Comparing the Effectiveness of Two Maternal Supplements: IFA (Iron and Folic Acid) and MMN (Multiple Micronutrient)

By

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Table of Contents

Figures

Tables

Abbreviations

AfrD	African sub region
AmrB	South American sub region
CI	Confidence interval
DALY	Disability-adjusted life-year
DHS	Demographic and Health Survey
DW	Disability weight
EurA	European sub region
GB	Gilgit-Baltistan
GBD	Global Burden of Disease
GDP	Gross domestic product
IDA	Iron-deficiency anemia
IFA	Iron and folic acid
Int'l$	International dollars
KPK	Khyber Pakhtunkhua
LiST	Lives Saved Tool
LBW	Low birth weight
MMN	Multiple micronutrient
NNS	National Nutrition Survey
NI	Nutrition International
RR	Risk ratio
RRR	Relative risk ratio
SearD	Southeast Asian sub region
SGA	Small-for-gestational-age
UNICEF	United Nations Children's Fund
UNIMMAP	United Nation International Multiple Micronutrient Preparation
WHO	World Health Organization
YLD	Years lost due to disability
YLL	Years of life lost

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Abstract

Iron and folic acid supplementations is the recommended intervention from the WHO since 1968 to target and reduce anemia. It is a very cost-effective intervention that can reduce anemia by up to 70%. However, recent research has showed that populations in low-income countries suffers from several other micronutrient deficiencies. To address these deficiencies a multiple micronutrient supplementation formula has been developed to simultaneously provide the required doses of 15 vitamins and minerals, including iron and folic acid. The marginal benefits of multiple micronutrient interventions have the potential of being quite large, however they come at an additional cost.

Many organizations are questioning if replacing iron supplements with multiple micronutrient tablets would be a cost-effective program to implement. In the goal of providing a framework to address this question, this paper uses meta-analysis and Monte Carlo simulations on a cost-effectiveness model adaptable to different health and socioeconomic context and able to measure the marginal health benefits of multiple micronutrient programs compared to iron supplementation. The cost-effectiveness of such interventions was analyzed in the context of Pakistan. The results showed that, with 89% confidence, multiple micronutrient would result in more health benefits than iron supplements and that it would only cost an additional 4.99 Int'l $ per disability-adjusted life-year averted (units measuring health impacts) to implement the intervention. Based on the WHO's guidelines, this is highly cost-effective.

To test the external validity of the model, the inputs were adapted to reflect the context of India. The model was able to tailor its result to a different setting and estimated, with 97% confidence, that a multiple micronutrient supplementation program in the context of India would generate more health benefits than iron supplementation. The cost-effectiveness analysis estimates that it would cost 5.33 Int'l$ per disability-adjusted life-year averted. Once again, this is very cost-effective.

Introduction

Issue

In response to the increasing disparities between developed and developing countries regarding socioeconomic and health statuses, the United Nation launched the Millennium Development Goals in 2000 and the Sustainable Development Goals in 2012. The latter is a group of 17 goals, covering a range of sectors, from poverty to climate change, with global targets to be reached by each country before 2030. The third Sustainable Development Goal, "Good Health and Well-Being," encompasses maternal and child health. The primary objectives for this goal are a reduction of maternal mortality to 70/100,000 live births, a reduction of neonatal mortality to 12/1,000 live births, and a reduction of under-5 mortality to 25/1,000 (United Nations, 2017).

Every year, 6 million children will die before they reach the age of five, most of them during their first 28 days of life. The majority of these infant deaths occur in Sub Saharan Africa and in South Asia. As for mothers, despite the recent progress in access to prenatal care, the risk of maternal mortality is still 14 times higher in developing countries. A significant contributor to maternal and child mortality and morbidity are communicable diseases, like nutrient deficiencies and HIV. A communicable disease is a disease which is automatically transmitted from the mother to their child during pregnancy or delivery (United Nations, 2017; WHO, 2017).

Iron deficiency is the most widespread nutrient deficiency in the world, affecting more than two out of three people in developing countries and targeting 50% of pregnant women in low-income countries (Baltussen et al., 2004). When iron-deficiency reaches a certain level, it is classified as iron-deficiency anemia (IDA). IDA decreases productivity and increases the risk of infections; it also causes 20% of maternal mortality (WHO, 2017). Maternal anemia causes birth defects in newborns and impedes the cognitive development of children. This, in turn, impacts their school performance and their ability to participate in the work force as adults fully. IDA is considered an important cause of intergenerational poverty in many developing countries.

Interventions Targeting Anemia

International practices

Food fortification and iron supplementation have been identified by the WHO and the international community as interventions that could help reduce the prevalence of IDA. Food fortification is a process in which micronutrients are added to foods. Food fortification in developed countries has been a common practice since the 20th century (Uauy et al., 2002). Due to the globalization in recent decades, it has also become a popular practice in developing countries. If done properly, food fortification can be an efficient and cost-effective way to tackle malnutrition in the targeted population. However, the success of such interventions depends on many factors. Firstly, the fortified food must reach the target population, but consumers must also be educated on the availability of such products and their benefits to accepting to bear the additional costs of fortified items (Hill and Nalubola, 2002).

Countries in Latin America have succeeded to implement fortification programs due to public-private partnerships in various sectors. For example, the addition of vitamin A to sugar since the 1970s in Guatemala, Costa Rica, Honduras, and El Salvador has been a success. They were estimated to reach 80-95% of the population, depending on the country, in 2002. However, the fortification of sugar with vitamin A was not as successful in the Philippines. The international market price of sugar declined significantly in February 1997, sending companies into financial crisis, preventing the continuation of the program (Hill and Nalubola, 2002).

Specific barriers to food fortification with iron are the bioavailability of iron (proportion of iron that has an active effect), the selection of a right vehicle, and the monitoring and surveillance of quality (Uauy, 2002). Finding a vehicle that is low-cost, present in the daily diet of targeted population and that is compatible with the absorption of iron can be a long and complicated process, requiring frequent evaluation. Unfortunately, many programs use arbitrary criteria to choose a vehicle, and monitoring of the quality is rarely done. Moreover, the leakage of non-fortified, and therefore cheaper, foods from surrounding countries is always a risk with fortification interventions (Hill and Nalubola, 2002).

As for iron supplementation programs, they are straightforward and efficient ways to target IDA. Iron supplementation has been a recommended WHO intervention since 1968 (WHO, 2016), with different specificities for each beneficiary. Recipients can include children, adolescent girls, women of reproductive age, pregnant women and men. Each group has different iron intake requirements, and therefore receiving various types of supplements.

Iron supplements can come in different dosage and accompanied with other vitamins or minerals. The most common vitamin added to iron tablets is folic acid. Folate is a B vitamin, and its deficiency is also linked to maternal anemia and neural tube defects in children. There are no known side effects of folate. Therefore it is often added to iron supplements during pregnancy. The recommended tablets from the WHO contain a daily dose of 30 mg to 60 mg of iron and 0.4 mg of folic acid. However, in countries where the prevalence of anemia is relatively high, above 40%, the upper dose of iron (60 mg) is recommended (WHO, 2016).

The success of iron supplementation programs depends on the coverage and on the adherence of the beneficiaries. A recurrent problem with iron and folic acid (IFA) supplements, is the availability of antenatal care and of the supplements. Shortages of tablets is a widespread problem inhibiting the beneficiaries of taking the complete regimen, and jeopardizing the coverage of target populations (Baltussen et al., 2004). According to K4Health, no country has been able to achieve the equivalent of public health care with IFA supplements, 80%, and only

Nepal and Senegal have been able to have a coverage above 50% (P-DHS, 2006-07 to 2012-13). Moreover, even if the tablets are available, it doesn't mean that beneficiaries will adhere to the regime. Multiple factors influence uptake, such as the quality of the tablets, the packaging, the education received by the recipients, and the support from the family and community.

Nutrition International (NI), an international organization focusing on malnutrition in developing countries, was able to successfully implement an iron supplementation program in Nepal that reached 80% coverage, with a baseline of 23%. However, the effects of iron supplementation were disappointing in many countries due to noncompliance, costs, and inadequate education on the program (Phuc, 2008). For example, an intervention in Vietnam identified the lack of compliance as a high-risk factor of IDA and as a cause of the stagnant prevalence of anemia (43%) between 1995 and the time of the intervention, 2003 (Aikawa, 2006), despite the national programs put in place.

Iron and folic acid and multiple micronutrient supplements

Publications like the Demographic and Health Surveys (DHS) and National Nutrition Surveys (NNS) highlighted the high prevalence of deficiencies in other vitamins and minerals such as vitamin A, iodine, and zinc, in most developing countries. Therefore, UNICEF, WHO and the United Nations developed a multiple micronutrient (MMN) supplement to target the most prevalent deficiencies in low-income countries efficiently. The United Nation International Multiple Micronutrient Preparation (UNIMMAP) is the recommended formula for MMN supplements and provides the complete daily requirement of the 15 vitamins and mineral. Table 1 summarizes the ingredients contained in the formula (WHO, 2016).

Table 1: UNIMMAP Formula

Vitamins and Minerals	Quantity	Vitamins and Minerals	Quantity
Vitamin A	800 µg	Vitamin C	70 mg
Vitamin D	5 µg	Niacin	18 mg
Vitamin E	10 mg	Zinc	15 mg
Vitamin B1	1.4 mg	Copper	2 mg
Vitamin B2	1.4 mg	Selenium	65 µg
Vitamin B6	1.9 mg	Iodine	150 µg
Vitamin B12	0.26 mg	Iron	30 mg
Folic	400 µg		

Due to the lower dose of iron in MMN supplements, their impact on maternal anemia and related adverse pregnancy outcomes can be questioned. Another concern with MMN is the unknown relationship between all of the nutrient, which could potentially create an adverse effect on the mother and the fetus. Various studies were conducted to better understand the relationship between MMN supplements and their impact on health outcomes. However, the results weren't consistent. The main point of concern with MMN supplements is their effect on neonatal mortality rates. Bhutta (2009) and Christian (2003) found an increase of neonatal mortality rates of 64% and 74%, respectively, for MMN compared to IFA. However, both didn't reach statistical significance. Other studies, in Bangladesh and Guinea-Bissau, found no statistically significant impact of MMN on neonatal mortality (Tofail, 2008; Kaestel, 2005). To gain a more thorough understanding of the role of MMN on neonatal mortality, the Supplementation with Multiple Micronutrient Intervention Trial (SUMMIT) Study Group conducted a large trial in Indonesia to compare the outcomes of IFA and MMN. They reported a statistically significant positive impact of MMN on post neonatal mortality (RR: 0.70), on infant mortality (RR: 0.82), and on infant mortality within babies born of anemic women at enrollment (RR: 0.62). However, they found the evidence for neonatal mortality to be statistically insignificant. The SUMMIT's hypothesis for this positive impact of MMN on mortality relative to other studies was their use of a much greater sample size (Lancet, 2008).

A recent publication in the Cochrane Library (2017) also looked at the effect of MMN supplements compared with IFA. It found that the ability of MMN tablets in reducing anemia and most of its health outcomes were similar to IFA tablets, expect for low birth weight (LBW) and small-for-gestational-age (SGA). In these two cases, MMN's had a higher impact on the reduction of SGA and LBW prevalence in infants.

The disparities between results of such analysis still call for more studies to keep building evidence towards the benefits of MMN supplements as a tool to target anemia. As of 2016, MMN isn't a recommended practice for antenatal care by the WHO (WHO, 2016). However, the WHO's recommendations state that:

"Although the GDG [Guideline Development Group] agreed that overall there was insufficient evidence to warrant a recommendation, the group agreed that policymakers in populations with a high prevalence of nutritional deficiencies might consider the benefits of MMN supplements on maternal health to outweigh the disadvantages, and may choose to give MMN supplements that include iron and folic acid."

Seeing as these recommendations don't give clear guidelines as to when and where MMN supplements are appropriate, it is at the discretion of governments and international organizations to determine which supplements are best suited for the context in which they operate. The entities who are considering implementing MMN supplements need to keep in mind that they are subject to the same obstacles as IFA supplementation programs, uptake, and coverage. MMN, in some context, can bring additional health benefits when compared to IFA but the extent of the benefits entirely relies on the implementation of the program.

Policy Question

Pakistan is a country with a very high prevalence of maternal anemia, and subsequent health conditions. IFA supplementation programs are already in place in most regions. However, some organizations are wondering if, keeping all organizational components equal, Pakistan would qualify as a country where the context warrants the use of MMN.

This paper summarizes a cost-effectiveness study comparing two alternative micronutrient supplements in the context of Pakistan. The first option is to provide IFA tablets containing 60 mg of iron and 0.4 mg of folic acid, and the second is to provide MMN using the UNIMMAP formula. The potential additional health benefits of MMN come at a greater cost. Thus, the analysis will allow for the comparison of the interventions and determine which type of supplements would be optimal in Pakistan.

The model uses meta-analysis to determine the expected benefits of MMN on the reduction of maternal anemia, premature birth, small for gestational age infants, low birth weight, stunting, stillbirth, neonatal mortality, infant mortality, and maternal mortality. Health and socioeconomic data specific to the context of Pakistan will be use to quantify the health impacts in this context. Monte Carlo simulations will then be used to conduct a probabilistic analysis and to the determine the level of confidence of the analysis. Using cost estimates from Baltussen (2004) the model will estimate the level of cost-effectiveness of and intervention replacing IFA supplements with MMN tablets in the context of Pakistan.

Key Findings

The analysis presented in this paper highlighted two key findings. Firstly, a policy recommendation. MMN as a supplement for pregnant women in the context of Pakistan was found to be a more effective health intervention compared to IFA, with 88.90% confidence. Secondly, MMN has significant positive effects on child morbidity. Morbidity is where MMN provides the most substantial impact compared to IFA, which is usually not captured by commonly used tools for assessing health and nutrition interventions, such as the Life Saved Tool (LiST). LiST only reports the impact of interventions on mortality, therefore it wouldn't be able to highlight the marginal benefit of MMN compared to IFA. However, the model used in this paper is able to quantify both mortality and morbidity effects, thus capturing a higher proportion of health benefits from MMN supplementation.

Pakistan

Socioeconomic Context

Despite Pakistan's fast urbanization rate (DW, 2014), 61.2% of the population lives in rural areas where agriculture is very present (CIA, 2017). Agriculture is the main employer in the country, representing 21% of the GDP (P-DHS, 2012-13), making it essential to the economic development. However, even with agriculture being a central component of the economy, around 60% of the population is food insecure, meaning they don't have physical access or monetary means to consume a healthy diet. It is estimated that even with an average household spending 40-50% of their monthly income on food (P-DHS, 2012-13), 22% of the population is undernourished (FAO, 2017).

In Pakistan, only 51% of the population is employed in the formal sector, and only 22% of women are in the formal job market (World Bank Data, 2017). The GDP per capita was estimated at 1,468.99 USD in 2015, which is beneath the World Bank's average for Lower Middle-Income countries (2,075 USD). About 30% of the population was below the national poverty lines in 2013 (NNS, 2011), and undernutrition was identified as the main contributor to inter-generational poverty (NNS, 2011).

Inequalities in Pakistan are high and two-fold, between rural and urban areas, as well as between men and women. Poverty rates in urban areas (18%) are much lower than in rural areas (35%) (World Bank Data, 2017). Similar trends are noticed for employment and education. However, one thing is consistent in both urban and rural regions; poverty has a "woman's face." There are large inequalities within households related to food distribution and other resources. In Pakistan, boys are considered more important than girls since they eventually earn income for the family. Therefore, under nutrition starts at a very young age for females, and continue throughout their adolescence and adult lives, resulting in poor pregnancy outcomes and continuing the cycle of malnutrition.

The most widespread health condition that comes from poverty and undernourishment is anemia, being particularly prevalent in pregnant women due to the increased requirements for vitamins and minerals coming from the fetus. Women who do not have access to education are usually unaware of the optimal antenatal care behavior to adopt and the importance of a proper diet during pregnancy. Moreover, most women do not have the necessary income to consume nutrient-rich foods. The dynamic between men and women in the household is also an obstacle for good antenatal practices. In multiple surveys, lack of support from husbands and from the family in law was identified as a barrier to seeking professional services during pregnancy (P-DHS, 2012-13; NNS, 2011).

Reproductive Health Care of Pakistan

The public health expenditure in Pakistan is one of the lowest in the world, 0.9% of GDP (IMF, 2017), which amounts to US$ 36 per capita. This level of expenditure is very low compared to countries in similar health and economic position. For example, India and Afghanistan spend 1.4% and 2.9% of their GDP on health expenditure respectively, representing 75$ and 57$ per capita. Bangladesh is one of the few countries with lower public spending in health. What is even more worrying is that health expenditure as a percentage of GDP in Pakistan has been a downward trend in the past few years with no sign future improvements, whereas other countries are increasing their share or keeping them constant (World Bank Data, 2017).

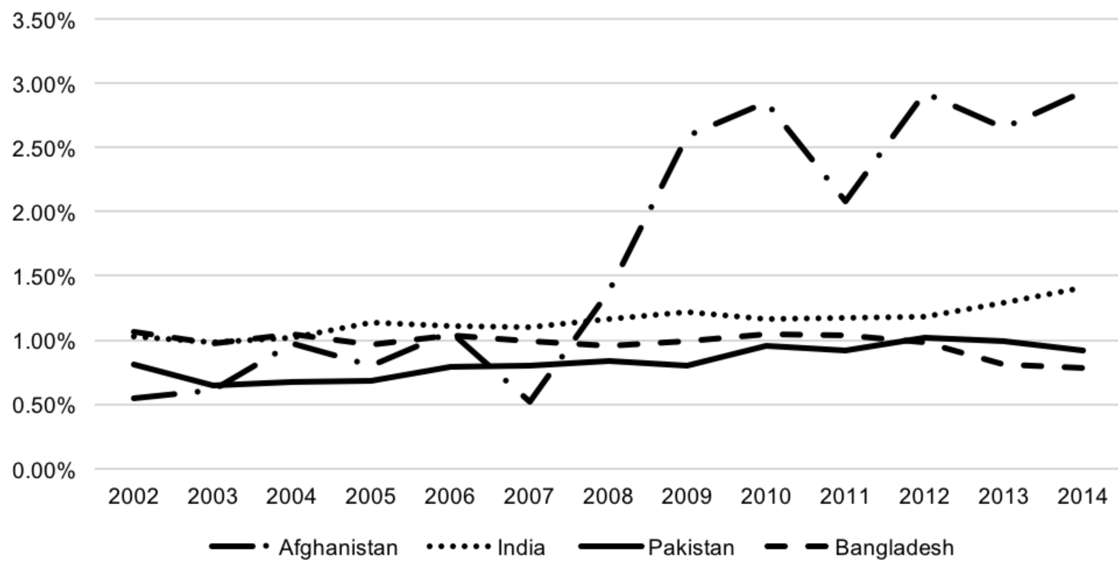

Figure 1: Health Expenditure, % of GDP

Other characteristics of Pakistan's health expenditure are that it mostly focuses on curative interventions instead of preventive interventions and 75% of the investment comes from private entities, making it difficult to align programs and policies across regions and to ensure a uniform quality, exacerbating the already precarious financial and nutritional situation of the country.

