
Unsafe abortion	7.6%	7.6%

Cost-effectiveness analyses

Reducing unmet need for contraception & increasing access to safe abortion services: In the model, reducing unmet need for contraception had a substantial impact on fertility as well as maternal deaths. At the most extreme, eliminating all stated unmet need decreased the TFR from 3.12 (status quo) to 1.62, and the number of maternal deaths decreased by nearly half (48.1%). Smaller reductions in unmet need had proportionally smaller effects on changing health outcomes, as shown in Table 2-4. It should also be noted that increased use of family planning affects the MMR statistic in both the numerator (number of deaths) and denominator (number of births)—which is why this indicator did not change as family planning use was scaled up in the model (shown in Table 2-4), even as it reduced maternal deaths.

Modeled health outcomes improved when the likelihood of a safe abortion was increased, but the gain was modest compared to those discussed above for reducing unmet need for contraception: eliminating all unsafe abortions reduced the MMR from 257 to 238, and decreased deaths from maternal causes by 6.8%. Results are shown in Table 2-4. Also, when these approaches were paired, reducing unmet need had a

spillover effect onto abortion-related deaths: even with no change in abortion safety, eliminating unmet need for contraception halved the number of maternal deaths from unsafe abortion. All family planning and abortion strategies were cost-saving over baseline.

Table 2-4: Health effects of reducing unmet need for family planning and increasing safe abortion provision

	% decrease, deaths from maternal complications	TFR	MMR	% risk
Family planning				
Status quo (unmet need: 15.7% overall)	-- (reference)	3.12	257	13%
Reduce unmet need by 25% (to 11.8% overall)	11.9%	2.74	258	11%
Reduce unmet need by 50% (to 7.85% overall)	24.0%	2.38	258	10%
Reduce unmet need by 75% (to 3.93% overall)	36.0%	2.01	257	8%
Reduce unmet need by 100% (to 0% overall)	48.1%	1.62	257	7%
Safe abortion*				
Status quo (unsafe abortions: 25%)	-- (reference)	3.12	257	13%
Reduce unsafe abortions by 25% (to 18.75%)	1.7%	3.12	253	12%
Reduce unsafe abortions by 50% (to 12.5%)	3.4%	3.14	248	12%
Reduce unsafe abortions by 75% (to 6.25%)	5.1%	3.14	243	12%
Reduce unsafe abortions by 100% (to 0%)	6.8%	3.15	238	12%
Family planning & safe abortion				
Status quo	-- (reference)	3.12	257	13%
Reduce unmet need & unsafe abortions by 25%	13.5%	2.75	253	11%
Reduce unmet need & unsafe abortions by 50%	26.6%	2.39	247	9%
Reduce unmet need & unsafe abortions by 75%	39.4%	2.00	244	8%
Reduce unmet need & unsafe abortions by 100%	51.8%	1.63	238	6%

Improving intrapartum care and packaged interventions: Significant reductions in the MMR will likely only occur with health system improvements, and increases in institutional and attended childbirth, accompany such pregnancy-related behavior change. This is true both from a conceptual level

* Note that abortion interventions were modeled as reductions in unsafe abortions. The baseline probability of an abortion being unsafe was 25% (due to lack of such data, this is an estimate and was adjusted during sensitivity analyses as discussed below); this was reduced by 25% (to 18.75%), by 50% (to 12.5%), by 75% (to 6.25%) and by 100% (no unsafe abortions).

(particularly for the MMR indicator of the MDGs, since this is especially insensitive to changes in fertility patterns), and as indicated by the model. Additionally, decreased fertility—due to less unmet need for family planning and/or safer abortion care—could also lessen the need for emergency obstetric care, since higher risks are seen among older women with high-parity births. Results suggest that, in the extreme scenario of zero unmet need for family planning and eliminated unsafe abortions, maternal deaths in Nepal could be approximately halved (51.8%), but the MMR would only decline from 257 to 238. Further reductions would require increasing utilization and quality of intrapartum care, and access to emergency obstetric care.

We estimated health impacts of packaged improvements in intrapartum care, including: starting delivery locations and attendance, recognition of complications by different types of birth attendants, availability of transportation between delivery site types, and availability of emergency obstetric services at different facility types. Results for these packaged improvements ("upgrades"), when introduced incrementally and with associated improvements in family planning and safe abortion care, are shown in Table 2-5.

The most intensive upgrade alone could achieve a 54.8% reduction in maternal deaths (MMR decline from 257 to 116); when coupled with the most extreme family planning and abortion increases (i.e., eliminated unmet need and eliminated unsafe abortions), 80.5% of maternal deaths in the model were averted and the MMR dipped below 100, as shown in Table 2-5.

We calculated incremental cost-effectiveness ratios for each upgrade, with and without accompanying improvements in family planning and safe abortion. Because these changes are stepwise and likely to be implemented in sequence (i.e., not directly from baseline to the fullest increase in all parameters, but rather via smaller progressive improvements), the incremental cost-effectiveness of each packaged option is presented as a comparison with the next-best strategy. Table 2-5 shows that the upgrades alone—intrapartum care improvements—were always cost-effective (ranging from US$650 to US$1071 per YLS,

from smallest to largest upgrade); but, when paired with accompanying family planning and safe abortion interventions, all options were incrementally cost saving.

Table 2-5: Variable inputs, plus health outcomes (maternal death decrease, MMR) and economic outcomes (incremental cost-effectiveness ratio versus next-best option), for health system upgrades (intrapartum improvements) with and without accompanying improvements in family planning and safe abortion

	Base case	Upgrade 1		Upgrade 2		Upgrade 3		Upgrade 4	
INPUTS									
Facility births, %	35.3%	50.2%		65.2%		80.1%		95%	
Transport from home, %	20%	38.8%		57.5%		76.3%		95%	
Transport from facility, %	35-50%	50-61.3%		65-72.5%		80-83.8%		95%	
Expedient care at facility, %	50-70%	61.3-76.3%		72.5-82.5%		83.8-88.8%		95%	
Unmet need reduction, %	--	none	25%	none	50%	none	75%	none	100%
OUTPUTS									
Decrease in maternal deaths, %	--	9.6%	21.9%	21.8%	43.3%	37.1%	63.3%	54.8%	80.5%
MMR	257	232	227	201	191	162	147	116	97
ICER ($/YLS)	--	650	CS	871	CS	978	CS	1071	CS

Table 2-6 below presents all combinations of upgrades (intrapartum strategies) and family planning/abortion increases. The uppermost left-hand cell represents status quo (baseline). The values shown are mortality reductions over baseline; and the cells are color-coded to indicate incremental cost-effectiveness over baseline. Increasing family planning and safe abortion were always cost-saving, but in the absence of intrapartum improvements, only achieved a maximum mortality reduction of 51.9%. When improvements in intrapartum care were introduced (the "upgrades"), greater mortality gains were seen over status quo; also, incremental cost-effectiveness was reduced although it never exceeded the threshold of triple-pcGDP. It might therefore be prudent to introduce policies in Nepal that seek impact along the

downward diagonal axis: scaling up family planning and safe abortion services, plus incremental improvements in intrapartum care—this could result in savings that could then be invested into the requisite health system improvements necessary for achieving the greatest gains.

Table 2-6: Health effects (percentages) and incremental cost-effectiveness ratios versus status quo (cell shading), of paired family planning/abortion care and intrapartum improvements

		Improvements in facility attendance, referral, transport, quality EmOC				
		Base case	Upgrade 1	Upgrade 2	Upgrade 3	Upgrade 4
Reduction in unmet need for family planning & increased safe abortion	Base case	--	9.6%‡‡	21.8%†††	37.1%†††	54.9%†††
	Reduce unmet need for FP & increase safe abortion, 25%	13.4%†	21.9%†	32.7%‡	46.1%‡‡	61.8%‡‡
	Reduce unmet need for FP & increase safe abortion, 50%	26.6%†	34.0%†	43.3%†	55.0%‡	68.5%††
	Reduce unmet need for FP & increase safe abortion, 75%	39.4%†	45.6%†	53.5%†	63.3%†	74.6%†
	Reduce unmet need for FP & increase safe abortion, 100%	51.9%†	56.8%†	63.2%†	71.1%†	80.5%†

Legend:

† Cost-saving (vs. status quo)

‡ ICER <100/YLS (vs. status quo)

†† ICER <300/YLS (vs. status quo)

‡‡ ICER <700/YLS (vs. status quo)

††† ICER <1000/YLS (vs. status quo)

Cost changes

Geographic heterogeneity: First, we re-ran the main analyses using three different cost levels to reflect the geographic heterogeneity of Nepal, and weighted the results based on the population distribution to attain aggregate values. The results, as shown in Table 2-7, remained similar to those presented above, even

though these scenarios reflected the potential for substantial investments in transportation infrastructure, health worker deployment, referral mechanisms, and care quality (equipment and supplies, etc). The addition of intrapartum improvements decreased the incremental cost-effectiveness (over status quo)—but, such an approach would be necessary to see the largest mortality reductions, and the most intensive option still rendered an ICER of below US$1200/YLS, which is less than twice Nepal's per capita GDP, making it highly cost-effective.

Table 2-7: Health effects (percentages) and incremental cost-effectiveness ratios versus status quo (cell shading), of paired family planning/abortion care and intrapartum improvements—with differential cost increases to reflect geographic diversity of Nepal

		Improvements in facility attendance, referral, transport, quality EmOC				
		Base case	Upgrade 1	Upgrade 2	Upgrade 3	Upgrade 4
Reduction in unmet need for family planning & increased safe abortion	Base case	--	9.6%†††	21.8%†††	37.1%‡‡‡	54.9%‡‡‡
	Reduce unmet need for FP & increase safe abortion, 25%	13.4%†	21.9%†	32.7%††	46.1%‡‡	61.8%†††
	Reduce unmet need for FP & increase safe abortion, 50%	26.6%†	34.0%†	43.3%†	55.0%††	68.5%‡‡
	Reduce unmet need for FP & increase safe abortion, 75%	39.4%†	45.6%†	53.5%†	63.3%†	74.6%‡
	Reduce unmet need for FP & increase safe abortion, 100%	51.9%†	56.8%†	63.2%†	71.1%†	80.5%†

Legend:
†Cost-saving (vs. status quo)
‡ICER <100/YLS (vs. status quo)
††ICER <300/YLS (vs. status quo)
‡‡ICER <700/YLS (vs. status quo)
†††ICER <1000/YLS (vs. status quo)
‡‡‡ICER <1400/YLS (vs. status quo)

Health system costs: When doubled bed-day costs were incorporated into the model, the results remained largely the same as those presented above: the most intensive option (highest levels of family planning, safe abortion, and intrapartum strategies) had an ICER versus status quo of US$ 215/YLS, which is well below the cost-effectiveness threshold. Without any family planning or safe abortion improvements, the most substantial intrapartum option ("upgrade 4") had an ICER versus status quo of US$ 2265/YLS (just above the threshold of triple per capita GDP)—and combining this with even a modest improvement (25% increase) in family planning and safe abortion yielded ICERs below US$ 1500/YLS.

Additionally, even with doubled health worker salaries, most options were still cost-effective: the most intensive set had an ICER over status quo of US$ 3086/YLS, but with improvements in family planning and safe abortion (of 25% and 50%), the ICERs decreased to within the threshold of triple GDP per capita (US$ 2211/YLS and 1526/YLS, respectively).

Intervention threshold analyses

The model targets use of family planning in terms of reducing unmet need. Interventions to achieve this would therefore increase access to contraception for those with latent demand: through supply chain strengthening and management, for example, or by increasing women's awareness of where supplies can be obtained. In other words, an improvement strategy in this model would seek to meet the existing stated level of demand among women in Nepal, not to stimulate new demand by changing norms or acceptability in the general population.[†] So how much could be spent on a family planning program, to reduce unmet need, for the modeled results to indicate the intervention was no longer cost-saving?

[†] This is, of course, not a comprehensive approach to increasing use of family planning—which would target latent demand (addressing unmet need), while also stimulating new demand, for example through changing people's attitudes towards contraception (i.e., increasing the number of women with stated need for family planning).

An intervention that could reduce unmet need by 25% (versus baseline) would no longer be cost-saving if it cost more than US$ 18 per woman; at the population level, this would cost approximately US$ 26.9 million (given the real-world size of the model's starting population of 1.49 million 15-19 year old women in Nepal [34]). If we sought to eliminate unmet need, this would need to cost US$ 69 per woman (versus baseline), and US$ 102.2 million at the population level, to no longer qualify as cost-saving over baseline. A report from the Guttmacher Institute estimated that, for the Asia region, the cost of improving services for all women with unmet need for contraception—including program and system costs, as well as the commodities themselves—would be approximately US$ 7.61 per woman of reproductive age [35]. The model results indicate that we could spend up to US$ 69 per woman (in the 15-19 age group, with costs incurring over the span of reproductive years) on a family planning intervention to eliminate unmet need and it would still qualify as cost-saving; the Guttmacher results suggest that this could be achieved for US$ 7, which would provide a wide budgetary margin for addressing bottlenecks and other structural constraints in the Nepal context.

Likewise, a strategy that increased utilization of improved intrapartum care would be non-cost-effective (i.e., ICERs would be greater than the triple-pcGDP threshold) if it cost more than an additional US$ 20 per woman (or US$ 30.3 million at the population level, for women aged 15-19 who then advance through their reproductive years) for an increase from baseline to the 25% level; or an additional US$ 88 per woman, or US$ 131.4 million at the population level, to move from baseline to the 100% level. An early year (FY 2011/2012) of the Aama program increased the proportion of institutional deliveries from 15% to 34%, and cost approximately US$ 8.1 million [36]. The magnitude of this program effect is approximately equivalent to the modeled shift from baseline to a 25% improvement, as the model captured linear increases in absolute percentage point changes (with no assumptions about relative change); the first upgrade increased institutional delivery could increase from 35% to 50%, or a fifteen percentage point increase. So, comparing this program budget to our modeled program cost threshold (US$ 8.1 versus 30.3 million), would leave a large budgetary margin for increasing care quality (which

was not strongly addressed by the demand-focused Aama program, but would be necessary to achieve mortality effects). Additionally, a full scale-up of the Aama program might fall well below the above-stated cost-effectiveness thresholds, particularly if the average per-woman cost function followed a U- or J-shaped curve as coverage increased, versus the model's linear assumptions about coverage and cost.

Lastly, for combined strategies of reducing unmet need plus increasing intrapartum care to reach the non-cost-effective level, these would need to cost US$ 77 per woman to shift from baseline to the 25% level of each (reduced unmet need and improved intrapartum care) and US$ 272 per woman to shift from baseline to 100% of each. At the population level, these strategies would need to cost, respectively, US$ 114.4 million and US$ 405.6 million to no longer qualify as cost-effective. According to the WHO, total health expenditures in Nepal are approximately US$ 1 billion per year, or 5% of GDP, and approximately US$ 400-500 million of this is spent by the government (of which around 50% is from the Ministry of Health, and the remainder) [37].

Sensitivity analyses

First, we changed parameters around family planning. Eliminating unmet need for spacing at all ages achieved a mortality reduction of 19.8% versus status quo; eliminating unmet need for limiting at all ages reduced mortality by 27.4% versus status quo—and a combined approach that halved, or eliminated, unmet need for spacing at young ages and for limiting at older ages achieved mortality reductions of 17.5% and 35.2% respectively. We also examined the effect of changing patterns of contraceptive use: by shifting women toward methods with lower failure rates (without changing rates of use), this achieved a mortality reduction of 0.9%; if unmet need was halved, there was a mortality reduction of 24.9%; and, if unmet need was eliminated, by 49.1%.

Second, we examined changes in abortion variables. Increasing the likelihood that abortions were unsafe, from 25% to 30% or 50%, increased the number of maternal deaths by 1.3% and 6.7% respectively—but

implementing improvements in abortion care alongside decreases in unmet need for family planning (as in the earlier model results, e.g., shown in Table 2-4), still resulted in cost-saving strategies even at these lower levels of safety. Likewise, decreasing the probability of elective abortion (at the main model's levels of abortion safety) increased the number of maternal deaths, but was still cost-saving.

Third, we examined the sensitivity of our results to assumptions made about intrapartum care. With universal recognition of symptoms and no other interventions, mortality reduced by only 1.2%; pairing this with eliminated unmet need and unsafe abortions achieved a mortality reduction of 52.6%—even without other intrapartum strategies—and was cost-saving versus status quo. Eliminating only the second delay (transportation to and between health facilities) resulted in a 2.9% mortality reduction in the absence of other improvements, and 53.4% when paired with universal family planning and safe abortion (and was also cost-saving versus status quo). Addressing the third delay (likelihood of appropriate care) by decreasing the percentage of EmOC-capable facilities, cost savings (versus baseline) were achieved but health outcomes were worsened (and MMR increased). On the other hand, if almost all facilities were upgraded to include EmOC care, and half of these were bEmOC capable, even with no corresponding improvements in family planning or safe abortion care, this would be highly cost-effective (ICER of US$ 1234/YLS, versus status quo) and would achieve a mortality reduction of 10.3%. If this same expansion in EmOC care were to be achieved alongside an increase in family planning and access to safe abortion, mortality reductions could be as high as 57.2% (and this would be cost saving over status quo).

Discussion and conclusion

Nepal has made enormous strides in reducing its maternal mortality ratio, and the results here indicate that further improvements will depend on continued reductions in unmet need for family planning, ensuring abortion safety, and strengthening intrapartum care around the "three delays." A strategy that encompassed these three factors could achieve up to an 80% reduction in maternal deaths—from an estimated 1100 [1] in 2013 to only 220—and would decrease the MMR in Nepal to 97 maternal deaths

per 100,000 live births. Attaining this degree of improvement would be highly cost-effective: full improvements in intrapartum care would result in an incremental cost-effectiveness ratio of US$ 997/year of life saved versus status quo, and adding antepartum improvements (eliminating unmet need and unsafe abortions) would be cost-saving versus baseline.

Other studies of how to improve maternal health in resource-poor settings have also concluded that a comprehensive approach would be necessary to see major improvements [9, 21, 22]. These results from Nepal echo this, even in a country that has already significantly expanded the use of family planning, and enacted a variety of programs and policies to increase access to safe abortions and to facility childbirth care (and has correspondingly seen lower fertility and MMR) [14].

We also found that the overall findings were robust to changes in cost inputs. Achieving the maximum set of improvements remained cost-effective subsequent to increased health system investments—both to better account for geographic challenges within Nepal, as well as to assess the impact of uncertainty around key inputs (i.e., health worker salaries and facility costs). This suggests that substantial investments into the health system—such as raising health worker salaries (which could increase the attractiveness of such employment, and might improve retention and deployment)—may not render less-favorable options, from a cost-effectiveness standpoint.

We also considered how to achieve the improvements modeled here, and the cost implications of doing so. Using a threshold analysis approach, we estimated how much the accompanying interventions would need to cost to render non-cost-effective results. A strategy that eliminated all unmet need and unsafe abortions, and achieved universal improvements across the intrapartum period (including delivery site and skilled attendance, complication recognition and referral, transport availability, and emergency obstetric care) could add up to US$ 272 per woman in costs and would remain cost-effective at the population level, given the health benefits that would accrue (i.e., ICER versus baseline below the triple-pcGDP

cutoff value). This suggests a maximum intervention "price tag," which is well above literature-based estimates for the cost of such programs in Nepal. The cost-effectiveness values themselves are, however, based on a utility-maximizing framework that estimates willingness-to-pay, and thus are not interpretable as actual monetary amounts; and the threshold (of triple pcGDP) which is used as the basis for these "price tag" analyses is widely used but not without controversy. So these results should be interpreted as exploratory in nature, and further analyses will be required to estimate actual budgetary impact and the opportunity cost of investing in these scenarios versus status quo spending in the health sector.

There is wide agreement in the global public health community about effective interventions to reduce maternal deaths [9], but much less is known about how to implement these ideal recommendations in specific contexts. In other words, there is evidence on specific approaches that result in better health outcomes, but there is limited knowledge of how to actually deliver these interventions, particularly at-scale. The multitude of contextual factors that affect utilization and quality of care—including individual behavioral characteristics and health system constraints—may offer insights into why some interventions may see more impact in one setting than another. And little is known about effective ways to accomplish such improvements at scale. A systematic review of family planning interventions found that most published studies have not found (and in many cases, have not analyzed) effects on actual utilization of contraception, nor health effects such as fertility or pregnancy-related outcomes—and found a dearth of information on "the effectiveness (and cost-effectiveness) of different modes of implementation of both demand-side and supply-side interventions" [38]. Similarly, a systematic review of strategies to improve maternal and neonatal health concluded: "Demand and supply-side strategies can be cost-effective in enhancing the utilization and provision of MNH care and improving health outcomes, though the evidence available is limited by the lack of high quality studies using comparable cost-effectiveness measures. Direct comparison of alternative strategies was also limited by how the studies were framed, as there was substantial variation in how researchers approached, designed and analyzed cost-effectiveness" [39]. While it may be impossible to fully account for all the important contextual issues, a decision

analytic modeling exercise such as the one presented here can help bridge data sources and create hypothetical counterfactual scenarios for the exploration of the costs and benefits in a way that direct empirical analyses cannot [21, 22].

Although the methods presented here have been used elsewhere and evidence is growing on the model's validity and reliability [21, 22], the research has some limitations that must be noted. First, the model only examines maternal outcomes, so impact and cost-effectiveness may in fact be larger if we also considered maternal morbidity, and/or neonatal outcomes. Second, this modeling approach relies on extensive inputs and assumptions, and data quality is an unavoidable challenge. We used recently-collected, Nepal-specific data whenever possible, to minimize this barrier; and, where assumptions were required, we conducted sensitivity analyses and determined that our findings were not significantly affected by these changes. Third, the model includes some important simplifying assumptions—for example, it assumes that the health system can be scaled infinitely (in terms of service availability and quality); this is an important limitation, particularly in a context such as Nepal where the existing health system could not accommodate universal demand in its current state. Lastly, the scenarios modeled here do not account for all possible changes that might result in improved outcomes. For example, the improved intrapartum care upgrades do not alter the "mix" of facilities in Nepal, i.e., no facilities are upgraded to offer a higher level of care. This may also help explain why the maximum attainable MMR for these modeled scenarios—even with the most intensive set of improvements—is still above 90 maternal deaths per 100,000 live births. Further reductions might be possible if more facilities were bEmOC or cEmOC capable.

This study also suggests areas for future research. For example, more nuanced models may be helpful for better representing sub-national variation in population and health system distribution and characteristics; as well as changes over time, given younger generations' different demographic characteristics, particularly those which may affect maternal health (more education, urbanization). Additionally, more research is needed around scaling up proven interventions across the continuum of reproductive health,

and both the costs and impacts of doing so. There is considerable uncertainty around the estimates used here, which also indicates areas where further study would be instructive—including epidemiologic data on complication rates and severity, information on elective abortion (prevalence and safety, particularly in settings where abortions are legal), and costs of health system inputs.

Nepal has already made very impressive strides in reducing maternal deaths and in increasing access to services across the continuum of reproductive health care, i.e., family planning, safe abortion, and obstetric care. It is likely to be one of the only countries to meet the Millennium Development Goal of reducing maternal mortality by three-quarters between 1990 and 2015. But if Nepal seeks continued reductions, additional improvements will be necessary. This paper highlights the importance of further strengthening all three aspects of care. A combined approach across the continuum will achieve the largest mortality reductions—and although improvements in obstetric care will require additional monetary investments, such strategies will remain cost-effective (even with significantly increased health worker salaries and health facility bed-day costs) until a cost threshold that is approximately equivalent to half of one year's total national health spending. There would be large and numerous benefits of eliminating unmet need for family planning, and achieving universal access to obstetric care—not only for the mortality endpoints measured here, but also in maternal morbidity, quality of life and in possible spillover effects across generations and time.

References for Chapter 2

1. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2013*. 2014.
2. Ronsmans, C. and W.J. Graham, *Maternal mortality: who, when, where, and why.* The Lancet, 2006. **368**(9542): p. 1189-1200.
3. World Bank. *Millennium Development Goals: Improve Maternal Health by 2015*. 2014.
4. Center for Global Development. *MDG Progress Index: Gauging Country-Level Achievements*. 2011.
5. United Nations, *The Millennium Development Goals Report 2013*. 2014: New York.
6. United Nations, *The Millennium Development Goals Report: Addendum, Goal 4, Reduce child mortality*. 2014.
7. Lawn, J.E., et al., *Every Newborn: progress, priorities, and potential beyond survival.* The Lancet, 2014. **384**(9938): p. 189-205.
8. Lawn, J.E., et al., *Stillbirths: Where? When? Why? How to make the data count?* The Lancet, 2011. **377**(9775): p. 1448-1463.
9. Campbell, O.M.R. and W.J. Graham, *Strategies for reducing maternal mortality: getting on with what works.* The Lancet, 2006. **368**(9543): p. 1284-1299.
10. Grepin, K.A. and J. Klugman, *Closing the deadly gap between what we know and what we do: Investing in women's reproductive health*, ed. The World Bank. 2013, Washington, D.C.
11. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2008*. 2010.
12. Measure DHS, *Nepal DHS 2006*. 2006.
13. Measure DHS, *Nepal DHS 1996*. 1996.
14. Hussein, J., et al., *An Appraisal of the Maternal Mortality Decline in Nepal.* PLoS ONE, 2011. **6**(5): p. e19898.
15. Measure DHS, *Nepal DHS 2011*. 2011.
16. World Health Organization, *Safe abortion: technical and policy guidance for health systems*. 2012.
17. Ministry of Health and Population (MOHP) [Nepal], New ERA, and ICF International Inc., *Nepal Demographic and Health Survey 2011*, Ministry of Health and Population, New ERA, and ICF International, Editors. 2012: Kathmandu, Nepal.
18. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc., *Nepal Demographic and Health Survey 2006*, Ministry of Health and Population, New ERA, and Macro International Inc., Editors. 2007: Kathmandu, Nepal.
19. Ministry of Health and Population (MOHP) [Nepal], New ERA, and Macro International Inc, *Nepal Family Health Survey 1996*, Ministry of Health and Population, New ERA, and Macro International Inc., Editors. 1997: Kathmandu, Nepal.
20. Powell-Jackson, T. and K. Hanson, *Financial incentives for maternal health: Impact of a national programme in Nepal.* Journal of Health Economics, 2012. **31**(1): p. 271-284.
21. Carvalho, N., A.S. Salehi, and S.J. Goldie, *National and sub-national analysis of the health benefits and cost-effectiveness of strategies to reduce maternal mortality in Afghanistan.* Health Policy and Planning, 2013. **28**(1): p. 62-74.
22. Goldie, S.J., et al., *Alternative Strategies to Reduce Maternal Mortality in India: A Cost-Effectiveness Analysis.* PLoS Med, 2010. **7**(4): p. e1000264.
23. World Bank, *World Development Indicators*. 2014.
24. Thaddeus, S. and D. Maine, *Too far to walk: Maternal mortality in context.* Social Science & Medicine, 1994. **38**(8): p. 1091-1110.
25. UNFPA, *Reproductive Health Costing Tools Model*, version 1.1 MP, Editor. 2005.
26. Society for Local Integrated Development Nepal (SOLID Nepal) and M. Nepal, *Barriers to Effective Policy Implementation and Management of Human Resources for Health in Nepal: Working Conditions of the Health Workforce in Nepal*, SOLID Nepal, Editor. 2012: Lalitpur.

27. World Health Organization, *Health service delivery costs*, Cost effectiveness and strategic planning (WHO-CHOICE), Editor. 2014.
28. Central Bureau of Statistics, *National Population Census 2011*, Government of Nepal, Editor. 2011: Kathmandu.
29. UNICEF Supply Division, *UNICEF Supply Catalogue*. 2009.
30. Management Sciences for Health (MSH), *International Drug Price Indicator Guide (IDPIG)*. 2009.
31. Mehata, S., et al., *Nepal Household Survey 2012*, Ministry of Health and Population Government of Nepal, Editor. 2013: Kathmandu, Nepal.
32. World Health Organization, *Life tables for member states, 2009*. 2012.
33. UNICEF Statistics and Monitoring Section Policy and Practice, *Country Profile Nepal - Maternal, Newborn & Child Survival*. 2012.
34. Central Bureau of Statistics, *National Population Census 2001*, Government of Nepal, Editor. 2001: Kathmandu.
35. Singh, S. and J. Darroch, *Adding It Up: Costs and Benefits of Contraceptive Services*, Guttmacher Institute and UNFPA, Editors. 2012.
36. Lamichhane, P. and S. Tiwari, *Progress Report on the Aama 4ANC Demand Side Financing Program*, NHSSP, Editor. 2012, Ministry of Health and Population.
37. World Health Organization, *Global Health Expenditure Database*. 2012.
38. Mwaikambo, L., et al., *What Works in Family Planning Interventions: A Systematic Review.* Studies in Family Planning, 2011. **42**(2): p. 67-82.
39. Mangham-Jefferies, L., et al., *Cost-effectiveness of strategies to improve the utilization and provision of maternal and newborn health care in low-income and lower-middle-income countries: a systematic review.* BMC Pregnancy and Childbirth, 2014. **14**(1): p. 243.
40. Amowitz, L.L., C. Reis, and V. Iacopino, *Maternal mortality in Herat Province, Afghanistan, in 2002: an indicator of women's human rights.* JAMA, 2002. **288**(10): p. 1284-1291.
41. Bartlett, L.A., et al., *Where giving birth is a forecast of death: maternal mortality in four districts of Afghanistan, 1999–2002.* The Lancet, 2005. **365**(9462): p. 864-870.
42. Population Reference Bureau (PRB), *World Population Data Sheet*. 2004, Population Reference Bureau: Washington DC.
43. Dreyfuss, M.L., et al., *Hookworms, Malaria and Vitamin A Deficiency Contribute to Anemia and Iron Deficiency among Pregnant Women in the Plains of Nepal.* The Journal of Nutrition, 2000. **130**(10): p. 2527-2536.
44. Brabin, B.J., M. Hakimi, and D. Pelletier, *An analysis of anemia and pregnancy-related maternal mortality.* The Journal of Nutrition, 2001. **131**(2): p. 604S-615S.
45. Graham, W.J., et al., *Chapter 26, Maternal and Perinatal Conditions*, in *Disease Control Priorities in Developing Countries 2nd edition*, D.T. Jamison, et al., Editors. 2006, The World Bank: Washington, DC.
46. Biswas, A.B., et al., *Availability and use of emergency obstetric care services in four districts of West Bengal, India.* Journal of health, Population and Nutrition, 2005: p. 266-274.
47. Johns, B., et al., *Estimated global resources needed to attain universal coverage of maternal and newborn health services.* Bulletin of the World Health Organization, 2007. **85**(4): p. 256-263.
48. Cahuana-Hurtado L, Sosa-Rubi S, and B. S, *The Application of the Mother Baby Package Reproductive Health Costing Spreadsheet in Morelos*, National Institute of Public Health, Editor. 2004, Division of Health Economics and Policy: Mexico.
49. Khan, K.S., et al., *WHO analysis of causes of maternal death: a systematic review.* The Lancet, 2006. **367**(9516): p. 1066-1074.
50. Pradhan, A., et al., *Nepal Maternal Mortality and Morbidity Study 2008/2009.* 2010, Family Health Division, Department of Health Services, Ministry of Health and Population, Government of Nepal: Kathmandu.

51. World Health Organization, *Revised Global Burden of Disease (GBD) 2002 estimates, Incidence*. 2004.
52. UNICEF, *State of the World's Children.* 2004.
53. Dolea, C., C. AbouZahr, and C. Stein, *Global burden of maternal hemorrhage in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
54. Chandhiok, N., et al., *Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India.* International Journal of Gynecology & Obstetrics, 2006. **92**(2): p. 170-175.
55. Derman, R.J., et al., *Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial.* The Lancet, 2006. **368**(9543): p. 1248-1253.
56. Hofmeyr, G.J., et al. (2013) *Postpartum misoprostol for preventing maternal mortality and morbidity*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD008982.pub2.
57. Mousa Hatem, A., et al. (2014) *Treatment for primary postpartum haemorrhage*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD003249.pub3.
58. Adam, T., et al., *Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries.* BMJ, 2005. **331**(7525): p. 1107.
59. Dolea, C. and C. Stein, *Global burden of maternal sepsis in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
60. Pagel, C., et al., *Estimation of potential effects of improved community-based drug provision, to augment health-facility strengthening, on maternal mortality due to post-partum haemorrhage and sepsis in sub-Saharan Africa: an equity-effectiveness model.* The Lancet, 2009. **374**(9699): p. 1441-1448.
61. Dolea, C. and C. AbouZahr, *Global burden of obstructed labour in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
62. Hofmeyr, G.J., M. Hannah, and A. Lawrie Theresa (2003) *Planned caesarean section for term breech delivery*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000166.
63. Hofmeyr, G.J. and R. Kulier (2012) *External cephalic version for breech presentation at term*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000083.pub2.
64. AbouZahr, C., *Global burden of maternal death and disability.* British Medical Bulletin, 2003. **67**(1): p. 1-11.
65. Dolea, C. and C. AbouZahr, *Global burden of hypertensive disorders of pregnancy in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
66. Duley, L., *Magnesium sulphate and other anticonvulsants for women with pre-eclampsia.* Cochrane Database of Systematic Reviews, 2010(11).
67. Duley, L., J. Henderson-Smart David, and D. Chou (2010) *Magnesium sulphate versus phenytoin for eclampsia*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000128.pub2.
68. Duley, L., et al. (2010) *Magnesium sulphate versus diazepam for eclampsia*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000127.pub2.
69. Magpie Trial Follow-Up Study Collaborative Group, *The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at 2 years.* BJOG: an international journal of obstetrics and gynaecology, 2007. **114**(3): p. 300.
70. Abalos, E., L. Duley, and D.W. Steyn (2014) *Antihypertensive drug therapy for mild to moderate hypertension during pregnancy*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD002252.pub3.
71. Hofmeyr, G.J., et al. (2014) *Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD001059.pub4.
72. Duley, L., et al. (2010) *Magnesium sulphate and other anticonvulsants for women with pre-eclampsia*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000025.pub2.

73. World Health Organization, *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2008*. 2011.
74. Puri, M., et al., *"Sometimes they used to whisper in our ears": health care workers' perceptions of the effects of abortion legalization in Nepal.* BMC Public Health, 2012. **12**(1): p. 297.
75. Samandari, G., et al., *Implementation of legal abortion in Nepal: a model for rapid scale-up of high-quality care.* Reproductive Health, 2012. **9**(1): p. 7.
76. Henderson, J.T., et al., *Effects of Abortion Legalization in Nepal, 2001–2010.* PLoS ONE, 2013. **8**(5): p. e64775.
77. Rocca, C.H., et al., *Unsafe abortion after legalisation in Nepal: a cross-sectional study of women presenting to hospitals.* BJOG: An International Journal of Obstetrics & Gynaecology, 2013. **120**(9): p. 1075-1084.
78. Singh, A., et al., *Providing skilled birth attendants and emergency obstetric care to the poor through partnership with private sector obstetricians in Gujarat, India.* Bulletin of the World Health Organization, 2009. **87**(12): p. 960-964.
79. Ram, F. and A. Singh, *Is antenatal care effective in improving maternal health in rural uttar pradesh? Evidence from a district level household survey.* J Biosoc Sci., 2006. **38**(4): p. 433-48.
80. Soubeiga, D., D. Sia, and L. Gauvin, *Increasing institutional deliveries among antenatal clients: effect of birth preparedness counselling.* Health Policy and Planning, 2013.
81. Nawal, D. and S. Goli, *Birth Preparedness and Its Effect on Place of Delivery and Post-Natal Check-Ups in Nepal.* PLoS ONE, 2013. **8**(5): p. e60957.
82. Dhakal, S., et al., *Utilisation of postnatal care among rural women in Nepal.* BMC Pregnancy and Childbirth, 2007. **7**(1): p. 19.
83. Sedgh, G., et al., *Induced abortion: incidence and trends worldwide from 1995 to 2008.* The Lancet, 2012. **379**(9816): p. 625-632.
84. Mills, S., et al., *Obstetric Care in Poor Settings in Ghana, India, and Kenya*, W. Bank, Editor. 2007: Washington, DC.
85. Lule, E., S. Singh, and S.A. Chowdhury, *Fertility regulation behaviors and their costs: Contraception and unintended pregnancies in Africa and Eastern Europe & Central Asia*, W. Bank, Editor. 2007: Washington, DC.
86. Campbell, O.M.R. and W.J. Graham, *Strategies for reducing maternal mortality: getting on with what works.* The Lancet, 2007. **368**(9543): p. 1284-1299.
87. Sibley, L.M., T.A. Sipe, and D. Barry (2012) *Traditional birth attendant training for improving health behaviours and pregnancy outcomes*. Cochrane Database of Systematic Reviews.
88. Lassi, Z.S., B.A. Haider, and Z.A. Bhutta (2010) *Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes*. Cochrane Database of Systematic Reviews.
89. Hundley, V.A., et al., *Should oral misoprostol be used to prevent postpartum haemorrhage in home-birth settings in low-resource countries? A systematic review of the evidence.* Bjog., 2013. **120**(3): p. 277-85; discussion 86-7. doi: 10.1111/1471-0528.12049. Epub 2012 Nov 27.
90. Rajbhandari, S., et al., *Expanding uterotonic protection following childbirth through community-based distribution of misoprostol: Operations research study in Nepal.* International Journal of Gynecology & Obstetrics, 2010. **108**(3): p. 282-288.
91. West Jr, K.P., et al., *Double blind, cluster randomised trial of low dose supplementation with vitamin A or βcarotene on mortality related to pregnancy in Nepal.* BMJ, 1999. **318**(7183): p. 570-575.
92. Manandhar, D.S., et al., *Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial.* The Lancet, 2004. **364**(9438): p. 970-979.
93. Osrin, D., et al., *Implementing a community-based participatory intervention to improve essential newborn care in rural Nepal.* Transactions of The Royal Society of Tropical Medicine and Hygiene, 2003. **97**(1): p. 18-21.

94. Christian, P., et al., *Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial.* BMJ, 2003. **326**(7389): p. 571.
95. Bolam, A., et al., *The effects of postnatal health education for mothers on infant care and family planning practices in Nepal: a randomised controlled trial.* BMJ, 1998. **316**(7134): p. 805-811.
96. Mullany, L.C., et al., *Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial.* The Lancet, 2006. **367**(9514): p. 910-918.
97. Andersen, K., et al., *Early pregnancy detection by female community health volunteers in Nepal facilitated referral for appropriate reproductive health services.* Global Health: Science and Practice, 2013. **1**(3): p. 372-381.
98. Danel, I. and A. Rivera, *Chapter 3: Honduras, 1990-1997.*, in *Reducing maternal mortality: learning from Bolivia, China, Egypt, Honduras, Indonesia, Jamaica, and Zimbabwe*, M. Koblinsky, Editor. 2003, The International Bank for Reconstruction and Development/The World Bank: Washington, DC.
99. Thapa, D.K. and A. Niehof, *Women's autonomy and husbands' involvement in maternal health care in Nepal.* Social Science & Medicine, 2013. **93**(0): p. 1-10.
100. Mullany, B.C., M.J. Hindin, and S. Becker, *Can women's autonomy impede male involvement in pregnancy health in Katmandu, Nepal?* Social Science & Medicine, 2005. **61**(9): p. 1993-2006.
101. Mullany, B.C., S. Becker, and M. Hindin, *The impact of including husbands in antenatal health education services on maternal health practices in urban Nepal: results from a randomized controlled trial.* Health Education Research, 2007. **22**(2): p. 166-176.
102. Baral, Y.R., et al., *Determinants of skilled birth attendants for delivery in Nepal.* Kathmandu Univ Med J (KUMJ). 2010. **8**(31): p. 325-32.
103. Mehata, S., et al., *Service Tracking Survey 2012*, Ministry of Health and Population Government of Nepal, Editor. 2013: Kathmandu, Nepal.
104. Morrison, J., et al., *Exploring the first delay: a qualitative study of home deliveries in Makwanpur district Nepal.* BMC Pregnancy and Childbirth, 2014. **14**(1): p. 89.
105. Jahn, A., et al., *Maternity care in rural Nepal: a health service analysis.* Tropical Medicine & International Health, 2000. **5**(9): p. 657-665.
106. McPherson, R.A., et al., *Are birth-preparedness programmes effective? Results from a field trial in Siraha district, Nepal.* J Health Popul Nutr., 2006. **24**(4): p. 479-88.
107. Brunson, J., *Confronting maternal mortality, controlling birth in Nepal: The gendered politics of receiving biomedical care at birth.* Social Science & Medicine, 2010. **71**(10): p. 1719-1727.
108. Thatte, N., et al., *Traditional birth attendants in rural Nepal: Knowledge, attitudes and practices about maternal and newborn health.* Global Public Health, 2009. **4**(6): p. 600-617.
109. Falle, T.Y., et al., *Potential role of traditional birth attendants in neonatal healthcare in rural southern Nepal.* J Health Popul Nutr., 2009. **27**(1): p. 53-61.
110. The World Bank, *World Development Indicators*. 2013.
111. Central Bureau of Statistics, *Nepal Living Standards Survey 2010/11*, National Planning Commission Secretariat, Editor. 2011, Government of Nepal: Kathmandu, Nepal.
112. Borghi, J., et al., *Financial implications of skilled attendance at delivery in Nepal.* Tropical Medicine & International Health, 2006. **11**(2): p. 228-237.
113. Borghi, J., et al., *Coping with the Burden of the Costs of Maternal Health*, in *Nepal Safer Motherhood Project*. 2004, Options, DFID, HMGN: Kathmandu, Nepal:.
114. Ministry of Health and Population (MOHP) [Nepal], *Nepal Health Sector Programme - Implementation Plan II (NHSP-IP 2) 2010-2015*, Government of Nepal, Editor. 2010: Kathmandu, Nepal.
115. Choulagai, B., et al., *Barriers to using skilled birth attendants' services in mid- and far-western Nepal: a cross-sectional study.* BMC International Health and Human Rights, 2013. **13**(1): p. 49.

116. Wagle, R., S. Sabroe, and B. Nielsen, *Socioeconomic and physical distance to the maternity hospital as predictors for place of delivery: an observation study from Nepal.* BMC Pregnancy and Childbirth, 2004. **4**(1): p. 8.
117. Hotchkiss, D.R., *Expansion of rural health care and the use of maternal services in Nepal.* Health & Place, 2001. **7**(1): p. 39-45.
118. Pradhan, A., et al., *Nepal Maternal Mortality and Morbidity Study 2008/09*, Family Health Division Department of Health Services, Editor. 2010, Ministry of Health and Population, Government of Nepal: Kathmandu Nepal.
119. Lekhak, S.C. and B. Budhathoki, *Quality and Accessibility of Reproductive Health Services in Nepal*, South Asian Institute for Policy Analysis and Leadership & Department of Health Services Family Health Division, Editor. 2010: Kathmandu, Nepal.
120. Rai, S.K., et al., *The health system in Nepal—An introduction.* Environmental health and preventive medicine, 2001. **6**(1): p. 1-8.
121. Acharya, L.B. and J. Cleland, *Maternal and child health services in rural Nepal: does access or quality matter more?* Health Policy and Planning, 2000. **15**(2): p. 223-229.
122. Barker, C.E., et al., *Support to the Safe Motherhood Programme in Nepal: An Integrated Approach.* Reproductive Health Matters, 2007. **15**(30): p. 81-90.
123. Mesko, N., et al., *Care for perinatal illness in rural Nepal: a descriptive study with cross-sectional and qualitative components.* BMC International Health and Human Rights, 2003. **3**(1): p. 3.
124. Hogan, M.C., et al., *Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5.* The Lancet, 2010. **375**(9726): p. 1609-1623.
125. Hill, K., et al., *Estimates of maternal mortality worldwide between 1990 and 2005: an assessment of available data.* The Lancet, 2007. **370**(9595): p. 1311-1319.
126. Thapa, S., J. Poudel, and S. Padhye, *Triaging Patients with Post-abortion Complications: A Prospective Study in Nepal.* Journal of Health, Population and Nutrition, 2004. **22**(4): p. 383-398.
127. Basnet, I., et al., *Evolution of the postabortion care program in Nepal: the contribution of a national Safe Motherhood Project.* International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 2004. **86**(1): p. 98-108.
128. Michael Vlassoff, et al., *Estimates of Health Care System Costs of Unsafe Abortion In Africa and Latin America.* International Perspectives on Sexual and Reproductive Health, 2009. **35**(3).
129. Devkota M, et al., *Readiness of Comprehensive Obstetric and Neonatal Emergency Care in Nepal*, National Health Sector Support Programme, Editor. 2011, Ministry of Health and Population of Nepal: Kathmandu.
130. Regmi, M.C., et al., *Loading dose versus standard regimen of magnesium sulphate in eclampsia--a randomized trial.* Nepal Med Coll J., 2010. **12**(4): p. 244-7.
131. Choudhary, P., *Eclampsia: a hospital based retrospective study.* Kathmandu Univ Med J (KUMJ). 2003. **1**(4): p. 237-41.
132. Travis, P., et al., *Overcoming health-systems constraints to achieve the Millennium Development Goals.* The Lancet, 2004. **364**(9437): p. 900-906.
133. Elzinga, G., M.C. Raviglione, and D. Maher, *Scale up: meeting targets in global tuberculosis control.* The Lancet, 2004. **363**(9411): p. 814-819.
134. Gilks, C.F., et al., *The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings.* The Lancet, 2006. **368**(9534): p. 505-510.
135. Brugha, R. and G. Walt, *A global health fund: a leap of faith?* BMJ, 2001. **323**(7305): p. 152-154.
136. Lu, C., et al., *Absorptive capacity and disbursements by the Global Fund to Fight AIDS, Tuberculosis and Malaria: analysis of grant implementation.* The Lancet, 2006. **368**(9534): p. 483-488.

