A cost effectiveness analysis of maternal multiple micronutrient supplementation in South Africa

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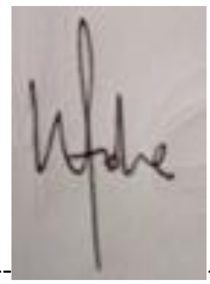
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, South Africa, in part fulfilment of requirements for the degree of Master in Public Health (Health Economics)

Johannesburg, October 2022

I Winfrida Mdewa declare that this research report is my own, unaided work. It is being submitted for the Master in Public Health specialising in Health economics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

-------------

24th day of October 2022 in Johannesburg, South Africa

DEDICATION

In memory of my dear husband

Humphrey Dumisani Mdewa

Thank you for loving us completely and unconditionally.

ABSTRACT

Objectives

Recent evidence has demonstrated that multiple micronutrient supplementation in pregnancy has greater benefits than iron and folate supplementation with recommendations being made to the South African government to consider switching from the current iron and folate regimen to multiple micronutrients. The objective of the study was to evaluate the cost-effectiveness of replacing iron and folate supplementation with multiple micronutrient supplementation in antenatal care in the South African public health care system.

Methods

A cost-utility analysis was conducted using a decision analytical model from a public healthcare payers perspective. The target population for the analysis was pregnant women attending antenatal clinics in the public health sector. Health outcomes considered in the analysis were obtained from a systematic review and include low birth weight, small for gestational age, still births and diarrhoea in children under 1 year. Direct medical costs considered in the analysis were incurred in one year and benefits accrued over a person's lifetime. Resource utilisation, cost estimates, length of hospitalisation, probabilities of health outcomes, and measures of effectiveness were sourced from literature. Costs were expressed in South African rand and effectiveness was measured in DALYs. One way and probabilistic sensitivity analysis were conducted to explore key model assumptions and parameters.

Results

Multiple micronutrient supplementation was the dominant strategy being more effective and less costly than iron and folate supplementation. Sensitivity analysis showed that base-case results were robust to variations of key model parameters. The South African government should consider replacing iron and folate supplementation with multiple micronutrient supplementation in South African public health facilities.

ACKNOWLEDGEMENTS

I would like to thank God for his guidance and giving me the strength to walk this journey. If it were not for him, this would have not been possible.

Dr Ijeoma Edoka, supervisor and former manager. Thank you for confidence in me, for your encouragement and for your patience. You held my hand during a very difficult time in my life and I will never forget that. Words cannot express my gratitude, and may God remember you for the role you have played in my life.

Immeasurable appreciation and deepest gratitude are extended to the following persons who in one way or another made this study possible :

Heather Fraser, former work colleague and friend, for being my sounding board, supporting and guiding me in developing my model.

Dr Karen Hofman, Director at the SAMRC/Wits Centre for Health Economics and Decision Science and the team ,for supporting me in my journey through my coursework and project write up. I could not have asked for a better employer.

NHIR Southampton. For financial support for this Masters report.

Doctor Pamela Machingaidze-Chamboko, for your clinical advice.

Tinashe-Tombe Nyahuma, sister for landing me in the Health Economics field.

Wadzanai Mamutse, best friend and assistant mum to my sons. You are my biggest cheerleader.

My family, for your love, unwavering support, encouragement, and prayers throughout this journey.

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List of Abbreviations

Abbreviation	Definition
DALY	Disability Adjusted Life Year
AFS	Animal Source Food
ANC	Antenatal care
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CPI	Consumer Price Index
GDP	Gross Domestic Product
ICER	Incremental Cost Effectiveness Ratio
IGUR	Intra Uterine Growth Restriction
INMB	Incremental Net Monetary Benefit
LMICs	Lower Middle-Income Countries
mg	Milligrams
MINIMat	Maternal and Infant Nutrition Interventions in Matlab
MMS	Multiple Micronutrient Supplementation
NGO	Non-Governmental Organisation
ORS	Oral rehydration Solution
QALY	Quality Adjusted Life Years
SGA	Small for gestational age
UNICEF	United Nations Children' Education Fund
UNIMMAP	United Nations Multiple Micronutrient Preparation
WHO	World Health Organisation
YLD	Years Lost Due to Disability
YLL	Years of life Lived
ZAR	South African Rand

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CHAPTER 1: INTRODUCTION

Micronutrient malnutrition, referred to as the "hidden hunger", affects nearly 2 billion people worldwide [1]. Micronutrients are essential vitamins and trace minerals needed to support cellular and molecular functions in humans [1]. The major cause of multiple micronutrient deficiencies is a poor quality diet that lacks variety often characterized by inadequate intake of fruits, vegetables, animal source foods (ASF) [2,3]. In addition factors such as infection, disease and inflammation affect nutrient absorption, utilization and excretion contribute to micronutrient deficiency [1].

Pregnancy results in exponential increases in micronutrient demands due to major physiological and metabolic change [4,5] .Vitamins A, B^{6},B^{9},B^{12},C, D, and E, and minerals copper, iodine, zinc, selenium, and iron play extremely important roles in maternal health, neonatal growth and lactation and recommended intakes could increase by up to 50% during pregnancy [4,6].In pregnant women adverse events caused by micronutrient deficiency include intra-uterine growth restriction, pregnancy loss, low birth weight ,pre-term birth and birth effects restriction [4]. These birth outcomes result in higher perinatal and infant morbidity and mortality in the short term [7,8]. In the medium term, small for gestational age and low birth weight have been found to have a higher risk of underweight, stunting and wasting in children [9]. Long term effects of impaired antenatal nutrition include the increased likelihood of developing chronic diseases such as obesity, type 2 diabetes and cardiovascular disease in offspring of mothers with micronutrient deficiency but the understanding of the molecular mechanisms of these effects has not been fully explored [10].

Women and children are mostly at risk with populations in low and middle-income countries (LMICs) bearing the largest burden of micronutrient deficiency [11].Most micronutrient deficiencies in low and middle income countries co-exist during the antenatal period because of poor diets and South Africa is no exception [12]. According to review of the South African adult dietary intake, fruit, vegetables and dairy are the most commonly deficient food groups and there is a high prevalence of micronutrient deficiencies[13].Pregnant women are particularly vulnerable as they experience higher levels of poverty and food insecurity .Compared to other women of reproductive age, pregnant women in South Africa are 45.6 % less likely to have an income and 66.9 % of them reside in households that received the child support grant [14]. In addition, a national study found that 25% of pregnant women lived in a household that suffered from food inadequacy and households with pregnant women suffered from elevated levels food insecurity characterised by missed meals or reduced food portions [14]. 23% to 33% of South African women are already anaemic when they fall pregnant with 50% of these anaemic cases attributable to iron deficiency[15]. In South Africa ,40% of all maternal deaths are attributed to anaemia [16].Closely related to maternal death is neonatal death and not much improvement has been made to reduce neonatal mortality despite increased government investment [17]. The neonatal death rate is estimated to have consistently hovered between 11 and 12 % from 2012 to 2015 [17]. Premature birth complications accounted for nearly 48% of neonatal deaths and 60% of premature birth deaths were low birth weight [17].

LMICs have disproportionately high rates of low birth weight with 95% of births occurring in these regions [18].In South Africa,15% of the live births are low birth weight [19]. Most of low birth weight births in developing countries are as a result of intra uterine growth restriction (IGUR) caused by maternal undernutrition and/or malnutrition [20]. Low birth weight has great public health significance as it is an indicator of maternal health and is a risk factor for morbidity and mortality in infancy and childhood .In the short term, low birth weight has been associated with higher risk of neonatal mortality and a number of neonatal morbidities.60%-80% of global neonatal deaths occur in low birth weight babies [21].

In LMICs, 27% of all births are small for gestational age, a figure that is twice as high as general low birth weight prevalence in the world [22].Small for gestational age can be as a result of being constitutionally small, maternal nutritional deficiencies, abnormal placental function, infections during pregnancy, and foetal genetic factors [22,23].Small for gestational age has an increased risk of perinatal mortality and morbidity with the most adverse outcomes occurring in the growth restricted group.

Stillbirth makes up a large percentage of preventable deaths but has been mostly overlooked as a public health priority [24]. Stillbirth rate is indicative of maternal health and quality of care a country's health system [25]. 41% of the 2,6 million third trimester stillbirths globally occurred in Africa and 98% of all stillbirths are in LMICs [7]. Improved nutrition prior to and during pregnancy has been suggested as a means of preventing stillbirths. Multiple micronutrient supplementation is suggested in the continuum of care from preconception to birth of a child to prevent still births[24,26].

Despite significant reductions in mortality as a result of diarrhoea over the decade, it is the fifth leading cause of death in children under 5 in the world [27]. In South Africa approximately 10% under 5 of deaths are attributable to diarrhoeal illness [22].Interventions to address diarrhoeal disease in children include breastfeeding, Vitamin A and Zinc supplementation, vaccination and water and hygiene interventions[28].A recent study has found that antenatal supplementation with multiple micronutrient supplementation results in significant reductions in diarrhoeal illness in children under 5 [29].

The main public health interventions for improving micronutrient intake are food fortification and supplementation [30]. Food fortification is a sustainable, cost-effective way of reaching a wider population without necessarily changing their consumption patterns [31]. However, inaccessibility and unavailability of fortified foods to poor populations limits the effectiveness of such interventions [32]. Increasing dietary variety as a long term strategy has been suggested as the most ideal strategy for preventing micronutrient deficiency in populations [33].It however has slow returns and is hampered by the need for people to change their dietary patterns in addition to issues of affordability especially in poor populations [33].

Supplementation is a short term strategy where large quantities of micronutrients are dispensed as syrups, capsules or pills [31].Supplementation is used in the prevention or treatment of severe forms of micronutrient deficiency because it supplies an ideal amount of nutrients in a highly absorbable form [1]. It is for this reason that they are recommended during pregnancy to combat nutrient deficiencies[1].The current micronutrient supplementation regimen recommended for pregnant women by the WHO (World Health Organisation) is daily iron and folic acid for the prevention of "maternal anaemia, puerperal sepsis, low birth weight, and preterm birth"[34].Multiple micronutrient supplements combine various micronutrients into one supplement in the form of capsules, tablets or syrups and are used in place of iron and folate supplementation [35].Their use in pregnancy is common in high income countries [35].Use of multiple micronutrient supplements could address the range of micronutrient deficiencies present during the gestation period [36].

Micronutrient intake recommendations in pregnancy in LMICs are next to impossible to meet during pregnancy through dietary intake alone due to poor diets [4]. Most LMICs use iron and folate supplementation as part of their antenatal care package. The current supplementation regimen in the South African public health system consists of 200 mg ferrous sulphate, 1000 mg calcium and 5 mg folic acid [12]. Considering the high likelihood of micronutrient deficiencies in the pregnant women in the SA population, iron and folate alone might not be sufficient to fully address micronutrient deficiencies in pregnant women. Recent studies comparing iron and folic acid supplementation with multiple micronutrient supplementation for pregnant women in LMICs have found evidence that multiple micronutrient supplementation provides greater health benefits for birth outcomes, infant mortality and childhood health outcomes compared to iron and folic acid supplementation [29,35,37]. Replacing iron and folate supplementation with multiple micronutrient supplementation in South Africa could address the micronutrient deficiencies in pregnancy in South Africa.

In 2020 the World Health Organization Guidelines for Antenatal Care were updated, and recommendations were made to use antenatal multiple micronutrient supplements that include iron and folic acid "in the context of rigorous research"[38].Further research to this end includes clinical trials and implementation research. In order to make a decision on whether to switch to multiple micronutrient supplementation ,policy makers need to know not only the health benefits but the costs involved and if the switch represents good value for money [34].It is in this context that a cost effectiveness analysis was conducted to assess the value for money of replacing the current supplementation regimen in the South African public health system with multiple micronutrient supplementation [12].

The multiple micronutrient supplement under review is the United Nations Multiple Micronutrient Preparation (UNIMMAP) tablet. It is made up of the recommended daily allowance of vitamin A, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium and iodine with 30 mg of iron and 15 mg of zinc for pregnant women [35]. It was formulated and recommended for tackling micronutrient deficiencies in countries with large populations that are nutritionally deficient [39].

This study compares the costs and benefits associated with of each of the supplementation regimens. Costs considered include the costs of supplementation and treatment of adverse health outcomes that result from lack of supplementation. The benefits considered include reductions in low birth weight, small for gestational age, stillbirths, and diarrhoea in children under 5 as well as potential cost savings from averting these health outcomes.

1.2 Literature Review

A literature review was conducted of the clinical effects and cost-effectiveness of multiple micronutrient supplementation using the PICO (Participants, Intervention, Comparison, Outcome) framework as outlined below:

Table 1 : 1 PICO framework for literature search

Element	Description
Population	Pregnant women of any age or parity anywhere in the world
Intervention	Micronutrient supplementation (single or multiple)
Comparator	Micronutrient supplementation with iron, folate and calcium
Outcome	Anaemia/iron deficiency in pregnancy, low birth weight, small for gestational age, perinatal mortality, stillbirths, maternal and infant mortality, costs, disability weights

I conducted an electronic database search on Google scholar, Pub Med and the Cochrane library.