The federal and provincial governments of Pakistan are jointly responsible for the health and nutrition sector. Various public programs are currently active in this partnership; however provincial governments are responsible for identifying the needs, leading to varying coverage levels by regions (Annual Action Program, 2016-17). The main health program in place, which has a women's health component, is the National Programme for Family Planning and Primary Care, also known as the Lady Health Workers Programme (PHNP, 2017). It was implemented in 1994 to provide unmet preventive health services for rural populations. However, inconsistent criteria to register as a Lady Health Worker brings disparities in the coverage across provinces (WHO, 2008). For example, the region with the highest coverage is Gilgit-Baltistan (72%), and the lowest is in Balochistan (24%) (Hafeez et al., 2011).

National reproductive health care services, which mainly regroups preventive services, suffers from the same inconsistency and from a lack of funding. Seven out of ten women visit a prenatal clinic at least once during their pregnancy. However only 37% of them have four or more visits during their pregnancy, which is the recommended amount, and six in ten women expressed having difficulties accessing health care. As for birth and postnatal assistance, only half of women are accompanied by a skilled health professional during delivery, and only 20% of newborns receive postpartum check up (World Bank Data, 2017).

The lack of reproductive health services throughout pregnancy and postnatal periods, as well as the disparity between regions in the accessibility of such services, increases the prevalence of maternal anemia and its subsequent adverse health outcomes for the mother and the child.

Pakistan and surrounding countries all have very high prevalence of anemia within pregnant women, averaging around 50%. The marking difference between Pakistan and other similar South-Asian countries, like Bangladesh and India, is its increase in the prevalence of anemia throughout time and across all regions. The maternal mortality ratio in Pakistan is higher but, comparable to other South-Asian countries, sitting at 178/1,000. As for children's health conditions, the neonatal mortality ratio is significantly greater in Pakistan, 45.5/1,000, compared to India, 27.7/1,000, and to Bangladesh, 23.3/1,000. Malnutrition of children is often assessed by the prevalence low birth weight and stunting (World Bank Data, 2017). Once again, Pakistan has higher prevalence for both of these health conditions than surrounding countries, and they have increased over time. Table 1 compares these health conditions between Pakistan, India, and Bangladesh.

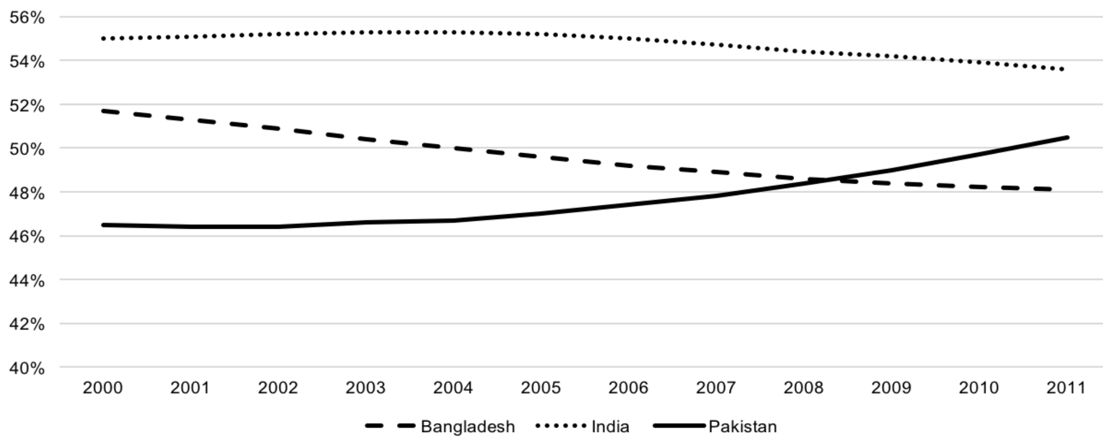

Figure 2: Maternal Anemia

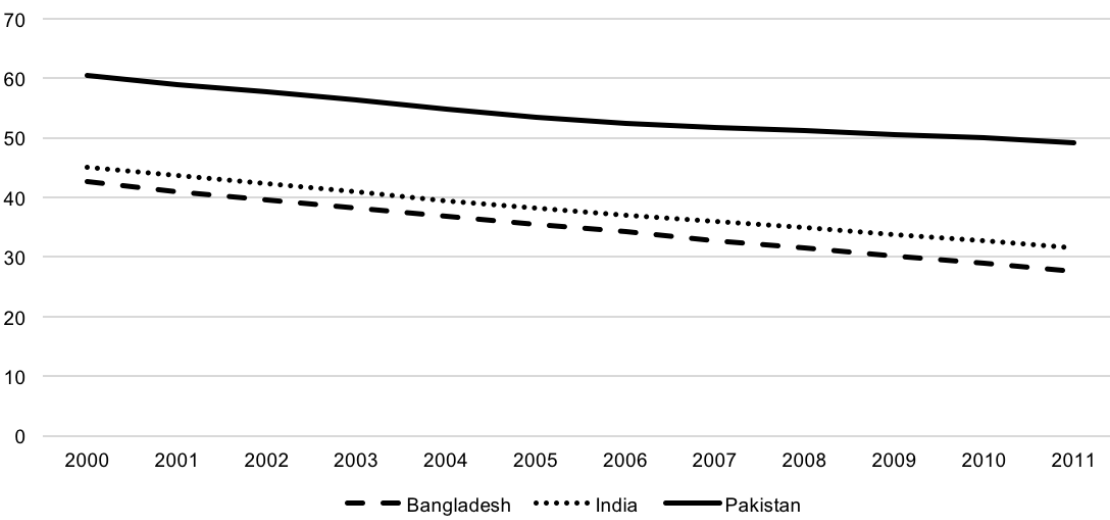

Figure 3: Neonatal Mortality Rate - per 1,000 live births

Table 2: Health Conditions in Southeast Asian Countries

Country	Maternal Anemia	Maternal Mortality Ratio	Neonatal Mortality Ratio	Low Birth Weight (LBW)	Small for Gestational Age (SGA)	Stunting
Pakistan	50.50%	178/100,000	45.5/1,000	32.00%	47.00%	45.00%
India	53.60%	174/100,000	27.7/1,000	28.00%	46.70%	38.70%
Bangladesh	48.10%	176/100,000	23.3/1,000	22.00%	39.60%	36.40%

Anemia

Risk Ratios

Risk ratios (RRs) are often used to report the impacts of health and nutrition interventions. RRs are a dichotomous measure representing the risk of having a health condition in an exposed group, compared to the risk of developing the same health condition in a non-exposed group. For example, the probability of dying during pregnancy while having moderate anemia, compared to the risk of death during pregnancy while not being anemic is 1.35 (Brabin et al., 2001). This analysis will estimate the marginal effectiveness of MMN compared to IFA using RRs reported for the morbidity and mortality outcomes of interest.

$$RR = \frac{risk\ of\ event\ in\ experimental\ group}{risk\ of\ even\ in\ control\ group} = \frac{S_E/_{N_E}}{S_C/_{N_C}}$$

Anemia

Nutrition and health sectors are regrouped under the same department in Pakistan since 2012 (Annual Action Program, 2016-17). Therefore, most preventative and curative interventions surrounding anemia are linked to the increase in coverage and quality of the health system. Since anemia plays a crucial role in pregnant women's health and in the development of the fetus, preventive interventions are directly linked to the accessibility of reproductive health care.

Anemia has various causes such as hookworm infection, malaria, low bioavailability of iron, and B12 deficiency due to poor absorption of iron by the body. However, more than half of all cases of anemia are caused by iron deficiency, IDA (Kalaivani, 2009).

IDA hinders the body’s capacity to produce red blood cell, which is a vital component to transporting oxygen throughout the body and to have a healthy immune system (Alton, 2005). Table 2 defines the thresholds for mild, moderate, and severe anemia defined by the WHO, using grams per deciliter (g/dL) as a unit of measure. Testing for serum ferritin, which indicates the amount of iron stored in the body, or for hemoglobin levels are the two most common and cost-effective ways to test for anemia (Alton, 2005).

Table 3: Levels of Anemia for Pregnant Women

Diagnosis	Mild	Moderate	Severe
Haemoglobin level	10.90 g/dL	9.90 g/dL	7.00 g/dL

Anemia causes fatigue, which decreases endurance, work capacity, and concentration (GBD, 2010). As the severity of anemia increases, the immune system is depressed, which increases the risk of contracting infections. IDA affects cognitive and motor development, having a sizable impact on a country's productivity level. Through a study including 10 developing countries, it was estimated that annual physical productivity losses due to IDA amount to 0.57% of GDP. However, when adding the cognitive capacities that are affected by anemia, the total losses can go up to 4% of GDP (Anand et al., 2013). As for Pakistan, it was estimated that the income lost due to iron deficiency is 5.2% of GDP (Horton and Ross, 2002).

Maternal consequences of anemia

The recommended daily intake of iron for women is 18 mg/day, whereas for expectant mothers the necessary intake increases to 27 mg/day since they need to provide sufficient iron stores for themselves and the fetus (Percy et al., 2016). In most cases, iron requirements during pregnancy become too high to be completely absorbed through a standard diet, putting women at risk of anemia. Moreover, the fetus' storage of iron is prioritized over the mother's during pregnancy, further depleting the iron levels of the women who were previously anemic.

In addition to the morbidity impacts of anemia, IDA is linked to maternal mortality. Women with mild anemia aren't at risk of dying during the delivery or the postpartum period. However, women with moderate and severe anemia are at a significantly higher risk. Moderate anemia is associated with a large proportion of women dying due to hemorrhage, hypertension, and sepsis during pregnancy, which causes 52% of all maternal deaths (Say et al., 2014). As for mothers with severe anemia, a blood loss as small as 200 ml can cause heart failures, shock, and death.

Risk ratios are often used to report the risk of having a health condition in an exposed group, compared to the risk of developing the same health status in a non-exposed group. For example, the probability of dying during pregnancy while having moderate or severe anemia, compared to the risk of death during pregnancy while not being anemic is 1.35 and 3.51 respectively (Brabin et al., 2001). In extremely severe anemia cases, where hemoglobin levels go below 5 g/dL, there is an 8-10 fold increase in the risk of maternal mortality (Kalaivani, 2009).

Table 4: Maternal Anemia and Mortality Risks

Severity Level	Mortality Risk
Mild Anemia	No increase in mortality rates.
Moderate Anemia	Increases risk of hemorrhage, sepsis, and hypertension. RR: 1.35
Severe Anemia	Increases risk of heart failure and hemorrhage. RR: 3.51

Child consequences of anemia

Women with anemia during pregnancy have a significantly higher risk of experiencing adverse birth outcomes, such as preterm birth, small for gestational age (SGA), low birth weight (LBW), and subsequently stunting, and mortality (neonatal, infant and under-five).

The mother's iron levels are positively correlated with the gestational time of pregnancies. Therefore, anemic mothers have a higher risk of having preterm deliveries (gestational time of 37 weeks or less). In a study conducted in India (Kumar et al., 2013), which looked at 1,000 mothers, the authors found that there was an increased risk of 11.5% for preterm deliveries in mothers who were anemic in their second and third trimester. Levy et al. (2005), also found higher rates of preterm births in anemic mothers, 10.7%, compared with non-anemic mothers.

The mother's poor nutrition and health during pregnancy impacts the weight of babies and often leads to LBW newborns (below 2,500 g). Levy et al. (2005), also looked at LBW as an outcome of maternal anemia through a retrospective population-based study of 13,204 anemic pregnancies. He found that within all the birth complications, 46% included both preterm births and LBW, and the remaining 54% were either preterm deliveries or LBW. Moreover, a study showed that anemic mothers have a 6.5% higher risk of giving births to LBW babies (Kumar et al., 2013). According to WHO (2004), LBW is "closely related to fetal and neonatal mortality and morbidity, inhibit growth and cognitive development, and chronic diseases later in life." Another study also related severe anemia (here defined as hemoglobin <8 g/dL) to a doubling of LBW rate and 2 to 3 fold increase in the perinatal mortality rates (Kalaivani, 2009).

A considerable impact of poor maternal nutrition and LBW is stunting. Stunting is defined as height for age below two standard deviations of the WHO median standards (WHO, 2017). Stunting cases are "associated with an underdeveloped brain, with long-lasting harmful consequences, including diminished mental ability and learning capacity, poor school performance in childhood, reduced earnings and increased risks of nutrition related chronic diseases, such as diabetes, hypertension, and obesity in future" (UNICEF, 2017). This condition is worsened by poor diet and inadequate sanitation and hygiene and is irreversible by the age of two. This significantly impacts the child's survival chances. A systematic review in reported that 20% of stunting cases in children are due to maternal undernutrition (Lancet, 2008). The impacts on anemia on the health conditions are summarized in Table 5.

In addition to birth defects, maternal anemia also leads to impairments in the cognitive development of their children. The infant's iron stores, for the first six months of life, is determined by the nutrients received in utero in combination with the nutrients received from breast milk. However, when mothers are anemic, they can't completely satisfy the infant's iron requirement, which leads to cognitive disturbances (Jáuregui-Lobera, 2014). Cognitive impairments in children related to iron deficiency are "attention span, intelligence, and sensory perception functions [...], as well as those associated with emotions and behavior" (Jáuregui-Lobera, 2014).

Prevalence rate in Pakistan

Due to the wavering commitment of the Pakistani government to health and nutrition programs, improvements in health indicators are slow or, in some cases, none existent. As expected, differ substantially between rural and urban populations. This has led Pakistan to have the third highest rate of maternal, fetal, and child mortality in the world, after Nigeria and the Democratic Republic of Congo. (Bhutta et al., 2013; Black, 2008; Rajaratnam; 2010).

Table 5: Child Morbidity due to Maternal Anemia

Morbidity	Increased Risk
Preterm Deliveries	11.5%
Low Birth weight	6.5%
Stunting	20.0%

Maternal anemia is highly present in all regions of Pakistan. Figure 1 shows the anemia prevalence in pregnant women throughout Pakistan. The national average of anemia and IDA in 2011 was 51%, and 37% respectively (NNS, 2011). Only the province of Khyber Pakhtunkhwa (KPK) and the Gilgit-Baltistan (GB) region had lower anemia prevalence, about 30%. In addition to the alarmingly high rates, we see an increase of anemia through time in Pakistan, instead of a reduction. Figure 2 shows the difference in prevalence of anemia between 2001 and 2011. We observe an increase of 20% of maternal anemia throughout Pakistan (NNS, 2011). Figure 3 and Figure 4 show the child mortality and morbidity prevalence in sub regions of Pakistan. According to the WHO, IDA causes 30% of all-cause maternal deaths.

Direct consequences of maternal anemia on newborns are preterm deliveries, LBW, and stillbirth, estimated to be 39%, 32%, and 43.15/1,000 live births respectively (UNICEF, 2013). Subsequent consequences of maternal under nutrition are stunting, affecting 44% of the population, and neonatal, infant, and under-5 mortality rates reaching 45.5/1,000, 65.8/1,000, and 81.1/1,000 respectively. These statistics are summarized in Table 6.

