PHASE I REPORT OF THE EARLY-LIFE NUTRITION LINKAGES TO NONCOMMUNICABLE DISEASE (ELN-NCD) MODEL

MATERNAL INTERVENTIONS TO IMPROVE BIRTHWEIGHT AND GESTATIONAL AGE, BANGLADESH

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APRIL 2014

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ABOUT SPRING

The Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) project is a five-year USAID-funded Cooperative Agreement to strengthen global and country efforts to scale up high-impact nutrition practices and policies and improve maternal and child nutrition outcomes. The project is managed by the JSI Research & Training Institute, Inc., with partners Helen Keller International, The Manoff Group, Save the Children, and the International Food Policy Research Institute. SPRING provides state-of-the-art technical support and focuses on the prevention of stunting and maternal and child anemia in the first 1,000 days.

RECOMMENDED CITATION

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CONTENTS

ACRONYMS

ANC	antenatal care
BDHS	Bangladesh Demographic and Health Survey
BMI	body mass index
BP	blood pressure
BPE	balanced protein energy
CEA	cost-effectiveness analysis
CER	cost-effectiveness ratio
CI	confidence interval
CVD	cardiovascular disease
CYP	couple-years of protection
DALY	disability-adjusted life year
DHS	Demographic and Health Surveys
DSBP	decrease in systolic blood pressure
ELN-NCD	early-life nutrition linkages to noncommunicable disease
ET	epidemiologic transition
FANTA	Food and Nutrition Technical Assistance (project)
FP	family planning
GDP	gross domestic product
GHI	Global Health Initiative
GNI	gross national income
HKI	Helen Keller International
ICER	incremental cost-effectiveness ratio
IFA	iron–folic acid
IHD	ischemic heart disease
IFPRI	International Food Policy Research Institute
IPI	interpregnancy interval
IUGR	intrauterine growth restriction
JSI	JSI Research & Training Institute, Inc.
LBW	low birthweight

LBWS	Low Birthweight Survey
LE	life expectancy
LMIC	low- and middle-income country
MFC	marginal fixed cost
mg	milligram
mmHg	millimeters of mercury
MMS	multiple micronutrient supplementation
MIYCN–FP	maternal infant young child nutrition–family planning
NCD	noncommunicable disease
N-RNCD	nutrition-related noncommunicable disease
OECD	Organisation for Economic Co-operation and Development
PTB	preterm birth
RDA	recommended daily allowance
RHD	rheumatic heart disease
SBP	systolic blood pressure
SC	Save the Children
SD	standard deviation
SPRING	Strengthening Partnerships, Results, and Innovations in Nutrition Globally (project)
SSA	sub-Saharan Africa
TBA	traditional birth attendant
TMG	The Manoff Group
UNICEF	United Nations Children's Fund
UNIMAP	UN Multiple Micronutrient Preparation
USAID	U.S. Agency for International Development
WHO	World Health Organization
WRA	women of reproductive age

DEFINITIONS

In the main report, terms defined below will be denoted at their first appearance with italics.

Balanced protein energy (BPE) supplementation: A nutritional supplementation during pregnancy in which proteins provide less than 25 percent of the total energy content (Kramer and Kakuma 2003). Examples tested for costing in this model include high-energy biscuits and corn–soy blends of varying content (CSB 14, CSB 13, CSB ++).

Cost-effectiveness analysis (CEA): A type of economic evaluation that examines both the cost and health outcomes of intervention strategies. Results are presented as a cost-effectiveness ratio (below; Centers for Disease Control and Prevention 2013).

Cost-effectiveness ratio (CER): The ratio of the cost of an intervention to a specified measure of effectiveness, such as disability-adjusted life years averted.

Decision tree: A graphic tool used to model the potential outcomes of different strategies (decisions). It includes each potential option under investigation and the probability of each potential outcome; it also may include differential probabilities for subpopulations, as well as costs associated with each strategy, to conduct cost-effectiveness analyses.

Disability-adjusted life years (DALYs): A measure of disease burden expressed as the number of years lost due to ill health or disability based on the population's life expectancy. As an example, if a person dies one year prematurely, one DALY is lost; and with one year lived with disability prior to death a fraction of a DALY is lost.

Discounting: In cost-effectiveness analyses of health services, researchers' practice of diminishing the valuation of costs and outcomes relative to their futurity—commonly by a compounded 3 percent deduction per year into the future (Edejer, Baltussen, and Adam 2003). The appropriateness of discounting has been extensively debated, particularly the discounting of benefits or health outcomes.

Empirical evidence: Evidence based on experience—for example, on controlled experiments or observational studies—rather than on theory.

Epidemiological transition (ET): The general phenomenon of disease burden shifting from predominantly communicable disease to noncommunicable and chronic disease, associated with economic development (Appendix A).

Extended time horizon: All cost-effectiveness analyses of strategies' expected costs and benefits specify a time horizon—for example, the maternal and child periods for most maternal and child interventions, from birth through adult death in the model discussed in this document.

Flat versus variable cost curve: For intervention strategies, costs per unit can be characterized as the same for different volumes for ease of calculation or lack of information. However, due to economies of scale and other logistic realities, costs per unit likely vary according to volume (i.e., a variable cost curve) and should be used to calculate total costs if possible.

Gestational age: The period of time between conception and birth, estimated through ultrasound, anthropometry, or by determining the date of the first day of the pregnant woman's last menstrual cycle.

Hypertension: A chronic condition of elevated blood pressure, generally defined as greater than 140 mmHg systolic and 90 mmHg diastolic. Hypertension is a common cause of cardiovascular disease.

Interpregnancy interval (IPI): The timing between one pregnancy and the next. Very short or very long IPIs are associated with pregnancy complications and adverse birth outcomes.

Low birthweight (LBW): Weight of less than 2.5 kg at birth.

Marginal cost: The change in the total cost of a production run to make one additional unit. In this report, that additional unit would be coverage of one more woman. The marginal cost includes labor, materials, and an allocation of fixed costs associated with production of that unit of health.

Markov model: A type of decision tree that models recurring probabilities of potential outcomes over an extended period. Markov models are often used to represent changes in occurrence of chronic disease or when risk is ongoing. A Markov model will illustrate multiple cycles, with differing risk for each.

Multiple micronutrient supplementation (MMS): The practice of administering dietary supplements containing trace elements such as folate, iron, zinc, and various vitamins during pregnancy to address deficiencies that result from intake of meat, fruits, and vegetables inadequate to support both the health of the mother and her baby. This report explores the UN Multiple Micronutrient Preparation (UNIMAP), a set mixture of 14 micronutrients at dosages that approximate the recommended dietary allowances (RDA) for pregnancy (UNICEF, WHO, and UNU 1999).

Neonatal: Characterizing the period from birth to 30 days after birth. The likelihood of infant death is greatest at this time.

Noncommunicable disease (NCD): A disease that is not infectious and not transmissible among people. Examples include cardiovascular disease, type II diabetes, asthma, and cancer.

Nutrition-related noncommunicable diseases (N-RNCDs): Noncommunicable diseases resulting from nutrition, including cardiovascular diseases (CVDs), type II diabetes and other metabolic disruptions, and some cancers.

Pathway: A link between a particular condition and outcome, established through empirical evidence. In this document, pathways explored include the link between maternal nutrition and the likelihood of a baby being born with low birthweight and the link between increased adult blood pressure and preterm birth.

Preterm birth (PTB): Infants born at fewer than 37 weeks' gestational age.

Postneonatal: The period of infancy beginning at 31 days after birth and ending 364 days after birth.

Provider perspective: The point of view of the individual or institution offering care and treatment to a patient. In cost-effectiveness analysis, costs included in the evaluation of a strategy depend on whose perspective is being examined or to whom the costs and benefits accrue. A cost-effectiveness analysis from a provider perspective would include the cost of providing the service or intervention, but not the costs to the intervention targets (i.e., the clients or patients) and not the costs to society as a whole.

Sensitivity analysis: A type of analysis used to test the empirical or theoretical assumptions underlying a simulation model. The testing is accomplished by altering individual values within the model over a plausible range and determining whether the predicted outcomes (e.g., cost-effectiveness ratios) are meaningfully different.

Simulation model: A tool for predicting outcomes of an event or events.

Systolic blood pressure (SBP): The measure of the pressure in the arteries immediately after the heart beats. Blood pressure is usually written as a ratio between two numbers: the SBP at the top and, at the bottom, the diastolic blood pressure—the pressure in the arteries while the heart is resting between beats.

1,000 days: The period between a child's conception and his or her second birthday. Many nutrition advocates view these thousand days as being a crucial time to prevent malnutrition and the associated risks, including child mortality and susceptibility to infectious disease and later-life NCDs. Details can be found here: http://www.thousanddays.org.

WHO thresholds for cost-effectiveness: Three ratios between the relative costs of a health intervention and its outcomes, as established by the World Health Organization (WHO) to guide resource allocation and policy decisions. An intervention is highly cost-effective if it is less than a country's annual gross domestic product (GDP) per capita per DALY; cost-effective if the ratio is between one and three times a country's annual GDP per capita per DALY; and not cost-effective if it is more than three times a country's annual GDP per capita per DALY (Edejer, Baltussen, and Adam 2003).

EXECUTIVE SUMMARY

Evidence has steadily grown to support the hypothesis that in utero, infant, and young child undernutrition increases the risk of developing nutrition-related noncommunicable diseases (N-RNCDs) later in life. Analysis of maternal and child nutrition programs, however, tends to look almost exclusively at a small set of direct outcomes over a short period of time, such as change in nutritional status or pregnancy outcomes. Focusing only on these direct outcomes can lead to the underestimation of the interventions' effectiveness.

FIRST-PHASE MODEL: DEVELOPMENT

To remedy this problem, the Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) project, under the U.S. Agency for International Development (USAID), has developed a model for early-life nutrition linkages to noncommunicable disease (ELN-NCD), a simulation model designed to yield a more complete understanding of the value of early-life nutrition interventions. By extending the timeframe for estimating treatment benefits, the ELN-NCD Model seeks to quantify an intervention's impact both on early-life conditions and on any resulting later-life N-RNCD risk—that is, to account for both short-term benefits (accruing during the period from birth to one year) and long-term benefits (realized from the age of 20 years onward).

The ELN-NCD Model is being created in two phases, using an adaptive process. SPRING has completed the first phase of the model, focusing on selected maternal nutrition interventions that affect birthweight and gestational age in Bangladesh and the long-term effects of those interventions on reducing morbidity and mortality relating to cardiovascular disease (CVD). SPRING used evidence reviews, expert consultations, and multiple country-specific and region-specific datasets to gather the best available evidence on intervention costs and on the effects of interventions on birth outcomes and how those birth outcomes then affect the relative risk of acquiring N-RNCD in adulthood in this specific country context.

SPRING chose to first elaborate the model for three maternal nutrition interventions in Bangladesh. Two interventions impact maternal nutrition directly during pregnancy, via nutrient supplementation; the other has an indirect effect, via an increased interpregnancy interval (IPI) that allows for interpregnancy growth of maternal nutrient stores (King 2003). The direct interventions include multiple micronutrient supplementation (MMS) and balanced protein energy supplementation (BPE). The indirect intervention consists of family planning (FP) between pregnancies to lengthen the IPI.

SPRING describes mortality results for two time periods: deaths or disability-adjusted life years (DALYs) averted for infants in the short-term period and deaths or DALYs averted for adults over the long-term period. Results are estimated with a dynamic model, where the two periods are allowed to interact; and with a static model, which estimates short-term and long-term effects separately. The total effect differs based on how results were modeled.

FIRST-PHASE MODEL: KEY RESEARCH FINDINGS

- **Static Model:** By reducing adverse birthweight outcomes, MMS appeared to avert about 13 percent of total modifiable short-term deaths. In addition, MMS was the most effective intervention in lessening the number of long-term deaths, averting approximately 10 percent of total modifiable long-term deaths in the static model. BPE was the next most effective at saving lives in the short-term and long-term periods, averting 9 percent and 8 percent, respectively. The indirect intervention, FP via IPI, did not produce notable decreases in either short- or long-term deaths.
- **Dynamic Model:** Short-term survival offsets deaths averted in the long-term period, since more children grow up to be adults at risk of developing CVD. In some cases, it appears as if more deaths were due to the intervention in the long-term period. However, because of the positive gains in disability averted, as measured in DALYs, the interventions still have a net positive effect on CVD outcomes.
- **Cost Estimates:** Based on the information available on fixed and variable costs, SPRING produced low and high marginal costs. FP was the least expensive at US$4 to US$6 per pregnancy or couple-years protection (CYP). MMS followed at US$7 to US$19 per pregnancy, with and BPE at US $16 to US$27 per pregnancy.
- **Cost-Effectiveness:** MMS appears to be the most cost-effective of the three interventions because of its relatively low marginal cost and its higher total effectiveness. Discounting the estimates by the traditional 3 percent, MMS was found to be highly cost-effective (ranging from US$160 per DALY to US$437 per DALY). BPE and FP via IPI were also both considered cost-effective in the low-cost scenario. Only BPE continued to be cost-effective in the high-cost scenario.

IMPLICATIONS, USES, AND FURTHER DEVELOPMENT

Analyzing the effects of nutrition interventions solely based on empirical evidence from randomized control trials, one would expect gains in life years over both the short-term and long-term periods. One might also assume that adding these gains to one another would yield an understanding of the total effect of an intervention over an individual's lifetime. However, by showing how interventions make themselves felt in multiple time periods, the ELN-NCD model provides a more accurate and complete picture of the effects. For example, the short-term effect of survivorship had a considerable confounding effect on interventions' impact on long-term outcomes. While more accurate, this complicates measurement of changes in CVD mortality for the long-term period, which is affected both positively and negatively by the same intervention: The 20,000 children saved during the short-term period can potentially die of CVD as adults.

The construction of the first-phase ELN-NCD model also identified major gaps in research, among them:

- Incomplete information on overlapping risk of combined adverse birth outcomes
- A lack of information on how the rate of weight gain post-birth modifies the N-RNCD risk of low birthweight /preterm birth babies and stunted children

- The margins of error around the date of conception and gestational age when using maternal recall, and therefore in assessing an intervention's efficacy in reducing PTB.

Recent papers published in *The Lancet* 2013 Series on Maternal and Child Nutrition, a series of four papers and a commentary from the authors, all available online,[1] have begun to fill gaps related to the first and second examples (Katz et al. 2013; Adair et al. 2013). Further work is needed to fully address the third example.

The ELN-NCD model will be expanded during SPRING's second phase to include the newly available evidence from *The Lancet* 2013 Series and other late-breaking birth outcome evidence. Potential additional extensions into other country settings, other interventions, and/or other long-term disease outcomes will be weighed in this second phase for feasibility and strength of evidence.

After work on both phases is completed, the results should provide valuable information to help program planners and policymakers strengthen advocacy for nutrition programs, improve planning and target setting for portfolios of maternal health and nutrition interventions, and inform the prioritization of these interventions.