Search terms used for effectiveness of supplementation strategies were "clinical effectiveness or efficacy or benefits " and " multiple micronutrient supplementation or UNIMAP " and "pregnancy, antenatal" .For the economic evaluation literature review search terms included "cost effectiveness or cost utility or economic evaluation" and "multiple micronutrient supplementation and iron and folate supplementation" and/or "pregnancy ,antenatal period". Study selection for clinical effectiveness was restricted to systematic reviews and randomised control trials for clinical effectiveness of multiple micronutrient supplementation. Cost effectiveness studies were restricted to full economic evaluations i.e. studies that employed the use of cost effectiveness analysis ,cost -benefit analysis and cost -utility analysis.

1.2.1 Methods of Economic Evaluation

Resource allocation decisions when faced with increasing healthcare demand and a limited budget can be quite challenging. Decision makers are faced with making choices of what to fund and which trade-offs are to be made in the health system. Consequently, maximising healthcare benefits from a given level of investment or value for money should be a priority especially in resource constrained settings like South Africa. Economic evaluation is a crucial and key element in facilitating efficient use and allocation of resources in healthcare. The following summary discusses the methods of full economic evaluations in current practice.

Cost minimization analysis involves comparison of two (or more) comparators are assumes that their outcomes are equal. As a result, the analysis is based solely on comparing the costs and choosing the cheapest option [40].Although it is easier to conduct, practically health outcomes are seldom identical and it is therefore not very popular in economics literature [41].

Cost Benefit Analysis (CBA) is used to address allocative efficiency and measures both the costs and consequences of interventions under consideration in monetary units. It addresses whether an intervention is worthwhile or not. Results are commonly expressed as a cost-benefit ratio. Because returns on investment are expressed in monetary terms ,it allows comparisons with returns in other sectors of the economy [42]. CBA ,however, presents difficulties in economic evaluation because of controversies surrounding measuring of health in monetary terms [43,44].

Cost effectiveness analysis addresses issues of technical efficiency making comparisons of at least two interventions within a fixed budget [43].It looks at one outcome measure or consequence of an intervention that is common to all alternatives being considered in the analysis. Outcomes are measured in natural units, either health outcomes or behaviours related to health outcomes (such as adherence to taking medicine) [45]. Results of a CEA are usually expressed as a ratio of the difference between the costs and benefits of the strategies under consideration. The ratio is called the incremental cost effectiveness ratio (ICER).A major disadvantage of CEA is that it is unable to compare interventions with differing natural effects meaning comparisons cannot be made across the health sector [45].

Cost utility analysis is similar to CEA but measures outcomes in terms of generic metrics that combine morbidity and mortality into single metrics namely “quality adjusted life years” (QALY) and “disability adjusted life years” (DALY).Health outcomes are measured in terms of utility which is the preferences that societies or individuals have for a particular set of health outcomes [45].It can also be used to analyse interventions or programmes with single or multiple outcome measures. Relative efficiency determined using an incremental ratio, a cost utility ratio [44].

1.2.2 Clinical Benefits of Multiple Micronutrient Supplementation compared to Iron and Folate supplementation

Several studies in LMICs over the years have assessed the clinical benefits of multiple micronutrient supplementation compared to iron and folate supplementation during pregnancy. Health outcomes considered in most analysis are preterm births, small for gestational age, low birth weight, perinatal mortality, stillbirths, neonatal mortality, maternal anaemia, and maternal mortality. Early studies found that compared to iron and folate supplementation, multiple micronutrient supplementation reduced the risk of low birth weight and small for gestational age births [(21-23)]. Some studies suggested that use of multiple micronutrient supplementation provided no extra health benefits when compared to iron and folic acid supplementation and others found increased perinatal mortality amongst multiple micronutrient supplementation takers [9,12,46] .

The 2016 World Health Organization Guidelines for Antenatal Care were informed by a 2025 Cochrane systematic review. Universal multiple micronutrient supplementation in pregnancy for improving maternal and perinatal outcomes were not recommended in the guidelines. They cited insufficient evidence to support its use and highlighted evidence of increased risk of perinatal mortality [21]. They, however, suggested policymakers consider its use in populations with high prevalence of nutritional deficits [21].

Since the WHO recommendation, an individual participant data analysis was conducted, and multiple micronutrient supplementation was found to be beneficial in more health outcomes than previously documented [37]. This study by Smith et al is commonly referred to as the Lancet review in literature [37]. Compared to iron and folate, multiple micronutrient supplementation had greater reductions in the risk of very low birth weight, low birth weight, early preterm birth, preterm birth, small for gestational age and stillbirths. Greater benefits (reduced low birth weight, small for gestational age births) were recorded in groups of anaemic and underweight women [37].Additionally, neonatal mortality, 6 month mortality and infant mortality risk reduction was greater among female infants compared to their male counterparts[37]. The Lancet review also found evidence of higher risk of large-for-gestational age infants in the multiple micronutrient supplementation group but noted that there was no association between multiple micronutrients and increased risk of stillbirth or mortality at any period.

Subsequently, a 2019 Cochrane review of 20 randomized control trials that evaluated multiple micronutrient supplementation during pregnancy and how it affected pregnancy outcomes was published [35].All trials were conducted in LMICs. The review reported improved outcomes in low birth weight (RR: 0.88; 95% CI: 0.85–0.91) and small for gestational age (RR: 0.92; 95% CI: 0.88–0.97) for multiple micronutrient takers [35]. Preterm birth, stillbirth, miscarriage, maternal mortality, maternal anaemia, perinatal mortality, and neonatal mortality showed no significant differences between the two supplementation groups. They did not find any adverse effect of multiple micronutrient supplementation on perinatal or neonatal mortality as had been previously suggested in other studies.

The most recent systematic review (2020) on effects on maternal, birth, child health, and developmental outcomes reported similar findings to the 2019 Cochrane Review [29]. Oh, et al reported a 15% reduction in the risk of low birth weight (RR 0.85, 95% CI 0.77 to 0.93),7% reduction in the risk of small for gestational age birth (average RR 0.93, 95% CI 0.88 to 0.98) and a 9% reduction in the risk of stillbirths (average RR 0.91, 95% CI 0.86 to 0.98). There was no effect on premature births, perinatal and infant mortality. They also reported a reduction in diarrhoea in children aged 6-59 months and some improvement in child serum/plasma retinol concentration levels .This review like other studies also refuted the occurrence of adverse consequences previously suggested indicating no increases in perinatal mortality as a result of multiple micronutrient supplementation use [35,37].

8 of the studies were in the Cochrane review, the lancet review as well as in the review by Oh and colleagues. The review by Oh et al 34 of the three latest reviews and 10 of these studies were conducted in Sub-Saharan Africa. All the systematic reviews clearly explained the methods used in the analysis. The review by Oh et al, however, provided current and updated evidence, including newly completed trial data. They also provided updated clinical effectiveness data on child health and developmental outcomes.

1.2.3 Cost Effectiveness Studies

The efficient use of resources to maximize population health is crucial especially in settings where resources are limited. Economic evaluation is a tool used to systematically analyse the costs and benefits of alternatives courses of action in health in order to inform optimal resource allocation[45]. It facilitates prudent decisions about investments in health that bring about high returns.

There is consensus in the literature that investing in nutrition interventions represents good value for money [30,31]. A panel of distinguished economists known as the Copenhagen Consensus ranked 30 interventions to tackle the greatest global challenges and the provision of micronutrients was found to be the world's second best investment for development, after controlling infectious disease[47] .Micronutrient fortification ranked third best investment, higher than vitamin A and zinc supplementation in children [47].

Most cost-effectiveness studies on micronutrient supplementation assess individual micronutrients and the benefits of investing in them, mostly in children. Studies have looked at zinc, vitamin A, iron and iodine supplementation in young children [48–50].Studies investigating investment returns on supplementation of pregnant women have mostly focused on iron and folate supplementation as well as folic acid during the preconception period [51,52].All these studies found supplementation to be cost effective.

There is, however, a paucity of studies on the cost effectiveness of multiple micronutrient supplementation. A review of the literature found a few studies, all conducted in LMICs. All studies derived their estimates of effectiveness from the Cochrane or Lancet systematic reviews

Two studies in Bangladesh assessed the cost effectiveness of multiple micronutrient supplementation using data from one randomized control trial, the Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial [53,54]. Participants in the trial were followed for a period of 5 years. The interventions assessed were early provision of prenatal food and multiple micronutrient supplementation to pregnant women in rural Bangladesh. They were put into random groups of either early (9 weeks of pregnancy) invitation to food supplementation plus daily doses of 30 mg, or 60 mg iron with 400 µg of folic acid, or multiple micronutrient supplementation with 15 micronutrients including 30 mg iron and 400 µg of folic acid or usual invitation (20 weeks of pregnancy). The two studies reported different times for distribution of supplements to pregnant women with Svefors et al reporting distribution at 14 weeks of gestation and Shaheen at 20 weeks [53,54] . Outcome measures were under-five mortality and stunting in one study and infant survival in another [53,54].

The first study by Shaheen et al investigated whether early invitation to foods supplements with multiple micronutrient supplementation was cost effective compared to normal invitation to food plus iron and folic acid supplementation. Pregnant women randomly assigned to early (about 9 weeks of pregnancy), or usual invitation (about 20 weeks of pregnancy) to daily (6 days a week) food supplements and micronutrient supplements. The health outcome of interest was infant survival. Most costing data was derived from another study (Khan et al) which used a bottom-up approach to costing [55]. Shaheen et al presented cost estimates from non-governmental organisation (NGO) run and community nutrition centres run by the government as well as a theoretical highest cost scenario. They reported that annualization of capital costs at a 5% discount rate had been applied in original costing study but no further discounting was applied in their study [55].Costs were adjusted to their relevant year price levels using the consumer price index. Life years gained and infant mortality averted were used as a measure of health benefit [54]. Years lived were discounted at 3% and at 5%. One way sensitivity analysis was conducted varying discount rates on year of life lived and hazard ratios of infant mortality. They did not conduct a probabilistic sensitivity analysis.

The second study was a follow-on study from Shaheen et al' s work. The analysis, like Shaheen et al was on the cost effectiveness of the interventions in the MINIMat trial. The health outcomes of interest were under 5 mortality and stunting. Costing data was derived from the study by Shaheen et al but Svefors et al considered only the highest cost scenario which combined the highest costs per item estimated for NGO run or government run community nutrition centers[54]. They like Shaheen et al, also reported the annualization of capital costs in the original study by Khan and no further discounting was applied in their study [54]. They adjusted costs to their relevant year price levels using the consumer price index. Svefors et al estimated the effects measure of the interventions terms of disability adjusted life years (DALYS). They estimated DALYs by combining years of life lost due to premature under 5-year mortality and years of life lived (YLL) with disability (stunting). Analysis was done for the 5 years that the program ran and extrapolated over a lifetime horizon [53].A 3% discount was applied to the YLL and the YLD for stunting only. No mention of sensitivity analysis in the study was made. Although they did not use a composite measure of effectiveness such as the DALY or QALY in their analysis, they proposed that their ICER estimate of between US$797 to US$907 to avert one case of infant mortality and US$27 to US$30 to save one extra life year was cost effective as it fell below the country's gross domestic product (GDP) per capita of Bangladesh in the year of study.

Overall, both studies showed that multiple micronutrient supplementation was cost effective in Bangladesh. The threshold used to assess the incremental cost effectiveness ratios (ICER) was the country's gross domestic product (GDP) and the interventions were considered cost effective as they fell below the annual GDP for that year [38,39].

Engle- Stone and colleagues modelled the effects of replacing iron-folic acid supplementation with multiple micronutrient supplementation for one year in Burkina Faso and Bangladesh using a decision analytical modelling approach [56]. The UNIMMAP formulation was supplement reviewed and the time horizon for the analysis was one year. The base case assumed 100% coverage and adherence of supplements for 6 months i.e., 180 tablets consumed. Outcomes of interest were stillbirths, neonatal and infant mortality, and birth outcomes (low birth weight, small for gestational age and preterm) for which associated benefits were calculated using evidence obtained from the literature on the magnitude of effect of multiple micronutrient supplementation (compared to iron and folate) on these outcomes[37]. DALYs associated with each outcome were estimated without age weighting. They assumed that the effects of low birth weight and prematurity would last a lifetime but there was no mention of discounting applied.