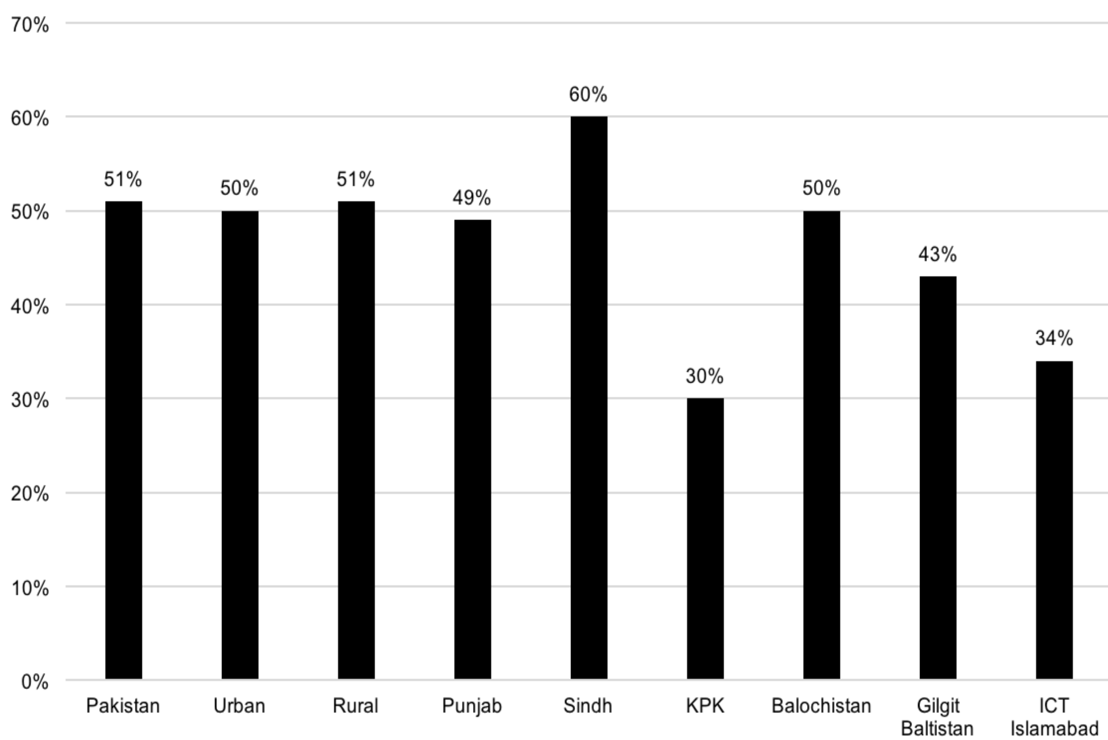

Figure 4: Maternal Anemia in Sub Regions of Pakistan

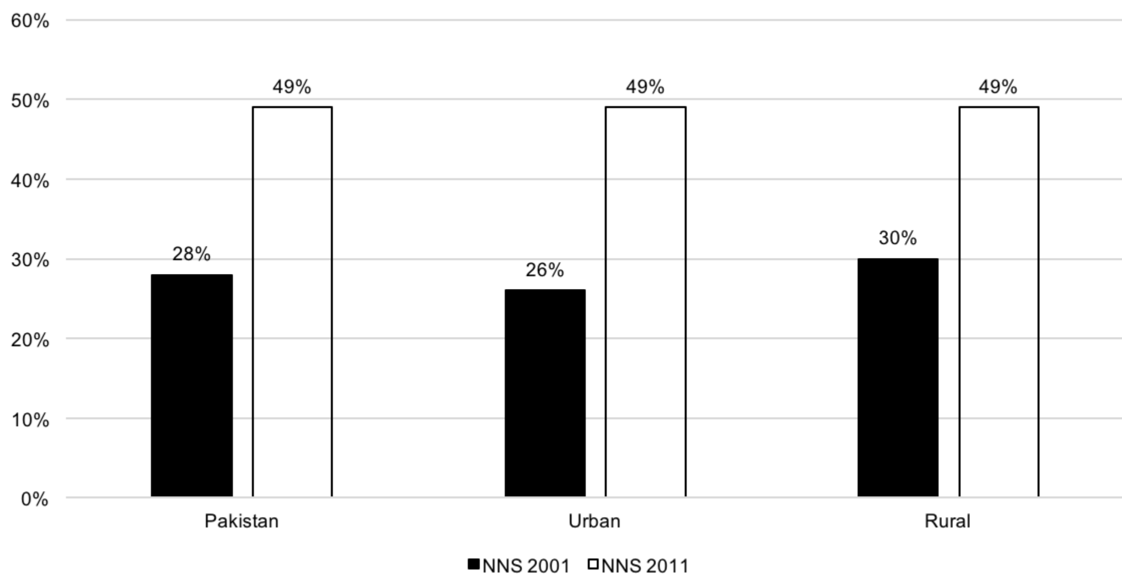

Figure 5: Anemia Prevalence Over Time

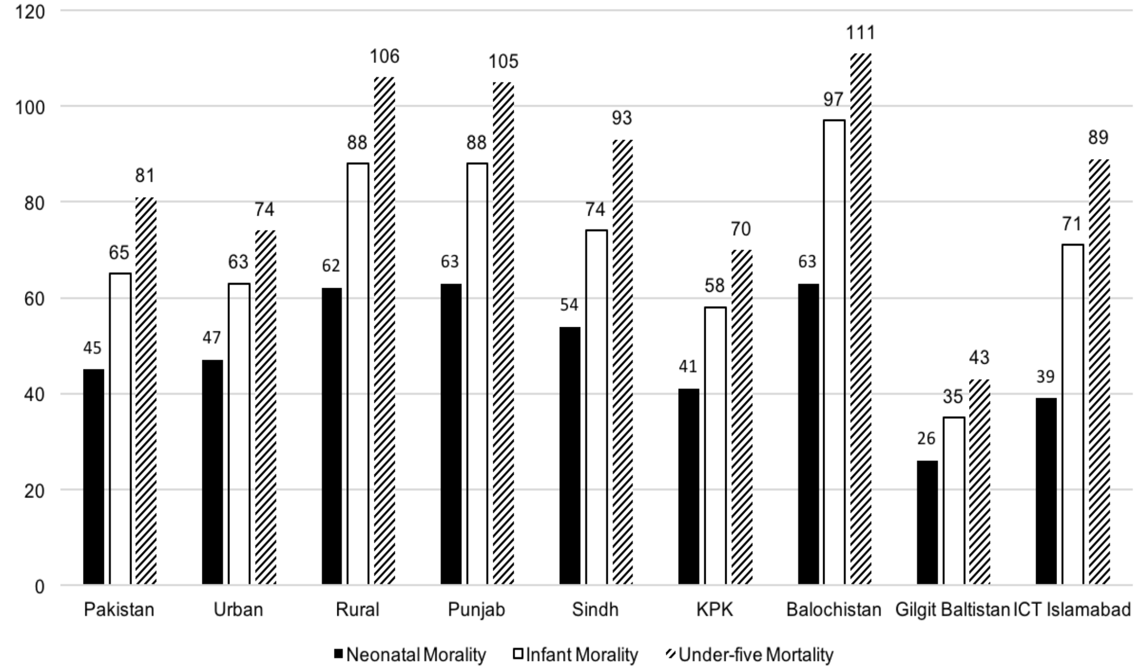

Figure 6: Child Mortality Rate - per 1,000 live births

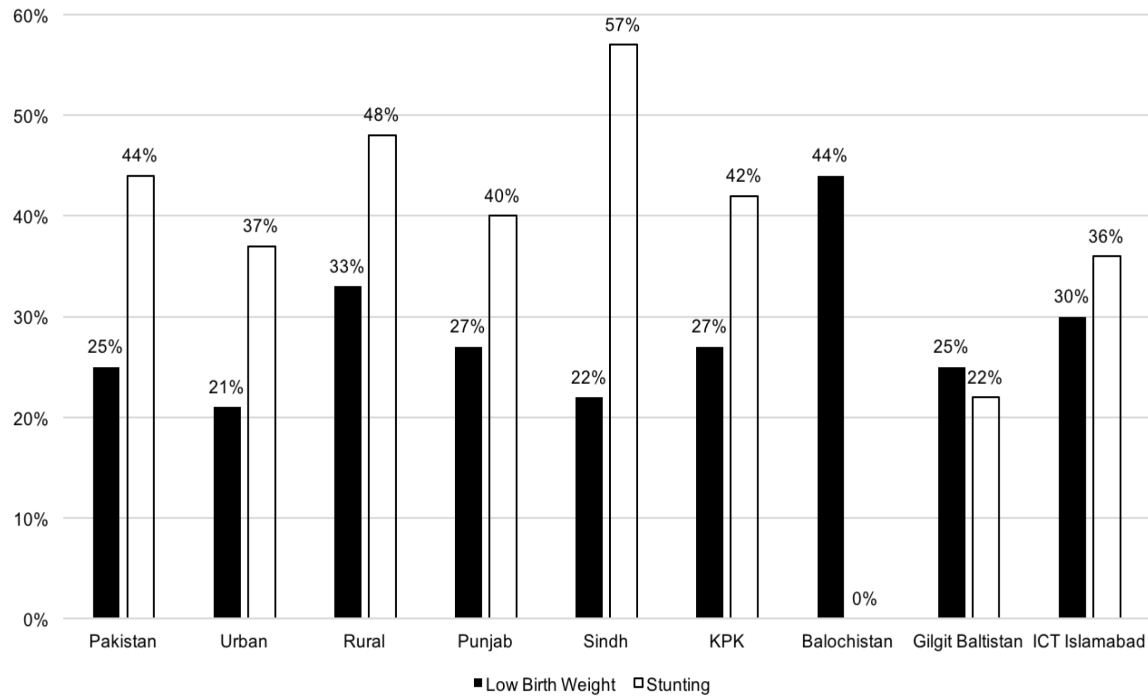

Figure 7: Child Morbidity

Table 6: National Prevalence of Conditions Related to Maternal Anemia in Pakistan

Health Conditions	Prevalence
Iron Deficiency Anemia in Pregnant Women	37%
Preterm Deliveries	39.28%
Low Birth weight	32%
Small for Gestational Age	46.99%
Stunting	44%
Maternal Mortality Ratio	178/100,000 live births
Stillbirths	43.15/1,000 live births
Neonatal Mortality Ratio	45.5/1,000 live births
Infant Mortality Ratio	65.8/1,000 live births
Under-five Mortality Ratio	81.1/1,000 live births

Methodology

Sources of Benefits

IFA and MMN can affect beneficiaries through various channels and with different effectiveness level. Through a thorough literature review, relevant stakeholders benefiting from interventions and the effectiveness level of interventions on each health outcomes were identified. Table 7 shows the Benefit, Cost & Stakeholder table, which gathers the primary beneficiaries and the health and financial channels through which they are impacted. Table 8 shows the full impact channels.

Table 7: Benefit, Cost & Stakeholder

	Implementers	Parents	Infants
Benefits			
Morbidity		✓	✓
Mortality		✓	✓
Costs			
Intervention Costs	✓	✓	

Table 8: Detailed Impact Channels

Impact Channels	
Morbidity	IFA and MMN will decrease child and maternal morbidity through the following channels: ● Maternal anemia ● Preterm deliveries ● Small-for-gestational-age infants ● Low birth weight infants ● Stunting (Indirect impact)
Mortality	IFA and MMN will decrease child and maternal mortality through the following channels: ● Maternal mortality ● Stillbirth ● Neonatal mortality ● Infant mortality
Medical Expenses	The reduction in morbidity and mortality will impact medical expenses through the following channels: ● Decrease in morbidity will reduce the medical services required by infants ● Reduction in mortality will increase medical services for each life saved Based on expert interviews, it was concluded that the impact on medical expenses is negligible in the context of Pakistan and is therefore excluded from the analysis.
Cognitive Development	Iron supplements can influence the cognitive development of children through an increase in the iron stores of the mother, which is passed on to the fetus during pregnancy. Due to the lack of scientific evidence on the direct impact of MMN on cognitive development, compared to IFA, and to the fact that MMN has the same impact as IFA on maternal anemia, we make the assumption that MMN will lead to the same benefits on cognitive development. Therefore, cognitive impacts are not included in the model.

Impacts of IFA in Pakistan

Several trials and systematic reviews report different RRs on the health condition listed above when comparing MMN to IFA. The RR reported significantly vary according to the sample size, to the randomizing method, and to the context of the trial. Choosing the optimal RRs in a coherent and impartial manner might be challenging and taking a weighted average of the RRs reported in systematic reviews would double count the overlapping trials in each research and bias the results. Therefore, two scenarios were constructed to obtain an overall marginal impact of MMN on IFA for each health outcomes.

The first scenario is a systematic review published in the Cochrane database in 2017 (Haider and Bhutta). It was chosen because it is the most recent systematic review published that compared both IFA and MMN and it is the review that covered the most health outcomes included in this model. The analysis reports a significant decrease in SGA and LBW prevalence and finds insignificant changes for preterm births, maternal anemia, maternal mortality, stillbirths, and neonatal mortality when comparing MMN to IFA. The countries represented in the review are Pakistan (Bhutta, 2009), Nepal (Christian, 2003; Osrin, 2005), Tanzania (Fawzi, 2007), Zimbabwe (Friis, 2004), Guinea-Bissau (Kaestel, 2005), China (Lui, 2014; Zeng, 2008), Mexico (Ramakrishnan, 2003), Burkina Faso (Roberfroid, 2008), Indonesia (SUMMIT, 2008; Sunawang, 2009), Bangladesh (Tofail, 2008; West, 2014), and Niger (Zagre, 2007). It regroups 15 trials that compares MMN with a control (iron supplements with or without folic acid) and converts all dichotomous measures used in the trials in RRs. A disadvantage of using this systematic review is that some trials use different formulas for the MMN supplements. This paper reproduces the meta-analysis conducted in the Cochrane review to ensure that the methodology employed is adequate. This first scenario will be referred to as Cochrane.

The second scenario, referred to as Cochrane+, is an updated version of the meta-analysis in the Cochrane review. A search through PubMed and Medline was conducted to find all relevant trials reporting the estimates of the impact of MMN compared to IFA for pregnant women in developing countries. The following 8 outcomes were of interest: maternal anemia, preterm deliveries, small-for-gestational-age infants, low birth weight infants, stunting, maternal mortality, stillbirths, neonatal mortality, and infant mortality. Only trials using randomized trials, and reporting their measures in RRs were included. All 15 trials reported in the Cochrane scenario were selected for the Cochrane+, and two additional studies were also included. Gupta (2007), conducted a trial in India comparing MMN and IFA. However it was excluded from the Cochrane review because it included women with severe anemia, which are considered an at-risk group. However, the assumption that many severely anemic women in Pakistan goes undetected and receive the same prenatal care as other women were made. It is therefore relevant to add it in the second scenario. Andersen (2010), conducted a follow-up of the trial in Guinea-Bissau from Kaestel (2005) and reported a different RR for neonatal mortality than the one included in Cochrane. The value estimated by Anderson for neonatal mortality will replace the one estimated by Kaestel in the meta-analysis. The rest of the estimates of Kaestel (2005) remained unchanged.

Infant mortality isn't included as an outcome of interest in the Cochrane scenario. However, it is an outcome in our model. The value estimated by Cochrane+ for infant mortality is used in both scenarios.

Meta-Analysis

Table 9: Risk Ratios by trials for Cochrane+

Cochrane/Cochrane+	Country	Population	Intervention	Comparisons	N	Preterm	SGA	LBW	Stillbirths	Neonatal Mortality	Maternal Anemia	Maternal Mortality	Infant Mortality
						RR (SE)	RR (SE)	RR (SE)	RR (SE)	RR (SE)	RR (SE)	RR (SE)	RR (SE)
Bhutta (2009a)	Pakistan	Pregnant women in developing countries.	Cluster randomised trial	MMN vs IFA	2378	1.07 (0.17)	0.97 (0.12)	0.82 (0.13)	1.15 (0.30)	1.44 (0.38)			
Christian (2003)	Nepal	Pregnant women in developing countries.	Double-blind cluster-randomised trial	MMN vs IFA	4,926	0.87 (0.09)	1.06 (0.05)	1.03 (0.10)	1.44 (0.47)	1.49 (0.46)	1.45 (0.36)		
Fawzi (2007)	Tanzania	Pregnant women in developing countries.	Double-blind trial	MMN vs IFA	8428	1.01 (0.06)	0.79 (0.05)	0.83 (0.07)	0.87 (0.12)				
Friis (2004)	Zimbabwe	Pregnant women in developing countries.	Randomised Trial	MMN vs IFA	1669	0.79 (0.17)	0.81 (0.24)	0.74 (0.24)	1.98 (4.48)				
Kaestel (2005)	Guinea-Bissau	Pregnant women in developing countries.	Randomised Trial	MMN vs IFA	2100	1.06 (0.26)	0.76 (0.25)	0.88 (0.21)	0.49 (0.20)			0.56 (0.65)	
Lui (2013)	China	Pregnant women in developing countries.	Double-blind randomised control trial	MMN vs IFA	18775	0.91 (0.08)		0.9 (0.13)	0.93 (0.33)	0.81 (0.27)			1.02 (0.27)
Osrin (2005)	Nepal	Pregnant women in developing countries.	Women attended a designated antenatal clinic	MMN vs IFA	1200	0.87 (0.20)	0.79 (0.18)	0.75 (0.10)	0.83 (0.41)	1.53 (0.87)	0.86 (0.10)		
Ramakrishnan (2003)	Mexico	Pregnant women in developing countries.	Randomised controlled Trial	MMN vs IFA	873	1.14 (0.44)	0.86 (0.24)	0.96 (0.32)	1.24 (1.67)		1.12 (0.16)		
Roberfroid (2008)	Burkina Faso	Pregnant women in developing countries.	Randomised controlled Trial	MMN vs IFA	1426	1.04 (0.20)	0.83 (0.12)	0.91 (0.18)	1.74 (0.99)	2.10 (1.81)			
SUMMIT (2008)	Indonesia	Pregnant women in developing countries.	Double-blind cluster-randomised trial	MMN vs IFA	31272	1.07 (0.06)	0.97 (0.08)	0.87 (0.09)	0.90 (0.09)	0.90 (0.09)		1.03 (0.32)	
Sunawang (2009)	Indonesia	Pregnant women in developing countries.	Cluster randomised trial	MMN vs IFA	843	1.13 (0.18)	0.87 (0.17)	1.22 (0.30)	0.90 (0.72)	0.54 (0.47)			
Tofail (2008)	Bangladesh	Pregnant women in developing countries.	Randomised controlled Trial	MMN vs IFA	2489	0.75 (0.13)	0.90 (0.14)	0.86 (0.09)	1.00 (0.38)	1.34 (0.51)			
West (2014)	Bangladesh	Pregnant women in developing countries.	Community-based, cluster-randomised, double-blind trial	MMN vs IFA	45000	0.85 (0.03)	0.98 (0.02)	0.88 (0.02)	0.89 (0.05)	0.98 (0.11)			0.95 (0.06)
Zagre (2007)	Niger	Pregnant women in developing countries.	Cluster-randomised, double-blind controlled programmatic study	MMN vs IFA	3670	1.02 (0.06)	0.82 (0.13)	0.87 (0.15)	1.18 (0.29)			1.12 (2.19)	
Zeng (2008)	China	Pregnant women in developing countries.	Community-based, cluster-randomised trial	MMN vs IFA	5828	1.06 (0.19)	0.89 (0.08)	0.90 (0.19)	1.35 (0.31)	1.15 (0.56)	0.96 (0.12)		
Gupta (2007)	India	Pregnant women in developing countries.	Randomised-control trial	MMN vs IFA	200	0.60 (0.15)		0.38 (0.01)					
Andersen (2010)	Guinea-Bissau	Pregnant women in developing countries.	Randomised-control trial	MMN vs IFA	2100					1.18 (0.45)			

Table 9 shows all 17 trials included in Cochrane+, as well as the RRs each trial reported for all eight outcomes. Using a random-effect method, a meta-analysis was conducted in R to obtain average values for each outcome of interest.

Morbidity

Table 10: Morbidity Risk Ratios for IFA and MMN

Morbidity	RR for IFA versus placebo†	RR for MMN versus IFA (Cochrane)‡	RR for MMN versus IFA (Cochrane+)
Maternal Anemia	0.33	1.03	1.03
Preterm Deliveries	0.93	0.96	0.95
Small-for-gestational-age	0.85	0.92	0.92
Low Birth Weight	0.80	0.88	0.87

† Cochrane, 2015; Lancet, 2013
‡ Haider et Bhutta, 2017

Maternal anemia

Parents, mainly mothers, affected by IDA and malnutrition will see their health improved through supplementation. They will gain in physical and cognitive capacity, increasing their opportunity to work and to participate in community life. Multiple studies and systematic reviews look at the impact of IFA on maternal anemia. Akhar (2013), found that iron supplementation decreased anemia in pregnant women by 73% in Pakistan. This result is the highest reduction of anemia prevalence found in Pakistan. Other articles report a reduction in anemia between 66-70% for pregnant women (Cochrane, 2015; Imbad, 2012; Lancet,2013).