1 http://globalnutritionseries.org/

INTRODUCTION AND RATIONALE

With a large proportion of the global population living in a context of rapid economic expansion and industrialization, traditional disease patterns have undergone a shift. These economic changes—bringing with them social upheaval, greater urbanization, and increasing prosperity—are helping to enact a transition in disease burden from communicable to *noncommunicable disease* (NCD),[2] including cardiovascular disease (CVD; Gersh et al. 2010). At the same time, in utero and young child undernutrition in many low- and middle-income countries (LMICs) has been linked to vulnerability to adult *nutrition-related noncommunicable disease* (N-RNCD; Barker 1992; Gluckman, Hanson, and Buklijas 2010).

"The facts are unequivocal and disturbing," point out Gersh et al. (2010). "CVD disease remains the leading cause of death in the world, far outstripping deaths due to malaria, HIV/AIDS, and tuberculosis." The authors note that about 80 percent of the 35 million deaths caused by NCDs each year and a similar percentage of the 16.7 million deaths caused by CVD occur in LMICs. These countries struggle with a daunting dual burden of chronic diseases and communicable diseases, both of which require complex, long-term medical care and consume vast amounts of these countries' limited health care resources. Adding to this dual burden is the loss of productive years of life. The resulting set of economic constraints can be crippling, both in the private and the public sectors (Gersh et al. 2010).

To help address the burden of CVD and other N-RNCDs, researchers, donors, and policymakers are beginning to look more closely at the effects of early childhood indicators of health in later life. With increased funding and coordination for nutrition interventions in the first *1,000 days* (i.e., from conception to two years of age) and with developments such as the World Health Assembly NCD resolution and the Global NCD Action Plan 2013–2020 of the World Health Organization (WHO), interest has grown in quantifying the relationship between N-RNCDs and early-life nutrition interventions.

An obstacle to quantifying this relationship is the way in which analysis of such interventions has been carried out. Maternal and child nutrition programs are often evaluated by looking at a small set of direct outcomes occurring over a short period of time, such as change in nutritional status or pregnancy outcomes. Only occasionally is evaluation extended to include changes in mortality in the near term. Basing estimation of benefits only on these direct outcomes creates a real risk of underestimating the effectiveness of early-life nutrition interventions.

To achieve a truer, more useful picture of such interventions' effectiveness, SPRING has developed a model for early-life nutrition linkages to noncommunicable disease (ELN-NCD), which extends the timeframe in which benefits are identified. Specifically, the model aims to quantify an intervention's value-added benefit—its impact on any resulting N-RNCD risk level in adulthood in addition to its impact early-life conditions, the conditions it was originally designed to resolve. Model creation is proceeding in two phases using an adaptive process.

SPRING has completed the first phase of the model, looking at selected maternal nutrition interventions that affect birthweight and *gestational age* in Bangladesh, and their long-term effects on reducing CVD. The relatively strong theoretical and *empirical evidence* for this linkage makes it

2 Terms with definitions will be denoted in the text at their first appearance with italics

a logical first relationship to model (e.g., Christian and Stewart 2010; Eckhardt 2006). SPRING used evidence reviews, expert consultations, and multiple country-specific and region-specific datasets to gather the best available empirical evidence on interventions' costs, their effects on birth outcomes, and how these birth outcomes then affect the relative risk of acquiring an N-RNCD in adulthood in this particular country context.

Then SPRING used this empirical evidence to develop a multilevel simulation model to estimate lifetime health burden based on birth outcomes across a series of categories of birthweight and gestational age. When combined, the model's results allow comparison of each intervention's impacts and present a more complete measure of value for money, or benefits per dollar, than traditional models, which account only for short-term effects.

The first-phase ELN-NCD model identifies variations in cost-effectiveness among the chosen interventions, variations related primarily to the costs of the commodities, to existing levels of intervention coverage, and to initial effectiveness in reducing adverse birth outcomes. There were also key technical findings related to using an *extended time horizon*. These findings will help improve understanding of future models that look at an individual's full life course when calculating effectiveness and costs.

RATIONALE

In SPRING's literature review, a limited number of studies on the cost-effectiveness of nutrition interventions were found; these studies focused on child nutrition interventions or food fortification (e.g., Allen and Gillespie 2001; Baltussen, Knai, and Sharan 2004). The latest work by the Food and Nutrition Technical Assistance Project (FANTA) with PROFILES separately estimated effectiveness and costs for several health and nutrition interventions (Howlander et al. 2012). SPRING did not find any literature that provided cost-effectiveness estimation like that of the ELN-NCD Model, which reflects both short- and long-term mortality and morbidity reductions resulting from particular interventions. Specific to maternal nutrition, no studies were found that estimated the cost-effectiveness of the three interventions modeled by SPRING in this exercise, with respect to either short- or long-term health outcomes.

The ELN-NCD model makes several unique contributions.

First, by extending the timeframe for evaluating nutritional interventions, it enables a more inclusive and dynamic understanding of the relative value of the interventions it examines, producing effectiveness and cost-effectiveness estimates based on the extended period and it providing greater technical understanding of the complexity of the life-course perspective on maternal interventions.

Second, findings produced by this model have been used to identify the most critical of the research gaps that inhibit further understanding of how adverse birth outcomes (and prevention of those outcomes) affect later-life risk for N-RNCD morbidity and mortality.

Third, from a programmatic perspective, the model can be viewed as a tool to evaluate the relative value of various maternal nutrition interventions and as a guide to prioritize such interventions. The results can be used for advocacy and planning (specifically, for target setting) by governments, international agencies, and donors.

The findings in this report are based on the results of a *simulation model*. A simulation model is used in lieu of a longitudinal dataset because relatively few longitudinal studies have looked at this topic in a developing country context. Although several cohort studies related to nutrition and/or N-RNCDs have been done in LMICs, none have yet matured to the point of providing information on linkages between observed birth outcomes and adult mortality outcomes.[3] The ELN-NCD model enables findings from shorter time periods to be linked into a simulated life course for a synthetic cohort of newborns.

The ELN-NCD model provides the following information not previously available in the literature:

- **The impact of reductions in adverse birth outcomes:** Approximate estimates on both short- and long-term health outcomes, regardless of intervention.
- **The effectiveness of specific maternal nutrition interventions:** Approximate estimates for both short- and long-term health outcomes as related to birth outcomes in a metric comparable to those used in cost-effectiveness evaluations of other health interventions—that is, disability-adjusted life years (DALYs).
- **Interventions' cost-effectiveness:** Approximate estimates in a metric comparable to those used in *cost-effectiveness analyses* of other health interventions (DALYs).

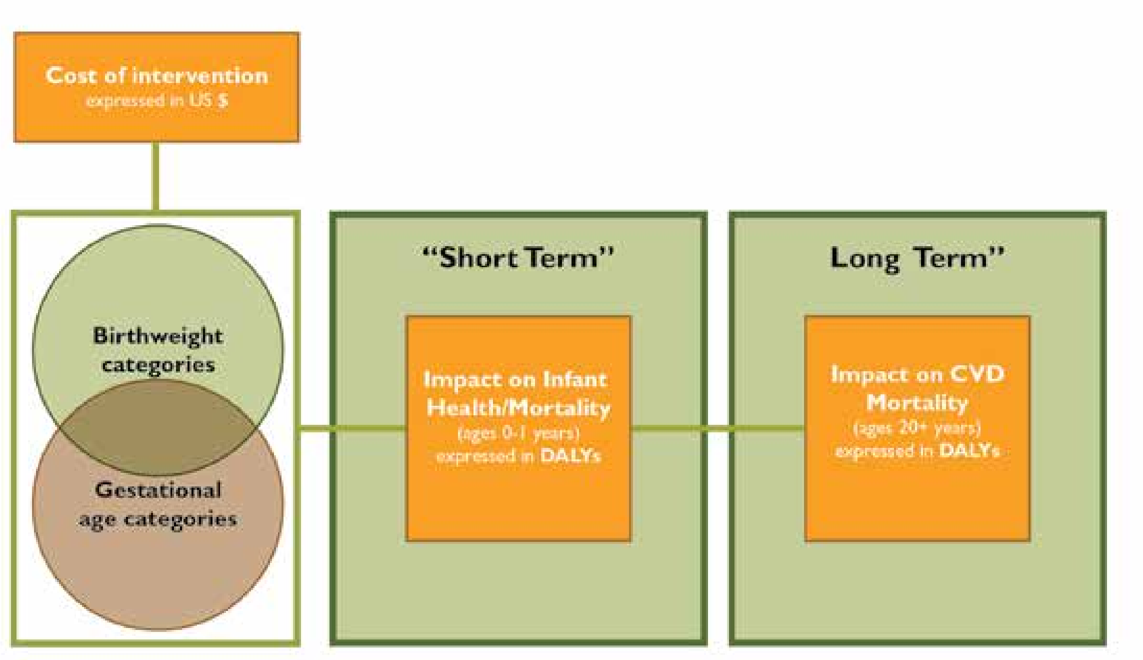
3 The longest active published cohorts in Southeast Asia (SPRING model phase 1 region) are the New Delhi Birth Cohort; the Lahore Slum cohort; the Cebu Longitudinal Health and Nutrition Survey cohort; the Pune child cohort; and the Mysore Adult birth cohort. Most of these studies began between 1979 and 1995. Surveillance data from Matlab, Bangladesh, are also available—these data are collected routinely and data on some indicators have been collected since 1966. Although not a cohort study, some data were collected during randomized controlled trials exploring micronutrients and family planning outcomes.

METHODS SUMMARY

This section summarizes the methods used in the model. For a more extensive exposition of the methods, please see the appendices noted in each section.

The model is designed to look at the population from a *provider perspective* and to be useful to potential funders of maternal nutrition interventions. The model provides information related to the short-term and long-term effectiveness and cost-effectiveness of maternal nutrition interventions that modify birth outcomes. Figure 1 describes the terms and scope of the model.

Figure 1. Scope of the ELN-NCD Model



Ideally, all effects for children aged 0–4 years would be included in the short-term, but evidence of impact was found only for *neonates* (0–30 days) and *postneonates* (1–11 months). Thus, “short-term effects” are those occurring only during the first year of life.

Rather than looking separately at birthweight and gestational age, SPRING examined four categories of birth outcomes (*below and Appendix B*), created by combining two indicators:

- Normal birthweight combined with a term birth
- *Low birthweight* (LBW) combined with a term birth
- Normal birthweight combined with a *preterm birth* (PTB)
- LBW combined with a PTB.

Together, these categories achieve the greatest possible level of specificity using current evidence.

Evaluating interventions’ effect on LBW and PTB (and the combination of these two conditions) was the first step in analyzing short- and long-term effects.

In the following pages, for the sake of brevity, "short term" will be used as shorthand for infant morbidity and mortality and "long term" to indicate adult morbidity and mortality—which, because of the parameters of this first phase work, is entirely CVD related.

SETTING

The best available evidence among LMICs came from Southeast Asia. Countries in this region with significant USAID nutrition funding (via the Global Health and Feed the Future initiatives) include Bangladesh, Nepal, and Cambodia. Of these, Bangladesh received the most funding by far; in fact, it is the region's top recipient of nutrition funding from USAID this year.[4] In addition, the research and evidence for Bangladesh are some of the strongest available for an LMIC and among publicly available data those for Bangladesh are the most recent (DHS, HCES, UNICEF Low Birth Weight Survey).

4 According to Foreignassistance.gov, 2013 planned support for Bangladesh (State Dept, USAID, and Millennium Challenge Acct) is US$25.8 million. Nepal is the next most funded South Asian country, with US$6.6 million in funding (ranks eighth out of all country support) http://foreignassistance.gov/ObjectiveView.aspx?budTab=tab_Bud_Planned#ObjAnchor.

EVIDENCE REVIEW

All evidence used in the model was obtained via a two-step review. First, an exploratory review conducted across Cochrane and Cochrane-style meta-analyses searched out direct and indirect nutrition interventions that had had an effect on birth outcomes. After this review was completed and the strongest interventions selected, a systematic literature review was completed to learn more about those interventions. This review process continued with an exploration of additional linkages to evidence in the model (e.g., linking birth outcomes to blood pressure, blood pressure to CVD mortality).

Evidence from the completed searches was selected based on a hierarchy that took into account both its location source and its quality. Studies set in Bangladesh were preferred, followed by others in South/Southeast Asia and then by studies from other developing countries. If no quality studies could be found within these locations, evidence was selected from developed countries in Asia, and then—only as a last resort—from non-Asian members of the Organisation for Economic Co-operation and Development (OECD). Study quality was defined in terms of recency, sample size, study design, and/or controls for relevant characteristics. In certain instances where the published literature could not provide the evidence needed for the model, secondary survey data analysis was used instead.

EVIDENCE FOR EFFECTIVENESS

A relatively large body of literature addresses the linkages between maternal nutrition and birth outcomes, although many studies are not properly designed to capture birthweight or gestational age outcomes. The main issues revolve around accurate measurement of birth outcomes and comparability of the interventions included in the evidence. *Multiple micronutrient supplementation* (MMS) has the most uniform set of interventions, because there is an internationally accepted standard mixture (the UNIMAP presentation[5]); the components of *balanced protein energy* (BPE) *supplementation* vary widely.

Two intermediate outcomes are often theorized to have a significant effect on birth outcomes via improved maternal nutrient stores: age at first birth and the *interpregnancy interval* (King 2003). Of these two intermediate outcomes, the evidence linking to birth outcomes is strongest for IPI, and FP is the intervention that was found to have the biggest impact on IPI (DaVanzo et al. 2004; Conde-Agudelo et al. 2012; Conde-Agudelo 2006). Published evidence was not designed in a way that it could be incorporated into the ELN-NCD model. Thus, SPRING used data from the DHS reproductive calendar to model the effect of FP on IPI in a way that allowed for combination with the published evidence on IPI (more details on this analysis provided in Appendix D).

Table 1 shows the selected effect sizes for the three types of interventions.

For more information on how these three interventions were chosen and for full explanation of the evidence, see Appendix B.

5 UN Multiple Micronutrient Preparation (UNIMAP) is a set mixture of 14 micronutrients at dosages that approximate the recommended dietary allowances (RDA) for pregnancy (UNICEF, WHO, and UNU 1999).

Table 1. Selected Intervention Effect Sizes

INTERVENTION (SOURCE)	SELECTED EFFECT SIZE
MMS (Haider and Bhutta 2012)	17% reduced risk of LBW
	No effect found on PTB
BPE (Ota et al. 2012)	12% reduced risk of LBW
	No effect found on PTB
FP via IPI (DHS, UNICEF surveys)	Average of 5.2 month increase in IPI (affecting 24%–28% of mothers)
	2% reduced risk of LBW
	Not able to test PTB due to quality of gestational age data

EVIDENCE FOR COSTS

A similar review process was conducted for evidence on cost of MMS, BPE, and FP via IPI interventions in Bangladesh. However, no studies were found that would meet all of the following criteria: quality, timeliness, context, and comparability. In lieu of published evidence on costs for the selected interventions, SPRING developed a method that permitted each intervention's total and *marginal costs* to be estimated based on product costs for the intervention and delivery costs, based on the scale and coverage of each intervention across the population. In most previous studies, estimating delivery costs as a flat, static factor[6] across all scales of delivery created a false representation of costs. In reality, the marginal cost of delivering a service goes down as scale increases because fixed costs are distributed over a larger number of units (Johns and Torres 2005). SPRING used a dataset created from 300 USAID-funded public health and family planning delivery projects to estimate a marginal fixed cost (MFC) function. These data points included the transport, storage, and other additional costs related to the delivery of project services. For further information on this function, see Appendix E.