137. Yu, D., et al., *Investment in HIV/AIDS programs: Does it help strengthen health systems in developing countries?* Globalization and Health, 2008. **4**(1): p. 8.
138. Beaglehole, R., et al., *Priority actions for the non-communicable disease crisis.* The Lancet, 2011. **377**(9775): p. 1438-1447.
139. Eaton, J., et al., *Scale up of services for mental health in low-income and middle-income countries.* The Lancet, 2011. **378**(9802): p. 1592-1603.
140. Randive, B., V. Diwan, and A. De Costa, *India's Conditional Cash Transfer Programme (the JSY) to Promote Institutional Birth: Is There an Association between Institutional Birth Proportion and Maternal Mortality?* PLoS ONE, 2013. **8**(6): p. e67452.
141. Oestergaard, M.Z., et al., *Neonatal Mortality Levels for 193 Countries in 2009 with Trends since 1990: A Systematic Analysis of Progress, Projections, and Priorities.* PLoS Med, 2011. **8**(8): p. e1001080.
142. Rammohan, A., K. Iqbal, and N. Awofeso, *Reducing Neonatal Mortality in India: Critical Role of Access to Emergency Obstetric Care.* PLoS ONE, 2013. **8**(3): p. e57244.
143. Measure DHS and USAID, *STAT Compiler*. 2012.
144. Chaturvedi, S., et al., *Quality of Obstetric Referral Services in India's JSY Cash Transfer Programme for Institutional Births: A Study from Madhya Pradesh Province.* PLoS ONE, 2014. **9**(5): p. e96773.
145. Malik, J., et al., *Utilization of Health Services under Janani Suraksha Yojna in Rural Haryana.* International Journal of Medicine and Public Health, 2013. **3**(3): p. 176-179.
146. Ameh, C., et al., *Status of Emergency Obstetric Care in Six Developing Countries Five Years before the MDG Targets for Maternal and Newborn Health.* PLoS ONE, 2012. **7**(12): p. e49938.
147. Spector, J.M., et al., *Improving Quality of Care for Maternal and Newborn Health: Prospective Pilot Study of the WHO Safe Childbirth Checklist Program.* PLoS ONE, 2012. **7**(5): p. e35151.
148. Lavender, T., *Effect of partogram use on outcomes for women in spontaneous labour at term.* Cochrane Database of Systematic Reviews, 2013(7).
149. Windrim, R., et al., *A randomized controlled trial of a bedside partogram in the active management of primiparous labour.* J Obstet Gynaecol Can., 2007. **29**(1): p. 27-34.
150. Abalos, E., et al., *Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 14-24.
151. Calvert, C., et al., *Identifying Regional Variation in the Prevalence of Postpartum Haemorrhage: A Systematic Review and Meta-Analysis.* PLoS ONE, 2012. **7**(7): p. e41114.
152. Carroli, G., et al., *Epidemiology of postpartum haemorrhage: a systematic review.* Best Practice & Research Clinical Obstetrics & Gynaecology, 2008. **22**(6): p. 999-1012.
153. Vogel, J.P., et al., *Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 76-88.
154. Fantu, S., H. Segni, and F. Alemseged, *Incidence, causes and outcome of obstructed labor in Jimma University specialized hospital.* Ethiopian journal of health sciences, 2010. **20**(3).
155. Mondal, S., et al., *Fetomaternal outcome in obstructed labor in a peripheral tertiary care hospital.* Medical Journal of Dr. DY Patil University, 2013. **6**(2): p. 146.
156. Lumbiganon, P., et al., *Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007–08.* The Lancet, 2010. **375**(9713): p. 490-499.
157. Ohlsson, A., *Intrapartum antibiotics for known maternal Group B streptococcal colonization.* Cochrane Database of Systematic Reviews, 2014(6).
158. Witlin, A.G., et al., *Predictors of neonatal outcome in women with severe preeclampsia or eclampsia between 24 and 33 weeks' gestation.* American Journal of Obstetrics and Gynecology, 2000. **182**(3): p. 607-611.

159. The WHO Young Infants Study Group, *Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study.* The Pediatric Infectious Disease Journal, 1999. **18**(10): p. S17-S22.
160. Lee, A., et al., *Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect.* BMC Public Health, 2011. **11**(Suppl 3): p. S12.
161. Bhutta, Z.A., et al., *Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost?* The Lancet, 2014(0).
162. Porwal, R.G.S.K., *Obstructed labour: incidence, causes and outcome.* Int J Biol Med Res, 2012. **3**(3): p. 2185-2188.
163. Lawn, J.E., et al., *Two million intrapartum-related stillbirths and neonatal deaths: Where, why, and what can be done?* International Journal of Gynecology & Obstetrics, 2009. **107, Supplement**(0): p. S5-S19.
164. UNICEF. *Low Birthweight*. 2014; Available from: http://data.unicef.org/nutrition/low-birthweight.
165. Mondal, G.P., et al., *Neonatal septicaemia among inborn and outborn babies in a referral hospital.* The Indian Journal of Pediatrics, 1991. **58**(4): p. 529-533.
166. Zaidi, A.K.M., et al., *Hospital-acquired neonatal infections in developing countries.* The Lancet, 2005. **365**(9465): p. 1175-1188.
167. Kaushik, S.L., et al., *Neonatal sepsis in hospital born babies.* J Commun Dis., 1998. **30**(3): p. 147-52.
168. Chacko, B. and I. Sohi, *Early onset neonatal sepsis.* The Indian Journal of Pediatrics, 2005. **72**(1): p. 23-26.
169. Chandra, S., S. Ramji, and S. Thirupuram, *Perinatal asphyxia: multivariate analysis of risk factors in hospital births.* Indian pediatrics, 1997. **34**(3): p. 206-12.
170. Bang, A.T., et al., *Why Do Neonates Die in Rural Gadchiroli, India? (Part II): Estimating Population Attributable Risks and Contribution of Multiple Morbidities for Identifying a Strategy to Prevent Deaths.* J Perinatol, 2005. **25**(S1): p. S35-S43.
171. Joseph, N., et al., *Morbidity among infants in South India: A longitudinal study.* The Indian Journal of Pediatrics, 2010. **77**(4): p. 456-458.
172. Joshi, P., et al., *Impact of universal immunization programme on the incidence of tetanus neonatorum.* Indian Pediatr, 1992. **29**: p. 773-75.
173. Kaushik, S.L., et al., *Neonatal mortality rate: relationship to birth weight and gestational age.* Indian J Pediatr., 1998. **65**(3): p. 429-33.
174. Blencowe, H., et al., *Tetanus toxoid immunization to reduce mortality from neonatal tetanus.* International journal of epidemiology, 2010. **39**(suppl 1): p. i102-i109.
175. Smits, J. and C. Monden, *Twinning across the Developing World.* PLoS ONE, 2011. **6**(9): p. e25239.
176. Registrar General India, *Maternal mortality in India: 1997-2003; trends, causes and risk factors (Sample Registration System)*. 2006: New Delhi, India.
177. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2010*. 2012.
178. Tayade, S., et al., *Maternal Death Review To Know The Determinants Of Maternal Mortality In A District Hospital Of Central India*. 2012. Vol. 3. 2012.
179. Bangal, V.B., P.A. Giri, and R. Garg, *Maternal mortality at a tertiary care teaching hospital of rural india: a retrospective study.* International Journal of Biological and Medical Research, 2011. **2**(4): p. 1043-1046.
180. Puri, A., I. Yadav, and N. Jain, *Maternal mortality in an urban tertiary care hospital of north India.* The Journal of Obstetrics and Gynecology of India, 2011. **61**(3): p. 280-285.
181. World Health Organization, *Neonatal and perinatal mortality: Country, regional and global estimates*. 2007.
182. World Health Organization, *World Health Statistics 2014*. 2014.

183. World Health Organization, *World Health Statistics*. 2010.
184. World Health Organization and UNICEF, *Improving newborn survival in India*. 2010.
185. Flenady, V., *Antibiotics for prelabour rupture of membranes at or near term.* Cochrane Database of Systematic Reviews, 2012(3).
186. Hopkins, L., *Antibiotic regimens for management of intraamniotic infection.* Cochrane Database of Systematic Reviews, 2013(2).
187. Westhoff, G., M. Cotter Amanda, and E. Tolosa Jorge (2013) *Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD001808.pub2.
188. Hodnett, E.D., *Continuous support for women during childbirth.* Cochrane Database of Systematic Reviews, 2013(7).
189. Casey, B.M., D.D. McIntire, and K.J. Leveno, *The Continuing Value of the Apgar Score for the Assessment of Newborn Infants.* New England Journal of Medicine, 2001. **344**(7): p. 467-471.
190. Seward, N., et al., *Association between Clean Delivery Kit Use, Clean Delivery Practices, and Neonatal Survival: Pooled Analysis of Data from Three Sites in South Asia.* PLoS Med, 2012. **9**(2): p. e1001180.
191. Moore, E.R., *Early skin-to-skin contact for mothers and their healthy newborn infants.* Cochrane Database of Systematic Reviews, 2012(5).
192. Conde-Agudelo, A., *Kangaroo mother care to reduce morbidity and mortality in low birthweight infants.* Cochrane Database of Systematic Reviews, 2014(4).
193. International Institute for Population Sciences, *District Level Household and Facility Survey 3*, Ministry of Health and Family Welfare Government of India, Editor. 2008: Mumbai.
194. International Institute for Population Sciences, *India Facility Survey (Under Reproductive and Child Health Project) Phase II Report*, Ministry of Health and Family Welfare, Editor. 2005: India.
195. Montgomery, A.L., et al., *Maternal Mortality in India: Causes and Healthcare Service Use Based on a Nationally Representative Survey.* PLoS ONE, 2014. **9**(1): p. e83331.
196. Million Death Study Collaborators, *Causes of neonatal and child mortality in India: a nationally representative mortality survey.* The Lancet, 2010. **376**(9755): p. 1853-1860.
197. Souza, J.P., et al., *The WHO Maternal Near-Miss Approach and the Maternal Severity Index Model (MSI): Tools for Assessing the Management of Severe Maternal Morbidity.* PLoS ONE, 2012. **7**(8): p. e44129.
198. Firoz, T., et al., *Measuring maternal health: focus on maternal morbidity.* Bulletin of the World Health Organization, 2013. **91**(10): p. 794-796.
199. Say, L., R.C. Pattinson, and A.M. Gülmezoglu, *WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity (near miss).* Reproductive Health, 2004. **1**(1): p. 3.
200. Prual, A., et al., *Severe maternal morbidity from direct obstetric causes in West Africa: incidence and case fatality rates.* Bull World Health Organ., 2000. **78**(5): p. 593-602.
201. United Nations, *UNData.* 2014.
202. Jabir, M., et al., *Maternal near miss and quality of maternal health care in Baghdad, Iraq.* BMC Pregnancy and Childbirth, 2013. **13**(1): p. 11.
203. Purandare, C., et al., *Maternal near-miss reviews: lessons from a pilot programme in India.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 105-111.
204. Ganatra, B., K. Coyaji, and V. Rao, *Too far, too little, too late: a community-based case-control study of maternal mortality in rural west Maharashtra, India.* Bulletin of the World Health Organization, 1998. **76**(6): p. 591.
205. Padmanaban, P., P.S. Raman, and D.V. Mavalankar, *Innovations and challenges in reducing maternal mortality in Tamil Nadu, India.* Journal of health, population, and nutrition, 2009. **27**(2): p. 202.

206. George, A., *Persistence of High Maternal Mortality in Koppal District, Karnataka, India: Observed Service Delivery Constraints.* Reproductive Health Matters, 2007. **15**(30): p. 91-102.
207. Ministry of Health and Social Welfare - Government of India, *Indian Public Health Standards*. 2012, National Health Mission.
208. Ministry of Health and Social Welfare - Government of India, *Maternal and Newborn Health Toolkit*, Maternal Health Division, Editor. 2013.
209. Mathai, M., A.M. Gülmezoglu, and S. Hill, *Saving women's lives: Evidence-based recommendations for the prevention of postpartum haemorrhage.* Bulletin of the World Health Organization, 2007. **85**(4): p. 322-323.
210. World Health Organization, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*. 2012.
211. Duley, L., *The Global Impact of Pre-eclampsia and Eclampsia.* Seminars in Perinatology, 2009. **33**(3): p. 130-137.
212. Seal, S.L., et al., *Does route of delivery affect maternal and perinatal outcome in women with eclampsia? A randomized controlled pilot study.* American Journal of Obstetrics and Gynecology, 2012. **206**(6): p. 484.e1-484.e7.
213. Churchill, D., et al. (2013) *Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD003106.pub2.
214. Wall, S.N., et al., *Reducing Intrapartum-Related Neonatal Deaths in Low- and Middle-Income Countries—What Works?* Seminars in Perinatology, 2010. **34**(6): p. 395-407.
215. Mishra, U. and M. Ramanathan, *Delivery-related complications and determinants of caesarean section rates in India.* Health Policy and Planning, 2002. **17**(1): p. 90-98.
216. Souza, J., et al., *Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health.* BMC Medicine, 2010. **8**(1): p. 71.
217. Sreevidya, S. and B.W.C. Sathiyasekaran, *High caesarean rates in Madras (India): a population-based cross sectional study.* BJOG: An International Journal of Obstetrics & Gynaecology, 2003. **110**(2): p. 106-111.
218. Raman, P.S., et al., *Impact of a public–private performance-based financing partnership on the proportion of caesarean section deliveries: a cross-sectional study.* The Lancet, 2013. **381**: p. S121.
219. Yakoob, M.Y., et al., *The effect of providing skilled birth attendance and emergency obstetric care in preventing stillbirths.* BMC Public Health, 2011. **11**(Suppl 3): p. S7.
220. Lee, A., et al., *Care during labor and birth for the prevention of intrapartum-related neonatal deaths: a systematic review and Delphi estimation of mortality effect.* BMC Public Health, 2011. **11**(Suppl 3): p. S10.
221. Backes, C.H., et al., *Maternal Preeclampsia and Neonatal Outcomes.* Journal of Pregnancy, 2011. **2011**.
222. The Magpie Trial Collaborative Group, *Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial.* The Lancet, 2002. **359**(9321): p. 1877-1890.
223. Goldenberg, R.L. and C. Thompson, *The infectious origins of stillbirth.* American Journal of Obstetrics and Gynecology, 2003. **189**(3): p. 861-873.
224. Chan, G.J., et al., *Risk of Early-Onset Neonatal Infection with Maternal Infection or Colonization: A Global Systematic Review and Meta-Analysis.* PLoS Med, 2013. **10**(8): p. e1001502.
225. Lieberman, E., et al., *Intrapartum Maternal Fever and Neonatal Outcome.* Pediatrics, 2000. **105**(1): p. 8-13.
226. Alexander, J.M., D.M. McIntire, and K.J. Leveno, *Chorioamnionitis and the prognosis for term infants.* Obstetrics & Gynecology, 1999. **94**(2): p. 274-278.

227. Lawn, J.E., S. Cousens, and J. Zupan, *4 million neonatal deaths: When? Where? Why?* The Lancet, 2005. **365**(9462): p. 891-900.
228. Sheiner, E., et al., *Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study.* Journal of Maternal-Fetal and Neonatal Medicine, 2005. **18**(3): p. 149-154.
229. Rhee, V., et al., *Maternal and birth attendant hand washing and neonatal mortality in southern Nepal.* Archives of Pediatrics & Adolescent Medicine, 2008. **162**(7): p. 603-608.
230. Kusiako, T., C. Ronsmans, and L. Van der Paal, *Perinatal mortality attributable to complications of childbirth in Matlab, Bangladesh.* Bulletin of the World Health Organization, 2000. **78**: p. 621-627.
231. Ronsmans, C., et al., *Effect of parent's death on child survival in rural Bangladesh: a cohort study.* The Lancet, 2010. **375**(9730): p. 2024-2031.
232. Lindblade, K.A., et al., *Health and nutritional status of orphans <6 years old cared for by relatives in western Kenya.* Tropical Medicine & International Health, 2003. **8**(1): p. 67-72.
233. Braitstein, P., et al., *Nutritional Status of Orphaned and Separated Children and Adolescents Living in Community and Institutional Environments in Uasin Gishu County, Kenya.* PLoS ONE, 2013. **8**(7): p. e70054.
234. Whetten, K., et al., *More than the loss of a parent: Potentially traumatic events among orphaned and abandoned children.* Journal of Traumatic Stress, 2011. **24**(2): p. 174-182.
235. Whetten, R., et al., *Child work and labour among orphaned and abandoned children in five low and middle income countries.* BMC International Health and Human Rights, 2011. **11**(1): p. 1.
236. O'Donnell, K., et al., *A Brief Assessment of Learning for Orphaned and Abandoned Children in Low and Middle Income Countries.* AIDS and Behavior, 2012. **16**(2): p. 480-490.
237. Hosegood, V., *The demographic impact of HIV and AIDS across the family and household life-cycle: implications for efforts to strengthen families in sub-Saharan Africa.* AIDS Care, 2009. **21**(sup1): p. 13-21.
238. Yamin, A.E., et al., *Costs of Inaction on Maternal Mortality: Qualitative Evidence of the Impacts of Maternal Deaths on Living Children in Tanzania.* PLoS ONE, 2013. **8**(8): p. e71674.
239. Wang, H., et al., *Economic Impact of Maternal Death on Households in Rural China: A Prospective Cohort Study.* PLoS ONE, 2013. **8**(10): p. e76624.
240. Ye, F., et al., *The Immediate Economic Impact of Maternal Deaths on Rural Chinese Households.* PLoS ONE, 2012. **7**(6): p. e38467.
241. Storeng, K.T., et al., *Paying the price: The cost and consequences of emergency obstetric care in Burkina Faso.* Social Science & Medicine, 2008. **66**(3): p. 545-557.
242. Filippi, V., et al., *Effects of severe obstetric complications on women's health and infant mortality in Benin.* Tropical Medicine & International Health, 2010. **15**(6): p. 733-742.
243. Family Care International, International Center for Research on Women, and KEMRI-CDC Research and Public Health Collaboration, *A price too high to bear: The costs of maternal mortality to families and communities*. 2014.
244. Filmer, D. and L. Pritchett, *Estimating Wealth Effects Without Expenditure Data—Or Tears: An Application To Educational Enrollments In States Of India.* Demography, 2001. **38**(1): p. 115-132.
245. Medhin, G., et al., *Prevalence and predictors of undernutrition among infants aged six and twelve months in Butajira, Ethiopia: The P-MaMiE Birth Cohort.* BMC Public Health, 2010. **10**(1): p. 27.
246. Darmstadt, G.L., et al., *Evidence-based, cost-effective interventions: how many newborn babies can we save?* The Lancet, 2005. **365**(9463): p. 977-988.

Appendix for Chapter 2

2.1 Overview of Model

2.1.1 Analytic Overview

The best available data were synthesized using a computer-based model to assess the costs and health outcomes of different strategies to reduce disability and death due to pregnancy-related complications in Nepal. The model captures the natural history of pregnancy and relevant co-morbidities in an individual woman, aggregates clinical outcomes to the population or subgroup level, and reflects setting-specific epidemiology, and access to health care through factors such as infrastructure, human resources, technology, health facilities and transport. We prioritized data from Nepal or the South Asian region to estimate initial ranges for age-specific probabilities of pregnancy, miscarriage, abortion, risk of maternal complications, and case-specific fatality and morbidity rates. The model integrates data on coverage rates for prenatal care, antenatal care, family planning, facility births and skilled birth attendants [SBAs], and assumptions on the availability of transport, facilities, and quality of care, to project outcomes (e.g., maternal mortality ratio [MMR], total fertility rate [TFR]); and these are compared with available national data.

Strategies relied on improving coverage of effective interventions and providing access to key services. Interventions could be provided individually, paired, or packaged into a bundle of integrated services; phased approaches involved scaling up access to services over time. Model outcomes include clinical events (e.g., postpartum hemorrhage), aggregate population measures (e.g., life expectancy), and economic costs (e.g., average per person lifetime costs). Monte Carlo and Markov simulations were used;

outcomes included per-woman events such as pregnancies, live births, facility-based births, and maternal complications, plus measures and indicators such as TFR, MMR, proportionate mortality ratio (proportion of deaths among women aged 15-49 that are pregnancy-related), and lifetime risk of maternal death.

The comparative performance of alternative strategies is described using the incremental cost-effectiveness ratio, defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive strategy. Strategies are considered "inefficient" or dominated if they were more costly and less effective, or more costly and less cost-effective, than an alternative strategy. We followed standard recommendations for economic evaluation. [WHO CHOICE] Sensitivity analyses were conducted to assess the impact of parameter uncertainty on our results.

2.1.2 The Model

The Global Maternal Health Policy Model is a computer-based model that simulates the natural history of pregnancy (both planned and unintended) and pregnancy- and childbirth-associated complications. This model defines health states to reflect important characteristics that affect prognosis, quality of life, and resource use. The time horizon incorporates a woman's entire lifetime and is divided into equal time increments during which women transition from one health state to another. Non-pregnant girls enter the model and in each time period may become pregnant depending on age, use of contraception, and clinical history. Once pregnant, women have a chance of spontaneous abortion (i.e., miscarriage), induced abortion, or continued pregnancy. A proportion of induced abortions will be unsafe (i.e., surgical or medical abortion conducted by untrained personnel). Labor and delivery may be associated with a direct complication of pregnancy (e.g., hypertensive disorders of pregnancy, obstructed labor, hemorrhage, sepsis). Case fatality rates are conditional on the type and severity of complication (e.g., moderate sepsis requiring antibiotics in facilities offering basic emergency obstetric care [bEmOC] versus severe hemorrhage requiring blood transfusion in facilities offering comprehensive emergency obstetric care [cEmOC]) and underlying comorbidity (e.g., moderate versus severe anemia). Nonfatal complications include neurological sequelae, rectovaginal fistula, severe anemia, and infertility. In addition to death from maternal complications, women face an annual risk of death from age-specific all cause mortality.

Strategies in the model to reduce maternal mortality consist of improving coverage of effective interventions, which may be provided individually or packaged as integrated services. In addition to family planning, antenatal care, and safe abortion, the model includes both intrapartum interventions that reduce the incidence of a complication (e.g., misoprostol for postpartum hemorrhage [PPH], clean delivery for sepsis) as well as those that reduce the case fatality rate through appropriate management in a referral facility.

The effectiveness of interventions to either reduce the incidence of complications or to reduce case fatality rates associated with complications depends, in part, on access to specific services (e.g., trained SBA) and to specific levels of facilities (e.g., cEmOC capacity for blood transfusion). Accordingly, the ultimate impact of interventions depends on several setting-specific factors. These include delivery site, presence of birth attendant, quality and type of referral facility, as well as successful referral when necessary. The model therefore explicitly considers the location of delivery, type of assistance, access to basic or comprehensive obstetrical care, and the ability to overcome a series of barriers around the timing

of delivery (e.g., recognition of referral need, reliable transport, timely treatment at an appropriate facility); these factors collectively determine the health services a woman can access and the specific interventions that would be included.

Delivery setting is differentiated by provider (e.g., family member, traditional birth attendant [TBA], SBA) and by site (e.g., home versus facility). Facilities are categorized as (1) *primary-level facilities,* which may not provide all services necessary to qualify as a bEmOC facility, but could function as birthing centers with SBA staff who provide expectant management of labor, 24-hour intrapartum care, and reliable referral connections when necessary; (2) *secondary facilities* with bEmOC capacity, assumed to be capable of administering injectable antibiotics, oxytocics, and sedatives or anti-convulsants, performing manual removal of placenta, removal of retained products, and assisted vaginal delivery; and (3) *tertiary facilities* with cEmOC capacity, which are also able to provide blood transfusion, cesarean section, and management of advanced shock.

We recognize that some tertiary sites will not have a blood bank and some secondary sites may eventually be able to perform c-section; further, we recognize that in the strategies that include stepwise investments in infrastructure and facility improvements, not all facilities will be expected to be fully implemented as one of the three distinct types. However, because the costs, functions and staffing are fairly closely aligned with basic or comprehensive EmOC capacity, this simple categorization captured the most important dimensions for purpose of this analysis. Part II, Subsection B provides a stylized example of how public health facilities in Nepal may be superimposed on our general model framework.

This model also allows us to evaluate phased approaches that involve scaling up access to services over time; we designate such stepwise investments in infrastructure as "upgrades". In addition to reducing unmet need for family planning and unsafe abortion, these strategies incrementally shift home births to facilities, increase skilled attendance, and improve access to, and quality of, emergency obstetrical care. For women delivering at home or in birthing centers, these strategies also improve recognition of referral need, access to transport, and expedient referral to an appropriate facility.

All models were built using TreeAge Pro 2008 (TreeAge Software Inc., Williamstown MA) and analyzed using IBM/Lenovo Dual-Core VT Pro Desktop computers running Microsoft Windows XP, using Microsoft Excel 2007 and Visual Basic for Applications 6.5 (Microsoft Corp., Redmond WA). We used Monte Carlo simulation to generate the number of per woman events such as pregnancies, live births, facility-based births, and maternal complications. This output is useful for both calibration exercises, as well as for assessing internal consistency and projective validity of the model by generating outcomes in similar formats to clinical studies. We used first-order Monte Carlo simulation to assess first-order uncertainty and one- and two-way sensitivity analyses to assess parameter uncertainty.

2.2 Overview of Model Parameterization, Calibration, Performance

2.2.1 Data and Assumptions: Epidemiology

Age-specific probability of pregnancy: Natural fertility—rates of fertility in the absence of family planning—was estimated based on early 21st century data from Afghanistan; conditions approximated

those of natural fertility since use of contraception and of abortion was very uncommon, and there was low access to high-quality health care [40, 41]. Using baseline demographic data plus information about family planning and assumptions around miscarriage and stillbirths, we approximated an average annual natural fertility rate of 31.3% [42]. Data on incidence of spontaneous and elective abortion were taken from the 2011 Nepal DHS [15], disaggregated by age groups.

Table 2.2-1: Estimated spontaneous and induced abortion incidence among women (nationally representative sample), Nepal DHS 2011 [15]

Age group	Incidence of miscarriage	Incidence of induced abortion
15-19	7.9%	2.8%
20-34	6.1%	8.1%
35-49	9.9%	13.7%

We assumed that long-term complications (e.g., untreated obstetric fistula) resulted in infertility and no future pregnancies for women with these complications. We assumed that women with treated complications (e.g., surgically-repaired fistula) could become pregnant again.

Anemia, poor health, and young age at first pregnancy: The 2011 Nepal DHS calculated the prevalence of anemia, based on measured hemoglobin levels: for all age groups of women between 15 and 49, moderate anemia prevalence was approximately 5-6%, and severe anemia prevalence was approximately 0.3-0.4% [15]. Other surveys in Nepal have found higher rates of anemia in certain subpopulations—for example, a community-based survey of pregnant women in a district of east-central Nepal that calculated the prevalence of severe and moderate anemia to be 20% [43]—but the model uses the NDHS estimates for moderate and severe anemia, disaggregated by age group as indicated below, because these were recently collected and are nationally-representative of all reproductive-age women.

Table 2.2-2: Estimated anemia prevalence among women (nationally representative sample), Nepal DHS 2011 [15]

Age group	Moderate anemia prevalence	Severe anemia prevalence
15-19	5.7%	0.4%
20-29	5.9%	0.3%
30-39	5.2%	0.4%
40-49	6.0%	0.3%

Evidence indicates that relative risk of death from maternal complications is 3.5 times greater for women with severe anemia, and 1.35 greater for women with moderate anemia, versus women with no anemia [44]. We used a conservative assumption that severe and moderate anemia did not affect case fatality for

untreated obstructed labor or hypertensive disorders; it did affect mortality from postpartum hemorrhage and from sepsis, as well as complications following unsafe abortion.

Poor general health and malnutrition also contribute towards increased risk of dying from pregnancy- and delivery-related complications. Chronic malnutrition during childhood can cause stunting, leading to the development of a smaller than normal pelvis, and put a woman at increased risk of obstructed labor. According to the 2011 NDHS, approximately 12% of Nepali reproductive-age women surveyed were shorter than 145cm (the "at-risk" height cutoff), and 18% were classified as thin or undernourished (BMI < 18.5 kg/m^2) [15].

Pregnancies at a young age and high parity are also known to increase the risk of death from pregnancy- or delivery-related complications. Age at marriage is slowly increasing in Nepal: according to the 2011 NDHS, the median age at marriage for women age 35 and over was approximately 17 years, but for younger women (those under 25 years of age), the median age has increased to 18-19 years [15]. There is little change in women's age at first birth, which is 20.2 years; and adolescent pregnancy is quite common, with nearly one-fifth of women aged 15-19 in the 2011 NDHS either having already had a child or pregnant [15]. Median birth interval in the 2011 NDHS was reportedly 36.2 months, with intervals increasing with maternal age; only one-fifth of surveyed women had a birth interval of under 2 years, the minimum interval recommended by WHO [15].

Poor overall health status, malnutrition and associated risk factors (such as vitamin A deficiency), as well as young age at first pregnancy, likely contribute to increased relative risk of incidence and case fatality from maternal complications. Insight into the size of these increased risks across provinces came from a series of calibration exercises on models at the province level and is described in the following sections.

Pregnancy-related complications: Incidence, case fatality rates, interventions to reduce incidence and mortality

Estimates of incidence and case fatality rates associated with pregnancy-related complications were initially obtained from published data. Ranges of values for sensitivity analysis were also based on systematic review of the literature. Case fatality rates were adjusted based on complication severity (e.g., life threatening complications requiring cEmOC) and underlying severity of anemia, using methods described below.

Interventions' effectiveness in reducing the *incidence of complications* (e.g., active management of labor) was estimated from published studies, using methods described below. The effectiveness of interventions to reduce *case fatality rates* was derived from published studies and assumed treatment in an appropriate facility; a wide plausible range was used for sensitivity analyses, as described below. An intervention's effectiveness in either reducing the incidence of complications or reducing case fatality rates associated with complications depends partly on access to specific services (e.g., trained SBA) and to specific levels of facilities (e.g., cEmOC capacity for blood transfusion). Therefore, the ultimate impact of interventions is linked to several setting-specific factors, including: delivery site, presence of birth attendant and type, quality and type of referral facility, as well as successful referral when necessary. Data on facility births and birth attendants were from country-specific surveys, and are described in Subsection B.

Adjustment of case fatality rates for heterogeneity in severity and co-morbidity

Baseline estimates for cause-specific case fatality rates were from a review conducted by the Disease Control Priorities Project (DCP2) - maternal hemorrhage (1%), sepsis (1.3%), hypertensive disorders of pregnancy (1.7%), obstructed labor (0.7%) [45]. These case fatality rates are lower than those reported in other studies, implying they could be underestimates [46]. We assumed that some of the variation reported in the literature is attributable to the heterogeneity in severity, and estimates based on small sample sizes. Case fatality rates were thus first adjusted based on complication severity (e.g., life-threatening complications requiring cEmOC versus moderate to severe complications requiring bEmOC).

Among the estimated 15% of pregnant women in developing countries who experience pregnancy-related complications, 7% require care at centers with surgical capacity (cEmOC) and 2-3% will require surgery [47]. Initial estimates of the proportion of complications requiring basic versus comprehensive EmOC care were derived from a study providing WHO expert opinion-based estimates, for each maternal complication, of the proportion of complications that will require surgical intervention, blood transfusion, or management of shock [47].

Table 2.2-3: Percentage of complications requiring emergency obstetric care, by type

	Require bEmOC	Require cEmOC
Hypertensive disorders	85.8%	14.2%
Obstructed labor	8% (assisted delivery)	92% (cesarean section)
Postpartum hemorrhage	72.5%	27.5% (25% transfusion, 2% surgery)
Puerperal sepsis	63%	37% (10% transfusion, 27% shock)

We altered these proportions slightly, either using data about the availability of certain levels of care in basic and comprehensive facilities and extent of training of personnel, or from insights gained during the calibration exercises. (Subsections B and C) In certain cases, we had specific data to assist with modifying estimates. For example, Johns et al [47] assumed 85.8% of eclampsia cases (HTN) require bEmOC, while 14.2% require cEmOC. This estimate is similar to an earlier study, which showed that severe pre-eclampsia and eclampsia required treatment with intravenous hydralazine and magnesium sulfate and in addition, approximately 10% of all cases were assumed to require emergency cesarean section [48]. Initial assumptions (and ranges) used in Nepal with respect to severity and need for basic versus comprehensive EmOC are provided below; sensitivity analyses were conducted to assess the implications of using the upper and lower bounds.

Table 2.2-4: Assumptions about complications requiring bEmOC and cEmOC in Nepal (used in model)

Complication	Require bEmOC	Require cEmOC
Hypertensive	85.8% (75%-90%)	14.2% (10%-25%)
Obstructed labor	31% (5%-35%)	69% (65%-95%)
Postpartum hemorrhage	65.6% (60%-72.5%)	34.4% (27.5%-38%)
Puerperal sepsis	63% (60%-75%)	37% (25%-40%)

Using the assumptions above we adjusted the literature-based case fatality rates based on severity (e.g., necessity for cEmOC, need for transfusion, delay in reaching care, underlying moderate anemia, underlying severe anemia). For example, to calculate implied average case fatality rate (CFR) for PPH, we took the baseline CFR of 1%, applied relative risks based on severity (e.g., necessity for cEmOC, need for transfusion, underlying moderate anemia, underlying severe anemia) and then weighted these based on the percentage of women who would face that risk. Therefore, the implied average CFR in Nepal for maternal hemorrhage of 3.4% is calculated from the following: 62% non-anemic women not requiring cEmOC (CFR 1%), 32.5% non-anemic women requiring cEmOC (CFR 3.5%), 3.25% moderately anemic women not requiring cEmOC (CFR 1.5%), 1.25% moderately anemic women requiring cEmOC (CFR 5.25%), 0.5% severely anemic women not requiring cEmOC (CFR 3%), 0.5% severely anemic women requiring cEmOC (CFR 10.5%). We then expanded the plausible range for sensitivity analysis based on this adjusted CFR.

Table 2.2-5: Adjusted CFR (in the absence of interventions) and expanded range for sensitivity analysis

	Hemorrhage	**Obstructed labor**	**Hypertensive disorders**	**Sepsis**	**Unsafe abortion**
CFR (initial)	0.010	0.007	0.017	0.013	0.0082
Range	0.007 – 0.013	0.005 – 0.009	0.012 – 0.022	0.009 – 0.017	0.002 – 0.01
CFR (adjusted, national)	**0.019**	**0.01**	**0.024**	**0.023**	**0.0082**

Hemorrhage: Incidence and case fatality rate

In a systematic review of 34 datasets, representing over 35,000 maternal deaths, Khan et al. [2006] found hemorrhage to be the leading cause of death throughout the world, accounting for a range of 1.4% to 49.6% of all maternal deaths, and the cause of the highest proportion of deaths in Asia and Africa. In Asia, hemorrhage is the leading cause of maternal mortality and contributes to approximately 30.8% of all maternal deaths [49]. A recent community-based study of maternal health in Nepal found similar results, with hemorrhage accounting for 34.5% of maternal deaths from direct causes in survey areas [50]. Maternal hemorrhage is categorized according to its timing in relation to delivery: antepartum, intrapartum, or postpartum. The etiologies and management of maternal hemorrhage differ among these three categories.

Initial estimates for the overall incidence of PPH were based on data from the WHO's Global Burden of Disease (GBD) study specifically for the SEAR region. We calculated estimates for the incidence of PPH (0.10) using data on the number of cases (n=3,692,000) [51] and the total number of births (n=37,820,000) [52]. The risk of PPH was modified to reflect assumptions in the WHO's "Global burden of maternal hemorrhage in the year 2000" [Dolea 2003a], specifically that the incidence of PPH, defined as > 1000ml of blood loss in the oxytocin arm, was 2.85% within 1 hour postpartum in women who were actively managed, as estimated from the MISO trial [53]. We assumed that the incidence of PPH in women who are managed expectantly by a skilled birth attendant would be twice as high as found in the MISO trial, or 5.7% of births [53, 54], and that births without skilled attendance would be twice as high as those with skilled birth attendance [55]. Extrapolating from these data, we assumed all births in a facility with emergency obstetrical care would be actively managed with a 2.85% risk of PPH, all other

births with a skilled attendant would be expectantly managed with a 5.7% risk of PPH, and all births attended by a family member or traditional birth attendant, or when delivery was alone, would be associated with an 11.4% risk of PPH. This approximates the range of 8% to 15% reported in the literature.

The initial estimate for case fatality rate of hemorrhage was from a review conducted by the DCP2 [45], which reported an average of 1%; this estimate was adjusted according to case severity and underlying morbidity (e.g., severe anemia) by calibrating the model to fit multiple epidemiologic targets simultaneously. [see section above on *Adjustment of case fatality rates for heterogeneity in severity and co-morbidity*] Our adjusted CFR widened the implied plausible range. While the literature-based range around the 0.01 (1%) average CFR from DCP2 was 0.007 – 0.013, the expanded adjusted CFR was 0.019 (1.9%). Model-projected mortality due to maternal hemorrhage, as well as MMR and TFR, closely approximated the empiric data.

To account for the uncertainty in our initial estimates, we established a plausible range for all the above parameters based on our literature review. There have been multiple studies and systematic reviews about the incidence and case fatality rate of maternal hemorrhage.

Hemorrhage: Reduction in mortality

In this model, the *incidence of maternal hemorrhage* is dependent on the delivery setting, and the use of expectant or active management. To *reduce mortality* from PPH, the model incorporates two approaches: by expectant or active management or labor (on the basis of delivery setting); and by successful referral and access to quality care (at an appropriate facility with basic or comprehensive emergency obstetrical care). Recent Cochrane reviews found no significant improvement in outcomes for women who received misoprostol for prevention or treatment of PPH [56, 57]—so use of misoprostol was not explored in the present analysis.

We assumed optimal treatment of maternal hemorrhage in an appropriate facility with EmOC capacity consisted of intramuscular or intravenous oxytocin immediately after delivery, uterine massage, repair of any perineal or vaginal tears, and fluid replacement or blood transfusion [48]; consistent with assumptions made by [58] and [45], we assumed an average reduction of 75% in the CFR. We varied this estimate from 60% to 90% for optimal management (i.e., bEmOC or cEmOC as necessary for severity).

Inclusion of antepartum hemorrhage

Johns et al. [47] estimate antepartum hemorrhage requiring management will complicate 2.2% of pregnancies; more specifically 0.11% pregnancies will be complicated by antepartum hemorrhage requiring caesarean section and 0.726% pregnancies will be complicated by antepartum hemorrhage requiring transfusion. As with postpartum hemorrhage, the course of antepartum hemorrhage can be unpredictable and a recurrent bleed can occur at any time and any severity level. Antepartum hemorrhage was not considered as a *separate category* in our model because we felt there were insufficient data on its epidemiology, natural history, and the impact of interventions *in developing countries*. For these same

reasons, incidence, prevalence and mortality rate estimates attributable to antepartum hemorrhage were not included in the WHO's global burden of maternal hemorrhage [53].

In contrast to postpartum hemorrhage, for which WHO region-specific incidence and mortality rates are available, the frequency of antepartum hemorrhage has been difficult to establish at the population level in developing countries due to a lack of: (1) widely accepted diagnostic criteria for this condition and (2) reliable ascertainment, which is grossly affected by the quality and availability of maternal care. Empirical data regarding the natural history of antepartum hemorrhage are also lacking. For example, the proportion of antepartum hemorrhages that present as severe or life-threatening is unknown, as is the proportion of cases that ultimately require transfusion and/or cesarean section. The percentage of cases of antepartum hemorrhage that resolve only to recur is also unknown. In addition, the mortality or morbidity risk of antepartum hemorrhage in the absence of medical care has not been determined. Finally, data are scarce with regard to the impact of interventions targeting antepartum hemorrhage. In developed countries, management of antepartum hemorrhage is frequently determined on a case-by-case basis since its etiology varies and management is dependent on multiple factors including etiology, the status of the mother and fetus, the amount of bleeding, gestational age, and in the case of placenta previa and abruption, the degree of separation between the uterus and the placenta. In developed countries, where comprehensive maternal care is not only high quality but also widely and promptly available, the mortality risk of antepartum hemorrhage has been reduced to <1%. This low mortality risk is attributable to a highly vigilant approach to this condition, generally consisting of: (1) emergency caesarean section for patients with refractory hemorrhage, poor fetal status, or significant bleeding after 34 weeks gestation; (2) hospitalization with close monitoring and supportive care for actively bleeding patients; (3) expectant management as an inpatient (or outpatient if the patient lives within 5-10 minutes of a comprehensive medical center) with close follow-up and planned caesarean section (or vaginal delivery, if possible) at 36 weeks (after documentation of fetal lung maturity) or sooner, if necessary, for patients with a resolved episode of antepartum hemorrhage due to placenta previa or abruption. The level and intensity of care required are not feasible for most developing countries. Additionally, there are currently no established guidelines or effectiveness data concerning the management of antepartum hemorrhage using a less vigilant approach in resource-poor settings.

Sepsis: Incidence and case fatality rate

Globally, puerperal sepsis and infection are estimated to contribute to nearly 10% of all maternal deaths in Africa (9.7%), Asia (11.6%), and Latin America and the Caribbean (7.7%) [49]. Recent regional estimates attributed 7% of maternal deaths to sepsis [33].

Initial estimates for the overall incidence of puerperal sepsis were created using data from the 2002 edition of the WHO's Global Burden of Disease study specifically for the SEAR region (containing Nepal). We calculated estimates for the observed incidence of puerperal sepsis (0.04) by using data on the number of cases (n= 1,573,000) [51] and data on the number of births (n= 37,820,000) [52]. We base our estimates for the risk of puerperal sepsis on the 2000 GBD estimates [59], that births occurring inside facilities with SBA were assumed to have a risk of puerperal sepsis of 2.5%. We assumed skilled birth attendants can still adhere to clean delivery practices outside a health facility, and therefore home deliveries attended by SBA had half the effectiveness of SBAs in a facility. Those delivering at home

with an untrained attendant had double the risk, at 5.0%. To account for the uncertainty in our initial estimates, we established a range of 4.2% - 6% for sensitivity analysis.

The initial estimate for the case fatality rate was from a review conducted by the Disease Control Priorities Project (DCP2) [45], which reported an average CFR of 1.3% and CFR 3.9% for severe sepsis; these estimates were then adjusted according to heterogeneity in severity and underlying morbidity (e.g., severe anemia) by calibrating the model to fit multiple epidemiologic targets simultaneously [see section above on *Adjustment of case fatality rates for heterogeneity in severity and co-morbidity*]. Our adjusted CFR widened the implied plausible range. While the literature-based range around the 0.013 average CFR from DCP2 was 0.009 – 0.017, the expanded adjusted CFR was 0.023. Model-projected mortality due to sepsis, as well as MMR, TFR, and calendar deaths for 2005, closely approximated the empiric data.

Sepsis: Reduction in mortality

We assumed the treatment regimen for puerperal sepsis (e.g., 2-day intravenous course of ampicillin, gentamycin, and metronidazole followed by an 8-day course of intramuscular gentamycin and oral metronidazole) had an overall treatment efficacy of 90% [45, 58]. A similar estimate was used in a recently published modeling analysis [60]: assuming an 11% case fatality rate for sepsis following delivery in sub-Saharan Africa, an 8-fold higher case fatality rate for sepsis without antibiotics compared to with antibiotics, and a 40% rate of antibiotic use, they estimated an 87.6% reduction in mortality from sepsis.

Obstructed labor: Incidence and case fatality rate

The two major causes of obstructed labor are cephalopelvic disproportion and abnormal fetal presentation (i.e., breech or brow presentation). Major complications of obstructed labor include endometritis, rectovaginal or vesicovaginal fistula, and ruptured uterus with consequent hemorrhage, shock or death. If the obstruction cannot be resolved by manipulation (to reposition the fetus) or instrumentation (with forceps or vacuum to deliver the fetus), cesarean section is required. Women who are malnourished, marry young, or engage in childbearing at an early age before the pelvis has reached adult proportions, are at high risk for obstructed labor.

Globally, obstructed labor is estimated at 4.6% of live births, although this varies considerably among different regions of the world [49, 61]. Using 2002 GBD data from the SEAR region, we estimated the incidence of obstructed labor (0.047) by using data on the number of cases (n=1771) [51] and data on the total number of births (n =37820) [52]. To account for the uncertainty in our initial estimates, we established a range of 3% - 7% for sensitivity analysis.

The initial estimate for the case fatality rate was from a review conducted by the Disease Control Priorities Project (DCP2) [45], which reported an average CFR of 0.7%; this estimate was adjusted according to heterogeneity in severity and underlying morbidity by calibrating the model to fit multiple epidemiologic targets simultaneously [see section above on *Adjustment of case fatality rates for heterogeneity in severity and co-morbidity*]. Our adjusted CFR widened the implied plausible range. Our

adjusted CFR was 0.01. Model-projected mortality due to obstructed labor, as well as MMR, TFR, and calendar deaths for 2005, closely approximated the empiric data.

Obstructed labor: Reduction in mortality

We assumed a 95% reduction in maternal mortality when obstructed labor was managed in an appropriate facility (assisted vaginal delivery with forceps or vacuum and, if necessary, cesarean section) [45, 58, 62, 63]. To account for the uncertainty in our initial estimates, we established a range of 76% - 100% for sensitivity analysis.

Severe pre-eclampsia and eclampsia: Incidence and case fatality rate

Hypertensive disorders of pregnancy refer to a range of conditions associated with high blood pressure, proteinuria and, rarely, seizures. Severe pre-eclampsia and eclampsia have the highest case fatality rates of the hypertensive disorders of pregnancy, and can lead to placental abruption, disseminated intravascular coagulopathy (DIC), adult respiratory distress syndrome (ARDS), cerebral hemorrhage, seizures, and death. Globally, the incidence of pre-eclampsia is estimated at 3.2% of live births and eclampsia at 0.5% [64] While in some parts of the world, such as Latin America and the Caribbean, hypertensive disorders of pregnancy are the leading causes of maternal deaths (25.7% of all maternal deaths) [49], globally they represent 13% of all maternal deaths [65]. UNICEF estimates that approximately 17% of maternal deaths in the SEAR region are attributable to hypertensive disorders [33].

