Establishing a Framework to Assess the Cost-Effectiveness of IIPH's Folic Acid Interventions for Women of Reproductive Age

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
in the Duke Global Health Institute
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ABSTRACT

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Abstract

There is a very high prevalence of folic acid deficiency in developing countries and women suffering from this deficiency during their pregnancies are at an increased risk of having a child with neural tube defects (NTDs). NTDs affect approximately 400,000 births annually. Newborns affected by neural tube defects suffer lifelong physical and mental handicaps, and in cases of severe NTDs, die. NTDs, however, are preventable with proper folic acid interventions for women of reproductive age, often reducing the risk of having a child with NTDs by 72%. This paper aims to conduct a systematic review in order to understand, formulate and propose a framework for assessing the cost-effectiveness of the Indian Institute of Public Health's (IIPH) prospective folic acid interventions in India. Several limitations to the proposal of such a framework (particularly on efficacy vs. effectiveness) are highlighted alongside key findings on integral components to include when conducting a cost-effectiveness analysis on folic acid interventions. These findings (costs/benefits/effectiveness), best practices, and lessons from a programmatic and post-hoc perspective are reported and discussed in the results section. Findings are succinctly summarized into a framework in the discussion section as a recommended checklist for IIPH to utilize when conducting a cost-effectiveness analysis on their future intervention.

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Acknowledgements

This paper is a component of a larger study being conducted by the Indian Institute of Public Health (Hyderabad branch) in conjunction with researchers from the London School of Hygiene and Tropical Medicine and the University of Bristol. The greater study is titled: *The public health consequences of folic acid deficiency in mothers and benefits of periconceptual folic acid supplementation on pregnancy outcomes, with special reference to neural tube disorders and oro-facial clefts in India*.

The Indian Institute of Public Health (IIPH) and its collaborators' multifold study aims to focus on determining the prevalence of and conducting descriptive studies of folic acid deficiency; identifying risk factors for specific congenital anomalies through case-control studies; and identifying and conducting folic acid interventions through a RCT involving folic acid and vitamin B_{12} supplementation.

The rise for this paper stems from the third leg of the aforementioned description of IIPH's larger study. In this paper, I aimed to understand the costs, benefits, and effectiveness of folic acid interventions, and then to strategize a framework to assess the cost-effectiveness of folic acid interventions in improving maternal and child health in India. Special consideration was paid to the logistic feasibility of adopting and implementing folic acid interventions at a population level.

I want to acknowledge the support of my thesis committee comprised of Drs. Mohanan, Kinra and Jeuland. I would like to thank my mentor, Dr. Manoj Mohanan, for all his invaluable advice, guidance, and support throughout my thesis journey. I would also like to extend my appreciation towards Dr. Sanjay Kinra for helping me identify the research opportunity at IIPH for my thesis and Dr. Marc Jeuland for exposing me to the proper resources for understanding cost-effectiveness analysis.

I am indebted to the Indian Institute of Public Health for providing me with the opportunity to explore my thesis within the context of their larger overarching study. I want to express gratitude towards Drs. B.R. Shamanna and Komal Allagh for their contributions and input towards my thesis. Of course, many thanks to the Duke Global Health Institute for all their input throughout my time in its Master of Science in Global Health program and their support during my surprise emergency in the field.

1. Introduction and rationale

There is a very high prevalence of folic acid deficiency in developing countries. Folic acid deficiency is associated with a myriad of health complications including, but not limited to, cancers, physical and cognitive developmental disorders, and birth defects. The incidence of neural tube defects due to folate deficiency affects about 400,000 births annually. Newborns affected by neural tube defects (NTDs) suffer lifelong physical and mental handicaps such as paralysis of the leg, brain injury and learning disabilities, and in cases of severe NTDs, die within 48 hours of birth. NTDs, however, are preventable with proper folic acid interventions.

India has one of the highest incidence rates of NTDs in the world at 6.57-8.21 per 1000 live births [73]. Depending on which part of India is being examined, the incidence of NTDs varies from 0.5-11 cases per 1000 live births [42]. With India's incidence rate of NTDs being far larger than the global estimate (between 0.56-1.70 cases per 1000 live births), the implementation of folic acid interventions for women aimed to prevent NTDs in their newborns is critical in India [81].

While a folic acid intervention is being implemented in India, it is not being implemented at a national level and very little economic data is available on the intervention. Currently, upon a preliminary search, there is no evidence addressing the cost-effectiveness of folic acid interventions in India. For scaling up and broader policy implementation, lack of cost-effectiveness information for folic acid interventions makes it difficult for policymakers in India to be convinced to prioritize interventions, prescribe policies and appropriate money to address the severity of NTDs.

Given this limitation, a team of researchers from the Indian Institute of Public Health (IIPH), the London School of Hygiene and Tropical Medicine and the University of

Bristol has developed an intervention study to address folic acid deficiency in women of reproductive age. This study ultimately aims to conduct a cost-effectiveness analysis on its interventions.

Therefore, the deliverable of the paper at hand will highlight essential information to gather, take into consideration and understand in order to effectively conduct a cost-effectiveness analysis of the larger study's folic acid interventions. Should the deliverable of this paper be applied, this paper will contribute towards assessing the cost-effectiveness of IIPH's intervention, learning best practices, and addressing limitations to improve interventions. In turn, improved interventions, which fall under the parameters of the federal government's assessment of what it considers cost-effectiveness, can become focuses of future health policy initiatives in India to minimize the adverse public health consequences of folic acid deficiency among mothers in India and strengthen the evidence base in childhood disability resulting from NTDs.

The objective of this paper is to conduct a systematic review in order to understand the general benefits and importance of folic acid consumption by women of reproductive age (as discussed in the literature review section of this paper), and to develop a framework that provides information on:

1. the primary health outcomes required to measure the consequences and impacts of folic acid consumption;
2. the costs associated with implementing effective periconceptual folic acid interventions;
3. the costs borne due to a lack of folic acid interventions leading to NTDs;
4. the benefits and effectiveness associated with periconceptual folic acid interventions;

5. and the background and contextual fabric of India (as this is where the study will take place).