Product unit costs were gathered from the latest-year estimates for the commodities used by the interventions described in the literature. Mode of delivery and scale were defined by the literature and analysis of the most recent Demographic and Health Survey (DHS). When two different legitimate estimates of unit cost or mode of delivery were available, SPRING allowed for that variation in the cost function, resulting in low and high cost estimates for each intervention. If an additional value for unit cost was available but of lesser quality or of unknown location, it was tested in the *sensitivity analyses*.

Table 2 shows the evidence selected for commodity costs and delivery methods of the three interventions. For further details on this evidence, see Appendix E.

For results of the evidence review beyond the intervention stage (for those stages that link interventions to outcomes), see Appendices B and C.

6 See definitions list, under flat versus variable cost curve.

Table 2. Selected Commodity Costs and Details

INTERVENTION	COMMODITY COST*	COMMODITY CONTENT	DAYS OF SUPPLEMENTATION
MMS	US$0.015–0.035 per sachet	UNIMAP Presentation	196 days
SOURCE	*Sprinkles Global Health Initiative (2013)*	*UNICEF, WHO, and UNU (1999)*	*UNICEF, WHO, and UNU (1999)*
BPE	US$0.13 per daily dose	CSB 14	112 days
SOURCE	*Webb et al. (2011)*	*Webb et al. (2011)*	*Mean from interventions reviewed in Ota et al. (2012)*
FP VIA IPI	Varied by method	Representative method mix	N/A—one CYP**
SOURCE	*USAID | DELIVER PROJECT (2012)*	*Analysis of BDHS 2011*	*USAID CYP conversion factors*

* Primary commodity costs were adjusted from source data to 2012 prices (if source was not 2012); if secondary estimates were available, they were used in the sensitivity analyses. **CYP = Couple-Years of Protection

SIMULATION MODEL

Evidence collected during the review was input into a combined *decision tree* and *Markov model*, which analyses a hypothetical population of individuals over the course of their lives. In essence, a decision tree is a form of analysis where each "branch" represents a possible health state or occurrence, and the likelihood of an individual ending on any given branch hinges on the probabilities entered into the model. A Markov model builds off a similar tree structure but repeats cyclically at a certain rate—for instance, every year. As each individual enters the Markov model, he or she will be "at risk" for the undesirable health state in each cycle, with varying risk, depending on such factors such as beginning health status, age in the cycle, and demographics.

In the ELN-NCD model, after the mothers receive one of the three interventions (or none), the cohort is born into four combinations by birthweight and gestational age. Intervention effect sizes are modified by the mother's nutritional status during pregnancy and her location (urban or rural), where the information was available. A baby's probability of being born preterm depends on weight; the ELN-NCD model revealed that if an intervention increases birthweight but does not reduce PTB independently, the child's likelihood of being PTB *and* LBW decreases.

A proportion of each of the four groups will die during the short-term period, either in the neonatal or postneonatal stage. This marks the first point at which LBW/PTB status can affect model outcomes; both outcomes independently increase the probability of death. To estimate long-term effects, the age and cause of death for individuals in the remaining cohort are determined within the Markov model with one-year cycles. In each cycle, individuals in the cohort die from CVD-related causes, die from other causes, or survive to the next cycle.

The probability of death from any cause is age- and sex-specific. Based on consultations with experts, SPRING further altered the model to include epidemiological shifts. The ELN-NCD model takes into account that its cohort undergoes an *epidemiological transition* (ET) whereby economic development brings decreases in overall mortality (primarily through control of infectious diseases), accompanied by increases in the proportion of CVD-related mortality. The probability of CVD-related death is dependent on blood pressure, which is estimated based on increases in Bangladesh's current mean *systolic blood pressure* (SBP). This is how PTB/LBW affects long-term health outcomes: Both birth outcomes are hypothesized to increase the probability of CVD-related death by increasing individuals' blood pressure (Appendix C).

BASE CASE DATA SOURCES AND ASSUMPTIONS

The cohort under study consists of births to all mothers in Bangladesh in a year that would be targeted for the three interventions. Since 2011 is the latest DHS for Bangladesh and coincides with the year of several other pieces of evidence, it was chosen as the index year. The birth cohort size for that year was an estimated 3,643,951 (U.S. Census, International Database estimate).[7]

The sociodemographic characteristics in the index year were taken from two datasets: the 2011 Bangladesh Demographic and Health Survey (BDHS) and the National Low Birth Weight Survey of Bangladesh 2003–2004, which was conducted by UNICEF (hereafter, "UNICEF LBWS"). Male–female ratios were obtained from the *CIA World Factbook* (1.04:1). The probability for being born LBW (36 percent) was taken from the proportion of LBW babies from the UNICEF LBWS. Note that although its birth outcome data for Bangladesh is the most recent birth outcome data found, current proportions may be lower, as indicated by Bangladesh's recent improvements in infant survival (National Institute of Population Research and Training, Mitra and Associates, and ICF International 2013). The survey also found conditional probabilities of 20.71 percent PTB given LBW, and 9.11 percent PTB given normal birthweight. Although these figures should be interpreted with caution (because the publicly available survey data did not appear to contain weights appropriate for making the results nationally representative), an unpublished community-based study in 2003–2004 found similar proportions of LBW and PTB (Barros et al. 2011), despite the study location being in Dhaka, an urban area.

Outcomes are reported in terms of short- and long-term deaths averted and DALYs. In accordance with current practice for calculating DALYs, maximum possible life expectancies (LEs) were used (specifically, those of Japan—79 for men, 86 for women, per Wang et al. 2012) and discounted at 3 percent (and at 0 percent for sensitivity analyses) to arrive at DALY estimates associated with each infant death and adult death. For each infant who, because of an intervention, does not die, approximately 31–32 DALYs would be saved (3 percent scenario). The number of DALYs saved per CVD death averted will vary based on the age at death. The results of the ET model find that by the time the cohort reaches adult age (20), Bangladeshi life expectancy will approximate that of present-day Malaysia, the country in Southeast Asia most closely aligned with projected Bangladeshi SBP and gross national income (GNI) levels. Thus, the time horizon for the model is the current Malaysian life expectancy (74 years). In reality, a small percentage of the cohort will survive past that age, but it is assumed additional benefits (i.e., DALYs) are negligible after that point and may be distorted by the Markov model as it "kills off" the remainder of the cohort.

7 More information on calculations here: http://www.census.gov/population/international/data/idb/estandproj.php.

OUTCOME CALCULATIONS AND DEFINITIONS

A key consideration for the use of the ELN-NCD model is the effect of survivorship related to long-term CVD outcomes. It was apparent while running the simulation that effects in multiple time periods create a more complex result. It becomes difficult to compare deaths averted or DALYs saved strictly in the long-term period because of the way changes in the short-term period affect the number of individuals reaching adulthood. The text below summarizes this dynamic.

A VERY SIMPLE EXAMPLE

Cohort A starts with 100,000 children.

- In the base case (with no intervention), 40,000 will die short-term due to birth outcomes (given 40 percent infant mortality) and 30,000 will die long term (given 30 percent CVD mortality).
- Intervention A is able to avert 20,000 deaths during the short-term period and 5,000 in the long-term period (because of the reduction in LBW and PTB). With these deaths averted, mortality rates are 20 percent for infants and 25% for adults (from CVD).

One might say the total deaths averted by Intervention A are 25,000. But if the Intervention A CVD mortality rate (i.e., 25 percent) is applied to the additional children who have survived (.25 * 20,000), 5,000 of those "saved" infants will also die of CVD—cancelling out the CVD deaths averted by the intervention.

This primarily affects the calculation of deaths (life years lost); the DALY will still partially capture morbidity reductions resulting from Intervention A. However, both deaths averted and DALYs will be reduced because of the dynamic explained in the boxed text above. As a result of the issue of short-term survivorship, this report looks at results derived from the ELN-NCD model in two ways:

- **Dynamic model:** The dynamic model produces the results gained by running the full model with all effects (both short-and long-term) allowed to interact. This model is used to produce the final *cost-effectiveness ratios* (CERs) and all DALY calculations. Stated another way, the 20,000 additional infants who survive due to an intervention will be among the adults at risk of developing CVD later in life. This situation, although close to reality, complicates the ability to examine how the intervention affects CVD mortality—with the reductions being the intervention's unique value added.
- **Static model:** This model separately highlights the short- or long-term effects of an intervention—in essence examining what happens to the cohort if the intervention's effects occur only in the short-term period or only in the long-term periods. Short-term survivorship stays constant across interventions and the baseline to eliminate the confounding negative effect on this outcome. It is important to note when modeling the short-term period and long-term period separately, one cannot add together the lives saved or DALYs to understand the final outcome. Only the dynamic model, with its combined estimates, can provide this understanding.

SENSITIVITY ANALYSES

After a simulation model is run and results are produced, it is important to run sensitivity analyses. These analyses test how sensitive the model results are to the assumptions used and evidence entered. One-way sensitivity analyses were conducted to test alternative model input values and assumptions. The results of these tests were used to create "plausible range" around the ELN-NCD model results (see Results). The greater the range of alternative evidence, or the weaker the assumptions, the wider the plausible range will be, and as such can be interpreted in a way similar to confidence intervals around regression results.

Assumptions and evidence tested in the sensitivity analyses:

- **Effect of MMS on LBW and PTB:** Evidence for a Bangladesh-specific study is available but was not preferred over a stronger meta-analysis, as the results were not significant. Given the hierarchy favoring local evidence, it is included in the sensitivity analyses.
- **Effect of LBW on SBP:** The model assumes that the effects of PTB and LBW on SBP found in the literature are completely independent. This assumption is tested by making LBW's effect on SBP 0 and half of the increase stated in the literature (1.29 mmHg).
- **Effect of epidemiological transition on SBP:** Lower and higher growth rates based on other possible matched countries in the ET model were tested, which will result in different changes in SBP over time for the model cohort.
- **Cost of MMS:** The generic micronutrient tablet cost and the more expensive Sprinkles© sachet cost were also tested.
- **No discounting of DALYs:** CERs with no discounting for future outcomes (as opposed to the standard 3 percent) were also tested, in accordance with the alternate calculations conducted as part of the *Global Burden of Diseases, Injuries, and Risk Factors Study* 2010 (Institute for Health Metrics and Evaluation).

RESULTS

This section is organized by the list of unique contributions given in the earlier Rationale subsection. It includes comparable results for the three interventions: multiple micronutrient supplementation, balanced protein energy supplementation, and family planning via interpregnancy interval.

IMPACT OF REDUCTIONS OF LBW AND PTB ON HEALTH OUTCOMES, REGARDLESS OF INTERVENTION

Prior to modeling the outcomes by intervention, it is important to describe the percentage of total deaths in each time period that are actually avertable, or modifiable, by reducing LBW and PTB. Figures 2a and 2b show the scope of mortality and morbidity that could feasibly be changed by reducing LBW and PTB. Figures 2a and 2b display the maximum deaths during the short-term period (a) and the long-term period (b) that could potentially be averted by eliminating LBW and PTB or by reducing these conditions by 20 percent increments. Note that the long-term deaths in Figure 2b were derived from the static model.

Figure 2a. Short-Term Deaths Averted Due to Incremental Reductions in LBW and PTB

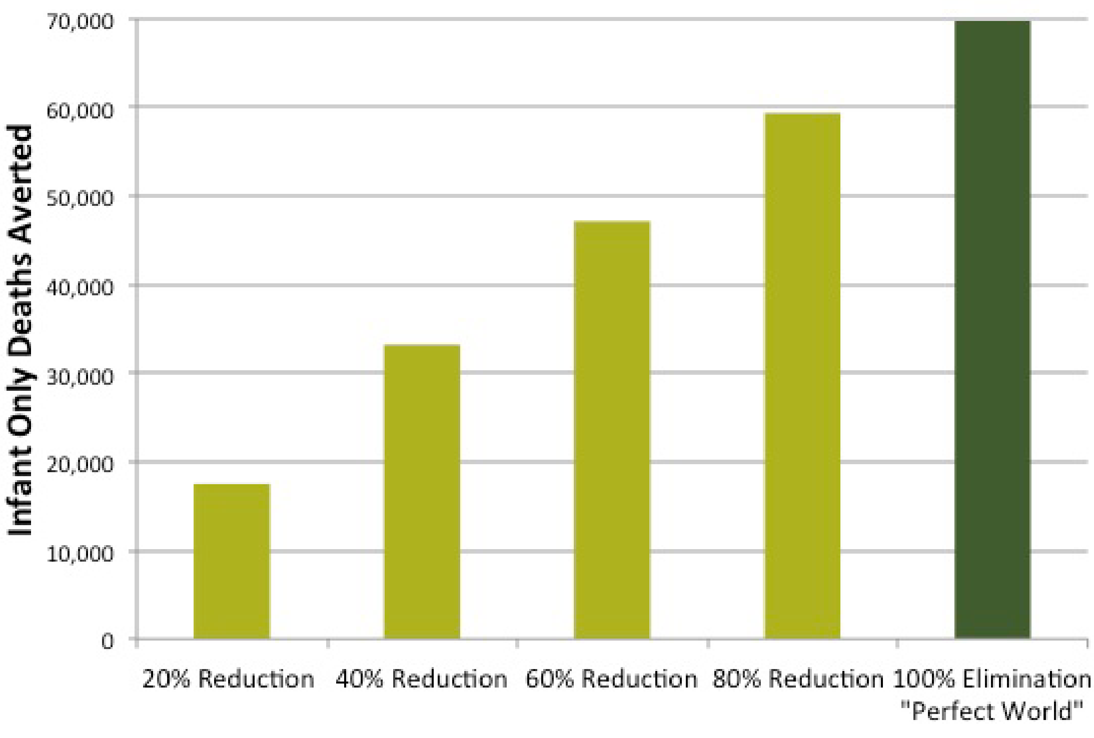
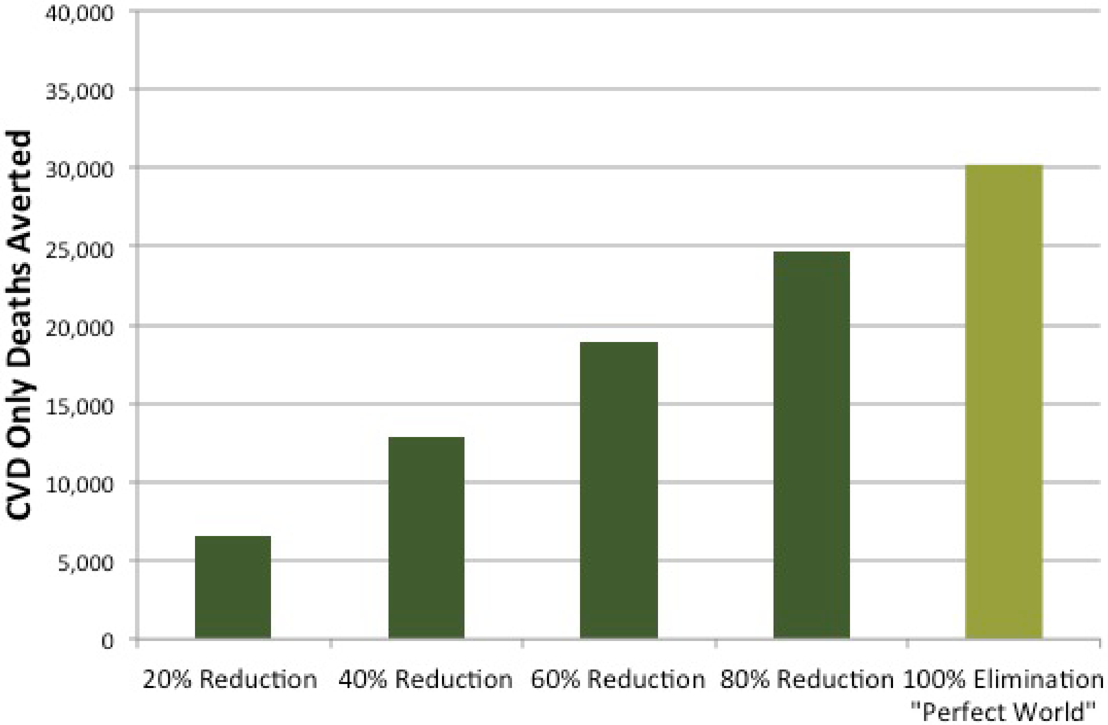


Figure 2b. Long-Term Deaths Averted Due to Incremental Reductions in LBW and PTB, Static Model



Based on the ELN-NCD model cohort of 3.6 million births, there are an estimated 115,000 total infant deaths and approximately 1.5 million deaths from CVD. LBW/PTB is responsible for 60 percent of all infant deaths (approximately 70,000) and for 2.3 percent of all CVD deaths (approximately 30,000). In the "perfect world" scenario in which LBW and PTB conditions are eliminated, these percentages translate directly to lives saved or deaths averted. Based on the model's assumptions, there is a very steady and linear decrease in the deaths averted per 20 percent decrease in LBW/PTB during the short- and long-term periods. In reality, as a condition comes closer to elimination, those most at risk are reached, thus the relationship likely follows more of a curve that accelerates upward with relatively few deaths averted in the lower quintiles and relatively more deaths averted in the quintiles closest to total elimination.