Costs of replacing iron and folic acid with multiple micronutrient supplementation were calculated as the marginal cost of providing multiple micronutrient tablets compared with iron and folic acid tablets. No programmatic costs involved in transitioning were included in the analysis. No discounting was applied to the costs because of the one-year time horizon adopted by the analysis. Incremental costs and incremental benefits (DALYs averted) were estimated across different coverage rates. The analysis reviewed four strata in each country: Urban, Male Child; Urban, Female Child; Rural, Male Child; Rural, Female Child [56]. Although the study covered a narrow time frame and marginal costs, it found that investing in multiple micronutrient supplementation for both countries was cost effective and a policy shift towards multiple micronutrient supplementation was worth considering [56]. The cost per DALY averted in both countries ranged from USD3 to 15 and the estimate was dependant on the country and subgroup effects[56].

In another study, Kashi et al developed a decision model to assess the cost-effectiveness of transitioning from iron and folic acid supplementation to multiple micronutrient supplementation in Pakistan ,Bangladesh and India [57].Iron and folate supplementation was defined as 60 mg of elemental iron and 400 mg folate taken orally and multiple micronutrient supplementation as the United Nations International Multiple Micronutrient Preparation (UNIMMAP) formulation .They assumed 95% coverage of supplements with 100% adherence for at least 6 months meaning 180 tablets per pregnant woman. The effectiveness of the supplements was based on relative risk estimates from meta-analysis by Cochrane and The Lancet reviews in 2017 [12,37]. They considered 8 health outcomes in the analysis: maternal anaemia, preterm delivery, small-for-gestational-age new-borns, low birth weight, stillbirths, and maternal, neonatal, and infant mortality. A deterministic model was used to calculate DALYs, and they reported present values of DALYs by applying discounting at a rate of 0%, 3%, and 5% on the years lived with disability. Figures for low birth weight were adjusted to account for small for gestational age and prematurity and avoid double counting. Unlike Engle-Stone and colleagues ; this study considered costs of purchasing supplements, -costs of patients accessing supplements at the primary health care facility, program costs and changeover costs (retraining of staff, updating national guidelines). This study, as the MINIMat studies, also used the WHO recommended threshold of 3 times GDP per capita to determine the cost- effectiveness of the interventions. To account for model input uncertainty, they conducted a probabilistic sensitivity analysis using 200 000 Monte Carlo simulation runs. This study also found that multiple micronutrient supplementation is a cost-effective strategy in the three countries 57. Under the Cochrane scenario, the incremental cost-effectiveness ratio of transitioning from iron and folate supplementation to multiple micronutrient supplementation for Pakistan, India, and Bangladesh was USD 41.54, 31.62, and 21.26 per DALY averted respectively. Under the Lancet scenario, the incremental cost-effectiveness ration decreased to USD 9.61, 14.99, and 10.74 per additional DALY averted in Pakistan, India, and Bangladesh, respectively. The most DALYs were averted through a reduction in small for gestational age under the Cochrane scenario and low birth weight under the Lancet scenario. Stillbirths and neonatal mortality produced the most uncertainty in both scenarios. The authors did not explicitly state the time horizon of the study or the perspective, but our deduction was that it was a lifetime horizon, and it was done from a healthcare payers' perspective.

In 2020, Nutrition International published a policy brief on an investment case and the cost effectiveness of transitioning from iron and folate supplementation to multiple micronutrients in South Africa [58]. Using the Nutrition International MMS Cost-Benefit Tool they estimated the necessary investment, cost-effectiveness and return on investment. The analysis consisted of the total population of pregnant women in a year. Multiple micronutrients were of the UNIMMAP formulation. Like other studies, it was assumed that women took 180 tablets during their pregnancy, but they assumed only 30 % coverage. Health outcomes in the study included stillbirth, female neonatal mortality and male neonatal mortality, preterm, low birth weight, small for gestational age, maternal mortality, and maternal anaemia. Benefits were calculated over a 10-year period and expressed as DALYs averted. Additional effect sizes for the supplements were based on the Cochrane and Lancet reviews [35,37]. Costs included in the analysis were supplement costs, costs of providing supplements using the existing public health antenatal system and program costs (administration and training of healthcare workers). There was no discounting or sensitivity analysis reported. Switching to multiple micronutrient supplementation resulted in an incremental cost of USD 15.80 per DALY averted (approximately ZAR 233.68 per DALY averted). Using the WHO threshold for cost effectiveness, they came to the conclusion that multiple micronutrient supplementation was very cost effective [58].

The evidence so far suggests that multiple micronutrient supplementation can be cost effective in low and middle-income countries and specifically in South Africa. However , the Nutrition

International report, did not provide a detailed account of the methods employed to come to their conclusions [58].Issues such as sensitivity analysis to test the robustness of the model as well as discounting of costs and benefits were not mentioned. Furthermore, a time horizon of 10 years could be too narrow to account for what most studies have considered to be lifetime benefits of multiple micronutrient supplementation [54,57,59].Cost estimates in this study did not include health system costs associated with the health outcomes under review. These studies also based its cost effectiveness conclusion on the 3 times GDP threshold and since then a South African specific threshold has been estimated [60]. Furthermore, recent studies on the efficacy of multiple micronutrient supplementation have been published since the Cochrane and Lancet reviews which includes its effect on child health outcomes and further investigations are needed. It is considering these observations, that we conducted a detailed cost effectiveness study of replacing iron and folate supplementation with multiple micronutrients in South Africa.

Details of cost-effectiveness studies included in the review are outlined in the table below:

First author, year	Type of study, country	Intervention and comparator	Measure of benefit	Result	Threshold	Sensitivity analysis
Shaheen (2015)	Cost-effectiveness Bangladesh	Provision of prenatal food supplementation early in pregnancy (9weeks) combined with multiple micronutrients vs usual invitation (20weeks)	Infant survival	Non-governmental organisation run centres-US$907 per case of infant mortality averted Government run community run centres - US$797 per infant mortality case averted US$ 27 to US3$0/life year saved	US$958 (GDP 2013)	One -way
Svefors (2018)	Cost-utility Bangladesh	Provision of prenatal food supplementation early in pregnancy (9weeks) combined with multiple micronutrients vs usual invitation (20weeks)	Under 5 child mortality and stunting	*5-year scenario -US $ 187/DALY averted* *Lifetime scenario- US$24/DALY averted*	US$1190 (GDP 2015)	Not mentioned
Engle-Stone (2019)	Cost-utility Burkina Faso, Bangladesh	Iron and folate supplementation vs multiple micronutrient supplementation	Stillbirths Neonatal mortality Infant mortality Very low birth weight Low birth weight Very preterm birth Preterm birth, Small for gestational age	Cost/DALY averted ranged from US$3 to US$15 depending on the country and consideration of subgroup effects	Not mentioned	One-way

Kashi et al (2018)	Cost-utility Pakistan, Bangladesh and India	Iron and folate supplementation vs multiple micronutrient supplementation (UNIMMAP)	Maternal anaemia Preterm delivery (births before 37 weeks of gestation), Small for gestational age Low birth weight Stillbirths Maternal mortality Neonatal death Infant mortality (death	Cochrane scenario-Pakistan, India and Bangladesh was 41.54,31.62 and 21.26 USD per additional DALY averted respectively Lancet scenario -Pakistan, India and Bangladesh was 9.61,14.99 and 10.74 USD per additional DALY averted respectively	GDP (2016) Pakistan US$5429 India US$6570 Bangladesh US$3580	Probabilistic
Nutrition International (2020)	Cost-utility South Africa	Iron and folate supplementation vs multiple micronutrient supplementation (UNIMMAP)	Stillbirth Neonatal mortality (Female) Neonatal mortality (Male) Low Birth Weight Small for gestational age Maternal mortality Maternal anaemia	US$15,80/DALY averted	South African GDP (actual figure not stated)	Not mentioned

Table 1.2 Literature review of Cost-effectiveness of Multiple Micronutrient Supplementation

1.3 Statement of the problem

Multiple micronutrient deficiencies exist in pregnant women in South Africa because of a lack of dietary diversity[15] . Multiple micronutrient supplementation has been proposed as a promising strategy for reducing adverse maternal and infant outcomes resulting from such deficiencies during the gestation period. If the South African government is to consider switching from current supplementation with iron and folate to multiple micronutrient supplementation information on whether this represents good value for money is needed. A cost-effectiveness analysis would provide information on whether the benefits of replacing iron and folate supplementation with multiple micronutrient supplementation in the South African public health care system outweighs the costs.

1.4 Justification of study

Recent evidence that included studies of pregnant women in low and middle income countries found that multiple micronutrient supplementation had better health outcomes compared to iron and folate supplementation [29,35,37]. New evidence also suggests that there is no increased risk to the mother or the child from taking multiple micronutrient supplements [35,37]. As the South African National Department of Health considers changing the current antenatal care guidelines in line with new evidence, context-specific evidence on the cost effectiveness of multiple micronutrient supplementation will be crucial for informing policy decisions on the replacement of iron and folate supplementation with multiple micronutrient supplementation in South Africa.

1.5 Research Question

From a public health system perspective, is it cost effective to replace iron and folic acid supplementation with the United Nations International Multiple Micronutrient Preparation (UNIMMAP) formulation in South Africa?

1.6 Study Aim

To determine whether it is cost-effective to replace iron and folic supplementation currently offered to pregnant women in government primary health care facilities in South Africa with the UNIMMAP formulation.

1.7 Study Objectives

Objective 1:

To estimate DALYs associated with adverse birth and child health outcomes due to micronutrient deficiency – low birth weight, small for gestational age, stillbirth and diarrhoea - in pregnant women attending government primary health care facilities in South Africa in 2020.

Objective 2:

To estimate supplementation costs and health service utilisation, clinical care management costs of adverse birth and child health outcomes due to micronutrient deficiency – low birth weight, small for gestational age, stillbirth and diarrhoea - in pregnant women and children attending government primary health care facilities in South Africa in 2020.

Objective 3:

To estimate the incremental cost effectiveness ratio (ICER) of replacing iron and folate supplementation with the UNIMMAP supplement formulation in antenatal care in government primary health care facilities in South Africa.

CHAPTER 2: METHODOLOGY

2.1 Study design

A cost utility analysis was conducted from the South African public health care payer perspective because the analysis intends to inform the National Department of Health (NDOH) decision making. When there is insufficient evidence on costs and health outcomes from a single source ,decision analytical modelling can be used to synthesize information from multiple sources [45]. A model provides a structure that allows extrapolation of data beyond the clinical trial period, extrapolation of intermediate clinical endpoints to final health outcomes ,generalization of results to other settings or patient groups and the inclusion plus management of uncertainty [45,61,62].I made use of decision analytical modelling in order to be able to synthesize data from multiple sources in a structured and systematic way. An excel based decision tree model was used to establish the incremental costs and benefits of replacing current antenatal supplementation in government primary health care facilities in South Africa with supplementation with the UNIMMAP formulation. The choice of a cost-utility analysis using DALYs as the outcome measure was made to facilitate comparison of cost-effectiveness across disease groups, settings as well as other public health interventions the government might want to consider.

The target population in the analysis was pregnant women seeking antenatal care at public health care facilities in South Africa in 2020. The analytic time horizon in economic evaluations is the period in which costs and benefits are evaluated [63] .Ideally, economic evaluation studies should adopt a time horizon that accommodates all the costs and benefits relevant to the decision problem and for differential timing of costs and benefits [64].In this study a lifetime horizon was adopted .Although all costs associated with the health outcomes were incurred in the first year of life, benefits accrued over a lifetime.

The study comparators are presented in Table 2.1. In both interventions, supplements are given to pregnant women by a nurse when they attend antenatal care at government primary health care facilities. It was assumed that patients will take supplements daily for at least 6 months of the pregnancy.

Table 2:1 Supplementation formulation

Current Intervention	Proposed Intervention
200mg of Ferrous sulphate tablets 5g of folic acid tablets	UNIMMAP formulation that contains Vitamin A 800 pg, Vitamin D 200 IU, Vitamin E 10 mg, Vitamin C 70 mg , Vitamin Bi 1.4 mg ,Vitamin B2 1.4 mg ,60mg of iron ,Niacin 18 mg,30mg of zinc , Vitamin B6 1.9 mg ,Vitamin B12 2.6 pg ,Folic Acid 400 pg ,Iron 30 mg ,Zinc 15 m ,Copper 2 mg ,Selenium 65 pg conjunction and Iodine 150 pg.

The health outcomes used as a measure of benefit for both supplementation regimens were informed by the systematic review by Oh and colleagues [29]. The choice for using health outcomes from this review was informed by Oh et al providing the latest evidence effectiveness data that included newly completed trial data not previously included in previous reviews. They also provided updated clinical effectiveness data on child health and developmental outcomes.

Health outcomes considered were low birth weight, small for gestational age, stillbirths and diarrhoea in children under 5.Although multiple micronutrient supplementation was cited as probably having an impact on reducing premature births in the review , prematurity was left out of the analysis as its effect was not statistically significant [29] .The assumption made was that the consequences of low birth weight and small for gestational age lasted for a person’s lifetime. For diarrhoea however ,only illness experienced during the first year of life was considered because diarrhoea incidence in children under 5 peaks between 6 and 11 months [65–67]. The effect of multiple micronutrient supplementation was not found to be statistically significant on maternal health outcomes in Oh et al's review and therefore were excluded from this analysis [29].