The next section of this paper provides a discourse on current literature in the field to set the background stage. Following, the Study Design section will provide an overview of the methodology utilized for the systematic review. After this paper conducts a systematic review on the costs-effectiveness of existing folic acid interventions aimed towards women of reproductive age, those results will be presented and discussed. Concluding, a recommendation providing IIPH with a set of guidelines of important items to consider when collecting information on costs and effectiveness of its folic acid interventions will be drafted in the discussion section. This framework will better equip the IIPH for its next steps.

2. Review of current literature

2.1 General importance of folic acid

Folic acid deficiency is associated with the increased risk of chronic diseases, developmental disorders, birth defects and complications [1] and also several cancers: colon, colorectal, breast, pancreas, brain and lung [2]. High intake of folic acid has been associated with lower breast cancer incidence [5, 6]. Folic acid supplementation has also shown to reduce the risk of stroke by 18% [7]; effectively reduce the risk of osteoporosis by 64% [8]; and assist a variety of physiological processes [13, 14]. Cognitive impairments [9, 10, 11] and fetal, infant and child underdevelopment [12] also result from folic acid insufficiency. The incidence of neural tube defects due to folate deficiency, characterized by abnormal neural tube closure, affects about 1 to 5 cases per 1000 pregnancies [1, 3, 4].

2.2 Folic acid deficiency in India and its effect on maternal and child health

Low and middle-income countries witness a high prevalence of folic acid deficiency [15]. In many developing countries, national surveys indicate high levels of folic acid and vitamin B12 deficiencies, hence posing these deficiencies as public health concerns [16, 17, 18, 19]. Studies on pregnant mothers in India show that the prevalence of folic acid deficiency ranges between 20-30%, and this is much higher than that of other low- and middle-income countries [21, 22, 23]. Furthermore, many South Asians have low folate levels due to their common vegetarian diets, which include a limited array of vegetables [20].

Mothers, during their pregnancy, undergo the depletion of folate, which results in adverse outcomes during and later in their pregnancies [28, 29]. This is important as empirical research shows that even a slight folate deficiency can result in poor pregnancy outcomes: spontaneous abortions, recurrent pregnancy loss, stillbirth [30, 31, 32], and

increased risk of preterm birth [33]. Furthermore, folic acid insufficiency is a determinant of birth weight and pregnancy wastage [34], where a child is stillborn or dies within the first week of its birth, which is of concern in India—Uttar Pradesh's prevalence of late pregnancy wastage was 18% [35].

Based on numerous studies conducted in developed countries, neural tube defects (NTDs) are the second most common group of serious birth defects [43], and over 400,000 children are born with NTDs annually [47]. NTDs result from failure of the neural tube to close properly approximately 28 days postconception [43]. This is typically before a woman is even aware of her pregnancy [44, 45], calling for increased interventions for folic acid supplementation preconception.

2.3 Neural tube defects

There are two common forms of NTDs: spina bifida and anencephaly. NTDs are a group of birth defects that occur in utero during the development of the brain and spinal cord [55]. Spina bifida results from the failure of the fusion of the posterior (caudal) neural tube, whereas anencephaly results from the failure of the fusion of the anterior (cranial) neural tube. Anencephaly is fatal and many children with anencephaly are stillborn or die shortly after birth. Children with spina bifida suffer lifelong physical and mental handicaps such as paralysis of the leg, brain injury and learning disabilities, and only a minority are able to function independently in adulthood [46]. Individuals with NTDs often have problems related to hydrocephalus, neurogenic bladder, kidney involvement, orthopedic complications and psychosocial consequences [43]. These complications are often burdens to patients with NTDs and their families [43]. Folic acid supplementation, based on the studies conducted in developed countries, acts towards the prevention of the aforementioned adverse conditions. Furthermore, according to a systematic review from The Cochrane Library, folic acid

supplementation has been proven to show a protective effect on the prevention of NTDs [61]. While it is known that folic acid consumption can reduce the risk of NTDs by 72% [1], there is limited knowledge of the effectiveness and consumption of folic acid in India. It is critical that this knowledge gap is addressed because the incidence rate of NTDs in India is between 6.57-8.21 cases per 1000 live births, making this rate one of the highest in the world [73]. Even more startling is that the incidence rate of NTDs can be up to 11 cases per 1000 live births depending on the region in India [42]. This high incidence rate is often found in impoverished regions where there is a lack of education, appropriate food sources and supplementation.

In an older study, Kulkarni et al. report that the incidence of NTDs was significantly higher in consanguineous families – families that are comprised of members from a common ancestor where interfamily marriages are common. [78]. This prospective study suggests that there may be a genetic component to the etiology of NTDs [78]. In India particularly, inbreeding has been a popular cultural practice for almost 2000 years, so genetic factors may even be important to consider for non-consanguineous couples [78]. However, it is important to keep in mind that this study is quite dated and additional study on this subject has not been conducted.

2.4 Sources of folic acid—dietary and supplementation

Dietary folic acid intake is poor for most people [24]. Folic acid intake from natural food sources can be unstable due to cooking practices, which deteriorates the nutritional content of natural food sources even before their ingestion [25]. Folic acid is found dark green leafy vegetables and a select few other vegetables such as asparagus, broccoli, and beets. While a diet rich in natural sources of folic acid may be beneficial in improving folic acid status [26, 27], the difficulty in actually consuming natural sources lies in the fact that

there is a general poor bioavailability of natural food folates [24]. Compounded by the said limitation in folate accessibility, local South Asian norms and cultural practices may challenge the consumption of specific natural folate-rich food sources. Therefore, an alternate source of folic acid would be through folic acid supplements. Folic acid supplementation would provide a stable and highly bioavailable source of folic acid [24].