EFFECTIVENESS OF MATERNAL NUTRITION INTERVENTIONS ON LBW- AND PTB-RELATED HEALTH OUTCOMES

The prior analysis allows for comparison of each intervention's relative ability to reduce deaths and DALYs in each time period to the ideal situation of total elimination of the two adverse birth outcomes. Figures 3a and 3b show how many of the total modifiable short- and long-term deaths could be averted by the three interventions.

Figure 3a. Short-Term Deaths Averted by Selected Interventions

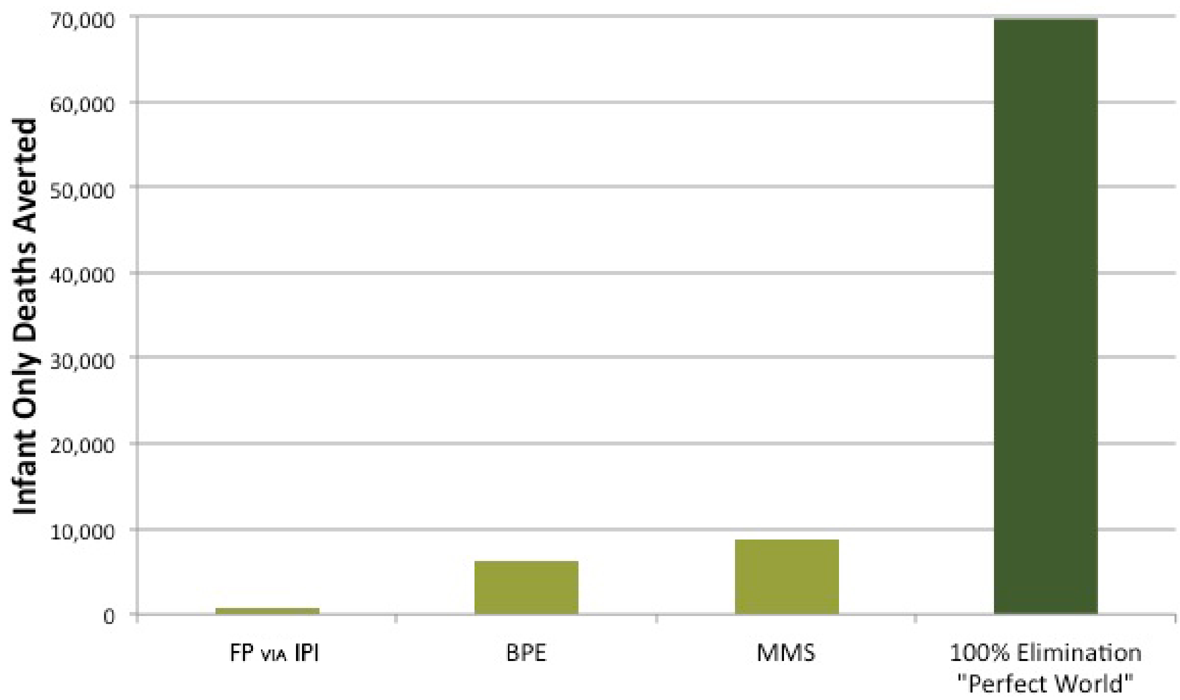
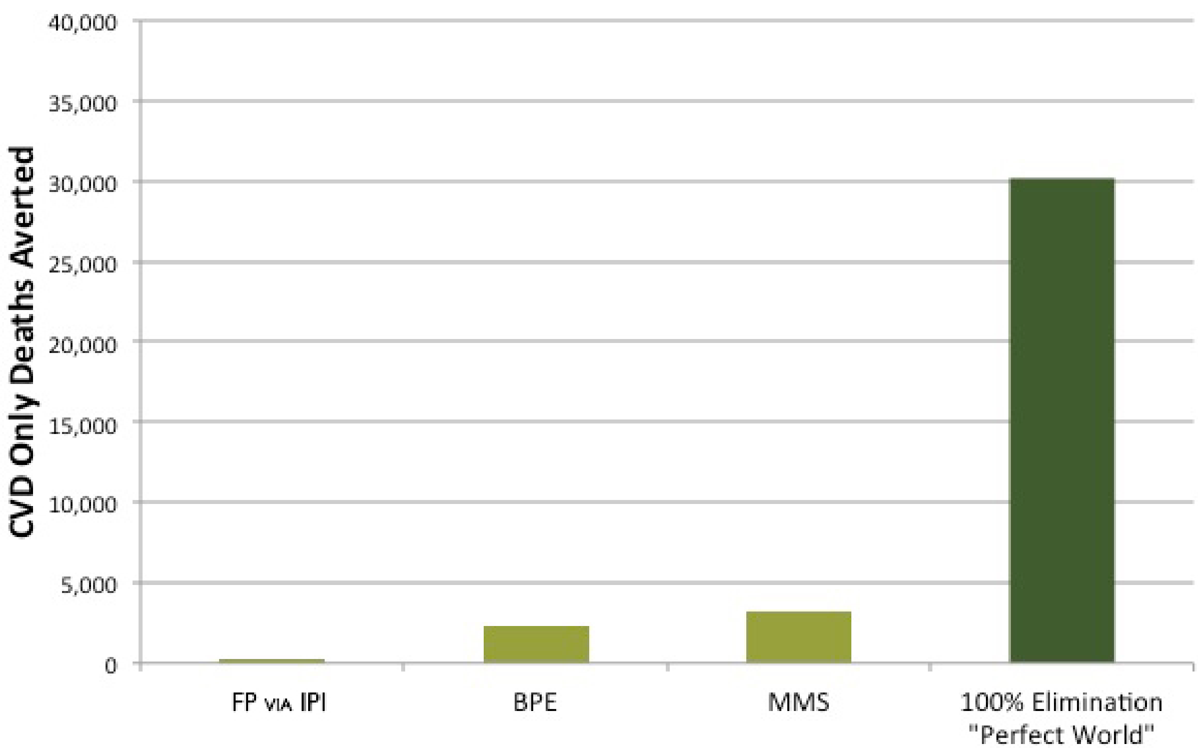


Figure 3b. Long-Term Deaths Averted by Selected Interventions, Static Model



These results come from the static model to allow for consideration of the separate effects of the interventions in each time period. Out of the total modifiable short-term deaths, MMS was most effective at saving lives. By reducing LBW incidence by 17 percent, MMS appeared to avert about 13 percent of total modifiable infant deaths. MMS also was most successful at reducing CVD deaths, averting approximately 10 percent of total modifiable CVD deaths.

BPE was the second-most effective intervention for saving lives during both the short- and long-term periods, averting 9 percent and 8 percent of total modifiable deaths, respectively. The indirect intervention, FP via IPI, did not produce notable decreases in deaths during the short- or long-term periods, primarily because of the minimal effect sizes found for FP on IPI. An additional factor was that the relatively low unmet need for FP in Bangladesh significantly reduced the potential intervention population. From analysis of the BDHS 2011 reproductive health indicators, approximately 30 percent of women from 15 to 49 years of age were not covered by FP and would have had a need for this intervention, compared to the 99 percent and 92 percent of pregnant women who needed and received MMS and BPE, respectively. Other studies have specifically focused on FP and its many benefits (Singh 2009). Table 3 shows the results of the dynamic model converted to DALYs. A small but nontrivial additional value-added is seen by the inclusion of long-term effects.

Table 3. DALY Totals

OUTCOMES	SHORT-TERM DALYS	LONG-TERM DALYS
Total DALYs due to LBW and PTB "modifiable DALYs"	2,188,975	39,781
Total DALYs averted due to MMS intervention	274,416	2,976
Total DALYs averted due to BPE intervention	198,678	2,263
Total DALYs averted due to FP via IPI intervention	24,857	270

COST-EFFECTIVENESS ANALYSIS OF MATERNAL NUTRITION INTERVENTIONS ON LBW- AND PTB-RELATED HEALTH OUTCOMES

Cost-effectiveness ratios are obtained by combining the DALY estimates above with the marginal cost of the interventions. The WHO *threshold for cost-effectiveness* is used to judge whether results are cost-effective.[8] Interventions that are deemed cost-effective cost less than three times the gross domestic product (GDP) per capita per DALY—US$2,229 for Bangladesh. Interventions deemed highly cost-effective cost less than GDP per capita, or US$743.[9] Table 4 shows the resulting CERs.

8 Pulled from WHO's CHOICE model documentation, found at http://www.who.int/choice/costs/CER_thresholds/en/index.html.

9 World Bank 2011 GDP per capita for Bangladesh.

Table 4. Cost-Effectiveness Ratios for Selected Interventions in 2011 US$ per DALY Averted[11]

	LOW MARGINAL COST	HIGH MARGINAL COST
LONG- AND SHORT-TERM BENEFITS		
MMS	160.03	437.37
BPE	529.76	889.45
FP via IPI	1,952.41	2,722.94
SHORT-TERM BENEFITS ONLY		
MMS	161.99	442.73
BPE	536.47	900.73
FP via IPI	1,976.12	2,756.01

Table 5. Cost-Effectiveness Ratios for Selected Interventions, in 2011 US$ per DALY Averted, 0% Discount

	LOW MARGINAL COST	HIGH MARGINAL COST
LONG- AND SHORT-TERM BENEFITS		
MMS	59.64	162.99
BPE	197.29	331.24
FP via IPI	727.77	1,014.99
SHORT-TERM BENEFITS ONLY		
MMS	61.83	168.98
BPE	204.76	343.79
FP via IPI	754.26	1,051.93

The MMS intervention was found to be "highly cost-effective" for Bangladesh under both low and high marginal cost scenarios, as was the BPE intervention under the low marginal cost scenario. All three interventions were "cost-effective" under the low marginal cost scenario. Under the high marginal cost scenario, FP via IPI was not considered cost-effective. Incorporating long-term benefits improved the CER calculation by a nontrivial amount, ranging from US$1.96 per DALY (MMS, low marginal cost) to US$33.07 per DALY (FP, high marginal cost).

The sensitivity analyses provide some idea of the potential range around the estimates. The most important sensitivity analyses relating to this calculation are the rates at which the DALYs are

10 Fewer US dollars per DALY means that it is a more cost-effective intervention.

discounted. The model uses the standard 3 percent, a figure that many have questioned in recent years because it undervalues long-term effects compared to shorter-term payoffs. Consequently, the 2010 *Global Burden of Diseases, Injuries, and Risk Factors Study 2010* (Institute for Health Metrics and Evaluation 2013) now also presents its findings with 0 percent discounting, and this practice may become more common in the future. When figured based on 0 percent discounting, CERs change dramatically (Table 5). Note that because all intervention costs are accrued during the present period, changes in discounting affect only effectiveness estimates.

There are substantial improvements in the CERs for all interventions, with gains of more than 60 percent. All but the FP via IPI intervention (high cost) are highly cost-effective for total benefits. These can be compared to only analyses of other nutrition and health interventions that also use 0 percent discounting, which may become more common going forward.

Other sensitivity analyses were conducted to test the assumptions of the model and, in some cases, the ranges found for some key effect sizes. The results of these additional tests provide a plausible range around the original 3 percent estimates (Table 6).

Table 6. Cost-Effectiveness Ratios for Selected Interventions in 2011 US$ per DALY Averted, and Plausible Range (Sensitivity Analyses)

	LOW MARGINAL COST		HIGH MARGINAL COST	
	BASE ESTIMATE	PLAUSIBLE RANGE	BASE ESTIMATE	PLAUSIBLE RANGE
LONG- AND SHORT-TERM BENEFITS				
MMS	160.03	(109.53–252.77)	437.37	(299.35–530.11)
BPE	529.76	(529.36–542.58)	889.45	(331.24–900.06)
FP via IPI	1,952.41	(1,950.99–2,007.49)	2722.94	(1,014.99–2,760.73)
SHORT-TERM BENEFITS ONLY				
MMS	161.99	(111.07–255.88)	442.73	(303.57–536.61)
BPE	536.47	536.47	900.73	900.73
FP via IPI	1,976.12	1,976.12	2,756.01	2,756.01

Note: None of the sensitivity analyses affected the short-term BPE and FP via IPI CERs, so no plausible ranges were created for these outcomes.

MMS results, which were found to be the most cost-effective in terms of averting infant- and CVD-related DALYs, were somewhat sensitive to the product cost assumptions (the higher end of the plausible range occurred under a high-cost Sprinkles® scenario). Moreover, if the results from the MMS study conducted in Bangladesh were used instead of those from the meta-analysis, the estimated cost per DALY averted would be US$50 to US$268 lower.

LIMITATIONS

Research into the effects of changes in birth outcomes over time is still an evolving area of inquiry. In creating the ELN-NCD model, SPRING has attempted to collect the best available evidence and create a structure flexible enough to accommodate improved information as it becomes available.

That said, it is critical to understand both areas of evidence where consensus is lacking and some of the gaps found in the research and to remember that simulation models can never exactly approximate human behavior and conditions and that there are limitations in how the model's structure may affect outcomes.