Initial estimates for the overall incidence of hypertensive diseases of pregnancy were based on data from the 2002 edition of the WHO's Global Burden of Disease study specifically for the SEAR region: 0.028 and 0.008 for preeclampsia and eclapmsia, respectively. The estimate derived from this data for hypertensive diseases was 0.066 [51, 52]. This appears slightly higher than the estimate used in the 2000 GBD, but is in fact very close once a correction is made to account for the proportion of hypertensive disorders that are preeclampsia and eclampsia.

Eclampsia has a high case fatality rate, which varies among regions of the world, presumably as a function of the access to and quality of health care [65]. The initial estimate for the case fatality rate (CFR) was from a review conducted by the DCP2 [45], which reported an average CFR of 1.7%; this estimate was adjusted according to heterogeneity in severity by calibrating the model to fit multiple epidemiologic targets simultaneously [see section above on *Adjustment of case fatality rates for heterogeneity in severity and co-morbidity*]. Our adjusted CFR widened the implied plausible range and was 0.024.

Severe pre-eclampsia and eclampsia: Reduction in mortality

We assumed that severe pre-eclampsia and eclampsia required treatment with intravenous hydralazine and magnesium sulfate; in addition, approximately 10% of all cases were assumed to require emergent cesarean section [48]. Evidence indicates that magnesium sulfate can prevent and control eclamptic

seizures, and for pre-eclampsia, reduces the risk of eclampsia; a recent Cochrane review found a 59% reduction in risk of eclampsia among women with pre-eclampsia, although a non-significant reduction in risk of death (RR 0.54), for women who received magnesium sulfate versus placebo [66].

A review showed that magnesium sulfate was the better anticonvulsant choice when treating women with eclampsia, and substantially reduced the risk of further seizures when compared to phenytoin or diazepam [67, 68]. A study by one collaborative group found that the use of magnesium sulphate for women with pre-eclampsia was associated with a 16% reduction in the risk of death or serious morbidity related to pre-eclampsia two to three years later [69]. Evidence on other interventions remains weak, including treatment with antihypertensive drugs during pregnancy [70], and antenatal calcium supplementation (although this has shown promise, the evidence base is not robust due to studies' small sample sizes) [71].

We assume that aside from the use of magnesium sulphate, induction of labor could occur in facilities capable of basic and comprehensive emergency obstetric care for women who do not require emergency cesarean section. Thus we rely on the higher effect size from the Cochrane Review, although still perhaps a conservative estimate, for the reduction in the case fatality rate of severe pre-eclampsia. We assumed severely pre-eclamptic/eclamptic women who received treatment had a 59% reduction in disease-specific mortality compared to those without treatment [45, 58, 72].

Long-term morbidity

Aside from mortality outcomes, the model considers the following non-fatal outcomes associated with pregnancy- and delivery-related complications. We obtained incidence rates for these non-fatal complications from the GBD project, as presented in the table below.

Table 2.2-6: Initial estimates for morbidity (GBD data)

Neurological sequelae from hypertensive disorders	0.0008
Severe anemia from PPH [a]	0.090
Sheehan's syndrome from PPH	0.008
Infertility from sepsis [b]	0.086
Fistula from obstructed labor [c]	0.021

a	This estimate takes into account the rate of severe and moderate anemia, the overall incidence of PPH, and the overall incidence of severe anemia in pregnant women, during the postpartum period, and in the general reproductive age group. We assume that women with pre-existing moderate anemia contribute disproportionately to the subsequent severe anemia observed following PPH.
b	Represented by the risk of pelvic inflammatory disease (PID) of 0.40 multiplied by the risk of infertility (0.22) given PID, to yield the estimate of 0.086
c	We assume at national average of 25% are treated.

Maternal deaths due to unsafe abortion

The World Health Organization (WHO) defines "unsafe abortion" as "a procedure for terminating an unintended pregnancy carried out either by persons lacking the necessary skills or in an environment that

does not conform to minimal medical standards, or both" [73]. Unsafe abortion is estimated to account for 13% of all maternal deaths worldwide [73]. The vast majority of unsafe abortions occur in developing countries where the access to safe abortion may be restricted by law, lack of adequate facilities, or sociocultural factors preventing easy access to legal abortions.

In 2002, the Nepal government passed legislation to legalize abortion, up to 12 weeks' gestation at the woman's request, and with certain medical conditions thereafter. The law went into effect in 2003, and the first abortion facilities were opened in 2004. Legalization and availability of services was a complex process, involving a number of partners and requiring significant health system capacity scale-up; additionally, in 2009, medical abortion was introduced (first as a pilot, then scaled up) as an alternative to surgery for early abortions [74].

By 2012, there were over 1200 clinicians and 530 clinical sites trained and certified to provide legal and safe abortion services in Nepal, and it has been estimated that approximately a half-million women had received abortion services by that time [75]. A recent analysis found that rates of severe abortion complications, as seen at public referral hospitals in Nepal, are declining over time—despite the likely increasing number of women obtaining abortions and seeking treatment, indicating that abortions are becoming safer [76].

But many women are still unaware of the laws and services: in the 2011 Nepal DHS, only 38% of women believed that abortion is legal in Nepal and less than 60% were aware of a place to receive a safe abortion—in both cases, older and rural women were the least aware [15]. Stigma also remains an issue, among women as well as among health care providers; and there are health system challenges, for example access to trained providers and safe abortion sites [74]. And there is concern that women are still utilizing unsafe services for illegal, and risky, later-term abortions. Additionally, data indicate that many women still utilize "unsafe, ineffective or unknown substances" for medical abortions [77].

Limited data are available on the rate of elective abortion (safe or unsafe) in Nepal. Due to increasing knowledge and availability of safe abortion services, we assume in our base case analysis that 25% of abortions are unsafe. Due to the lack of Nepal-specific data on the proportions of maternal deaths due to unsafe abortion, we were unable to perform calibration exercises to check the face validity of our estimates. However, we vary both the probability of elective abortion and the proportion unsafe in sensitivity analyses to account for the uncertainty surrounding these estimates. These estimates were varied from 10-25% (abortion ratio), and from 20-30% (proportion of unsafe abortions), respectively.

We used Asia-specific estimates from the WHO, and assumed that illegal/unsafe abortion is associated with a mortality of 300 per 100,000 procedures [73]. In addition, we assumed a proportion of safe and unsafe abortion, 2.8% and 14.7% respectively, was associated with post-abortion complications requiring hospitalization and incurring quality of life decrements and costs [47, 78].

We use earlier-estimated mortality risk from safe abortion, based on U.S. data in the early 1970s (when elective first-trimester abortion was legalized in most U.S. states), and results from other studies in the U.S. and elsewhere [22]. We assume a crude average of 1.55 per 100,000 for the risk of mortality from safe abortion; however, we acknowledge the actual risk may be higher in developing countries.

2.2.2 Data and Assumptions: Coverage Inputs and Selected Services

Delivery setting

In the model delivery setting is differentiated by site including (1) home; (2) birthing center or health center (used interchangeable here), (3) facility with bEmOC, (4) facility with cEmOC; and differentiated by health provider including (1) family member, (2) traditional birth attendant [TBA], (3) skilled birth attendant (doctor, nurse, nurse/midwife). Facilities classified as birthing centers or health centers are assumed to be staffed by SBA with expectant management of labor but do not have all signal functions to qualify as bEmOC.

Using data from NDHS-2011 (displayed below), more than half of births occur at home, and only 2.9% of home births are delivered by a skilled provider (defined as doctor, nurse, nurse/midwife). [17]

Table 2.2-7: Selected Model Parameters

Variable	Baseline value
% delivered in a health facility	35.3%
% non-health facility deliveries with attendance by doctor or nurse/midwife	2.9%
% non-health facility deliveries with attendance by lower-cadre health worker or traditional birth attendant	29.9%

To obtain the breakdown of births by facility type, we relied on data from the Nepal HMIS. We estimated for the status quo that 42.4% of facility delivers occur in an EmOC-capable site, of which 25% are bEmOC. In strategies that shift home births to facilities, additional analyses are conducted using several alternative assumptions. For example, as shown below, we explore in a scenario analysis the impact of (a) changing the distribution of routine deliveries that occur in primary facilities lacking EmOC (health posts and sub health posts) and facilities with EmOC, and (b) changing the distribution of deliveries in EmOC that occur in bEmOC versus cEmOC.

Table 2.2-8: Sensitivity Analyses, Birth distribution among facilities

	Analysis 1		Analysis 2		Analysis 3		Analysis 4	
	A*	B*	A*	B*	A*	B*	A*	B*
Total facility births								
Begin HP/SHP**	58%	58%	75%	75%	90%	90%	0%	0%
Begin bEmOC**	10%	21%	6%	12%	3%	5%	25%	50%
Begin cEmOC**	32%	21%	19%	13%	7%	5%	75%	50%
* A = 25% bEmOC, 75% cEmOC (base case); B = 50% bEmOC, 50% cEmOC								
** HP = health post, SHP = sub health post, bEmOC = basic emergency obstetric care, cEmOC = comprehensive emergency obstetric care.								

Antenatal care

Data on antenatal care (ANC) from the Nepal DHS 2011 were used for coverage rates, and were stratified by age group when available. We assumed in our analyses that antenatal care includes 4 or more visits with a skilled provider, tetanus vaccination, syphilis, gonorrhea, chlamydia screening (and treatment), urinalysis, blood tests, treatment for anemia, counseling (e.g., family planning, spacing, intrapartum care). Among women aged 15-49 who had a live birth in the preceding 5 years, 50.1% of them attended 4 or more antenatal care visits during pregnancy prior to their most recent live delivery. It was assumed that all women received treatment of anemia during their antenatal care. [17]

There is some evidence that utilizing antenatal care services may lead to the utilization of other maternal health services such as institutional delivery, delivery with skilled attendance, and advice-seeking behavior for pregnancy-related complications and postpartum complications [79], particularly in areas where few women seek institutional childbirth [80]. These findings were echoed in a recent study from Nepal, which found that birth preparedness was significantly associated with increased likelihood of institutional delivery [81]. Sensitivity analyses were conducted to explore the range of potential benefits associated with the scenarios that antenatal care increases facility over home births and the use of SBAs for those remaining at home.

Postpartum care

In a recent household survey, women who had recently given birth were asked about postpartum complications: approximately 10% of respondents reported at least one problem in the six weeks after birth, most commonly fever, anemia and hemorrhage; but only half of these women sought care for the postpartum complication [31]. Similar rates of postpartum careseeking have been reported by a community-based survey [82] and in the 2011 Nepal DHS; the model uses the national average of 32% of women who received postnatal care for most recent live birth within prior 2 years. [17]

Family planning: Coverage level of contraceptive method

We include a comprehensive strategy of enhanced family planning to reduce the unmet need for contraception for purposes of *both* limiting and spacing pregnancies. The effectiveness of family planning is incorporated into the model as a set of variables that reflect (i) coverage level of contraceptive method; (ii) distribution of contraceptive type; (iii) type-specific failure rate. We use nationally representative data to represent the current met need for contraception and the distribution of methods used by age. Failure rates are conditional on the method used. Contraceptive methods included traditional methods (withdrawal or rhythm) and modern methods such as the pill, intrauterine device (IUD), male condoms, injectables, vasectomy, and tubal ligation.

Estimates relating to unmet need for family planning are from the Nepal DHS 2011. Approximately 27 percent of currently married women in Nepal have an unmet need for family planning, with limiting (17.4%) approximately double that of spacing (9.6%) using average national estimates. Unmet need declines with age, from 41.5% (ages 15-19) to 13.2% (ages 45-49); and women below age 24 have a greater unmet need for spacing than for limiting. In our base case analysis, this age pattern is incorporated. [17] We do explore age-specific focused interventions in sensitivity analyses, specifically, focusing efforts to increase modern contraception in younger women. The motivation for these

exploratory analyses was based on NDHS data showing that although over 40% of currently married women reported using modern contraception, family planning is used mainly for the purpose of providing long-term contraception: among married women, the main contraceptive type is female sterilization (15.2% of modern method users overall), and consequently modern method use is lowest in the youngest age groups. The median age for women undergoing sterilization is 27 years, which sheds light on the childbearing pattern of Nepalese women. [17]

Family planning: Distribution of contraceptive type

Table 2.2-9: Selected model parameters, Baseline Value (%) among married women [17]

			Age groups						
		Nepal, overall	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**
Family planning									
	Any method	49.7%	17.6%	29.5%	46.3%	59.6%	67.4%	68.1%	53.7%
	Modern methods	43.2%	14.4%	23.8%	39.8%	52.2%	59.9%	59.9%	48%
		Pill	4.1%	3%	3.7%	5.4%	5.5%	4.5%	3%	1.7%
		IUD	1.3%	0%	1%	1.8%	1.3%	1.9%	1.2%	0.6%
		TOL	15.2%	0%	4%	11.8%	18.7%	23.8%	27.1%	22.9%
		Condom	4.3%	6.5%	5%	5.7%	4.5%	3.5%	2.3%	1.3%
		Injectable	9.2%	4.9%	8.5%	9.9%	11.1%	10.9%	9.5%	5.7%
	No. women surveyed	9608	792	1761	1914	1659	1461	1190	832
a	IUD: intrauterine device; TOL: female sterilization								

Family planning: Type-specific failure rate

We used contraceptive failure rate estimates from the UNFPA's Reproductive Health Costing Tool. [UNFPA 2007; Trussell 1990] Failure rates by method are: IUD (4%), oral contraceptives (8%), condoms (19%), injectables (2.9%), female sterilization (0.5%), and male sterilization (0.2%).

Family planning: Overview of increasing contraceptive use

Our main intervention target was to reduce unmet need, thus describing the effect of increasing access and uptake of modern contraception by reflecting two groups of women: (a) women who are not using any method of contraception but who do not want any more children - unmet need for *limiting* and (b) those who are not using contraception but want to wait two or more years before having another child - unmet need for *spacing*. (The sum of the unmet need for limiting and the unmet need for spacing is the modeled unmet need for family planning.)

For Nepal as a whole over the past two decades, there has been a slight decrease in unmet need for family planning among married women, from 32.4% in the 1996 DHS to 27.8% in 2001 to 24.7% in 2006 and,

as discussed above, 27% in 2011. Unmet need for limiting methods remained virtually unchanged over this period, but unmet need for spacing has fallen (from 14.8% in the 1996 survey to just below 10% in 2011), and this change has been seen in all age groups. [17]

The table below illustrates differences in baseline model assumptions about access to family planning (e.g., the unmet need for spacing and limiting births) and the magnitude of stepwise increases characterizing different strategies.

Table 2.2-10: Modeling increases in use of family planning

	Status quo	**Step 1**	**Step 2**	**Step 3**	**Step 4**
% reduction in unmet need		25%	50%	75%	100%
	% of women using contraception				
15-19	17.6%	28.0%	38.4%	48.7%	59.1%
20-24	29.5%	38.7%	47.9%	57.1%	66.3%
25-29	46.3%	53.9%	61.6%	69.2%	76.8%
30-34	59.6%	66.1%	72.6%	79.1%	85.6%
35-39	67.4%	72.6%	77.8%	82.9%	88.1%
40-44	68.1%	72.1%	76.0%	80.0%	83.9%
45-49	53.7%	57.0%	60.3%	63.5%	66.8%

Relationship between abortion and contraception

The risk of unsafe abortion is reduced through the use of contraception, legalization of elective abortion, and the use of safe abortion methods by a high-quality and trained provider.[83] Access to safe, effective contraception can substantially reduce the need for abortion to regulate fertility. [84, 85] Women who reported having a recent abortion in the NDHS were asked their reason for the abortion: 20% did not want any more children, 12% had a husband who did not want the child, 10% wanted a longer birth interval, 7% were trying to delay childbearing, and 10% cited health-related reasons [17].

Impact of community-based interventions

There is generally weak data about the potential of community-based interventions to improve maternal and neonatal health outcomes (e.g., the use of misoprostol by TBAs to reduce PPH in the home setting, or clean birth kits in reducing death from sepsis in the home) [86, 87] – but a recent study modeled the potential gains of such community interventions alongside health system strengthening, and found that it would likely save lives as a complementary activity in sub-Saharan Africa [60].

A Cochrane review identified 18 randomized and quasi-randomized trials to evaluate the impact of community-based interventions to prevent maternal and neonatal death and illness [88]. Most of the studies had occurred in south Asia (Nepal, India, Bangladesh, Pakistan), and focused on improving skills for TBAs and community health workers around antenatal and intrapartum care; the review did not find a

significant effect on maternal mortality, although the interventions were associated with improvements in maternal morbidity as well as neonatal outcomes.

There have also been a number of studies looking at community-level use of misoprostol to reduce mortality from PPH. A recent Cochrane review of these found that the use of uterotonics in the home birth setting was associated with a significant decreased risk of PPH, although the studies have so far been too small to identify effects on maternal mortality [89]. A study was done in Nepal to assess the operational feasibility of this approach, and the authors found positive results, particularly for women in the poorest and most remote households—but the study did not look at any process measures or outcomes. [90]

Coverage of community-based interventions in Nepal

Aside from the need for convincing evidence on the effectiveness of community-based interventions to improve maternal health, additional evidence on the potential reach of such interventions across a large portion of the population is required to justify policy relevance of these strategies. The above-mentioned community-based misoprostol study was conducted in only 1 district of Nepal and included 840 women [90]. There have been larger studies, including a study to assess mortality effects of micronutrient supplementation, which involved nearly 45,000 women in one area of Nepal [91]. Additionally, a large study assessed the potential impact of women's groups on neonatal outcomes, with almost 30,000 women in a single district of Nepal [92, 93]. There have been a number of other smaller studies also looking at neonatal outcomes, as associated with micronutrient supplementation [94], as well as postnatal women's groups [95] and postnatal umbilical cord care [96]. A recent study used community health volunteers to provide pregnancy tests (otherwise often unavailable and unaffordable in rural areas) plus follow-up counseling and referral for services, in six Nepal districts; in a relatively short follow-up period (only 8 months), the volunteers provided the test, counseling and referral to over 4500 women [97]. It is noteworthy that even the larger studies reported here had very limited spatial reach—the geographic characteristics of Nepal may make it especially challenging to implement widespread experiments, and this may have important implications for taking community-based interventions to scale.

2.2.3 Data and Assumptions: Intrapartum care and the "three delays"

Effective referral relies on the ability to overcome three critical delays: (a) recognition of referral need, willingness to be referred and permission to seek care (varies by provider and delivery location); (b) expedient transfer to referral facility (determined by distance, affordability, available transport); and (c) timely treatment in an appropriate facility capable of high-quality emergency obstetrical care (e.g., 6 signal functions in bEmOC, blood transfusion and surgery in cEmOC; also includes 24-hour accessibility, trained providers, female providers). We expanded Thaddeus and Maine's [1994] "three delays" framework to reflect the multidimensional nature of each of these delays and the heterogeneity between and within countries as to which delays and components are most critical. A successful referral in our model incorporates a series of elements, each of which could act as a barrier to the care a woman with pregnancy-related complications requires.

Delay Category 1. Recognition of need for referral and/or willingness and/or permission to be referred

We include in this category failure and/or delay in any or all of the following: (1) recognition of the need for referral by the birth attendant; (2) willingness to be referred on the part of the woman and her family; (3) obtaining permission to seek care by the husband, male head of the household, or other family member. We assumed the recognition rate for complications developing during home deliveries would vary based on the level and skill of the birth attendant. Based on data from Honduras regarding traditional (untrained) birth attendants, we assumed a 10% recognition rate for unskilled delivery at home, and a 20% recognition rate for skilled birth attendants at home [45, 98]. For referrals from health posts and sub health posts, we assume a 50% recognition rate for skilled attendants in these settings. We assumed life-threatening complications (e.g., those needing cEmOC capability) occurring at bEmOC were recognized as needing transfer to a facility with cEmOC. We also included an analysis assessing the impact of delays in facility transfers (i.e., incorporating the delay due to transport problems, logistics, or fees). In addition, we assumed an "erroneous" referral rate (in the absence of complications), owing to misdiagnosis and lack of patient monitoring support, that varied from 2.5% to 10% based on location of delivery and skill level of birth attendant.

Based on literature and Nepal-specific data, we established a plausible range for sensitivity analysis. There are many determinants of where and with whom women deliver, including autonomy about household decisions. Studies in Nepal have found that decision-making roles are associated with care-seeking behavior during pregnancy and childbirth. The extent of a woman's sole household decision-making authority has been associated greater likelihood of non-accompanied ANC attendance [99, 100]; joint spousal decision-making is associated with greater discussion of pregnancy health issues within the household and greater likelihood of birth preparation [100], although one study that saw this identical result also found an opposite effect for economic autonomy on discussion of pregnancy health [99]. An evaluation of an intervention to increase antenatal health education among husbands in Nepal found that joint antenatal education resulted in greater birth preparations (although found no significant effect on number of antenatal care visits, nor institutional birth or skilled attendance) [101]. A recent review article also found that decision-making power, socioeconomic autonomy and gender inequality were determinants of maternal care-seeking behaviors in Nepal [102].

When women in Nepal are asked about their care-seeking behaviors, both generally for health care and for childbirth specifically, it is becoming less common for women to cite barriers due to permission. In the 2006 NDHS, 12.6% of women reported that "getting permission to go for treatment" was a serious problem in accessing health care for themselves when ill, and this number fell to 7% by the 2011 NDHS. The 2011 NDHS also asked women who had recently delivered at home why they had not sought institutional delivery, and only 2.8% said that "husband/family did not allow." In 2010, the National Living Standard Survey (NLSS) in Nepal asked women who was involved in the decision to access health care during pregnancy: 24.5% of respondents said that they made the final decision alone, 9.6% said that their spouse made the decision, and 56.3% reported joint decision-making (9.6% responded "other," which probably indicates involvement of other family members, for example mothers-in-law).

Decisions about childbirth care-seeking among laboring women in Nepal are often made by family members: a household survey indicated that, among women who had recently given birth, the majority

(77%) of their husbands had been involved in the decision about where to seek care, and 35% of women also had input from their in-laws [31]. Another recent survey asked postpartum women at a health facility about who participated in this decision: 47% of women said they themselves had input into the decision, 65% of decisions involved spouses, and 44% involved in-laws [103]. In this same survey, 6% of women who had delivered at home attributed this birth site to a lack of permission from other household members for care-seeking at a facility. In the 2011 NDHS, women were asked about problems faced in general health careseeking, and 13% reported difficulties with getting permission to go for treatment [17].Qualitative research from Nepal also supports these findings that the choice about location for childbirth and utilization of clinical care is highly influenced by spouses and in-laws [104].

Additionally, those in the home setting may not know when care is necessary: only half of women of reproductive age know at least three pregnancy-related danger signs [31]. Birth preparedness should be part of antenatal care, but direct observation of antenatal services in Nepal found that danger signs were only discussed 12% of the time and birth planning only 17% of the time [105].

Larger studies have found, however, that birth preparedness has increased alongside antenatal care utilization in Nepal: in the 2011 NDHS, among women who had received antenatal care for their most recent birth (within the prior 5 years), 75.5% had been "informed of signs of pregnancy complications," which is a considerable increase over 57.7% reporting the same in the 2006 NDHS [17]. This overall statistic does mask considerable variation across education groups: in 2011, information about signs of complication during ANC was near-universal among the highest-educated group of women (92.8%) versus only 63.9% in the lowest education group. Also, among women who had delivered in the prior 5 years, 35.4% of women had made no specific preparations for the delivery—this is down from 45.8% of women who reported the same in 2006. In another study, women who acknowledged the importance of an attendant at birth, but have not used one, were asked why; "did not think it was necessary" was the most commonly-cited reason, followed by cost [106]. Additionally, gender norms and household hierarchical structures may suppress women's expression of suffering if complications in the home birth setting do arise, so they do not request, and sometimes even refuse, transfer to a health facility for medical attention [107].

Evidence also suggests that TBAs in Nepal may not be identifying and referring complications optimally. One study found that TBAs report having no standard practice to identify maternal complications nor the severity of these [108]. In another, one-quarter of TBAs reported that they would not send a woman to a health facility if a complication arose during delivery that they could not manage—and only half of the surveyed TBAs had ever actually referred a woman with delivery-related complications to a health facility or doctor [109].

The table below shows the initial *range* of baseline estimates used in sensitivity analyses, and the initial *range* across which stepwise improvements were made in the temporal strategies evaluated. These ranges were expanded in a series of exploratory analyses.

Table 2.2-11: Recognition of referral need

	Value used in baseline model	Range of stepwise increases in recognition of need/willingness for referral	Range of baseline estimates for status quo used in sensitivity analysis
Family at home	10%	n/a	5-30%
TBA at home	10%	n/a	5-40%
Skilled at home	20%	20-90%	10-40%
Skilled at birthing center	50%	50-100%	40-100%
At bEmOC	95%	n/a	75-100%

Delay Category 2. Expedient transfer from birth location to facility

We include in this category availability of timely and affordable transportation from birthing location to facility, functioning vehicle with fuel, and if necessary, provision of interim lifesaving care en route. The availability of transport is assumed to be a function of infrastructure (ambulances or private vehicles, neighborhood emergency transport networks, road densities, distance to hospitals, etc.). Based on available data, we made assumptions about effective transfer that varied by delivery location (home, HC, bEmOC), and were intended to reflect access to transport, reliable fuel and accompanying person en route, and interim care if necessary. We assigned 95% (and not 100%) as the baseline rate of "expedient accurate referral" in a lower-level facility, to reflect delays attributable to multiple transfers between facilities, and delays related to being turned away from one hospital and having to travel to another. We established a plausible range for sensitivity analysis based on the broader and Nepal-specific literature.

Nepal's population is largely rural, with challenges in access to health facilities and to roads. According to recent estimates from the World Bank, the majority of Nepal's population is rural: 82.7% of households in 2012 [110]. Access to paved roads is quite low, particularly in rural areas. The World Bank estimates that only around half of Nepal's road network is paved [110]. The 2010 Living Standard Survey found that the average time to reach a paved road for rural households was approximately 3 hours. (Only half of rural households reported access to a paved road in under an hour, and for nearly one-quarter of rural households, the nearest paved road is over 3 hours away.) Road access also exhibited a strong relationship with household wealth: the average time to reach a paved road among the richest quintile was reportedly 66 minutes, versus 253 minutes for households in the poorest quintile [111]. Likewise, households in urban settings reported an average time to reach a hospital of under 30 minutes, but this rose to over two hours for rural households [111].

Distance and transport to health facilities for childbirth have long been acknowledged as significant barriers to accessing care in Nepal. Women in the mountainous areas of Nepal have reported spending over 8 hours (on average) traveling to comprehensive obstetric care facilities, versus 5.6 hours in the hills and 2.8 hours in the terai [112]. In contrast, women reported that birth attendants reached their homes within one hour on average [113]. Studies such as these prompted the government of Nepal to reconsider geographic access to childbirth services. More recently, the government of Nepal identified poor transportation in rural areas as a significant barrier to utilization of services including health care [114]. And articles about determinants of maternal care-seeking behavior in Nepal repeatedly find that transportation and distance (including road quality) are high on the list of obstacles to care [102].

In the 2011 NDHS, nearly half (49.8%) of women respondents in the mountain areas and 43.3% of those in the hills reported traveling more than one hour (the maximum response category) to a facility for their most recent childbirth. And among women who reported "serious problems" in accessing care when ill, half of these women attributed this problem to health facility distance—and when women who had not recently delivered in a health facility were asked why not, 14% reported that the facility was too far and/or they did not have transport, and 8% delivered their baby before reaching the facility [17]. Similar values were reported in the 2012 Household Survey: among women who had recently delivered at home, 17% said this was because the facility was too far away and an additional 8.4% said the reason was lack of transport [31]. In this same survey, 38% of women who reported having experienced a complication during pregnancy or labor did not seek care for this complication, and 30% said it was because the facility was too far away—and when women did deliver at a health facility, the most common modes of transport were walking, ambulance, and public transport (together encompassing nearly three-quarters of all surveyed women who had delivered at a public health facility within the prior year). Many studies have also found that women cite distance and transport challenges as barriers to institutional delivery [115-117].

A recent qualitative study in Nepal found that facility characteristics—including distance and access challenges—were key determinants of a woman's choice of maternal care; and among women who had died from maternal causes at home, nearly one-quarter had encountered transportation and/or distance challenges [118]. Among maternal deaths included in this study, 42% occurred at home and 7% while in transit to a facility. For women who paid for transportation to a health facility for childbirth care, the median cost in a recent study was 400 Nepali rupees [103] (approximately 4 USD); this is clearly unaffordable for many in a country where over half the population is below the 2 USD/day poverty line [110].

Despite these far distances and long travel times, few women in Nepal report making transportation arrangements in advance of birth. Only 2% of 2011 NDHS mountain respondents (and only 2.3% of hill) made specific transport arrangement preparations before delivery [17]. As part of the government's effort to increase utilization of institutional delivery services, there is a new transportation reimbursement incentive. Use of this incentive is not yet universal: between two-thirds and three-quarters of recently delivered women reported receiving this payment in recent surveys [17, 103]. Additionally, according to the 2011 NDHS, only 2.3% of surveyed households owned automobiles, 10.9% owned motorcycles, and 39.7% owned bicycles/rickshaws—limiting a woman's transportation options from home to a health facility in the case of complications during a home birth. And transfers between facilities may likewise be hindered by lack of transport: fewer than 10% of health posts and sub health posts surveyed in the 2011 STS had an ambulance available (although approximately half had stretchers available for transport), and just over one-third of PHCCs and three-quarters of hospitals had a functional ambulance [103].

These factors may explain why childbirth events—both delivery and maternal death—occur before reaching a facility. In the 2011 NDHS, 8% of respondents said that, for their most recent birth, the child was born before reaching a health facility [17]. An audit of maternal deaths in 2008 found that 41% had occurred at home, 7% in transit to a facility and 5% in transit from a facility [118]. This analysis was a follow-up to a decade-earlier study about maternal mortality in Nepal, and the later results showed an increase in the percentage of maternal deaths that had occurred at a health facility—from 14% in 1998 to 42% in 2008—and, accordingly, a decline in the percentage occurring at home (from 70% to 41%). This

implies that more women are going to facilities when they experience a complication, but this decision may be occurring too late or the facilities are unable to treat them.

Accordingly, women who decide to seek care at a health facility may be referred elsewhere, particularly if they begin by accessing the lowest-level health facility closest to them. In the 2012 Household Survey, approximately 10% of women who had delivered at a government health facility within the prior year had been referred there, mostly from other, lower-level public health facilities [31]. A facility-based survey from the same year similarly found that between 10 and 20% of women who delivered at a facility had been referred there [103]. Complex cases are commonly referred to other facilities, even by hospitals: a recent facility survey found that over half of hospitals referred women needing assisted deliveries (only 40-55% of lower-level facilities referred such women), and referral facilities were on average two hours away [103].

Such a high referral rate carries risks. First, logistics for coordinating referrals can be complex. A recent assessment of reproductive health care quality in Nepal found that very few facilities use referral forms [119]. Transportation is also a challenge: only 30% of studied health facilities had ambulances available for referral transport [119]. In another survey, ambulance availability was disaggregated by type of facility, and availability was significantly lacking at lower-level facilities (i.e., those more likely to provide out-referrals): approximately 90% of health posts and sub-health posts studied had no ambulance available at all (versus 6% of hospitals) [103]. Qualitative research indicates that the referral system for obstetric care is perceived as not well-functioning [118].

The table below shows the initial *range* of baseline estimates used in sensitivity analyses, and the initial *range* across which stepwise improvements were made in the temporal strategies evaluated. These ranges were expanded in a series of exploratory analyses.

Table 2.2-12: Ability to transfer to appropriate facility expediently (reflecting transport, supportive care en route, no delays)

	Value used in baseline model	Range of stepwise increases in recognition of need/willingness for referral	Range of baseline estimates for status quo used in sensitivity analysis
From home	20%	20-95%	5-40%
From HP/SHP	35%	35-95%	10-50%
From bEmOC	50%	50-95%	30-60%

Delay Category 3. Availability and quality of services at EmOC facilities

We include in this category availability and quality of services at EmOC facilities, including the presence of a facility open 24 hours per day with adequate staffing and supplies, expedient attention (e.g., without delay to collect fees or requirement for family to bring supplies), and care that is evidence-based and of high-quality. In general, assumptions for this category are challenging as even in locations where there might be adequate numbers of doctors, or an adequate number of facilities, attributes such as round-the-clock availability, expedient care without delay, adequate supplies, and high-quality practice are critically influential on the effectiveness of health service delivery. The facility categories are flexibly modeled

such that particularities of the public health infrastructure in different settings (e.g., country, province, rural versus urban areas) can be accurately represented in terms of capacity and cost.

For input into the model, facilities are categorized as (1) *primary-level facilities*, or health centers (HC), which may not provide all services necessary to qualify as a bEmOC facility, but could function as birthing centers with SBA staff who provide expectant management of labor, 24-hour intrapartum care, and reliable referral connections when necessary; (2) *secondary facilities* with bEmOC capacity, assumed to be capable of administering injectable antibiotics, oxytocics, and sedatives or anti-convulsants, performing manual removal of placenta, removal of retained products, and assisted vaginal delivery; and (3) *tertiary facilities* with cEmOC capacity.

Delivery setting is differentiated by site including (1) home, (2) health centre (HC; used interchangeably with "birthing center" here), (3) facility with bEmOC, (4) facility with cEmOC; and differentiated by health provider including (1) family member, (2) traditional birth attendant (TBA), (3) skilled birth attendant (doctor or nurse/midwife). Facilities classified as HC are assumed to be staffed by SBA with expectant management of labor but do not have the signal functions to qualify as bEmOC. Facilities with basic EmOC (bEmOC) are assumed to be capable of administering injectable antibiotics, oxytocics, and sedatives or anti-convulsants, performing manual removal of placenta, removal of retained products, and assisted vaginal delivery. Facilities with comprehensive EmOC (cEmOC) also are able to provide blood transfusion, cesarean section, and management of advanced shock.

Some tertiary sites will not have a blood bank and some secondary sites may eventually be able to perform c-section; further, we recognize that the strategies include stepwise investments in infrastructure and facility improvements, but not all facilities may be fully implemented as among the three distinct types. However, because the costs, functions and staffing are fairly closely aligned with basic or comprehensive EmOC capacity, this simple categorization captures the most important dimensions for purposes of this analysis. Below is a stylized example of how public health facilities in Nepal (categorizations as found in, e.g. [120]), may be superimposed on our general model framework. Note that some primary health care centers (PHCC) function essentially as health centers while others have bEmOC capacity; likewise, some district hospitals have bEmOC capacity while others have cEmOC capacity.

Table 2.2-13: Framework to differentiate facilities

Health facilities in Nepal	Facility Level	Model Category	Staff Assumptions	Facility Capacity Assumptions
Sub-health post, Health post	1st	Health center (HC)	Medical Officers, Staff Nurse, Health workers	SBA expectant-management of labor
Primary health care center (PHCC)	2nd	bEmOC	Above, plus physicians	Capabilities of 1st level facility plus active-management of labor
District hospitals				
Higher-level hospitals, plus some district hospitals	3rd	Tertiary facility with cEmOC	Above, plus specialists, Obstetricians/ Gynecologists (Ob/Gyn)	Capabilities of 2nd level facility plus availability of blood transfusion, surgery (e.g., c-section), intensive hemodynamic support

The health system in Nepal faces obstacles in delivering high-quality childbirth care. One key constraint is the health worker shortage, especially for lower-cadre health workers and for specialists—both necessary for obstetric care. Across all facility levels, low-level staff, e.g. health assistants, are in short supply. And among hospitals, one-third has unfilled obstetrician posts and two-thirds have unfilled anesthesiologist posts. Staff shortages are perceived by providers to impact service delivery: one-quarter of hospitals cited staffing shortages as affecting the provision of safe motherhood services, and approximately 50-60% of lower-level facilities reported the same [103].

Data shown below are from a recent nationally-representative survey of health facilities in Nepal. [103] One-third of surveyed hospitals and the majority of lower-level facilities do not have consistent electricity; many lower-level health facilities do not offer basic EmOC services around the clock; and 25% of hospitals and more than 80% of health posts and below do not have overnight accommodation for nurses, with obvious implications for lack of 24-hour care.

Table 2.2-14: Facility types and characteristics [103]

Facility type	24/7 power supply	bEmOC services available 24/7	Overnight nurse accommodations	Separate delivery room	Adequate delivery room, table	Adequate delivery kit
Hospital	63%	100%	75%	100%	75%, 69%	88%
Primary Health Care Centre (PHCC)	36%	36%	54.8%	93.6%	72%, 66%	79%
Health Post (HP)	23%	6%	17.7%	48.1%	61%, 61%	79%
Sub Health Post (SHP)	11%	0%	2.8%	13.9%	40%, 70%	70%

Care quality is repeatedly cited as the key constraint for improving rates of institutional delivery: quality both affects a woman's willingness to seek formal health care, and outcomes among those women who receive services [104, 121, 122]. In the 2006 NDHS, among women who reported serious problems in accessing health care when they are sick, 57.1% felt there would be no provider available (50.4% had a concern specifically about availability of a female provider) and 53.6% thought there would be no drugs available. These issues are especially acute in mountain areas: 70.3% of respondents in the mountains mentioned concerns about provider availability, versus only 51.7% of women in terai who chose this response; and drug supply concerns were mentioned by 74.2% of mountain respondents versus 44.3% of women in the terai [18].

Some analyses suggest that increasing the number of facilities would only modestly impact service utilization behaviors, because of poor facility quality due to such under-staffing and under-stocking of supplies [117, 121]. Women ascribe these quality indicators to their non-use of health facilities for maternal care: government primary health facilities are seen as low-quality, lacking supplies, and only able to assist with minor issues; and although district hospitals are seen as a better option, women report physical distance as a barrier [123]. Similar findings have persisted over the past decade, as found in a recent qualitative study where women who delivered at home often attributed this choice to health system quality issues, including opening hours and human resource skill and demeanor [104]. Women have stated a preference for home deliveries for reasons of cost and distance, as well as attendant characteristics (familiarity and same-sex) [112, 113].

We conducted both sensitivity analyses on alternative baseline assumptions, as well as an analysis at every stepwise point. The table below shows the initial *range* of baseline estimates used in sensitivity analyses, and the initial *range* across which stepwise improvements were made in the temporal strategies evaluated. These ranges were expanded in a series of exploratory analyses.

Table 2.2-15: Availability of care

	Value used in baseline model	Range of stepwise increases in recognition of need/willingness for referral	Range of baseline estimates for status quo used in sensitivity analysis
bEmOC	50%	50-95%	30-80%
bEmOC at cEmOC	70%	70-95%	50-95%
cEmOC	70%	70-95%	50-90%

2.2.4 Calibration Exercises and Model Performance

Calibration targets are established based on survey data and published studies, and include the distribution of causes of maternal mortality (e.g., PPH, obstructed labor, sepsis), maternal mortality ratio (MMR), and the total fertility rate (TFR). The MMR is adjusted directly in the model for indirect causes of maternal-related mortality, as explained below. The importance of using multiple indicators is that each reflects a different aspect of maternal mortality. For example, the MMR is not age-standardized, nor does it incorporate repeated exposure to risk, nor does it robustly account for risk reduction due to fertility decline. The model can be used to project a range of maternal health indicators and these can be used as calibration targets, or can be compared to survey data to assess an approximation of face validity or projective validity. These include:

- Maternal mortality rate: Defined as the number of maternal deaths per 1,000 women or 100,000 women of reproductive age (ages 15-45) or woman-years of risk exposure, and designed to be an indicator of risk of maternal death (i.e., cause-specific death rate)

- Proportionate mortality ratio: Defined as the proportion of all female deaths among women of reproductive age due to maternal causes

- Lifetime risk of maternal death: Reflects the probability of a maternal death during a woman's reproductive lifespan (the probability that a 15-year-old will eventually die from a maternal reason up to age 45, for example) and is described in terms of odds (it accounts for the probability of dying from maternal causes each time a woman experiences a pregnancy, and so takes into account fertility as well as obstetric risk)

- Lifetime risk of dying from maternal causes: The calculation of lifetime risk assumes no changes in fertility or mortality; estimates are generated from the maternal mortality rate, and do take into account the competing causes of death. In contrast, in our model, the simulation over time does take into account the changes in fertility and background mortality, including changes in maternal mortality.

MMR: We used published data for the baseline Nepal model MMR calibration target. The range of MMRs for Nepal from different sources and methods is provided below. It is widely accepted that the error and uncertainty in these measures is formidable, and trends should be interpreted with grave caution. During calibration exercises, we prioritized the recent MMR point value of 190 from the interagency estimates of global maternal mortality [1].

Table 2.2-16: Recent documentation of maternal mortality ratios (MMR) for Nepal reported in the literature

	MMR	Range
[1] WHO et al 2014 (2013)[a]	190	(110-340)
[124] Hogan et al 2010 (2010)[b]	240	(149-370)
[12] NDHS 2006 (2006)	281	(178-384)
[125] Hill et al 2007 (2005)	830	(290-1900)
a	Also reported were estimates from 2005 (310), 2000 (430), 1995 (580), and 1990 (790). Data from earlier years are less relevant for comparison to the data above for purposes of calibrating a baseline.	
b	Also reported were estimates for 2000 (343, range 213-533), 1990 (471, range 290-722) and 1980 (865, range 536-1351). Data from earlier years are less relevant for comparison to the data above for purposes of calibrating a baseline.	

Distribution of causes of maternal deaths: Systematic reviews of the magnitude and causes of maternal deaths have documented variation both across and within geographical regions. Estimates of specific causes of death in Nepal are hindered by the same methodological challenges as in global estimates, further complicated by the considerable heterogeneity that exists. We used Khan et al.'s (2006) regional estimates based on the large sample sizes and the complete accounting for a range of causes of maternal death, both direct and indirect [49].

Table 2.2-17: Cause of maternal death

Maternal mortality causes	Khan et al [49]	WHO [33]
Maternal hemorrhage	30.8% (5.9%-48.5%)	35%
Hypertensive disorders	9.1% (2.0%-34.3%)	17%
Obstructed labor	9.4% (0.0%-12.0%)	--
Sepsis	11.6% (0.0%-13.0%)	7%
Abortion	5.7% (0.0%-13.0%)	10%
Subtotal	*66.6%*	*69%*
Other direct	1.6% (0.0%-25.9%)	11%
Anemia	12.8% (0.0%-17.3%)	--
Other indirect	12.5% (0.0%-29.2%)	19%
Unclassified	6.1%(0.0%-16.2%)	1%

The MMR is adjusted directly in the model for indirect causes of maternal-related mortality. We assume that the proportion of mortality that is categorized as indirect and attributable to anemia will be reduced with strategies that include enhanced family planning, increases in appropriate antenatal care with completed courses of treatment for anemia, facility-based births with quality intrapartum care, and reliable access to basic and comprehensive EmOC. We conservatively assume that the proportion of mortality that is categorized as indirect and attributable to other causes will not be affected.

Model performance was assessed by comparison of model-based projections with reported measures such as total fertility rate, life expectancy, maternal mortality ratio, proportionate mortality ratio.

2.3 Overview of Costs and Estimates

Direct health care costs include the cost of a normal pregnancy (e.g., prenatal visits, normal labor and delivery), the cost of treating pregnancy-related complications (e.g., eclampsia, hemorrhage, sepsis), salaries of health care providers (e.g., counseling, skilled birth attendants, clinician time); costs related to prenatal care (e.g., additional prenatal visits, nutritional supplementation, treatment of anemia or other existing disease, screening for sexually-transmitted diseases [STDs]), providing safe abortion (e.g., manual vacuum aspiration) or family planning options (e.g., sterilization, intrauterine device [IUD], oral contraceptives), the cost of treating abortion-related complications, and emergency obstetric care (e.g.,

facilities with the capacity for transfusion, parental antibiotics, surgery, anesthesia). Direct non-health care costs include, but are not limited to, the costs of transportation to and from the clinic or provider.

Cost estimates are broken down by input (e.g., drugs, vaccines, salaries, infrastructure), by intervention (e.g., management of a normal birth, hemorrhage, eclampsia, sepsis), and by service location or level (e.g., hospital, health center, health post).

Facility costs are country-specific from data publicly available from the World Health Organization [27]. Originally presented in 2008 US Dollars, facility costs were converted to 2006 US dollars using currency exchange rates. Personnel cost (salaries) were obtained from a recent survey and report about the Nepal health workforce [26]. Originally reported in 2011 local currency units, salaries were converted to 2006 US dollars. When possible, we conducted literature reviews for costs associated with different services and complications; these costs were extrapolated and adjusted to the same year and currency to facilitate comparison and generate plausible ranges for each cost estimate.

Costs are presented in currency units that remove price inflation, and for analyses intended to inform resource allocation and compare studies from multiple countries, costs are expressed as US dollars or international dollars. While exchange rates may reflect under- or overvaluation of the local currency, they represent what is actually paid for locally-produced inputs. Purchasing-power parity rates, in contrast, attempt to express what the local currency is worth in purchasing power, and therefore account for differences in price levels across countries. The exchange rate for domestic currency into international dollars is the amount of domestic currency required to purchase the same quantity of goods and services as $1 could purchase in the US.

2.3.1 Documentation of costs used in the Nepal model

Country-specific cost estimates of all maternal interventions explored in the current model were drawn from the UNFPA's Reproductive Health Costing Tools Model (RHCTM) [25]. This model is designed to help countries estimate the cost of scale up for a basic package of reproductive health services – ranging from family planning, antenatal and delivery care to emergency obstetric care and HIV/STI prevention and treatment.

The RHCTM consists of two main parts. The first part estimates the direct costs associated with providing an essential package of 45 reproductive health interventions. Interventions evaluated in the current RHCTM include: (1) family planning; (2) antenatal care, including treatment for chlamydia, gonorrhea and anemia; (3) abortion (incomplete and elective) and post-abortion complications; (4) delivery care; (5) emergency/pre-referral care; (6) assisted vaginal delivery (EmOC treatment of obstructed labor); (7) cesarean section; (8) postpartum hemorrhage; (9) puerperal sepsis; (10) severe pre-eclampsia/eclampsia; (11) treatment of long-term complications such as PID and obstetric fistula; and (12) postpartum care. The RHCTM also includes costs for additional maternal complications including: (1) premature rupture of membranes; (2) prolonged labor; (3) trichomoniasis and (4) antepartum hemorrhage.