2.2 Study Site

The study site was public primary health care facilities in South Africa. Public primary health care is delivered through a non- fee paying ,nurse-based, doctor-supported framework of over 3500 clinics and community health centres [68].

2.3 Measurement of health outcomes – Objective 1

To measure the health benefits resulting from both supplementation interventions, I made use of the disability adjusted life year (DALY). This is a generic measure of health effect that combines morbidity and mortality into one health metric (46). DALYs allow for comparability with previous cost effectiveness studies conducted. They also allow decision makers to compare health gains across different populations, diseases and interventions (48).

One DALY lost is interpreted as one year of healthy life lost. Consequently, one DALY averted is equivalent to the gain of one year of healthy life. DALYs are the sum of years of life lost due to premature mortality (YLL) and years lost due to disability (YLD) resulting from the disease. In this study, DALYs were estimated as YLL due to low birthweight, small for gestational age, stillbirth, and diarrhoea plus YLD due to low birth weight, small for gestational age and diarrhoea. The formula for calculation of DALYs is the following:

$$\mathrm{DALY} = \mathrm{YLL} + \mathrm{YLD}$$

where YLL and YLD are further expressed as follows:

$$\text{DALYs} = \sum YLL_{hs}(m_{hs}, LE) + \sum YLD_{hs}\,(dw_{hs}, L)$$ [69]

Where ***hs*** are health outcomes (stillbirth, low birth weight, small for gestational age and diarrhoea) , YLL_{hs} a function of mortality rate (m_{hs}) and the remaining life expectancy (LE) at age and YLD_{hs}, a function of the disability weight (dw_{hs}) associated with each health outcome and average duration of the health outcome until remission or death,(L). Benefits of supplementation were realised in the future in the form of averted mortality (neonatal mortality and stillbirths) and morbidity (small for gestational age and low birth weight) and lasted a lifetime. In order to estimate the present value of these benefits, a discount factor of 5% was applied to the length of effect, in line with the South African Pharmacoeconomic guidelines [70].

Life expectancy estimates for South Africa were obtained from the WHO life tables [71].Duration of disability associated with low birth weight and small for gestational age was assumed to be for their entire lifetime. YLD for the neonatal period were included in the DALYs calculation. Mortality as a result of low birth weight and small for gestational age was considered to occur only during the neonatal period because excess risk in mortality for this phenotype and in all children occurs during the first 28 days of life [72,73]. Three levels of diarrhoea were included in the analysis, mild diarrhoea with no treatment, moderate diarrhoea with outpatient care and severe diarrhoea with hospitalisation. Diarrhoea illness duration per episode was obtained from a systematic review that estimated diarrhoea duration and severity in children in LMICs. The case fatality rate for diarrhoea hospitalisation was also obtained from literature. [74].There is no evidence of long-term disability as a result of diarrhoeal illness in the literature and therefore, DALYs associated with diarrhoea were mostly based on the years of life lost, with YLD making a small contribution to diarrhoea-related DALYs [75].I assumed the same disability weight for low birth weight and small for gestational age obtained from the Global Burden of Disease 1990 as we could not find any recent estimates [76] .For diarrhoea disability weights, 2017 Global burden of Disease study estimates were used [75].DALY calculations were conducted in Microsoft Excel. Disability weights used in the study are represented in Table 2.2.

Table 2.2 Key input parameters for estimating DALYs

Parameter	Estimate	Source
Disability Weights		
Low birth Weight	0.11	57
Small for gestational age	0.11	57
Severe diarrhoea	0.25	77
Moderate diarrhoea	0.19	77
Mild diarrhoea	0.07	77
Mean duration of illness		
Severe diarrhoea	0.02301	74
Moderate diarrhoea	0.01753	74
Mild diarrhoea	0.01178	74
Life expectancy	65.25	71
Case fatality ratio diarrhoea hospitalisation	0.02	78

2.4 Measurement of supplementation Costs, health service utilisation and clinical management costs – Objective 2

An ingredients-based costing approach was adopted to estimate the economic burden associated with each study health outcome and the cost of the new intervention. Health care resources used, and quantities were identified from the national standard treatment guidelines and literature. The analysis considered only direct medical costs from a South African public healthcare system perspective. Direct health system costs considered included the price of supplementation, initial hospitalization at birth and costs of treating diarrhoea in hospital and in outpatient care in the first year of life. Initial costs of hospitalisation were considered because they represent the largest medical costs incurred by infants during the first year of life provided there is no serious illness experienced. Economic studies have found that gestational age is an important cost driver for hospitalisation costs [79].

As with previous studies, this analysis assumed that there was an immediate, absolute, 1-year switch from iron and folate supplementation to multiple micronutrient supplementation [56]. Because of unavailability of cost estimates, change over program costs involved such planning and rolling out the new program such as training of staff, costs of meetings and information, education and communication were not considered in the analysis. The assumption was made that these costs were negligible as the new intervention would make use of the same infrastructure and human resources as the old intervention. In the base case scenario, all pregnant women received and consumed 180 tablets and 100% of iron and folate tablets were replaced with multiple micronutrient tablets.

Supplementation prices for iron and folate supplementation were obtained from the Master Health Product List [80]. Multiple micronutrient supplement prices were obtained from the UNICEF Supply Catalogue and converted to South African rand using the average exchange rate in 2020[81] (1 USD = ZAR 14.79). Supplementation costs per patient were the product of the price of the supplement and the number of days the supplement was taken (180 days). Because no program costs were included in the analysis, the incremental costs associated with the supplementation program came from higher multiple micronutrient supplement costs.

For initial hospitalisation at birth , previous studies have found a longer hospital stay for low birth weight and small for gestational age babies compared to normal weight as they need special monitoring and care in the first few days or weeks of their life [79,82,84].We made the same assumption in our study [84].Due to a dearth of literature on complications due to low birth weight and small for gestational age infants, these cost of managing complications were excluded. South African-specific general ward daily facility fee cost estimate at secondary level hospitals were used and it was assumed that a specialist medical practitioner would be in attendance. Because the study population was made up of full-term babies, I assumed that incubation or special equipment would not be necessary for care. Hospitalised infants would receive care in a general neonatal ward. The daily facility fee accounts for overhead costs of providing care within general wards [83].Faciilty and professional fees were obtained from the

Uniform Patient Fee Schedule and length of stay estimates were obtained from the literature [83,84].Total costs of initial hospitalisation were calculated as follows :

$$
\begin{aligned}
&Direct\ medical\ costs\ for\ initial\ hospitalisation \\
&\qquad = (Facility\ fee\ per\ day\ \times length\ of\ stay) \\
&\qquad + (Practioner\ fee\ per\ day\ \times length\ of\ stay)
\end{aligned}
$$

Diarrhoeal illness was estimated for three levels of severity - that is severe, moderate and mild illness. Care pathways in the Standard Treatment Guidelines and Essential Medicines List at primary care level and hospital level paediatrics were used to identify resources used in treating diarrhoea [85].

Severe illness was defined as passing more than 10 watery stools in 24hours [86].Patients with severe diarrhoea suffer from severe dehydration and are assumed to be managed as inpatients. Length of hospital stay was identified from literature[93].Patients were assumed to be hospitalised for 4,09 days based on a previous study[93] .Inpatient costs for diarrhoea hospitalisation were the sum of health care facility fees, human resource costs, diagnostic tests and medication.

Secondary level hospital facility fees per day were used in the analysis and obtained from the Uniform patient fees schedule[83].Diagnostic tests included creatinine, potassium, sodium, HIV rapid test, blood acid base assessment and urine test strip [85]**.**Tests were assumed to be conducted once during the hospital stay. Diagnostic test prices were obtained from the National Health Laboratory Service 2018 state price list and prices were inflated to 2020 prices using the Consumer Price Index using the following formula [88].

$$Adjusted\ cost_{2020} = \ Cost_{2018}\, X\ \frac{CPI_{\ 2020}}{CPI_{2018}}$$

Where CPI is the Consumer Price Index, obtained from Statistics South Africa [89].

CPI_{2020}= 115.9; $CPI_{\ 2018}$ = 107.8

Specialist medical practitioner fees per day from the uniform patient fee schedule were used to estimate the human resource costs. Using data obtained from previous studies, and primary healthcare level standard treatment guidelines ,we assumed that each hospitalised diarrhoea case would receive six sachets of oral rehydration solution (ORS) treatment per day in the facility and two of dextrose 5% intravenous (IV) solutions during their stay[90].In addition, each patient would take 20mg of zinc supplements for 10 days[90].

Total costs for severe diarrhoea were calculated as follows:

$$\begin{aligned} &\mathit{Direct\ medical\ costs\ for\ inpatient\ care} \\ &\quad = (\mathit{Facility\ fee\ per\ day} \times \mathit{length\ of\ stay}) \\ &\quad + (\mathit{Practioner\ fee\ per\ day} \times \mathit{length\ of\ stay}) \\ &\quad + (\mathit{cost\ of\ diagnostic\ test} \times \mathit{number\ of\ tests}) \\ &\quad + (\mathit{cost\ of\ medication} \times \mathit{quantity\ used}) \end{aligned}$$

Moderate diarrhoea cases were defined as passing 6 to 9 stools in a day [86]. I assumed that mild dehydration was experienced, and care was sought at primary health care clinics. Patients were attended to by a primary health care nurse. Total costs per visit were calculated as below:

$$\begin{aligned} &\mathit{Direct\ medical\ costs\ for\ outpatient\ care} \\ &\quad = (\mathit{Facility\ fee\ per\ visit}) + (\mathit{Nurse\ Practioner\ fee\ visit}) \\ &\quad + (\mathit{cost\ of\ medication} \times \mathit{quantity\ used}) \end{aligned}$$

Facility fees and nurse practitioner fees were obtained from the uniform patient fee schedule. Using the primary healthcare level standard treatment guidelines, we assumed that patients would be prescribed 20mg oral Zinc for 14 days and were given 6 ORS sachets a day for 2 days [87].Treatment regimens were verified by a clinical paediatric expert.

Mild diarrhoea cases were defined as passing 3 stools in a day; no dehydration was experienced, and no treatment was sought for illness and therefore there were no costs incurred because of mild illness.

There was no discounting applied to any of the costs in the analysis as all expense were incurred during the first year of life. All costs were expressed in 2020 South African Rand (ZAR).

All resource-use inputs and costs were collated and analysed using Microsoft excel.

Table 2.3 Key input parameters for estimating healthcare costs

Parameter	Unit of measurement	Base Case	Source
Cost of supplements in ZAR			
Iron and folate	Per pregnancy	0.16	[80]
Multiple micronutrient supplements	Per pregnancy	0.26	[91]
Length of hospital stay in days			
Initial hospitalisation low birth weight & small for gestational age	Per stay	9.4	[84]
Initial hospitalisation low birth weight & appropriate for gestational age	Per stay	4.7	[84]
Initial hospitalisation normal weight & small for gestational age	Per stay	2.9	[84]
Initial hospitalisation normal weight & appropriate for gestational age	Per stay	1.9	[84]
Stillbirth	Per stay	2.80	[92]
Severe Diarrhoea	Per episode	4.09	[93]
Facility fees/day in ZAR			
Inpatient general ward	Per day	1073.00	[83]
Outpatient consultation	Per visit	104.00	[83]

Cost of human resources in ZAR			
Specialist medical practitioner	Per day	305.00	83
Nursing practitioner	Per visit	66.00	83
Costs of treatment in ZAR			
Diagnostic tests for severe diarrhoea	Per stay	243.14	94
Medication for diarrhoea	Per stay	38.71	80

2.5 Estimating Incremental Cost-Effectiveness Ratios - Objective 3

A decision tree developed in Microsoft excel was used to estimate the ICER of multiple micronutrient supplementation compared to iron and folate supplementation from a public health system perspective. The model estimates the expected costs and benefits of micronutrient supplementation and the comparator- iron and folate supplementation for a cohort of 100 000 pregnant women.