It is also important to bear in mind the assumptions that had to be made to complete the model—among them:

- **Birth phenotypes:** Until recently, LBW was considered the primary modifiable birth outcome that affected health outcomes, as a proxy for interuterine growth retardation (IUGR), and thus is the most studied in the literature. However, a significant minority of this literature also asserts PTB as an important contributor to adverse health outcomes. In the 2013 *The Lancet* Series, the small for gestational age syndrome has been put forth as the primary modifiable birth outcome with potential for improving later health. The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project will be producing vital information on standards for interuterine growth (IUG), phenotypes of birth outcomes, and potentially an alternative growth standard for children born with IUGR. INTERGROWTH-21st relies on five large cohorts of pregnant women who are monitored by sonogram to gain the most accurate measurement of these conditions. SPRING hopes this work will help clarify which conditions or combination of conditions are most important to track in order to improve later-life health (MedSciNet 2011).
- **Preterm birth:** Gestational age is difficult to assess for various reasons, including sometimes faulty maternal recall and reproductive cycle heterogeneity. Because of difficulties with measurement, PTB and small for gestational age are often omitted from current evidence or found to have minimal or or no effects. Theory suggests there should be some impact, and with new methods for assessing preterm birth (e.g., sonogram), future research may be more successful in identifying effects.
- **Maternal nutrition intervention coverage:** Aside from information on iron–folic acid, little appears to have been written on maternal nutrition interventions, particularly those included in this model.
- **Cross-intervention coverage:** This is an issue in many areas of health impact research. Few studies looking at several interventions also examine their interactions in depth. Yet information on these interactions is vital in SPRING's model addressing ELN-NCD and others, to inform a decision on whether nutrition interventions can have additive or multiplicative effects on outcomes. This information would permit estimates of combined intervention effects—for instance, if MMS and BPE were to be provided together.

- **Cross-birth outcome effects:** To modify evidence on how one intervention might affect a child who is both LBW and preterm, some assumptions were made. Evidence suggests these conditions overlap and are related, but without clear evidence on how they interact, estimates on their combined effect will not necessarily be accurate. During the ELN-NCD project's second phase, evidence published in *The Lancet's* 2013 Series on Maternal and Child Undernutrition will be used to try to improve estimates of these cross-outcome effects (Katz et al. 2013).
- **Differentials in blood pressure:** Based on the evidence available, the assumption built into the ELN-NCD is model is that the differentials in blood pressure found in infants due to different birth outcomes remain over each individual's life. Some animal studies suggest that structural changes to the vascular system caused by higher blood pressure could lead to increasing differentials over time (Kuneš et al. 2012; Kuneš et al. 2013). Human studies have noted an increase in differentials in adults when weight gain is considered, but with mixed findings as to when weight gain is most influential (Adair et al. 2009; Law et al. 2002).
- **Cost functions for nutrition interventions:** As noted in the evidence review, few studies have tracked the costs of implementing or scaling up maternal nutrition interventions. Better evidence is available for child interventions, but the effects of scale and coverage are often absent, and a flat cost curve, which belies efficiencies of scale, is assumed.
- **Inherent uncertainties of later-life mortality rates:** The drawback of models with a shorter time horizon is the risk of missing interventions' later-life consequences or benefits. The drawback of models with longer time horizons, such as the ELN-NCD model, is the increase in the uncertainty around the estimates. As with any forecasting, the inherent uncertainties can derail the mathematical trends and estimates that feed the model. For instance, the epidemiological transition model predicts mortality rates based on projected economic growth and its association with *current* mortality rates around the world. If Bangladesh's future economy and epidemiology differ significantly from those seen in worldwide historical trends, the country's future mortality rates could be either overestimated or underestimated.

These limitations notwithstanding, results of the ELN-NCD model analyses should provide acceptable approximations of the three interventions' short-term effectiveness, combined short- and long-term effectiveness, and cost-effectiveness. As new data and evidence become available, the model's flexible design will permit SPRING to incorporate the new information.

SUMMARY AND DISCUSSION

So far, the ELN-NCD model has provided important information regarding the impact of maternal nutrition interventions on early- and later-life health outcomes. It has also provided a better understanding of the dynamics across a lifetime cohort. Analyses of interventions' effectiveness using the model also identified major gaps in research, most notably for measurement and efficacy regarding PTB, and how rate of weight gain post-birth modifies N-RNCD risk of LBW/ PTB babies, stunted children, and wasted children. SPRING will be able to incorporate findings published in *The Lancet* 2013 Series on Mother and Child Nutrition to begin to fill some of these gaps. Others await further evidence.

SUMMARY OF KEY FINDINGS

- By reducing LBW outcomes in Bangladesh, MMS appeared to avert about 13 percent of total modifiable short-term deaths—that is, infant deaths. MMS was also the most successful at reducing long-term deaths from CVD, averting approximately 10 percent of total modifiable long-term deaths in the static model. The interventions had only a negligible effect on reducing PTB, a lack of impact that could have resulted from issues of measurement related to gestational age.
- BPE supplementation was second most effective at saving lives in both the short- and long-term periods, averting 9 percent and 8 percent, respectively.
- The indirect intervention, FP via IPI, produced no notable decreases in deaths in either the short- or the long-term periods, primarily because FP appears to have a minimal effect on IPI.
- When short-term and long-term effects were allowed to interact in the dynamic model, survivorship during the short-term period offset deaths averted in the long-term period. In some cases, this means there were more adult deaths due to the intervention than in the absence of that intervention. However, when converted to DALYs, the positive gains in disability averted meant the interventions still had a net positive effect on CVD outcomes.
- Looking only at cost, FP was the least expensive at US$4 to US $6 per pregnancy (or CYP); followed by MMS, at US$7 to US$19 per pregnancy); and then by BPE, at US$16 to US$27 per pregnancy. The differences in price between MMS and BPE were driven primarily by the cost of the supplements rather than by duration of treatment or the duration of provider visits.
- MMS appeared to be the most cost-effective of the three interventions because of its relatively low marginal cost and higher total effectiveness. SPRING estimated effectiveness both with the traditional 3 percent discounting and discounting of 0 percent.
- Using the traditional 3 percent discounting, MMS was found to be highly cost-effective, ranging from US$160 per DALY to US$437 per DALY. Throughout the sensitivity analyses, at US$743 per DALY, MMS never exceeded WHO's threshold for being highly cost-effective.

BPE and FP via IPI were also both considered cost-effective in the low-cost scenario, but only BPE continued to be cost-effective in the high-cost scenario. When 0 percent discounting was posited, all interventions were considered highly cost-effective except for FP via IPI in the high-cost scenario.

MODEL PERFORMANCE

The model provides useful information about the dynamic effects of an intervention over time. Solely using empirical evidence from randomized trials, one might expect gains in life years in both the short- and long-term periods. One might also assume that these gains could be simply added together to determine the total effect of that intervention on the life course. By allowing effects to occur during multiple time periods, the model yields a much more dynamic and complete picture of how an intervention actually affects morbidity and mortality. Although this picture is more accurate, it complicates measurement of changes in CVD deaths over the long-term period.

This has implications for the future Bangladesh CVD burden, as hypothesized in the epidemiological transition literature. The NCD burden is increasing at the same time that the burdens of communicable diseases and undernutrition decrease. An increasing NCD burden, without similar changes in GNI per capita, will prematurely saddle Bangladesh's healthcare system with additional cases of complex, long-term disease and higher per-person medical costs.

As noted in the 'Limitations' section of this document, significant deviation from forecasted economic and epidemiological growth will make it necessary to revise the model estimates. In particular, if CVD-related adult conditions increase at more rapidly than previously seen in the pool of countries used to model the epidemiological transition, because of a more rapid nutrition transition—as explained in such nutrition transition research as Popkin, Adair, and Ng 2012—or as a result of other factors. This type of limitation applies to any simulation model. To refine modeled mortality estimates, this exercise can be repeated over time, including new evidence, changes in epidemiological and economic factors, and more sensitive measures of birth outcome categories. The ELN-NCD model's flexibility will facilitate the continued monitoring.

CONTRIBUTION TO DISCOURSE ON COSTS SPENT AND COSTS SAVED

It is worth noting the cost estimation results on their own, since no current literature is available on the two direct interventions. Table 7 below shows the results of SPRING's cost function for estimated per pregnancy costs of each intervention, along with some comparison estimates from the literature for other nutrition interventions.

Other empirical research on maternal nutrition interventions was also reviewed to see whether the estimates in Table 7 could be validated via similar delivery interventions. Two studies on iron folate supplementation were found (Baltussen, Knai, and Sharan 2004; Zeng et al. 2009). The first found that for countries falling within the WHO-defined SEARO D region, which includes Bangladesh, supplementation would cost approximately US$12.53 per pregnancy, adjusted to 2011 US dollars. Zeng et al. found a similar figure in rural western China, US$13.36 per pregnancy, again adjusted for 2011 US dollars. Both figures fall in the middle of SPRING's estimated cost range for MMS, supporting the plausibility of the results.

The ELN-NCD model explored the cost-effectiveness of the two direct interventions, weighing their merit based on the ratio of intervention costs to health outcomes (here defined by DALYs averted). One could also examine the cost–benefit of the interventions, which compares intervention costs to quantified benefits (or costs saved). A 2006 study by two well-known economists

Table 7. Cost Estimates for Selected Interventions

	MARGINAL COST (U.S.$ IN 2011)
MMS intervention (per pregnancy)	6.95–19.00
BPE intervention (per pregnancy)	16.25–27.25
FP via IPI intervention (per pregnancy, or CYP)	4.03–5.63
FOR COMPARISON, FROM "WHAT WILL IT COST?" (HORTON ET AL. 2010)	
Breastfeeding promotion (per year)	5.00–15.00
Vitamin A supplementation (per child per year)	1.20

attempted to quantify the benefits of averting LBW from an economic perspective, a perspective that reflects a broader range of outcomes than health alone (Alderman and Behrman 2006). They estimated total benefits (the present discounted values of expected economic benefits) by looking at seven major classes of benefits that might be expected by shifting a single infant from LBW to non-LBW status:

- Reduced infant mortality
- Reduced neonatal care
- Reduced costs of infant/child illness
- Productivity gain from reduced stunting
- Productivity gain from increased cognitive ability
- Reduction in costs of chronic diseases
- Intergenerational benefits

With discounting of 5 percent, the researchers found a benefit of US$510 for every infant shifted from LBW to non-LBW. Reduction in the cost of chronic disease care and treatment and inter-generational benefits made up 10 percent of those savings. If traditional 3 percent discounting is applied, the calculated benefit rises to US$832, and the savings accruing from long-term benefits increase to 17 percent of that total.

When inflated to current US dollars[11] and applied to SPRING's estimate of the number of children shifted from the LBW state, the MMS intervention would save Bangladesh US$76 million and the BPE intervention would save US$53 million.[12] By comparison, Bangladesh currently spends US$4.14 billion on health.[13] Speaking about their work, Alderman and Behrman concluded that the economic benefits of cost saved are fairly substantial for low-income countries, and that alone, these savings justify supporting interventions that reduce LBW (Alderman and Behrman 2004).

11 Using most recent complete year data, 2012.

12 Using 3% discounting to match SPRING's assumptions.

13 Calculated using 2011 WHO estimate for the percentage of GDP spent on health (3.7%) and 2011 World Bank estimate of total GDP at US$112 billion (WHO Global Health Observatory Data Repository 2011 and World Bank Database 2011).

APPLICATIONS FOR DONORS, ADVOCATES, AND POLICYMAKERS

Results from the ELN-NCD model can be viewed as another tool for evaluating the relative value of different maternal nutrition interventions. They can also help in prioritizing such interventions in Bangladesh and countries with similar epidemiological, health system, and demographic profiles. Testing this model in other countries can broaden its usability, producing contextually relevant results that help to determine which interventions are most suitable for specific countries.

The results can provide key information for advocacy and for target setting and other planning for donors and other organizations. For instance, by providing information on total modifiable deaths (Figures 2a and 2b), this model provides a more accurate denominator with which to compare expected performance of maternal nutrition interventions. It also will ultimately allow donors to achieve evidence-based three- and five-year target reductions in morbidity and mortality.

Finally, the ELN-NCD model exemplifies how to develop longer-term cost-effectiveness estimates for resource allocation and program planning. Specifically, Phase 1 results suggest that investing in MMS, and to a lesser extent in BPE, may be effective in saving DALYs in both the short term and the long term—that is, in reducing both morbidity and mortality in children and NCD among adults. Results also indicate that beginning to promote MMS in pregnancy over iron–folic acid alone would improve DALYs-averted rates overall in both the short-term and long-term time periods.

NEXT STEPS

In Phase 2, SPRING will explore the feasibility of some key extensions to the model. First, SPRING will test the baseline demographic parameters to see if any country might have a disease burden such that the issue of survivorship would not so heavily counter-balance the DALY gains made in adulthood. Second, based on evolving evidence, SPRING will provide a picture of the evidence linking birth outcomes to other long-term disease outcomes, such as diabetes mellitus. Third, SPRING will update the Phase 1 model with any new evidence that emerges during work on Phase 2. If this new evidence justifies adding another intervention to the model, this will be done in Phase 2.

Given SPRING's Phase 1 findings on survivorship, the project will continue to explore measurement of CVD age of onset, or age of onset of *hypertension*. This measurement would allow for consideration of additional years without "disability" (i.e., without hypertension) that individuals gain from the intervention. These DALYs could help provide a measure of long-term improvement that is less prone to distortion by short-term survivorship.

After both project phases are complete, SPRING will produce a final report, an article to be submitted for journal publication, and actionable guidance for maternal nutrition programs based on the model results. SPRING will also work to disseminate these findings to the key nutrition and NCD-prevention advocacy groups in Bangladesh.

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APPENDIX A: EPIDEMIOLOGICAL TRANSITION REGRESSIONS

The epidemiological transition, described in detail elsewhere (Yusuf et al. 2001; Gersh et al. 2010), is outlined in Table A1 below; there are four phases.

- **Stage 1:** In this pre-transition stage of ET, stage 1, infectious diseases dominate, and the proportion of deaths from cardiovascular disease is minimal, generally 5 to 10 percent.
- **Stage 2:** In the first stage of economic growth, associated with a fast-growing urban population, life expectancy rises and the pandemic of infectious disease starts to recede; hypertensive disease becomes prominent, and CVD accounts for between 10 percent and 35 percent of all deaths.
- **Stage 3:** This stage marks the "normalization" of CVD. It becomes the primary cause of death within a population, accounting for 35 to 65 percent of all deaths.
- **Stage 4:** The final stage sees a plateau in deaths attributable to CVD, even a fall, sometimes to less than 50 percent, as symptom management and prevention interventions begin taking effect. The most notable change characterizing stage 4 is the increase in CVD deaths occurring after the age of 70 to between 70 and 80 percent—compared to 20 to 30 percent in countries in stages 2 and 3.

Study of the epidemiological transition has been most complete in countries of the Organisation of Economic Co-Operation and Development, where wide-scale health surveillance has been ongoing for decades. The ET in the United States (from stage 1 to 4) was thought to have taken between 50 and 70 years (Gaziano 2010); evidence shows that the ET is happening much more quickly in Latin American and Asian countries. If this rate of change is not taken into account, there is a risk of grossly underestimating future total health burden.