Cochrane (2017) report an average RR of having maternal anemia when taking MMN compared to IFA. The expected mean estimated by this scenario is 1.03, indicating that there would be an increase in the probability of having maternal anemia by 3% when taking MMN (Haider and

Bhutta, 2017; Bhutta, 2011). Cochrane+ didn't include additional studies reporting maternal anemia as an outcome. Therefore the expected value is the same for both scenarios. The RR obtained isn't significant (Confidence Interval (CI) at 95%: 0.85, 1.24). We can assume that IFA and MMN have relatively the same impact on maternal anemia. Maternal anemia is the primary reason for supplementing pregnant women with IFA or MMN. Therefore, it will be included in our model. As more evidence emerges, the inputs can be updated.

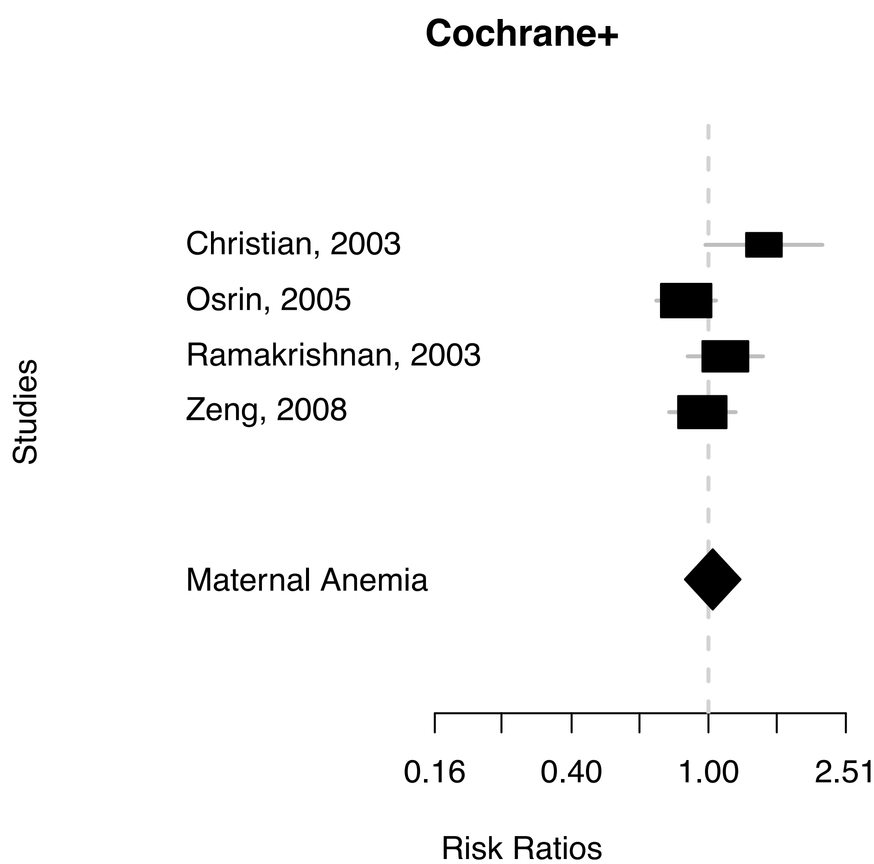

Figure 8: Random-Effect Meta-Analysis for Maternal Anemia

Preterm deliveries

Newborns also benefit from IFA supplements through a reduction in morbidity. Women without anemia, or with a lower severity level, are able to transfer a higher amount of iron to the fetus which increases their health and nutrition status. This translate into a lower probability of premature births, small for gestational age and low birth weight infants.

Fewer studies address the impact of IFA on preterm births. A Cochrane systematic review in 2015 reported an average decrease in preterm birth by 7% for women taking IFA supplements compared to no intervention. When comparing IFA and MMN, Cochrane estimates an average RR of 0.96 (2017), which doesn't reach significance (CI: 0.90, 1.03). Cochrane+ includes Gupta (2007) as an additional study, which results in an average RR of 0.95 (CI: 0.88, 1.02).

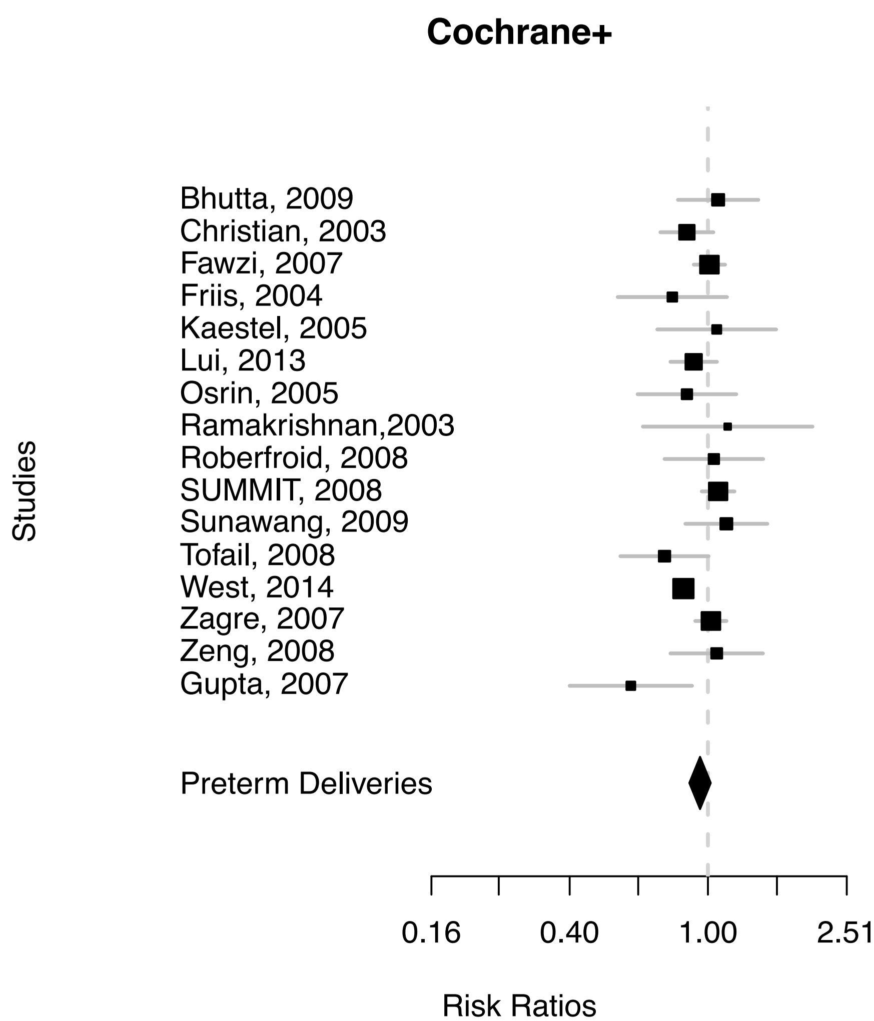

Figure 9: Random-Effect Meta-Analysis for Preterm Deliveries

Small-for-gestational-age

The values regarding the impact of IFA on small-for-gestational-age infants were taken from the WHO's cost-effectiveness tool. They estimate that, in the context of Pakistan, IFA can reduce the prevalence of SGA by 15%. Multiple systematic reviews and scientific studies report the relative risk of giving birth to an SGA infant when taking MMN compared to IFA. The RR reported by Cochrane is 0.92 (CI: 0.86, 0.98). Cochrane+ didn't bring in any other evidence on stillbirths. Therefore it reports the same RR and confidence interval.

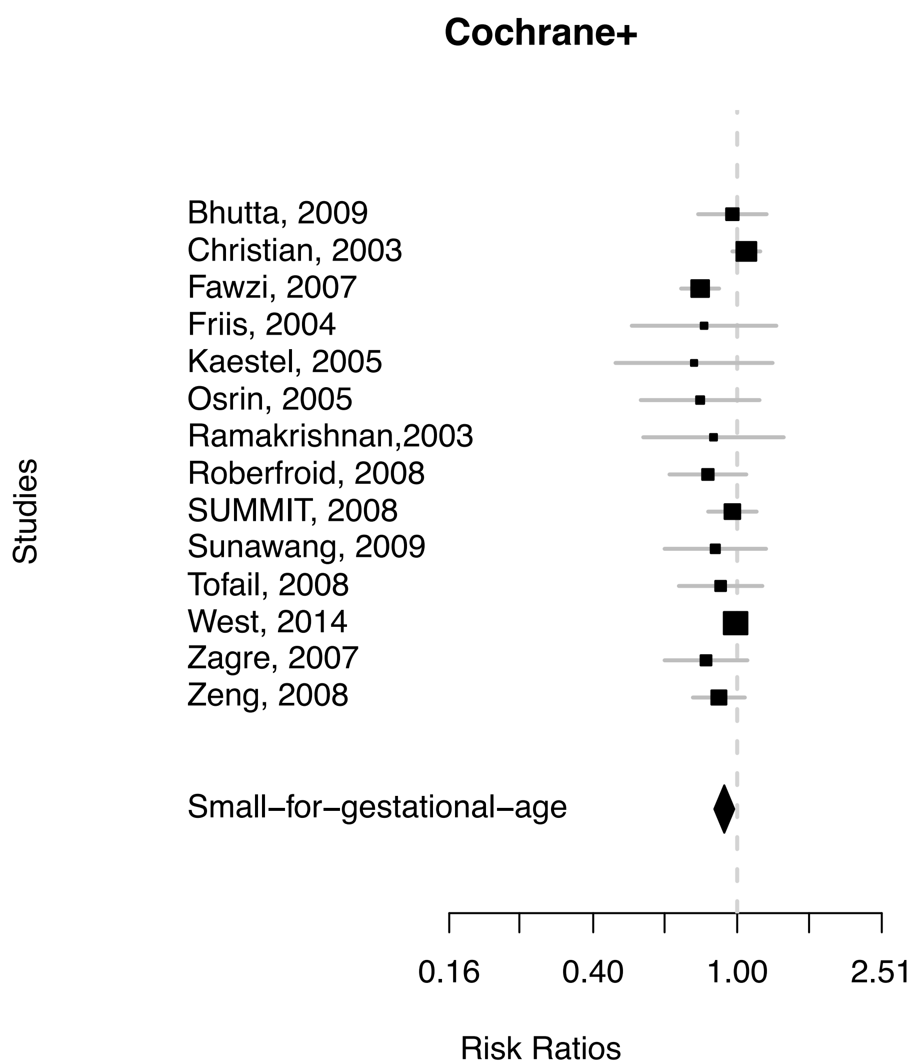

Figure 10: Random-Effect Meta-Analysis for Small-for-gestational-age Infants

Low birth-weight

Since low birth weight is often used as a proxy to estimate the overall health status of children, more studies focus on this birth outcome. IFA supplements were reported to decrease LBW by 16-20% (Cochrane, 2015; Imbad, 2012; Lancet, 2013). As for MMN, they enable the mothers to transfer higher levels of iron to the fetus, as well as 14 other vitamins and minerals. This can significantly increase the nutritional status of newborns and can potentially have higher impacts on child morbidity than IFA supplements. An RR of 0.88 (CI: 0.85, 0.91) was reported by Cochrane. As for Cochrane+, the trial form Gupta (2007) reported LBW as an outcome. The expected value from Cochrane+ is 0.87 (CI: 0.83, 0.92)

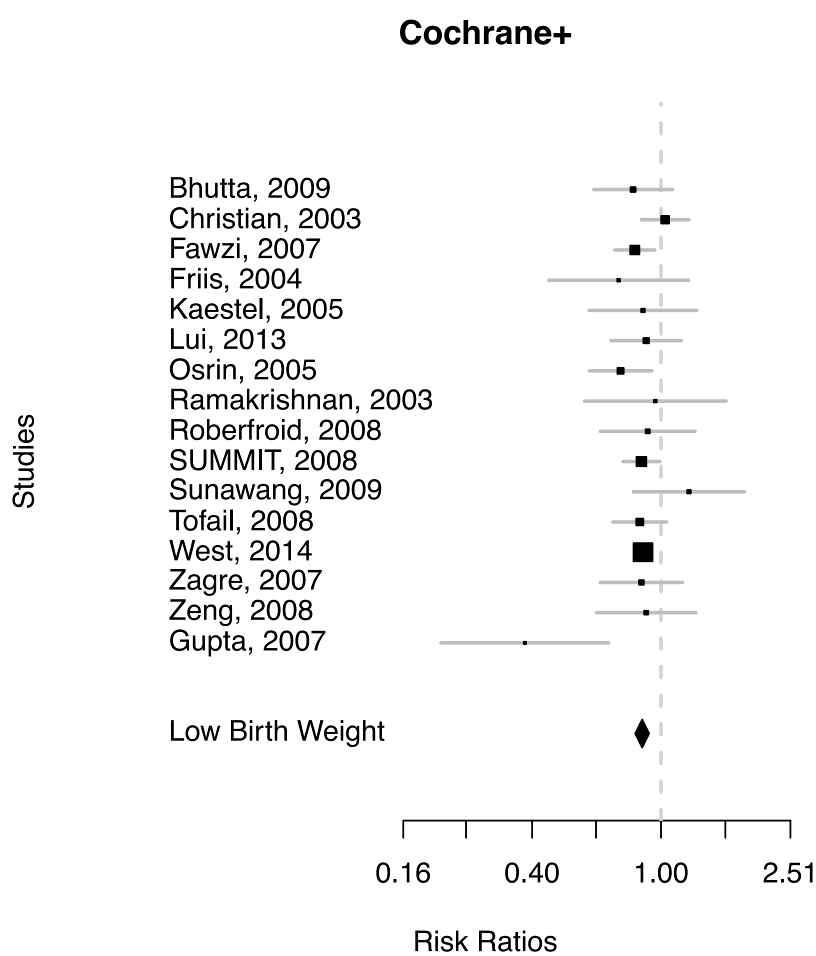

Figure 11: Random-Effect Meta-Analysis for Low Birth Weight Infants

Stunting

Another benefit from iron supplementation is the prevention of stunting. However, little literature reports the impact of IFA or MMn on stunting, since follow-ups must be conducted 2 years after the intervention to assess the impacts. One study in Nepal estimated that IFA reduced stunting in children under two years of age by 14% (Nisar, 2016). The DHS-2011 in Zimbabwe compared IFA to no intervention and found a reduction in stunting of 20%.

The impacts of MMN compared to IFA on stunting were assessed in Vietnam, and it was estimated that the treatment group had an 8.6% lower prevalence of stunting (Nguyen, 2009). In Bangladesh, a trial found a decrease in stunting due to MMN in boys, but not girls (Khan, 2011). Another trial in Nepal found no significant impact of MMN on height-for-age (stunting), but significant effects on head circumference. This might indicate that MMN has positive impacts on child cognitive growth, translating into increased performance in school and in the job market (Vaidya, 2008).

Due to the lack of convincing evidence, the model will look at the indirect impact of MMN on stunting through the reduction in LBW. An extensive study in Bangladesh (Rahman et al., 2016) estimated that 50% of LBW infants grow up to become stunted due to insufficient nutrients available in their environment. Since Bangladesh has a similar socioeconomic and health context as Pakistan, this value will be used as a proxy. However, it is acknowledged that the prevalence of LBW and stunting is lower in Bangladesh (22% and 36.4%) than in Pakistan (32% and 45%). Therefore this estimate could be an underestimation. Using the RR of MMN compared to IFA for LBW, we can obtain the amount of averted LBW cases. Assuming that 50% of those averted cases would have become stunted, we can deduce the indirect impact of MMN on stunting.

Mortality

Table 11:Mortality Risk Ratio for IFA and MMN

Mortality	RR for IFA versus placebo †	RR for MMN versus IFA (Cochrane) ‡	RR for MMN versus IFA(Cochrane+)
Maternal Mortality	0.33	0.97	0.97
Stillbirth	0.91	0.97	0.97
Neonatal Mortality	-	1.06	1.06
Infant Mortality	-	-	0.95

†Cochrane, 2015
‡Haider et Bhutta, 2017

Maternal mortality

Iron supplementation is expected to decrease maternal mortality due to anemia. Women with lower levels of anemia are expected to sustain less hemorrhage during and after delivery, a significant cause of maternal death. However, a paucity of evidence exists. A Cochrane systematic review in 2015 reported an RR of 0.33 for women receiving IFA, but the 95% CI was very large (CI: 0.01, 8.19).

Only Cochrane looked at the impact of MMN on maternal mortality compared to IFA and found an RR of 0.97. However, this RR wasn't significant (CI: 0.63, 1.48). The three trials included in the study also reported non-significant RRs of 0.56 (CI: 0.17, 1.84), 1.03 (CI: 0.64, 1.66), and 1.21 (CI: 0.27, 5.42) (Kaestel, 2005; SUMMIT, 2008; Zagre, 2007). Cochrane+ didn't include any additional trials that looked at maternal anemia and reports the same expected value. Maternal mortality is an important outcome of IFA and MMN that should be taken into account when selecting interventions. Therefore, we included the RR in the model. Again, as this area of research develops, assumptions in the cost-effectiveness analysis can be adjusted to reflect emerging evidence.

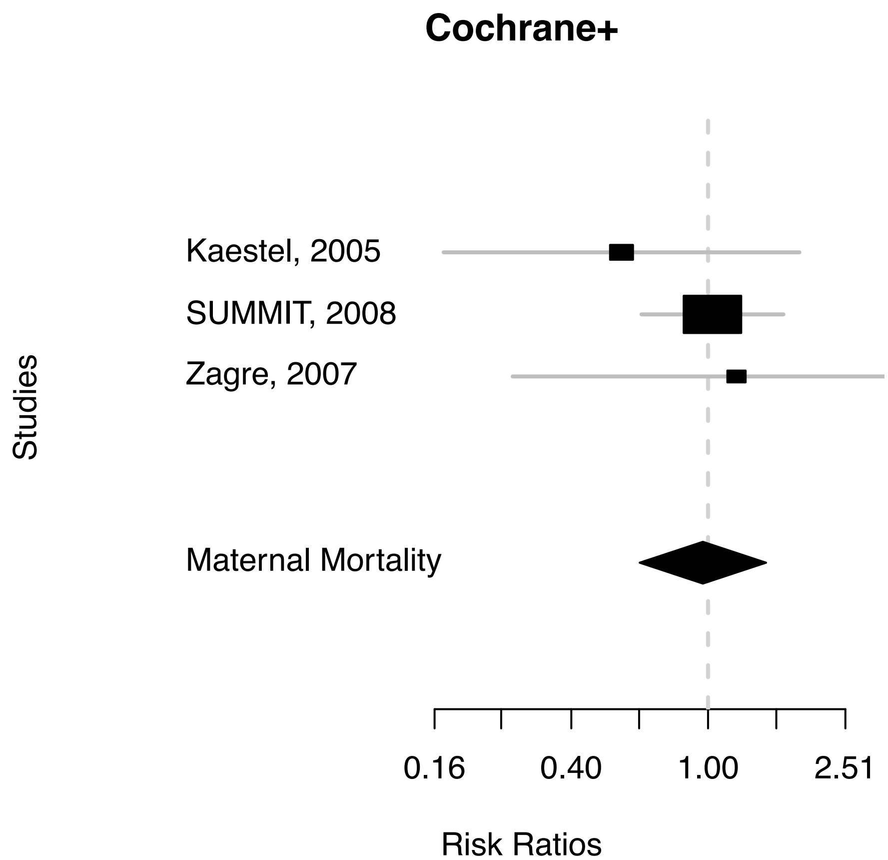

Figure 12: Random-Effect Meta-Analysis for Maternal Mortality

Stillbirths

The impact of iron supplements on child mortality has been extensively studied. Children with low iron stores are at risk of stillbirth, neonatal mortality, and infant mortality. And at each age group, the causes of death differ.