2.5 Nutritional supplementation programs in India today

In the 1970s, the National Nutritional Anemia Prophylaxis Program was initially implemented in India to provide pregnant women iron-folic acid supplementation for three months during their pregnancy. Although reasons are unknown, this program's utilization was quite low; three states in India witnessed that the proportion of pregnant women given iron-folic acid supplements and the proportion of pregnant women consuming the iron-folic acid supplements were low [37]. Today, this program now focuses on delivering vitamin A supplementation to women [43] and the supplementation is provided through primary healthcare centers throughout the country [36]. The program's inceptive goal of providing iron-folic acid supplementation was revised in 2003 after recognizing an overwhelming burden of vitamin A deficiency in infants, adolescents and school-age children [46].

However, there is the National Pilot Program on Control of Micronutrient Malnutrition, which is being implemented in a few states, specifically in Northern India [73]. However, a major flaw in this program is that the administered dosage of folic acid (between 75 and 168 micrograms) is way below the 400 micrograms recommended to prevent birth defects [73].

2.6 Cost-effectiveness analysis

2.6.1 A general overview of cost-effectiveness analysis

Cost-effectiveness analysis (CEA) aims to look how effective an intervention is compared to its cost [50]. According to a World Bank publication: "cost-effectiveness analysis is a method for assessing the gains in health relative to the costs of different health interventions" [50, 51, 53]. The importance of CEA lies in its ability to help policymakers, researchers and academics "identify neglected opportunities by highlighting interventions that are relatively inexpensive, yet have the potential to reduce the disease burden substantially" in order to better serve neglected communities [50]. Furthermore, CEA establishes "not only the utility of allocating resources from ineffective to effective interventions, but also the utility of allocating resources from less to more cost-effective interventions" [50].

For CEA, health interventions are categorized as: "deliberate activities that aim to improve someone's health by reducing the risk, the duration, or the severity of a health problem" [50]. In general, the mathematical basis for a CEA ratio is in terms of U.S. dollars per DALY (disability-adjusted life year), or in other words, the "basic calculation involves dividing the cost of an intervention in monetary units by the expected health gain measured in natural units such as the number of lives saved" [50], and outcomes are measured in natural units [76]. A DALY thus measures not only the additional years of life gained by an intervention, but also the improved health that people enjoy as a consequence [50].

Alternative methods of assessing cost-effectiveness calculate cost-effectiveness by using the number of life years lost as the unit for measuring the how effective an intervention is [50], and by utilizing QALYs (quality-adjusted life year) instead of DALYs [51]. QALYs

are an alternative measure of how much a life year is worth if a person suffers from one or more limitations of various kinds and degrees [51].

2.6.2 Understanding the context of cost-effectiveness analyses

The paradigm of CEA for healthcare is embedded in pharmacoeconomics. When evaluating the cost-effectiveness of a drug therapy (or supplementation program for the context of this paper), several perspectives (patient, provider, payer and society) are taken into account [76]. Patient perspectives, both positive and negative, are especially important, as they represent views on the effectiveness of interventions as consumers of services or commodities [76]. Furthermore, patient perspectives are integral when assessing the impact of drug therapy on the quality of life [76]. Provider perspectives represent the actual expenses of providing a commodity or service [76]. Payer perspectives include those of insurance companies, employers, or most relevant, the government [76]. The primary costs for payers are of main concern [76]. Lastly, there is the societal perspective, which considers the benefit or costs to society as a whole [76].

2.6.3 Direct versus indirect costs in cost-effectiveness analyses

When looking at the costs (in U.S. dollars) in CEA, customarily only direct costs are included. When looking at direct costs associated with health interventions it is imperative to define the level of care at which it is delivered, the particular supplies and processes involved, the types of healthcare workers and any associated services (such as laboratory tests) required [50]. Direct medical costs are the costs incurred for medical products and services used to prevent, detect and/or treat a disease or condition [76].

There are also indirect nonmedical costs, which range in their definitions and inclusiveness. The most common indirect costs include those borne from an illness, disease or condition, but do not involve purchasing medical services; these costs include resources

spent by patients on transportation to reach facilities, child or family care expenses, etc. [50, 76]. Another indirect cost could be the value of the time patients and family members spend in obtaining a service [50]. Other indirect costs could be those resulting from morbidity and mortality such as reduced productivity [76]. There are intangible costs that include pain, suffering, inconvenience and grief, and also opportunity costs that include lost opportunities and revenue forgone [76].

Indirect costs are often disregarded because it is difficult to quantify and attach values to these indirect costs due to lack of data [50, 51]. Assessing indirect costs is even more problematic when trying to make comparisons over large cultural and income differences [51]. Moreover, indirect costs are often also disregarded as when indirect costs are high, it becomes difficult to accurately estimate the cost-effectiveness of an intervention [50]. Further, when more costs are included, the cost per unit of health gain will be higher and the intervention will appear to be less cost-effective [50, 51].

However, indirect costs can play a large role in assessing the cost-effectiveness of an intervention [50]. Indirect costs are particularly important to consider when assessing interventions and programmatic efforts in rural spaces of developing countries where logistical capabilities may be limited and require additional resources, or where accessing health interventions located in urban centers is difficult. Even if indirect costs are not included in the actual CEA, it is imperative that they are addressed and taken into account when examining an intervention. This will help contextualize the intervention and also allow for a more holistic examination of the intervention.

2.6.4 Role of cost-effectiveness analysis in developing countries

It is important to keep in mind that when evaluating the cost-effectiveness of an intervention, the effectiveness of an intervention is partially dependent on the degree of its

need in a health setting and also dependent on how culturally appropriate or acceptable the population it is intended to benefit considers them [51]. This requires a thorough assessment of the local space and context for which the intervention is intended. Furthermore, due to the complexity between the different stakeholders when considering a CEA, an intervention that is cost-effective may be infeasible to deliver and vice versa [51].

As previously mentioned, indirect costs become substantive and important to take into consideration examining the cost-effectiveness of interventions in developing countries [51]. Especially in developing countries, where interventions often make beneficiaries mentally or physically more productive, better able to continue in and learn from school, or to work and earn more, interventions that do not seem cost-effective may have tremendous nonhealth benefits, vice versa [51]. Interventions that do not seem cost-effective upfront may actually have positive economic benefits in the lives of impoverished beneficiaries [52]. Arguably, this is because healthy workers are more productive than workers who are similar but not healthy [52]. Economic research demonstrates that low-income countries that have high levels of health experience faster rates of economic growth as their incomes adjust [52].