The primary ET indicators are the proportion of total deaths in a given year due to CVD and the proportion of total CVD deaths that occur in the population under the age of 70. Unfortunately, in many countries, indicators are not routinely collected every year. The primary interest in this indicator is the rate of change of rate of growth over time (the speed with which countries move from stage to stage). As a result, sporadically missing data is a substantial hurdle.

A number of other indicators could act as a proxy. Epidemiologically, using key CVD risk factors such as body mass index (BMI), blood pressure, and cholesterol levels as proxies makes sense, but the association is often complex because prevalence data are often estimated from small samples. These risk factors will be influenced not just by changes in prevalence but also by the degree to which the health system manages or treats these conditions.

Another sign of transition is how the burden of CVD shifts from subtype to subtype. BMI is strongly correlated with ET during stages 1, 2, and 3, whereas the correlation is lost as ET moves into stages 3 and 4. Similarly, high blood pressure has a much stronger association in stages 3 and 4 than in 1 and 2.

Table A1. Stages of Epidemiological Transition as it Pertains to Cardiovascular Diseases

DESCRIPTION	LIFE EXPECTANCY	PROPORTION OF DEATHS DUE TO CVD (%)	DOMINANT FORM OF CVD DEATH
STAGE 1: PESTILENCE AND FAMINE			
• Malnutrition • Infectious diseases	35 years	< 10	• Infectious: rheumatic heart disease (RHD) • Nutritional
STAGE 2: RECEDING PANDEMICS			
• Improved nutrition and public health • Chronic disease • Hypertension	50 years	10–35	• Infectious (RHD) • Stroke—hemorrhagic
STAGE 3: DEGENERATIVE AND MAN-MADE DISEASES			
• Rising fat and caloric intake • Tobacco use • Chronic disease deaths exceed deaths from infections and malnutrition	> 60 years	35–65	• Ischemic heart disease (IHD)* • Stroke—hemorrhagic, ischemic
STAGE 4: DELAYED DEGENERATIVE DISEASES			
• Leading causes of mortality: CVD and cancer deaths • Prevention and treatment delays onset • Age-adjusted CVD deaths reduced	> 70 years	40–50	• IHD** • Stroke—ischemic • Congestive heart failure

* Greater in higher socioeconomic groups
** Younger patients—lower socioeconomic status; elderly patients—higher socioeconomic status
Source: Gersh et al. 2010

METHODS AND FINDINGS

SPRING compiled a global dataset of 193 countries and classified them by stage using gross national income per capita, proportion of deaths due to CVD, proportion of deaths due to infectious disease, and proportion of noncommunicable disease deaths under 70 years in 2008.[14]

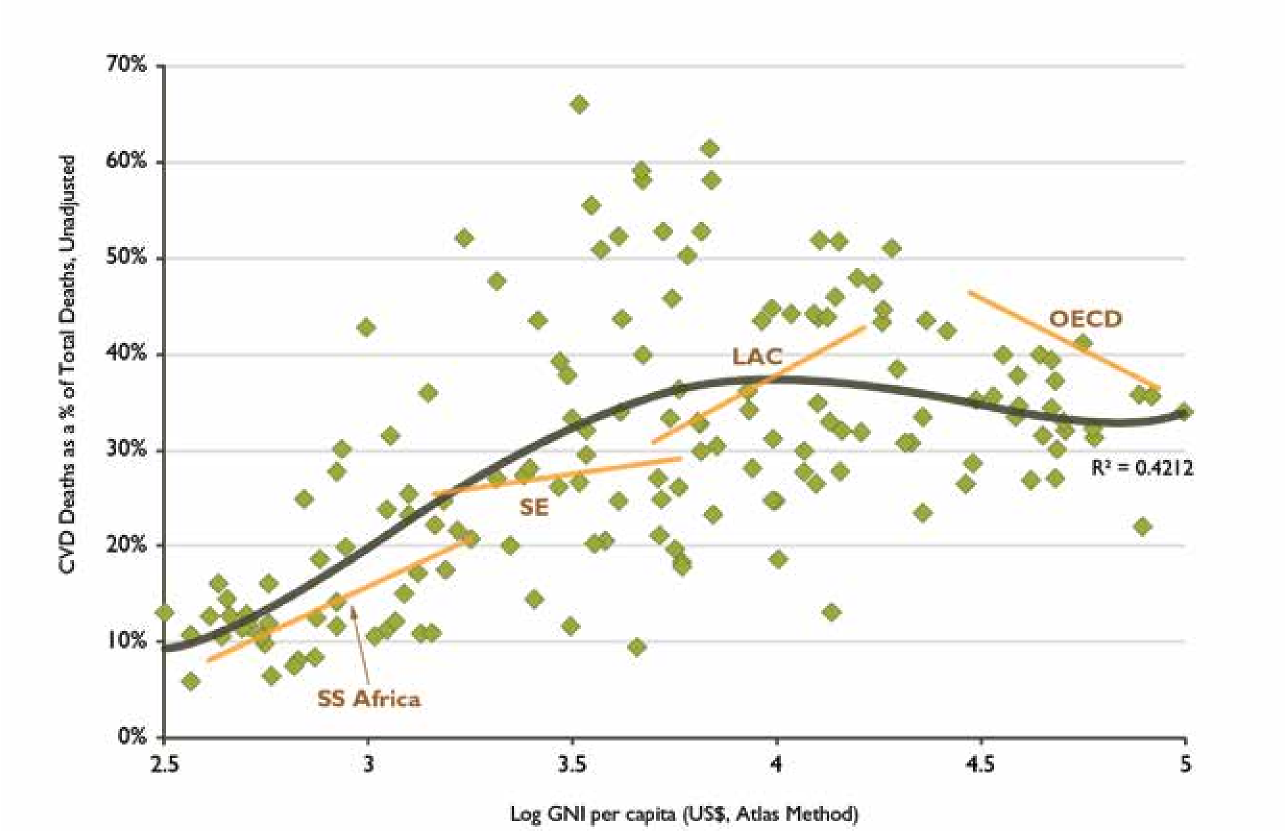
When regressions were run, two sets of distinct outlier countries skewed results. The first set includes countries with high HIV prevalence (above 25 percent), because this skewed the CVD death proportion estimates relative to the level of economic development. The second set of outliers consisted of countries whose mean female body mass index was at or above 30; these were mainly Pacific Island countries with small populations. Egypt, Kuwait, and Belize were excluded by this measure.

14 This measure is used in lieu of available data on CVD deaths under 70 years as a proportion of total deaths.

Bivariate analysis of the proportion of CVD deaths that makes up all deaths and the proportion of NCD deaths that occurs in individuals under 70 provides a good idea of where different countries fall in their ET. Generally speaking, fast-growing, urbanizing countries in sub-Saharan Africa and south Asia seem to be at stage 2; Latin American and East Asian countries seem to fall into stage 3. These conclusions are supported by analysis of BMI, meaning by country, and the proportion of adults with high blood pressure. Correlation with BMI is much stronger in stage 2 countries, whereas in stage 3 countries, deaths correlate more strongly with high blood pressure.

As shown in Figure A1, a polynomial trend line represents the best fit trend for the relationship (r^2=0.4212) between proportion of total deaths in a given year due to CVD and log of GNI per capita in US dollars (estimated using the Atlas method). This trend seems to validate the epidemiological regression curve described in Table A1, with steep growth in the middle of the transition, followed by a plateauing and eventual fall of deaths due to CVD.

Figure A1. Subregion Trends Superimposed on Global Epidemiological Transition Analysis Results



Source: Author calculations

There is a strong geographical pattern when countries are separated out into subregions, and those trend lines are drawn against the global trend line. The bulk of sub-Saharan African countries straddle stages 1 and 2. Progress toward reducing maternal death and infectious death in children over the last two or three decades has meant that very few countries remain far from entering stage 2. Southeast Asian countries are mainly in stages 2 and 3; separated out, South Asian countries are predominantly in stage 2, and East Asian countries are predominantly in stage 3. Like Latin America and the Caribbean, many South American countries are well into stage 3 and bordering stage 4. Much of Central America is in stage 2. Countries marked as OECD are primarily in the countries of North America, western Europe, and Oceania.

For the purpose of the model, the countries of greatest interest are primarily in stages 1, 2, and 3. The key to estimating future CVD burden is to find both the country's current stage and its rate of change within the transition. The majority of the CVD burden occurs among those aged 30 to 60 (in countries in stages 1 to 3), so knowing what the burden of CVD will be in the future is paramount in defining the burden relative to the overall aggregate at that time.

After countries' stages were classified in this dataset, those in stage 4 were removed, leaving 91 countries (39 from sub-Saharan Africa, 10 from South Asia, 8 from South America, 3 from North Africa and the Middle East, 13 from East Asia and the Pacific, and 18 from Central America and the Caribbean).

When running the same regressions by subregion, the goodness of fit (R^2) was generally better. The model with best fit for south Asia gives the following equation (R=0.585):

$$\text{ET stage (\%CVD deaths)} = 9.784 \text{ GNI pc At (log)} + 0.7787$$

Using this equation, SPRING estimated the countries' rate of growth throughout stages 2 and 3. To estimate ET rate of change, SPRING looked at countries at the end of stage 2; countries in stage 3; and countries in stage 3 where CVD deaths constituted more than 30 percent of all deaths and where more than 40 percent of deaths caused by NCDs occurred before age 70.

Next, a model was fit to predict ET at various stages of GNI development to approximate the change in systolic blood pressure over time for Bangladesh. The model focused on the countries' mean growth rates of GNI per capita throughout the end of stage 2 (where Bangladesh currently falls) and through stage 3 (where Bangladesh would be expected to fall in the future). In Bangladesh, the mean growth rate was 6.9 percent. It is known that high blood pressure is associated with a higher proportion of CVD disease in stage 3 than in stages 1 and 2, and the rate of increase in high blood pressure as a result is then much higher than the CVD death change rate (as a proportion of total deaths).

For Bangladesh, the model predicts a population mean SBP of about 124 mmHg. When the ET model is applied to Bangladesh to estimate its ET position in 20 years and its growth rate, the figure that emerges is 30.67 percent CVD deaths and a resulting mean SBP of around 130 mmHg.

Finally, data on age distribution around the mean SBP of a population were used to break this summary down by age for the Markov model.

APPENDIX B: SELECTION AND EFFECTIVENESS OF INTERVENTIONS

MATERNAL NUTRITION TO BIRTH OUTCOMES

There is a relatively large body of literature on the linkages between maternal nutrition and birth outcomes, although many studies are not properly designed to capture birthweight outcomes. The main issues are related to imprecise measurement of outcomes and the existence of comparable intervention evidence. Of the interventions studied, multiple micronutrient supplementation interventions are the most uniform, offering greater comparability, as there is an internationally accepted standard mixture for the supplement (the UNIMAP presentation).

SPRING began by reviewing all Cochrane or similar meta-analyses for any type of supplementation or nutritional intervention during pregnancy to gauge the strength of evidence around the following interventions: calcium, iron–folic acid, B vitamins, vitamin C, vitamin A/carotenoids, and zinc. Based on this initial review, SPRING chose to pursue further investigation of MMS, balanced protein energy supplementation, and family planning via interpregnancy interval.

Based on this evidence and discussions with area experts, the single binary outcome of low birthweight versus normal birthweight has been expanded to four types of birth outcomes, as shown in Table B1.

Table B1. Birth Outcome Categories

Normal birthweight (>=2,500 g) X term birth (>=37 weeks)	Low birthweight (<2,500 g) X term birth (>=37 weeks)
Normal birthweight (>=2,500 g) X preterm birth (<37 weeks)	Low birthweight (<2,500 g) X preterm birth (<37 weeks)

These four categories provided the highest level of specificity possible while utilizing the current evidence available. In addition, while there are implications for later-life outcomes when a baby is born too big (>3,500 g), the population of Bangladeshi babies in these categories is so small that risk of these conditions in this context cannot be estimated accurately.

MULTIPLE MICRONUTRIENT SUPPLEMENTATION[15]

Although research into MMS effect on birth outcomes has increased substantially over the past few years, several studies were not powered to detect significant differences in effects on low birthweight and preterm birth. One such study was set in Bangladesh (Tofail et al. 2008) and found a 0.86 RR for LBW and 0.75 RR for PTB—neither effect statistically significant. SPRING then used a meta-analysis (Haider and Bhutta 2012), which found a 0.78 RR for LBW among mothers with a body mass index under 20 kg/m^2 and 0.88 RR for LBW among mothers with a BMI of 20 or more. These figures were weighted by proportions of Bangladeshi women in each category (48 percent and 52 percent, respectively, according to the 2011 Bangladesh Demographic and Health Survey) to arrive at a final LBW RR of 0.832 among infants born to mothers who

15 All effect sizes, which are reported as risk ratios, were incorporated in the model using the ProbtoProb function in TreeAge.

received MMS. The same meta-analysis found no effect of MMS on PTB (RR=0.99, 95% CI 0.97–1.02).

Use of the meta-analysis has benefits and drawbacks. Although the power to detect a consistent effect is greater, the studies reviewed span a wide geographic range, with varying pre-existing maternal nutrition levels. The included studies varied somewhat in the timing of MMS administration as well as in what was administered to control groups. Several used iron–folic acid for the control group; others used a placebo or a vitamin with two or fewer micronutrients. Because the relative micronutrient deficiencies and the current iron–folic acid use of the Bangladeshi cohort compared to those of the other study populations are not known, it is difficult to predict whether the effect is under- or overestimated.

No information was available on current coverage levels of MMS in Bangladesh, which are needed to determine the additional benefit of MMS. Thus, the analysis assumed it as 0 percent. For both direct nutrition interventions, optimal coverage was defined at 99 percent to match the assumptions and levels in 2008's *The Lancet* Maternal and Child Undernutrition series, modeling of other nutrition interventions (Bhutta et al.)

BALANCED PROTEIN ENERGY SUPPLEMENTATION

As for MMS, little information is available on current use of BPE in Bangladesh. SPRING used the latest estimate of coverage for supplementary foods as a proxy and defined it at 8.3 percent (DGHS and MHFW 2012).

Although no published studies in Bangladesh exist for BPE's effect on LBW and PTB, a 2012 *Cochrane Review* meta-analysis (Ota et al. 2012) found a 66.96 g increase in birthweight among children born to undernourished mothers and a 15.93 g increase among those born to adequately nourished mothers. The weighted average increase in birthweight was then added to the mean birthweight in Bangladesh (2,638 g, according to the UNICEF LBW Survey). Assuming a normal distribution of birthweight, this increase in mean birthweight translates to a 4.9 percent reduction in LBW, or a RR of 0.88 among infants whose mothers were supplemented with BPE during pregnancy. Ota and colleagues found a small and statistically insignificant effect of BPE on PTB (0.96, 95% CI: 0.80, 1.16).