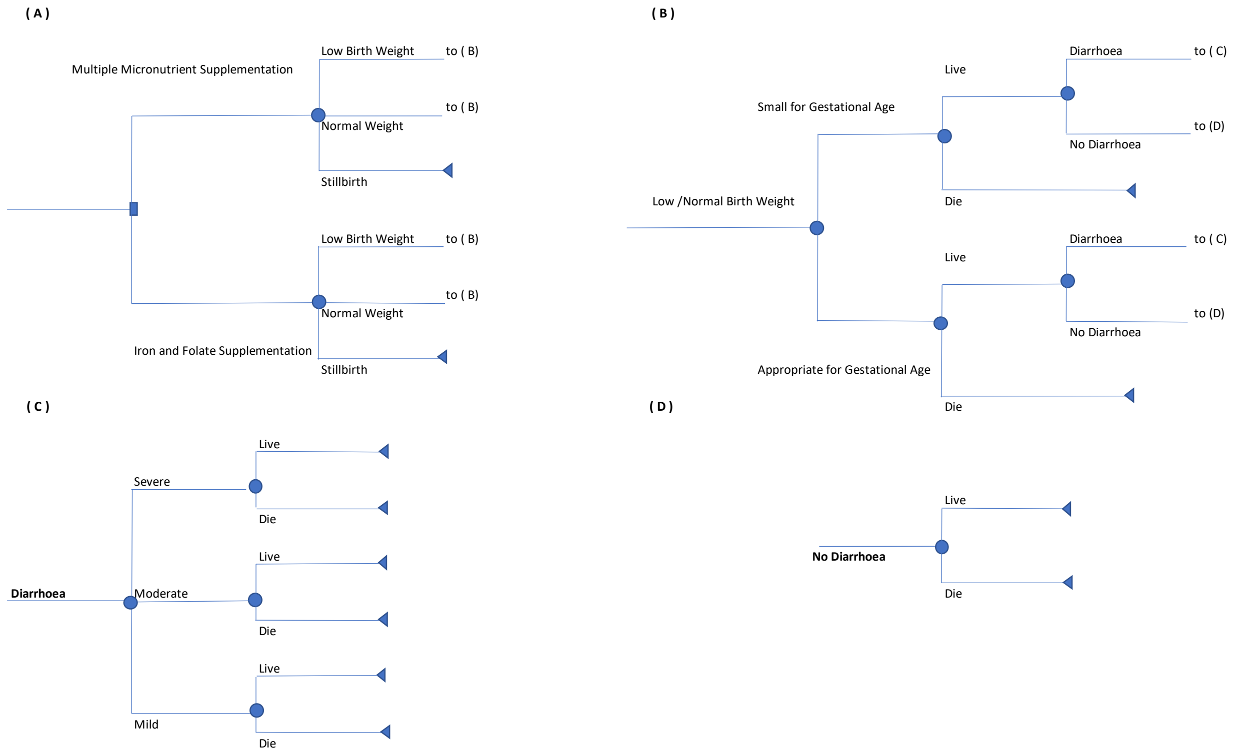

Figure 2.1 Decision analysis tree for multiple micronutrient supplementation versus iron and folate supplementation

Figure 2.1 represents the structure of the model. The model consists of two arms -current practice which is iron and folate supplementation and alternative practice which is multiple micronutrient supplementation (Figure 2.1A). At the initial decision node (represented by a square, Figure 2.1A), a cohort of 100 000 pregnant women either receives iron and folate supplementation or multiple micronutrient supplementation. Thereafter, they follow the respective arm or pathway leading to a chance node (circles) which represents possible consequences of the initial decision made. Pregnant women can either give birth to an infant that is low birth weight or normal weight or stillborn (Figure 2.1A). Those born low-birth weight or normal weight can either be small for gestational age (SGA) or appropriate for gestational age (AGA) (Figure 2.1B). They can either live or die during the neonatal period. If they live, they can proceed to develop diarrhoea or not in the first year of life. Those who develop diarrhoea may experience one of three levels of illness (Figure 2.1C) over the study's one-year time horizon: mild illness and they do not seek any form of medical treatment; moderate illness and they seek outpatient care and severe illness, and they are hospitalised. Patients can either live or die after diarrhoea illness (Figure 2.1D). Figure ID represents the mortality rate from diarrhoeal illness of children under 1.

The probabilities on each pathway stipulate the number of pregnant women that follow each branch, where the total probability for all the branches leaving a chance node is equal to 1 (or 100%). The joint probability of the sequences in the tree are calculated by multiplying all the probabilities for each path. The joint probability of each path was multiplied by the corresponding cost/health benefit and added up for each intervention to estimate the expected cost/health benefit for each pathway.

In the comparator arm of the model, baseline epidemiological data of the probabilities of low-birth weight, small for gestational age, diarrhoea and under 1 mortality rate were used to estimate cumulative probabilities for each chance node. In the multiple micronutrient supplementation arm of the model, these baseline estimates were modified by relative risk ratios representing the efficacy of multiple micronutrient supplementation against the four study health outcomes. In addition to probabilities, the model was populated with DALYs, and costs estimated from Objective 1 and 2, respectively. In the base case scenario, the model assumes that all pregnant women receive supplements and take them i.e., 100% coverage and adherence.

Table 2.4 Key input parameters for decision analytical model

Parameter	Base case value	Source
Probabilities		
Probability of LBW	0.15	[23]
Probability of LBW & SGA	0.79	[95]
Probability of Diarrhoea	0.648	[96]
Probability of severe diarrhoea	0.05	[74]
Probability of moderate diarrhoea	0.347	[74]
Probability of mild diarrhoea	0.648	[74]
Probability of stillbirth	0.04	[19]
Risk ratio		
Efficacy of MMS on LBW	0.85	[29]

Efficacy of MMS on SGA	0.93	[29]
Efficacy of MMS on stillbirths	0.91	[29]
Efficacy of MMS on diarrhoea	0.84	[29]
Mortality rates		
Neonatal mortality full term births	0.01	[97]
Neonatal mortality in normal weight infants	0.0069	[97]
Relative risk		
Neonatal mortality in low birthweight, SGA infants	8.2	[73]
Neonatal mortality in low birth weight, AGA infants	3.4	[73]
Neonatal mortality in normal weight, SGA infants	2.3	[73]

Incremental costs were estimated as the difference between the expected costs of the multiple micronutrient supplementation and iron and folate arms of the decision model; DALYs averted, as the difference between expected DALYs lost in the multiple micronutrient and iron and folate supplementation arms. Finally, the incremental cost effectiveness ratio (ICER) was estimated as the ratio between incremental costs and DALYs averted:

$$ICER = \frac{Costs^{Multiple\ Micronutrient\ Supplementation} - Costs^{Iron\ and\ Folate\ supplementation}}{DALYs^{Multiple\ Micronutrient\ Supplementation} - DALYs^{Iron\ and\ Folate\ supplementation}} = \frac{\Delta\ C}{\Delta\ E}$$

where C = Costs and E = Effects

The results of the cost effectiveness analysis were represented graphically on a cost effectiveness plane. The cost-effectiveness plane is divided into four quadrants as seen in Figure 2.2 [98].In Fig 2.2 the north-west(NW) and south-east (SE) quadrants have negative ICERs and are easy to interpret. In the (NW) quadrant, multiple micronutrient supplementation costs more but is less effective i.e., averts less DALYs than iron and folate supplementation. Iron and folate supplementation dominates multiple micronutrient supplementation, and the recommended decision would be to retain iron and supplementation. If the ICER falls in the (SE) quadrant, this implies that multiple micronutrient supplementation is less costly and is more effective i.e., averts more DALYs compared to iron and folate supplementation. In this instance, multiple micronutrient supplementation dominates iron and folate supplementation, and the recommendation would be to switch to multiple micronutrient supplementation. Figure 2.2 north-east (NE) and south-west (SW) quadrants have positive ICERs. In Figure 2.2 (SW) multiple micronutrient supplementation is less costly but also less effective than iron and folate supplementation. In the (NE) quadrant, multiple micronutrient supplementation is more costly and more effective than iron and folate supplementation [45]. There is generally an unwillingness by policy makers to pursue an intervention if it is less effective than existing interventions (SW) and therefore most attention is focussed on treatments with ICERs falling in the (NE) quadrant [99]. The question that we face is whether the additional benefits realised from the new intervention are worth the additional costs incurred to achieve them[61].In order to make this decision we make use of the cost effectiveness threshold.

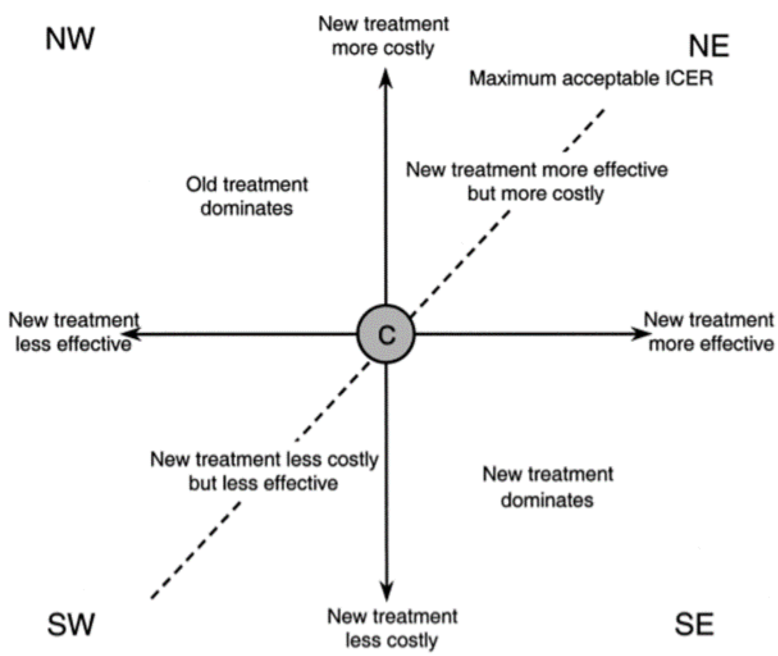

Figure 2.2 Decision rules and the cost effectiveness plane[45]

2.6 Cost effectiveness threshold

The ICER is typically compared to a reference ICER or a "benchmark" value called the cost-effectiveness threshold (λ) in order to determine whether the new intervention is cost effective [60].The threshold represents the value of health given up elsewhere in the health system if the health system incurs additional costs on a fixed budget [100,101]. The most widely cited threshold to date is the WHO recommendation of one- and three-times GDP per capita per DALY averted. This is a "demand side" value,based on estimates of individual or societal willingness to pay for additional health benefits. It is representative of what society or individuals are willing to give up 'outside' the health system for additional health gains [60]. Considering the resource constraints faced by the South African government, introducing new health interventions would most likely lead to displacement of other health services. I therefore used a South African specific threshold that reflected the health opportunity cost of health spending or marginal productivity of health spending instead[60].This is a "supply-side" threshold that represents the value of health forgone in the health system when additional costs are imposed on with a fixed budget [60].This marginal productivity of health spending is represented by the gradient of the dashed line in Figure 2.2 [98] Health interventions with ICERs that lie below the threshold are considered to be cost-effective or represent good value for money and should be adopted and the opposite is true for those that lie above the threshold [102].A South -African specific cost per DALY averted threshold of ZAR 38 500.00/DALY averted was used in order to determine whether multiple micronutrient supplementation was cost effective or not..

2.7 Sensitivity analyses

A deterministic sensitivity analysis in the form of one-way analysis was be performed to assess the impact of parameter uncertainty on the ICER. Univariate sensitivity analysis varied the base case values of a parameter one at a time whilst keeping all other model inputs constant [45].For upper and lower variable estimates for probabilities and relative risks of health outcome variables, supplementation efficacy estimates and length of hospital stay, I used upper and lower 95% confidence limits derived from the literature [103]. In the absence of confidence intervals around cost parameters,+/- 50% was used as it provides a wide interval for cost variation. Initial hospitalisation costs for all disease pathways and treatment of diarrhoea costs were included in the analysis.

For ease of interpretation, I applied univariate sensitivity analysis on the incremental net monetary benefit (INMB). INMB was calculated as follows:

$$INMB = \Delta E \times \lambda - \Delta C$$

where E = effectiveness (expressed in DALYs), λ = willingness to pay threshold and C = Cost

A positive INMB indicates that multiple micronutrient supplementation is the preferred strategy. In addition to the one-way sensitivity analysis, a probabilistic sensitivity analysis was conducted to evaluate the uncertainty in model inputs jointly. Probabilistic sensitivity analyses were conducted to quantify the combined uncertainty around the model inputs and model parameters and how this affects the ICER. I did this by assigning probability distributions to each uncertain parameter and using Monte Carlo simulation to repeatedly draw from each distribution 1000 times, each time calculating respective ICERs. For probabilities and disability weights, beta distributions were used as they restrict values range between 0 and 1. Log-normal distributions were assumed for relative risks and gamma distributions were used for costs to avoid negative values.

The results of the probabilistic sensitivity analysis are presented on a cost-effectiveness plane as a scatter plot and cost-effectiveness acceptability curves (CEAC). The CEAC is a graphical representation summarizing uncertainty on the result of an economic evaluation. It is constructed by plotting the proportion of the costs and effect pairs that are cost-effective for a range of values of λ.