2.7 Brief overview of cost-effectiveness analysis of nutritional interventions and supplementation trials

Many studies have determined certain types of folic acid interventions of being cost-effective [40]. For instance, organizations such as the American Academy of Family Physicians, have argued that folic acid supplementations are cost-effective [40]. A study examining public education programs, as a strategy to increase folic acid consumption through supplementation, estimated that compared to no program, supplementation saved approximately $5,000 per quality adjusted life year per case [40]. However, recent

publications have argued that there is limited data on cost and cost-effectiveness of population-based weekly supplementation programs [54].

In order to understand methods of evaluating costs and effectiveness of nutritional intervention trials, it is critical to evaluate other studies [38] and explore systematic reviews that have been conducted on those studies [38, 39]. A variety of cost-effectiveness analysis models can be utilized to assess those intervention trials (e.g. CHOICE, which allows comparison of interventions and programs across more than one disease area) [38]. When evaluating the costs and effectiveness of interventions, examining the delivery mechanisms of the interventions and their costs are important to consider [38]. Thereafter, outcomes, the number of people impacted, and the effectiveness should be evaluated [38].

Costs and effectiveness of other folic acid interventions, namely fortification of flour, as seen in Chile, have been evaluated based on the strategy of fortification with the baseline alternative of no fortification [41]. Birth surveillance data was used to evaluate the effectiveness in reducing neural tube defect risk in all births (live and fetal deaths). The case of Chile utilized a cost-effectiveness analysis framework provided by the Disease Control Priorities Project supported by the World Health Organization, World Bank and the guidelines used in the WHO-CHOICE generalized cost-effectiveness analysis program [41].

In other studies, incremental costs of each intervention were measured by inputs of resources such as program administrators, health professionals, materials and folic avid supplements [55]. Other costs include costs of training, equipment and supplies [55]. These costs and the benefits were compared to a base case model and the study showed no reduction in Australia or New Zealand, however in the UK, such cost-effective results have been illustrated [55].

Therefore, it then becomes extremely important for each country to conduct their own cost-effectiveness analysis, as contextual actors help determine the cost-effectiveness of

each trial. The framework, which will be established in later parts of this paper, will highlight key elements to include when trying to conduct a CEA in a localized context.

3. Study design

3.1 Research aim and objective

The overarching aim of this paper is to develop a framework of key information that IIPH should collect in order to evaluate the cost-effectiveness of their preconception folic acid interventions for women of reproductive age.

More specifically, the framework aims to:

1. Provide an understanding of the primary health outcomes associated with periconceptional folic acid interventions to be classified as appropriate measures of consequences and effectiveness;
2. Identify costs associated with implementing effective periconceptual folic acid intervention;
3. Identify costs borne due to a lack of folic acid interventions leading to NTDs; and
4. Lay out information and background about folic acid interventions in the context of India, as this is the country IIPH's folic acid interventions are concerned with.

3.2 Methods

The study was conducted over the course of ten weeks from September through December (year 2012) at IIPH's Hyderabad regional office in the district of Mahbubnagar in the state of Andhra Pradesh, and also off-site in San Francisco, California, United States of America.

Available published data and studies focusing on understanding the cost-effectiveness of periconceptional folic acid interventions were reviewed.

A broad search was initially deployed to set the context for the study, but searches progressively became more focused to narrow down results to those focusing on low and middle-income countries, and ultimately on India. Available literature was sought out utilizing two key databases: NCBI archives (i.e. PubMed databases) and The Cochrane Library. Specific filters and terms were utilized.

Snowball searching was used whereby literature was crosschecked in Google Scholar's 'Citation Index' and Web of Science databases to ensure a comprehensive inclusion of available published literature. This method was utilized to ensure all recent publications citing said articles were included in this paper. Key articles and evidence were summarized systematically. Furthermore, articles sourced from the reviews were.

The second reviewer for a systematic review approach (for the inclusion and exclusion of key papers) was Dr. Komal Allagh, a Research Associate at the Indian Institute of Public Health (Hyderabad branch). This study was supervised under Dr. B.R. Shamanna, the Senior Public Health Specialist at the Indian Institute of Public Health (Hyderabad branch).

For a comprehensive approach, two reviews were conducted:

- Review 1: to obtain information on general economic (benefits and costs) data and evidence revolving around folic acid interventions during pre-, post- and periconception; and
- Review 2: to obtain information revolving around CEA of folic acid interventions (individually or combined with other micronutrients) within the context and space of India.

3.2.1 Methodology for Review 1

For the first review, a search was conducted through PubMed and The Cochrane Library to identify a broad range of economic data concerning folic acid supplementation during pre-, post-, and periconception. This review included both, an examination of the benefits or impacts of interventions and also the economic burden inflicted on patients due to the conditions arising from the lack of supplementation. Upon snowball searching for this review, one article was sourced, as discussed in the results section. Details can be found in Figure 1.

3.2.2 Inclusion and exclusion criteria for Review 1

During the first round of searches (as per Table 3) for this review, a general search on all articles concerning the cost-effectiveness analysis of folic acid interventions was conducted on both databases. Articles were included if they generally concerned economic data on interventions for pregnant women, interventions during or for pregnancy or interventions for women of reproductive age. Articles had to be in English, published, and available in their full texts. No publication date was instated as an exclusion criterion.

In order to refine the yield of publications while searching, additional search terms were added to the next round of article search (as per Table 4). All articles in this search were included if they focused on cost-effectiveness of folic acid supplementation (independently or combined with other mineral or vitamin supplementation) for pregnant women, folic acid supplementation during or for pregnancy or folic acid supplementation for women of reproductive age *all in relation to the supplementation's impact (or potential impact) on their pregnancy or offspring*. Therefore, articles concerning the aforementioned search terms combined with variations of the following terms were included: folic acid supplementation, micronutrient supplementation, iron supplementation, pregnancy, pregnant women,

preconception, periconception, postconception, NTDs, neural tube defects, anencephaly, encephalocoeles, spina bifida, hydranencephaly, iniencephaly, schizencephaly, oro-facial cleft, cleft palate, cleft lip and cost effectiveness analysis. These terms were selected to better define the impacts and expand the breadth of conditions that were desired to be examined within the cost-effectiveness analysis scope of this paper. All articles concerning both the benefits and costs of supplementation, or the lack of supplementation, were included for review. Included articles had to be in English, published, and available in their full texts. No publication date was instated as exclusion criteria.