The WHO estimates that the average reduction in stillbirths due to IFA supplements, compared to no intervention, is 9%. The RR reported in the Cochrane review, and included in the model is 0.97 (CI: 0.87, 1.09). Cochrane+ reported the same value.

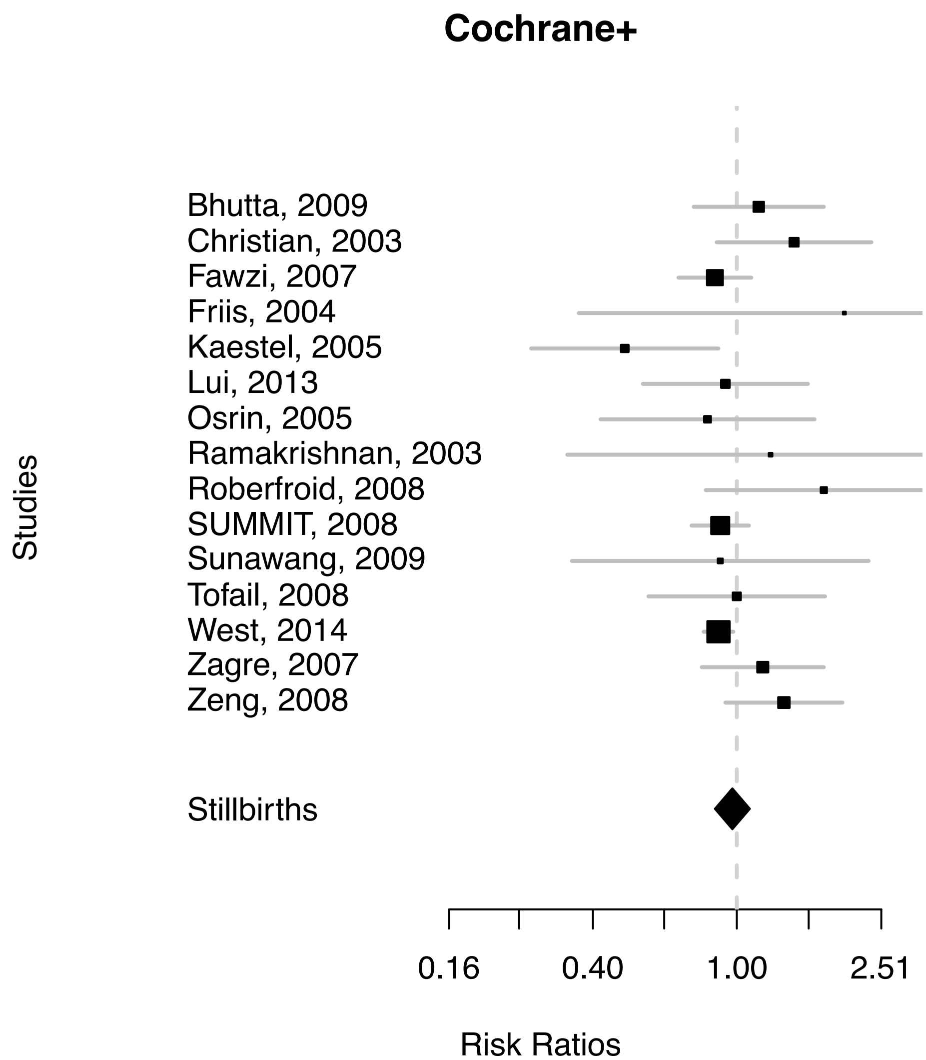

Figure 13: Random-Effect Meta-Analysis for Stillbirths

Neonatal mortality

Neonatal mortality, defined as death within the first 28 days of life, has not been a health outcome frequently assessed when analyzing the impacts of IFA. A study conducted in Jamaica found that IFA can prevent 50% of neonatal deaths, but no other study was conclusive (Allen, 2000).

As discussed above, the impacts of MMN on neonatal mortality differ considerably and have been at the center of many debates. The RR ranges from 0.53 to 1.64 (Kawai, 2011; Bhutta, 2009; Bhutta, 2006; Tofail, 2008; Keith, 2015; Bhutta, 2011; Cochrane, 2017; Lancet, 2008; Gupta, 2007). Cochrane reports an RR of 1.06 (CI: 0.92, 1.22). Cochrane+ included Andersen (2010), which is a follow-up of a trial conducted in Guinea-Bissau (Kaestel, 2005), which is included in Cochrane. Andersen (2010), reports an updated measure of neonatal mortality and will replace the estimate provided by Kaestel (2005). However, the changes in included studies do not result in a different RR. Cochrane+ reports an expected mean of 1.06 (CI: 0.93, 1.22). Due to the divergence in results, and the tendency of the RR to be higher than one, without reaching significance, sensitivity analysis will be conducted around this value.

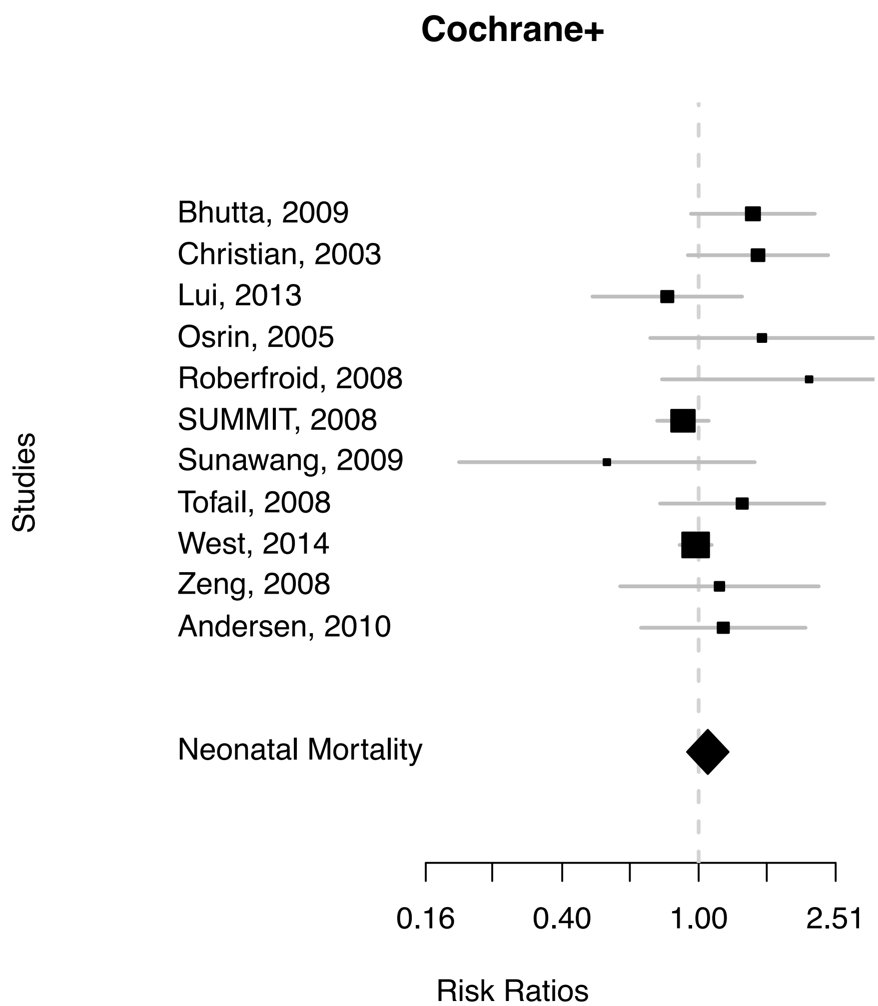

Figure 14: Random-Effect Meta-Analysis for Neonatal Mortality

Infant mortality

If a child dies during the first year of life, it is recorded as infant mortality. Infant mortality has rarely been estimated as an outcome of IFA or MMN supplementation. It is the only health outcomes that weren't included in Cochrane. However, two studies in Cochrane did estimate the impact of MMN on infant mortality (Lui, 2014; West, 2014). Cochrane+ conducted a meta-analysis using these two studies and found an RR of 0.95 (CI: 0.86, 1.06).

IFA and MMN supplements most likely lead to a reduction in under-five mortality rates, however, to date there is no study looking at this outcome. The reason for the lack of evidence is most likely the same as for stunting. Follow-ups must be conducted two to five years after the intervention, and localizing all the infants used in the initial trial can be difficult.

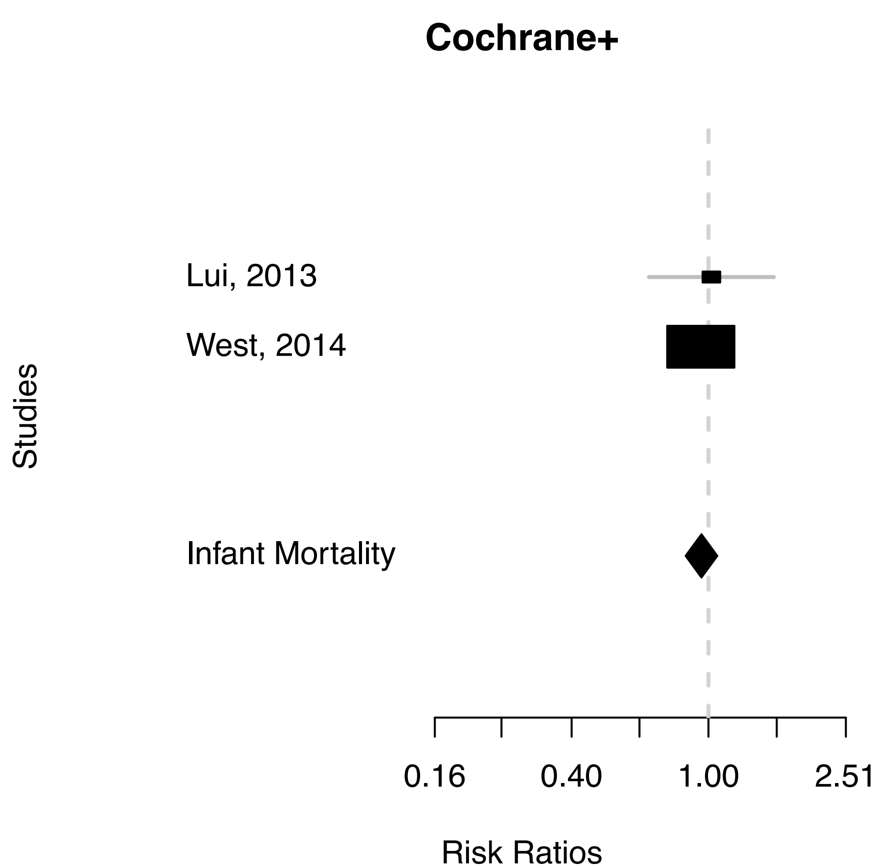

Figure 15: Random-Effect Meta-Analysis for Infant Mortality

The following figures represent the difference in distribution density of the RRs between Cochrane and Cochrane+ for each morbidity and mortality outcome. The figures show the confidence interval at 95% around the mean for each outcome of interest obtained through meta-analysis (Cochrane+). The area to the left of the vertical line at 1.00 shows the probability of MMN to have a positive marginal impact compared to IFA.

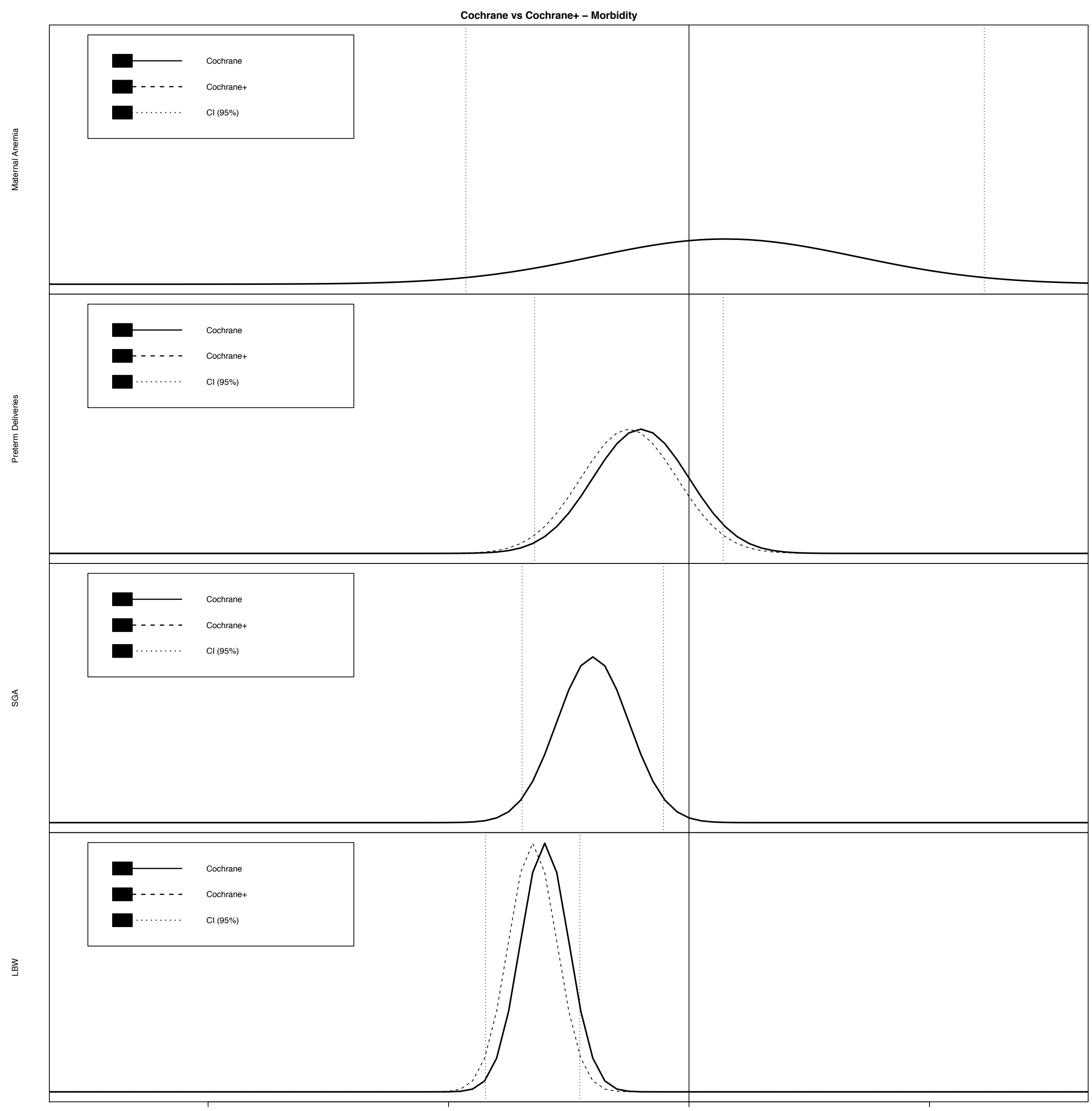

Figure 16: Overlay Charts of Cochrane and Cochrane+ for Each Morbidity Outcome

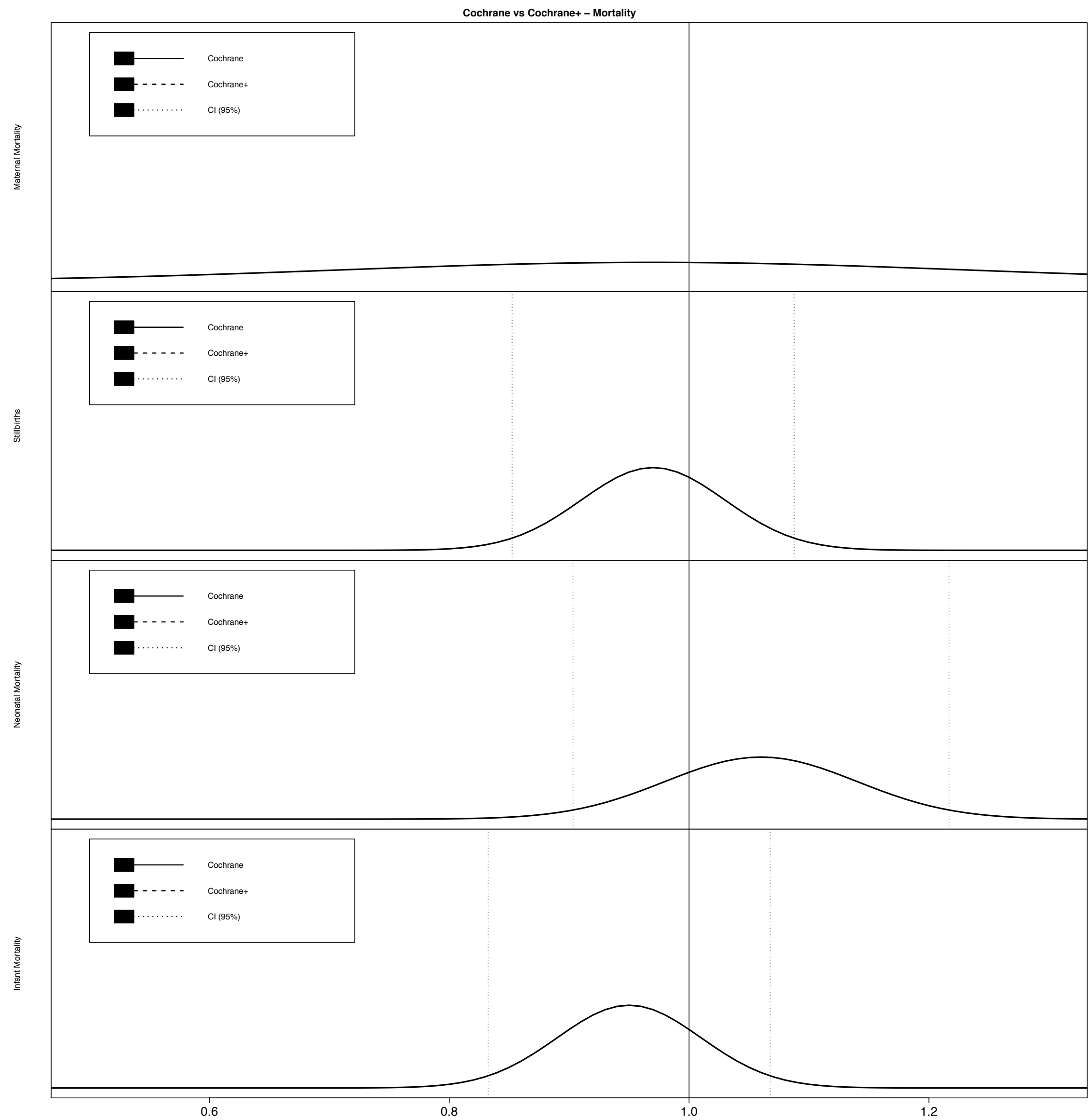

Figure 17: Overlay Charts of Cochrane and Cochrane+ for Each Mortality Outcome

Medical expenses

Medical expenses can either increase due to averted mortality or decrease due to averted morbidity. Pregnant women who no longer suffers from anemia are less likely to have preterm deliveries, as well as LBW and stunted infants. Children are less prone to developing subsequent health problems, such as diabetes and pneumonia, and therefore will require fewer medical services in the future. McCormick (1985), looked at the difference of average stay in hospitals between normal-birth-weight and low-birth-weight infants in the United States. The average stay for a child with adequate weight is 3.5 days. Infants weighing below 2000g, 1500g, and 1000g have an average stay of 24 days, 57 days, and 89 days respectively. McCormick specifies that the birth weight of infants does not affect the nature of the medical services required. For example, congenital anomalies, respiratory infections, and gastrointestinal problems are all common conditions among low birth weight and normal-birth-weight infants. The reason for the increase in medical services is explained by the higher number of cases of such conditions among LBW newborns compared to normal weight infants. As for averted mortality, the child whose life was saved due to the intervention will require standard medical services during his lifetime.