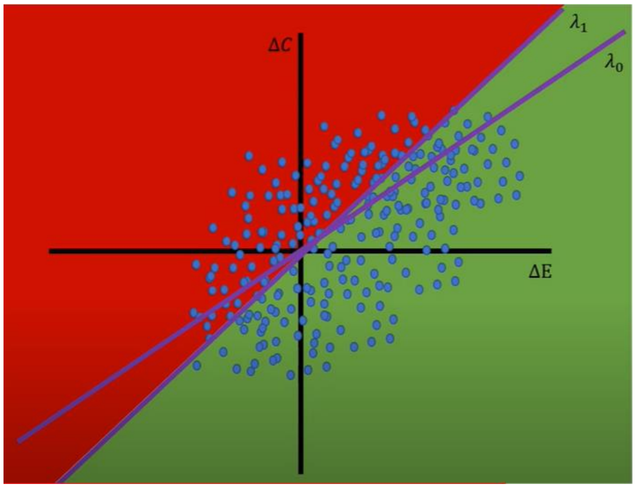

Figure 2.3 Cost-Effectiveness plane[104]

On the incremental cost-effectiveness plane (Fig 2.3), cost-effective pairs are represented by the proportion of incremental cost-effect pairs lying to the south and east of the purple line that runs through the origin (slope equivalent to the x-axis i.e., λ = 0). This is then repeated for λ values until the slope of the line is equivalent to the y-axis (infinity is reached)[105] .The output is shown as the cost-effectiveness acceptability curve in Figure 2.4.

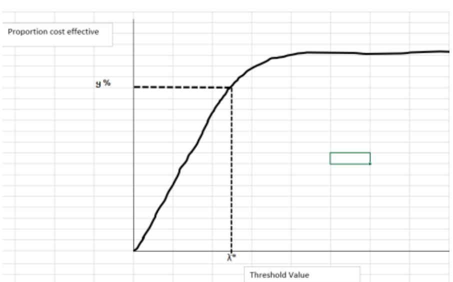

Figure2.4 Cost-effectiveness acceptability curve[104]

At a threshold value of λ*, the probability that the new intervention is cost effective is y%.

CHAPTER 3: RESULTS

3.1 DALYs associated with study health outcomes

Table 3.1 shows the DALYs averted per pregnancy estimates for decision pathways in the model. Low birth weight and SGA had the same DALY estimates because the same disability weight was used in their estimation. A disability weight for small for gestational age could not be found and therefore the assumption was made that it was the same as low birth weight. The length of effect of low birth weight and SGA was assumed to last a lifetime. The highest number of DALYs per pregnancy were recorded in decision pathways that ultimately resulted in death. Low birth weight and SGA infants that died from severe diarrhoea had the highest DALY estimates of 21.29. YLL contributed nearly 100% to the DALY estimates in this pathway as the total years of life lived with low birth weight or SGA was only 2.04 DALYs. Years lived with diarrhoea was negligible. Stillbirths had the second highest DALY estimate and because there is no time lived with disease, YLL made up the entire DALY estimate. Low birth weight and SGA infants who died during the neonatal period had the third highest DALY estimate and again, YLD estimates were negligible due to the short duration of survival. There was a marginal difference in DALY estimates for health outcomes that did not result in death.

Table 3.1 Discounted DALY estimates

	Low birth weight & / SGA		Diarrhoea		Total Discounted DALYs
	YLD	YLL	YLD	YLL	
Low birth weight & / SGA – Severe Diarrhoea	2.05	0	0.0057	0	2.04
Low birth weight & / SGA – Severe Diarrhoea - Death	2.05	0	0.0057	19.21	21.29
Low birth weight & / SGA – Moderate Diarrhoea	2.04	0	0.0033	0	2.04
Low birth weight & / SGA – Mild Diarrhoea	2.04	0	0.0009	0	2.04
Low birth weight & / SGA – Death	0.01	19.15	0	0	19.16
Stillbirth	0	19.23	0	0	19.23

3.2 Supplementation costs and clinical care management costs of study health outcomes

3.2.1 Costs of supplementation

The health system costs associated with the respective supplementation regimens are presented in Table 3.2. Only supplementation costs were considered and no program costs. Multiple micronutrient supplement cost was found to be higher than Iron and folate with the incremental cost estimated at R0.10/tablet and R18/pregnancy.

Table 3.2 Supplementation costs

	Iron and folate supplementation	Multiple Micronutrient supplementation	Incremental Costs
Cost/tablet (ZAR)	0.16	0.26	0.10
Quantity	180	180	180
Total cost/pregnancy (ZAR)	28.74	46.69	18

3.2.2 Costs of treatment

Table 3.3 shows the direct medical costs associated with normal weight, low birth weight, small for gestational age, still birth and diarrhoea.

Table 3.3 Costs of healthcare utilization

Health Outcomes		Total cost/stay
Initial hospitalisation	Low birth weight & SGA	12953
	Low birth weight & AGA	6477
	Normal weight & SGA	3996
	Normal weight & AGA	2618
Still birth		3858
Moderate diarrhoea-outpatient care		225
Severe diarrhoea - hospitalisation		5918

Costs for initial hospitalisation per stay were highest in infants with both low birth weight and small for gestational age estimated at R 12 953.20 per infant. Compared to appropriate for gestational age babies, SGA babies cost significantly more. The cost of hospitalisation for infants that are low birth weight & SGA (R 12 953) was double that of low birth weight & AGA infants. Still birth deliveries cost R 3858.40 per delivery more than normal weight & AGA infants. Stillbirth infants cost the health system R1 240.20 more than normal weight & AGA infants and slightly less than normal weight & SGA at R137.80.

We considered costs for severe and moderate diarrhoeal illness only and assumed that mild cases did not seek treatment. Severe cases were hospitalised, and moderate cases received treatment at an outpatient facility. Treatment at an outpatient facility for moderate diarrhoea cost R 225.17 per incident. Hospitalisation from severe illness resulted in a total cost per hospital stay of R 5917.87.

3.3 Incremental cost effectiveness ratio

In Table 3.4, the number of cases of each health outcome per 100 000 pregnancies are shown. Switching to multiple micronutrient supplementation resulted in a decrease in the number of cases for all the health outcomes except for normal weight. The highest number of cases averted was recorded for normal weight children who were small for gestational age with 2 138 cases averted per 100 000 pregnancies. Multiple micronutrient supplementation also resulted in a higher number of normal weight and appropriate for gestational (AGA) age infants. An additional 4721 normal weight AGA were recorded.

Table 3.4 Number of cases averted per 100 000 pregnancies

	Multiple micronutrient supplementation	**Iron and folate supplementation**	**Cases averted**
Number of cases			

Low Birth Weight & SGA	10073	11850	1778
Low Birth Weight	2678	3150	473
Normal weight & SGA	50707	52845	2138
Normal weight & AGA	33176	28455	-4721
Stillbirths	3367	3700	333
Diarrhoea	7856	9449	1593

Table 3.5 shows the incremental costs and incremental DALYs from the simulation of 100 000 pregnancies. The table shows the total costs and DALYS associated with each health state for each supplementation regimen for example costs associated with low birth weight and SGA infants in the multiple micronutrient supplementation arm who suffered from severe diarrhoea totalled ZAR 1468979.80. Approximately 1493 DALYs from this population group were averted. The same population group under the iron and folate arm, incurred ZAR 2055442.54 in costs and 2090 DALYs were averted. Stillbirths represented by far the highest DALYs averted with 6 403.95 DALYs averted per 100 000 births. Following stillbirths were infants that born SGA. Infants born SGA who did not experience diarrhoeal illness had the second and third highest number of DALYs averted with normal weight SGA infants recording 2432 DALYs averted and low birth weight SGA with 2412 DALYs per 100 000 pregnancies. The lowest estimate for DALYs averted were recorded for infants born normal weight and AGA because there was no disability or years of life lost attached to normal weight AGA. Total DALY estimates were derived solely from diarrhoeal illness. Normal birth weight AGA infants who suffered from mild diarrhoea had 0 DALYs averted and those with moderate diarrhoea averted 2.88 DALYs per 100 000 pregnancies. Severe diarrhoea DALY estimates were lower than moderate diarrhoea at 1.02 DALYs averted per 100 000 pregnancies because of the lower incidence of severe diarrhoea in normal birth weight AGA compared to moderate diarrhoea.

The highest incremental cost estimates were for normal birth weight AGA infants who did not experience diarrhoeal illness. Despite having shorter hospital stays and no additional costs from diarrhoeal illness, normal weight AGA infants had the largest number of incremental cases ,4 721 per 100 000 pregnancies (see Table 3.4), translating into higher costs of initial hospitalisation. An increase in the number of normal weight AGA infants also led to a higher cost of death during the neonatal period. Multiple micronutrient supplementation does not influence neonatal mortality and thus mortality rate remained the same. Highers numbers of normal weight AGA infants in the multiple micronutrient supplementation arm translated to higher mortality figures in the neonatal period compared to the iron and folate arm and higher incremental costs.

Table 3.5 Base case cost effectiveness results (ZAR 2020)

		Multiple micronutrient Supplementation		Iron and Folate Supplementation			
Health State		Costs	DALYs Lost	Costs	DALYs Lost	Costs averted	DALYs averted
Low birth weight & SGA	Severe Diarrhoea	1468979.80	1492.39	2055442.54	2090.18	586462.73	597.79
	Moderate Diarrhoea	5656302.50	873.40	7911240.00	1223.26	2254937.50	349.85
	Mild Diarrhoea	9453599.31	1483.28	13222053.16	2077.42	3768453.86	594.14
	Live No Diarrhoea	107509678.39	16861.13	122721689.14	19273.50	1521201.75	2412.37
	Die	7408663.96	10921.09	8704040.26	12848.12	1295376.30	1927.04
Low birth weight & AGA	Severe Diarrhoea	265817.88	51.88	371756.80	72.66	105938.93	20.78
	Moderate Diarrhoea	794176.11	240.32	1109332.92	336.58	315156.81	96.26
	Mild Diarrhoea	1305273.02	408.13	1823083.09	571.61	517810.07	163.48
	Live No Diarrhoea	14844026.91	4639.42	16921111.54	5303.20	2077084.63	663.77
	Die	409754.92	1203.71	480738.12	1416.11	70983.20	212.40
Normal weight & SGA	Severe Diarrhoea	1885178.01	386.93	2334658.63	570.11	449480.61	183.17
	Moderate Diarrhoea	5605956.94	2682.25	6925860.96	3327.78	1319904.02	645.52
	Mild Diarrhoea	9227817.65	4655.56	11397795.13	5775.98	2169977.47	1120.43
	Live No Diarrhoea	186447336.42	94024.95	190420621.64	96456.92	3973285.21	2431.98
	Die	3253412.35	15421.01	3375516.53	16070.86	122104.18	649.85
Normal weight & AGA	Severe Diarrhoea	1070208.35	48.62	1092766.06	49.65	22557.71	1.02
	Moderate Diarrhoea	37767,18	0.04	2543137.64	2.92	2505370.46	2.88
	Mild Diarrhoea	4015846.09	1.31	4072871.72	1.34	57025.63	0.03
	Live No Diarrhoea	81139857.20	0.00	68044631.04	0.00	-13095226.17	0.00
	Die	610026.67	4378.42	519698.88	3762.41	-90327.79	-616.01
Still birth		13148438.03	64751.04	14382418.00	71154.99	1233979.97	6403.95

Compared to iron and folate supplementation, micronutrient supplementation averted an additional 24264.67DALYs and resulted in a cost saving of R26 106 326.08 per 100 000 pregnancies.

Table 3.6 summarizes the cost-effectiveness results of the model. Assuming base case values across all variables, multiple micronutrient supplementation proved to be dominant over iron and folate supplementation being both less costly and more effective than its comparator. Multiple micronutrient supplementation averted an additional 0.24 DALYS and a cost saving of R248.72 per woman compared to iron and folate supplementation.

Table 3.6 Summary of cost-effectiveness results

	Multiple micronutrient Supplementation		Iron and Folate Supplementation			
Health State	Costs	DALYs Lost	Costs	DALYs	Costs	DALYs
				Lost	averted	averted
Low birth weight & SGA	131497224	31631.29	154614465.1	37512.48	9426432	5881.19
Low birth weight & AGA	17619048.84	6543.46	20706022.47	7700.16	3086974	1156.69
Normal weight & SGA	206419701.4	117170.7	214454452.9	122201.65	8034751	5030.95
Normal weight & AGA	86873705.49	4428.39	76273105.34	3816.32	-1.31	-612.08
Still birth	13148438.03	64751.04	14382418	71154.99	1233980	6403.95
Total/100000	468706555.7	289275.92	494812881.8	313540.59	26106326,08	24264.67
Total/person	**4687.07**	**2.89**	**4948,128818**	**3.14**	**261.06**	**0.24**

3.4 Sensitivity analysis

Univariate sensitivity analyses were conducted on all variables by varying input values between the lower and upper bound presented in Table 3 and Table 12. Results in terms of incremental costs, incremental DALYs, and incremental net monetary benefit (INMB) are summarised in Table 3.7 and presented as a tornado diagram in Figure 3.1.