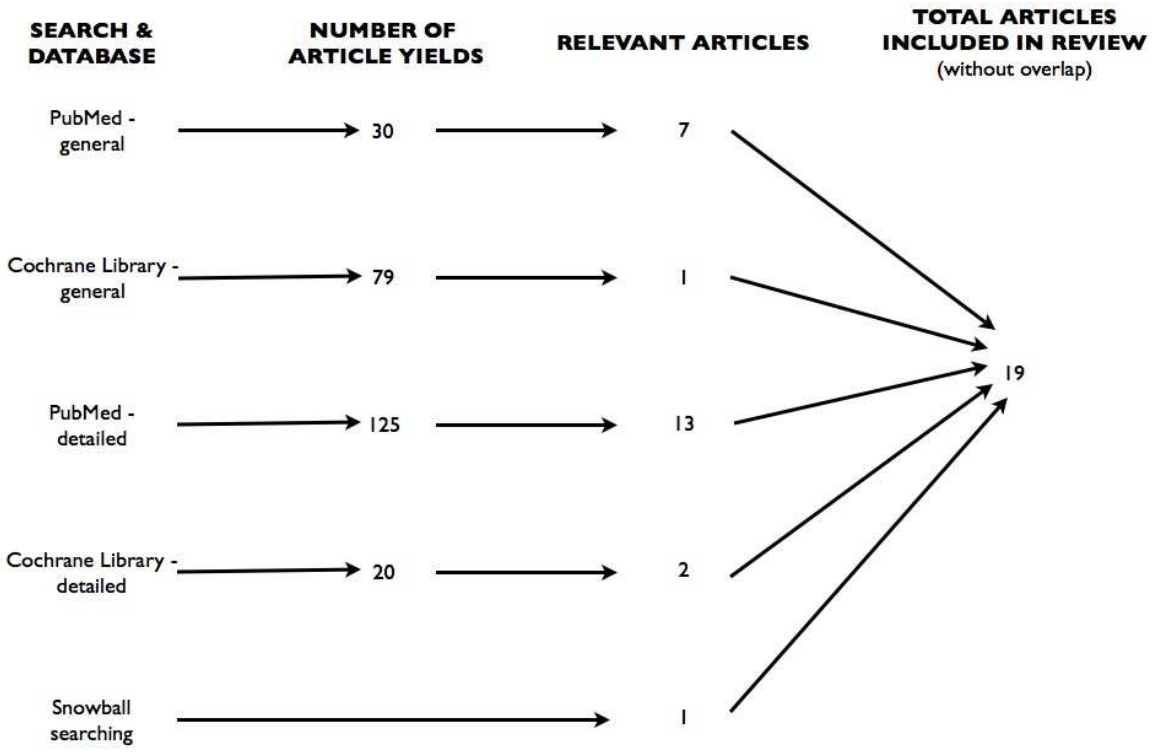

Figure 1: Process of selecting articles into Review 1.

3.2.3 Methodology for Review 2

A second (as per Table 5) review was conducted to source literature to better understand the landscape of folic acid interventions and supplementation (independently or

with other micronutrients) in India for pregnant women. This review was conducted to develop and establish a context for a cost-effectiveness analysis on folic acid supplementation in India. The aim is to obtain a clear understanding on the inputs required for the cost-effectiveness analysis, and how the outputs fit specifically an Indian landscape. Details can be found in Diagram 2.

3.2.4 Inclusion and exclusion criteria for Review 2

Articles were included if they were concerned with folic acid interventions specifically in India for pregnant women. Included articles had to be in English, published, and available in their full texts. No publication date was instated as an exclusion criterion.

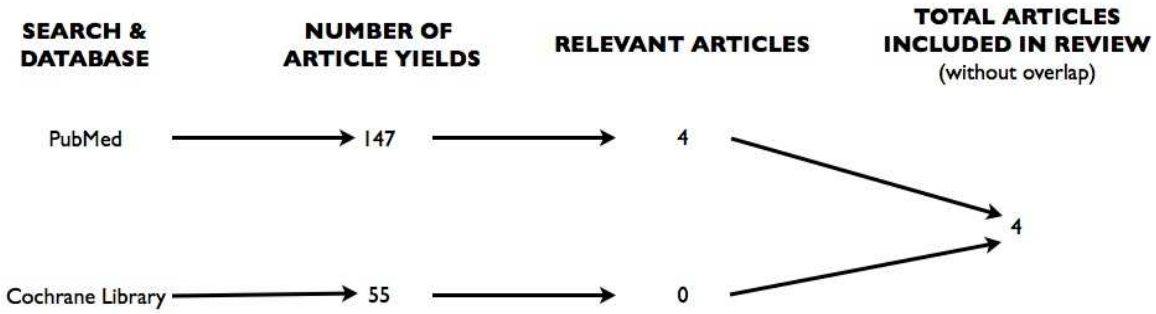

Figure 2: Process of selecting articles into Review 2.

4. Results and analysis

Over the course of this section, all discourse derived from the literature should be underpinned with the caveat that it is important to keep in mind the limitations in the quality of the studies and their external validity. The quality of studies was assessed by looking at the significance of the data reported, the strength of the data presented, and limitations presented within the articles themselves. Some of these studies' results and conclusions were not particularly convincing, yet had relevant statistics for reporting. Many of the studies included report outstanding statistics that may be a result from efficacious studies that may prove ineffective when extrapolated and applied to a larger context.

4.1 Review 1: general economic data and evidence focusing on folic acid interventions for pre-, post-, and periconception

After following the methodology as highlighted in the Study Design section for Review 1, 18 articles were considered relevant and in accordance to the inclusion and exclusion criteria, and hence are included in this paper. Upon snowball searching, one article was sourced. Table 1, included below, briefly highlights key information about the 19 selected articles for Review 1.