Figure 2.3-1: RHCTM Essential package of 45 reproductive health interventions

FAMILY PLANNING	ANC and Delivery Care	Obstetric Complications
Short-Term Methods	11 Antenatal Care (ANC)	18 Emergency Pre-Referral Care
1 Oral Contraceptives (Pill)	12 Treatment of Severe Anaemia	19 Prelabour Rupture of Membranes
2 Injectables	13 Hypertensive Disorders of Pregnancy	20 Prolonged Labour (>18 hours)
3 Condom - Male	14 Malaria Prevention within ANC	21 Forceps or Vacuum-Assisted Delivery (AVD)
4 Condom - Female	15 Malaria Treatment within ANC	22 Cesarean Section (C-Section)
Long-Term Methods	16 Delivery Care	23 Antepartum Haemorrhage
5 Intrauterine Device (IUD)	17 Postpartum Care	24 Postpartum Haemorrhage
6 Implant		25 Puerperal Sepsis
7 Sterilization - Female		26 Eclampsia/Severe Pre-eclampsia
8 Sterilization - Male		27 Postabortion Complications (PAC)
Other Methods		
9 Other		
10 Emergency Contraceptives (EC)		
Other Maternal Conditions	**HIV-related Interventions**	**Sexually Transmitted Infections**
28 Obstetric Fistula (OF)	Condom Programs targeting	40 Chlamydia
29 Urinary Tract Infection (UTI)	35a Commercial Sex Workers	41 Gonorrhea
30 Mastitis	35b Men who have Sex with Men (MSM)	42 Syphilis
	35c Adolescents (age 15-24)	43 Trichomonas
Newborn Interventions	35d Other vulnerable population	44 Pelvic Inflammatory Disease (PID)
31 Routine Newborn Care	36a Antiretroviral Therapy (ARV) First Line	45 Cervical Cancer Screening
32 Newborn Sepsis / Infections	36b Antiretroviral Therapy (ARV) Second Line	
33 Birth Asphyxia / Breathing Difficulties	37 Prevention of Mother-to-Child Transm. of HIV (PMTCT)	
34 Low Birth Weight	38 Voluntary Counseling and Testing for HIV (VCT)	
	39 Post-Exposure Prophylaxis (PEP)	

The RHCTM uses an ingredients approach to estimate the costs associated with an intervention. Each complication is associated with drug, supplies, and personnel requirements for treatment. However, the estimate does not include costs associated with occupying a health facility bed or an outpatient visit; these costs were obtained from the WHO CHOICE database and Nepal-specific estimates were used.

Most of the data in WHO CHOICE are from UN sources such as the UN Population Division, WHO's Global Burden of Disease and other databases, UNICEF's maternal health database, and Demographic and Health Surveys. The lists of drugs and supplies required to provide the interventions are based on WHO treatment guidelines [58]. Costs are presented in 2006 United States dollars (USD), and drug prices are based on quotes from the UNICEF Supply Catalogue and the MSH International Drug Price Indicator Guide [29, 30].

Personnel costs/salaries used in the Nepal model are based on a 2012 report on health worker salaries, and are listed in the table below [26]. Salaries are presented in local currency units and in 2006 USD.

Table 2.3-1: Annual personnel costs by category and source

	2011 NPR	**2006 US$**
Auxiliary/ Attendant	15300	1510
Nurse/ Midwife	21030	2080
General physician	22410	2215
Specialist physician (obstetrician pediatrician)	25000	2470
Lab Technician	15300	1510

The RHCTM does not include estimates of facility costs per case. For this, we drew on the Nepal-specific estimates of unit costs for patient services provided in WHO-CHOICE. Since many interventions can occur outside a 20-minute visit time frame (e.g., 5 minutes or 30 minutes), we broke down the cost for outpatient visits according to an estimated cost per minute.

Facility costs originally presented in 2008 US dollars were assumed to be the same in 2006 US dollars; those presented in 2005 local currency were converted to 2006 local currency units using a GDP deflator, and to 2006 US dollars using exchange rates. Since health center costs across coverage levels were very similar, to simplify, the model used an average cost (i.e., 0.076 USD per minute).

Table 2.3-2: WHO CHOICE facility costs

	2006 US$		
Bed day cost by hospital level			
Primary	2.65		
Secondary	2.76		
Tertiary	3.57		
Outpatient visit by hospital level			
Primary	1.08		
Secondary	1.12		
Tertiary[a]	1.50		
Health center costs (by coverage level)		**2005 NPR**	**2006 US$**
50%		93.71	1.47
80%		93.71	1.47
95%		101.08	1.59
[a] WHO-CHOICE does not give a value for tertiary hospitals in Nepal, so this was assumed as a value greater than that of a secondary hospital.			

In the following intervention-specific sections, we present cost estimates used in the model, and tables outlining how these costs were derived from the RHCTM for the following intervention components: (1) drugs and supplies per case; (2) personnel costs per case; and (3) facility costs per case. Where no additional cost estimates were available with which to inform a range surrounding base case costs, we assume a range consisting of 0.5 times to 1.5 times the base case cost.

Family Planning

Oral Contraceptives: The 2011 NDHS reported that most women using oral contraceptives took monophasic pills (e.g., Levonorgestrel 0.15 mg + Ethinylestradiol 0.03 mg), so the costing model reflected this. Additionally, the most common place to obtain pills as reported in the 2011 NDHS was the public sector outpatient setting (health posts and sub-health posts). The cost of oral contraceptives for this model is therefore $7.24 per year.

Injectables: According to the 2011 NDHS, most women obtained injectable contraceptives from health posts and sub-health posts; the cost as estimated by the model is $7.39 per year.

Condoms: The cost of providing condoms is $5.87 per year. We assumed that condoms are obtained at an outpatient health post/sub-health post visit. In a scenario where the use of family planning is increased, costs could be reduced through alternative delivery methods that eliminate this visit and its associated costs.

Intrauterine device (IUD): According to the 2011 NDHS, the most common IUD in Nepal is the copper IUD; and women obtain these either at hospitals or at health posts/sub-health posts, so the costing model incorporated this split. The annual cost of IUD use is $4.63.

Female sterilization: The cost for female sterilization is $10.42, assuming that all procedures are conducted at the hospital level (as per data from 2011 NDHS) with follow-up visit at a lower-level health facility.

Male sterilization: The total cost for male sterilization is $5.77, using the assumption (based on 2011 NDHS data) that all procedures are conducted at the hospital level, with follow-up visit at a lower-level health facility.

Antenatal care, including treatment for chlamydia, gonorrhea and anemia: The average cost of four antenatal care visits under the current standard of care is $7.99. This total reflects the cost of all four visits, including drugs and personnel for tetanus vaccination, syphilis testing and treatment if necessary, urinalysis for glucose, ketones, pH, and includes counseling and education (family planning, birth spacing, parenting, etc). Health personnel providing antenatal care reflected the distribution in the 2011 NDHS: approximately one-third of women reported receiving antenatal care from an auxiliary nurse-midwife, one-third from a nurse, and one-third from a physician (some small fraction of whom saw a specialist). The majority of women received antenatal care at a health post/sub-health post, and some women (those consulting with an obstetrician, for example) visited a hospital. The duration of each antenatal visit was assumed to be 15 minutes; this was the maximum duration observed in a study from Nepal [105]. The cost of treatment for anemia is added to the cost of prenatal care shown above. The management of severe anemia is not specified in the RHCTM, but was adapted based on the PPH protocol of the RHCTM and the total cost summed to $0.44: $0.34 for anemia prophylaxis during pregnancy (iron supplementation) for all women, plus treatment for severely and moderately anemic women that totaled $0.10.

Incomplete abortion: We assumed all women with incomplete abortion from miscarriage were managed with manual vacuum aspiration, and stayed in a hospital for one day. Total cost was $6.00, as detailed below.

Elective abortion: No data were found on the cost of abortion in Nepal. Past modeling exercises with the Global Maternal Health Policy Model have used a cost of elective abortion between $22-32 (2006 USD), based off modified estimates found elsewhere in the literature—due to low salaries of health workers in Nepal, the bottom end of this range ($22) was used in the model.

Post-abortion complications: We assumed all women requiring care for post-abortion complications were managed with manual vacuum aspiration, and that a fraction of these women required repair of lacerations and/or treatment of sepsis. The model assumes that half of women requiring PAC are treated by doctors and half are treated by nurses, and varies length and location of stay—both according to

findings from the literature in Nepal [126, 127]. Total cost was $12.03 as detailed below. This cost produced by the RHCTM may be an underestimate. An analysis of post-abortion care in Africa and Latin America found per-patient costs of approximately $80-90 (2006 USD) [128]; this was however estimated in the context of unsafe abortion, where required post-abortion care may be considerably more complex than in Nepal.

Delivery Care

We assume that for births that take place at home can be assisted by a family member, by a TBA, or by a SBA. For home deliveries, we include the cost of the attendant's time but there are no facility charges. Per Nepal government definition, the classification SBA only refers to nurse/midwives and doctors. Births with an SBA (but not a TBA) in the home setting were assumed to utilize supplies, such as gloves, and lidocaine anesthetic. The model assumes that some births (15% with a TBA, 75% with a SBA) also involve a clean delivery kit; these inputs are based on data from the 2012 Household Survey among recently-delivered women [31].

Deliveries at health posts and sub health posts are assumed to be attended by skilled staff, and functions of bEmOC are not assumed to be present although the facility are assumed to have mechanisms for referral to facilities with EmOC. The model assumes that care at these facilities is given by auxiliaries and nurses, and that basic supplies are used (gloves, antiseptics, clean delivery kits, paracetamol; and sometimes use of partograph, of oxytocin to prevent hemorrhage, of lidocaine anesthetic, and of suture supplies in case of episiotomy). Likelihood of using these supplies was assumed to reflect availability, and this was based on data from the 2012 Service Tracking Survey, which calculated rates of availability for key drugs at surveyed health facilities (by type) [103].

The Nepal government policy is that women remain at health facilities for 1 day after a normal delivery (and 3 days after assisted delivery, and 7 days after a Cesarean section)—but this is not always followed. In the model, length of stay is based on data as reported by recently delivered women in the 2012 Household Survey [31]. Among women with uncomplicated deliveries at health posts and sub health posts, only 5% of women stayed for longer than 24 hours after birth. The model shifts these values upward to also include labor time, and assumes that three-quarters of women stay at the facility for less than a day, one-fifth are there for 36 hours, and the remainder are there for 2 days.

For normal deliveries at BEONC and CEONC facilities, the above supplies are assumed to be present, and care sometimes also involves a doctor (general physician or obstetrician). Facility costs are also more expensive, both due to bed-day costs and because women in the 2012 Household Survey reported longer lengths of stay at hospitals: usually at least 24 hours after childbirth.

Results are shown below. All costs were varied in sensitivity analysis.

A 2004 report analyzed the costs of different types and aspects of delivery for women in Nepal [113]. For women who had home deliveries, either with trained TBAs or with SBAs, drug and other costs were on average 100 NPR ($1.60 in 2006 USD) which is close to the model average value.

Costs for transportation include the cost of transportation for a woman with a recognized complication that cannot be treated at the original birthing location (either true complication or false referral), and the cost for an attendant to accompany the woman during transport in some circumstances. Costs of transportation to a health facility for childbirth were estimated from a recent household survey of Nepali women, who reported spending approximately 1000 NPR (median value) ($8 2006 USD) on transportation for delivery [31]; this is higher than findings from a recent facility-based survey, in which the median reported transport cost for childbirth was 400 NPR [103]. It should also be noted that the Aama Programme offers monetary incentives to help with transport costs, from 500 NPR in the terai to 1000 and 1500 NPR in hills and mountains, respectively.

We assume these costs represent costs from home to a bEmOC facility, and that the cost of transport from home to a health center would be 10% less, while the cost from home to a cEmOC facility would be 10% more, on average. Inter-facility costs are also estimated to be 10% lower than these baseline costs. The transport costs used in the model are shown below.

Table 2.3-3: Transport costs for Nepal model (2006 $US)

Cost from home to HC	$7.20
Cost from home to bEmOC	$8.00
Cost from home to cEmOC	$8.80
Cost from HC to bEmOC or cEmOC, or from bEmOC to cEmOC	$7.20

Management/treatment of complications

There are certain assumptions made for medical procedures across the model. When women in the model have assisted delivery (either with forceps or vacuum), their length of stay at the bEmOC facility ranges between 1.5 and 5 days according to reports by recently-delivered women in a recent household survey [31]. For all c-sections in the model (at cEmOC facilities), the following assumptions were made. First, the majority of women receive spinal anesthesia and the rest get general anesthesia, per findings from a recent survey of cEmOC facilities in Nepal [129]. Second, one-quarter of women have hospital stays of 5 days, while three-quarters stay for 7 days, reflecting findings from a recent household survey of recently-delivered women [31].

Management/treatment obstructed labor: Management of obstructed labor at bEmOC consists of assisted vaginal delivery with vacuum or forceps. In addition to obstructed labor costs, we also included the cost of prolonged labor, which precedes the diagnosis of obstructed labor. At the bEmOC level (where cesarean section is not available), the total cost is $16.14. At the cEmOC level, the cost of treating obstructed labor with c-section is $39.87. Length of stay is estimated based on data from the 2012 Household Survey [31].

Management/treatment for postpartum hemorrhage: Managing PPH with basic services at a bEmOC-level facility costs $17.41; for those cases needing transfusion, advanced shock management, and/or surgery at cEmOC, the cost is $103.22. The difference in the cost of management/treatment for PPH

reflects primarily the lack of capacity to perform emergency transfusions at a bEmOC facility and increased personnel and facility charges at cEmOC facilities.

Management/treatment of puerperal sepsis: At a bEmOC-level facility, the cost is $21.70; for cases needing transfusion, advanced shock management, and/or surgery at cEmOC, the cost is $48.26. Borghi et al. [2003] report the cost for treatment of sepsis in Benin (75.88-184.17, 2006 USD) and Ghana (177.71, 2006 USD) and Weissman et al. [1999] for Uganda (11.23-36.11, 2006 USD). When these costs are converted to 2006 US$ using the methods described earlier, our estimates fall within this range.

Management and treatment of severe pre-eclampsia/eclampsia: The cost of managing hypertensive disorders and treating eclampsia at bEmOC facilities is $23.57 and $61.02 in cEmOC. Half of women with eclampsia treated at cEmOC facilities in the model are assumed to receive a c-section, as per rates found in hospital-based studies from Nepal [130, 131]; which increases costs, primarily via length of hospital stay.

Treatment of pelvic inflammatory disease: The cost associated with treating PID is $2.91, assuming all PID is treated on an outpatient basis.

Treatment of obstetric fistula: The model estimates the cost of repairing an obstetric fistula at $28.33. There are reportedly very few facilities offering fistula repair in Nepal, so the model assumes only care at cEmOC sites and with an obstetrician.

Postpartum care: Postpartum care includes a 30-minute visit by a skilled health provider and distribution of iron/folate supplementation. Type of provider was informed by the 2011 NDHS: among women who received postnatal care, one-third of women reported its provision by a doctor, half saw a nurse/midwife, and approximately 10% each saw an auxiliary and an obstetrician. With these inputs, the model estimated the cost of postnatal care as $2.94.

Table 2.3-4: All items, cost components and totals, in model

Item	Component cost (2006 US$)			Total cost
	Drugs and supplies	Personnel	Facility charges	
Contraception				
Oral Contraceptives	$4.14	$0.46	$2.64	$7.24
Injectables	$3.85	$0.52	$3.02	$7.39
Condoms	$2.85	$0.38	$2.64	$5.87
IUD	$0.64	$0.75	$3.24	$4.63
Female sterilization	$4.73	$1.79	$3.89	$10.42
Male sterilization	$0.88	$1.11	$3.78	$5.77
Health care				
Antenatal care (4 visits)	$2.83	$0.91	$4.25	$7.99
Postpartum care	$0.23	$0.45	$2.27	$2.94
Incomplete abortion	$2.19	$1.23	$2.65	$6.00
Elective abortion	--	--	--	$22
Post-abortion complications	$6.03	$1.81	$4.19	$12.03
Delivery care				
Home with TBA	--	$2.92	--	$2.92
Home with SBA	--	$6.00	--	$6.00
1^{ary} health center	$3.62	$4.92	$2.98	$11.52
2^{ary} health center	$3.72	$4.72	$3.73	$12.18
3^{ary} health center	$4.16	$5.19	$6.25	$15.60
Treatment of complications				
OL – bEmOC	$4.39	$0.49	$7.87 + $3.38 (for prolonged labor)	$16.14
OL – cEmOC	$12.20	$2.86	$21.41 + $3.38 (for prolonged labor)	$39.87
PPH – bEmOC	$9.13	$2.87	$5.41	$17.41
PPH – cEmOC	$87.34	$3.22	$12.66	$103.22
Sepsis – bEmOC	$13.71	$2.58	$5.41	$21.70
Sepsis – cEmOC	$33.21	$2.71	$12.34	$48.26
HTN – bEmOC	$5.33	$4.03	$14.21	$23.57
HTN – cEmOC	$8.88	$1.27	$41.15	$61.02
PID	$0.64	$0.38	$1.89	$2.91
Fistula	$12.58	$4.71	$11.04	$28.33

2.3.2 Costs of scaling up and costs in sensitivity analysis

Investments for strategies that included stepwise improvements in intrapartum care fall into the following general categories:

(1) average normal delivery (differentiated by site) to reflect (a) recruiting and training cadre of SBA, (b) improving recognition of referral need via training of SBA, as well as education for woman and family, and (c) interim care by SBA prior to transport;

(2) transfer from delivery site to referral facility (differentiated by origin and destination) to reflect (a) transport cost; (b) vehicle use and fuel; and (c) interim care en route separate from routine SBA training;

(3) expedient attention at appropriate referral facility (differentiated according to bEmOC or cEmOC services) to reflect (a) new and/or improvements in existing primary facilities (bEmOC) including ensuring 24-hour access; (b) new/and or improved secondary and tertiary facilities (cEmOC); (c) blood bank and transfusion capability, enhanced surgical capacity, intensive care support functions for shock in cEmOC; and (d) improved quality of care in bEmOC and cEmOC with adequate supplies and personnel.

3 Providing safe childbirth care: Readiness of the Indian health system

Abstract

Background: Reducing childbirth-related deaths is a global priority. The largest volume of all peripartum deaths (maternal, stillbirths, and immediate postpartum neonatal) occur in India. Even with increased rates of institutional delivery, improvements in health outcomes may lag if the health system cannot provide adequate high-quality care. The Safe Childbirth Checklist (SCC) includes 29 behaviors that should be provided as part of high-quality routine (non-emergency) intrapartum care; the checklist itself is part of a broader SCC quality improvement intervention, which also includes training and coaching on the relevant behavior change. The checklist guides clinicians through the provision of care, from when a laboring woman is admitted to a health facility until she and the newborn are discharged. Pilot results indicate that the SCC can improve quality of care by increasing the frequency with which providers conduct these 29 activities, but studies have not yet quantified how the SCC may result in improved outcomes. And it is unclear whether health facilities in India have the relevant inputs—in terms of medicines, infrastructure and equipment—to administer all activities and, correspondingly, the impact of a more limited or modified SCC intervention. This study aimed to estimate SCC impact, both if all health facilities in India could implement all checklist items, and how this would attenuate given health system capacity.

Methods: The Indian District-Level Household & Facility Survey (2007-08) provided information about health facility infrastructure (supplies, equipment, medicine), as well as population-level data on the probability of childbirth at different facility types, and facility-based data on care volume. SCC impact was estimated through a decision tree representing childbirth; outcomes included maternal survival or death (and if the latter, cause of death), intrapartum stillbirth or live birth, and early neonatal survival or death. Four main maternal complications were modeled, and neonatal outcomes were modeled as either contingent upon these or due to competing events (complications that arise independently). The potential

impact of the SCC was assessed as the sum of each item's effectiveness, which was based on evidence from the literature.

Results: The model estimated that, at the population level, implementation of key SCC activities could avert up to 33.6% of facility-based maternal deaths, and up to 42.9% of facility-based early neonatal deaths. These are "best-case" scenarios, assuming that an SCC intervention results in maximum behavior change, and assuming that all necessary health system inputs are available. But not all health facilities in India could implement this full suite of SCC activities: in fact, a set of key items (maternal antibiotics, magnesium sulfate, oxytocin, hand washing, baby drying, clean cord cutting, and resuscitation) may only be available at 29.1% of district hospitals, 11.4 or 21.5% of rural or urban (respectively) community health centres, and 5.0% of primary health centres. Subtracting any of these key items from the set of SCC interventions has a detrimental effect on the possible impact that could be achieved. An additional analysis with a subset of middle-level facilities (community health centres) found that if the SCC were deployed in the current health system, it would avert only half as many facility-based maternal deaths compared to if it were implemented in a system with no such infrastructure constraints, and only two-thirds as many facility-based neonatal deaths.

Discussion: The Safe Childbirth Checklist is an intervention that could significantly reduce the number of intrapartum-period deaths. The activities within the SCC are focused on routine (non-emergency) care that should be provided to all women undergoing childbirth—but the current state of the health system in India is insufficient for achieving the most possible benefit from the SCC. If implemented fully in India, the SCC activities could save up to 12,000 women's lives and up to 63,700 early neonates. But many health facilities have system constraints, so actual impact of the SCC might be substantially attenuated.

Introduction

During recent decades, there have been debates about health system capacity to deliver interventions with demonstrated effectiveness. These questions have arisen about major infectious diseases including HIV/AIDS, tuberculosis and malaria, as well as non-communicable diseases and mental health, and in the context of global initiatives including the Global Alliance for Vaccines and Immunizations, the Millennium Development Goals, and the Global Fund to Fight AIDS, Tuberculosis and Malaria [132-139]. A well-functioning health system is necessary to achieve substantial improvements in maternal and infant health: even routine (non-emergency) childbirth care is resource-intensive from a systems perspective, requiring infrastructure, pharmaceuticals, supplies and equipment, and health workers. This paper revisits these ongoing discussions about health system capacity and scale-up of care, specifically in the context of providing routine intrapartum care for mothers and their babies in India.

India contributes more annual maternal deaths, neonatal deaths and stillbirths than any other country [8]. Although the maternal mortality ratio has declined (from 560 deaths per 100,000 live births in 1990, to 190 in 2013) [1], this masks substantial regional variation: nine of India's 29 states account for almost two-thirds of the nation's, and 12% of global, maternal deaths [140]. Additionally, nearly 28% of all neonatal deaths worldwide occur in India [141], and most (80%) within 1 week of birth (so-called "early neonatal deaths"). There is also a very high stillbirth rate, particularly intrapartum-related and during the third trimester, and also with regional variation: ranging from below 20 per 1000 births in Kerala to 66 per 1000 births in central India [8]. Progress on reducing neonatal deaths in India has been slow, and these have increased as a share of childhood mortality (a trend that has also been observed at a global level) [142].

Rates of institutional delivery in India have increased: in the 2005-06 DHS, 40% of births during the prior three years had occurred at health facilities, versus 34% in the 1998-99 DHS and 26% in the 1992-93 DHS; although rates for rural women lag those of urban women, at 31% and 69% respectively [143]. The

Indian health system is structured to provide basic emergency obstetric care (bEmOC, or the ability to administer parenteral antibiotics, uterotonics and anticonvulsants, as well as conduct manual placenta removal, assisted vaginal delivery, basic neonatal resuscitation, and removal of retained uterine products) at primary health centers (PHCs), and comprehensive emergency obstetric care (cEmOC, which includes all of the above-stated bEmOC activities plus provision of caesarean section and blood transfusion, and more advanced neonatal resuscitation and care) at community health centers (CHCs) and at tertiary District Hospitals (DHs). Women utilize all these levels of care for childbirth [144, 145].

But increased utilization alone is not sufficient to yield improved health outcomes: the care must be high-quality. An analysis of Janani Suraksha Yojana (JSY, the Indian conditional cash transfer program aimed to encourage institutional delivery) found no health outcome improvements associated with increased rates of institutional childbirth, and concluded that essential care quality was lacking [140]. This finding was explored further in a recent analysis that found a higher risk of maternal mortality following obstetric referral in India [144]. Such challenges in providing high-quality obstetric care are not uncommon: an analysis of bEmOC and cEmOC services in 6 countries with high maternal mortality burden (including India) found that fewer than 25% of cEmOC-designated facilities could provide this care in full, and only 2.3% of bEmOC facilities could offer all related services [146].

The Safe Childbirth Checklist (SCC) was developed by WHO and partners to improve adherence to well-known best practices for quality intrapartum care. It is a 29-item list that guides health care providers through the provision of obstetric care, from when a laboring woman is admitted to the hospital until she is discharged (see Appendix, section 3.1). Additionally, the list itself is accompanied by coaching and training, to ensure behavior adoption and adherence. The SCC is thus a quality improvement initiative, targeted at resource-poor settings, that aims to reduce the risk of major causes of maternal and neonatal death, as well as severe outcomes related to these. The SCC focuses on upstream approaches to prevent and mitigate complications just before and during labor (“safety checks”). In other words, it does not

address complication management via emergency obstetric care, but rather aims to encourage provision of quality routine obstetric care. The aforementioned training and coaching therefore do not teach new skills, but rather encourage checklist use as a behavior prompt for already-familiar activities. The SCC can therefore be viewed as a model set of routine childbirth practices.

A pilot study was conducted to assess the feasibility of implementing the SCC, and to estimate its effect on provider behavior. This pilot was conducted at a sub-district level hospital in Karnataka state, India; data were collected via direct observation of health workers attending to women in labor, before and after introduction of the SCC (in July and December 2010, with a sample size of 499 birth events and 795 events, respectively). The results were promising and indicated that such behavior change is possible: at baseline, most of the interventions on the SCC were rarely performed, but by follow-up, many were near-universal [147]. However, it would be impossible to enact all checklist items if the health system lacks certain inputs (e.g., supplies, medicines, infrastructure), which may result in lesser improvements than what was seen in the pilot.[‡] The study authors commented on this, noting that their results may not generalize since the site had good access to supplies and equipment, which "undoubtedly contributed to implementation success" [147].

The aim of this study is to explore the capacity of the Indian health system to implement SCC activities, as emblematic of high-quality, routine obstetric care. Given this research objective, there are 2 main research questions. First, does the health system have capacity to provide quality obstetric care, as exemplified by the SCC? How many, and what types of, health facilities have the available medicines, equipment and infrastructure to perform the SCC (each item, and combinations therein)?

[‡] The SCC also aims to also help local decision-makers see gaps in capacity to deliver routine care, and work to close these gaps as the intervention unfolds. However, because the pilot site was well-equipped, this type of behavior change has not yet been observed nor quantified in the context of the SCC. This is explored further in the Discussion section.

Second, to what degree could the SCC result in improved health outcomes? In other words, how might maximum impact attenuate given real-world system constraints? Using known rates of complication incidence and severity, and overlaying these with intervention evaluation results, we can model the possible impact of the checklist to improve delivery care and health outcomes.

Methods

Overview

The analysis proceeded in four steps, which are summarized here and explained in more detail below. First, we built a decision tree to represent childbirth, to estimate the joint probability of maternal and neonatal deaths, based on rates of complications, severity and management. Second, we reviewed the literature for information on the SCC items, to estimate the possible impact these activities might have on health outcomes. Third, we estimated what proportion of health facilities in India could implement the activities on the checklist. A facility was considered able to implement a checklist item when it had all requisite supply components for that item (for equipment, available and functional; for medicines, in-stock). We assessed each item independently for each facility, and also calculated a joint probability of availability for all items ("maximum SCC implementation"). Lastly, we assessed how implementation of the SCC might reduce the number of intrapartum deaths (maternal, stillbirths, early neonatal), in an unconstrained scenario (full SCC utilization at all health facilities in India) and then adjusted to reflect health system readiness (based on results from the first analysis, described above). We also estimated the potential impact of the SCC on severe maternal morbidity ("near-miss" cases), and conducted a set of sensitivity analyses to assess how parameter uncertainty may affect the main results.

As described above and shown in the Appendix (section 3.1), the checklist includes 29 items; due to repetition, there are 14 unique items on the checklist. Some are not supported by robust effectiveness data from the literature (i.e., partograph use [148, 149], and confirming that the mother and birth attendant can call for help if there are danger signs); and others were not relevant for this analysis (i.e., nevirapine for

mothers and neonates, and discussion of family planning options, since these interventions would not impact intrapartum-period outcomes; and assessments for obstetric and neonatal referral, since these women and babies would then not receive routine care). So, this paper analyzes the remaining 7 checklist items: provision of antibiotics to women with suspected infection, provision of magnesium sulfate to women with suspected eclampsia, encouragement of birth companion presence, preparation of birth supplies for the mother (supplies for hand washing, and for oxytocin administration) and for the baby (sterile blade, and neonatal resuscitation equipment), postpartum checking of maternal bleeding, and encouragement of early initiation of breastfeeding and skin-to-skin contact[§]. Four of these items explicitly require health system inputs: use of maternal antibiotics, use of maternal magnesium sulfate, preparation of maternal birth supplies, and preparation of neonatal birth supplies.[**] The focus checklist items for this analysis, and the requisite supply components, are shown in Table 3-1.

Table 3-1: Safe Childbirth Checklist (SCC) items analyzed in this paper, and the supply requirements to successfully execute each item

SCC item	Supply component(s)
1. Mother antibiotics	a) Obstetric antibiotics
2. Magnesium sulfate	a) Urine tests b) Blood pressure apparatus c) Magnesium sulfate
3. Mother supplies	a) Water b) Oxytocin
4. Neonatal supplies	a) Towel b) Sterile blade c) Resuscitation kit
5. Birth companion	*No supplies required*
6. Check bleeding	
7. Breastfeeding, skin to skin contact	

§ Data on neonatal antibiotic availability were not included in the dataset used here, so although this is an SCC item with robust evidence of effectiveness, it was excluded from this analysis.

** Supply availability may not perfectly or entirely capture potential for implementation; for example, if health workers are not trained on, or comfortable with, the requisite clinical skills to perform SCC item(s), this will also be a barrier to implementation. Human resources are not included in this analysis, although they are an essential health system component.

Modeling childbirth events and outcomes

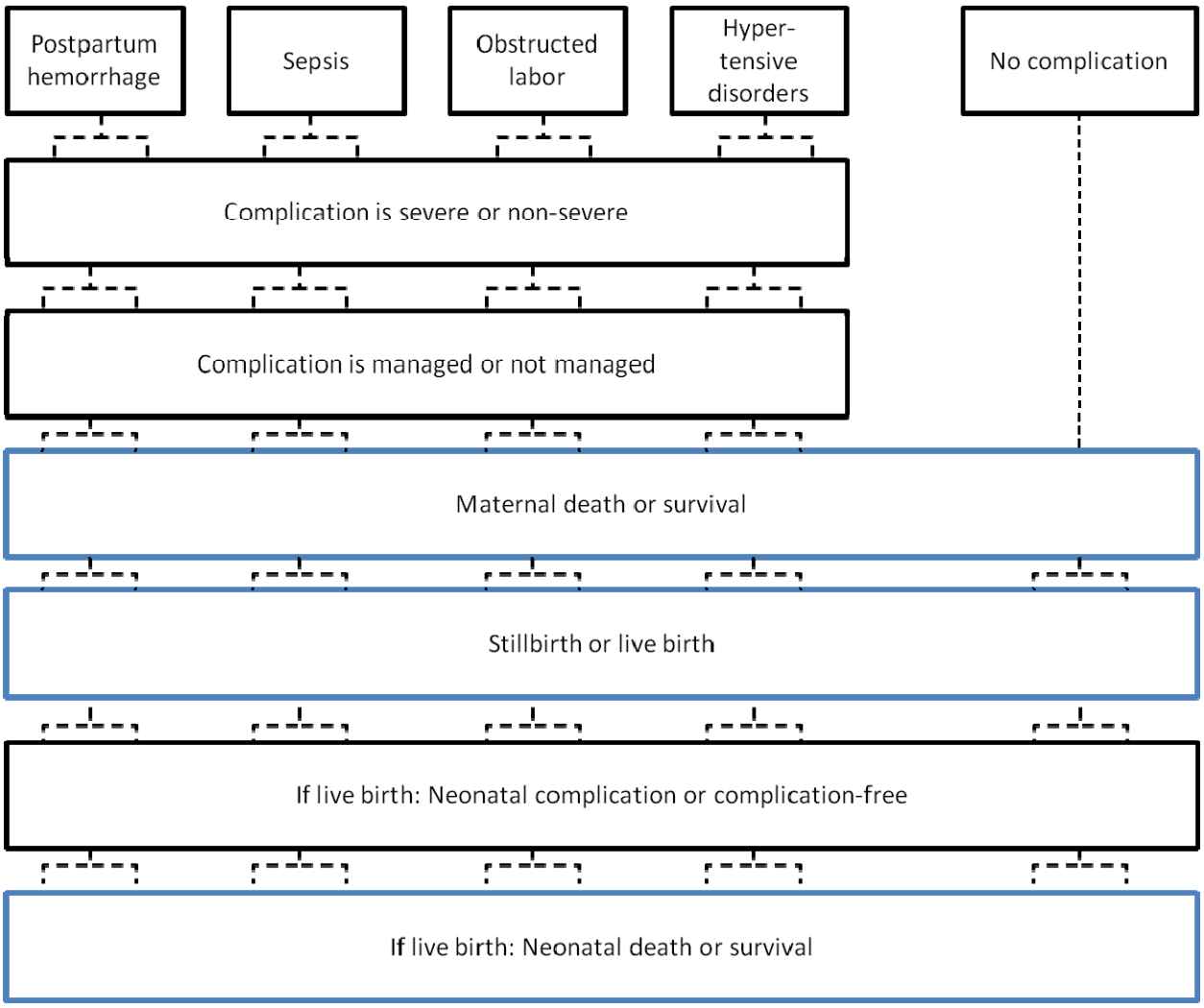
Model overview: A decision tree for childbirth was constructed, to model the likely progression of a woman from the onset of labor through childbirth, as well as the fetal outcome and progression through the early neonatal period. The key outcomes of interest were: maternal survival or death (and cause of death), intrapartum-related stillbirths versus live births, and early neonatal survival or death. All possible branches of the tree were specified, and Microsoft Excel was used to generate probabilities for each path.

In the base (natural event) model, a childbirth event begins with risk of a major obstetric complication: postpartum hemorrhage, obstructed labor, sepsis, or pre-eclampsia. The probability of each complication is derived from the epidemiologic literature. Some of these complications are severe; likelihoods of severity for each type of event were also based on the literature. Each complication (whether severe or non-severe) is associated with a likelihood of progressing to death, sometimes conditional on treatment, based on case fatality rates from the literature.

The tree also captures neonatal events, both linked with maternal complications (modeled as described above), and in the absence of any maternal complications. Neonates first face a probability of intrapartum stillbirth; then some live births experience a complication, and some progress to death. In cases where the mother has experienced a complication, these incidence and case fatality rates are associated with her complication (as per data from the literature). The model allows likelihood of death (whether stillbirth or early neonatal mortality) to be mitigated through treatment if the literature supports this assumption.

A simplified visual representation of the tree is presented in Figure 3-1. Outcome variables of interest have blue borders (i.e., all deaths).

Figure 3-1: Decision tree schematic diagram



Because some parameters might differ by facility type (for example, ability to manage hemorrhage), four trees were specified, each with some differences in input parameters, based on the literature: one to represent births at district hospitals (DH), another to represent births at urban community health centres (CHC), a third for births at rural CHCs, and a fourth for births at primary health centres (PHC)[††]. For outcomes at the health system or population level, the results of all models were combined using weighted proportions of births at and across facilities, as per DLHS-3 data.

[††] In the dataset, district hospitals are predominantly urban, and PHCs are mostly located in rural areas, so a geographic distinction was not made for these facility types.

Model data and assumptions: The model input values were informed by published data on incidence, severity and case fatality rates for maternal and neonatal complications. Priority was placed on India-specific or regional data whenever possible. Table 3-2 below shows key model input values; full details on these and all assumptions can be found in the Appendix (sections 3.2 and 3.3, for maternal and neonatal outcomes respectively).

A number of simplifying assumptions were made for these models; these are also described in the Appendix (sections 3.2 and 3.3), but a few key assumptions are highlighted here.

1. We assumed that women in the model were experiencing complication-free childbirth events and planned on natural vaginal delivery. The first SCC item asks the provider to assess whether the woman requires obstetric review (i.e., if she is experiencing a complication), so such women would not receive "normal" childbirth care, which is the target of the SCC.
2. We assumed that women would only face one major complication per birth event, plus some additional competing mortality risk from other causes (less-severe complications)—for example, women in the model would not see any increased risk of sepsis following obstructed labor.
3. We examined only public health facilities, and assumed no out-referrals.
4. We assumed that mortality risk would be nearly eliminated by appropriate management; as well as some attenuation in facilities' actual complication management capacity (so-called "signal function availability").
5. It was assumed that assisted delivery would occur only following obstructed labor.
6. We assumed that neonates would face only one main complication subsequent to a maternal complication, and would otherwise follow the trajectory of babies born to complication-free mothers.
7. For both the maternal and neonatal models, we assumed no underlying heterogeneity in risk.

8. We used literature-based assumptions about how values (of incidence, fatality, and rates of stillbirth or neonatal complications) might vary by facility type, but many of these are largely not empirically derived, but rather are estimates by experts on likely effectiveness.

Table 3-2: Maternal and neonatal model, key inputs and assumptions

	Postpartum hemorrhage	**Sepsis**	**Obstructed labor**	**Hypertensive disorders**	**No/other maternal complication**
MATERNAL MODEL					
Complication	6.5-13% (*FT) [53]	3.5% [59]	5.5% [61, 64]	5% [64, 65, 150]	--
Severity	15% [151, 152]	--	--	2.3% [65]	--
Management	0-60% (*S, FT)	10-60% (*FT)	10-60% (*FT)	0-60% (*S, FT)	--
Fatality	0.05-3% (*S, M) [45, 60]	0.05-3% (*S, M) [45, 60]	0.035-0.7% (*M) [45]	0.4-3.5% (*M) [150]	0.01%
NEONATAL MODEL					
Stillbirth	*(assume same as "no/other" complication category)*	1.25-3.5% (*FT, M) [153]	7.5-21% (*FT, M) [154, 155]	1.5-8.4% (*FT, S) [150]	0.25-0.7% (*FT) [8, 150, 156]
Neonatal complication		2.5-5% (*M) [157]	--	18% [158]	*(varied by neonatal complication)*
Fatality		10.8-24% (*FT, M) [45, 157, 159-161]	6-24% (*FT, M) [155, 156, 162, 163]	4-16% (*FT, S) [72, 150]	
In absence of maternal complication:					

	Prematurity, low birth weight	**Neonatal infection**	**Birth asphyxia**	**Neonatal tetanus**	**Other**	**None**
Neonatal complication	20% [164]	2% [165-168]	1-1.9% (*FT) [169-171]	0.7-1.4% (*FT) [172]	7%	--
Fatality	4-8% (*FT) [170, 173]	14-28% (*FT) [45]	10-20% (*FT) [45, 170]	20-40% (*FT) [45, 174]	4-8% (*FT)	0.01%

Notes:
"Management" here indicates the likelihood that a complication would be appropriately treated if it were to arise.
* FT indicates this parameter varied by facility type (DH/CHC urban or rural/PHC)
* S indicates this parameter varied by maternal complication severity (severe/non-severe)
* M indicates this parameter varied by maternal management status (yes/no)

Model calibration: Model outputs were determined by counting maternal, stillbirth and neonatal deaths from the base (natural history) model; these were converted to summary statistics (maternal mortality ratio [MMR], intrapartum stillbirth rate [ISBR] and early neonatal mortality rate [ENMR]). Live births

were calculated based on total model births minus stillbirths, and we applied a twinning rate for India from the literature to account for multiple births [175].

These model outputs were then compared to values from the literature. Published estimates of MMR and ENMR have considerable variance, so these ranges were considered feasible targets. The maternal cause of death distribution was compared to Asia regional estimates from Khan et al [49], which are very similar to others found in the literature [84, 176]. Since many model input values were assumptions, these were adjusted until the distribution of cause of death among women in the model looked similar to the figures from Khan et al. Likewise, assumptions about facility capacity to manage peripartum infant death, and about fatality of neonatal complications, were adjusted until the ISBR and ENMR reflected values from the literature. (The adjusted values are reflected in Table 3-2 values, and described in the Appendix, sections 3.2 and 3.3.) The endpoint of this calibration exercise is shown in Table 3-3.

Table 3-3: Model performance, compared to published values in the literature

	Model output	**From literature**
MMR	231.4	190-200 [1, 177], 242 [178], 303 [179], 690 [180], 314 [140]
Cause of maternal death		From [49]
Postpartum hemorrhage	30.1%	30.8%
Sepsis	10.9%	11.6%
Pre-eclampsia/eclampsia	9.0%	9.1%
Obstructed labor	9.2%	9.4%
Other	40.9%	33.5%
Abortion	--	5.6%
ISBR	16.6	13 [8]
ENMR	24.9	23-30 [7, 181-184]
MMR: maternal mortality ratio (per 100,000 live births) ISBR: intrapartum stillbirth rate (per 1000 births) ENMR: early neonatal mortality rate (per 1000 live births)		

Assumptions about SCC impacts

It must be first noted that the checklist itself (and the 7 activities listed therein, which are the focus of this analysis) is only one aspect of the SCC intervention. The SCC also includes up-front training and ongoing coaching for clinical workers and managers, as well as feedback mechanisms for quality improvement. This paper uses the findings from the pilot study to inform its assumption that, at baseline, few of the checklist items are performed with regularity—but, when the SCC intervention is implemented in a well-equipped hospital, providers will nearly always perform the 7 activities examined here [147]. Thus this analysis conflates the SCC intervention with the activities listed on the checklist, and assumes that behavior change is perfect in the presence of the unconstrained intervention. So here the impact of the SCC intervention is represented as the sum of the impact of each component activity of the checklist, as outlined below, because we assume universal behavior change from zero at baseline to perfect after intervention uptake. (The Discussion section explores the implications of this assumption.)

The literature was reviewed for evidence on the effectiveness of each SCC item, and these values were used to adjust model parameters for the SCC implementation scenarios. Evidence related to the 7 key interventions is presented below; full details for all items are presented in the Appendix (section 3.4). Table 3-4 maps the literature review results onto model values.

A Cochrane review examined use of antibiotics following premature rupture of membranes at or near term (an indication also highlighted by the SCC) and found a reduction in maternal infection, with a risk ratio of 0.43 for chorioamnionitis or endometritis [185]. The model therefore assumes a reduction in incidence of sepsis following implementation of SCC item 3. Also, since the treatment of sepsis is likewise provision of antibiotics, the model assumes that this SCC item increases sepsis management.

Evidence suggests that intrapartum antibiotics for women with group B streptococcus infection, or with intraamniotic infection, result in lower neonatal infection (RR of 0.17 and 0.08 respectively) [157, 161,

186]. The model thus assumes that likelihood of neonatal sepsis decreases if SCC item 3 is implemented. (Neonatal sepsis treatment requires provision of pediatric antibiotics, so this was not assumed to change when SCC item 3 was implemented.)

Magnesium sulfate significantly reduces the likelihood that pre-eclampsia progresses to severe or eclampsia (risk ratio 0.41) [72, 161]. The model assumes that women who receive SCC item 4 have a reduced risk of severe pre-eclampsia/eclampsia (by RR 0.41), and that treatment—also provision of magnesium sulfate—is near-universal when cases do occur.

Provision of oxytocin after childbirth significantly reduces the risk of regular and severe postpartum hemorrhage: a Cochrane review estimated the magnitude of this effect as 0.53 for regular PPH and as 0.62 for severe PPH [187]—the model uses these same values to decrease the probability of PPH and of severe PPH.

Birth attendant hand washing has been found to reduce the risk of neonatal infection (RR of approximately 0.7 for both tetanus and omphalitis) [161], so the model assumed a reduction in probability of neonatal sepsis associated with SCC item 11.

Continuous support during labor has been shown to be linked with shorter labor duration, and lower rates of instrumental delivery and c-section (RR 0.9 and 0.8, respectively), although no maternal health outcome changes were identified in this review [188]—so the model assumes a reduced likelihood of obstructed labor. Additionally, continuous labor support may be associated with higher Apgar scores for the newborn (RR 0.7 for a low 5-minute Apgar score) [188], which are associated with greatly reduced neonatal mortality risk [189]. It is assumed that all benefits to the newborn, however, accrue via this decreased probability of obstructed labor (and, associated, caesarean section).

There is no evidence from the literature about the impacts of checking for maternal blood loss as a stand-alone intervention, so for the purposes of this model, it is assumed to be associated with a decreased probability of severe PPH.

Neonatal resuscitation has seldom been examined as a stand-alone intervention; a recent article used a Delphi process and estimated a 20% reduction in intrapartum-related deaths following immediate newborn assessment and stimulation at a health facility [160]. A recent review article used an estimated effect for facility-based neonatal resuscitation of 0.7 (95% CI 0.59-0.84) [160, 161]. This analysis thus assumed a reduction in case fatality rates, due to all neonatal complications.

The same SCC item also includes supplies for clean cord cutting. The use of a clean blade for cutting the umbilical cord is also associated with reduced neonatal mortality: a recent analysis found use of a boiled blade following home birth reduced the risk of neonatal mortality (global RR 0.73, India RR 0.74), and in particular mortality due to sepsis (OR 0.28) and asphyxia (OR 0.51) [190]. The model therefore assumed small additional reductions in case fatality of sepsis and asphyxia.

Skin-to-skin contact for neonates has been found to significantly improve cardio-respiratory stability [191]; additionally, for low birth weight babies, “kangaroo care” is linked with reduced neonatal severe sepsis (RR 0.56) and reduced early neonatal mortality (RR 0.6) [192]. The model thus assumes reduced case fatality for low birth weight babies.