Table 3.7 One -way sensitivity analysis (INMB in ZAR)

Parameter	Low	High
Base case incremental net monetary benefit	712509438	
Discount Rate	20 073	9786,45
Efficacy of MMS on SGA	480 032 834	944 985 510
Efficacy of MMS on stillbirths	535 095 974	839 233 340
Efficacy of MMS on LBW	631 316 719	793 702 141
Probability of LBW	667 204 892	792 662 796
Probability of severe diarrhoea	697 665 168	737 249 888
Probability of LBW & SGA	689 339 093	716 074 106
Initial hospitalisation costs LBW SGA	700 997 282	724 021 595
Multiple micronutrient supplementation costs	745 501 150	767 614 345
Efficacy of MMS on diarrhoea	707 307 267	717 710 894
Initial hospitalisation costs normal weight SGA	708 238 047	716 780 829
Initial hospitalisation costs normal weight AGA	717 571 221	709 883 621
Initial hospitalisation costs LBW AGA	710 979 294	714 039 535
Initial hospitalisation costs stillbirth	711 867 014	713 151 862
Probability of moderate diarrhoea	712 109 965	712 909 854
Costs of treatment severe diarrhoea	712 249 513	712 769 364
Costs of treatment moderate diarrheal diseases	712 449 762	712 581 428
Probability of diarrhoeal illness	712 509 438	712 509 438

The results of the univariate sensitivity analysis (Table 3.7 and Figure 3.1) showed that multiple micronutrient supplementation had a positive INMB over the complete range of parameters and was therefore cost effective. Model results were most sensitive to uncertainty on discounting of health benefits followed by the efficacy of multiple micronutrient supplementation on small for gestational age. The model also showed sensitivity to efficacy of multiple micronutrient supplementation on stillbirths and low birth weight and the probability of low birth weight. The costs of multiple micronutrients had some impact on model results and the probability of diarrhoeal illness and costs of treating diarrhoea had no impact on model results.

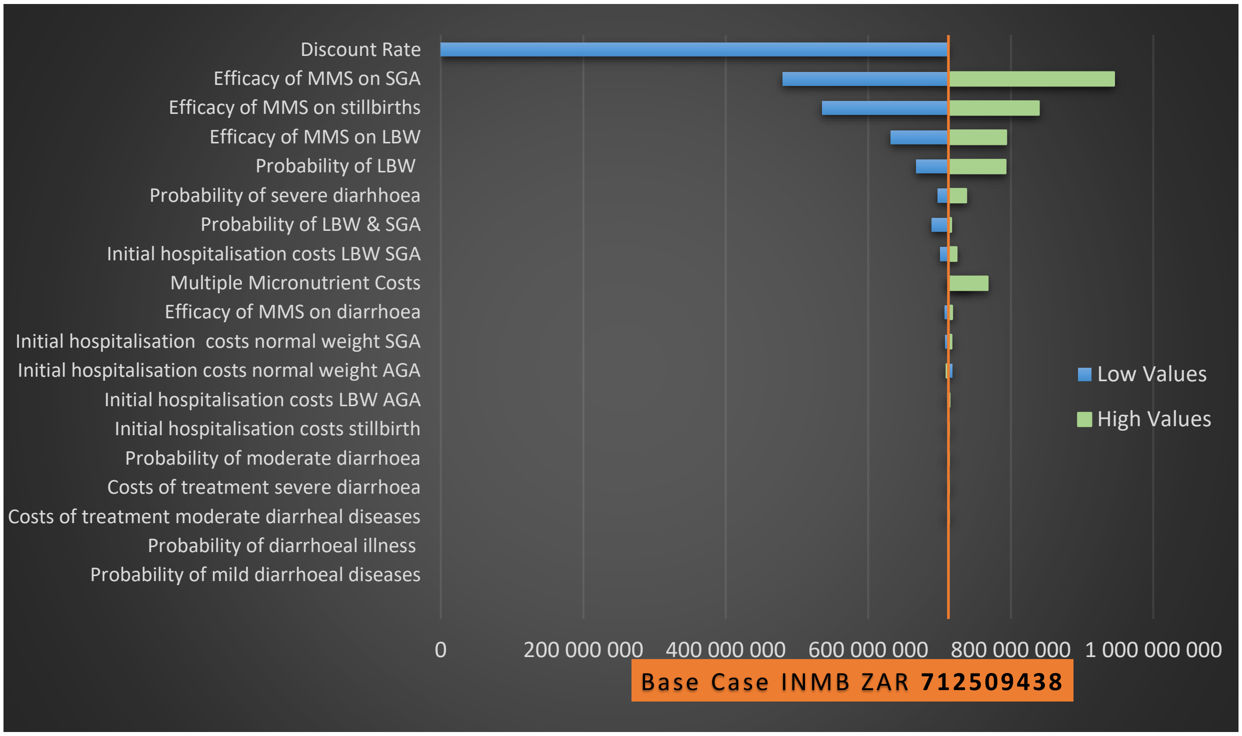

Figure 3.1 Tornado diagram summarizing one-way sensitivity analysis

Probabilistic sensitivity analysis

To assess the uncertainty in model input parameter estimates simultaneously, we conducted a probabilistic sensitivity analysis by fitting distributions (shown in Table 3.8) to the deterministic estimates of the variables and running 1000 iterations of a Monte Carlo simulation. The results are presented in Figure 3.2.

Table3.8 Model parameters: Base case and sensitivity analysis

Parameter	Base case value	Low Estimate	High Estimate	Standard error	Distribution	alpha	beta	Source
Probabilities								
Probability of LBW	0.15	0.085	0.265	0.045918367	Beta	8.920444444	50.54918519	23

Probability of LBW & SGA	0.79	0.53	0.83	0.076530612	Beta	21.58706389	5.73833344	95
Probability of Diarrhoea	0.648	0.0403	0.14	0.025510204	Beta	226.4769315	123.024506	96
Probability of severe diarrhoea	0.05	0.02	0.10	0.020408163	Beta	5.65238	107.395125	74
Probability of moderate diarrhoea	0.347	0.297	0.397	0.025510204	Beta	120.47451	226.7142826	74
Probability of mild diarrhoea	0.648	0.598	0.698	0.025510204	Beta	226.47693	123.024506	74
Risk Ratio								
Efficacy of MMS on LBW	0.85	0.77	0.93	0.040816327	Log-normal	-0.163670524	0.047991561	29
Efficacy of MMS on SGA	0.93	0.88	0.98	0.025510204	Log-normal	-0.072946763	0.027425169	29
Efficacy of MMS on stillbirths	0.91	0.86	0.98	0.030612245	Log-normal	-0.094876179	0.033630318	29
Efficacy of MMS on diarrhoea	0.84	0.76	0.92	0.040816327	Log-normal	-0.175532532	0.04856222	29
Relative risk/Hazard Ratios								
Neonatal mortality in LBW & SGA	8,20	8	8,4	0,102040816	Log-normal	2,104056734	0,01244352	74
Neonatal mortality in LBW & AGA	3,40	3,1	3,7	0,153061224	Log-normal	2,103959975	0,018664377	74
Stillbirth rate	2,80	1	5,6	1,173469388	log-normal	0,948712383	0,402261195	92
Total Cost/patient/day								
Initial Hospitalisation LBW SGA	12953.20	6476.6	19429.80	3304.39	Gamma	16.39	816.30	
Initial Hospitalisation LBW AGA	6476.60	3238.3	9714.90	1652.19	Gamma	16.39	408.15	
Initial Hospitalisation Normal Weight SGA	3996.20	1998.1	5994.30	1019.44	Gamma	16.39	251.84	
Initial Hospitalisation Normal weight AGA	2618.20	1309.1	3927.30	667.91	Gamma	16.39	165.00	
Severe Diarrhoea	5917.87	2958.94	8876.81	3304.39	Gamma	16.39	816.30	
Moderate Diarrhoea	216.59	108.30	324.89	1509.66	Gamma	16.34	373.50	
Still birth	3858.40	192.2	5787.60	55.25	Gamma	15.37	14.10	
Disability Weights								
Low birth weight	0.11	0,0265	0,1325	0,027	Beta	13,63	114,97	76
Small for gestational age	0.11	0,0265	0,1325	0,027	Beta	13,63	114,97	76
Mild diarrheal diseases	0.07	0.049	0.104	0.014	Beta	25.68	321.40	77
Severe diarrheal diseases	0.25	0.164	0.348	0.047	Beta	20.60	62.81	77

Moderate diarrheal diseases	0.19	0.125	0.264	0.035	Beta	22.64	97.77	77

The simulated cost effectiveness pairs are represented in the cost-effectiveness plane (Figure 3.2). 99% of the simulations fell below the threshold indicating that the ICERs are robust to uncertainty in model parameters and multiple micronutrient supplementation is cost effective (Figure 3.2).

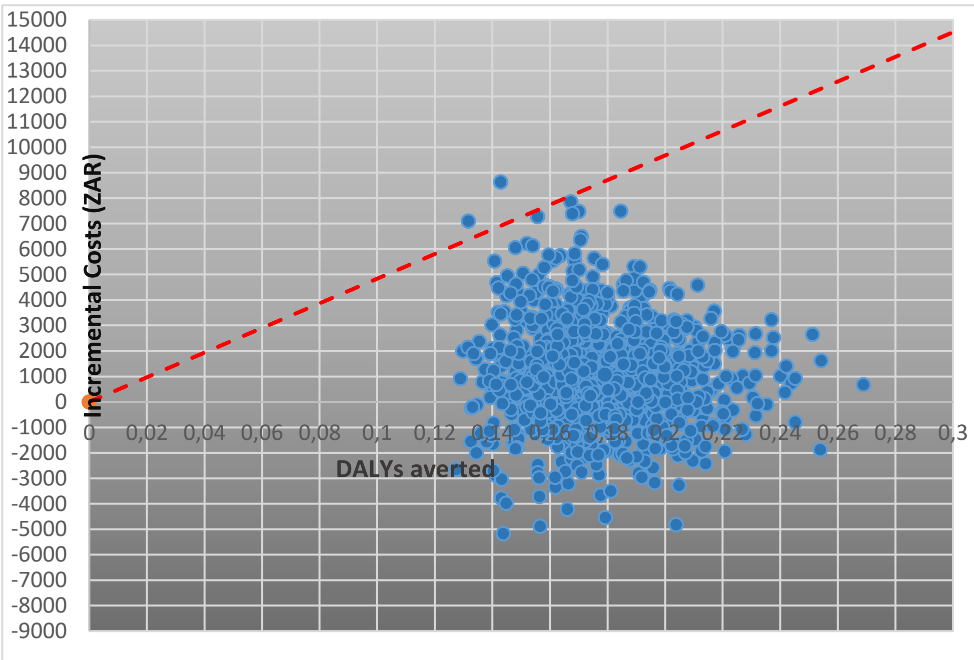

Figure 3.2 Probabilistic sensitivity analysis- cost effectiveness place

Figure 3.3 is a CEAC which shows the probability that multiple micronutrient supplementation is cost-effective compared with iron and folate supplementation at different cost-effectiveness thresholds. The horizontal axis represents a range of cost-effectiveness thresholds and the vertical axis is the probability of the intervention being cost-effectiveness [105].Figure 3.3 shows that at R38 500, 99% of all simulations fell under the cost effectiveness threshold and multiple micronutrient supplementation was the cost-effective option across all simulations. Therefore, our analysis suggests that multiple micronutrient supplementation is cost effective and should be recommended for use in pregnant women.