Table 1: Key findings and summaries of articles included in Review 1.

Author, Year, Country, Article Reference Number	Study Design or Article Type	Folic acid intervention cost-effective?	Concerned with NTDs?	Summary of Relevant Information Provided and Additional Notes
1. Casey 2011, Vietnam [54]	Economic evaluation	Yes	No	Casey et al. conclude that weekly iron-folic acid supplementation with de-worming medication is cost-effective and viable for grassroots level populations affected by anemia and iron deficiency and low malaria infection rates. Study identified key components it included (and their approximate costs) when conducting its CEA but did not include quantitative data directly relating to the CEA of the supplementation for the purposes of this paper (addressing NTDs, etc.).
2. Dalziel 2010, Australia & New Zealand [55]	Economic evaluation	Insignificant results	Yes	Dalziel et al. aim to propose an optimal strategy for reducing the rate of NTDs in Australia and New Zealand. They concluded that several options for reducing NTDs are cost effective although their data analyses deemed their conclusions insignificant. Although the CEA of mandatory fortification in Australia was inconclusive and was not cost-effective in New Zealand, the two countries' have proceeded with this option with a rigorous economic evaluation plan in place.
3. Zeng 2009, China [56]	Double-blind RCT	N/A	No	This study aims to primarily examine reports of side effects and rates of adherence to prenatal multivitamin supplementation in

				China. A secondary objective of the study is to describe the inputs and costs associated with prenatal supplementation by tracking them. This study concluded that one of the most important inputs in prenatal supplementation interventions, which also significantly impacted the rates of adherence, was ensuring mothers' accessibility to trained health workers and a reliable supply of supplements. A CEA was not conducted.
4. Stockley 2008, United Kingdom [57]	Systematic review	N/A	No	This study analyzes existing articles on the consumption of folic acid supplementation to provide a basis for recommending strategies to improve the use of folic acid supplements by low-income and young women. Stockley et al. found that campaigns and interventions should be comprised of certain key and crucial elements.
5. Postma 2002, The Netherlands [58]	Economic evaluation and literature review	Yes	Yes	This article is possibly the most relevant to this paper. It clearly identifies how a CEA was conducted on periconceptional folic acid supplementation in The Netherlands. All information needed to estimate the cost-effectiveness – such as costs, inputs, probabilities of NTDs, etc. – was estimated using Dutch registrations and international literature. The study found that periconceptional supplementation of folic acid is cost-effective.
6. Jentink 2008, The Netherlands [59]	Economic evaluation and literature review	Yes	Yes	Jentink et al. aim to estimate the cost-effectiveness of folic acid fortification in The Netherlands. Costs and inputs were

				estimated using Dutch registrations, Dutch guidelines for costing, international literature and other expert opinions. Results indicate that bulk folic acid fortification can be cost-effective. Other benefits to folic acid fortification were also identified.
7. Sayed 2008, South Africa [60]	Ecological study	Yes	Yes	This study aims to document the prevalence of NTDs before and after folic acid fortification in South Africa. The study shows a significant decline in the prevalence of NTDs following folic acid fortification, and these results are consistent with decreases observed in other countries that have also fortified their foods.
8. De-Regil 2010 [61]	Systematic review	N/A	Yes	While this systematic review did not comment on the cost-effectiveness of folic acid supplementation, it did comment on the immense protective effect that folic acid interventions can have on NTDs.
9. Yi 2011 [62]	Literature review	Yes	Yes	Yi et al. take another route in assessing the cost-effectiveness of folic acid interventions by understanding the economic burden of NTDs and the economic impact of preventing NTDs with folic acid interventions. This review shows that folic acid interventions can be cost-effective ways to reduce the incidence and prevalence of NTDs.
10. Bentley 2009, United States [63]	Economic evaluation	Yes	Yes	This study's aim was to quantify the health and economic outcomes associated with changes in folic acid consumption following

				the fortification in the United States. The study finds that the health and economic gains of folic acid fortification outweigh the costs, hence making fortification cost-effective.
11. Hertrampf 2008, Chile [64]	N/A – Policy piece	Yes	Yes	This policy piece focuses on folic acid fortification in Chile. The prevalence of NTDs was reported to have declined after folic acid fortification. The impact of folic acid fortification on other health statuses and conditions – elderly health, blood levels, etc. – were also examined.
12. Grosse 2005, United States [65]	Economic evaluation and literature review	Yes	Yes	This evaluation and review estimates that folic acid fortification provides the United States with an annual economic benefit of about $312-425 million. Cost-savings have been estimated to be about $88-145 million. Extensive economic data was not provided in the study's paper.
13. Hodges 2000, Uganda [66]	Prospective study	N/A	Yes	This study did not comment on the cost-effectiveness of folic acid interventions, but instead focused on the inputs needed and costs associated with treating effects of NTDs, such as cleft lips.
14. Romano 1995, United States [67]	Economic analysis	Yes	Yes	This study concludes that averting NTDs, which is a costly birth defect, by folic acid fortification of grain provides the United States with substantial economic benefits. Benefits discussed in this paper may actually be underestimated due to the unmeasured costs of NTDs and unmeasured benefits of

				higher folate intake.
15. Tilford 2009, United States [69]	Population-based analysis	N/A	Yes	This study estimates the labor market productivity costs for caregivers of children and adolescents with spina bifida. The study concludes that caregivers of children with spina bifida work an annual average of 7.5-11.3 hours less per week, and that difference in work hours by caregivers of children with spina bifida can translate into lifetime costs as high as $133,755. Hence, due to this huge economic cost resulting from NTDs, caregiver costs must be included in CEA.
16. Grosse 2008, United States [70]	Economic evaluation	Yes	Yes	This study aims to examine the cost-effectiveness of NTD reoccurrence programs, and finds that recurrence program costs are much less than the costs associated with children with NTDs.
17. Thakkar 2010, India [68]	N/A – Letter	N/A	Yes	This letter does not comment on the cost-effectiveness of folic acid interventions, but instead comments on the other numerous costs associated with treating a child with spina bifida and cleft lip. It also briefly comments on the lack of consistency in quality of care and surgery for these children.
18. Whitworth 2009 [71]	Systematic review	Yes	Yes	This review comments on not only the benefits of consuming folic acid, but also on the need for rigorous monitoring and aggressive interventions for such interventions to be cost-effectiveness.