Table 3-4: Model input values and outcomes, by SCC item

SCC item	Evidence	Model input changes
MATERNAL OUTCOMES		
Mother antibiotics	Sepsis RR 0.43 [185]	Reduce probability of sepsis by 57%, Increase management of sepsis to 90%
Magnesium sulfate	Eclampsia RR 0.41 [72]	Reduce probability of eclampsia by 59% (severity), Increase management of pre-eclampsia and eclampsia to 90%
Birth companion	Lower rates of instrumental delivery and c-sec (RR 0.9 and 0.8) [188]	Reduce probability of obstructed labor by 10%
Mother supplies	Oxytocin regular PPH RR 0.53, severe PPH RR 0.62 [187]	Reduce probability of PPH by 47%, Reduce probability of severe PPH by 40%
Check bleeding	(No evidence)	Reduce probability of severe PPH by 25%
NEONATAL OUTCOMES		
Mother antibiotics	Neonatal sepsis RR 0.1 [157, 161, 186]	Reduced probability of neonatal sepsis by 90%, subsequent to managed maternal sepsis
Mother supplies	Hand washing: Neonatal infection RR 0.7 [161]	Reduced probability of neonatal sepsis by 30%
Neonatal supplies	Resuscitation: Neonatal mortality 0.7-0.8 [160, 161] Sterile blade: Neonatal mortality RR 0.73, sepsis-attributable OR 0.28, asphyxia-attributable OR 0.51) [190]	Reduced all CFR by 25% (resuscitation) Reduced CFR from sepsis and asphyxia by an additional 20%
Breastfeeding, skin to skin contact	For low birth weight babies: Neonatal mortality RR 0.6 [192]	Reduced CFR from low birth weight by 40%

Analyses

Quantifying health system capacity to deliver quality obstetric care: This analysis used data from the Indian District-Level Household & Facility Survey conducted in 2007-08 (DLHS-3, or DLHS unless otherwise specified) [193]. Sampling units were identified from the 2001 Indian Census sampling frame

(all districts), stratified by household size, caste composition and female literacy; a subset of sampling units was then selected using probability proportional to size, and households within these were randomly selected for individual surveys. Primary and secondary health facilities near the selected households were also surveyed[‡‡], and data were collected on staffing, training, infrastructure and supplies (tailored by facility type). Data for supplies and infrastructure were collected via direct observation, supplemented with information from a health worker respondent, for example, about frequency of drug stockouts. Descriptive information for each facility (catchment area, number of beds, number of deliveries) was used directly as recorded in the DLHS.

The DLHS-3 questionnaire did not collect all necessary data for this analysis from all facility types—namely, no relevant data were collected from DH, and the PHC questionnaires did not contain all necessary items. So, an additional analysis was undertaken to fill these data gaps. First, rural CHC data were used to estimate the relationship between sub-items and composite items, and these ratios were applied to the available sub-item availability at PHCs, to estimate the full item availability for these SCC activities at PHCs. We also imputed missing data points for district hospitals, making estimates across facility types and also across time, as follows. Ratios, as described above, were first calculated for urban CHCs in DLHS-3. Then, we calculated an "inflation factor" (to reflect increasing supply availability at health facilities over time), as the change in these ratios at urban CHCs between the second and third rounds of the DLHS [194]. Each sub-item ratio was multiplied by the relevant sub-item availability measured at DHs in DLHS-2, and the "inflation factor" was applied to estimate availability of these full SCC items in the DLHS-3. (Full details of all calculations are in the Appendix, section 3.5).

[‡‡] According to the DLHS-3, among women who delivered babies at public health facilities, very few did so at sub-centres (SCs) (only 2.4% of all surveyed women overall, and 75.8% of SCs in the sample had conducted no deliveries during the prior month)—so SCs were not included in this analysis.

Additionally, the joint probability of all 4 of these items was also estimated for PHCs and DHs. The CHC data indicated that items 4 and 12 were relatively uncorrelated, and the joint probability of these two items' availability approximately estimated the all-item probability—so this same relationship was assumed to be true for DHs and PHCs.

Additionally, 3 of the SCC items analyzed here—encouraging presence of a birth companion, checking for maternal blood loss, and encouraging early initiation of breastfeeding and skin-to-skin contact—do not require any health systems inputs, so would be "available" at all health facilities.

Estimating health outcome changes, with unconstrained and partial SCC implementation: The above-described model first estimated the number of maternal deaths, intrapartum stillbirths, and early neonatal deaths at baseline (i.e., in the absence of any SCC interventions), by facility type and then weighted by the percentage of births that occur at that facility type (according to the DLHS-3). This provided baseline facility-based intrapartum deaths, with the above-described assumption that no SCC items were implemented at baseline.

We then assessed the unconstrained and "maximum SCC implementation" scenario, in which all SCC interventions were implemented in concert with no health system constraints. The model parameters were all adjusted as indicated in the last column of Table 3-4. Each tree was re-run, and mortality probabilities were calculated and, as above, generated into an all-facility weighted summed value using the distribution births indicated by DLHS-3. The total number of deaths was compared to the baseline values, and the percentage reduction in each type of death was calculated. We also examined the effect of eliminating each SCC item from the "maximum" package, one at a time, to estimate how much possible impact might be lost per SCC item not implemented; the weighted sum of deaths, by type, for each of these scenarios was compared with baseline to calculate percent reductions in mortality.

We also calculated the impact of the SCC on the maternal mortality ratio, the intrapartum stillbirth rate, and the early neonatal mortality rate. Since these are population-based metrics, they also include deaths that occur outside health facilities (and are therefore unaffected by the SCC)—so we used estimates from the literature on the proportion of births, and of maternal and neonatal deaths (49.5% and 22.2% respectively) [195, 196], in India that occur within health facilities.

Readiness-adjusted health outcomes: The above analyses could only examine the maximum possible benefit of all SCC items together, and the effect of subtracting one item at a time. But since each combination of SCC items may confer a different level of health benefit, we sought to explore the distribution of facilities, births and deaths by a "readiness score": how much of the maximum possible SCC impact would be seen at a given facility, given its supply/infrastructure capacity. Restrictions of data availability from the DLHS only allowed this analysis among CHCs.

The above methods assume a random distribution of birth events across the health system—but if women are not randomly distributed (for example, if they are more likely to choose to deliver at a better-equipped facility) program impact may in fact differ from the "maximum SCC implementation" scenario.

We assessed the prevalence of each possible combination of SCC items at CHC facilities. Then we estimated the percentage mortality reduction versus baseline (by type of death, by rural/urban CHCs) for each unique combination of SCC items. Each such combination of SCC items, and the facilities with this exact combination, was assigned a "readiness score": the fraction of maximum impact it achieves. So for example, a facility with a 100% score can implement all 7 SCC items analyzed here and sees the largest possible improvement in health outcomes; a facility with a score of 50% has a reduced capacity to implement the SCC items, and can achieve only half the maximum benefits. This was calculated separately for all outcomes (maternal deaths, intrapartum stillbirths, and early neonatal deaths), so each facility received three "readiness scores."

Estimating SCC effect on "near-miss": The SCC trial (currently underway in Uttar Pradesh) is also measuring maternal near-miss as an outcome. Maternal deaths may only represent the "tip of the iceberg" of the burden of intrapartum complications—so cases of morbidity may be important both for generating research sample size, as well as for indicating something important about the quality of childbirth care [197]. When maternal morbidity almost results in death, these are called near-miss cases, or severe acute maternal morbidity (SAMM). The global community is working to adopt universal classification methods for SAMM [198]; much of the existing epidemiologic literature on SAMM uses differing criteria and approaches, so systematic reviews have been stymied [199].

Here we estimated the prevalence of SAMM, at baseline and with SCC implementation. A West Africa regional study, which used standardized measurement approaches on a large cohort of pregnant women, calculated maternal morbidity ratios (per 100 live births) for postpartum hemorrhage (1.74, 95% confidence interval 1.56-1.93), eclampsia (0.19, 95% confidence interval 0.14-0.26), sepsis (0.09, 95% confidence interval 0.05-0.14), and other causes related to caesarean section (0.80, 95% confidence interval 0.69-0.94) [200]. We applied this to the volume of annual live births in India [201], to attain a baseline estimate of SAMM. Next, we estimated how the "maximum SCC implementation" might reduce prevalence of SAMM. Because SAMM varies by setting and because there are no systematic reviews with standardized rates, as discussed above, this analysis relies upon a "death-to-SAMM ratio" measure, calculated from a study in Iraq [202]. This is a smaller study than the Prual analysis used to calculate the baseline prevalence of SAMM, so the estimated impact of the SCC on reducing SAMM should be interpreted with caution.

Sensitivity analyses: Many of the input values for the model have uncertainty, and the above-listed model assumptions might also introduce error. We therefore conducted a set of sensitivity analyses. First, we halved and doubled each model input variable in turn, and assessed how each of these changes affected the main results: the number of maternal deaths, intrapartum stillbirths, and early neonatal deaths, at

baseline, with maximum SCC implementation, and the readiness-adjusted number of deaths at CHCs. Table 3-5 presents the lower and upper bound values used for all input variables in sensitivity analyses. We also assessed the impact of changing our assumptions about how the SCC items would affect health outcomes, by halving and doubling the effect of each.

Table 3-5: Parameter ranges, all variables with lower and upper bound values explored in sensitivity analyses

Parameter	Lower bound	Upper bound
Maternal complications & severities		
pr(HTN)	0.025	0.1
pr(severe|HTN)	0.0115	0.046
pr(obstructed labor)	0.0275	0.11
pr(PPH)	0.0325-0.065*	0.13-0.26
pr(severe|PPH)	0.075	0.3
pr(sepsis)	0.0175	0.07
Maternal complication management		
pr(management|non-severe|HTN)	0	0.2
pr(management|severe|HTN)	0.05-0.3*	0.2-0.9*
pr(management|obstructed labor)	0.05-0.3*	0.2-0.9*†
pr(management|non-severe|PPH)	0.05-0.3*	0.2-0.9*†
pr(management|severe|PPH)	0.025-0.3*	0.1-0.9*†
pr(management|sepsis)	0.05-0.3*	0.2-0.9*†
Maternal complication case fatality rates		
pr(maternal death|other complication)	0.0005	0.002
pr(maternal death|unmanaged|non-severe|HTN)	0.002	0.008
pr(maternal death|unmanaged|severe|HTN)	0.0175	0.07
pr(maternal death|managed|severe|HTN)	0.0009	0.0035
pr(maternal death|unmanaged|obstructed labor)	0.0035	0.014
pr(maternal death|managed|obstructed labor)	0.0002	0.0007
pr(maternal death|unmanaged|non-severe|PPH)	0.005	0.02
pr(maternal death|managed|non-severe|PPH)	0.0003	0.001
pr(maternal death|unmanaged|severe|PPH)	0.015	0.06
pr(maternal death|managed|severe|PPH)	0.0008	0.003
pr(maternal death|unmanaged|sepsis)	0.0065	0.026
pr(maternal death|managed|sepsis)	0.0003	0.0013
Neonatal complications subsequent to maternal complications		
pr(neonatal complication|maternal HTN)	0.09	0.36
pr(neonatal complication|maternal managed sepsis)	0.0125	0.05
pr(neonatal complication|maternal unmanaged sepsis)	0.025	0.1

Table 3-5 (Continued)

Neonatal complications, competing with or absent maternal complications		
pr(asphyxia)	0.004-0.008*	0.016-0.032*
pr(low birth weight)	0.1	0.4
pr(neonatal sepsis)	0.01	0.04
pr(neonatal tetanus)	0.003-0.006*	0.012-0.024*
pr(other neonatal complications)	0.035	0.14
Neonatal complication case fatality rates		
pr(neonatal death|asphyxia)	0.05-0.1*	0.2-0.4*
pr(neonatal death|low birth weight)	0.02-0.04*	0.08-0.16*
pr(neonatal death|neonatal sepsis)	0.07-0.14*	0.28-0.56*
pr(neonatal death|neonatal tetanus)	0.1-0.2*	0.4-0.8*
pr(neonatal death|no neonatal complication)	0.0005	0.002
pr(neonatal death|other neonatal complications)	0.02-0.04*	0.08-0.16*
pr(neonatal death|maternal non-severe HTN)	0.02-0.04*	0.08-0.16*
pr(neonatal death|maternal severe HTN)	0.04-0.08*	0.16-0.32*
pr(neonatal death|maternal managed obstructed labor)	0.03-0.6*	0.12-0.24*
pr(neonatal death|maternal unmanaged obstructed labor)	0.06-0.12*	0.24-0.48*
pr(neonatal death|maternal managed sepsis)	0.054-0.108*	0.216-0.432*
pr(neonatal death|maternal unmanaged sepsis)	0.06-0.12*	0.24-0.48*
Stillbirths		
pr(stillbirth|maternal non-severe HTN)	0.0075-0.021*	0.03-0.084*
pr(stillbirth|other maternal complication)	0.0013-0035*	0.005-0.014*
pr(stillbirth|maternal managed obstructed labor)	0.0375-0.105*	0.15-0.42*
pr(stillbirth|maternal unmanaged obstructed labor)	0.15	0.6
pr(stillbirth|maternal severe HTN)	0.015-0.042*	0.06-0.168*
pr(stillbirth|maternal sepsis)	0.0063-0.0175*	0.025-0.07*

** This variable value varied by facility type (DH, versus urban CHC, versus rural CHC, versus PHC).*

† Truncated at 0.9.

Abbreviations: PPH – postpartum hemorrhage, HTN – hypertensive disorders (pre-eclampsia, eclampsia)

Results

Quantifying health system capacity to deliver quality obstetric care

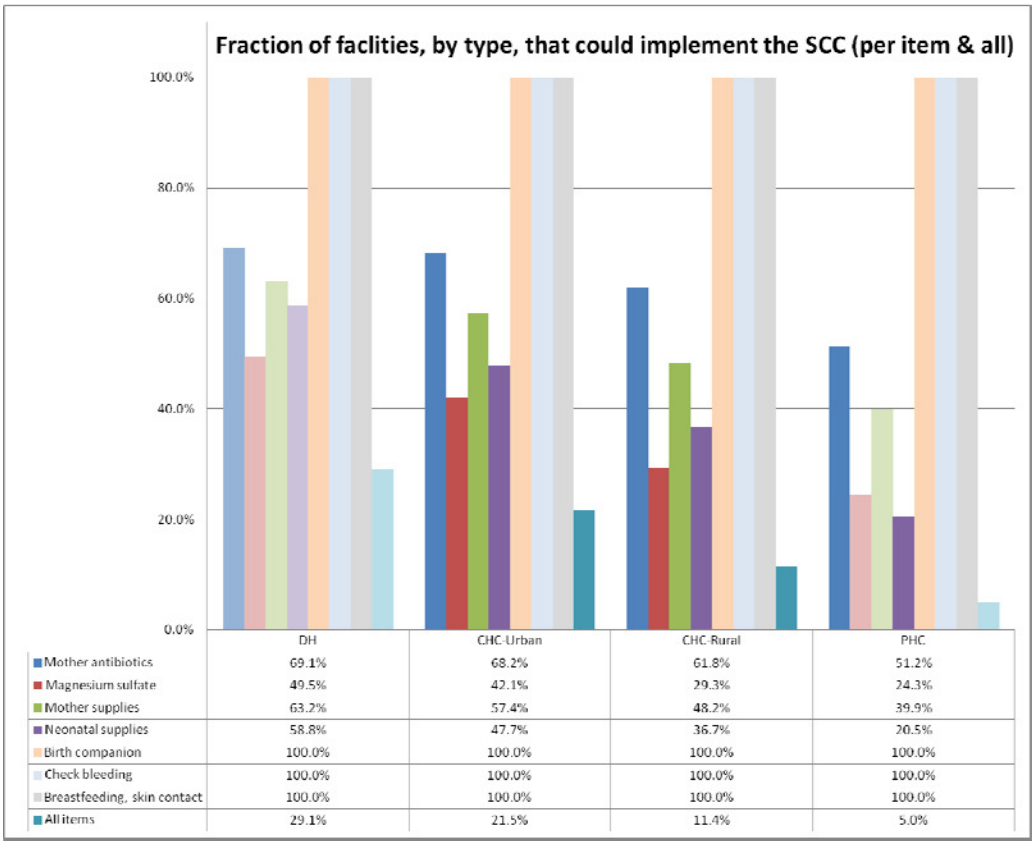
Table 3-6 presents descriptive information on the sample of facilities included in this analysis.

Table 3-6: Description of the health system sample from the DLHS-3

	DH	CHC, Rural	CHC, Urban	PHC
n	594	3090	1072	8619
Catchment area population (mean)	1,444,633	127,242	131,568	49,142
Rural (%)	--	100%	0%	94.7%
Number of beds (mean)	206.3	21.4	29.1	5.2
Number of deliveries during prior month (mean)	223.1	44.0	62.1	26.2
% with zero deliveries during prior month	6.4%	12.3%	5.0%	27.6%
Number of caesarean sections during prior month (mean)	44.9	39.5	55.3	--

Facility capability to implement the SCC items analyzed in this paper is shown in Figure 3-2. Only 29.1% of DH, 21.5% and 11.4% of urban and rural (respectively) CHCs and 5.0% of PHCs would be able to provide all SCC items.

Figure 3-2: Capacity to implement the SCC, by health facility type, per item and as a set



	DH	CHC-Urban	CHC-Rural	PHC
Mother antibiotics	69.1%	68.2%	61.8%	51.2%
Magnesium sulfate	49.5%	42.1%	29.3%	24.3%
Mother supplies	63.2%	57.4%	48.2%	39.9%
Neonatal supplies	58.8%	47.7%	36.7%	20.5%
Birth companion	100.0%	100.0%	100.0%	100.0%
Check bleeding	100.0%	100.0%	100.0%	100.0%
Breastfeeding, skin contact	100.0%	100.0%	100.0%	100.0%
All items	29.1%	21.5%	11.4%	5.0%

Estimating health outcome changes, with full and partial SCC implementation

The "maximum SCC implementation" scenario—assuming unconstrained implementation of the 7 SCC items analyzed here (in terms of supplies and equipment)—resulted in 33.6% fewer maternal deaths at facilities, 8.75% fewer intrapartum stillbirths, and 42.9% fewer early neonatal deaths at facilities, versus baseline (i.e., no SCC). The population-level impacts of implementing the SCC in full are shown below, in Table 3-7.

Table 3-7: Population-level estimates of SCC impact

	Maternal deaths	Intrapartum stillbirths	Early neonatal deaths
Deaths (baseline), India	69,400 [195]	347,230 [8]	670,000 [196]
Averted deaths with full SCC, India	11,714	15,291	63,747
% fewer facility-based deaths versus baseline, India	33.56%	8.75%	42.86%
Population-based metric with full SCC	MMR: 211.3	ISBR: 12.2	ENMR: 22.2

But, as shown in Figure 3-2, few facilities have the requisite health system inputs to provide all SCC items. When SCC items were individually "subtracted" to reflect this supply/infrastructure availability, the impact of the checklist attenuated for both maternal and neonatal deaths (less so for intrapartum stillbirths) (Table 3-8).

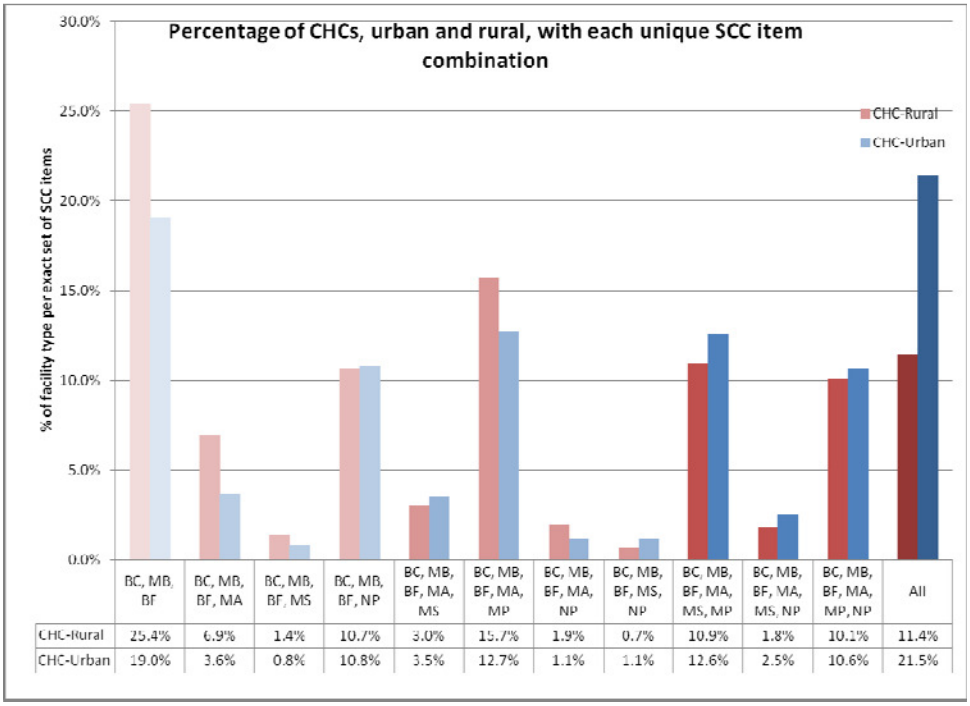
Table 3-8: Effect of eliminating one SCC item per scenario, compared to baseline (no SCC), by health facility type

	All SCC (i.e., 7 items)	Minus antibiotics	Minus MgSO4	Minus mom supplies	Minus neonatal supplies	Minus these 4 items (i.e., 3 items)
MATERNAL DEATHS – Change n over baseline						
DH	-29.40%	-20.77%	-19.57%	-20.41%	-29.40%	-1.94%
CHC-u	-38.56%	-27.74%	-31.63%	-20.98%	-38.56%	-3.23%
CHC-r	-35.99%	-27.29%	-27.41%	-20.97%	-35.99%	-3.69%
PHC	-41.16%	-30.28%	-35.21%	-20.34%	-41.16%	-3.50%
INTRAPARTUM STILLBIRTHS – Change n over baseline						
DH	-8.88%	-7.27%	-8.80%	-8.88%	-8.88%	-7.19%
CHC-u	-8.68%	-6.79%	-8.58%	-8.68%	-8.68%	-6.70%
CHC-r	-8.77%	-7.00%	-8.68%	-8.77%	-8.77%	-6.91%
PHC	-8.46%	-6.26%	-8.35%	-8.46%	-8.46%	-6.15%
NEONATAL DEATHS – Change n over baseline						
DH	-43.17%	-42.74%	-43.16%	-40.75%	-21.56%	-16.93%
CHC-u	-42.63%	-42.11%	-42.62%	-40.35%	-20.63%	-16.12%
CHC-r	-42.97%	-42.52%	-42.95%	-40.60%	-21.15%	-16.58%
PHC	-42.11%	-41.58%	-42.10%	-39.94%	-19.74%	-15.41%

Readiness-adjusted health outcomes

Figure 3-3, below, presents combinations of the 4 main SCC items among CHCs (rural and urban). The most common state for rural CHCs was to have none of the supplies required for the 4 study SCC interventions; at urban CHCs, it was most common to have all 4 items.

Figure 3-3: Availability of SCC items, alone and in combination, at CHCs; color saturation increases from left to right, signifying increasing number of items within each package



BC: birth companion; MB: maternal bleeding; BF: breastfeeding/skin-to-skin contact; MA: mother antibiotics; MS: magnesium sulfate; MP: mother supplies; NP: neonatal supplies

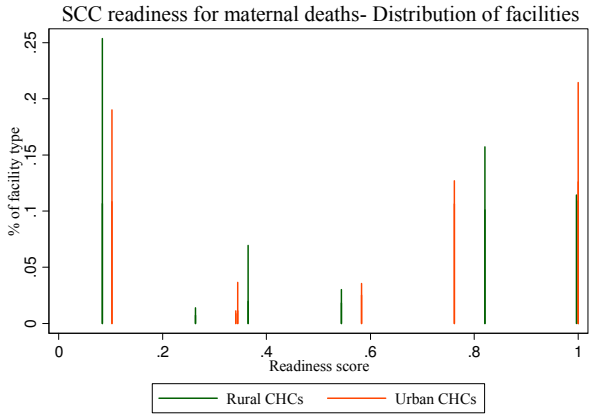
Figures 3-4, 3-5 and 3-6 show the distribution, respectively, of CHC facilities, births at CHC facilities, and deaths at CHC facilities, by "readiness score" for each of the three outcomes. Figure 3-4 highlights characteristics of the health system: what is the probability of a randomly-selected urban or rural CHC having full, or some degree of attenuated, ability to deliver full benefits from the SCC. The x-axis can be interpreted as follows: in the top figure, having a readiness score of 0.8 means that the facility has available health system inputs (medicines, supplies, infrastructure) that enables them to implement SCC

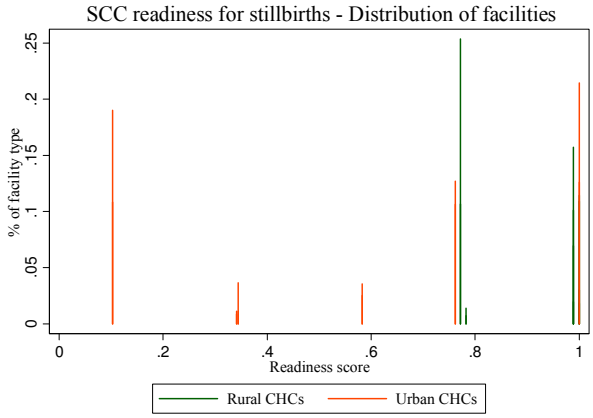
items to the degree that they can capture no more than 80% of the full potential impact of the SCC with respect to maternal deaths; in the middle graph, a readiness score of 0.8 means that the inputs will enable SCC implementation to attain no more than 80% of the full potential in reducing stillbirths; and in the bottom graph, a facility with readiness score of 0.8 has available inputs to see no more than an 80% reduction in early neonatal deaths versus full potential.

Since childbirths are perhaps not randomly distributed across facilities (if better-equipped facilities see a greater share of births), Figure 3-5 shows the distribution of births across readiness scores for rural and urban CHCs. Birth distribution was calculated based on prior-month birth volume, as recorded in the DLHS; it is therefore assumed that the sampled facilities are representative of all facilities of that type. Each facility's readiness score has the same interpretation as above, but this figure plots birth volume by score (rather than number of facilities with each score).

Figures 3-5 and 3-6 demonstrate that women do not all deliver at well-equipped facilities: in fact, the largest birth volumes are seen at low-readiness-score facilities (for both urban and rural CHCs). When this is translated into mortality (given the high birth volume and low readiness), the highest proportion of deaths occur at low-readiness facilities. This is particularly evident for early neonatal deaths, where nearly all deaths are estimated to occur at facilities grouped at the low end of the readiness scale.

Figure 3-4: Distribution of CHC facilities (urban and rural) by "readiness score" for reducing maternal deaths, intrapartum stillbirths, and early neonatal deaths (i.e., reduction in health outcomes relative to maximum possible level at facilities able to fully implement the SCC)





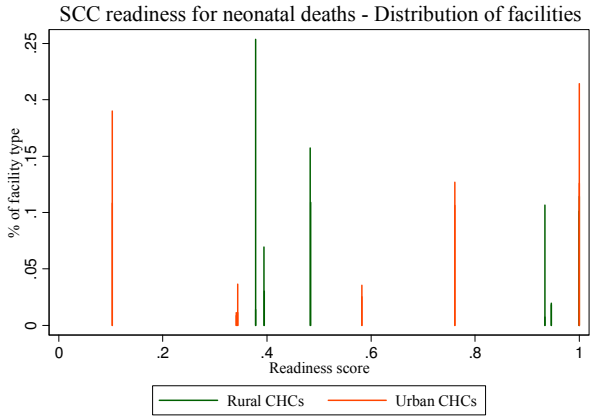
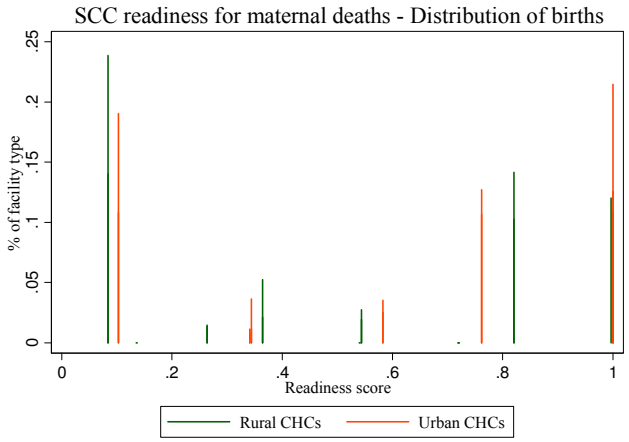
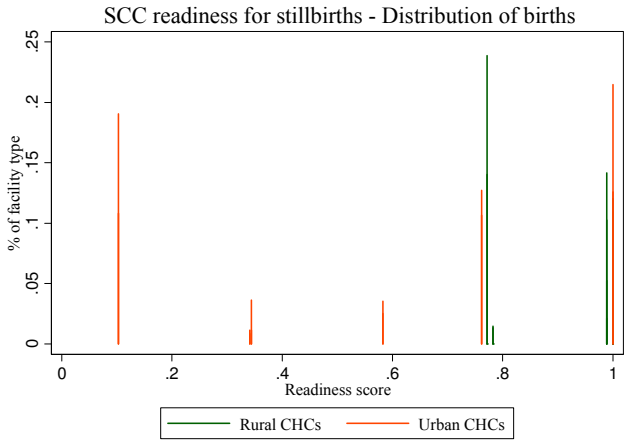


Figure 3-5: Distribution of births at CHC facilities (urban and rural) by "readiness score" for reducing maternal deaths, intrapartum stillbirths, and early neonatal deaths (i.e., reduction in health outcomes relative to maximum possible level at facilities able to fully implement the SCC)





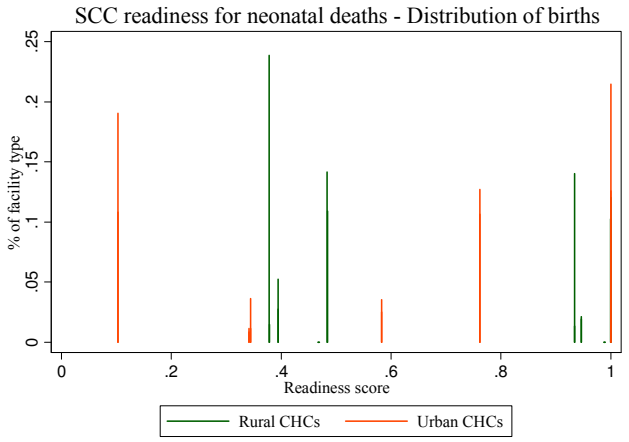
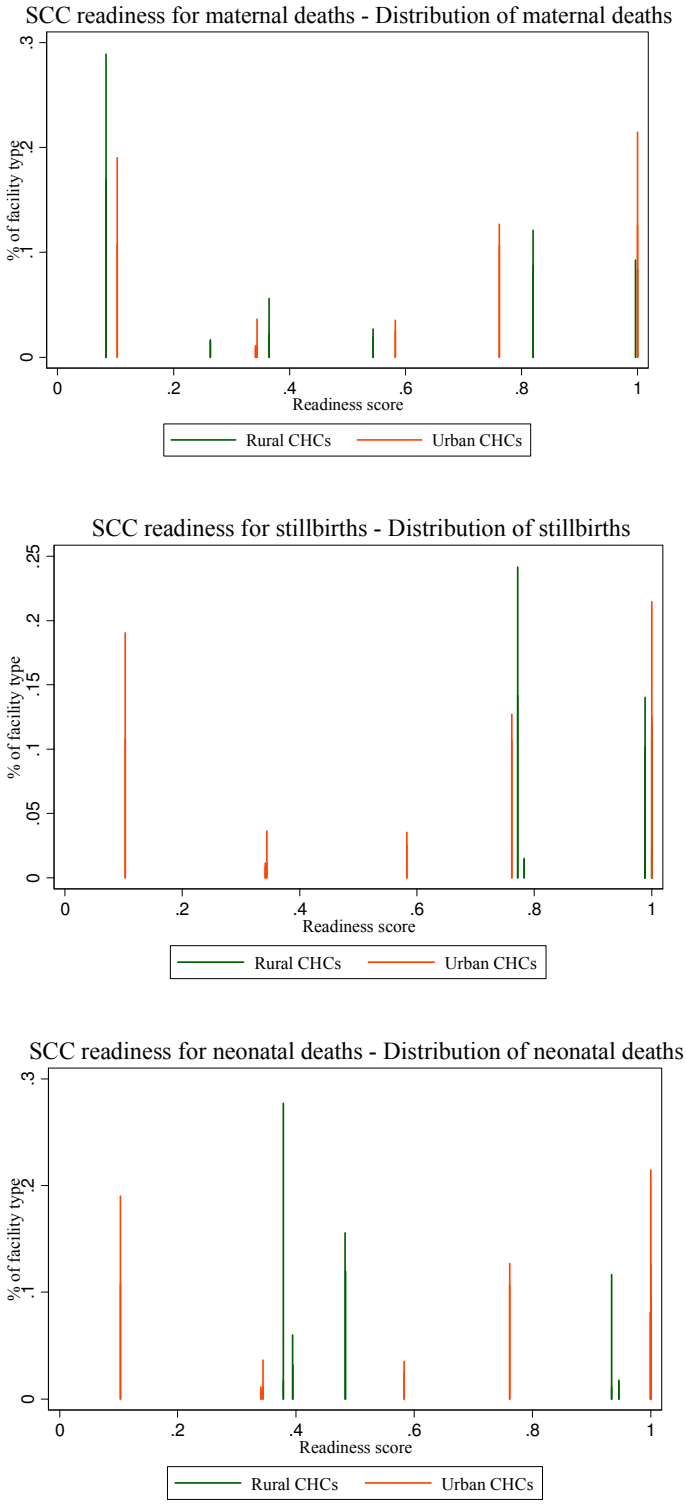


Figure 3-6: Distribution of deaths at CHC facilities (urban and rural) by "readiness score" for reducing maternal deaths, intrapartum stillbirths, and early neonatal deaths (i.e., reduction in health outcomes relative to maximum possible level at facilities able to fully implement the SCC)



Lastly, we calculated the likely effect of deploying the SCC at CHC facilities only: the maximum number of averted deaths with full SCC implementation, versus the likely benefits seen given the distribution of facilities by readiness score. These results are shown in Table 3-9. It is estimated that deploying the SCC in the current health system ("readiness-adjusted") could avert only approximately half (53%) the number of maternal deaths as if the SCC could be implemented in full, and two-thirds (66%) of early neonatal deaths.

Table 3-9: Facility-level estimates of SCC impact

	Maternal deaths	**Intrapartum stillbirths**	**Early neonatal deaths**
Deaths (baseline), at CHC facilities	6790	33,971	28,930
Averted deaths (with full SCC), at CHC facilities	2585	2954	12,352
Averted deaths (readiness-adjusted), at CHC facilities	1382	2683	8156
Ratio adjusted : full	0.53	0.91	0.66

Estimating SCC effect on "near-miss"

The baseline estimate of severe acute maternal morbidity (SAMM, also called "near-miss") is shown in Table 3-10. The relative distribution of cause-specific SAMM estimated here are similar to those found in the literature from India; e.g., a recent study that pooled data from 6 medical colleges in India to calculate the prevalence and causes of SAMM found that, among near-miss cases, 72% were related to PPH, 3.8% to sepsis, and 26.5% to HTN [203]. The bottom half of Table 3-10 shows the estimate of how the SCC might reduce prevalence of SAMM. It suggests that the "maximum SCC implementation" scenario in India could avert a substantial number—approximately 85.3% on average—of "near-miss" cases from these major obstetric complications.

Table 3-10: Estimated prevalence of severe acute maternal mortality (SAMM), or near-miss cases, among modeled population of women

	N	%
n births (annual in India)	27,098,000	--
Baseline		
SAMM, all causes (estimated)	764,164	100%
Related to PPH	471,505	61.70%
Related to HTN	51,486	6.74%
Related to sepsis	24,388	3.19%
Other causes (OL, other)	216,784	28.37%
With full SCC implementation	**Δ n SAMM, %**	
SAMM, PPH and HTN and Sepsis (average)	-85.30%	
SAMM, PPH	-76.39%	
SAMM, HTN	-92.11%	
SAMM, Sepsis	-87.39%	

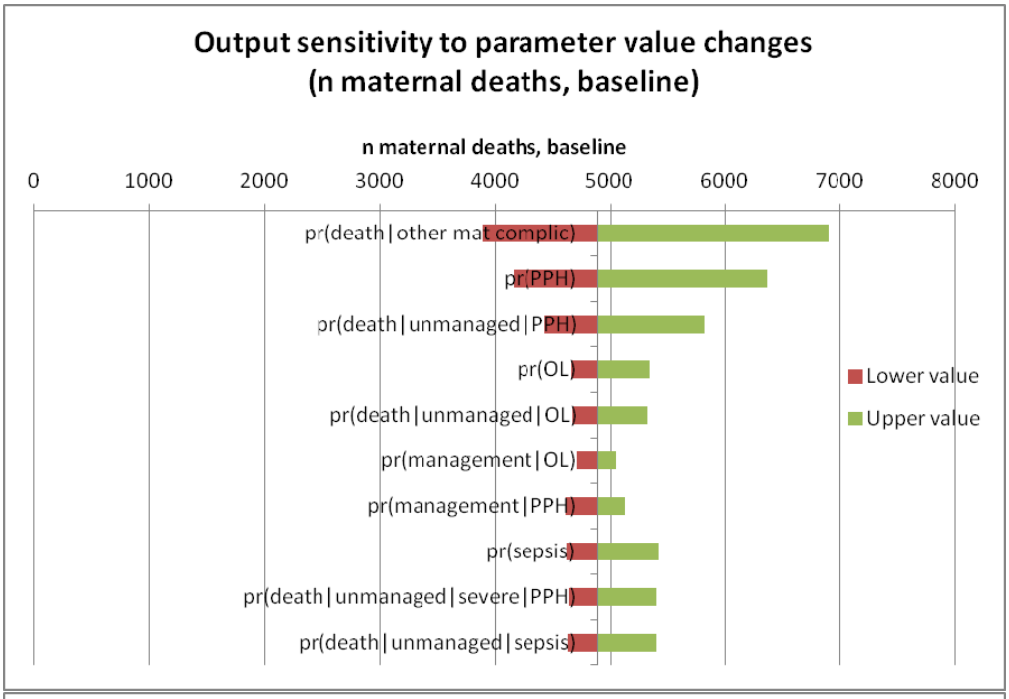
Sensitivity analyses

The first set of sensitivity analyses focused on the degree to which each input parameter value affected the main outcomes (number of deaths by type) under different scenarios (baseline at all health facilities, with maximum SCC implementation at all health facilities, and readiness-adjusted SCC implementation at CHC facilities), by doubling and halving each value, as described in the Methods section.

Figures 3-7 and 3-8 illustrate these results. Additional results are also presented in the Appendix (section 3.6). The most influential variable for maternal death, in all scenarios, was the case fatality rate of other/no complications, as well as the prevalence, and consequences, of postpartum hemorrhage. The number of stillbirths was most strongly affected by parameters around obstructed labor (shown in Appendix), and early neonatal deaths were most sensitive to input values around the most common (and critical) neonatal complications of low birth weight, tetanus, and neonatal sepsis.

We also assessed the impact of changing our assumptions about how the SCC items would affect health outcomes; these results are shown in the Appendix (section 3.6). The possible impact of the SCC on maternal death was most heavily influenced by changes in assumptions around the effectiveness of oxytocin to reduce likelihood of postpartum hemorrhage, both regular and severe. Early neonatal death changes were most strongly influenced by assumptions about the effectiveness of breastfeeding/skin-to-skin contact, and neonatal resuscitation, as well as the spillover effects of antibiotics for maternal sepsis.

Figure 3-7: Number of deaths (maternal and early neonatal) at baseline, with different input variable (parameter) values



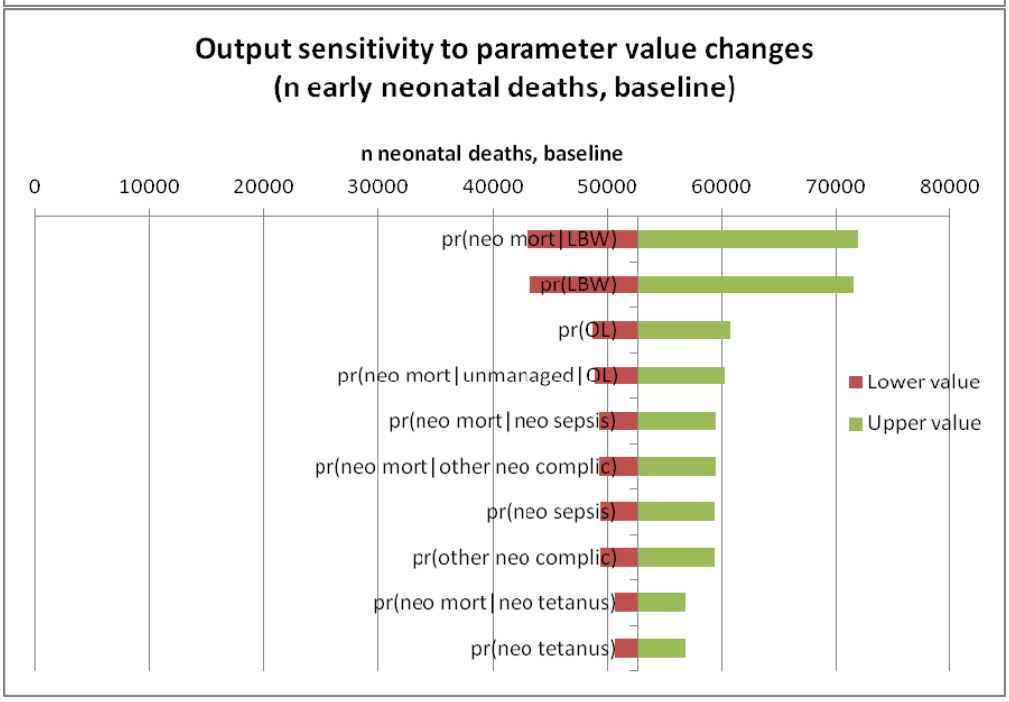
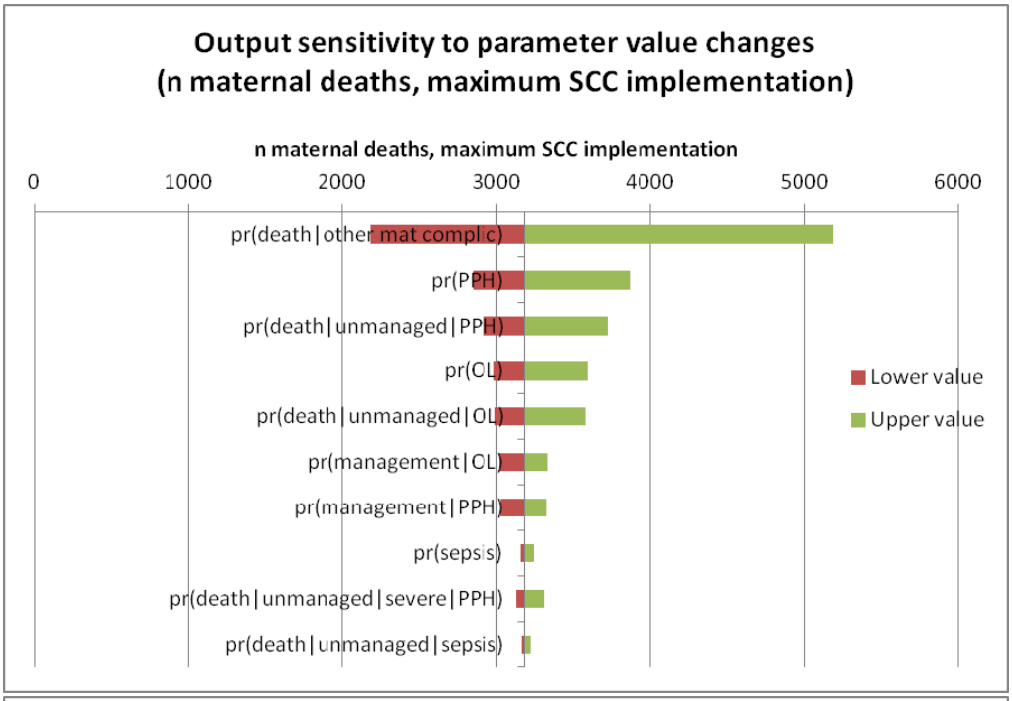
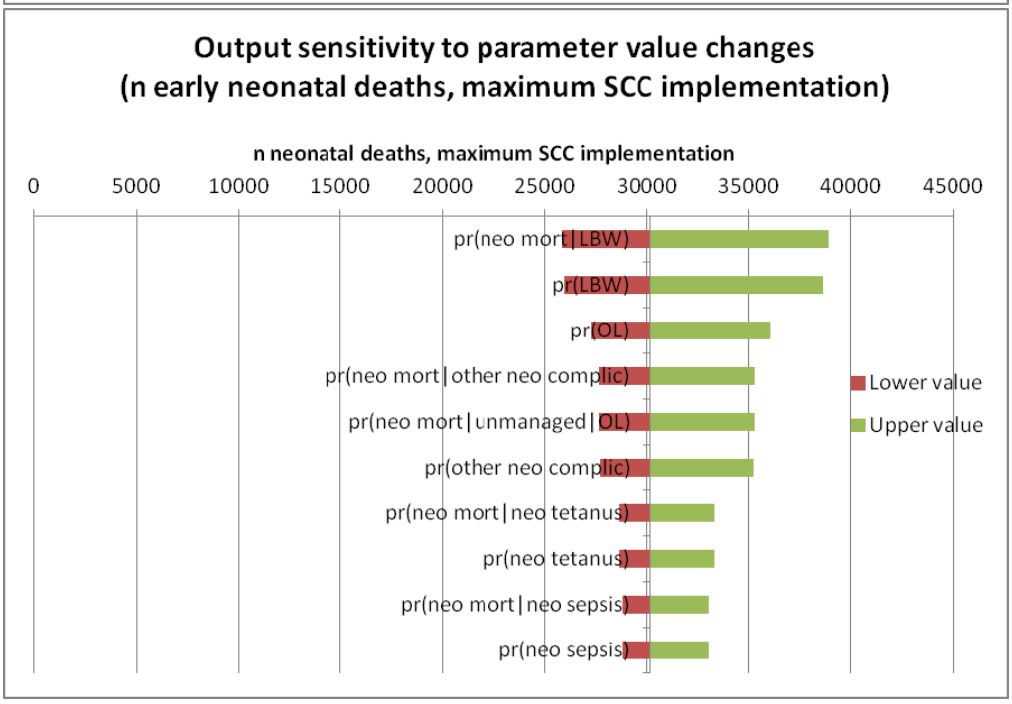


Figure 3-8: Number of deaths (maternal and early neonatal) with maximum SCC implementation, with different input variable (parameter) values





Discussion

As the Millennium Development Goals deadline approaches, it is evident that childbirth remains extremely dangerous: many countries will fail to meet their Goal for maternal mortality, and neonatal deaths have increased as a share of childhood mortality. The provision of high-quality obstetric and postpartum care is critical for addressing this mortality burden. But there are few proven large-scale effective interventions to improve care quality. This paper aimed to estimate the potential impact of an intervention with promising pilot data on provider behavioral change—the Safe Childbirth Checklist—and to explore how health system capacity might limit the intervention's effectiveness when delivered at-scale in India.