The cost for additional medical services required due to birth defects, as well as medicine, are minimal in low-income countries, including Pakistan. Moreover, households rarely have the income necessary to access medical services. Therefore, even by averting mortality and morbidity medical expenditure wouldn't be significantly affected. For this reason, it will not be included as a benefit channel in our analysis. However, we acknowledge that in another context, medical expenses might potentially impact the results.

Cognitive development

The marginal impact of MMN on cognitive development, compared to IFA is uncertain. As previously mentioned, iron deficiency can have significant impacts on cognitive abilities of children. The MMN supplements contain both iron and zinc which were thought to compete in bioavailability, which could potentially negate the positive effects of iron. However, recent studies have shown that the combination of both micronutrients does not impact the efficacy of MMN on maternal anemia, and therefore on anemia prevalence and cognitive development of children (Nguyen et al., 2012; Haider and Bhutta, 2017). Even though the impact of MMN on cognitive development has not been studied, this leads us to believe that MMN has the same impact as IFA on cognitive development.

Due to the lack of evidence, and the assumption that MMN and IFA generate the same impacts, cognitive development will not be included as an the model. As more trials look as this outcome, it can be added in the model. However, DALYs do not account cognitive impacts. Therefore this outcome would need to be quantified through the increase in productivity or school performance.

Spatial and Other Influential Factors

The effectiveness of IFA and MMN interventions can vary depending on intervention- and region-specific factors.

The design of interventions will impact the adherence and the coverage which are critical to the success of IFA and MMN supplementation (Baltussen et al., 2004). Side effects are often thought of as a primary cause for non-adherence. The level of iron in supplements impact the intensity of side effects. Therefore, it is expected that when IFA tablets, with 60 mg of iron, are substituted by MMN tablets, with 30 mg of iron, that the uptake would increase. This would increase the cost of MMN intervention since more tablets would be required. However, a trial conducted in Pakistan comparing the effectiveness of IFA and MMN reported that women consumed 75% of the tablets in both groups (Bhutta, 2009). Moreover, side effects are reported to have a small impact on adherence compared to other factors (Shrimpton and Schultink, 2002; Schultink et al., 1993; Galloway and McGuire, 1995; Ekstrom et al., 1996).

Table 12: Influential Factors

Influential Factors	
Intervention-specific	• Design • Side Effects • Training & Education • Packaging & Marketing
Regional-specific	• Prevalence • Socioeconomic Factors • Diet

The design of interventions will impact the adherence and the coverage which are critical to the success of IFA and MMN supplementation. Side effects are often thought of as a primary cause for non-adherence. The level of iron in supplements impact the intensity of side effects. Therefore, it is expected that when IFA tablets, with 60 mg of iron, are substituted by MMN tablets, with 30 mg of iron, that the uptake would increase. This would increase the cost of MMN intervention since more tablets would be required. However, a trial conducted in Pakistan comparing the effectiveness of IFA and MMN reported that women consumed 75% of the tablets in both groups (Bhutta, 2009). Moreover, side effects are reported to have a small impact on adherence compared to other factors (Shrimpton and Schultink, 2002; Schultink et al., 1993; Galloway and McGuire, 1995; Ekstrom et al., 1996).

Education seems to be one of the biggest cause of non-adherence. Health workers who are not trained properly do not see the benefits of iron supplementation and are less likely to distribute the tablets regularly; this also impacts the coverage of interventions (Shrimpton and Schultink, 2002). Often, women who are prescribed iron supplements are not aware of the benefits or the reason why they are required to take the tablets, which impacts their compliance (Galloway, 2002). A trial conducted in China reported an adherence rate of 90% and attributed this success to the frequent contact between mothers and health workers and a reliable supply of the supplements.

Lastly, the packaging and marketing of supplements play a major role in uptake. Women in impoverished communities usually do not understand the causes of iron-deficiency anemia and the benefits of supplements. Therefore, having tablets with an appealing taste, smell, and color can increase the uptake and the coverage (Galloway, 2002).

The prevalence of anemia is a primary factor in the effectiveness of IFA and MMN, which is mainly determined by region-specific elements (Baltussen et al., 2004). The principal determinant of maternal anemia is socioeconomic status. Baig-Ansari (2008) conducted a study in Pakistan and found a significant increase in the prevalence of anemia in women who have low levels of formal education, of income, and are unemployed. Another study made by Akhtar et al. (2013) found a correlation between anemia rates, diets, and socioeconomic status of women in Pakistan. These findings are consistent with other trials conducted in other developing countries (P-DHS, 2012-13; WHO, 2004).

Socioeconomic conditions of women also affect the age at which they get married, when they start having children, and how many children they have, which are all determinants of maternal anemia. Women in impoverished communities tend to get married at a younger age, which leads to early pregnancies. Adolescent girls and young women are still in their growth period and require a higher level of iron to sustain their development and so are at greater risk of maternal anemia. Women who start having children early are also likely to have more children. Short intervals between childbirth, and having more than 5 children are important risk factors for maternal anemia and mortality (Brabin et al., 2001; Abu-Ouf and Jan, 2015; Anand et al., 2013; Akhtar et al., 2013; Baig Ansari et al., 2008).

Finally, the diet of women will directly influence their iron stores. Not all food contains the same amount of bioavailable iron. Fish and poultry, for example, contain heme iron which is easily absorbed by the body. Whereas, all plant foods contain nonheme iron which is hard to absorb. Fiber and phytate rich foods also interfere with the absorption of iron. The Pakistani diet mostly relies on plant food and whole wheat flour which is rich in phytate. This partly explains the high prevalence of anemia across both urban and rural regions of Pakistan (Kalaivani, 2009; Anand et al., 2013; Akhtar et al., 2013). Evidence of the impact of phytate on anemia was put forward by Baig Ansari et al. (2008) when they found that one particular ethnic group in Pakistan, the Pashto, had a significantly lower prevalence of moderate and severe anemia than other ethnic groups. Pashto-speaking communities are the only ones who use a different type of flour to cook, which contains a much lower level of phytate. These findings were consistent with results from the NNS (2001-02), that found a more moderate prevalence of anemia in the Khyber Pakhtunkhwa (KPK) province where Pashto is the main ethnicity.

Measure of the Overall Impact

A Comparable Measure of Impact on Mortality and Morbidity (DALY)

The model uses the following formula to calculate the marginal cost-effectiveness of MMN supplements compared to IFA:

$$CEA = \frac{C^{MMN} - C^{IFA}}{\Delta DALY}$$

The numerator represents the marginal cost of using MMN instead of IFA supplements, and the denominator represents the marginal benefits of the MMN supplements over IFA. Benefits of health interventions are quantified using disability-adjusted life-years (DALYs), which is a unit that encompasses both the years of healthy life lost due to morbidity (YLDs) and due to mortality (YLLs). DALYs in of themselves are a negative concept; they represent the loss of health.

Interventions seek their reduction. Therefore, the marginal benefits are the DALYs averted when going from IFA tablets to MMN tablets. DALYs are the only measure able to quantify both morbidity and mortality benefits in one unit, enabling policy makers to assess the overall impact of an intervention. The WHO's LiST module uses DALYs has its measure of health impacts. However, it only takes into account the mortality portion of the DALY calculation, since those are usually the outcomes with the most benefits.

General Formulas

Table 13: Formulas to Calculate DALYs

Formulas	Variables
$DALY = YLD + YLL$	YLD: Years lived with disability YLL: Years of life lost
$YLD = Pr \times DW$	Pr: Prevalence DW: Disability Weight
$YLL = L \times N$	L:Years of life lost due to death N:Number of cause specific deaths

The Global Burden of Disease (GBD) is a research program institutionalized by the WHO and was initiated to develop a robust methodology to quantify and compare disease burdens across cultures and countries, which would enable policymakers to formulate appropriate policies (WHO, 2017). The goal of the GBD is to quantify the importance of premature death and years lived with a disability in a single metric, to facilitate the consistent comparison by age, sex, and region.

The first report of the GBD in 1990 came up with the disability-adjusted life-years (DALYs) to assess the health burden of more than 100 diseases and injuries across various regions. DALYs are the sum of the years of life lost due to premature death (YLL) and the years of life lived with a disability (YLD), using time as a common measure of burden (Lajoie, 2015; WHO). The 1990 results were updated in 2000-2002 and 2004 (GBD, 2010; WHO, 2017). In 2010, the GBD developed a new method for calculating DALYs and extended the calculations to 280 diseases and injuries and 1160 sequelae. An update of the 2010 GBD results was published in 2015, comparing the DALYs lost for all causes across regions between 2000 and 2015 (Lajoie, 2015; WHO, 2017). The formula to calculate YLLs is the following:

$$YLL = L \times N$$

The GBD study separates morbidity and mortality burden by age cohorts (grouped by 5 years) and determines the life expectancy for each cohort (L). L is equivalent to the amount of years lost due to premature death for each age group. The new method published in the 2010 GBD study established a standardized loss function table to use in YLL calculations. The life expectancies reported in this table are based on the highest projected life expectancies, and the life expectancy at birth is 86.01. Then, by estimating the incidence of death by age group for each mortality causes (N), we can calculate the total years of life lost by age and cause for a specific region.

As for YLDs, different perspective exists to calculate them. The first edition of the GBD suggested the incidence perspective which uses the following formula:

$$YL\mathrm{D} = I \times L \times DW$$

The incidence (I) represents the amount of new cases per year, within an at-risk population. The incidence per age group multiplied by the length of the disease (L) gives the total amount of years lived with a disability. Each diseases or injuries have a different “disability weight” (DW), which needs to be taken into account if we want the morbidity measure (YLD) to be comparable to the mortality measure (YLL). Therefore, the total amount of years lived with a disability for a morbidity and, an age cohort is weighted by its health burden relative to death. DW will be discussed more extensively in the following section.

A problem with the incidence perspective is the availability of data. Firstly, determining the exact length of a disease, per sex and age can be very difficult. The length can vary depending on various factors like nutrition, accessibility of health care, comorbidity, and socioeconomic status. Secondly, the “at-risk” population required to calculate the incidence rate can be hard to narrow down, especially when it comes to birth defects like SGA and LBW. In these cases, the at-risk population is every fetus that reaches a stage where it is possible to develop birth defects. Taking into account that around one in five pregnancy end without the woman knowing she was pregnant, and an additional 10-15% end in spontaneous abortion, estimating the total amount of at-risk infant is impossible (Mason et al., 2005). To counter these problems, some studies have turned to a prevalence perspective. This has created inconsistencies in methodology across studies and, therefore, failed the original purpose of the GBD research.

In 2010, the GBD officially changed the method of calculating YLDs to a prevalence perspective:

$$YLD = Pr \times D\mathrm{W}$$

The prevalence (Pr) represent the proportion of the population suffering from a morbidity, or the probability of having a morbidity within a population. Under certain conditions, incidence times the length of the disease equals the prevalence. The prevalence is much easier to calculate, and usually more readily available. In the case of birth defects, the prevalence represents the amount of infants born with a morbidity over all live births. The cost-effectiveness analysis conducted in this paper will take a prevalence perspective.

Disability weights

The purpose of DW is to establish a ranking between diseases and to compare their health burden with death. The GBD released the first set of DW in 1990 for about 100 injuries and diseases. The DW was determined with the help of a panel of economists, philosophers and health expert (GBD, 2010). The 2004 GBD update incorporated DW for LWB (0.106), stunting (0.002) and developmental disability due to stunting (0.024), moderate iron deficiency (0.011) and cognitive impairment due to iron deficiency (0.024).

As the methodology and research evolved, DW needed to be attributed to more morbidities. In the 2010 GBD study, Salomon et al. extended the database for 289 disease and injuries and 1160 sequelae. To obtain the DW, they used a large-scale population survey in various communities and cultures to have a normalized perception of disease burden (Lajoie, 2015). “Each respondent had to consider two hypothetical individuals with different, randomly selected health states and indicated which person they thought were healthier. Salomon et al. used these responses to develop a DW scale from 0 (no loss of health) to 1 (health loss is equivalent to death)” (WHO, 2004). The DW for iron-deficiency anemia was changed to 0.052, and the DW for LBW and stunting were taken out. Replacing them is a DW attributed to motor and cognitive development disability due to preterm birth complications (moderate: 0.061).

Table 14: Disability Weights for Morbidity and Mortality Related to Maternal Anemia

Conditions	Mild	Moderate	Severe
Iron-deficiency anemia	0.040	0.052	0.149
Preterm birth complications (motor and cognitive)	0.031	0.061	0.402

Discounting

DALYs in themselves are a negative concept; they represent the number of years lost due diseases and injuries. When health programs are introduced, they aim to avert the loss of DALYs. The DALYs averted are then used to quantify the benefits of interventions in cost-effectiveness studies. To avoid inconsistencies when comparing the benefits and the costs, the original GBD methodology discounted future DALYs averted at a rate of 3% (WHO, 2013). Alternative discount rates of 0% and 5% were recommended for sensitivity analysis.

Discounting was criticized by many who thought that the loss of one year of good health today should have the same value as one year of good health lost tomorrow (WHO, 2013). Moreover, the choice of a discount rate is regarded as subjective, since not all cultures view the value of current and future years of health in the same way (Lajoie, 2015).

In the case of maternal supplements, the mortality benefits will be observed within the first five years of birth. As for morbidity benefits, they will impact the infants throughout their entire life, which will be further impacted when discounted. When MMN are compared to IFA, a significant component of their marginal benefits is related to averted morbidity. Discounting the marginal benefits would result in a decrease of the cost-effectiveness of MMN and could favor the implementation of IFA.

These issues and divergence in opinions less to an inconsistent methodologies among studies. Sensitivity analysis are rarely done, making comparisons difficult (Fox-Rushby and Hanson, 2001). Therefore, the current GBD method disregards discount rates. This decision was more easily accepted once the GBD clarified the definition of DALYs as a quantitative measure of resulting morbidity and mortality, rather than the social value of health losses. The model will include a discount rate 0%, 3%, and 5% to enable comparisons with other studies.

Aggregation problem

When an intervention only affects one disease or one injury, it is straightforward to calculate the DALYs averted. However, when an injury or a disease leads to another morbidity, referred to as sequelae, it can be difficult to aggregate the health burden without overlaps. To avoid overestimating the benefits, adjustments must be made to the methodology.

When looking at the benefits of IFA and MMN supplements, we need to look at the prevented maternal anemia, which averts maternal mortality. Infants born to non-anemic mothers are less likely to be premature, SGA, or LBW, and are less likely to die during infancy. If we look at the direct impact of IFA on the reduction of each of these conditions, there will be significant overlaps. For example, preterm deliveries and SGA infants are primary causes of LBW. Therefore, the prevalence of LBW needs to be adjusted for the proportion of LBW-SGA and LBW-preterm babies in the model to avoid bias results. The same needs to be done for overlaps between neonatal and infant mortality.

The analysis conducted in this paper reflects the mortality and morbidity losses averted in infants. The health and nutrition benefits will follow the children throughout their whole life, not only for the duration of the supplementation. Therefore, even if the YLDs will be calculated using a prevalence perspective, they will be multiplied by the life expectancy of the infants. This leads to another aggregation problem. There exist overlaps between the length of birth defects when calculating the YLDs, and the morbidity resulting in child mortality in the first year of life, when calculating YLLs. Adjustments for the percentage of each birth defects resulting in infant mortality would be the ideal scenario. However, the literature mainly estimates the impact of birth defects on neonatal death (0 - 28 days) and not on infant mortality (within the first year of life). Therefore, the adjustment will not be included in the model. We acknowledge that this might result in a slight overestimation of the benefits. However, since the model is reporting the relative effectiveness, this is not going to affect the results in a significant way.