19. *via snowball searching* – Rabovskaja 2013, Australia [77]	Economic evaluation and policy	Yes	Yes	This study found that mandatory folic acid fortification can be cost-effective, however folate intake will still remain below recommended levels.

4.1.1 An overview of cost-effectiveness of folic acid interventions

According to a study done in Australia and New Zealand, several interventions for folic acid supplementation and fortification were analyzed to be cost-effective against NTDs [55, 77]. This paper also presented important statistics about folic acid fortification across a number of other countries; in Canada, after fortification in 1998, there was a 48% reduction in NTDs; Chile's fortification program in 2000 was followed by a 51% decrease in the birth prevalence rate of spina bifida and a 42% decrease in the birth prevalence rate of anencephaly; and Costa Rica's fortification of wheat flour and corn flour in 1997 and 1999, respectively, resulted in a reduction in NTD cases from 9.7 cases per 1000 live births to 6.3 per 1000 live births [55].

However, it is critical to acknowledge that the aforementioned statistics may products of highly regulated and monitored studies that proved to be efficacious. There may be additional factors contributing to such drops in NTD rates alongside the mentioned folic acid interventions.

4.1.2 Cost assessment of folic acid interventions

According to a study that distributed iron-folic acid supplementation as a part of a larger package aimed to address anemia in Vietnam, a comprehensive list of costs—both programmatic costs and health systems cost—was created [54, 55]. Furthermore, a study in China clearly provides program inputs and costs for micronutrient supplementation [56]. In addition to training service providers (including village doctors and staff at different levels) and free supplements, in China, access to three antenatal and one postnatal service was provided for free to encourage high adherence to the supplementation program [56].

A study that utilized a pharmacoeconomic evaluation method (as discussed in Review 1), expressed the outcome in net costs per life-year gained [58]. Here, net costs

display the cost of the folic acid supplementation minus the benefits of averted lifetime costs of care for children with NTDs from a public and social perspective; life-years gained resulted from comparing life-years lost with and without supplementation [58]. In this analysis, however, only direct costs were included.

Below, a break down of direct costs (programmatic costs and health systems costs) is provided to conceptualize the complexity of intervention costs for folic acid interventions (focusing on folic acid supplementation):

Programmatic costs:

- Cost of supplements packaged appropriately [54, 55, 56];
- Distribution and storage costs for receiving the supplements and then transporting them to key locations for dissemination [54];
- Promotional and educational materials costs including the development and production of posters and flip-charts to be distributed to health centers via the public health system [54, 55, 56];
- Cost of training national staff to conduct training for provincial health workers [54, 55, 56]; and
- Cost of monitoring and evaluation which included printing forms, distributing them to relevant staff, collecting appropriate data, and then ensuring all information and forms were reported back to intervention headquarters [54].

Health systems costs:

- Institutional administrative costs which included personnel costs at a district, commune and village level [54, 56]; and
- Health worker (including health professionals) income costs [54, 55].

4.1.3 Direct and indirect costs borne due to the repercussions of no folic acid interventions

To understand the economic burden of NTDs and the economic impact of preventing NTDs with folic acid, a systematic review conducted by Yi et al. indicated three things:

- The lifetime direct medical costs for patients with NTDs is significant [62];
- The lifetime indirect cost for patients with spina bifida is even greater due to increased morbidity and premature mortality [62];
- There are some costs, which may be categorized as "indirect costs" on a surface level, that should actually be considered direct costs (i.e. caregiver time costs) [62].

Yi et al. points out that children with spina bifida have a high probability of lifelong physical and mental handicap, and only a minority of these children are able to function independently as adults [62]. Children with NTDs regularly have problems related to hydrocephalus, neurologic bladder, kidney involvement, orthopedic complications, and psychosocial consequences [62]. Considering the said economic points, folic acid fortification and supplement consumption are cost-effective ways to reduce the incidence and prevalence of NTDs [62]. Again, it is instrumental to acknowledge and further study contributing factors that add to the cost-effectiveness of the said interventions in reducing the incidence of NTDs. Folic acid fortification and supplementation may be efficacious from a

regulated intervention perspective, but ineffective, and even cost-ineffective, from a implemented policy perspective.

Direct costs for children with NTDs and their families include:

- Hospital-care costs including:
  - Hospital admission directly after birth [58, 59, 62];
  - Surgery to close the neural tube [58, 59, 62, 66], including the need for anesthesia [66]; and
  - Placement of the shunt and outpatient follow-up [58, 62, 66];
- Cost of accommodations for physically and mentally handicapped patients and also the cost of special education [58, 62];
- Travel costs [59]; and
- Patient mobilization including the need of community outreach teams, and of radio, church, and public announcements [66].

Indirect costs that can be considered when folic acid interventions are not provided, and a child with NTDs is born:

- Production losses for parents taking care of children with spina bifida [58, 62];
- Caregiver costs [62];
- Costs due to premature loss of life [62]; and
- Significant and high hospitalization and necessary service costs for comorbidities resulting from NTDs (including urologic infections, renal calculi, pressure ulcers, osteomyelitis, and wheelchair and walking aids) [62].

In essence, the costs due to a case of NTDs can pose a significant economic burden on families, and public and private healthcare providers.

Expanding on the costs of surgery, an article written by researchers from India specifically addresses the high costs of cleft-lip and palette surgeries, and the process in order to obtain one in India. Not only are the costs of surgeries high, but there is also the issue of inconsistency in the levels of surgical skills and competence represented by surgeons [68]. Furthermore, assuming the costs of surgery were omitted (as surgeries in the article were subsidized by Operation Smile), just the cost of travel and local stay to the patient summed over $261, making it quite expensive to obtain care [68].