Based on these findings, only between 5 and 29% of health facilities in India, by type, have all the available supplies to perform 7 key SCC interventions: provision of maternal antibiotics for cases of suspected infection, provision of magnesium sulfate to laboring women with signs of eclampsia, preparation of safe childbirth supplies for mothers (water for hand washing, and oxytocin for prevention of postpartum hemorrhage) and for neonates (sterile blade for cord cutting, clean towel for drying the baby, and resuscitation equipment)—as well as encouraging presence of a birth companion, checking for maternal blood loss, and encouraging early breastfeeding and skin-to-skin contact for newborns.

In an ideal "maximum implementation scenario" that assumes no health system constraints, these results suggest that the SCC activities could achieve potential reductions in maternal and early neonatal mortality. The SCC intervention was estimated to potentially reduce the number of facility-based maternal deaths by 33.6%, intrapartum stillbirths by 8.8% and early neonatal deaths by 42.9%. It also may reduce near-miss cases by 85%. But when key interventions were "subtracted" from the full SCC package, to reflect supply unavailability, health benefits would likely be reduced. The example analysis among CHCs demonstrates that a considerable fraction of births occur at facilities with low-to-medium "readiness," defined as degree to which SCC impact may be attenuated due to implementation capacity

(given health system constraints). Implementing the SCC at CHCs, given actual health system capacity, would avert only half the number of maternal deaths, and two-thirds the early neonatal deaths, as if the SCC could be utilized in full.

The Safe Childbirth Checklist includes 29 items that represent routine quality obstetric care—in other words, care that all women during childbirth should receive. The SCC does not include emergency obstetric care behaviors, such as blood transfusion or caesarean section, which are more resource-intensive than the routine obstetric care outlined by the SCC.[8] But these results show that health facilities in India may still lack adequate supplies and infrastructure to provide this regular (non-emergency) obstetric care—and, without such capacity, the potential impact of interventions like the SCC could be substantially lessened.

This analysis relied on the assumption that the effect of SCC project implementation was equivalent to the sum of each checklist item's impact, and that each item was never implemented at baseline versus always implemented in the presence of the SCC, unless health system constraints made this impossible. This assumption about perfect intervention uptake, in terms of the magnitude of behavior change, was informed by the pilot study [147]—but may not be a reasonable assumption, as future results on the SCC emerge. If additional results indicate that the SCC intervention does not universally result in a never-to-always behavior shift, this model can be adjusted to reflect realistic empirically-informed probabilities of each item's implementation. Additionally, the pilot site was unique in its access to supplies and equipment; future data from SCC projects may provide insights on how health system ingredients and SCC-related behavior change are correlated. This model assumed that perfect behavior in the presence of

[8] This analysis did not include the SCC item that refers high-risk women for emergency obstetric care—thereby possibly underestimating the potential impact of the SCC intervention, if such referral systems function well and if high-quality emergency obstetric care is available.

the SCC intervention was only constrained by lack of health system inputs—but future results may indicate the degree to which this assumption is realistic, and this model can be adjusted accordingly.

These findings suggest areas for future intervention. This analysis demonstrated gaps in important health system components for high-quality intrapartum care in India; these results (and others from the DLHS) can be used to underscore emphasis on health system strengthening. The SCC intervention aims to increase awareness of such shortcomings, by providers and managers, and provide an impetus for making system improvements—for example, as noted in the conclusions of the pilot study: "[A]fter introduction of the program it became apparent that no structure was in place to adequately monitor women and newborns immediately after delivery, which brought to light the difficulty in reliably completing crucial assessments and practices at that time. In response, the local staff took the initiative to convert an underutilized room adjacent to the labor ward into a postpartum bay where women and newborns were observed for at least one hour after delivery." [147] They also cited similar improvements around availability of medicines and supplies near the labor ward. The results of this analysis reinforce the importance of highlighting such barriers during the SCC intervention, and empowering stakeholders at different levels of the health system to make improvements. A hospital administrator, for example, may be able to ensure that soap is always available for hand-washing, but higher-level system managers must be involved to resolve medicine supply chain issues.

This paper also points to lessons for research. This presents a new approach to estimating impact at-scale for interventions with only pilot data. It uses decision modeling as a means to fill in a knowledge gap, using the best-available information and assumptions that can be systematically explored as part of the analysis. This type of analysis may be useful for a range of topics, since many interventions have not been assessed via large-scale randomized control trials so their anticipated impact may not be well understood. Also, trials have limited generalizability, so policymakers and program managers may still seek additional locally-relevant information, which an analysis like the one presented here could provide.

There are some limitations to this analysis. First, the supply and infrastructure estimates were based on data from a national survey of health facilities, but some imputations were required to map these findings onto the SCC, which may introduce bias or error. Second, these results necessarily have limited external validity since all estimates and analysis were constructed to be India-specific. Third, the data from the DLHS are from 2007/08; although these are the most recent nationally-representative data available in India, a newer dataset would offer a more current snapshot of supplies and infrastructure in the Indian health system.

Fourth, a key assumption undergirding this model is that SCC implementation is equivalent to uptake of the checklist items, from never to always, unless there are health system constraints. These results should therefore be seen as the most generous estimates of SCC impact, since in reality, some items may be partially implemented at baseline, and SCC implementation may not always result in full and perfect behavior change. There may also be other limiting factors, such as human resource availability and/or skill level, which were not explored here but could diminish SCC effectiveness. So these findings represent the uppermost bound of how many lives might be saved if the SCC were to be implemented.

Lastly, the decision tree model included assumptions—and one in particular merits further discussion here: how emergency obstetric care is handled in the model. In an environment of non-universal facility-based childbirth, such as India, the population that presents at facilities for delivery may especially include high-risk women, such as women who intended to deliver at home but experienced a complication mid-labor. In reality, many such women would receive emergency obstetric care—and since the first SCC item is to assess for such a need and to refer out, women who have a complication already underway at admission would not "receive" the 7 SCC items modeled here, and they are omitted from the analysis. The model does capture treatment of complications that arise after admit (via the "complication is managed or not managed" variable shown in Figure 3-1), where likelihood of management reflects the

probability that each facility type can offer emergency obstetric care—but its starting population may be a lower-mortality group than the actual population of women undergoing facility-based childbirth in India. This has implications for how the model was calibrated, as well as extrapolating to population-level metrics. The main results should also be interpreted with caution, although it is impossible to know whether they are over- or under-estimates. For the former, the estimates of facility-based mortality reduction would be only applicable to a population of women who presented without a complication underway. And on the latter, SCC impact may be greatest at lower-level facilities because it identifies high-risk women early and prevents serious complications (like postpartum hemorrhage through timely oxytocin)—both reducing the need for emergency obstetric care.

Conclusion

Global efforts to reduce maternal and early neonatal deaths have been progressing slowly. Quality of care may be a significant barrier, and this is associated with the strength of the health system. This paper examined how certain health system characteristics (medicines, supplies, and infrastructure) may affect the potential to implement an intervention that enables the provision of quality routine obstetric care—namely, the Safe Childbirth Checklist. This analysis aims to shed light on how health system constraints may attenuate an intervention's ability to achieve maximum possible impact. Additionally, it demonstrates a new approach to anticipating program effectiveness in the absence of robust outcome data, by using decision modeling. There are other important health system "inputs" that were not considered here, for example human resources, and there are other interventions for improving intrapartum care quality—and this analysis does not aim to comprehensively address these questions, but rather to offer a stylized example of one potential approach to consider important questions about program scale-up and health system constraints.

References for Chapter 3

1. Travis, P., et al., *Overcoming health-systems constraints to achieve the Millennium Development Goals.* The Lancet, 2004. **364**(9437): p. 900-906.
2. Elzinga, G., M.C. Raviglione, and D. Maher, *Scale up: meeting targets in global tuberculosis control.* The Lancet, 2004. **363**(9411): p. 814-819.
3. Gilks, C.F., et al., *The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings.* The Lancet, 2006. **368**(9534): p. 505-510.
4. Brugha, R. and G. Walt, *A global health fund: a leap of faith?* BMJ, 2001. **323**(7305): p. 152-154.
5. Lu, C., et al., *Absorptive capacity and disbursements by the Global Fund to Fight AIDS, Tuberculosis and Malaria: analysis of grant implementation.* The Lancet, 2006. **368**(9534): p. 483-488.
6. Yu, D., et al., *Investment in HIV/AIDS programs: Does it help strengthen health systems in developing countries?* Globalization and Health, 2008. **4**(1): p. 8.
7. Beaglehole, R., et al., *Priority actions for the non-communicable disease crisis.* The Lancet, 2011. **377**(9775): p. 1438-1447.
8. Eaton, J., et al., *Scale up of services for mental health in low-income and middle-income countries.* The Lancet, 2011. **378**(9802): p. 1592-1603.
9. Lawn, J.E., et al., *Stillbirths: Where? When? Why? How to make the data count?* The Lancet, 2011. **377**(9775): p. 1448-1463.
10. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2013*. 2014.
11. Randive, B., V. Diwan, and A. De Costa, *India's Conditional Cash Transfer Programme (the JSY) to Promote Institutional Birth: Is There an Association between Institutional Birth Proportion and Maternal Mortality?* PLoS ONE, 2013. **8**(6): p. e67452.
12. Oestergaard, M.Z., et al., *Neonatal Mortality Levels for 193 Countries in 2009 with Trends since 1990: A Systematic Analysis of Progress, Projections, and Priorities.* PLoS Med, 2011. **8**(8): p. e1001080.
13. Rammohan, A., K. Iqbal, and N. Awofeso, *Reducing Neonatal Mortality in India: Critical Role of Access to Emergency Obstetric Care.* PLoS ONE, 2013. **8**(3): p. e57244.
14. Measure DHS and USAID, *STAT Compiler*. 2012.
15. Chaturvedi, S., et al., *Quality of Obstetric Referral Services in India's JSY Cash Transfer Programme for Institutional Births: A Study from Madhya Pradesh Province.* PLoS ONE, 2014. **9**(5): p. e96773.
16. Malik, J., et al., *Utilization of Health Services under Janani Suraksha Yojna in Rural Haryana.* International Journal of Medicine and Public Health, 2013. **3**(3): p. 176-179.
17. Ameh, C., et al., *Status of Emergency Obstetric Care in Six Developing Countries Five Years before the MDG Targets for Maternal and Newborn Health.* PLoS ONE, 2012. **7**(12): p. e49938.
18. Spector, J.M., et al., *Improving Quality of Care for Maternal and Newborn Health: Prospective Pilot Study of the WHO Safe Childbirth Checklist Program.* PLoS ONE, 2012. **7**(5): p. e35151.
19. Lavender, T., *Effect of partogram use on outcomes for women in spontaneous labour at term.* Cochrane Database of Systematic Reviews, 2013(7).
20. Windrim, R., et al., *A randomized controlled trial of a bedside partogram in the active management of primiparous labour.* J Obstet Gynaecol Can., 2007. **29**(1): p. 27-34.
21. Dolea, C., C. AbouZahr, and C. Stein, *Global burden of maternal hemorrhage in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
22. Dolea, C. and C. Stein, *Global burden of maternal sepsis in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
23. AbouZahr, C., *Global burden of maternal death and disability.* British Medical Bulletin, 2003. **67**(1): p. 1-11.

24. Dolea, C. and C. AbouZahr, *Global burden of obstructed labour in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
25. Dolea, C. and C. AbouZahr, *Global burden of hypertensive disorders of pregnancy in the year 2000*. 2003, GBD 2000 Working Paper, World Health Organization, Geneva.
26. Abalos, E., et al., *Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 14-24.
27. Calvert, C., et al., *Identifying Regional Variation in the Prevalence of Postpartum Haemorrhage: A Systematic Review and Meta-Analysis.* PLoS ONE, 2012. **7**(7): p. e41114.
28. Carroli, G., et al., *Epidemiology of postpartum haemorrhage: a systematic review.* Best Practice & Research Clinical Obstetrics & Gynaecology, 2008. **22**(6): p. 999-1012.
29. Graham, W.J., et al., *Chapter 26, Maternal and Perinatal Conditions*, in *Disease Control Priorities in Developing Countries 2nd edition*, D.T. Jamison, et al., Editors. 2006, The World Bank: Washington, DC.
30. Pagel, C., et al., *Estimation of potential effects of improved community-based drug provision, to augment health-facility strengthening, on maternal mortality due to post-partum haemorrhage and sepsis in sub-Saharan Africa: an equity-effectiveness model.* The Lancet, 2009. **374**(9699): p. 1441-1448.
31. Vogel, J.P., et al., *Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 76-88.
32. Fantu, S., H. Segni, and F. Alemseged, *Incidence, causes and outcome of obstructed labor in Jimma University specialized hospital.* Ethiopian journal of health sciences, 2010. **20**(3).
33. Mondal, S., et al., *Fetomaternal outcome in obstructed labor in a peripheral tertiary care hospital.* Medical Journal of Dr. DY Patil University, 2013. **6**(2): p. 146.
34. Lumbiganon, P., et al., *Method of delivery and pregnancy outcomes in Asia: the WHO global survey on maternal and perinatal health 2007–08.* The Lancet, 2010. **375**(9713): p. 490-499.
35. Ohlsson, A., *Intrapartum antibiotics for known maternal Group B streptococcal colonization.* Cochrane Database of Systematic Reviews, 2014(6).
36. Witlin, A.G., et al., *Predictors of neonatal outcome in women with severe preeclampsia or eclampsia between 24 and 33 weeks' gestation.* American Journal of Obstetrics and Gynecology, 2000. **182**(3): p. 607-611.
37. The WHO Young Infants Study Group, *Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study.* The Pediatric Infectious Disease Journal, 1999. **18**(10): p. S17-S22.
38. Lee, A., et al., *Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect.* BMC Public Health, 2011. **11**(Suppl 3): p. S12.
39. Bhutta, Z.A., et al., *Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost?* The Lancet, 2014(0).
40. Porwal, R.G.S.K., *Obstructed labour: incidence, causes and outcome.* Int J Biol Med Res, 2012. **3**(3): p. 2185-2188.
41. Lawn, J.E., et al., *Two million intrapartum-related stillbirths and neonatal deaths: Where, why, and what can be done?* International Journal of Gynecology & Obstetrics, 2009. **107, Supplement**(0): p. S5-S19.
42. Duley, L., et al. (2010) *Magnesium sulphate and other anticonvulsants for women with pre-eclampsia*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD000025.pub2.
43. UNICEF. *Low Birthweight*. 2014; Available from: http://data.unicef.org/nutrition/low-birthweight.

44. Mondal, G.P., et al., *Neonatal septicaemia among inborn and outborn babies in a referral hospital.* The Indian Journal of Pediatrics, 1991. **58**(4): p. 529-533.
45. Zaidi, A.K.M., et al., *Hospital-acquired neonatal infections in developing countries.* The Lancet, 2005. **365**(9465): p. 1175-1188.
46. Kaushik, S.L., et al., *Neonatal sepsis in hospital born babies.* J Commun Dis., 1998. **30**(3): p. 147-52.
47. Chacko, B. and I. Sohi, *Early onset neonatal sepsis.* The Indian Journal of Pediatrics, 2005. **72**(1): p. 23-26.
48. Chandra, S., S. Ramji, and S. Thirupuram, *Perinatal asphyxia: multivariate analysis of risk factors in hospital births.* Indian pediatrics, 1997. **34**(3): p. 206-12.
49. Bang, A.T., et al., *Why Do Neonates Die in Rural Gadchiroli, India? (Part II): Estimating Population Attributable Risks and Contribution of Multiple Morbidities for Identifying a Strategy to Prevent Deaths.* J Perinatol, 2005. **25**(S1): p. S35-S43.
50. Joseph, N., et al., *Morbidity among infants in South India: A longitudinal study.* The Indian Journal of Pediatrics, 2010. **77**(4): p. 456-458.
51. Joshi, P., et al., *Impact of universal immunization programme on the incidence of tetanus neonatorum.* Indian Pediatr, 1992. **29**: p. 773-75.
52. Kaushik, S.L., et al., *Neonatal mortality rate: relationship to birth weight and gestational age.* Indian J Pediatr., 1998. **65**(3): p. 429-33.
53. Blencowe, H., et al., *Tetanus toxoid immunization to reduce mortality from neonatal tetanus.* International journal of epidemiology, 2010. **39**(suppl 1): p. i102-i109.
54. Smits, J. and C. Monden, *Twinning across the Developing World.* PLoS ONE, 2011. **6**(9): p. e25239.
55. Khan, K.S., et al., *WHO analysis of causes of maternal death: a systematic review.* The Lancet, 2006. **367**(9516): p. 1066-1074.
56. Mills, S., et al., *Obstetric Care in Poor Settings in Ghana, India, and Kenya*, W. Bank, Editor. 2007: Washington, DC.
57. Registrar General India, *Maternal mortality in India: 1997-2003; trends, causes and risk factors (Sample Registration System)*. 2006: New Delhi, India.
58. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2010*. 2012.
59. Tayade, S., et al., *Maternal Death Review To Know The Determinants Of Maternal Mortality In A District Hospital Of Central India*. 2012. Vol. 3. 2012.
60. Bangal, V.B., P.A. Giri, and R. Garg, *Maternal mortality at a tertiary care teaching hospital of rural india: a retrospective study.* International Journal of Biological and Medical Research, 2011. **2**(4): p. 1043-1046.
61. Puri, A., I. Yadav, and N. Jain, *Maternal mortality in an urban tertiary care hospital of north India.* The Journal of Obstetrics and Gynecology of India, 2011. **61**(3): p. 280-285.
62. World Health Organization, *Neonatal and perinatal mortality: Country, regional and global estimates*. 2007.
63. Lawn, J.E., et al., *Every Newborn: progress, priorities, and potential beyond survival.* The Lancet, 2014. **384**(9938): p. 189-205.
64. World Health Organization, *World Health Statistics 2014*. 2014.
65. World Health Organization, *World Health Statistics*. 2010.
66. World Health Organization and UNICEF, *Improving newborn survival in India*. 2010.
67. Flenady, V., *Antibiotics for prelabour rupture of membranes at or near term.* Cochrane Database of Systematic Reviews, 2012(3).
68. Hopkins, L., *Antibiotic regimens for management of intraamniotic infection.* Cochrane Database of Systematic Reviews, 2013(2).
69. Westhoff, G., M. Cotter Amanda, and E. Tolosa Jorge (2013) *Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD001808.pub2.

70. Hodnett, E.D., *Continuous support for women during childbirth.* Cochrane Database of Systematic Reviews, 2013(7).
71. Casey, B.M., D.D. McIntire, and K.J. Leveno, *The Continuing Value of the Apgar Score for the Assessment of Newborn Infants.* New England Journal of Medicine, 2001. **344**(7): p. 467-471.
72. Seward, N., et al., *Association between Clean Delivery Kit Use, Clean Delivery Practices, and Neonatal Survival: Pooled Analysis of Data from Three Sites in South Asia.* PLoS Med, 2012. **9**(2): p. e1001180.
73. Moore, E.R., *Early skin-to-skin contact for mothers and their healthy newborn infants.* Cochrane Database of Systematic Reviews, 2012(5).
74. Conde-Agudelo, A., *Kangaroo mother care to reduce morbidity and mortality in low birthweight infants.* Cochrane Database of Systematic Reviews, 2014(4).
75. International Institute for Population Sciences, *District Level Household and Facility Survey 3*, Ministry of Health and Family Welfare Government of India, Editor. 2008: Mumbai.
76. International Institute for Population Sciences, *India Facility Survey (Under Reproductive and Child Health Project) Phase II Report*, Ministry of Health and Family Welfare, Editor. 2005: India.
77. Montgomery, A.L., et al., *Maternal Mortality in India: Causes and Healthcare Service Use Based on a Nationally Representative Survey.* PLoS ONE, 2014. **9**(1): p. e83331.
78. Million Death Study Collaborators, *Causes of neonatal and child mortality in India: a nationally representative mortality survey.* The Lancet, 2010. **376**(9755): p. 1853-1860.
79. Souza, J.P., et al., *The WHO Maternal Near-Miss Approach and the Maternal Severity Index Model (MSI): Tools for Assessing the Management of Severe Maternal Morbidity.* PLoS ONE, 2012. **7**(8): p. e44129.
80. Firoz, T., et al., *Measuring maternal health: focus on maternal morbidity.* Bulletin of the World Health Organization, 2013. **91**(10): p. 794-796.
81. Say, L., R.C. Pattinson, and A.M. Gülmezoglu, *WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity (near miss).* Reproductive Health, 2004. **1**(1): p. 3.
82. Prual, A., et al., *Severe maternal morbidity from direct obstetric causes in West Africa: incidence and case fatality rates.* Bull World Health Organ., 2000. **78**(5): p. 593-602.
83. United Nations, *UNData.* 2014.
84. Jabir, M., et al., *Maternal near miss and quality of maternal health care in Baghdad, Iraq.* BMC Pregnancy and Childbirth, 2013. **13**(1): p. 11.
85. Purandare, C., et al., *Maternal near-miss reviews: lessons from a pilot programme in India.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. **121**: p. 105-111.
86. Ganatra, B., K. Coyaji, and V. Rao, *Too far, too little, too late: a community-based case-control study of maternal mortality in rural west Maharashtra, India.* Bulletin of the World Health Organization, 1998. **76**(6): p. 591.
87. Padmanaban, P., P.S. Raman, and D.V. Mavalankar, *Innovations and challenges in reducing maternal mortality in Tamil Nadu, India.* Journal of health, population, and nutrition, 2009. **27**(2): p. 202.
88. George, A., *Persistence of High Maternal Mortality in Koppal District, Karnataka, India: Observed Service Delivery Constraints.* Reproductive Health Matters, 2007. **15**(30): p. 91-102.
89. Ministry of Health and Social Welfare - Government of India, *Indian Public Health Standards*. 2012, National Health Mission.
90. Ministry of Health and Social Welfare - Government of India, *Maternal and Newborn Health Toolkit*, Maternal Health Division, Editor. 2013.
91. Mathai, M., A.M. Gülmezoglu, and S. Hill, *Saving women's lives: Evidence-based recommendations for the prevention of postpartum haemorrhage.* Bulletin of the World Health Organization, 2007. **85**(4): p. 322-323.

92. World Health Organization, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*. 2012.
93. Duley, L., *The Global Impact of Pre-eclampsia and Eclampsia.* Seminars in Perinatology, 2009. **33**(3): p. 130-137.
94. Seal, S.L., et al., *Does route of delivery affect maternal and perinatal outcome in women with eclampsia? A randomized controlled pilot study.* American Journal of Obstetrics and Gynecology, 2012. **206**(6): p. 484.e1-484.e7.
95. Churchill, D., et al. (2013) *Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD003106.pub2.
96. Wall, S.N., et al., *Reducing Intrapartum-Related Neonatal Deaths in Low- and Middle-Income Countries—What Works?* Seminars in Perinatology, 2010. **34**(6): p. 395-407.
97. Mishra, U. and M. Ramanathan, *Delivery-related complications and determinants of caesarean section rates in India.* Health Policy and Planning, 2002. **17**(1): p. 90-98.
98. Souza, J., et al., *Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health.* BMC Medicine, 2010. **8**(1): p. 71.
99. Sreevidya, S. and B.W.C. Sathiyasekaran, *High caesarean rates in Madras (India): a population-based cross sectional study.* BJOG: An International Journal of Obstetrics & Gynaecology, 2003. **110**(2): p. 106-111.
100. Raman, P.S., et al., *Impact of a public–private performance-based financing partnership on the proportion of caesarean section deliveries: a cross-sectional study.* The Lancet, 2013. **381**: p. S121.
101. Yakoob, M.Y., et al., *The effect of providing skilled birth attendance and emergency obstetric care in preventing stillbirths.* BMC Public Health, 2011. **11**(Suppl 3): p. S7.
102. Lee, A., et al., *Care during labor and birth for the prevention of intrapartum-related neonatal deaths: a systematic review and Delphi estimation of mortality effect.* BMC Public Health, 2011. **11**(Suppl 3): p. S10.
103. Backes, C.H., et al., *Maternal Preeclampsia and Neonatal Outcomes.* Journal of Pregnancy, 2011. **2011**.
104. The Magpie Trial Collaborative Group, *Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial.* The Lancet, 2002. **359**(9321): p. 1877-1890.
105. Duley, L., *Magnesium sulphate and other anticonvulsants for women with pre-eclampsia.* Cochrane Database of Systematic Reviews, 2010(11).
106. Goldenberg, R.L. and C. Thompson, *The infectious origins of stillbirth.* American Journal of Obstetrics and Gynecology, 2003. **189**(3): p. 861-873.
107. Chan, G.J., et al., *Risk of Early-Onset Neonatal Infection with Maternal Infection or Colonization: A Global Systematic Review and Meta-Analysis.* PLoS Med, 2013. **10**(8): p. e1001502.
108. Lieberman, E., et al., *Intrapartum Maternal Fever and Neonatal Outcome.* Pediatrics, 2000. **105**(1): p. 8-13.
109. Alexander, J.M., D.M. McIntire, and K.J. Leveno, *Chorioamnionitis and the prognosis for term infants.* Obstetrics & Gynecology, 1999. **94**(2): p. 274-278.
110. Lawn, J.E., S. Cousens, and J. Zupan, *4 million neonatal deaths: When? Where? Why?* The Lancet, 2005. **365**(9462): p. 891-900.
111. Sheiner, E., et al., *Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study.* Journal of Maternal-Fetal and Neonatal Medicine, 2005. **18**(3): p. 149-154.
112. Rhee, V., et al., *Maternal and birth attendant hand washing and neonatal mortality in southern Nepal.* Archives of Pediatrics & Adolescent Medicine, 2008. **162**(7): p. 603-608.

Appendix for Chapter 3

3.1 Elements of the WHO Safe Childbirth Checklist

Checklist Item		Qualifying Caption
On admission of the mother to the birth facility		
Does mother need referral?	□ Yes, organized	According to facility's criteria
	□ No	
Partograph started?	□ Yes	Start plotting when cervix ≥ 4 cm, then cervix should dilate ≥ 1 cm/hr. Every 30 min: plot heart rate, contractions, fetal heart rate. Every 2 hours: plot temperature. Every 4 hours: plot blood pressure
	□ No, will start when ≥ 4 cm	
Does mother need to start antibiotics?	□ Yes, given	Give if temperature ≥ 38°C, foul-smelling vaginal discharge, rupture of membranes >18 hours, OR labor >24 hours
	□ No	
Does mother need to start magnesium sulfate?	□ Yes, given	Give if (1) diastolic blood pressure ≥110 mmHg and 3+ proteinuria, OR (2) diastolic blood pressure ≥90 mmHg, 2+ proteinuria, and any: severe headache, visual disturbance, OR epigastric pain
	□ No	
Does mother need to start anti-retroviral medicine?	□ Yes, given	Give if mother is HIV+ and in labor
	□ No	
□ Supplies available to clean hands and wear gloves for each vaginal exam		
□ Birth companion encouraged to be present at birth		
□ Confirm that mother/companion will call for help during labor if mother has a danger sign		Call for help if bleeding, severe abdominal pain, severe headache, visual disturbance, urge to push, OR difficulty emptying bladder
Just before pushing (or before Cesarean)		
Does mother need to start antibiotics?	□ Yes, given	Give if temperature ≥ 38°C, foul-smelling vaginal discharge, rupture of membranes >18 hours now, labor >24 hours now, OR cesarean section
	□ No	
Does mother need to start magnesium sulfate?	□ Yes, given	Give if (1) diastolic blood pressure ≥110 mmHg and 3+ proteinuria, OR (2) diastolic blood pressure ≥90 mmHg, 2+ proteinuria, and any: severe headache, visual disturbance, OR epigastric pain
	□ No	
Are essential supplies at bedside for mother?	□ Gloves	Prepare to care for mother immediately after birth: (1) Exclude 2nd baby, (2) Give oxytocin within 1 minute, (3) Controlled cord traction to deliver placenta, (4) Massage uterus after placenta is delivered
	□ Soap and clean water	

	□ Oxytocin 10 IU in syringe	
Are essential supplies at bedside for baby?	□ Clean towel	Prepare to care for baby immediately after birth: (1) Dry baby and keep warm, (2) If not breathing: stimulate and clear airway, (3) If still not breathing: cut cord, ventilate with bag-and-mask, (4) shout for help
	□ Sterile blade to cut cord	
	□ Suction device	
	□ Bag-and-mask	
□ Assistant identified and informed to be ready to help at birth if needed?		
Soon after birth (within 1 hour)		
Is mother bleeding too much?	□ Yes, shout for help	If bleeding ≥500 ml, or if ≥250 ml and severely anemic: massage uterus, consider additional uterotonic, start intravenous line, treat cause
	□ No	
Does mother need to start antibiotics?	□ Yes, given	Give if placenta manually removed, or if temperature ≥38°C and any: foul-smelling vaginal discharge. lower abdominal tenderness, rupture of membranes >18 hours at time of delivery, OR labor >24 hours at time of delivery
	□ No	
Does mother need to start magnesium sulfate?	□ Yes, given	Give if (1) diastolic blood pressure ≥110 mmHg and 3+ proteinuria, OR (2) diastolic blood pressure ≥90 mmHg, 2+ proteinuria, and any: severe headache, visual disturbance, OR epigastric pain
	□ No	
Does baby need referral?	□ Yes, organized	According to facility's criteria
	□ No	
Does baby need to start antibiotics?	□ Yes, given	Give if antibiotics were given to mother, or if baby has any: breathing too fast (>60 breaths/min) or too slow (<30 breaths/min), chest in-drawing, grunting, convulsions, no movement on stimulation, OR too cold (temperature <35°C and not rising after warming) or too hot (temperature >38°C)
	□ No	
□ Does baby need special care and monitoring?		Recommended if more than 1 month early, birth weight <2500 grams, needs antibiotics, OR required resuscitation
Does baby need to start an anti-retroviral medicine?	□ Yes, given	Give anti-retroviral medicine if mother is HIV+
	□ No	
□ Started breastfeeding and skin-to-skin contact? (if mother and baby are well)		
□ Confirm that mother/companion will call for help if:		Mother has bleeding, severe abdominal pain, severe headache, visual disturbance, breathing difficulty, fever/chills, OR difficulty emptying bladder
		Baby has fast or difficulty breathing, fever, unusually

		cold, stops feeding well, less activity than normal, OR whole body becomes yellow
Before discharge		
Is mother's bleeding controlled?	□ Yes	
	□ No, treat and delay discharge	
Does mother need to start antibiotics?	□ Yes, given	Give if temperature $\geq 38^{o}C$ and any: chills, foul-smelling vaginal discharge, OR lower abdominal tenderness
	□ No	
Does baby need to start antibiotics?	□ Yes, give antibiotics, delay discharge, and give special care or refer	Give if breathing too fast (>60 breaths/min) or too slow (<30 breaths/min), chest in-drawing, grunting, convulsions, no movement on stimulation, too cold (temperature $<35^{o}C$ and not rising after warming) or too hot (temperature $>38^{o}C$), stopped breastfeeding well, OR umbilical redness extending to skin or draining pus
	□ No	
Is baby feeding well?	□ Yes	
	□ No, help and delay discharge	
□ Family planning options discussed and offered to mother		
□ Confirm that mother/companion will call for help after discharge if:		Mother has bleeding, severe abdominal pain, severe headache, visual disturbance, breathing difficulty, fever/chills, OR difficulty emptying bladder
		Baby has fast or difficulty breathing, fever, unusually cold, stops feeding well, less activity than normal, OR whole body becomes yellow
□ Follow-up arranged for mother and baby		

(from [147])

3.2 Maternal tree, Complications and progression to mortality endpoints: Assumptions and values

3.2.1 Overall assumptions

- We assumed that women entering the model would not already be experiencing complications. In reality, the population of laboring women at a given health facility may experience greater probability and/or severity of complications—since complications during labor may be the impetus for a woman to arrive at a health facility (in environments where home birth is relatively common, such as India). But the model excludes these women, and assumes that the facility-based births were essentially planned in advance. This assumption was made because the first SCC item screens women for obstetric review, thereby removing such already-complicated cases from the universe of women who "receive" the remainder of the checklist intervention.
- There is no underlying heterogeneity in complication risk. Although there is evidence that a woman's demographic characteristics (e.g., age, parity) as well as clinical factors (e.g., anemia, HIV status) may affect the incidence and/or severity of complications, a simplifying assumption was made to not include these here.
- As a simplifying assumption, women in the model can only experience one complication per birth event.
- After a complication arises in the model, the woman is not referred elsewhere. Evidence from India has repeatedly shown that the referral system is not well-functioning, and some data indicate that women who are referred generally experience the worst outcomes [144, 204-206]. For this reason, it is assumed that all women begin and end their deliveries at the same type of health facility.
- Although many women in India deliver at home or at private health facilities, this analysis only looks at public health facilities. Additionally, it focuses on District Hospitals, Community Health Centers and Primary Health Centers. These are the types of facilities for which the DLHS collected infrastructure and supplies data—and understanding these characteristics is necessary for using the model to explore the relationship between health system constraints and SCC implementation. The DLHS also collected information from Sub-Centres, but since very few women deliver at SCs (only 2.4% of all those who delivered at public health facilities, according to the data reported to DLHS from the household level), SCs were excluded from the analysis.
- There are guidelines for services to be provided at all levels of the health system, as per Indian government regulations. Emergency obstetric care (EmOC) classification is based on "signal functions": facilities classified as offering basic emergency obstetric care (bEmOC) can provide parenteral antibiotics, uterotonic drugs, parenteral anticonvulsants, manual placental delivery, removal of retained products, assisted vaginal delivery (vacuum extraction and instrumental), and basic neonatal resuscitation; and comprehensive emergency obstetric care facilities (cEmOC) offer these plus caesarean delivery and blood transfusions. The correlation between facility type and EmOC status is shown below.

Table 3.2-1: Health facility types and emergency obstetric care status

	Referral level [207]	EmOC status [208]
District hospital (DH)	Secondary	Comprehensive (cEmOC)
Community health centre (CHC)	Secondary	Mix of comprehensive & basic
Primary health centre (PHC)	Primary	Some basic (bEmOC)

But actual signal function availability may not be universal at Indian health facilities classified as EmOC capable. A study found that only 43% of cEmOC facilities offered all 9 signal functions for that level, and only 15% of bEmOC facilities offered the requisite 7 signal functions [146]. Although these authors did not stratify by urban versus rural status, given the results of this analysis from Part I, we assumed that urban CHCs would be more likely to offer a full set of services than rural counterparts. So for the purposes of this model, it is assumed that among DHs, 60% bEmOC and/or cEmOC care; 15% of urban CHC facilities can offer cEmOC services and an additional 50% provide bEmOC care only; 5% of rural CHCs offer cEmOC care and 25% offer bEmOC care; and 10% of PHCs can provide bEmOC care.

- We assumed that treatment of complications—i.e, provision of emergency obstetric care—would nearly completely eliminate the risk of death. There are no published quantifications of the impact of EmOC services on reducing maternal mortality, but is it widely acknowledged as extremely efficacious, and maternal death is very rare in environments where women have access to high-quality emergency obstetric care. So we assumed a 95% reduction in case fatality rates (themselves conditional on each complication) for women who receive EmOC services.
- If women did not experience one of these 4 complications (postpartum hemorrhage, obstructed labor, sepsis or pre-eclampsia), it was assumed they would have a 99.99% chance of survival.

The probabilities included in this tree are:

- Pr(complication): the incidence of each complication
- Pr(severity|complication): the likelihood that each complication is severe
- Pr(management|complication, severity): the probability of receiving emergency obstetric care, for each complication given its level of severity
- Pr(survival|complication, severity, management): case fatality rate for each complication, severe and non-severe, and whether managed or not

3.2.2 Overview

Table 3.2-2 shows all input parameters used in the maternal tree.

Table 3.2-2: Input parameter summary, maternal tree

	Postpartum hemorrhage	**Sepsis**	**Obstructed labor**	**Hypertensive disorders**	**No/other maternal complication**
Complication					
DH	6.5%	3.5%	5.5%	5%	--
CHC (Urban & rural)	9%				
PHC	13%				
Severity	15%	--	--	2.3%	--
Management					
DH	60% (severe and non-severe)	60%	60%	60%	--
CHC -Urban	15% (severe), 50% (non-severe)	50%	50%	50%	
CHC - Rural	5% (severe), 25% (non-severe)	25%	25%	25%	
PHC	0% (severe), 10% (non-severe)	10%	10%	10%	
Fatality					
Unmanaged	1% (non-severe), 3% (severe)	1.3%	0.7%	0.4% (non-severe), 3.5% (severe)	0.01%
Managed	0.05% (non-severe), 1.5% (severe)	0.065%	0.035%	0% (non-severe), 2% (severe)	

3.2.3 Postpartum hemorrhage

Postpartum hemorrhage (PPH, i.e., the vaginal loss of more than 500 mL of blood during the first 24 hours postpartum, or, for severe postpartum hemorrhage, the loss of more than 1000 mL of blood in this same period) is a leading direct cause of maternal death worldwide, and the foremost direct cause of maternal death in Asia [49]. PPH is usually caused by a failure of the uterus to contract sufficiently after birth, so-called atonic PPH, which can be prevented through management of labor: most effectively via active management (which includes aspects of prophylactic uterotonics postpartum, controlled cord

traction and early clamping and cutting—versus expectant management, which entails attended and assisted placental delivery) [209].

Incidence: The incidence of PPH has been difficult to calculate: estimates are confounded by this association with delivery care, and objective measurement of blood loss is difficult and rare. There is thus little consensus in the literature about PPH burden. The GBD 2000 estimates used assumptions about rates of PPH that varied by birth setting, based on clinical trial results: among women with active management of labor, 2.85% were estimated to experience severe PPH, and this was estimated to double (to 5.7%) for women who receive expectant management, and double again (to 11.4%) without skilled birth attendance [53, 64].

Regional estimates of PPH have estimated that 8.5% of women who give birth in Asia will experience PPH (this review include two studies from India, with incidence of 6.4% and 12%) and an additional 1.9% will have severe PPH [151]; another review estimated the south-central Asia regional incidence at 4.35% for regular PPH and 0.68% for severe PPH [152]. A global analysis that did not differentiate between birth location nor region estimated an overall PPH incidence of 10.5% [64].

- For the baseline model, we used the same assumptions as the GBD 2000 study, so this could vary with delivery location (and could exclude women with home births). We assumed that women at hospitals always receive expectant management, and sometimes active management—so used 4% (the midpoint of the above estimates associated with expectant and active management) as the point estimate for PPH incidence. At CHCs, we assumed all women receive expectant management so assigned an incidence of 5.7%; at PHCs, we used an incidence of 8%, assuming that approximately half of women receive expectant management and others receive basic birth attendance.
- During calibration, these values were adjusted upward, to 6.5% at DH, 9% at CHCs, and 13% at PHCs.

Severity: Among cases of PPH, some fraction of these women experience severe PPH (i.e., more than 1000 mL of blood loss). A large systematic review found that prevalence of PPH was 6.09%, and 1.86% for severe PPH, or 10.55% and 3.04% when blood loss was objectively measured [152]: in either case, approximately 20% of PPH cases were classified as severe. The above-mentioned regional PPH estimates indicates conditional probabilities for severe PPH of 18% [151] and 14% [152].

- The conditional probability of severe PPH in this model was assumed to be independent of delivery location; we assumed a starting point estimate that 15% of all PPH cases are severe.

Management: Management of PPH cases includes medical treatment—first uterotonics, followed by prostaglandin or other drugs—then surgical interventions and blood transfusions if needed [210]. These are associated with signal functions for bEmOC and cEmOC facilities, respectively, so were classified according to the overall model assumptions (as outlined above).

Fatality: The Disease Control Priorities Project used literature reviews and expert reviews to determine an estimated case fatality rate (CFR) for PPH of 1% [45]; this is a global average, but specific local estimates are largely lacking in the literature. Severe PPH is more fatal, and has been estimated at approximately 3% [60].

- The CFR for PPH was assumed to be conditional on severity and on lack of management (but not delivery location). For un-managed PPH and severe PPH, the model used an estimated CFR of 1 and 3%, respectively. It was assumed that management would almost completely reduce the risk of death (by 95%), so the CFR for managed cases of PPH and severe PPH were 0.05 and 0.15%, respectively.

3.2.4 Sepsis

Following PPH, sepsis is the next-leading direct cause of maternal mortality in Asia, estimated to be responsible for 11.6% of deaths [49]. A number of infections are classified within the maternal sepsis definition, which makes classification difficult, and may limit cross-study comparability (adding to the challenge of estimating burden attributable to sepsis).

Incidence: The GBD 2000 estimates included a likelihood of sepsis within health facilities of 2.5% [59]. A global analysis estimated that the overall incidence of sepsis is 4.4% (this includes births without skilled attendance) [64]. Evidence generally points to a lower incidence of sepsis in health facilities than at home (even in resource-poor settings), since unhygienic practices during childbirth can increase the likelihood that a woman acquires an infection [59].

- For the initial base model, we assumed this same value for the point estimate of incidence (2.5%); during calibration, this was increased to 3.5%.

Management: Sepsis cases can be managed through provision of antibiotics, which is a signal function of bEmOC and cEmOC facilities. We use the same standard assumptions as for management of other complications; all bEmOC and cEmOC facilities should be capable of providing parenteral antibiotics, but not all facilities classified as such actually provide all signal functions.

Fatality: The GBD 2000 estimates use a CFR for sepsis of 1.3%, with a plausible range of 0.9-1.7% [45, 64].

- We assume this same value for the CFR point estimate (1.3%). For managed cases of sepsis, it was assumed that there was a reduction in fatality (0.065%).

3.2.5 Obstructed labor

Obstructed labor causes 9.4% of maternal deaths in Asia [49]; it is generally a consequence of a physiological mismatch between the fetal head (e.g., due to gestational diabetes) and the mother's birth canal (e.g., due to malnutrition and/or young maternal age), or malposition of the fetus. Without clinical intervention, such as assisted delivery (instrumental or vacuum extraction) or caesarean section, risk of maternal death arises due to infection, uterine rupture and hemorrhage [61]. There are also serious morbidities that can arise following obstructed labor such as obstetric fistula, although these are not represented in the model.

Incidence: It has been challenging to develop robust estimates of OL burden, due to inconsistencies in recognition and reporting. The GBD studies have estimated incidence between 3 and 6%, using the higher

value in countries with more frequent adolescent-age childbearing and higher rates of malnutrition [61]. A global analysis estimated that the overall incidence of OL is 4.6% [64].

- At baseline, we assumed the higher incidence of 6% due to prevalence of early childbearing and maternal malnutrition in India. During calibration exercises, this was adjusted downward, to 5.5%.

Management: When OL arises, it requires basic or comprehensive emergency obstetric care, available in bEmOC or cEmOC facilities. We use the same assumptions here as for management of other complications

Fatality: The GBD 2000 estimates use a CFR for OL of 0.7% [45].

- We assume this same value for the CFR point estimate (0.7%) at all facility types for unmanaged OL. We assume that management of OL is effective at eliminating 95% of the risk of death, so estimated a CFR for managed OL of 0.035%.

3.2.6 Hypertensive disorders

Hypertensive disorders of pregnancy include several conditions—the most dangerous of which are pre-eclampsia and eclampsia. Pre-eclampsia can arise during pregnancy and cause dangerously high blood pressure as well as problems with organ failure and clotting abnormalities, and the fetus can be affected via the placenta; one possible consequence is eclampsia, which is characterized by convulsions and can be fatal [211]. Pre-eclampsia can also be fatal, and constitutes a larger fraction of mortality burden (compared to eclampsia) in settings with lower (versus higher) maternal mortality rates [211]. It is estimated that hypertensive disorders cause approximately 9.1% of maternal deaths in Asia [49].

Incidence and Severity: As with other model parameters, burden of hypertensive disorders is complicated due to lack of uniform definitions and difficulties in measurement. GBD 2000 used an unpublished literature review, which sought uniform definitions and high-quality measurement; it estimated that pre-eclampsia occurs in 2.8% of births in the SEARO-D region (of which India is part) and eclampsia results in 2.3% of pre-eclampsia cases [65]. Likewise, a global analysis estimated that the overall incidence of pre-eclampsia/eclampsia is 3.2% [64]. A recent global analysis of hospital-based births found that 2.16% of women experienced pre-eclampsia and 0.28% of women experienced eclampsia, and the values for India were 1.97 and 0.43% for pre-eclampsia and eclapmsia respectively [150].

- At baseline, we assumed that the incidence of pre-eclampsia would be approximately 3%, regardless of birth location since it arises pre-labor so it likely unassociated with birth location. This was adjusted during calibration exercises, to 5%.
- Severity was modeled as a conditional probability, using the GBD estimate that 2.3% of pre-eclampsia cases progress to eclampsia, regardless of birth location.