DALYs averted (ΔDALY)

To obtain the number of DALYs averted by changing IFA to MMN, we would usually need to calculate the number of DALYs lost when IFA supplements are used (baseline scenario) then subtract the number of DALYs lost when MMN supplements are used. However, since the literature on MMN is mostly reporting its effectiveness on the prevalence of various disease relative to IFA, we are adjusting the formula to look at the averted DALYs by disease directly. To do so, we will calculate the relative risk reduction (RRR). The RRR expresses the probability of an event, dying or contracting a disease, in the treatment group (MMN) compared to the likelihood of the same event happening in the control group (IFA). The RRR calculation reflects the difference in the prevalence of mortality and morbidity events between the two groups.

Effectiveness Analysis

The Deterministic Model

Using the RR's mentioned above, for both Cochrane and Cochrane+, a deterministic model was built to estimate the averted DALYs for each health outcomes. Table 15 shows the detailed formulas used to calculate the health benefits. The YLDs calculated below use the prevalence perspective. However, the benefits are calculated for a cohort of women, and their infants, who receive the supplements for one year. The morbidity benefits received for the mother are only guaranteed for one year since they can return to a state of anemia once the supplementation is stopped. However, the morbidity benefits for the infants will last for their entire life (estimated life expectancy in Pakistan is 65.86), since they can't become preterm or low birth weight once the supplementation has stopped (United Nation, 2017). Therefore, the YLDs are multiplied by the life expectancy at birth for the children's morbidity outcome. As for maternal mortality, the mean age of pregnancy for Pakistan, 22 years old, was obtained through the United Nations Population Division (2017) and their estimate for life expectancy from 22 years of age was use to calculate the length of the benefits of averted maternal mortality.

Table 15: Detailed Formulas

Formulas	Variables
$\frac{YLD}{1{,}000} = \sum_i [(1 - RR_i) \times Pr_i \times L_i \times DW_i]$	i: Type of morbidity RR_i : Relative risk of having the disability (MMN vs IFA) Pr_i : Number of cases per 1,000 participants L_i : Length of the disease, adjusted for mortality within the first year of life
$\frac{YLL}{1{,}000} = \sum_j [(1 - RR_j) \times N_j \times L_j]$	j: Type of mortality RR_j: Relative risk of mortality (MMN vs IFA) N_j: Number of death of type j per 1,000 participants L_j : Amount of years of life lost due to premature death

Using the values from the Cochrane scenario, the total amount of averted DALYs (using the Cochrane+ value for infant mortality) discounted at 3% is 160.19. Whereas, the total number of DALYs averted, per 1000 participants, using the values reported by Cochrane+ discounted at 3% is 230.81. The scenarios discounted at 0% and 5% are shown in the appendix.

Table 16: Resulting Changes in Morbidity, YLDs per 1,000 Discounted at 3% (Cochrane)

i	RR_i	Pr_i †	DW_i	L_i	$(1 - RR_i) \times Pr_i \times DW_i \times L_i$
Anemia	1.03	510.00	0.052	0.97	-0.74
Preterm	0.96	392.80	0.061	28.58	26.94
SGA‡	0.92	434.70	0.061	28.58	59.62
LBW‡	0.88	201.60	0.061	28.58	41.48
Stunting		12.34	0.061	29.10	21.54
Total					148.84

† per 1,000 live births
‡ Adjusted for overlaps

Table 17: Resulting Changes in Mortality, YLLs per 1,000 Discounted at 3% (Cochrane)

j	RR_j	L_j	N_j †	$(1 - RR_i)\times L_i \times N_i$
Maternal Mortality	0.97	25.35	1.78	1.35
Stillbirth	0.97	28.58	43.15	36.99
Neonatal Mortality	1.06	28.58	45.50	-78.01
Infant Mortality‡	0.95	28.58	35.71	51.02
Total				11.36
Total Averted DALYs				160.19

† per 1,000 live births
‡ net of neonatal mortality (death after 28 days but within the first year)

Table 18:Resulting Changes in Morbidity, YLDs per 1,000 Discounted at 3% (Cochrane+)

i	RR_i	Pr_i †	DW_i	L_i	$(1 - RR_i)\times Pr_i \times DW_i \times L_i$
Anemia	1.03	510.00	0.052	0.97	-0.74
Preterm	0.95	392.80	0.061	28.58	33.67
SGA‡	0.92	434.70	0.061	28.58	59.62
LBW‡	0.87	201.60	0.061	28.58	44.93
Stunting		13.37	0.061	29.10	23.33
Total					160.82

† per 1,000 live births
‡ Adjusted for overlaps

Table 19: Resulting Changes in Mortality, YLLs per 1,000 Discounted at 3% (Cochrane+)

j	RR_i	L_i	N_i†	$(1-RR_i)\times L_i\times N_i$
Maternal Mortality	0.97	25.35	1.78	1.35
Stillbirth	0.97	28.58	43.15	36.99
Neonatal Mortality	1.06	28.58	45.50	-78.01
Infant Mortality‡	0.95	28.58	35.71	51.02
Total				11.36
Total Averted DALYs				172.18

† per 1,000 live births

‡ net of neonatal mortality (death after 28 days but within the first year)

Probabilistic Analysis

The average RRs used in the deterministic model all widely diverge in significance level. The benefits measure for LBW, which is significant at 95%, can't have the same weight as the benefit for maternal mortality, which has a large confidence interval. To take this into account, a probabilistic analysis was conducted on the deterministic model using Monte Carlo simulations. The sampling method used was Monte Carlo (more random) and the number of trials run was 200,000. The assumptions used for mean and standard error of each RR are the same as those presented before, and visually summarized in figure 16 and 17.

Running the Monte Carlo simulations gives us both the expected value and the standard error for the total averted DALYs for both Cochrane and Cochrane+. Cochrane resulted in an average 160.39 averted DALYs per 1,000 participants, with a standard error of 148.48. This result has an 87.02% success rate of MMN over IFA in the context of Pakistan. For Cochrane+, the simulations led to an average expected value of 172.40 DALYs averted, with a standard error of 144.81. This scenario implies an 88.88% chance that MMN will result in more health benefits than IFA in the context of Pakistan.

The following figure shows the density distribution of the total averted DALYs for both scenarios discounted at 3%, with a confidence band of 95% around the expected value of Cochrane+. The area to the left of the vertical line at 0.00, shows the probability of MMN resulting in fewer mortality and morbidity benefits for the mother and the infant.

The Monte Carlo simulations highlighted neonatal mortality, stillbirths, and infant mortality to be the most sensitive inputs. These results can provide decision makers with more information in choosing between MMN and IFA in the context of Pakistan.

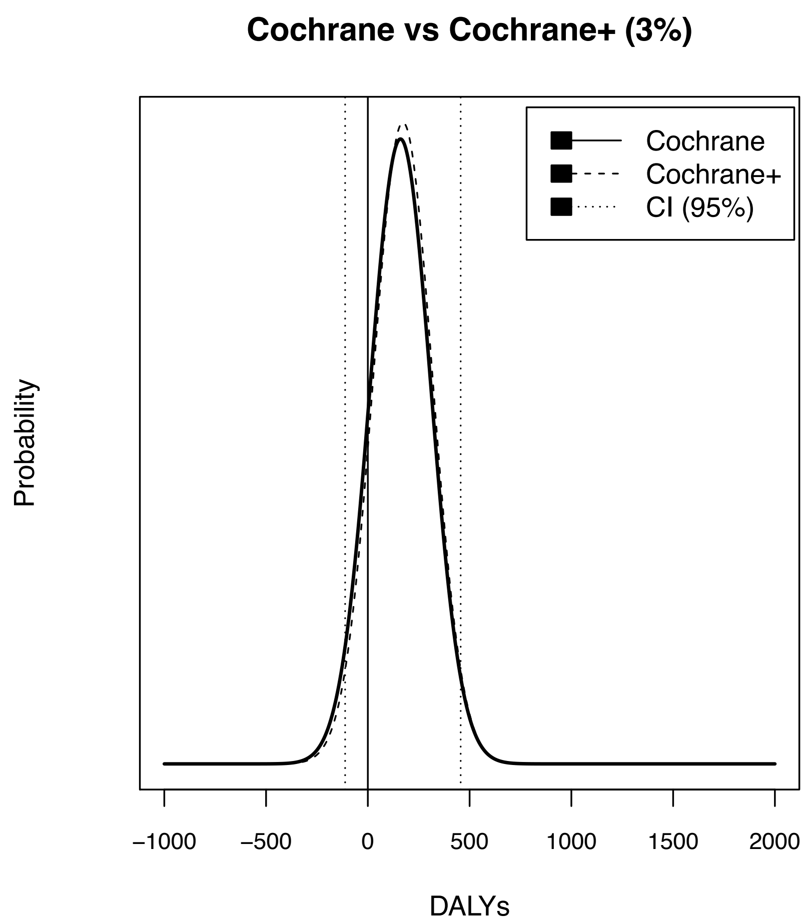

Figure 18: Overlay Charts of Averted DALYs of Cochrane and Cochrane+

The probabilistic analysis also enable the model to highlight the most sensitive inputs, the ones that yields the most variations in the expected value of total averted DALYs. As expected, the mortality estimates were the most sensitive, causing almost 95% of the total variation. Neonatal mortality, stillbirths, and infant mortality were the most critical inputs in the analysis. Table 20 reports the proportion of variation from each health outcome on the overall estimate.

Table 20: Sensitivity Analysis of Health Measures

	Variation (%)
Neonatal Mortality	51.90
Stillbirth	26.80
Infant Mortality	15.20
Preterm Deliveries	2.70
Small-for-gestational-age	2.40
Maternal Mortality	0.60
Low Birth Weight	0.30
Maternal Anemia	0.00
Stunting	0.00

Cost-Effectiveness Analysis

Program Costs for Iron Supplementation

Components of Cost

Cost data relating to iron supplementation programs are scarce and usually has little external validity due to the divergence of costs between regions due to the specificity of the context (Johns et al., 2003; Feidler et al., 2008). The cost of micronutrient supplementation programs all have a similar structure. They encompass both program costs and patient costs. Program cost covers most of the implementation costs, and represent the greater component of total expenses. They include administration and management costs, training for health workers, education programs and promotion campaign for women and communities, and monitoring of coverage. As for patient cost, they include costs related to the supply of the supplements and the delivery of the supplements, either through door to door programs, through antenatal care clinics, or through pharmacies. Fiedler et al. (2008) report a common cost structure for vitamin A supplements and argues that iron supplementation programs most likely have the same structure, with the exception of a higher total cost due to the necessity of supplying daily instead of weekly tablets. The following figure shows the cost decomposition of a standard supplementation program.

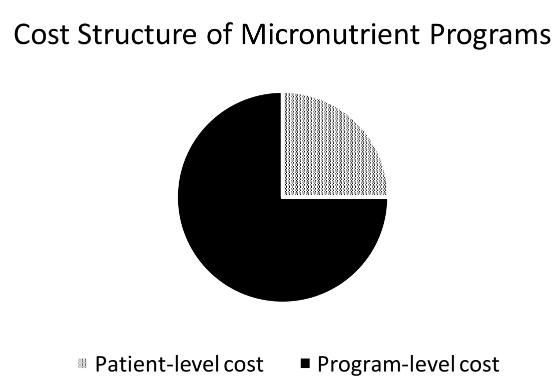

Figure 19: Decomposition of Cost for Micronutrient Interventions

Cost of IFA supplementation programs in Pakistan

Due to the lack of evidence for the cost of iron supplementations intervention in Pakistan, the WHO's WHO-CHOICE system will be used. The WHO established a database regrouping the overall cost for health and nutrition interventions for 14 sub regions of the world. The model uses the ingredient approach to calculate total costs, instead of total expenditure. The ingredient approach records the price and the quantity of each unit of input used in the implementation of health programs and classifies they input into three main categories: start up versus post start up cost, central versus lower levels cost, and recurrent versus capital costs. All of the costs are discounted at a rate of 3% (Adam et al., 2003).

Baltussen et al. (2004), in collaboration with WHO-CHOICE, estimated the cost of iron supplementation interventions for four of the fourteen sub regions of the world determined by the WHO. They looked at the African sub region (AfrD), the South American sub region (AmrB), the European sub region (EurA), and the Southeast Asian sub region (SearD). Pakistan is included in the SearD region. Therefore, the cost estimated will be used as a proxy for this cost-effectiveness model. The SearD region regroups 31,597,515 women taking iron supplementation annually.

The cost estimated by Baltussen were for geographical coverage of iron only, not IFA, at 95%. It is acknowledged that a program supplying IFA tablets would have a higher total cost due to the addition of folic acid to the supplement. However it is assumed that this marginal increase is negligible and will not impact the final results of the analysis. The delivery of iron supplements is assumed to be through four antenatal care visits at a health facility. The mothers will be supplied enough tablets for a regimen of six months during pregnancy and three months postpartum.

The costs are reported in International dollars (Int'l$), which are a currency unit relfecting the current exchange rate and purchasing power parity adjustments of a currency. They are discounted at 3% where the base year is 2000. The costs were estimated for the start-up of the intervention and an implementation over 10 years. Since costs will be higher during the start-up period, calculating an average annual cost of a 10-year project will give policy makers a better idea of the overall financial cost that needs to be incurred for this type of projects.

Costs were divided into the patient-level cost and program-level cost. Patient-level cost included antenatal visit costs when iron supplementation coverage surpassed prenatal care coverage estimates. Health facility unit cost estimates were based on an extensive study of hospital cost from Adam et al. (2002). Tablet costs were reported from the International Drug Price Indicator and were adjusted for transportation cost. It was estimated that the cost per recipient was 10.12 Int'l$ (total outpatient visit cost is 9.25 Int'l$ and tablet cost is 0.87 Int'l$). Therefore, the patient-level cost for 31,597,515 women is 319,741,462 Int'l$ per year. As for program-level cost, they included the management, training, education, promotion, and supervision components of the intervention and are estimated to be 9,448,557 Int'l$ per year for the SearD region. The total annual cost for an iron supplementation program at 95% coverage level for the SearD sub region is 329,190,020 Int'l$, resulting in 10.42 Int'l$ per women, per year (Baltussen, 2004).

Table 21: Calculation of Cost for Iron Supplementation Programs in SearD

	Patient level costs									
Region	Annual number of pregnant women receiving iron supplementation	Coverage of antenatal care	Cost per outpatient visit, at 95% coverage (Int'l$)	Total costs outpatient visits (Int'l$)	Costs of drugs (Int'l$)	Cost per recipient (Int'l$)	Total costs (Int'l$)	Program level costs (Int'l$)	Patient and program level costs (Int'l$)	Cost per pregnant women (Int'l$)
	1	2	3	4	5	6 = 4 + 5	7 = 6*1	8	9 = 7 + 8	10 = 9/1
SearD	31,597,515	57%	3.85	9.25	0.87	10.12	319,766,852	9,448,557	329,215,409	10.42

(Baltussen et al., 2004)

Program Costs for MMN

Components of Costs

It is estimated that program-level cost for MMN supplementation will be similar to those of iron supplementation due to the synergy between implementation. If we assume that a country already has in place an IFA supplementation program and is considering changing the distributed supplement to MMN, the delivery channels, storage facilities, and training for health care workers will be the same. The main difference in cost will come from the patient-level cost, specifically the tablets. MMN supplements are expected to be twice the cost of IFA supplements since they include 14 other vitamins and minerals.

Cost of MMN supplementation programs in Pakistan

From Baltussen's estimates, drug prices for one recipient in 0.87 Int'l$. If the drug price doubles for MMN supplements, one complete regimen for one recipient will cost 1.74 Int'l$. Using the same method as Baltussen, the total patient-level cost for one woman will be 10.99. Keeping program-level cost constant, the total annual cost of MMN supplements for one pregnant woman is 11.28 Int'l$.

To be consistent with the measure of averted DALYs, the cost of iron and MMN supplementation will be reported for 1,000 participants. Therefore, the annual cost for iron and MMN supplementation per 1,000 pregnant women in the SearD sub region, discounted at 3%, is 10,420 Int'l$ and 11,280 Int'l$ respectively.

Table 22: Calculation of Cost for MMN Supplementation Programs in SearD

	Patient level costs									
Region	Annual number of pregnant women receiving iron supplementation	Coverage of antenatal care	Cost per outpatient visit, at 95% coverage (Int'l$)	Total costs outpatient visits (Int'l$)	Costs of drugs (Int'l$)	Cost per recipient (Int'l$)	Total costs (Int'l$)	Program level costs (Int'l$)	Patient and program level costs (Int'l$)	Cost per pregnant women (Int'l$)
	1	2	3	4	5	6 = 4 + 5	7 = 6*1	8	9 = 7 + 8	10 = 9/1
SearD	31,597,515	57%	3.85	9.25	1.74	10.99	347,256,690	9,448,557	356,705,247	11.29

Cost-Effectiveness Analysis

To determine the marginal cost effectiveness of MMN supplementation compared to IFA supplementation we need the marginal benefits, measured through averted DALYs from Cochrane+, and the incremental cost.

$$CEA = \frac{C^{MMN} - C^{Iron}}{\Delta DALY} = \frac{11{,}280 - 10{,}420}{172.18} = 4.99\ I\$\ per\ averted\ DALY$$

The WHO uses a standard approach to determine if an intervention is cost-effective or not. If the cost/DALY averted is less than three times the national GDP/capita, the intervention is very cost-effective, and if it's less than the GDP/capita than the intervention is cost-effective (WHO, 2003). This method has many limitations. However, it is the most common way of determining the level of effectiveness of health and nutrition programs, therefore to enable comparison with other analysis the model will use the same method.

The GDP per capita of Pakistan in International dollars is 5,249.29 Int'l$ (World Bank Data, 2017). Therefore, replacing IFA supplements by MMN supplements is very cost-effective in the context of Pakistan.

External Validity

Many factors come into play in the external validity of the cost-effectiveness model. The average RRs estimated through meta-analysis, the other health inputs required to calculate DALYs averted, as well as the cost of the program, will influence the validity of the analysis.

Average Risk Ratios

The RRs derived in Cochrane+ are averages of 12 trials conducted developing countries. The estimates are tailored to low-income countries. However, they aren't context-specific. This implies that the RRs included in the deterministic model can be used in a context other than

Pakistan. However, it is important to note that the effectiveness of IFA and MMN supplementation will be significantly impacted by the prevalence of infections, like malaria and HIV, and by the diet of communities. Using these RRs in a context where the prevalence of diseases or diets diverges from the norm will not yield a result that is realistic for those settings.