FAMILY PLANNING

No articles were found examining the direct effect of family planning on PTB or LBW.[16] Rather, the literature in this area focuses on the impact of increasing the interpregnancy interval. Most studies found that IPIs of fewer than 6 months consistently increased risks of PTB and LBW (DaVanzo et al. 2004; Ferraz et al. 1988; Conde-Agudelo 2006; Wendt et al. 2012). However, these findings were difficult to translate into the ELN-NCD model because results were presented as a risk ratio for LBW/PTB against one reference group (around two years). Other studies examined the link between IPI or pregnancy spacing and infant and child mortality (Rutstein 2005; Conde-Agudelo et al. 2012); but because the ELN-NCD model examines intervention impact on

16 To ensure that the literature review was comprehensive, the Maternal Infant Young Child Nutrition–Family Planning (MIYCN–FP) Integration Toolkit (http://www.k4health.org/toolkits/miycn-fp) was also consulted to look for potential sources for the linkages between family planning and maternal and child nutrition.

the probability of LBW and PTB outcomes, these studies could not be used. Saha and van Soest (2013) included the impact of family planning use on IPI length and infant mortality, but since birth interval includes gestational age, the results could not be used to predict preterm status (Saha and van Soest 2013).

Thus, instead of using published literature findings for FP and LBW, SPRING conducted linear regressions using several DHS datasets and the UNICEF LBWS to determine the association between FP and IPI, and between IPI and LBW. The analysis resulted in an average 5.2 month increase in IPI and a 0.98 RR of LBW. For additional information on the regressions and results, see Appendix D.

Current FP use in Bangladesh was assessed based on the average 52 percent modern contraceptive prevalence as noted in the 2011 BDHS. Because the analysis examines the effect of increasing FP availability so as to totally eliminate unmet need, the coverage level was assumed to be equivalent to total unmet contraceptive need minus the modern contraceptive prevalence rate—again by location and BMI category (rural/normal weight or urban/underweight—23 percent to 28 percent, respectively, according to the 2011 BDHS).

LINKING EVIDENCE TO MORTALITY OUTCOMES

To link these effects to final outcomes, several other steps of evidence were defined, as detailed in Appendix C.

APPENDIX C: METHODS FOR LINKING BIRTH OUTCOMES TO MORTALITY

EFFECT OF BIRTH OUTCOMES ON INFANT MORTALITY

Preterm birth and low birthweight are known to substantially increase the likelihood of infant mortality, particularly in neonates. But because there have been few studies on the effects of either of these adverse birth outcomes on postinfancy mortality (one to four years), their impact (aside from their indirect effect through increasing blood pressure) was assumed to be nil.

To estimate the effect of PTB and LBW on mortality, Bangladesh-specific data were used when possible, because neonatal and infant causes of death vary widely by region and depending on the extent of access to health care. A study conducted in a Bangladeshi periurban setting found neonates who were both PTB and LBW were 4.78 times more likely to die than term LBW neonates (Yasmin et al. 2001). One would expect that this difference might be even greater for Bangladesh as a whole, because the study area probably had better accessibility of neonatal care than the rest of the country. This difference for preterm versus term was also used for neonates with normal birthweights.

For LBW, Ashworth (1998) found infants in Guatemala and India weighing between 2,000 g and 2,499 g at birth were four times more likely to die than those weighing between 2,500 g and 2,999 g (and 10 times more likely than those weighing between 3,000 b and 3,499 g) in the neonatal stage; and two times more likely to die at the postneonatal stage (four times more likely to die than those weighing between 3,000 g and 3499 g). Given the proportions of each weight category in the UNICEF LBWS, this translated to a 5.46 RR of neonatal mortality and a 2.48 RR of postneonatal mortality.

SPRING made an assumption that the findings of Ashworth et al. (1998) hold for LBW babies at term because it was not possible to parse out the percentage of study births that were term or preterm from the evidence published. Consequently, one can apply the relative risk given by Yasmin et al. (2001) to obtain the combined risk of a child born preterm and with LBW: they will be 19.12 (4.78 x 5.46) times more likely to die in the neonatal stage than a child born at term and with normal birthweight. This assumption is noted as one of the limitations of the model and the evidence base, and SPRING is working to translate evidence from Katz et al. (2013) to develop a more accurate measure of LBW/term relative risk. In turn, knowing this relative risk will provide a more accurate relative risk calculation for children born both preterm and LBW.

EFFECT OF BIRTH OUTCOMES ON SYSTOLIC BLOOD PRESSURE

Although the literature review yielded no studies linking LBW and PTB with cardiovascular disease events or CVD-related mortality, a number of studies analyzed the impact of LBW or PTB on systolic blood pressure. One systematic review found a 3.8 mmHg increase associated with PTB among its five highest-quality studies (de Jong et al. 2012). All but one were in developed countries, and ages studied ranged from the mid-teens to the late 20s. Similarly, a meta-analysis of birthweight and blood pressure found a 2.58 mmHg increase associated with LBW, but the age at the time of BP measurement varied more widely—from 4 to 70 years (Mu et al. 2012).

Two assumptions of the ELN-NCD model should be noted. First, the 3.8 mmHg increase due to PTB and the 2.58 mmHg increase due to LBW are assumed to be a permanent, static increase in SBP starting in the cohort's 20s and lasting through the rest of their lives. However, it is possible early stress on the cardiovascular system, brought on by PTB and/or LBW, may result in progressively worse outcomes over time, rather than a uniform increased risk throughout adulthood, as seen in some animal studies (Kuneš et al. 2012; Kuneš et al. 2013). The uncertainty of effect resulting from paucity of evidence may yield underestimates in CVD-related mortality.

Second, no information in meta-analyses reported on the overlap of PTB and LBW, so the effect of PTB and LBW was assumed to be cumulative (i.e., a 6.6 mmHg increase in SBP over the mean for PTB and LBW births). Because there is actually substantial overlap between LBW and PTB status, the effect is unlikely to be entirely cumulative. Sensitivity analyses following the meta-analyses showed LBW effect ranging from none to raising SBP by 2.58 mmHg.

MORTALITY PROBABILITIES

The probability of CVD-related death (CD) is modeled as

$$CD = CDB_{age,\ sex} * eSBP$$

Where $CDB_{age,sex}$ is the probability of death for those born with normal birthweight and at term. It is multiplied by the effect of increased systolic blood pressure (eSBP), which is calculated as

$$eSBP = e\hat{}\beta_{age,\ sex} * DSBP$$

$\beta_{age,sex}$ is the effect of increased SBP (in mmHg) on CVD-related mortality; decrease in systolic blood pressure (DSBP) is the increase of SBP over the population mean SBP for those born normal weight and at term at the beginning of the model (2011), calculated as

$$DSBP = eET\_SBP_{age,\ sET} + \_PTB * ePTB\_SBP + \_LBW * eLBW\_SBP$$

$eET\_SBP_{age,\ sET}$ is the predicted increase in SBP based on Bangladesh's predicted epidemiological transition (ET). PTB is a dummy variable for PTB, and ePTB_SBP is the effect of PTB on SBP (and similar for LBW).

BASELINE MORTALITY TABLE CREATION

To analyze the effect of the nutrition interventions on mortality rates, mortality probabilities must first be computed in a scenario where there is no PTB or LBW in the population (i.e., a baseline mortality table must be created) and then the effects added back in (the effects being dependent on the new proportions of PTB and LBW occurring as a result of the intervention). The baseline mortality table was created in several steps. First, current mortality probabilities for Bangladesh for 2008 were obtained from WHO Global Health Observatory (Life Expectancy: Life Tables Bangladesh); mortality proportions attributable to CVD for South Asia were obtained from the 2008 Global Burden of DiseaseNext, to obtain mortality probabilities for the same cohort, infant- and CVD-related mortalities were adjusted downward, with LBW eliminated, to reflect predicted effects on LBW of interventions' effects. These infant- and CVD-related mortalities were further adjusted down by the predicted effects of PTB interventions on mortality. Based on ET model regression results for economic growth, the ELN-NCD model predicted that by time the newborns reach the age of 20, Bangladesh's economic development will be similar to that of present-day Malaysia. To predict non-CVD-related mortality for this cohort of infants in adulthood, mortality tables from Malaysia were combined with cause-of-death data for Southeast Asia [17] to obtain probabilities for non-CVD-related death.

EFFECT OF INCREASED SYSTOLIC BLOOD PRESSURE ON CVD-RELATED DEATH

This model used findings from Lewington and colleagues (2002), who recorded blood pressure and CVD-related mortality from 1 million adults in 61 prospective studies. Generally, they found that a given increase in SBP has a greater impact on the probability of vascular death for men than for women and for younger people than for those who are older. In the same study, Lewington and colleagues presented hazard ratios for death due to stroke, ischemic heart disease, and other vascular heart diseases following a 20 mmHg decrease in SBP. To obtain the final $ß_{age, sex}$ described earlier, the natural log of each hazard ratio was divided by -20 for each mortality table. This provided the original modeled ß, as the hazard ratio function is exponential with base e. Dividing by (-1) yields the increased relative risk, rather than the decreased relative risk. Each age- and cause-specific ß was weighted by the number of deaths to acquire the $ß_{age, sex}$.

EFFECT OF EPIDEMIOLOGICAL TRANSITION ON SYSTOLIC BLOOD PRESSURE

The predicted population increase in SBP due to the ET was calculated in two stages of regression. The first regression, using World Bank GNI data for more than 90 countries, predicted the effect of economic growth (log GNI) on the percentage of CVD-related deaths (or ET stage); a 1 percent increase in GNI was associated with a 9.784 percentage point increase in CVD-related deaths. The second regression predicted the effect of ET stage on mean SBP and found a 1.08 percentage point increase in mean SBP per 1 percent increase in CVD-related deaths (Appendix A).

To predict Bangladesh's rate of economic growth over the adult lifetime of the cohort, we analyzed historic growth rates of 16 countries that made epidemiological transitions similar to that of Bangladesh to date over a similar time span. Depending on the timeframe used (10–43 years), the average annual economic growth rate ranged from 4.8 to 6.9 percent. The base case used the average of the highest and lowest estimates (5.9 percent). Bangladesh's GNI was predicted at every relevant age (>20) based on this growth rate, and the regression results were used to predict the population mean increase in SBP.

17 Country-level, disease-specific data from the GBD 2010 were not available to the public at the time the calculations were undertaken, so 2010 regional data were used

APPENDIX D: FAMILY PLANNING VIA INTERPREGNANCY INTERVAL REGRESSIONS

Because no publicly available datasets could be found for South Asian populations that included contraceptive use, interpregnancy interval, and accurately measured birth outcomes, SPRING conducted a two-step modeling process to better use available data to look at effects on birthweight. According to a USAID issue brief (USAID 2005), one of the best methods for ensuring healthy pregnancies and safe births is to enable women to space the births of their children through family planning. Although IPI's effect on birthweight and gestational age is not completely understood, researchers and implementers hypothesize that a longer IPI allows women's bodies to replenish micro- and macronutrients between pregnancies (Wendt et al. 2012).

Based on this information, a two-step regression process was used to develop SPRING's estimates. First we modeled the effect of contraceptive use (the intended outcome of FP interventions) on IPI, then the effect of changes in IPI on birthweight and gestational age.

STEP 1: MODELING THE EFFECT OF FAMILY PLANNING USE ON LENGTH OF INTERPREGNANCY INTERVAL

Unfortunately, few datasets track FP use and IPI in Bangladesh. Within the Demographic and Health Survey, SPRING was able to exploit the temporal aspect of the reproductive calendar variable (vcal). This variable is unique within the DHS in that it asks a woman to recall her reproductive and FP activity month by month for the past 59 months, providing detailed information on FP method used in each month as well as on all pregnancies and births. With these data, it is possible to construct variables on FP use prepregnancy, interpregnancy, and postpregnancy. Unfortunately, the sample size of women in Bangladesh who have had at least two children in the last five years (which allows for full IPI estimation and contraceptive use history from the DHS calendar data) is too small to perform a full analysis. For that reason, SPRING obtained data from outside the country. In keeping with the decision to use data from populations as similar to Bangladesh's as possible, the data selected for use were from India's 2005–2006 DHS. Using the Indian data allowed for a much larger sample size of mothers with multiple children on their calendar, similar to Bangladeshi mothers. Table D1, below, compares key variables.

Table D1. Characteristics of Women in Bangladesh and India

	BANGLADESH	INDIA
Total fertility ratio	3.0	2.66
Percentage of women who know a modern contraceptive method	100	96
Median age at first marriage	14.8	17.2 (17.7 at first cohabitation)
Mean household size	5.0	4.8
Percentage of women with no education	34.4	41.5
Median years of schooling completed	1.8	1.9

Source: Bangladesh DHS Final Report 2004 and India DHS Final Report 2005–2006

Although there are some differences between the two countries (most notably, median age at first marriage and the percentage of women with no education), the data are fairly similar; there is nothing to suggest that FP effects should differ greatly from one country to the other.

From the more than 124,000 women included in the India DHS, a subpopulation of just over 10,000 who reported at least two births during the five-year calendar and had at least six months of data on FP use before the penultimate birth. As might be expected, this subpopulation is slightly poorer, younger, and less educated than the population as a whole (Table D2). This discrepancy is not ideal, but in the absence of an original study of this issue, the results from this analysis can be used to obtain effect sizes for India's population of women of reproductive age (WRA) and, by extension, for the WRA population in Bangladesh.

Table D2. Characteristics of Sampled Women

	DIFFERENCE IN VALUES FOR WOMEN (REGRESSION SAMPLE)		HIGH MARGINAL COST (FULL DHS SAMPLE)	
	DIFFERENCE	SD	MEAN	SD
WEALTH				
Poorest	0.118***	(0.007)	0.163***	(0.004)
Poorer	0.054***	(0.006)	0.184***	(0.003)
Middle	0.004	(0.005)	0.201***	(0.003)
Richer	-0.039***	(0.005)	0.214***	(0.003)
Richest	-0.137***	(0.005)	0.238***	(0.005)
Age at first marriage	-0.364***	(0.042)	17.170***	(0.029)
Number of living children	1.181***	(0.024)	1.878***	(0.008)
Current age	-3.822***	(0.078)	29.425***	(0.036)
Education				
No education	0.162***	(0.007)	0.390***	(0.004)
Incomplete primary	-0.005	(0.003)	0.080***	(0.001)
Complete primary	0.002	(0.003)	0.067***	(0.001)
Incomplete secondary	-0.087***	(0.006)	0.336***	(0.003)
Complete secondary	-0.022***	(0.002)	0.049***	(0.001)
Higher	-0.050***	(0.003)	0.078***	(0.002)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

In the regression model, SPRING included controls for a large number of background and socioeconomic characteristics to determine their association with IPI. Developed after reviewing the literature, this list included age at first marriage, the number of living children, and age at current birth (as a squared term).[18] Although the literature does mention a few other variables, these were either not available in this dataset or were closely correlated with other covariates.

18 See RamaRao et al. 2006 for a discussion of birth interval correlates. Also, see reviews by Conde-Agudelo 2006 and Wendt et al. 2012 for variables in the included studies (RamaRao, Townsend, and Askew 2006).