Management: There is little evidence about mechanisms to effectively address risk due to pre-eclampsia alone, beyond provision of hypertensive drugs to reduce blood pressure during pregnancy. Eclampsia can be managed by treating the seizures with magnesium sulfate—the same drug used as a preventative anticonvulsant to prevent progression of pre-eclampsia. The ability to provide magnesium sulfate for women with pre-eclampsia and eclampsia is a signal function of bEmOC and cEmOC facilities. Pre-

eclampsia and eclampsia were also traditionally managed with early delivery and/or caesarean section whenever possible, but recent evidence has questioned whether practice improves outcomes for women [212, 213] so it was not considered a necessary step for management here.

- We assume no management of pre-eclampsia itself.
- For management of eclampsia, we use the same assumptions as for management of other complications: all bEmOC and cEmOC facilities should be capable of managing eclampsia.

Fatality: The GBD 2000 estimates use a CFR for hypertensive disorders of 1.7% but does not distinguish between pre-eclampsia and eclampsia [45]; the only study from SEARO region included in this review estimated a hospital-based CFR of 3.3% in Thailand [65]. A recent global analysis of women who gave birth in health facilities and experienced hypertensive disorders found that 0.43% of those with pre-eclampsia died, and 3.66% of women with eclampsia died [150].

- We use these type-specific rates for unmanaged cases of pre-eclampsia and eclampsia, assigning them CFR values of 0.4 and 3.5% respectively.
- Treatment with anticonvulsants has been shown to reduce risk of progression from pre-eclampsia to eclampsia, with a non-significant impact on mortality [72]; we assumed that managed cases of eclampsia would decrease the CFR.

3.3 Neonatal tree, Complications and progression to mortality endpoints: Assumptions and values

3.3.1 Overall assumptions

- These numbers have substantial uncertainty. Adverse neonatal events have only recently been quantified, particularly for stillbirths and differentiating causes of neonatal mortality (plus the terminology to do so) [8, 214]. Additionally, there are challenges to robust estimation, including inconsistent definitions and terminology, poor availability of cause-specific information, and lack of robust data on rates and volumes of neonatal deaths [163].
- Only intrapartum stillbirths are included here. Since the SCC begins at the childbirth event (i.e., no antenatal component), earlier fetal death is assumed to be unrelated to maternal and neonatal complications that arise during and after labor and thus targeted by the SCC.
- For the purposes of simplifying this model, it is assumed that assisted births *only* occur subsequent to obstructed labor. This is likely a conservative estimate, since rates of elective caesarean section in India are increasing [215], and outcomes (perinatal mortality, fetal death) are significantly worse for babies without medical indications who are delivered following a caesarean section versus vaginal birth [216]. But we made this assumption for simplifying purposes; and even without it, the model would pick up very caesarean sections for babies without medical indications, due to its exclusive focus on the public sector: these fast-increasing rates of caesarean section are concentrated in private facilities [215, 217, 218], which are not represented in this model. A recent study of delivery types across Asia found that only 0.2% of births by Caesarean section in India did not include intrapartum indications (versus the 13.9% with indications) [156].
- We assume that cases of cases of intrapartum stillbirth can sometimes be managed at health facilities. Expert opinion, cited in a systematic review (and used as an input for the Lives Saved [LiST] model), is that bEmOC facilities can reduce intrapartum stillbirths by 45%, and cEmOC facilities can achieve a 75% reduction [219]. These values were used in the baseline model; during calibration exercises, they were adjusted such that DH could reduce stillbirths by 75%, urban CHCs by 65%, rural CHCs by 50%, and PHCs by 30%.

Likewise, we use assumptions about care to reduce neonatal mortality: sources have estimated that bEmOC care is associated with a reduction of 40%, and cEmOC care by 85% [161, 220]. These values were used in the baseline model; during calibration, they were adjusted, and the resulting values were a 60% reduction at DHs, a 50% reduction at urban CHCs, a 40% reduction at rural CHCs, and a 20% reduction at PHCs.

We also make a number of simplifying assumptions. Namely:

- Each live birth resulting from a birth with a maternal complication only faces one possible neonatal complication, i.e. the predominant complication associated with each maternal complication. If the baby does not experience this complication in the model, it then faces the same likelihood of all other complications as babies born to mothers without complications.
- There may be maternal risk factors (e.g., age, anemia status) that put the baby at increased risk of complications and/or death—but as a simplifying assumption, those are not modeled here.

- There are ways in which risk factors may combine (e.g., low birth weight babies may have increased susceptibility to infection)—but as a simplifying assumption, those are not modeled here.
- If a woman experiences a complication and this is managed in the model, the neonate may face a different likelihood of complications (i.e., the maternal management strategy may have protective or harmful effects on the fetus) but only direct sequlae are modeled here.

The probabilities included in this tree are:

- Pr(stillbirth): likelihood of intrapartum fetal death
    - Some of these are Pr(stillbirth| maternal complication, maternal complication severity/management)
- Pr(complication|live birth): incidence of each neonatal complication
    - Some of these are Pr(complication|live birth, maternal complication, maternal complication severity/management)
- Pr(survival|complication, live birth): case fatality rate for each neonatal complication
    - Some of these are Pr(survival|complication, live birth, maternal complication, maternal complication severity/management)

3.3.2

3.3.3 Overview

A summary table of all values used in the model is displayed in Table 3.3-1.

Table 3.3-1: Input parameter values for neonatal tree

In presence of maternal complication:					
	Postpartum hemorrhage	**Sepsis**	**Obstructed labor**	**Hypertensive disorders**	**No/other maternal complication**
Stillbirth	*(assume same as "no/other" complication category)*	5%*	30%* (managed), 30% (not managed)	6%* (non-severe), 12%* (severe)	1%*
Neonatal complication		2.5% (managed), 5% (not managed)	--	18%	*(varied by neonatal complication)*
Fatality		27%* (managed), 30%* (not managed)	15%* (managed), 30%* (not managed)	10%* (non-severe), 20%* (severe)	

In absence of maternal complication:						
	Prematurity, low birth weight	**Neonatal infection**	**Birth asphyxia**	**Neonatal tetanus**	**Other**	**None**
Neonatal complication	20%	2%	2%*	1.5%*	7%	--
Fatality	10%*	35%*	25%*	50%*	10%*	0.01%

* Indicates that this parameter varied by facility type (DH/CHC urban or rural/PHC)

3.3.4 Pre-eclampsia/Eclampsia

Stillbirth: Pregnancies resulting in pre-eclampsia and eclampsia see an elevated risk of ending in stillbirth. One study estimated the stillbirth rate for women with eclampsia to be approximately 21 per 1000, and approximately 9 per 1000 for non-severe pre-eclampsia [221]. A recent cross-country study of facility-based births estimated that 6.36% of births to women with pre-eclampsia ended in stillbirth, as did 15.32% of births to women with eclampsia [150]. Thus the likelihood of stillbirth is approximately double for babies born to women with eclampsia versus non-severe pre-eclampsia. (These analyses did not distinguish between antepartum and intrapartum stillbirth, so the prevalence is assumed to be equivalent for these groups.)

A mother's treatment with magnesium sulfate does not appear to increase risk of stillbirth: a magnesium sulfate trial in South Africa did not stratify by severity, but found equivalent stillbirth rates for women with pre-eclampsia/eclampsia in both the placebo and intervention trial arms, of approximately 8-8.5% [222]. A recent review also found no significantly increased risk of stillbirth among women who received magnesium sulfate [161].

- Assume no different stillbirth prevalence for women treated with magnesium sulfate or not.

- Assume attenuation in intrapartum stillbirth rate by facility type, as described in assumptions section.

Neonatal complication: The main complication to arise from pre-eclampsia is low birth weight, largely due to intrauterine growth restriction [45]. Pre-eclampsia is in fact the leading cause of intrauterine growth restriction [221]. Overall, up to 18% of babies born to women with pre-eclampsia may experience intrauterine growth restriction [158].

The same assumption was made about prevalence of low birth weight among babies born to women with eclampsia. Since eclampsia arises during labor, it would have no differential impact on intrauterine growth. Accordingly, an analysis of predictors of neonatal outcomes found no significant correlation for any neonatal outcome and severity of maternal pre-eclampsia/eclampsia [158]. The Magpie trial in South Africa found no significant difference in mortality or morbidity outcomes for babies whose received magnesium sulfate, when compared to those who did not [222]; a systematic review found no significant difference in perinatal or neonatal mortality among babies born to women with pre-eclampsia/eclampsia with or without magnesium sulfate [161].

- Assume no different complication prevalence for women treated with magnesium sulfate or not.
- Assume no relationship between facility type and complication prevalence.

Death: The CFR for low birth weight babies ranges between 2 and 80%, depending on the sequelae [45]. A facility-based study found that 3.04% of babies born to women with pre-eclampsia and 8.61% of babies born to women with eclampsia experienced early neonatal death [150]. In a Cochrane review that pooled stillbirths and neonatal deaths, 19.7% of babies born to women with eclampsia (regardless of maternal treatment status) died, versus approximately 10% of babies born to women with non-severe pre-eclampsia [66]. This indicates that the approximate doubling of mortality exists throughout the intrapartum period, affecting both stillbirth rates (as discussed above) and neonatal deaths.

As discussed above, likelihood of neonatal death does not appear to be associated with the use of magnesium sulfate to manage maternal eclampsia.

- Assume no different mortality for babies of women treated with magnesium sulfate.
- Assume attenuation in mortality by facility type, as described in assumptions section.

3.3.5 Sepsis

Stillbirth: Maternal infection may result in fetal death indirectly (e.g., distress due to elevated body temperature or reduced respiration, or via placental damage) or directly (through transmission of pathogens across the placenta). A fetus is at risk throughout the gestational period, and may die as a direct consequence or may develop congenital abnormalities that result in a stillbirth (which itself may happen soon or may take time to reach a critical state). The etiology of stillbirth resulting from maternal infection is thus very complex and can be difficult to discern. [223] But these ongoing risks due to infection throughout the gestational period are not modeled here; rather, the model focuses on maternal sepsis with acute symptoms during the intrapartum period.

A bacterial infection of the amniotic fluid may cause maternal symptoms, including fever and/or rupture of membranes. In many cases, the resulting fetal infection will cause preterm labor (and women in preterm labor are not modeled here, since the model only analyzes normal deliveries)—though it can also result in stillbirth. It has been estimated that approximately 20-25% of stillbirths are caused by bacterial amniotic infection [223]. A recent multicountry facility-based study found that, among births to women with sepsis and systemic infections, 5.3% resulted in intrapartum stillbirths [153].

- Assume no difference in stillbirth rate for women who do and do not receive intrapartum antibiotics.
- Assume attenuation in intrapartum stillbirth rate by facility type, as described in assumptions above.

Neonatal complication: During the birth process, a neonate may inhale infected amniotic fluid and consequently experience respiratory distress and/or infection. (Infants may also be exposed to pathogens during the birth process that are not transmitted from the mother; these are included in the "Other" arm below since they are not associated with maternal sepsis.) It is challenging to diagnose early-onset neonatal sepsis in resource-poor settings since it requires a rapid blood culture, which may not be available and is itself based off clinical judgment; and definitions of sepsis vary, with different pathogens under investigation for different studies. The modeled likelihood of early-onset neonatal sepsis resulting from maternal infection is therefore largely based on assumptions.

A recent meta analysis found that babies born to women with infections were more likely to experience infection (compared to newborns of uninfected women), by approximately 6-9 times greater odds [224]. Another study found that infants of mothers whose fevers were clinically high (>101°F) were 3.8 times as likely to require resuscitation immediately after delivery, and this was robust to controlling for use of epidural drugs (which can elevate maternal fever even in the absence of an infection) and other covariates; no increased need for resuscitation was found for mothers with fever between 100.5°F and 101°F [225]. Another study found that clinical chorioamnionitis in the mother increased the odds of early neonatal sepsis by 2.9 [226]. The recent Lancet series on neonatal survival estimated that intrapartum maternal fever (>38°C) increased the odds of neonatal mortality by approximately 10 [227]—but this was a population-based value, and in fact the use of antibiotics to manage maternal sepsis may reduce incidence of infection among neonates.

The association between maternal treatment for sepsis and neonatal complications is also unclear. A recent Cochrane review found that intrapartum antibiotics in cases of known maternal Group B streptococcal (GBS) infection were associated with significantly lower incidence of early-onset GBS infection in neonates (risk ratio 0.17 compared with no treatment); the prevalence of probable early neonatal GBS infection was between 5-8% among the placebo group versus 0-2% in the treatment group [157]. Other reviews have not found significantly improved outcomes for babies whose mothers were treated with antibiotics following premature rupture of membranes at or near term, nor in cases of intraamniotic infection—although the sample sizes for these reviews were small [185, 186].

- If risk of neonatal infection is assumed to be very low in the absence of maternal sepsis (1%); and the literature converges on a magnitude of increased risk for babies of maternal sepsis of between 3 and 10—assumed a point estimate of 5% prevalence of complications (neonatal infection) for babies born to women with sepsis.

- Assumed a halving of neonatal sepsis prevalence among babies born to mothers with maternal sepsis who received treatment.
- Assumed no difference in complication rate by facility type (beyond what is already absorbed in the relationship between facility type and likelihood of maternal treatment for sepsis).

Death: The case fatality rate for neonatal sepsis (whether resulting from intrauterine or intrapartum infection) is estimated to be between 30-40% [45]; a similar value was found in a multicenter study, where 30% of neonates with positive blood cultures then died [159].

It is possible to reduce the risk of death following infection: neonatal resuscitation has been estimated to reduce mortality by approximately 30% [160], and neonatal antibiotics for sepsis reduces mortality by a factor of 0.35 [161]—which are not very different from the literature cited in the assumptions section about ability of bEmOC and cEmOC to reduce neonatal death (neonatal resuscitation is a basic signal function, and bEmOC care is estimated to reduce neonatal death by 40%).

Evidence is mixed on how maternal antibiotics may affect neonatal mortality (and certainly some data also incorporate earlier stages of the model, i.e. changed incidence of complications and/or management). One review article found that babies born to women who have received antibiotics for premature rupture of membranes were significantly less likely to experience neonatal mortality (risk ratio of 0.88 (CI 0.8-0.97) [161]); the earlier-cited study that found a decreased risk of neonatal infection with GBS after maternal antibiotics also found no significant mortality effect from this treatment [157].

- Assumed very small reduction (10%) in mortality for babies with sepsis whose mothers were given antibiotics. This assumes a perfect capture of sepsis cases (no misclassifications).
- Assume attenuation in mortality by facility type, as described in assumptions section.

3.3.6 Postpartum hemorrhage

Although evidence suggests there may be an association between hemorrhage (and varying by severity of hemorrhage) and infant outcomes [228], there is an overall paucity of robust data to inform this model's parameters. So it was assumed that babies born to women who experienced PPH faced the same risks (of stillbirth, neonatal complications, and death) as those born to women without any maternal complications.

3.3.7 Obstructed labor

Stillbirth: The structural causes that underlie most cases of obstructed labor—cephalopelvic disproportion and fetus malpresentation—can cause fetal asphyxiation, and in many cases the fetus dies before delivery has been completed. In one study, only 46% of women with obstructed labor birthed live babies [154], suggesting that the stillbirth rate may be as high as half; a study from a hospital in India identified a stillbirth rate of 18.2% among women with obstructed labor [155]. A recent review article found that 30-45% of intrapartum stillbirths were attributable to abnormal labor [8].

- Assumed that, at all facilities, non-managed cases of obstructed labor saw an equivalent rate of intrapartum stillbirth.

- For managed cases of obstructed labor, assume attenuation in intrapartum stillbirth rate by facility type, as described in assumptions above.

Neonatal complications and mortality: Hospital-based assessments in India have indicated that approximately one-quarter of babies born to women with OL may experience neonatal death [155, 162]. Population-based studies have indicated that the odds ratio for all-cause neonatal/perinatal deaths, associated with maternal OL, is between 7 and 85 [163]; and the case fatality rate for birth asphyxia—one possible outcome for babies born to women with OL—has been estimated at 20-30%, depending on exact sequelae [45].

Whether a woman with OL receives care (i.e., caesarean section or instrumental delivery) likely affects survival outcomes for her neonate. If such treatment is received promptly, this may attenuate the consequences of birth asphyxia and trauma—but assisted birth may also present new risks for these newborns. In a study of outcomes by delivery type for women and children in Asia, the odds of early neonatal mortality was approximately 2-2.6 (compared to spontaneous vaginal births) among babies who received operative vaginal delivery or Caesarean section with indications [156]; but in this same study, babies with abnormal or breech presentation experienced lower odds of neonatal mortality when the mother was given a Caesarean section versus spontaneous delivery (OR 0.4-0.6) and no significant difference for operative vaginal delivery.

- It is assumed that one-third of live births to women with unmanaged obstructed labor experience complications that lead to death, and that this is associated with facility type, with a reduction as per assumptions outlined above.
- Management of obstructed labor may indeed be protective against neonatal mortality. Assume a halving of likelihood of complication/mortality among obstructed labor cases that were managed.

3.3.8 No maternal complication

Stillbirth:

Some stillbirths occur in the absence of major maternal complications. A recent review estimated that, in higher-mortality settings, approximately 65% of antepartum stillbirths and 20% of intrapartum stillbirths were not correlated with any identified maternal condition [8]. Using these figures, plus the estimated stillbirth rate for the South Asia region of 26.7 per 1000 births, where 56.6% of these occur intrapartum: 0.75% and 0.3% of births to women without complications would result in antepartum and intrapartum stillbirth, respectively—for a total of 1.05% of births resulting in stillbirth when the mother does not experience a complication as outlined above. This rate is similar to others in the literature; for example, an earlier-cited large multicountry facility-based study about pre-eclampsia and neonatal outcomes found that among women without pre-eclampsia/eclampsia, 1.87% of their pregnancies ended in stillbirth [150]– which is slightly higher than our assumed value, but since it included stillbirths to women with other complications (e.g., sepsis, obstructed labor), this gap does not seem unreasonable. Additionally, in the Asia region, among pregnancies ending in spontaneous vaginal birth (e.g., not operative whether with or without indications), 0.9% were estimated to end in fetal death [156].

- Assume attenuation in intrapartum stillbirth rate by facility type, as described in assumptions above.

Neonatal complications and death:

Babies can also experience complications during and immediately after birth even if the mother does not. Analyses indicate that between 11% and 25% of neonatal deaths occur following a birth where the mother did not experience a complication [153, 227].

The main causes of neonatal death in India, all per 1000 live births, are prematurity/low birthweight (12 per 1000 live births), neonatal infections (10), birth asphyxia/trauma (7) (tetanus accounts for an additional 1.2 deaths per 1000 live births), with an overall neonatal mortality rate of 37 per 1000 live births [196]. These were therefore the main neonatal complications modeled here.

Prematurity/low birth weight: It has been estimated that approximately 28% of newborns in India are classified as low birth weight [164]; other studies have found rates of preterm plus low birth weight of approximately 30% [171]. A small newborn, whether due to birth before term or small size, is at increased risk of death via several mechanisms: from respiratory insufficiency to metabolic disorders. The Disease Control Priorities Project estimated that death would result in 50-80% of cases [45], but a study of low birth weight/premature babies in an Indian hospital found a case fatality rate of approximately 10-20% [173], and another found 33% case fatality [170]. The model used the 10% value. The prevalence of preterm birth and low birth weight was assumed not to vary by facility type (since this occurs outside the intrapartum period of interest and only presumed-normal births are included in the model), but the likelihood of death attenuated by facility type.

Neonatal infections: Studies of neonatal sepsis rates at Indian health facilities have found that approximately 1.5-4% of newborns acquire an infection [165-168]. The Disease Control Priorities Project estimates a case fatality of neonatal sepsis of 30-40% [45], and this is similar to rates found elsewhere in the literature (e.g., within the above-cited articles and [170]).

- Although sepsis rates may vary across facilities, we assume they are unlikely to vary systematically by facility type. The values used in the model are a facility average, and applied to all facility types. However, the ability to manage the complication and avoid death did vary by facility level.

Birth asphyxia/trauma: The prevalence of perinatal/birth asphyxia among babies in India has been found to be between 1.3-3.6% [169-171]. The case fatality rate for asphyxia is estimated to be approximately 20-30% according to the Disease Control Priorities Project [45], and a similar rate was found in a recent study among a rural community in India (38.5%) [170].

- The prevalence of birth asphyxia was assumed to be related to care during childbirth, so it varied by facility type in the model; as did the case fatality rate.

Tetanus: Despite availability of a vaccine to prevent neonatal tetanus, the disease remains a problem in India. The literature has estimated that approximately 1.5% of infants may experience neonatal tetanus [172], and 80-100% of cases progress to death [45, 174]. The likelihood of acquiring neonatal sepsis is likely lower at higher-level facilities, so this and the likelihood of death were assumed to vary by facility type. During calibration, the case fatality of neonatal sepsis was decreased (to 50%).

Other: These main complications comprise 82% of neonatal deaths; so 18% are due to other causes. Given the summed probability of experiencing one of these main complications in the model, this means that approximately 7% of babies face other complications; this was revised upward during calibration to 10%. We assume that this does not vary by facility type. We assume a moderate fatality rate for these other complications (25%) and allowed it to vary by facility type.

None: It is assumed that nearly all complication-free babies survive (99.99%).

3.4 Literature review, SCC item impact

The literature was reviewed to identify evidence about SCC item effectiveness. Recent systematic reviews and meta-analyses were prioritized.

A randomized trial of partograph use found no significant difference between groups in indicators of complications for mothers or babies: maternal temperature (intrapartum and postpartum), nor neonatal Apgar score or antibiotics receipt or NICU admission; as well as no change in duration of labor, or rates of c-section. [149] When these results were pooled with those from a study in Mexico, the overall risk ratio for Caesarean section was 0.64 (95% CI 0.24-1.70): women in the partograph arm of the study in Mexico had a lower rate of Caesarean section (RR 0.38, 95% CI 0.24-0.61) but this study was deemed to have a high risk of bias; and no other studies have compared partograph to no-partograph, with measured morbidity or mortality outcomes. [148, 161]

There are a number of reasons why women may exhibit symptoms (such as fever, abdominal pain) for which they would receive antibiotics during the intrapartum period. Most published results about antibiotic effectiveness focus on particular infections—but all may be relevant, since the SCC does not require laboratory confirmation of infection. A Cochrane review examined use of antibiotics following premature rupture of membranes at or near term (an indication also highlighted by the SCC) and found a reduction in maternal morbidity, with a risk ratio of 0.43 for chorioamnionitis or endometritis (95% CI 0.23-0.82); and no significant effect on neonatal outcomes was found [185]. A more recent Lancet review found significantly reduced early onset sepsis (RR 0.61, 95% CI 0.48-0.77) attributable to antibiotics following preterm PROM, and a borderline non-significant neonatal mortality effect (RR 0.9, 95% CI 0.72-1.12) [161]. In cases of maternal group B streptococcus infection, a Cochrane review found that intrapartum antibiotic use (versus no treatment) was associated with significantly reduced early onset neonatal group B streptococcus infection (RR 0.17, 95% CI 0.04-0.74), but there was no significant reduction in mortality (RR 0.19, 95% CI 0.01-3.82) (whether all-cause, from group B streptococcus infection, or from other infections) [157, 161]. Lastly, a Cochrane review found that women with intraamniotic infection who receive intrapartum antibiotics (versus women who received postpartum antibiotics) had the same rates of maternal bacteremia (RR 2.19, 95% CI 0.25-19.48) but there was reduced neonatal sepsis (RR 0.08, 95% CI 0.00-1.44) [186].

Magnesium sulfate significantly reduces the likelihood that pre-eclampsia progresses to severe or eclampsia; a recent Cochrane review estimated the order of magnitude at approximately half (risk ratio 0.41, 95% CI 0.29-0.58) [72, 161]. This was associated with a borderline non-significant decrease in maternal deaths (RR 0.54, 95% CI 0.26 to 1.10). The Cochrane review found no significant impact on stillbirth or neonatal death (RR 1.04, 95% CI 0.93 to 1.15) [72]; a more recent review estimated non-significant effects on neonatal mortality (RR 1.16, 95% CI 0.94-1.42), stillbirth (RR 0.99, 95% CI 0.87-1.12), and perinatal death (RR 0.98, 0.88-1.1) [161].

Provision of oxytocin after childbirth significantly reduces the risk of regular and severe postpartum hemorrhage: a Cochrane review estimated the magnitude of this effect as 0.53 for regular PPH (95% CI

0.38-0.74) and as 0.62 for severe PPH (95% CI 0.44-0.87) [187]; these studies did not examine maternal nor neonatal mortality outcomes.

Clean childbirth practices—e.g., hand washing—have been found to be associated with neonatal infection. Birth attendant hand washing reduces the risk of neonatal infection (RR of approximately 0.7 for both tetanus and omphalitis, with 95% CI of 0.48-0.70 and 0.56-0.87, respectively), and there is a borderline significant reduction in neonatal mortality as well (RR 0.93, 95% CI 0.85-1.01) [161]. Studies of clean birth practices for home births have found overall similar reductions in neonatal mortality among infants whose birth attendants washed their hands (global RR 0.89, 95% CI 0.73-1.09; India 0.69, 95% CI 0.51-0.94; Nepal RR 0.81, 95% CI 0.66-0.99) [190, 229]. There is no rigorous evidence of the impact of hand washing on maternal infection nor mortality.

The use of a clean blade for cutting the umbilical cord is also associated with reduced neonatal infection and mortality: a recent analysis found use of a boiled blade following home birth reduced the risk of neonatal mortality (global RR 0.73, 95% CI 0.59-0.90; India RR 0.74, 95% CI 0.51-1.08) [190].

Neonatal resuscitation has seldom been examined as a stand-alone intervention; a recent article used a Delphi process and estimated a 20% reduction in intrapartum-related deaths following immediate newborn assessment and stimulation at a health facility [160]. A recent review article used an estimated effect for facility-based neonatal resuscitation of 0.7 (95% CI 0.59-0.84) [160, 161].

Provision of antibiotics to neonates with suspected infection can significantly reduce mortality: a recent review article estimated an approximate halving of all-cause mortality risk for neonates with pneumonia who receive antibiotics (RR 0.75, 95% CI 0.64-0.89) [161].

3.5 Calculations to derive SCC item and subitem availability values

We imputed values for missing variables among PHC facilities, using data from DLHS-3 for rural CHCs. For item 11 (maternal birth supplies), DLHS-3 measured oxytocin availability but not the other sub-items, so we estimated composite item availability based on sub-item prevalence. We multiplied the ratio of oxytocin availability to the full composite item 11 among rural CHCs (i.e., what proportion of the overall unavailability of item 11 was due to unavailability of oxytocin specifically) by the unavailability of oxytocin among PHCs; this generated the likely prevalence of item 11 at PHCs.

- $Ratio_1$ = (%CHC_{rural} with full item 11 / % CHC_{rural} with oxytocin) = (0.482/0.618) = 0.780
- $Ratio_1$ * % PHC with oxytocin = (0.780 * 0.512) = 0.399

Additionally, the PHC data for DLHS-3 did not include any components relevant to SCC item 4 (magnesium sulfate), so we first estimated availability of the magnesium sulfate drug, then applied this to estimate the composite item availability. First, we created a ratio of a pharmaceutical item (antibiotics) availability at PHCs to its availability at rural CHCs. It was assumed that availability of magnesium sulfate would follow the same relationship, so we multiplied this ratio by the availability of magnesium sulfate among rural CHCs. This—the estimated availability of magnesium sulfate drug—was then applied in a similar fashion to step 1 above, multiplying composite item availability as a function of this sub-item for rural CHCs by availability of the sub-item among PHCs.

- $Ratio_2$ = (% PHC with antibiotics / % CHC_{rural} with antibiotics) = (0.512/0.618) = 0.829
- $Ratio_3$ = (% CHC_{rural} with full item 4 / % CHC_{rural} with magnesium sulfate) = (0.293/0.597) = 0.491
- $Ratio_2$ * $Ratio_3$ * % CHC_{rural} with magnesium sulfate = 0.491 * 0.829 * 0.597 = 0.243

There was no relevant information for DHs within DLHS-3—so we used DLHS-2 data and an inflation factor, to reflect increasing supply availability at public health sector institutions over the last decade. This inflation factor was estimated as equal to the change in urban CHC-level availability between DLHS-2 and DLHS-3, which assumes that DHs saw the same trend over this period. These inflation factors were calculated separately for drug-based items (using magnesium sulfate) and the neonatal supply item (using neonatal resuscitation equipment). Also, these calculations utilize "gap" measures to impute availability of checklist items based on data-derived availability of other items[9]. Gaps represent unavailability of an item; they are a measure of "non-prevalence" equal to one minus probability of item availability.

The inflated estimate of magnesium sulfate availability was applied to the "gap ratio" for magnesium sulfate as a proportion of SCC composite item 4 among urban CHCs in DLHS3, to estimate availability of SCC composite item 4 among DHs.

[9] The gap (i.e., degree to which each item was not present) was used rather than prevalence (where gap = 1-prevalence) so that items with a high degree of availability could not be extrapolated to values above 100%.

- Gap_1 = (1 - % CHC_{urban} with magnesium sulfate in DLHS3) = 1-0.68 = 0.32
- ΔGap_1 = 1+[(Gap_1 - % CHC_{urban} with magnesium sulfate in DLHS2) / (% CHC_{urban} with magnesium sulfate in DLHS2)] = 1+[(0.32-0.63)/0.63) = 0.51
- $GapRatio_1$ = (1 - % CHC_{urban} with full item 4 in DLHS3) / (1 - % CHC_{urban} with magnesium sulfate in DLHS3) = 0.421/0.68 = 1.81
- Gap_2 = [$GapRatio_1$ * (ΔGap_1 * (1 - % DH with magnesium sulfate in DLHS2))] = 1.81 * (0.51 * (1-0.55)) = 0.505

We then calculated a "gap ratio" to estimate likely availability of drugs as a function of another drug (antibiotics based on magnesium sulfate, among urban CHCs in DLHS3), and applied this to the above-estimated availability of magnesium sulfate to estimate availability of antibiotics. And since antibiotics and oxytocin are available in the same essential obstetric drug kit, we assumed equivalent availability for oxytocin; and used the "gap ratio" of the oxytocin subitem to the SCC composite item 11 (maternal supplies).

- $GapRatio_2$ = (1 - % CHC_{urban} with full item 4 in DLHS3) / (1 - % CHC_{urban} with full item 3 DLHS3) = (1-0.421 / 1-0.682) = 0.612
- Gap_3 = $GapRatio_2$ * (1 - Gap_2) = 0.612 * 0.495 = 0.309
- $GapRatio_3$ = (1 - % CHC_{urban} with full item 11 in DLHS3) / (1 - % CHC_{urban} with oxytocin in DLHS3) = (1-0.574 / 1-0.682) = 0.839
- Gap_4 = (1 - % DH with antibiotics in DLHS2) / $GapRatio_3$ = [(1-0.691) / 0.839) = 0.368

We also applied the inflated estimate of neonatal resuscitation equipment to the "gap ratio" for the neonatal resuscitation subitem to full composite SCC item 12, to estimate the availability of SCC item 12.

- Gap_5 = 1 - % CHC_{urban} with neonatal resuscitation in DLHS3 = 1-0.621 = 0.379
- ΔGap_2 = 1+[(Gap_5 - % CHC_{urban} with neonatal resuscitation in DLHS2) / (% CHC_{urban} with neonatal resuscitation in DLHS2)] = 1+[(0.379-0.71)/0.71) = 0.534
- $GapRatio_4$ = (1 - % CHC_{urban} with full item 12 in DLHS3) / (1 - % CHC_{urban} with neonatal resuscitation in DLHS3) = (1-0.477)/(1-0.621) = 1.38
- Gap_6 = [$GapRatio_4$ * (ΔGap_2 * (1 - % DH with neonatal resuscitation in DLHS2))] = 1.38 * (0.534 * (1-0.56)) = 0.413

3.6 Sensitivity analyses: Further details

Table 3.6-1: Changes in outcome variables, at lower and upper bounds for most influential input parameters

	n deaths, baseline		n deaths, maximum SCC		Δn deaths, readiness-adjusted SCC	
Parameter	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**
Maternal deaths	*Base value: 4893*		*Base value: 3184*		*Base value: -435*	
pr(PPH)	4158	6363	2845	3860	-473	-389
pr(obstructed labor)	4667	5344	2981	3590	-444	-420
pr(sepsis)	4626	5426	3155	3240	-496	-332
pr(severe|PPH)	4717	5245	3142	3268	-469	-376
pr(management|obstructed labor)	4707	5052	3017	3327	-441	-432
pr(management|non-severe|PPH)	4617	5127	3023	3320	-440	-432
pr(management|sepsis)	4674	5081	3184	3184	-485	-411
pr(maternal death|other complication)	3893	6893	2184	5184	-938	-322
pr(maternal death|unmanaged|non-severe|PPH)	4430	5819	2914	3722	-452	-411
pr(maternal death|unmanaged|obstructed labor)	4676	5327	2988	3574	-443	-420
pr(maternal death|unmanaged|severe|PPH)	4639	5400	3123	3305	-537	-354
pr(maternal death|unmanaged|sepsis)	4636	5406	3164	3223	-497	-330
Parameter	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**
Stillbirths	*Base value: 33304*		*Base value: 30406*		*Base value: -1043*	
pr(obstructed labor)	22066	55780	20292	50635	-1188	-927
pr(HTN)	32308	35296	29427	32366	-1074	-985
pr(sepsis)	32762	34389	30173	30873	-1100	-934
pr(severe|HTN)	33277	33358	30395	30428	-1043	-1043
pr(management|obstructed labor)	27708	38340	25369	34939	-1084	-1026
pr(stillbirth|maternal unmanaged obstructed labor)	24001	51910	22034	47152	-1159	-938

pr(stillbirth|maternal managed obstructed labor)	31156	37600	28473	34273	-1059	-1015
pr(stillbirth|maternal non-severe HTN)	32168	35576	29255	32710	-1081	-974
pr(stillbirth|maternal sepsis)	32626	34661	30115	30990	-1114	-908
pr(stillbirth|other maternal complication)	29971	39970	26975	37270	-1189	-823
Parameter	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**	**At lower bound**	**At upper bound**
Neonatal deaths	*Base value: 52706*		*Base value: 30199*		*Base value:-3169*	
pr(obstructed labor)	48706	60706	27276	36045	-3991	-1748
pr(PPH)	52706	52706	30199	30199	-3244	-3095
pr(low birth weight)	43247	71625	25966	38666	-3629	-2613
pr(neonatal sepsis)	49349	59421	28780	33037	-3178	-3155
pr(neonatal tetanus)	50656	56807	28649	33299	-3253	-3020
pr(other neonatal complications)	49395	59328	27697	35204	-4360	-2943
pr(neonatal death|low birth weight)	43061	71997	25825	38947	-3623	-2625
pr(neonatal death|neonatal sepsis)	49330	59458	28770	33057	-3178	-3154
pr(neonatal death|neonatal tetanus)	50648	56821	28770	33057	-3253	-3020
pr(neonatal death|other neonatal complications)	49395	59328	27697	35204	-4360	-2943
pr(stillbirth|maternal unmanaged obstructed labor)	48934	60251	27653	35292	-3252	-3038

Figure 3.6-1: Number of deaths (maternal, intrapartum stillbirth, early neonatal) at baseline, with different input variable (parameter) values

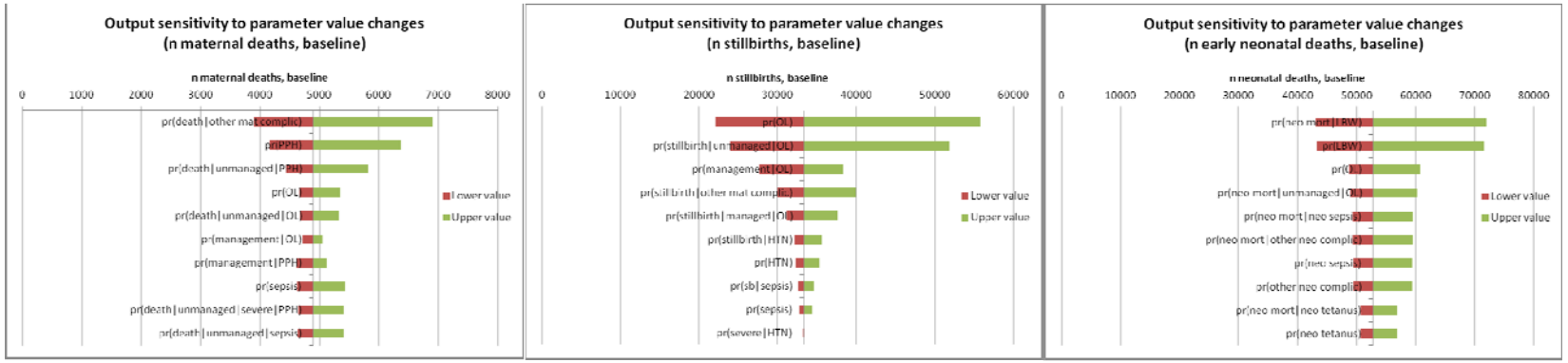


Figure 3.6-2: Number of deaths (maternal, intrapartum stillbirth, early neonatal) with maximum SCC implementation, with different input variable (parameter) values

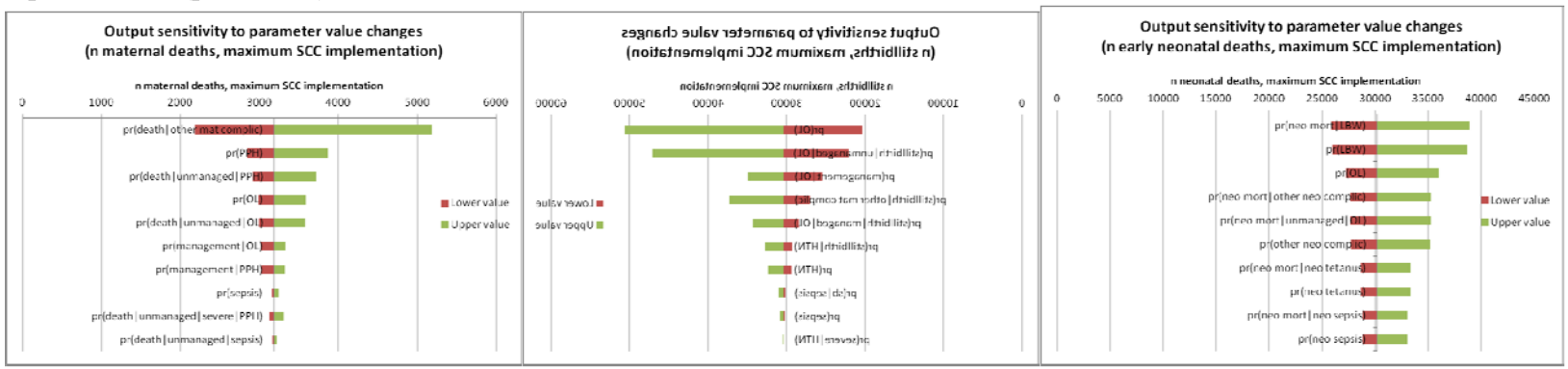


Figure 3.6-3: Number of deaths (maternal, intrapartum stillbirth, early neonatal) with readiness-adjusted SCC implementation versus baseline, at CHCs, with different input variable (parameter) values

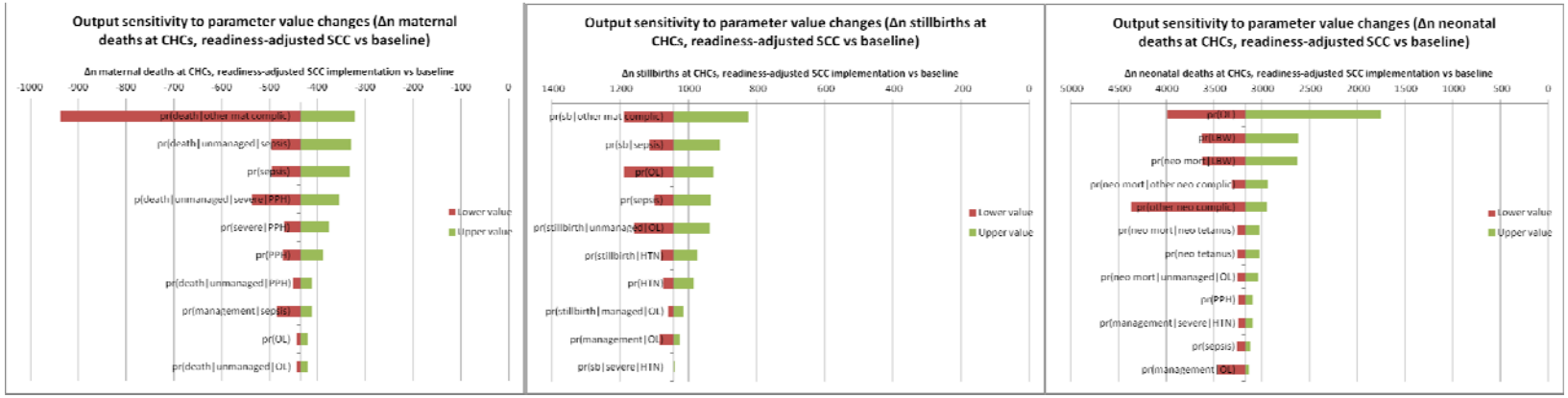
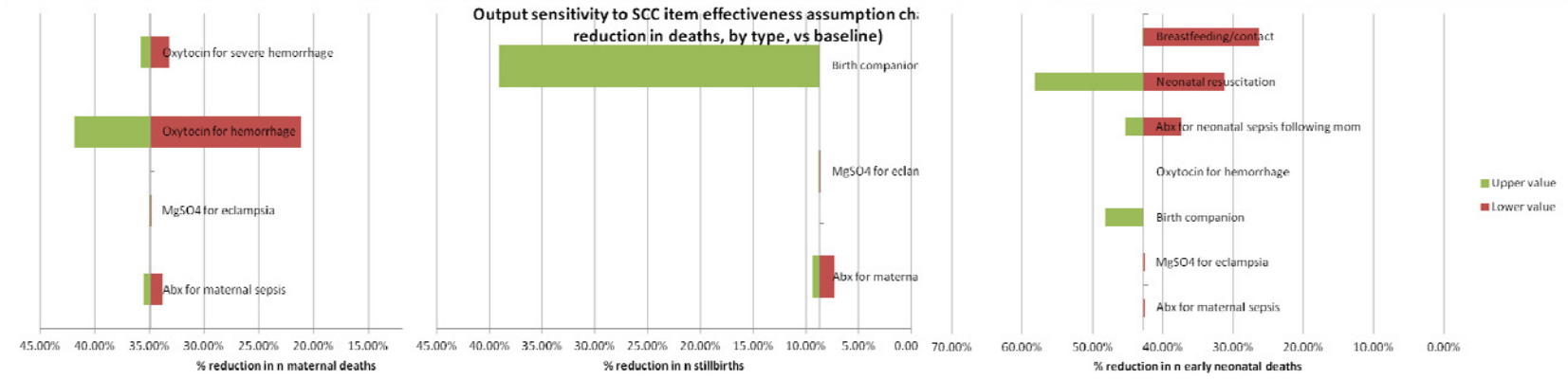


Figure 3.6-4: Percent reduction in number of deaths (maternal, intrapartum stillbirth, early neonatal) with maximum SCC implementation versus baseline, with different SCC item effectiveness variable values



4 Consequences of maternal mortality on infant and child survival: A 25-year longitudinal analysis in Butajira Ethiopia (1987-2011)[10]

Abstract

Background: Maternal mortality remains the leading cause of death and disability for reproductive-age women in resource-poor countries. The impact of a mother's death on child outcomes is likely severe but has not been well quantified. This analysis examines survival outcomes for children whose mothers die during or shortly after childbirth in Butajira, Ethiopia.

Methods: This study uses data from the Butajira Health and Demographic Surveillance System (HDSS) site. Child outcomes were assessed using statistical tests to compare survival trajectories and age-specific mortality rates for children who did and did not experience a maternal death. The analyses leveraged the advantages of a large, long-term longitudinal dataset with a high frequency of data collection; but used a strict date-based method to code maternal deaths (as occurring within 42 or 365 days of childbirth), which may be subject to misclassification or recall bias.

Results: Between 1987 and 2011, there were 18189 live births to 5119 mothers; and 73 mothers of 78 children died within the first year of their child's life, with 45% of these (n=30) classified as maternal deaths due to women dying within 42 days of childbirth. Among the maternal deaths, 81% of these infants also died. Children who experienced a maternal death within 42 days of their birth faced 46 times greater risk of dying within one month when compared to babies whose mothers survived (95% confidence interval 25.84-81.92; or adjusted ratio, 57.24 with confidence interval 25.31-129.49).

Conclusions: When a woman in this study population experienced a maternal death, her infant was much more likely to die than to survive—and the survival trajectory of these children is far worse than those of mothers who do not die postpartum. This highlights the importance of investigating how clinical care and

[10] Publication information for this chapter: Moucheraud C, Worku A, Molla M, Finlay JE, Leaning J, Yamin AE. (2015). Consequences of maternal mortality on infant and child survival: A 25-year longitudinal analysis in Butajira Ethiopia (1987-2011). *Reproductive Health*, 12(S1): S4.

socio-economic support programs can better address the needs of orphans, both throughout the intra- and post-partum periods as well as over the life course.

Background

Maternal mortality is a leading cause of death and disability for adult women worldwide, responsible for an estimated 289,000 deaths in 2013 [1]. It represents true excess burden of disease since the overwhelming majority of maternal deaths are due to preventable causes; and could be treated with well-understood interventions that have long been available in the global North. Maternal mortality highlights large inequalities between and within countries; the maternal mortality rate in resource-poor countries is 15 times higher than that in wealthy nations, and within countries, the poorest women see the greatest risk of dying during pregnancy or childbirth [2]. Reducing maternal mortality ratios (MMRs) by 75% from 1990 levels was therefore included in the United Nations' Millennium Development Goals, as integral to reducing global poverty. Less well-characterized, however, are the short- and long-term consequences of maternal deaths on children, families and communities. Often a maternal death can have spillover effects onto child health, via obstetric complications, infant feeding behaviors, and care for orphans. It thus is critically important to look beyond MMRs to fully characterize the harm caused by the loss of a mother.