Other Inputs

The additional inputs required to calculate the DALYs averted in this cost-effectiveness model are specific to the context of Pakistan. Therefore, the values used for the prevalence, incidence, and the life expectancy won't be valid in another context.

These data can be found in National Nutrition Surveys, in Demographic and Health Surveys, and in international databases like the World Bank database. By adapting the inputs, the cost-effectiveness model will estimate results relevant to specific regions and contexts.

Cost

The cost of supplementation interventions will differ widely both within and across countries. Many factors influence the cost, such as the drug prices, the delivery of supplements, the salaries for health care workers, etc. Having the exact cost of intervention will enable the model to give a more precise cost-effectiveness level. However, adjusting the cost comes to adjusting one input which doesn't require extensive changes to the model.

Example in the context of India

To test the external validity of the model, the analysis was conducted in the context of India using the RRs from Cochrane+. The most recent I-DHS (2005-06) estimated the prevalence rates of maternal anemia, LBW infants, neonatal mortality, and infant mortality. However, the data was older and didn't give results that reflected the current context of India. The World Bank Database, the LiST module, and United Nations Population Division had more current data available for the inputs listed above as well as for preterm deliveries, SGA infants, maternal mortality, stillbirths, and life expectancy. An updated version of the I-DHS for 2015-16 will be published soon.

Table 22 compares the health inputs in the deterministic model for the context of Pakistan and India. The deterministic model used the listed values for India and estimated 160.27 averted DALYs. The main difference between the Pakistani and the Indian cases is the averted mortality. In Pakistan, the contribution of prevented mortality to total DALYs averted is 11.36, whereas in India it is -11.95. In the case of Pakistan, even if the expected value of averted DALYs due to neonatal mortality is negative, the high prevalence of infant mortality and stillbirths compensates to give a positive value for total averted DALYs. However, in India, the prevalence of infant mortality and stillbirths is lower and doesn't generate averted DALYs big enough to compensate the expected increase in neonatal mortality. Table 23 and 24, as well as graph 20 show the deterministic model and the decomposition of averted DALYs for each health outcome.

Table 23: Comparison of health inputs between Pakistan and India

	Pakistan	India
Maternal Anemia	51.00%	53.41%
Preterm Deliveries	39.28%	12.95%
Small-for-gestational-age	43.47%	46.90%
Low Birth Weight	20.16%	28.40%
Stunting	45.00%	38.70%
Maternal Mortality Ratio	178/100,000	174/100,000
Stillbirths	43.15/1,000	23.03/1,000
Neonatal Mortality Ratio	45.50/1,000	27.70/1,000
Infant Mortality Ratio	35.71/1,000	10.20/1,000
Life Expectancy	66.38	68.35

Table 24: YLDs per 1,000 in the Context of India

i	RR_i	Pr_i [†]	DW_i	L_i	$(1 - RR_i) \times Pr_i \times DW_i \times L_i$
Anemia	1.03	534.10	0.052	0.97	-0.78
Preterm	0.95	129.50	0.061	28.81	11.19
SGA[‡]	0.92	469.00	0.061	28.81	64.86
LBW[‡]	0.87	284.00	0.061	28.81	63.82
Stunting		19.57	0.061	29.06	34.12
Total					173.22

[†] per 1,000 live births
[‡] Adjusted for overlaps

Table 25: YLLs per 1,000 in the Context of India

j	RR_j	L_j	N_i [†]	$(1 - RR_i) \times L_i \times N_i$
Maternal Mortality	0.97	25.59	1.74	1.34
Stillbirth	0.97	28.81	23.03	19.91
Neonatal Mortality	1.06	28.81	27.70	-47.88
Infant Mortality[‡]	0.95	28.81	10.20	14.69
Total				-11.95
Total Averted DALYs				161.27

[†] per 1,000 live births
[‡] net of neonatal mortality (death after 28 days but within the first year)

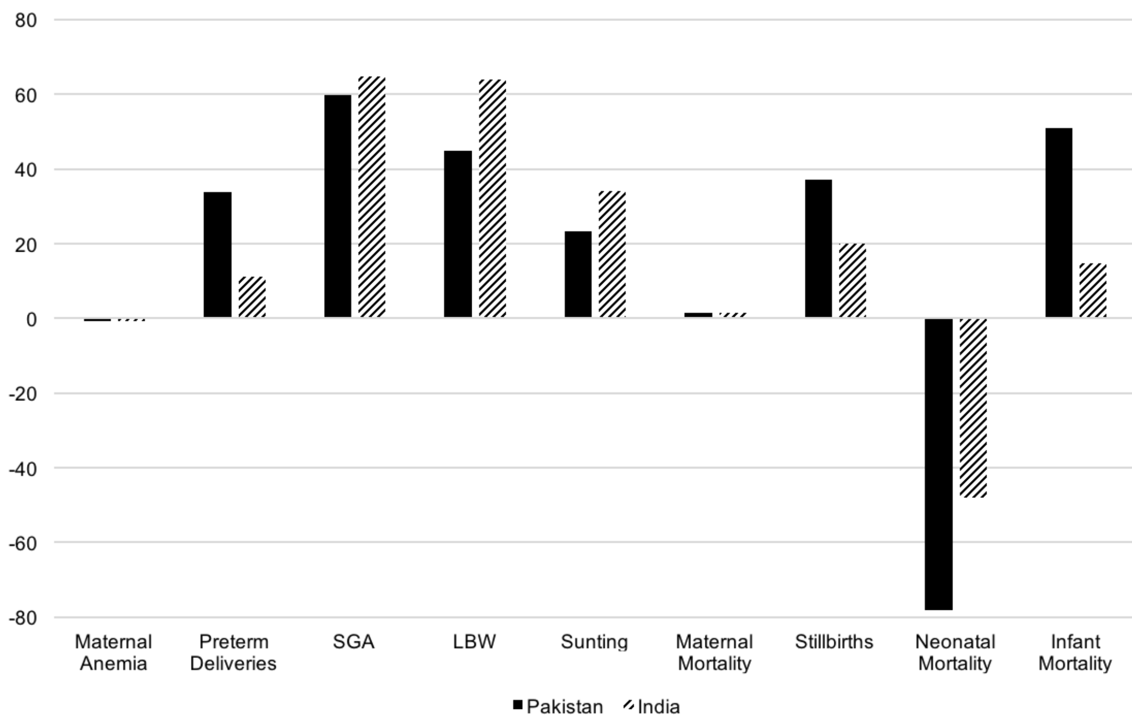

Figure 20: Decomposition of Averted DALYs per Health Outcome for the Case of India

Without conducting a probabilistic analysis, some policy makers could be reluctant to implement an MMN supplementation program in India due to the estimated increase in mortality. However, by running the deterministic model through Monte Carlo simulations we see that the expected value of averted DALYs comes with greater level of statistical significance, 97.5% (mean: 161.27; standard error: 82.14). This means, that even though the overall expected averted DALYs is lower, the chance of the health benefits of MMN to be equal or lower than IFA are close to zero. The higher level of confidence associated with the case of India is due to its lower prevalence of over all mortality. A lower prevalence results in less averted DALYs due to reductions in mortality. Through the probabilistic analysis, it was highlighted that the mortality outcomes were the ones causing most of the variation in the forecast. Since these outcomes now constitute a smaller portion of the total DALYs, the variance in the forecast decreases.

India also is a part of the SearD sub region, and has the same cost estimates for an IFA and MMN supplementation program. This allowed for a cost-effectiveness analysis for scenario in India.

The marginal cost-effectiveness analysis shows that it would cost 5.33 Int'l$ per averted DALY, which is highly cost-effective (GDP/capita of India: 6,572.34 Int'l$).

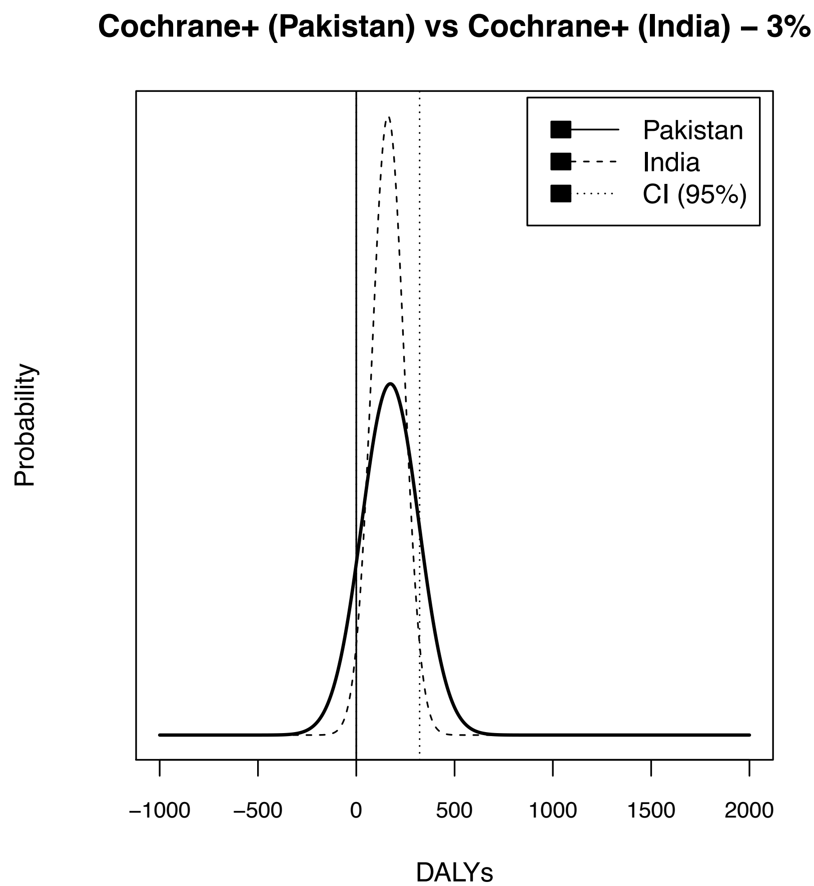

Figure 21: Overlay Charts of Averted DALYs of India and Pakistan

Conclusion

For the past 50 years iron and folic acid (IFA) supplements have been a recommended intervention to target anemia among pregnant women. IFA tablets are a cost-effective way to reduce anemia and is implemented in a majority of countries. However, the international community has noticed in the past years multiple other micronutrient deficiencies amongst low-income populations, especially during pregnancy. This has prompted the United Nation, UNICEF, and the WHO to develop a multiple micronutrient supplement (MMN) formula to simultaneously provide the required dose of 15 vitamins and mineral to pregnant women.

The impact of MMN supplements on anemia and subsequent health conditions are, to some extent, uncertain. It is believed that MMN has the same impact as IFA on maternal anemia, and has an even greater beneficial impact on child morbidity. However, some studies have shown the potential negative impacts of MMN child mortality. Even if the negative impacts of MMN on child mortality never reached statistical significance, more evidence is required before policy makers replace IFA supplementation. As for the WHO, their guidelines on prenatal supplements stipulate that the use of MMN could be justify in certain context. It is up to governments and implementing organizations to determine which supplements to use.

This study puts together a marginal cost-effectiveness model to assess the feasibility of such MMN supplementation intervention in the context of Pakistan. To assess the effectiveness of MMN to reduce negative health outcomes related to maternal anemia, the model quantifies the averted disability-adjusted life-years (DALYs), where the calculations of DALYs are modified to adequately measure the health benefits of micronutrient programs. Moreover, inputs specific to the context of Pakistan were chosen to adapt the results to the setting of interest. The risk ratios (RRs) quantifying the percentage decrease, or increase, of health conditions due to MMN supplementation were estimated through a random-effect meta-analysis. Seventeen trials conducted in developing countries were chosen through a thorough literature review. They all compared the effects of MMN supplementation with IFA and reported the impacts on various health outcomes. The meta-analysis enabled the model to have average RRs that could be used in the context of Pakistan, as well as others.

The analysis showed that MMN supplements has the biggest impact on child morbidity. The principal source of averted DALYs comes from a reduction in preterm deliveries, small-for-gestational-age, and low birth weight. Standard tools to assess the health benefits of interventions, such as the LiST module, only measures health impacts through a reduction of mortality when calculating DALYs. In most cases averted DALYs from reductions in morbidity is negligible compared to the those coming from reductions in mortality. However, when looking at the marginal benefits of MMN, we see an improvement in the reduction of morbidity. This strength of MMN supplements could not be quantified, or noticed, if standard tools were used to assess the impacts. The deterministic model reports that 172.18 additional DALYs could be averted if MMN tablets would replace IFA supplements in Pakistan.

Since health measures surrounding MMN in the model are in most cases not statistically significant, a probabilistic analysis was conducted to highlight the most sensitive inputs and to assess the probability of success of MMN supplementation interventions. Using Monte Carlo simulations it was found that with 90% confidence, in the context of Pakistan, MMN supplements would yield more health benefits than IFA supplements, with a mean value of 172.18 averted DALYs.

To assess the cost of iron supplementation programs, the model used cost estimates from Balussen (2004). These estimates were used to derive the cost of MMN supplementation programs for Pakistan. The marginal cost-effectiveness analysis showed that it would cost 4.99

Int'l$ per averted DALY to replace IFA supplements with MMN tablets. Based on the WHO's threshold, this would be a very cost-effective intervention.

Based on these findings replacing IFA supplements with MMN tablets is a recommended policy, in Pakistan, that could yield important additional health benefits at a low marginal cost.

To test the external validity of the model, the analysis was conducted in the context of India. The RRs obtained in the meta-analysis were used, however, the health inputs were changed to reflect the setting of India. Using the deterministic and the probabilistic analysis, we expect MMN supplementation to avert an additional 161.27 DALYs, with 97.5% confidence. The cost-effectiveness for India showed that it would cost 5 Int'l$ per averted DALYs to replace IFA and MMN supplements.

Through the sensitivity analysis, the RRs for neonatal mortality, stillbirths, and infant mortality were identified as the inputs yielding the most variance. Future research would be needed to increase the evidence of the impacts of MMN over IFA surrounding these three health outcomes.

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Appendix: Deterministic results with different discount rates

Table 26: YLDs per 1,000 Discounted at 0% (Cochrane)

i	RR_i	Pr_i	DW_i	L_i	$(1 - RR_i) \times Pr_i \times DW_i \times L_i$
Anemia	1.03	510.00	0.052	1.00	-0.77
Preterm	0.96	392.80	0.061	65.86	62.09
SGA‡	0.92	434.70	0.061	65.86	137.47
LBW‡	0.88	201.60	0.061	65.86	95.60
Stunting		12.34	0.061	69.79	51.67
Total					346.01

† per 1,000 live births
‡ Adjusted for overlaps

Table 27: YLLs per 1,000 Discounted at 0% (Cochrane)

j	RR_j	L_j	N_j	$(1 - RR_i) \times L_i \times N_i$
Maternal Mortality	0.97	25.35	1.78	2.58
Stillbirth	0.97	28.58	43.15	85.26
Neonatal Mortality	1.06	28.58	45.50	-179.80
Infant Mortality‡	0.95	28.58	35.71	117.59
Total				25.63
Total Averted DALYs				371.65

† per 1,000 live births
‡ net of neonatal mortality (death after 28 days but within the first year)

Table 28: YLDs per 1,000 Discounted at 0% (Cochrane+)

i	RR_i	Pr_i †	DW_i	L_i	$(1 - RR_i)\times Pr_i\times DW_i\times L_i$
Anemia	1.03	510.00	0.052	1.00	-0.77
Preterm	0.95	392.80	0.061	65.86	77.61
SGA‡	0.92	434.70	0.061	65.86	137.42
LBW‡	0.87	201.60	0.061	65.86	103.56
Stunting		13.37	0.061	69.79	55.99
Total					373.81

† per 1,000 live births
‡ Adjusted for overlaps

Table 29: YLLs per 1,000 Discounted at 0% (Cochrane+)

j	RR_j	L_j	N_j†	$(1 - RR_i)\times L_i\times N_i$
Maternal Mortality	0.97	25.35	1.78	2.58
Stillbirth	0.97	28.58	43.15	85.26
Neonatal Mortality	1.06	28.58	45.50	-179.80
Infant Mortality‡	0.95	28.58	35.71	117.59
Total				25.63
Total Averted DALYs				399.45

† per 1,000 live births
‡ net of neonatal mortality (death after 28 days but within the first year)

Table 30: YLDs per 1,000 Discounted at 5% (Cochrane)

i	RR_i	Pr_i †	DW_i	L_i	$(1 - RR_i) \times Pr_i \times DW_i \times L_i$
Anemia	1.03	510.00	0.052	0.95	-0.73
Preterm	0.96	392.80	0.061	19.20	18.10
SGA‡	0.92	434.70	0.061	19.20	40.05
LBW‡	0.88	201.60	0.061	19.20	27.86
Stunting		12.34	0.061	19.34	14.31
Total					99.60

† per 1,000 live births

‡ Adjusted for overlaps

Table 31: YLLs per 1,000 Discounted at 5% (Cochrane)

j	RR_j	L_j	N_j †	$(1 - RR_i) \times L_i \times N_i$
Maternal Mortality	0.97	18.11	1.78	0.97
Stillbirth	0.97	19.20	43.15	24.85
Neonatal Mortality	1.06	19.20	45.50	-52.40
Infant Mortality‡	0.95	19.20	35.71	34.27
Total				7.69
Total Averted DALYs				107.28

† per 1,000 live births

‡ net of neonatal mortality (death after 28 days but within the first year)

Table 32: YLDs per 1,000 Discounted at 5% (Cochrane+)

i	RR_i	Pr_i †	DW_i	L_i	$(1 - RR_i) \times Pr_i \times DW_i \times L_i$
Anemia	1.03	510.00	0.052	0.95	-0.73
Preterm	0.95	392.80	0.061	19.20	22.62
SGA‡	0.92	434.70	0.061	19.20	40.05
LBW‡	0.87	201.60	0.061	19.20	30.18
Stunting		13.37	0.061	19.34	15.51
Total					107.64

† per 1,000 live births
‡ Adjusted for overlaps

Table 33: YLLs per 1,000 Discounted at 5% (Cochrane+)

j	RR_j	L_j	N_j†	$(1 - RR_i) \times L_i \times N_i$
Maternal Mortality	0.97	18.11	1.78	0.97
Stillbirth	0.97	19.20	43.15	24.85
Neonatal Mortality	1.06	19.20	45.50	-52.40
Infant Mortality‡	0.95	19.20	35.71	34.27
Total				7.69
Total Averted DALYs				115.32

† per 1,000 live births
‡ net of neonatal mortality (death after 28 days but within the first year)