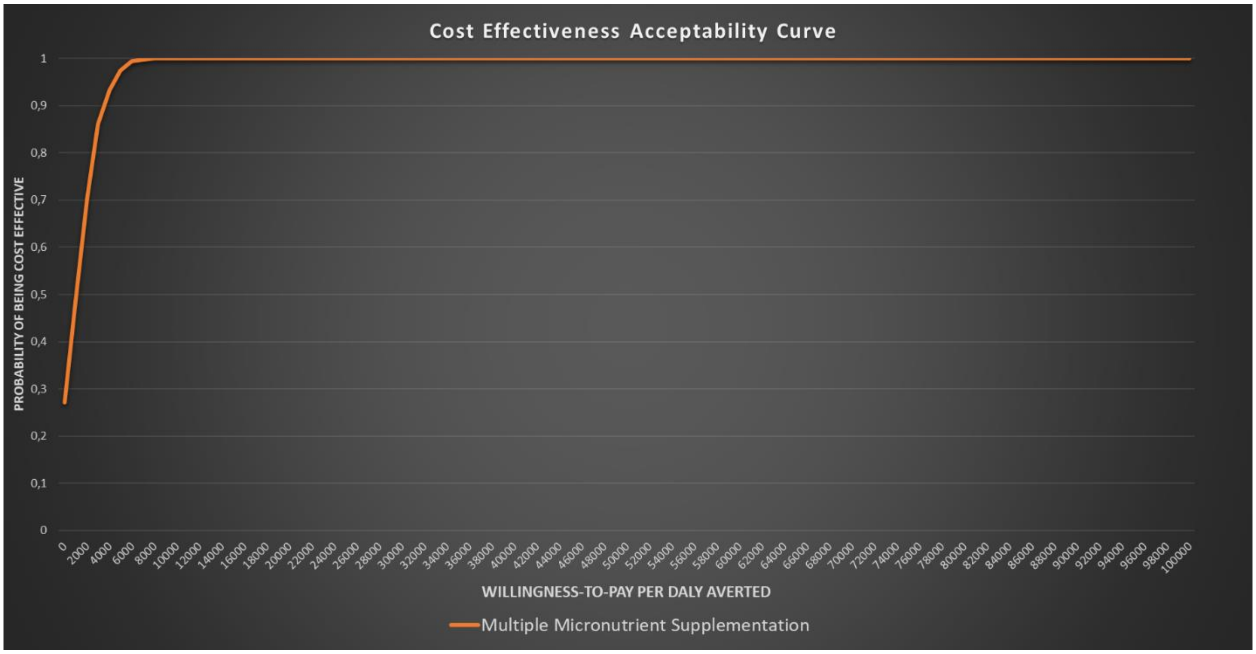

Figure 3.3 Cost-effectiveness acceptability curve

Chapter 4: DISCUSSION

4.1 Summary Key Findings

The primary aim of this study was to assess the cost effectiveness of introducing multiple micronutrient supplementation to replace iron and folate supplementation in the South African public health care system. The study was done from a public health care payers' perspective. We developed an economic model that analysed the costs and benefits associated. Our analysis found that multiple micronutrient supplementation was the dominant strategy.

There are considerable health benefits to be realised from switching supplementation regimens. A total of 1 778 low birth weight and SGA ,473 low birth weight and SGA ,2 138 SGA ,333 stillbirths and 1 593 diarrhoea cases per 100 000 pregnancies a year could be averted because of changing supplementation regimen. An estimated additional 4721 normal birth and AGA births were recorded. In total health, switching to multiple micronutrient supplementation resulted in 17860,70 DALYs averted per 100 000 pregnant women per year or 0.18 DALYs averted for each pregnant woman.

Multiple micronutrient supplementation was cost saving in our analysis. Costs associated with multiple micronutrient supplements were approximately R 4 555.58 vs approximately R 4804.30 for iron and folate supplementation per patient representing a total cost saving of R 248.72 per pregnant woman. The highest costs per day were incurred by low birth weight and SGA infants for both interventions. This was driven by longer lengths of hospital stays. There is a paucity of data available on complications arising from low birth weight or SGA infants that are full-term and therefore there was no costing of any complications associated with these outcomes nor were costs of further medical care after initial hospitalisation discharge included in this study. As a result, there is a likelihood that health system costs associated with low birth weight and SGA in the first year of life were underestimated and that multiple micronutrient supplementation is likely to be even more cost saving than the base case estimate.

The analysis by Nutrition International on replacing iron and folate supplementation with multiple micronutrients in South Africa assumed that all costs associated with the transition other than supplement costs were approximately USD $ 2 million in the first year and an additional investment of USD $5 096 423 over 10 years. Due to lack of methodological clarity as to the basis of this estimate, I didn't include it in this study. Although program costs associated with introducing multiple micronutrient supplementation into the public health system were excluded in this analysis, it is likely that health system cost savings from introducing multiple micronutrient supplementation will offset these additional costs and multiple micronutrient supplementation would still be the more cost-effective option. The same human resources, infrastructure and supply mechanisms used in the distribution of iron and folate supplements would be used for the multiple micronutrient supplementation. Additional program costs to be incurred would be 'information, education and communication" activities and staff training. To account for these potential costs in the analysis, cost figures for the parameters were inflated by 50% in the one-way sensitivity analysis and none of the variation in costs resulted in a negative net monetary benefit. However, program costs should be included in further analysis. and these would most likely not affect the dominance of the new intervention

The univariate sensitivity analysis suggests that the INMB is most sensitive to the discount rate. We analysed model results at a discount rate of 0% and 5% for years of life lost. Under both scenarios, multiple micronutrient supplementation was found to be cost effective. INMB values in all parameters varied in univariate analysis were positive and therefore multiple micronutrient supplementation was cost effective across all parameter inputs varied.

Probabilistic sensitivity analysis revealed some uncertainty surrounding the results of the cost-effectiveness analysis. The ICER values of the model varied greatly from the base-case estimate. Results ranged from dominance in the south-east quadrant to being more costly and more effective in the north-east quadrant. The cost effectiveness plane showed that most of the uncertainty in the ratios came from the difference in effect between multiple micronutrient supplementation and iron and folate supplementation. The cost effectiveness acceptability curves showed that at a willingness to pay threshold of R38 500, the probability that multiple micronutrient supplementation was cost effective was 100%

4.2 Consistency of results with previous economic literature

This study found results that were consistent with analysis of in other settings. Like previous studies, it was found that low birth weight and SGA infants incurred higher costs of hospitalisation compared to normal birth weight infants [106]. Compared to normal birth weight infants, low birth weight and SGA births incur higher rates and increased periods of hospitalization, rehospitalization and outpatient visits translating into higher health system utilization costs[106]. [106].Lim et al found that an inverse relationship existed between birth weight or gestational age and the cost of hospitalization during the neonatal period [82]. A study in Mozambique found that an increase of 100 gr in the average weight at birth of a low birth weight baby resulted in 53% reduction of the average costs incurred by households in seeking routine health care[107]. In Canada low birth weight accounted for 37% of the total cost of health system utilization despite being only 7% of the live births[106] .

In my analysis switching to multiple micronutrient supplementation was cost effective in the South African setting. Prior cost effectiveness studies in Bangladesh, Burkina Faso, South Africa, Pakistan, and India found multiple micronutrient supplementation to be more cost effective than iron and folate supplementation. ICERs were positioned in the northeast quadrant of the cost effectiveness plane, with multiple micronutrient supplementation costing more as well as having more benefits than iron and folate supplementation. This study found multiple micronutrient supplementation to be the dominant strategy costing less and having greater benefits compared to iron and folate supplementation. Unlike previous studies, our cost estimation for multiple micronutrient supplementation was less than its comparator because we used different costs estimates and health outcomes in our analysis. Shaheen and Svefors et al both considered only supplementation program costs and excluded any costs related to health benefits. Engle -Stone and colleagues only considered costs of supplementation tablets and no program costs or costs related to the health benefits. This study costed costs of supplementation tablets and costs associated with health benefits but did not include program costs. Our probabilistic sensitivity analysis reported ICERs that were consistent with other authors and the majority of our joint distribution results were cost effective and in the northeast quadrant of the cost effectiveness plane.

The Nutrition International analysis on South Africa found multiple micronutrient supplementation to be very cost effective at $15.80 per DALY averted. A number of differences existed between my analysis and theirs that resulted in the difference in results. They used the Lancet scenario for health effect while we used the latest review from Oh at el. As a result, additional health benefits such as neonatal mortality and preterm birth were included in their analysis. Higher DALY estimates would have made the intervention more cost effective. A time horizon of 10 years was considered for both costs and benefits and we considered costs incurred in one year and lifetime benefits accrued from that. Coverage estimates for supplementation in the Nutrition International analysis were quite low as they pegged it at 30% and we assumed 100% coverage. Lastly, there was no mention of discounting in their analysis, and our analysis discounted health benefits at a discount rate of 5 %. Our sensitivity analysis found discounting to have the greatest influence on the ICER value and excluding discounting from the analysis resulted in a higher estimate of the ICER. Prices of iron and folate supplementation in -The Nutrition International analysis were slightly higher compared to my analysis ($2.27 vs $ 1.94). This is because I used South African specific estimates in our study.

4.3 Strength of study

This analysis explicitly estimates the benefits and the costs associated with shifting from iron and folate supplementation to multiple micronutrient supplementation in South Africa. Although previous analysis in South Africa have been conducted our study differed in the following: It makes use of the latest efficacy data available in literature and looks at health benefits accrued over a person’s lifetime. Recent evidence has shown that multiple micronutrient supplementation reduces diarrhoea in children under 5. This study is the first to include diarrhoea as a health outcome in an analysis comparing the cost effectiveness of iron and folate with multiple micronutrient supplementation. It also used South African specific data for most of our cost estimates. Cost effectiveness was established by comparing results of the model to a South African specific cost-effectiveness threshold.

4.4 Limitations

Time constraints for this research project precluded primary data collection to ascertain full programme costs of the two interventions. It was assumed that costs of implementing the two interventions would be comparable. We have had to assume that the only program costs involved in changing from iron and folate supplementation to multiple micronutrient supplementation is the extra cost of the UNIMMAP supplement compared to iron and folate. It is assumed that the new supplement does not incur any additional supply chain, storage, or administration costs. It is also assumed that no additional activities are required in terms of training, planning, or monitoring and evaluation. Program costs and costs associated with the health outcomes such as follow up hospital visits beyond the one-year period could have been included in the analysis. These assumptions and exclusions likely biased our cost estimates.

Due to the unavailability of South African specific medical care price index, the consumer price index was used to adjust prices for inflation. This might not be an accurate reflection of the rate of change in the price for medical goods and could have biased our cost estimates.

The analysis of diarrhoeal disease was limited to only the first year of life because that is when peak prevalence has been reported in children[66,67] . It was also assumed that mortality between normal birth weight infants and those born low birth weight or small for gestational age was the same beyond the first year. The literature suggests that mortality rates differ between these two groups but a high-level estimation of the effect in our analysis revealed that differing mortality rates would result in more DALYs being averted under multiple micronutrient supplementation and therefore rendering it more cost effective than our current results. Since the new intervention is dominant, there was no need to include this in our analysis.

Another limitation is that there are no South African specific disability weights for the health outcomes under consideration. This means that I was not able to accurately estimate South African specific benefits resulting from introducing multiple micronutrient supplementation into the public health system. I however made use of published disability weights data in the absence of South African specific data to come up with the best possible DALY estimates for our context.

The assumption that there is 100% coverage and adherence of supplement taking is not a realistic one. Like other studies, we chose this threshold to demonstrate the expected benefits of supplementation. Studies in South Africa have shown varying adherence to prophylactic iron supplementation in pregnancy ranging from as low as 50% in some settings to as high as 93% in others [108,109].

A model provides a structure that allows extrapolation of data beyond the clinical trial period, extrapolation of intermediate clinical endpoints to final health outcomes ,generalization of results to other settings or patient groups and the inclusion plus management of uncertainty [45,61,62]. When making a model, assumptions are made on the structure of the model, which parameters to include and their respective values, and value judgements, for example the parameters included in the sensitivity analysis. Because of its subjective nature, decision analytical modelling aids in decision making and does not provide exact result estimates[61].To test the robustness of our results, we conducted sensitivity analyses and concluded that multiple micronutrient supplement was cost effective.

4.5 Future Research

Costs of complications, follow on health service utilisation and programmatic costs were excluded in the study and a more detailed analysis of the costs in future is recommended. A budget impact analysis would be useful in informing government of the financial consequences of adopting multiple micronutrient supplementation.

Value of information analysis quantifies the expected value of research in reducing decision uncertainty to inform whether a decision can be made based on existing evidence or if additional evidence is required and worthwhile. Although there was uncertainty in some of the parameter models, our sensitivity analysis showed that our results were robust and multiple micronutrient supplementation was the dominant strategy. As a result, there would be no value in in conducting a value of information study in this instance.

Further analysis could also do the evaluation from the societal perspective and include costs incurred by caregivers.

4.6 Conclusions

In summary, replacing multiple micronutrient supplementation with iron and folate supplementation would be cost effective in the South African health care system and the South African government should consider switching regimens. Further analysis is needed to establish programmatic costs involved in switching to multiple micronutrient supplementation and provide a complete picture of the actual costs involved should there be a switch. In view of the resource and budget constraints faced by the National Department of Health, a budget impact analysis is needed to estimate the expected changes in the expenditure and the financial consequences of adopting multiple micronutrient supplementation. A budget impact analysis will provide information on whether the new intervention is affordable. Budget impact analysis will ensure that a comprehensive economic assessment of a switch to multiple micronutrient supplementation in South Africa has been undertaken.

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6 : APPENDICES

Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

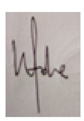
SENATE PLAGIARISM POLICY: APPENDIX ONE

I WINFRIDA MDEWA (Student number: 1820895) am a student registered for the degree Of Master

In Public Health specializing in Health Economics in the academic year 2018.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.



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HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

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TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: Ms W Mdewa
Student No. (if appropriate): 1820985
Staff No. (if appropriate):

Supervisor: Dr I Edoka

School: Public Health
Medical School
University

Project title: *A cost effectiveness analysis of maternal multiple micronutrient supplementation in South Africa*

Reason: Review of information in the public domain.
No human participants will be involved in the study.

CBPenny

Dr CB Penny
Chairperson: Human Research Ethics Committee (Medical)

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