There are a number of mechanisms through which a maternal death may affect outcomes for infants and children. The main direct causes of maternal mortality—obstetric complications such as eclampsia, sepsis, obstructed labor and hemorrhage—can also put neonates at increased risk of death [153, 224, 230]. If the infant survives birth but the mother does not, the resulting lack of nutritional support from breastfeeding leaves the baby vulnerable to malnutrition, which can itself be fatal or may increase the risk of disease or death from infection [231-233]. Older siblings also may suffer in many ways without maternal care: among orphans, the risk of child labor [234, 235], poor learning outcomes and lower educational attainment [236], and disrupted living arrangements [237] can impose trauma that has detrimental impacts on health and well-being. Qualitative research from rural Tanzania found that orphans of women who died of maternal causes—girls in particular—were likely to be undernourished in infancy and beyond, face education-related challenges, and receive compromised medical care [238]. This study also found adverse household effects, including economic drains—a finding echoed in a recent

study from China, where maternal death was associated with significant household income and expenditure declines [239, 240]. Detrimental household economic impacts were also seen in a study from Burkina Faso, where the high and unforeseen expense of emergency obstetric care was reported as difficult to repay, triggering long-term consequences on physical, psychological, social and economic well-being [241].

Infant and child mortality is thus only one adverse outcome associated with maternal death, but it is crucially important. An analysis from Bangladesh found a significantly worse survival trajectory of orphaned children—but cautioned about generalizing the findings, due to contextual factors that may differentially impact orphan survival such as household composition, the role of the father and HIV prevalence [231]. Recent analyses, however, have found similarly negative outcomes in sub-Saharan Africa. A cohort study in Benin found an elevated risk of mortality among infants born to women who experienced serious complications during childbirth (near-miss cases), even in the absence of maternal death [242]. Recent research in Kenya found an elevated mortality rate among babies of women who died after childbirth [243].

This analysis aims to provide evidence about the grave mortality consequences of maternal death on young children in Ethiopia between 1987 and 2011. By using a longitudinal demographic dataset—from a Health and Demographic Surveillance System (HDSS) site, comparable to the methods used in the Ronsmans study cited above [231]—we conducted a full survival analysis for all children of deceased mothers, examining additional outcomes for older children who become orphaned, and applying different definitions of maternal death in order to capture the consequences of a mother's death immediately after birth, as well as to examine a longer-range effect for late maternal deaths.

Methods

Study setting and data collection: This analysis uses a household-level longitudinal dataset, collected by the Butajira Rural Health Programme as a member center and founder in the INDEPTH network of HDSS sites. Butajira is a woreda (district) in south-central Ethiopia, approximately 130 kilometers south of Addis Ababa; the HDSS site consists of both rural- and town-based households. Data collection began in 1987 with monthly visits to approximately 28,000 individuals; the frequency was reduced to quarterly study visits in 2000. Date of closure for the current analysis was mid-2011, by which time the study population had grown to approximately 70,000 individuals. During household visits, study personnel collected information about vital and migratory events: births, deaths, and changes in household composition including marriage, and in- and out-migration. In the event of a parental death, the orphaned children were followed in subsequent rounds of data collection if they relocated within the Butajira study area. All those who moved out of the community were lost to follow-up; although such loss to follow-up is estimated to be low among reproductive-age women in Butajira [unpublished data].

Variable definition: A subset of the full Butajira HDSS dataset was used for the current analysis: children born to women during the study period (i.e., between January 1987 and June 2011). "Maternal death" was operationalized as a woman's death within a 42-day window of her most recent childbirth (or within 365 days, using the standard definition for late maternal death). It was necessary to use a date-based method to categorize maternal deaths because there are not reliable cause-of-death data available in the Butajira HDSS dataset. These categorizations were selected to correspond with the WHO definitions of maternal death, although the latter also includes deaths during pregnancy, which was not explored in the main analysis here (due to shortcomings in the quality and availability of these data).

The "index child" was defined as the reference birth for counting these 42 (or 365) days, and "non-index children" were all births prior to the one associated with the maternal death (i.e., elder siblings of the index child). Children's survival time was calculated as the number of days from their birth until their

death or out-migration, or the study period end. A woman's death during her pregnancy was reported as such by other members of her household during regular data collection.

Household characteristics were recorded only at baseline. For our analysis, women were classified into three wealth groups based on a principal component analysis of household assets (per [244]); the score included: number of rooms in the home, the presence of a separate kitchen, the presence of windows, use of piped or protected well water, use of a functional flush toilet, radio ownership, and a metal (non-thatched) roof.

Statistical methods: We used Kaplan-Meier survival analysis to calculate cumulative survival probabilities for index children of a maternal death versus those with surviving mothers from birth to 30 days (1 month), 183 days (6 months), 365 days (12 months), 1825 days (5 years) and 3652 days (10 years). Statistically significant differences between these survival functions were assessed using the log-rank test. We used a Poisson regression to compare death rates within each of these age groups for index children of a maternal death and children with a surviving mother; the unadjusted ratios used robust standard errors to account for clustering of births to the same mother, and the adjusted ratios added controls for other important covariates: household wealth, mother's age, mother's ever marital status, and mother's educational attainment. Confidence intervals at the 95% level are reported. All analyses were conducted using Stata 12.1 (StataCorp 2014).

Ethical clearance: Study protocols were approved by the Harvard T.H. Chan School of Public Health Institutional Review Board and the Addis Ababa University College of Health Sciences Institutional Review Board in Ethiopia.

Results

Table 4-1 presents information on the mothers and children analyzed in this study, including classifications of deaths and survival. Between 1987 and 2011, there were 17993 live births to 5084 mothers; 30 mothers of 104 children died within the first 42 days of childbirth.

Table 4-1: Characteristics of mothers and children in the Butajira cohort, 1987-2011

			n	**%**
Maternal death within 42 days n= 30	Index child n= 32	Deceased	26	81.25%
		Survived	6	18.75%
	Non-index children n= 72	Deceased	5	6.94%
		Survived	67	93.06%
Non-maternal death n= 335	Children n= 1014	Deceased	45	4.44%
		Survived	969	95.56%
Surviving women n= 4719	Children n= 16875	Deceased	1509	8.94%
		Survived	15366	91.06%

Note: The 26 deceased index children include 5 children who died on the day of their birth, and their mother's death occurred within the following 4 days. All other children classified as deceased in this analysis (i.e., non-index children of maternal deaths and all children of women who died from non-maternal causes) died subsequent to their mother's death.

Children born to women who died around the time of their childbirth experienced very high mortality: 81% of these children also died. This is significantly higher ($p<0.001$) than the proportion of deaths among older children of these women (7%). The mortality proportion among children of maternal deaths (combined index and non-index births) is significantly higher ($p<0.001$) than that among children of women who died non-maternal deaths (4.4%). And among children who experienced death of a mother (maternal or non-maternal causes), more of these children died than children of women who survived ($p<0.01$), among whom the proportion of deaths is around 9%. Notably, non-index children of maternal deaths do not have a significantly different ($p=0.6$) probability of death than children whose mothers survived (7% and 9%, respectively).

Characteristics of the study sample are presented in Table 4-2 for mothers, and Table 4-3 for children. Women who died during or shortly after childbirth are significantly ($p<0.001$) more commonly in the poorest wealth groups: 60% of deceased women were in the lowest household asset group (versus 30% of surviving women); note that this is a relative measure (relative asset index to other households in the community). The sex distribution of children is not statistically significantly different between the groups ($p=0.3$). Women were at increased risk of maternal death at first birth and at high parity: this is reflected in the birth order among index children of maternal deaths, where 34% of index children to maternal deaths were a first birth, and 38% were birth order five and beyond. Birth order and maternal age are likely associated, and this table presents only uncontrolled proportions.

Table 4-2: Characteristics of mothers in the Butajira cohort, 1987-2011

	Maternal death (42 days)	**Mother survived**
n	30	4719
Mother's age at most recent childbirth (years)		
10-19	2 (6.7%)	254 (5.38%)
20-24	5 (16.7%)	712 (15.09%)
25-29	6 (20.0%)	938 (19.88%)
30-34	8 (26.7%)	1216 (25.77%)
35-39	6 (20.0%)	989 (20.96%)
40+	3 (10.0%)	604 (12.80%)
Household asset group (at baseline)		
Poorest	18 (60.0%)	1433 (30.4%)
Middle	10 (33.3%)	1258 (26.7%)
Richest	1 (3.3%)	1778 (37.7%)
Missing	1 (3.3%)	250 (5.3%)
Mother's educational attainment (at baseline)		
No schooling	13 (43.3%)	2680 (56.8%)
Grades 1-5	1 (3.3%)	506 (10.7%)
Grades 6-9	1 (3.3%)	211 (4.5%)
Beyond grade 9	1 (3.3%)	140 (3.0%)
Missing	14 (46.7%)	1182 (25.1%)

Table 4-3: Characteristics of children in the Butajira cohort, 1987-2011

	Maternal death (42 days)		Mother survived
	Index children	**Non-index children**	**Children**
n	32	72	16875
Sex of child			
Boy	14 (43.8%)	38 (52.8%)	8679 (51.4%)
Girl	18 (56.2%)	34 (47.2%)	8196 (48.6%)
Birth order			
1	11 (34.4%)	18 (25.0%)	4719 (28.0%)
2	4 (12.5%)	18 (25.0%)	3614 (21.4%)
3	0	16 (22.2%)	2803 (16.6%)
4	5 (15.6%)	8 (11.1%)	2077 (12.3%)
5+	12 (37.5%)	12 (16.7%)	3662 (21.7%)

In data presented in the Appendix (Table 4.1-1), children who lost a mother (from any cause, maternal or not) were significantly more likely to have received no schooling: 55% of children with surviving mothers never attended school, versus 62% of children with deceased mothers (p-value <0.01). Note that, unlike vital and demographic events, education was not updated in the routine surveillance system, so this variable is often missing in the dataset and these data should be interpreted with caution. Additionally, cause of death is also largely missing (for two-thirds of deceased children) so differences between groups are too small to be analyzed—but, among all child deaths, the most common attributed causes included stillbirths, diarrhea/vomiting, sudden death, pneumonia, malaria, and malnutrition (presented in the Appendix, Table 4.1-2).

Maternal death had a large and significant impact on child survival, as shown in Table 4-4 and Figure 4-1. (These survival analysis results, and all that follow, compare index children from maternal deaths to children whose mothers survived.) All deaths among index children of women who died during or after childbirth occurred in the first year of life. These survival functions are significantly different (log-rank test p<0.001). Data from Table 4-4 are presented visually in a Kaplan-Meier survival curve, seen in

Figure 4-1. The survival function for non-index children of maternal deaths (see Appendix, Table 4.1-3) is not significantly different from that of their counterparts with surviving mothers (p=0.38)—indicating that the mortality effect of a maternal death was strongest among the index children, and, as seen in Table 4-4 and Figure 4-1, was concentrated during early infancy.

Table 4-4: Probability of survival to day x for index children by maternal mortality status, in the Butajira cohort, 1987-2011

	Maternal death		**Mother survived**	
Days since birth	Survival prob.	n died	Survival prob.	n died
0	0.6875	10	0.9848	274
30	0.3750	10	0.9760	159
183	0.1875	6	0.9638	218
365	0.1875	0	0.9558	142
1825	0. 1875	0	0.9279	463
3652	0. 1875	0	0.9167	152

Figure 4-1: Kaplan-Meier Survival Probability Curve by maternal mortality status in the Butajira cohort, 1987-2011

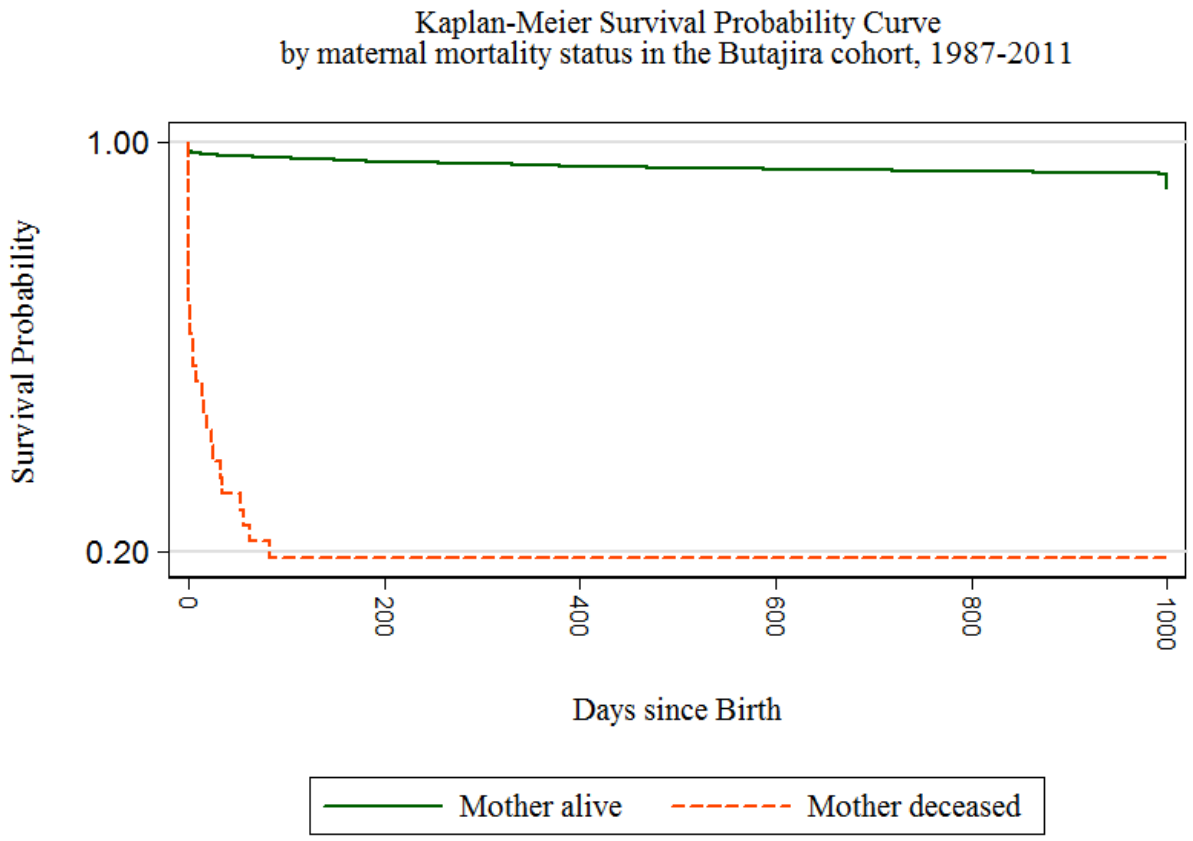


Table 4-5 presents age-specific mortality rates by mother survival status: the death rate from birth to 30 days was 81.92 per 100,000 child-days for children of surviving mothers, and 4210.53 deaths per 100,000 child-days for index children of maternal deaths. Thus, index children of maternal deaths were at 46 times greater risk of dying in the first month of life than their counterparts whose mothers survived; or, if adjusting for covariates, a 57 times greater risk of dying during the first 30 days of life.

Table 4-5: Age specific death rates in children according to survival status of the mother in the Butajira cohort, 1987-2011

Child age (days)	Deaths per 100000 child-days (Number of child deaths)		Crude death rate ratio (95% CI)	Adjusted death rate ratio (95% CI)
	Mother survived	Maternal deaths (index children)		
0-30	81.92 (433)	4210.53 (20)	46.01 (25.84-81.92)	57.24 (25.31-129.49)
31-183	8.17 (218)	565.50 (6)	65.96 (24.94-174.41)	80.38 (21.93-294.59)
184-365	4.58 (142)	.	.	.
366-730	2.94 (176)	.	.	.
731-1095	1.73 (99)	.	.	.

Note: Variables used for adjusted ratios include: household wealth, mother's age, mother's ever marital status, and mother's educational attainment.

In Table 4-6, we explore the potential for gender bias in child mortality rates by maternal survival status. Unadjusted ratios during the neonatal period were higher for index boys than for index girls (though confidence intervals overlap so these may not be statistically significantly different), which corresponds to the widespread generally higher mortality risk faced by infant boys.

Table 4-6: Gender bias in child survival in the Butajira cohort, 1987-2011

Child age (days)	Deaths per 100000 child days (number of child deaths)		Crude death rate ratio (95% CI)	Adjusted death rate ratio (95% CI)
	Mother survived	Maternal deaths (index children)		
0-30				
Male	95.59 (259)	11111.11 (12)	101.93 (43.03-241.46)	79.46 (33.62-187.82)
Female	67.54 (174)	2179.84 (8)	29.06 (13.36-63.20)	40.42 (9.37-174.42)
31-183				
Male	7.97 (109)	555.56 (1)	64.42 (6.50-638.64)	56.48 (5.10-625.39)
Female	8.38 (109)	567.54 (5)	64.92 (22.08-190.90)	64.81 (14.31-293.47)
184-365				
Male	4.53 (72)	.	.	.
Female	4.60 (70)	.	.	.

Note: Variables used for adjusted ratios include: household wealth, mother's age, mother's ever marital status, and mother's educational attainment.

Additionally, we explored the robustness of these results to an expanded definition of maternal death, up to 365 days postpartum (full results presented in Tables 4.1-4, 4.1-5, 4.1-6, and Figure 4.1-1). Among the 58 women who died in the year after childbirth (which, by definition, includes the women captured in the 42-day definition of maternal mortality), 38 (or 63%) of their index children experienced a subsequent death. The survival function for index children of these women was significantly different than that for children of surviving mothers ($p<0.001$). The one-month mortality rate ratio for these children versus those born to mothers who survived was 15.2 (95% confidence interval 8.96-25.74), or adjusted ratio of 19.42 (9.24-40.85); and for the 30-183 day period, the ratio was 24.94 (13.76-45.18), or adjusted ratio of 27.96 (11.11-70.39). Thus, even with an expanded definition of maternal mortality that includes deaths up to 365 days after childbirth, these children also experience greatly increased likelihood of dying.

Discussion

In this setting, there was a very high likelihood of infant mortality subsequent to a maternal death during the intra- and post-partum period. Children whose mothers died during or shortly after childbirth were at approximately 50 times greater risk of dying during the first month of life than babies whose mothers survived. A significantly elevated risk ratio was also found for children born to women who died within one year of childbirth. The results remained significant with the inclusion of control variables that might also be associated with higher mortality for both mother and child (maternal age, household wealth, maternal educational attainment)—indicating that these babies' risk was likely linked to the maternal death itself and not other covariates.

This highly elevated risk of death for infants of maternal deaths echoes, and even surpasses, findings from other settings [231]. Local characteristics around childbirth and infant care, as well as household structure, may offer hypotheses to help explain the added risk seen here. In a study of childbearing practices in Butajira, the overwhelming majority of women (90%) gave birth at home, not at a health facility, and just one-quarter of deliveries were attended by a skilled provider [245]. Low use of clinical obstetric care may put both mothers and babies at increased risk of death from childbirth-related complications. This same study in Butajira also found that breastfeeding was initiated within one hour of birth for one-third of women, and almost all infants (99.6%) were still breastfed at one year of age [245]; in this environment of prompt, near-universal and long-duration breastfeeding, a maternal death that compromises the availability of breast milk could have especially dire nutritional consequences for babies. Additionally, migratory patterns and household composition may leave orphaned infants at higher risk of death: male migration to urban centers, including Addis Ababa, is common in the study area, with outmigration incidence rate among males of 4.16 per 100 person years (95% confidence interval 4.10-4.22) [unpublished data]. If a mother dies, there is therefore a higher likelihood of decreased care and support in the household, which may contribute to the higher risk of child death in this group. Without formal social support mechanisms to assist families who suddenly find themselves caring for orphaned

children (e.g., nutritional support, assistance with education and health care), the level of care will vary based on what these guardians can provide, creating possible additional vulnerabilities for orphaned children.

Many women, and consequently children, could be saved by increasing availability and use of emergency obstetric and neonatal care. Because many obstetric complications arise unexpectedly, all women should be provided access to skilled attendants and emergency obstetric care. Interventions may need to target relevant barriers to use, including financial and time costs, accessibility issues (transportation availability), quality of care (including clinical indicators and treatment by staff), and psychic costs and social norms that may be limiting utilization of maternity care. It has been acknowledged that maximum impact requires pairing clinical care with community-based interventions [246], which is particularly important in a context such as Butajira where few women currently have institutional deliveries. Programs to address upstream risk factors for maternal death, including women's economic empowerment and increased female educational attainment [10], are likewise also important for child well-being. Although this study did not find mortality effects for the older children orphaned by a maternal death, the much lower rate of any educational attainment in this group indicates a potentially grave problem around orphan care and well-being. This also may perpetuate the cycle of poverty (and accordingly, the risk of maternal and infant mortality) from one generation to the next.

This study utilized the unique benefits of a large longitudinal dataset, with a high frequency of data collection over a long period of time, to examine the survival trajectories of children born to women who die during or shortly after childbirth. There are nonetheless some data limitations to note. First, there were ultimately few maternal deaths to analyze using either the 42- or 365-day cutoff values; this may limit the level of inference drawn from these analyses, and resulted in large confidence intervals around the results. Additionally, there are other possible confounding variables that could not be included in this analysis due to data availability. A third possible limitation is the use of a date-based method to code maternal deaths,

which is subject to measurement error due to recall bias and misclassification of deaths from other causes that occurred during the postpartum period. In the absence of a vital registry in Butajira, verbal autopsy methods could offer a more specific approach to classifying maternal deaths; but the Butajira HDSS site only recently began using verbal autopsy methods so these data were not included here. To match the full WHO definition of maternal death (i.e., occurring during pregnancy or up to 42 days postpartum), the analysis was repeated, adding women who were reportedly pregnant at the time of their death. These results are included in Table 4.1-7. the survival function of children with mothers who died during pregnancy or within 42 days (there were 48 such women) was significantly different than that of children born to women who survived ($p<0.001$).

Lastly, the external validity of these results should be carefully considered. Contextual factors that may be crucially important for explaining the dramatic survival effects shown here, likely vary by setting—so the results should be generalized with caution. For example, in settings with higher rates of institutional delivery, particularly where high-quality neonatal and postnatal care is offered, these results may not hold. Additionally, differing practices around infant care (feeding behaviors, for example, and social networks for care) may be protective against infant death even following the loss of a mother. Lastly, there may be underlying risk factors that could detrimentally affect both maternal and infant survival—HIV for example, or anemia—and although the data were not available to consider those here, such background risk is likely important (and setting-dependent).

There are several important areas for follow-up research identified by this analysis. First, more quantified evidence is needed from a variety of settings on the survival of children following a maternal death. Second, there is much to be learned about non-mortality outcomes—for example educational attainment, morbidities (for example, nutritional status) and household structure—for surviving orphans. Lastly, robust evaluation data are lacking on effective ways to improve child survival following death of a mother, with respect to both health system approaches and family-community interventions.

Conclusions

Saving mothers means saving children in this study context—a particularly salient finding given the slow progress in reducing neonatal mortality worldwide, which is seeing very little improvement in Africa and comprises approximately 40% of all under-5 deaths [141]. Infants of women who died during or shortly after childbirth were at significantly and dramatically elevated risk of death when compared to babies whose mothers survived; this relationship persists even after controlling for covariates. There appear also to be ill consequences for older orphaned children, notably in lesser educational attainment. The social and economic factors that undergird high maternal mortality rates also affect babies, both directly through the loss of a mother as well as indirectly over the life course. This study adds evidence—which has been noted as generally lacking [10]—on the broad consequences of maternal death. It highlights the urgent need to scale up clinical programs for safe childbirth and postpartum care that also meet the needs of newborns, as well as to eliminate the barriers to women's effectively utilizing such services. These results show that a maternal death has grave spillover effects, and the relationship between maternal and infant mortality merits further attention by policymakers and researchers.

References for Chapter 4

1. World Health Organization, et al., *Trends in maternal mortality: 1990 to 2013*. 2014.

2. Ronsmans, C. and W.J. Graham, *Maternal mortality: who, when, where, and why.* The Lancet, 2006. 368(9542): p. 1189-1200.

3. Chan, G.J., et al., *Risk of Early-Onset Neonatal Infection with Maternal Infection or Colonization: A Global Systematic Review and Meta-Analysis.* PLoS Med, 2013. 10(8): p. e1001502.

4. Kusiako, T., C. Ronsmans, and L. Van der Paal, *Perinatal mortality attributable to complications of childbirth in Matlab, Bangladesh.* Bulletin of the World Health Organization, 2000. 78: p. 621-627.

5. Vogel, J.P., et al., *Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health.* BJOG: An International Journal of Obstetrics & Gynaecology, 2014. 121: p. 76-88.

6. Ronsmans, C., et al., *Effect of parent's death on child survival in rural Bangladesh: a cohort study.* The Lancet, 2010. 375(9730): p. 2024-2031.

7. Lindblade, K.A., et al., *Health and nutritional status of orphans <6 years old cared for by relatives in western Kenya.* Tropical Medicine & International Health, 2003. 8(1): p. 67-72.

8. Braitstein, P., et al., *Nutritional Status of Orphaned and Separated Children and Adolescents Living in Community and Institutional Environments in Uasin Gishu County, Kenya.* PLoS ONE, 2013. 8(7): p. e70054.

9. Whetten, K., et al., *More than the loss of a parent: Potentially traumatic events among orphaned and abandoned children.* Journal of Traumatic Stress, 2011. 24(2): p. 174-182.

10. Whetten, R., et al., *Child work and labour among orphaned and abandoned children in five low and middle income countries.* BMC International Health and Human Rights, 2011. 11(1): p. 1.

11. O'Donnell, K., et al., *A Brief Assessment of Learning for Orphaned and Abandoned Children in Low and Middle Income Countries.* AIDS and Behavior, 2012. 16(2): p. 480-490.

12. Hosegood, V., *The demographic impact of HIV and AIDS across the family and household life-cycle: implications for efforts to strengthen families in sub-Saharan Africa.* AIDS Care, 2009. 21(sup1): p. 13-21.

13. Yamin, A.E., et al., *Costs of Inaction on Maternal Mortality: Qualitative Evidence of the Impacts of Maternal Deaths on Living Children in Tanzania.* PLoS ONE, 2013. 8(8): p. e71674.

14. Wang, H., et al., *Economic Impact of Maternal Death on Households in Rural China: A Prospective Cohort Study.* PLoS ONE, 2013. 8(10): p. e76624.

15. Ye, F., et al., *The Immediate Economic Impact of Maternal Deaths on Rural Chinese Households.* PLoS ONE, 2012. 7(6): p. e38467.

16. Storeng, K.T., et al., *Paying the price: The cost and consequences of emergency obstetric care in Burkina Faso.* Social Science & Medicine, 2008. 66(3): p. 545-557.

17. Filippi, V., et al., *Effects of severe obstetric complications on women's health and infant mortality in Benin.* Tropical Medicine & International Health, 2010. 15(6): p. 733-742.

18. Family Care International, International Center for Research on Women, and KEMRI-CDC Research and Public Health Collaboration, *A price too high to bear: The costs of maternal mortality to families and communities*. 2014.

19. Filmer, D. and L. Pritchett, *Estimating Wealth Effects Without Expenditure Data—Or Tears: An Application To Educational Enrollments In States Of India.* Demography, 2001. 38(1): p. 115-132.

20. Medhin, G., et al., *Prevalence and predictors of undernutrition among infants aged six and twelve months in Butajira, Ethiopia: The P-MaMiE Birth Cohort.* BMC Public Health, 2010. 10(1): p. 27.

21. Darmstadt, G.L., et al., *Evidence-based, cost-effective interventions: how many newborn babies can we save?* The Lancet, 2005. 365(9463): p. 977-988.

22. Grepin, K.A. and J. Klugman, *Closing the deadly gap between what we know and what we do: Investing in women's reproductive health*, ed. The World Bank. 2013, Washington, D.C.

23. Oestergaard, M.Z., et al., *Neonatal Mortality Levels for 193 Countries in 2009 with Trends since 1990: A Systematic Analysis of Progress, Projections, and Priorities.* PLoS Med, 2011. 8(8): p. e1001080.

Appendix for Chapter 4

List of supplemental tables

List of supplemental figures

Table 4.1-1: Education attainment of children in the Butajira cohort, by mother survival status (excludes children with missing value for education variable), 1987-2011

	Mother deceased	Mother survived
n	557	5028
No schooling	2784 (55.4%)	348 (62.5%)
Grades 1-5	1529 (30.4%)	168 (30.2%)
Grades 6-8	405 (8.1%)	26 (4.7%)
Grades 9+	310 (6.2%)	15 (2.7%)

Table 4.1-2: Cause of death among deceased children in the Butajira cohort (excludes children with missing value for cause of death), 1987-2011

Cause	n
Stillbirth	122
Diarrhea/vomiting	103
Sudden death	61
Pneumonia	61
Malaria	54
Malnutrition	54
Accident	27
Tuberculosis	21
Premature birth	14
Whooping cough	14
Hepatitis	9
Pregnancy/ delivery related	5
Measles	2
Meningitis	1
AIDS	1
Other	310

Table 4.1-3: Probability of survival to day x for non-index children by maternal mortality status, Butajira cohort, 1987-2011

	Maternal death		Mother survived	
Days since birth	Survival prob.	n died	Survival prob.	n died
0	1.0	0	0.9847	274
30	1.0	0	0.9759	159
183	1.0	0	0.9637	218
365	1.0	0	0.9557	142
1825	0.9861	1	0.9276	462
3652	0.9716	1	0.9165	151

Table 4.1-4: Characteristics of mothers and children in the Butajira cohort, expanded definition for late maternal death, 1987-2011

			n	%
Maternal death within 365 days n= 58	Index child n= 60	Deceased	38	63.33%
		Survived	22	36.67%
	Non-index children n= 151	Deceased	7	4.64%
		Survived	144	95.36%
Non-maternal death n= 298	Children n= 907	Deceased	31	3.42%
		Survived	876	95.58%
Surviving women n= 4719	Children n= 16875	Deceased	1509	8.94%
		Survived	15366	91.06%

Table 4.1-5: P**robability of survival to day x for index children by maternal mortality status, expanded definition for late maternal death in Butajira cohort, 1987-2011**

	Maternal death		**Mother survived**	
Days since birth	Survival prob.	n died	Survival prob.	n died
0	0.8333	10	0.9848	274
30	0.6667	10	0.9759	159
183	0.4667	12	0.9641	212
365	0.3833	5	0.9564	137
1825	0.3667	1	0.9284	462
3652	0.3667	0	0.9173	152

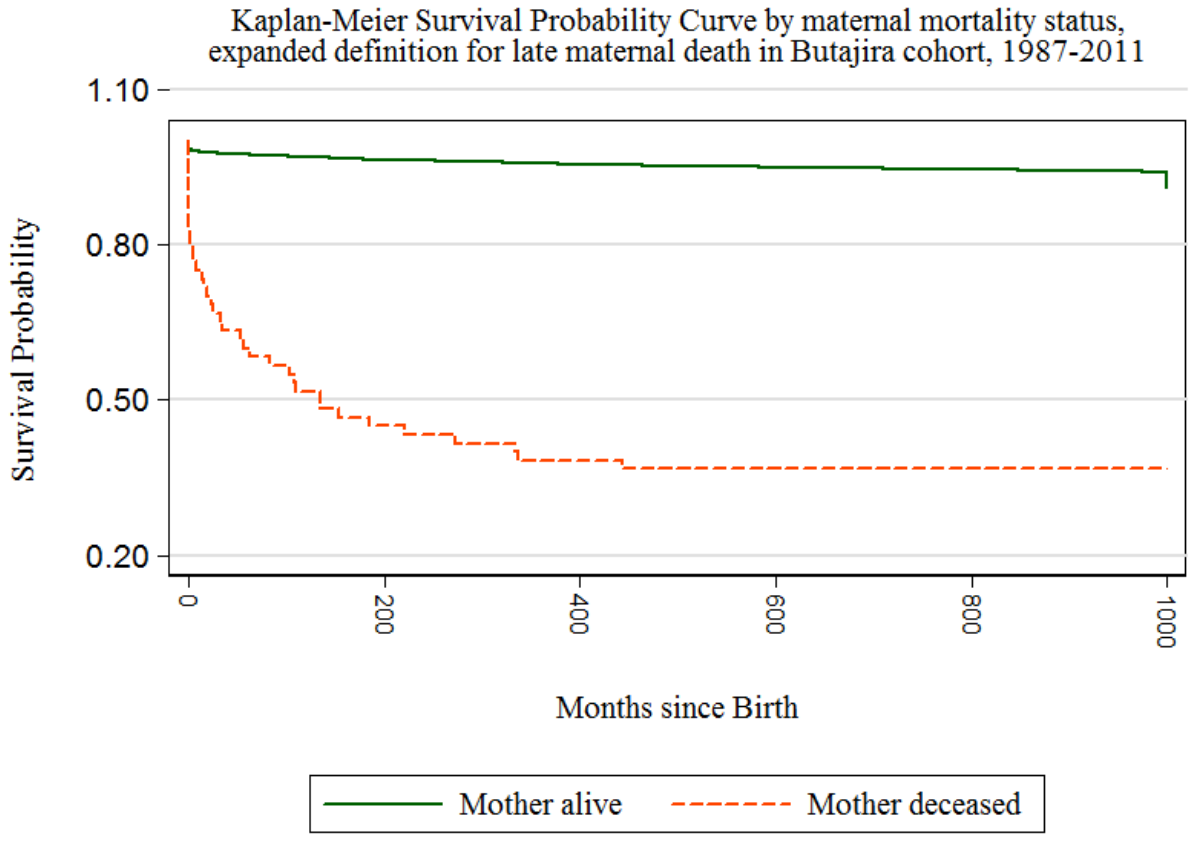
Table 4.1-6: Age specific death rates in children according to survival status of the mother, expanded definition for late maternal death in Butajira cohort, 1987-2011

Child age (days)	**Deaths per 100000 child-days (Number of child deaths)**		**Crude death rate ratio (95% CI)**	**Adjusted death rate ratio (95% CI)**
	Mother survived	Maternal deaths (index children)		
0-30	82.05 (433)	1520.91 (20)	15.20 (8.96-25.74)	19.42 (9.24-40.85)
31-183	7.96 (212)	240.48 (12)	24.94 (13.76-45.18)	27.96 (11.11-70.39)
184-365	4.42 (137)	108.27 (5)	22.30 (9.14-54.39)	19.47 (4.85-78.18)
366-730	2.92 (175)	12.52 (1)	3.11 (0.43-22.69)	0 (0-0)
731-1095	1.74 (99)	.	.	.

Table 4.1-7: Probability of survival to day x for index children by maternal mortality status, maternal deaths include those during pregnancy and up to 42 days postpartum in Butajira cohort, 1987-2011

	Maternal death		Mother survived	
Days since birth	Survival prob.	n died	Survival prob.	n died
0	0.9333	10	0.9847	274
30	0.8667	10	0.9758	159
183	0.8267	6	0.9636	218
365	0.8267	0	0.9555	142
1825	0.8199	1	0.9274	462
3652	0.8053	2	0.9163	150

Figure 4.1-1: Kaplan-Meier Survival Probability Curve by maternal mortality status, expanded definition for late maternal death in Butajira cohort, 1987-2011



5 Discussion and Conclusion

Overview

The three papers of this dissertation aimed to explore questions about maternal and child mortality, including the relationship between these outcomes, and context-specific approaches for addressing this burden, with a health systems focus. Deaths among mothers and children, particularly infants, represent excess and inequitable mortality burden: most of these deaths, which are concentrated among the most underserved populations and the poorest countries, could be averted with high-quality medical care. Most countries will fail to meet their Millennium Development Goals for maternal and child mortality by the end of this year. Weak health systems may be a barrier to achieving significant improvements for both Goals, as improvements in intrapartum-period care is crucial to better outcomes for mothers and infants.

To reiterate, the overarching research questions addressed in this dissertation were:

1) What is the effect of maternal health (morbidity and mortality) on infant outcomes? (Chapters 3 and 4)
2) What survival gains could be attained through improved interventions, across the continuum of care (Chapters 2 and 3)?
3) How do health system characteristics affect potential impact (Chapter 3) and cost-effectiveness (Chapter 2)?

Summary of findings

The first paper, in Chapter 2, explored the potential impact and cost-effectiveness of achieving improvements across the continuum of reproductive care in Nepal. How many lives could be saved if unmet need was reduced, safe abortions were increased, and access to quality intrapartum care was improved, and what would be the cost-effectiveness of doing so? The findings point to the importance of investing across the continuum: the largest mortality reductions—and particularly on the maternal

mortality ratio indicator—occur subsequent to a combined approach. This also carries the biggest price tag, since obstetric care improvements (in particular) can be costly, e.g. transportation and referral strengthening, staffing and care quality, etc. But even the most exhaustive, and expensive, level of eliminated unmet need for family planning and universal improvements in intrapartum care would still be highly cost-effective, with an incremental cost-effectiveness ratio over status quo of US$ 997/year of life saved—which is well under the triple-GDP threshold recommended by WHO for assessing cost-effectiveness (Nepal's per-capita GDP is approximately US$ 700).

We conducted additional exploratory analyses to assess the price at which an accompanying strategy to achieve such improvements would no longer render a cost-effective outcome. In other words, fully eliminating unmet need would likely require an accompanying intervention (to strengthen the supply chain, for example); likewise for any behavior change intervention or other approach to increase uptake of facility-based delivery, and/or provider training for recognizing complications and conducting referrals, etc. We estimated that any such accompanying interventions would need to add US$ 405.6 million to the total package cost for it to cross the cost-effectiveness threshold—and this is approximately equivalent to half of one year's health expenditures in Nepal. Such an investment could of course be spread over several years (and such a time span would likely be necessary to actually achieve the changes required for the resulting health outcome improvements). This could avert approximately 4 out of every 5 maternal deaths in Nepal.

The findings from Chapter 2 underscore the necessity of improving obstetric care if we are to achieve substantial reductions in maternal mortality. But evidence is generally weak on how to actually implement such changes effectively, particularly at-scale in resource-poor health systems. There are small studies, but only some have robust evaluation designs to permit causal attribution; and large "experiments"—such as Matlab in Bangladesh—have struggled to disentangle the separate effects of

various interventions. So while Chapter 2 estimates the health improvements that would result from obstetric care improvements, it does not assess how to achieve such changes.

Chapter 3 addressed this question: if an intervention (namely, the Safe Childbirth Checklist) were scaled up nationally in India, what is its potential maximum impact on health outcomes? And, given the state of India's health system, how might these results attenuate in the real-world setting? The Safe Childbirth Checklist (SCC) is a 29-item list, plus decision tools for each item, to guide clinicians through the provision of routine (non-emergency) obstetric care, from when a woman is admitted to a health facility, until she and her baby are discharged. A pilot study at a single hospital in India found that the SCC intervention (which includes the list itself, plus training and coaching for providers to encourage adherence to the SCC) improved quality of care by increasing the administration of the 29 SCC items. But this pilot study was not sufficiently large to assess health outcomes, nor did it explore the potential impact of health system characteristics, namely infrastructure, supplies and medicines.

The analysis in Chapter 3 utilized a four-step approach. First, we used a nationally-representative dataset (the Indian District-Level Household & Facility Survey, 2007-08) to analyze the presence and functionality of supplies, medicines and infrastructure necessary to execute a subset of evidence-based, high-impact SCC items: provision of antibiotics to women with suspected infection, provision of magnesium sulfate to women with suspected eclampsia, encouragement of birth companion presence, preparation of birth supplies for the mother (supplies for hand washing, and for oxytocin administration) and for the baby (sterile blade, and neonatal resuscitation equipment), postpartum checking of maternal bleeding, and encouragement of early initiation of breastfeeding and skin-to-skin contact. Second, we developed a decision tree to represent a birth event. Based on data from the literature, maternal complications occur in the model with some frequency, and progress probabilistically to a maternal endpoint of survival or death (based on likelihoods of complication severity, management, and the case fatality rate); neonates in the model face a risk of intrapartum-period stillbirth, and surviving neonates

may experience complications which may progress to death (again, due to probability of management and case fatality rate), both as a direct result of, and absent of, maternal complications during the birth. Third, we conducted a literature review to estimate the likely impact of each study SCC item on all intrapartum deaths (maternal, stillbirth, early neonatal). Fourth, we incorporated this information into the decision model to estimate the SCC's impact, both in a maximum scenario (assuming all health facilities could implement all of the SCC items explored here) and in a "readiness-adjusted" scenario (where each facility could only achieve a maximum level of improvements due to health system resource constraints).

The results from this paper indicate both the potential of an intervention like the SCC to significantly reduce mortality, as well as the likely importance of health system characteristics in facilitating this. Our "best case" estimate is that the SCC could avert up to one-third of facility-based maternal deaths, and up to 43% of facility-based early neonatal deaths. But we would not expect to see such effect sizes in practice, due to weaknesses in the health system: only 29.1% of district hospitals, 11.4 or 21.5% of rural or urban (respectively) community health centres, and 5.0% of primary health centres, have the sufficient supplies, medicines and infrastructure to fully implement the 7 SCC items studied here. In a sub-analysis among community health centres, which see approximately one-fifth of births at public health facilities in India, we estimated that these facilities could achieve only half the number of averted maternal deaths, and two-thirds the number of averted early neonatal deaths, versus maximum implementation in these facilities.

These findings suggest that interventions like the SCC for improving routine intrapartum care may offer significant potential for improving health outcomes, but likely require health system improvements in order to see maximum impact. This paper uses decision modeling to explore the scenario of scaling up a particular intervention in a specific context. It uses the best-available epidemiologic, intervention and health system data—but much of this information is highly uncertain. The sensitivity analyses in Chapter 3 highlight the degree to which this uncertainty may affect the results presented.

In particular, robust information is only recently emerging on the relationship between maternal and neonatal outcomes. Much is still unknown about how maternal complications affect infants, including the role of complication severity and of management approaches. At a more macro level, there is a newly developing evidence base about spillover effects of a maternal death. There are likely many ways in which children may be affected, including via health (both mortality and morbidity), development (psychosocial, economic), and social/structural mechanisms (household formation, marriage patterns, labor force participation). It is believed that these effects are likely severe, but they have not been well-quantified to date.

Chapter 4 offers some of the first evidence from a resource-poor setting on this topic. Using a large, long-term demographic dataset, from a Health and Demographic Surveillance Site (HDSS) in Butajira Ethiopia, we analyzed survival outcomes for children following a maternal death during or shortly after childbirth. The HDSS in Butajira has been collecting information from households since 1987, so this analysis leveraged the many decades of data to examine the intergenerational effects of the relatively rare event of a maternal death. In the study area, there were 30 maternal deaths over this period (classified as occurring within 42 days of a childbirth). Among the infants born to these deceased women, 81% of them also died. Thus a maternal death was virtually tantamount to the death of her infant. The risk of dying, particularly during infancy, was much greater for infants who had lost a mother than for those who had not (e.g., 46-57 times greater risk, in unadjusted and adjusted ratios).

These values exceed what has been reported elsewhere in the literature, e.g. from the HDSS dataset in Bangladesh—and this may be explained by the poor quality of intrapartum care in Butajira. Almost all women (90%) delivered their babies at home, and only one-quarter of births were attended by a skilled provider. This puts women at risk, and their babies may suffer as a direct result of these complications or from their own complications which are therefore also not attended to. There are also characteristics of

household composition and migration, as well as habits of prompt and long-duration breastfeeding, which may affect infant outcomes following the death of its mother. But it is likely that improved obstetric care could have a large effect on saving women's and infants' lives in Butajira.

Areas for future study

The methods and findings of this dissertation suggest several areas for future exploration. First, all three papers highlighted the need for additional data on the epidemiology of maternal and neonatal outcomes. Many values in the literature are estimates, extrapolated across geographic areas and/or across time—and it is critical to develop more specific measures, given the number of important contextual factors which may affect the prevalence and severity of these conditions. Such metrics are important for research purposes, as well as for developing more nuanced and robust measures of progress in reducing intrapartum-period mortality. Second, these papers also all point to a dearth of rigorous data about delivering effective interventions, particularly at-scale, for reducing mortality among mothers and infants. This dissertation offers new research approaches to considering these questions (i.e., the "threshold" analysis in Chapter 2 and the modeling exercise in Chapter 3), but direct empirical studies are also necessary—such as large-scale evaluations of programs that also include measurement of health system inputs (and associated costs) as well as measurement of long-term impacts, including intergenerational effects on fertility, morbidity and mortality.

Lastly, this dissertation underscores the importance of health system strengthening for improving maternal and neonatal outcomes. All three papers provide evidence on the association between intrapartum care and mortality—and strong health systems are needed to provide high-quality care. As the global community takes stock of progress toward the Millennium Development Goals, and considers a post-MDG agenda, the importance of health systems should be a foremost consideration.

Conclusion

Women and children continue to face substantial danger around the time of childbirth, and this mortality risk is particularly borne by those from the poorest households and in the poorest nations. Progress toward reducing the burden has been slow in many countries. This dissertation explored how to measure outcomes, and assess strategies, around maternal and infant mortality. The findings presented here highlight two main themes. First, outcomes for mothers and children are highly interconnected, so progress in reducing deaths among infants may depend in part on improving outcomes for the mother as well. Second, the provision of high-quality care during the intrapartum period will be essential for reducing both maternal and neonatal mortality—and this requires a well-functioning and strong health system. This dissertation identifies several areas for future research and exploration, from improved epidemiologic data, to better information on the costs and impacts of at-scale interventions. These findings and proposed next steps will, I hope, enrich the dialogue around how best to achieve improvements in reducing the excess burden of mortality seen by women and children, and will prove useful to other researchers and to policymakers seeking to make progress on this crucially important issue.