Table D3. Effect of Contraceptive Use on Length of IPI (Months) For All Women with Two Births and Six Additional Months on the Calendar

	RURAL UNDER-WEIGHT	RURAL NORMAL	RURAL OVER-WEIGHT	URBAN UNDER-WEIGHT	URBAN NORMAL	URBAN OVER-WEIGHT
IPI	**4.121*** (0.413)**	**3.758*** (0.424)**	**3.675* (1.663)**	**3.701*** (0.981)**	**5.281*** (0.680)**	**4.901*** (1.392)**
WEALTH INDEX	-0.765* (0.315)	-0.579* (0.268)	0.555 (0.874)	-0.4 (0.455)	-0.26 (0.378)	-0.221 (0.955)
MOTHER'S EDUCATION (REF: NONE)						
Incomplete primary	-0.301 (0.621)	-0.551 (0.604)	5.382** (1.665)	-0.278 (0.945)	-1.621 (0.871)	-0.269 (3.128)
Complete primary	-0.157 (0.630)	-0.153 (0.567)	0.915 (2.605)	-0.088 (1.440)	-0.41 (1.066)	6.140** (2.307)
Incomplete secondary	-0.763 (0.477)	-0.668 (0.427)	4.480** (1.607)	0.436 (0.842)	-1.623* (0.756)	1.841 (1.855)
Complete secondary	0.431 (1.417)	0.431 (1.000)	6.320* (2.720)	-0.098 (2.209)	-1.904 (1.239)	5.624* (2.490)
Higher	1.307 (2.540)	1.343 (1.161)	5.298 (2.784)	-0.543 (2.816)	0.574 (1.306)	5.540* (2.377)
NUMBER OF LIVING CHILDREN	1.433 (0.824)	1.116 (0.639)	2.517 (2.190)	-0.311 (1.838)	0.127 (1.050)	1.4 (2.484)
MOTHER'S AGE	5.103*** (0.209)	4.913*** (0.173)	4.264*** (0.711)	5.323*** (0.372)	4.901*** (0.287)	4.326*** (0.692)
INTERACTION OF LIVING CHILDREN AND MOTHER'S AGE	-0.04 (0.029)	-0.04 (0.021)	-0.098 (0.070)	0.01 (0.062)	-0.006 (0.035)	-0.014 (0.074)
MOTHER'S AGE AT FIRST MARRIAGE	-0.176* (0.081)	-0.207** (0.070)	-0.920** (0.303)	-0.27 (0.181)	-0.276* (0.125)	-0.542 (0.294)
MOTHER'S AGE AT BIRTH	-5.277*** (0.406)	-4.982*** (0.345)	-3.299* (1.556)	-5.595*** (0.874)	-4.890*** (0.545)	-2.041 (1.502)
MOTHER'S AGE AT BIRTH (SQUARED)	0.007 (0.008)	0.006 (0.007)	-0.003 (0.027)	0.009 (0.019)	0.001 (0.010)	-0.041 (0.027)
TOOK ANY IFA	0.297 (0.414)	0.097 (0.358)	1.094 (1.279)	-0.239 (0.764)	0.665 (0.623)	0.838 (1.272)
HAD AT LEAST ONE ANC VISIT	1.481*** (0.422)	0.588 (0.398)	-2.179 (2.240)	0.811 (1.122)	1.067 (0.685)	-1.184 (1.815)
SYMPTOMS EXPERIENCED DURING PREGNANCY (REF: NONE)						
Convulsions not from fever	-0.714 (0.574)	0.291 (0.346)	-0.093 (1.657)	0.282 (0.999)	1.277* (0.545)	-3.444* (1.747)
Leg, body, or face swelling	0.8 (0.435)	0.514 (0.358)	-1.304 (1.629)	-0.565 (0.803)	0.642 (0.576)	0.633 (1.350)
Excessive fatigue	-0.339 (0.313)	-0.181 (0.323)	-0.199 (1.338)	1.260** (0.485)	-0.218 (0.532)	-0.796 (0.540)
Vaginal bleeding	0.134 (0.316)	0.11 (0.580)	4.718 (2.948)	0.358 (0.678)	0.397 (0.608)	2.006 (2.152)
R-SQUARED	0.271	0.239	0.315	0.327	0.267	0.272
N	2,634	3,891	245	940	1,978	482

Clearly, this line of analysis operates under the assumption that the relationships seen in the Indian subpopulation are representative of the population of interest in Bangladesh. Although the Bangladeshi sample size was too small to conduct the same regression on Bangladesh DHS data, preliminary data from a modified regression suggest that the findings are comparable. Findings from Bangladesh suggest that the effect of using long-term FP methods on IPI is 3.6 (SD=0.757) additional months in Bangladesh. The effect of short-term methods is 4.6 (SD=0.933) additional months, findings that are comparable to those shown in Table D3.

In addition to developing estimates of the relationship for this sample of women, separate estimates based on weight and maternal residence were also developed. Knowing the risk levels for the separate subgroups of women allows for the conduct of more precise simulation estimates for the underlying population of interest. Ferraz and colleagues (1998) hypothesized that the mother's weight mediated the effects of short birth intervals, suggesting that the risk posed in Step 2 of this process of short IPI on birth outcomes may vary for women based on their overweight status as well as on their location. For this reason, analyses were run separately on women by weight and location. In cases where such information was available for the underlying population, the simulation is able to calculate more specific outcomes for each woman. Results are presented in Table D3. For flexibility within the model, the same analysis was also conducted as a logit model with dichotomous outcome variables for IPI above six months and IPI above one year (*not shown*).

STEP 2: MODELING THE EFFECT OF IPI LENGTH ON LOW BIRTHWEIGHT

Although the first step of obtaining estimates required use of the India DHS, the birth outcome measures in that dataset are self-reported from recall, and their accuracy has been an issue (Blanc and Wardlaw 2005). In response to the resultant need for another source for reliable birthweight data, SPRING used UNICEF's 2003–2004 Bangladesh National Low Birth Weight Survey to provide estimates on the effect of IPI length on birth outcomes. The UNICEF LBWS enrolled girls and women who had missed two periods and lived in one of 107 randomly selected clusters throughout the country. These women were followed until their delivery, where locally recruited resident field assistants took and recorded birth measurements within 72 hours of delivery (Bangladesh Bureau of Statistics and UNICEF 2005).

From that dataset, estimates of IPI were created from the variable that gives the number of months since the respondent's last pregnancy terminated and the date of the respondent's last menstrual period. Using IPI as the independent variable of interest, SPRING ran three models looking at birthweight outcomes. Due to the survey's sampling strategy and the very small number of urban women included, only women from the rural clusters were included in the final analysis.

The process for including covariates in the regressions was similar to the one described for Step 1. After a literature review and examination of covariance within the data, the following covariates were included in the continuous IPI model: squared and cubic terms for IPI; education level of the mother; mother's weight at first interview; an index of access to medical services (developed through principal components analysis of iron–folic acid supplementation, visits for antenatal care (ANC), and attendance by a skilled birth attendant at birth); mother's age (squared term); and an index of symptoms during pregnancy (principal components analysis of severe headache at time of birth and bleeding after six months of pregnancy). The results from this analysis are shown in Table D4.

Table D4. Birthweight in Grams as a Result of IPI Length in Months, From the Bangladesh LBWS, by Maternal Weight

	UNDERWEIGHT	NORMAL	OVERWEIGHT
IPI	-9.467 (10.400)	7.243* (2.868)	-1.344 (8.698)
IPI-SQUARED	0.139 (0.219)	-0.150** (0.055)	-0.104 (0.151)
IPI-CUBED	-0.001 (0.001)	0.001* (0.000)	0.001 (0.001)
EDUCATION LEVEL OF MOTHER	20.940* (10.319)	12.236** (4.157)	29.267* (11.224)
MOTHER'S AGE	49.197 (41.445)	33.64 (19.402)	98.642 (111.009)
MOTHER'S AGE SQUARED	-0.82 (0.733)	-0.542 (0.354)	-1.718 (1.958)
SEVERE HEADACHE AT DELIVERY	-13.198 (72.320)	-21.765 (33.845)	-109.632 (161.931)
BLEEDING AT SIXTH MONTH	-110.338 (126.531)	-102.98 (73.218)	-504.810** (162.938)
NUMBER OF ANC VISITS ATTENDED	10.625 (23.989)	17.615 (9.146)	-24.409 (29.320)
NUMBER OF IFA TABLETS TAKEN DURING PREGNANCY	1.322 (0.758)	0.997* (0.396)	1.278 (0.933)
SKILLED BIRTH ATTENDANT (DOCTOR, NURSE, FWV, TRAINED TBA)	-23.143 (111.848)	98.154** (32.170)	-48.238 (126.774)
CONSTANT	1,933.808** (587.267)	2,021.480*** (267.560)	1,657.756 (1,563.426)
R-SQUARED	0.077	0.056	0.229
N_SUB	261	1469	105

The dichotomous IPI models did not include the additional IPI terms suggested by the literature review. To mirror the form of the regressions developed in Step 1, SPRING conducted this analysis on subpopulations by mother's weight status, using the BMI cutoffs for underweight, normal weight, and overweight.

Unfortunately, measurements of gestational age in the dataset were inexact, relying on mothers' recall for date of last period. In addition, the measurements were not able to give the precision needed to estimate the effect of IPI length on gestational age. The risk ratio for FP's impact on the likelihood of PTB was therefore estimated as 0.

APPENDIX E: COST FUNCTION DETAILS

SPRING based the cost of each intervention on the actual product costs and the costs for delivery, varying by the scale and coverage product has across the population. Most previous studies have been limited by estimating delivery costs as a flat number across all scales of delivery. SPRING used a dataset from the delivery of public health and FP products and services funded by USAID to estimate a delivery/marginal fixed cost function between 10,000 and 1,000,000 units per delivery point. (Data beyond these levels were so few that they had to be dropped from the analysis.) The function to estimate delivery costs as a function of scale was:

$$\text{Log}_{10}(\text{MFC}) = 4.0253279 - [0.57198238 * \log_{10}(s)]$$

where (s) is scale or number of units of production per delivery point.

Estimating the total cost simply requires adding the cost of the intervention product (multiple micronutrient supplementation, balanced protein energy supplementation, or contraceptive) to the estimate of MFC based on program scale and on knowledge of the delivery mode/scale of rollout. The scale for delivery was calculated from the number of pregnant women predicted in 2013 (6,559,112); the number of health care centers (i.e., delivery points—884); and the number of health care visits to the centers required for the interventions.

For MMS and BPE, the number of visits was assumed to be ANC visits/health worker visits. Thus, there was a range of three ANC visits to approximately six community health worker contacts across 884 facilities or health posts (DGHS and MHFW 2012; National Institute of Population Research and Training, Mitra and Associates, and ICF International 2013). The total number of women in need of the intervention is based on the same calculations of current and ideal coverage that were used for the effectiveness estimates. Total visits per facility per intervention were estimated from this information by calculating:

Visits per facility/per intervention=Total users * ANC visits per pregnancy/health facilities

This translated to a range of about 22,036– 44,074 ANC visits per facility, which represent the "scale" of the intervention used in the delivery cost function for the "low" and "high" cost estimates, respectively.

For the family planning interventions, scale was based on the number of contact points from two sources: 1) a study in Bangladesh of family planning (3.7 visits per annum, [Janowitz et al. 1997]; and 2) expert opinion on usual number of contact points for oral contraceptives used by over 50 percent of contraceptive users (7 visits per annum) (DELIVER staff, personal communication).

The delivery cost function is based on data from 300 interventions in the areas of reproductive and maternal health, and thus fits the FP via IPI intervention best. Attempts to find more nutrition-specific programming data have not resulted in any data that could allow for a similar nutrition-only function; however, two studies looking at maternal iron supplementation during pregnancy using flat cost curves do produce estimates that are well within the range we get from the SPRING cost function for MMS (adjusted for 2012, they find between US$12 and US$14 per pregnancy in SEARO D countries and China) (Baltussen, Knai, and Sharan 2004; Zeng et al. 2009).

For this first phase, SPRING only looked at costs of the intervention compared to the benefits in the short- and long-term.

Currently, no discount rate is built into the cost function because all intervention costs are incurred in the present day. Data are from 2009 and 2010; thus, final results have been adjusted to 2011 dollar amounts using IMF-reported inflation rates (International Monetary Fund 2013).

For the direct nutritional interventions, the model envisions a scenario where 99 percent of pregnant women receive MMS and 92 percent receive BPE (based on current coverage-total population); thus the cost per birth is calculated by multiplying by the ratio of pregnancies to live births (1.8, as defined by Bangladesh-specific figures on ratio of crude births per 1,000 population to crude births plus abortion (spontaneous plus induced; National Institute of Population Research and Training, Mitra and Associates, and ICF International 2013). For the family planning intervention, total costs include coverage of all women in need of contraception at the time of the study, which was divided by the cohort size to get a cost per birth.

Further information elaborating on the data in Table 2 can be found below.

MULTIPLE MICRONUTRIENT SUPPLEMENTATION

The primary source for unit costs was the Sprinkles Global Health Initiative, which is a brand of multiple micronutrient sachets. The Sprinkles® estimate of US$0.015–0.035 per sachet is likely higher than that of a generic product, so our secondary source was the MSH International Drug Price Indicator Guide. This guide is the main source for drug cost information in developing countries. It reports recent supplier and buyer prices for most commodities on national official drug lists in USAID countries. The median buyer price for 2011 (accessed on March 1, 2013) was US$0.0060/tablet; however, SPRING could not confirm that these are the standard UNIMAP preparation.

For both nutrition interventions, the recommended coverage during pregnancy is one unit per day for the second and third trimesters. As such, assuming 40 weeks of pregnancy – 12 = 28 weeks = 196 days of coverage, this results in a product cost per pregnancy/intervention of US$2.94. SPRING chose the low end of the Sprinkles® range with the assumption that it represents a cost somewhere between the actual cost of a generic and the highest possible cost of Sprinkles®, in lieu of a Bangladesh-specific estimate of Sprinkles® or of a generic. We included in our sensitivity analyses the high estimate (US$0.035) and the unverified generic preparation (US$0.0060) because of this assumption.

BALANCED PROTEIN ENERGY SUPPLEMENTATION

As detailed in the Ota et al. 2012 review, there was a wide range of supplements used in the trials, all called "BPE" interventions. For the sake of costing, SPRING used the USAID corn-soy blend mixture named "CSB14," which contains corn meal, soy flour, soy oil, and whey concentrate. The total protein-to-total energy ratio of CSB14 was 15 percent. Based on a 2011 report on food aid, the cost of CSB14 is US$585 per metric ton and the appropriate dose is 200g, so the unit cost would be US$0.12 per daily dose (Webb et al. 2011).

As with MMS, unit cost to cost per pregnancy/intervention is converted based on recommended coverage during pregnancy. There is no published recommendation for coverage, and the trials reviewed by Ota et al. (2012) varied in their length of coverage, so 16 weeks of once-daily supplementation (or 112 days) is used instead. This results in a cost per pregnancy/intervention of US$13.44. The assumptions for mode of delivery and scale were the same as MMS.

FAMILY PLANNING

For method mix, SPRING obtained the breakdown from the 2011 BDHS and used the top four methods, which account for 94 percent of FP users. Costs of these four types were pulled from the most recent contraceptive commodity catalog (USAID|DELIVER PROJECT 2012) and were averaged using normalized weights representing market share. These were converted into unit cost per couple-years of protection (CYP) using the conversion factors given by USAID (2014), resulting in an average cost per CYP/intervention of US$3.50.

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