The costs to the labor market, due to a loss in productivity because caregivers and parents have to take care of children with spina bifida, should also be examined [69]. Because many cost-effectiveness analyses exclude caregiver time costs and other "family spillover effects" from cost-effectiveness analyses, the value of preventing NTDs and spina bifida may be understated [69]. According to a study conducted in Arkansas, there was a substantial impact of caring for a child with spina bifida on the labor force; participation rates in the labor force were 21 to 27% lower for groups where caregivers had to attend to children with spina bifida [69]. The total lifetime labor market productivity costs can be up to $412, 965 per child with spina bifida [69]. Of course, there may be other factors that are currently unaccounted for that impact of NTDs on a child's life.

4.1.4 Benefits and effectiveness of folic acid interventions

According to a study conducted on the United States' folic acid fortification intervention, projected results indicate that between 182 and 1,423 cases of NTDs could be prevented, depending on the dosage of folic acid fortification [63]. Hence, the U.S.' fortification program would be gaining about 3,436 to 26,899 QALYs, also depending on the

dosage of folic acid fortification [63]. Another study in the U.S. establishes that the total economic benefit from the reduction of NTDs after folic acid fortification is estimated to be $425 million per year [65]. The study conducted an economic evaluation by surveying the number of NTD births averted and then multiplying this figure by total cost per NTD birth [65]. Total costs included both indirect and direct costs – medical costs, caregiving time costs, hospitalization costs, etc. Subtracting the cost of folic acid fortification ($3 million per year) from the amount gained, the net monetary benefit of fortification is $422 million [65]. The studies concluded that the projected health and economic benefits gained from preventing NTDs in the U.S. population far exceeded those lost due to fortification itself, ultimately providing a remarkable return on investment [63, 65, 67].

A study from Chile comments on the correlation between folate consumption and NTD rate [64]. Since 99% of births in Chile occur in institutional settings, Chile's vital registration system is well maintained and NTD registry is a part of regular neonatal care [64]. According to the NTD registry, after the fortification mandate in 2000, NTD rates were seen to decline by 43% compared to pre-fortification [64]. Before the fortification mandate, there were 17.1 cases of NTD per 10,000 births, and post-fortification, the number of cases declined to 9.7/10,000 births [64].

4.1.5 Additional lessons learned

Along with the inherent components necessary in evaluating the cost-effectiveness of folic acid interventions, studies included in this review also identified other best practices that could have implications on the CEA of folic acid interventions. First, a successful supplementation program must include the training of healthcare system workers, provision of accessible educational materials for the target group and the broader community and a reliable distribution system for commodities [54]. Additionally, one study concluded that

supplementation programs were cost-effective with high adherence when mothers had frequent contact with trained health workers and a reliable supply of supplements [56]. Another study shows that active and aggressive interventions with high levels of monitoring made folic acid interventions cost-effective [71].

Evidence from the United Kingdom shows that cost-effective folic acid interventions for young and lower-income women should [57]:

- Include a 'package' of complementary components including different communication channels, locations and health promotion approaches to ensure sustainability of interventions [57];
- Focus on high-risk and vulnerable groups [57];
- Involve the families of beneficiaries in the intervention process [57];
- Incorporate folic acid education into school-based sex education [57];
- Work with youth development programs [57];
- Consider peer-delivered approaches [57];
- Provide practical support such as easy access to supplementation [57]; and
- Encourage for the consistent use of folic acid supplements [57].

While the above list does come from a developed setting, lessons can be drawn and customized for applicability in resource poor settings. Therefore, these costs and considerations should be incorporated into the overall cost of an intervention program [54].

Overall take-home lessons from studies focusing solely on the cost-effectiveness of periconceptional supplementation of folic acid establish that periconceptional supplementation of folic acid can result in health gains and that lifetime care costs of spina bifida can be prevented [58]. According to a study conducted in The Netherlands, the costs

of providing periconceptional folic acid supplementation was less than the costs borne due to a case of NTDs, justifying the cost-effectiveness of folic acid supplementation [58].

As stated by a study administered in rural South Africa, which examined the impact of folic acid fortification on NTD prevalence after fortification, found that there was a significant decline of about 66% in NTD related perinatal mortality after fortification [60]. The study effectively estimated the cost-effectiveness of fortification by comparing the direct cost of fortification against the direct cost of minimal medical intervention in the short term, which resulted in a tremendous economic saving [60]. Essentially, the economic benefit from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification [60]. All the aforementioned studies have demonstrated that folic acid interventions have protective effects on the prevention and reoccurrence of NTDs [61].

On the other hand, Grosse et al. clarifies the need to evaluate the harm associated with folic acid intervention programs [65]. It has been recently become a major concern that high folic acid statuses can mask individuals' vitamin B12 deficiencies; individuals with vitamin B12 deficiency can often go undiagnosed with hematologic manifestation of anemia while allowing neurological damage to proceed untreated [65].

4.2 Review 2: CEA of folic acid interventions within the context and space of India

As per the methods section, after Review 2 was conducted, only 4 articles were relevant for inclusion in this paper. The Cochrane Library yielded 55 articles, however upon screening, none were relevant for inclusion for this paper. Search terms and histories can be found in the Methods section above.

Table 2, included below, briefly highlights key information about the selected articles for Review 2.

Table 2: Key findings and summaries of articles included in Review 2.

Author, Year, Country, Article Reference Number	Study Design or Article Type	Folic acid intervention cost-effective?	Concerned with NTDs?	Summary of Relevant Information Provided and Additional Notes
1. Deb 2011, India [75]	Case-control study	N/A	Yes	This study comments on important facts about the policy and programmatic space revolving around folic acid interventions in India. There is no mandatory fortification program in India. It also comments on essential statistics about the prevalence of NTDs in India.
2. Muthayya 2009, India [74]	Literature review	N/A	Yes	This review comments primarily on the status of folic acid consumption in India, which is low mainly due to a lack of folic acid interventions in India.
3. Salvi 2005, India [73]	N/A – Research letter	N/A	Yes	Salvi et al. write this letter to address the major problems with folic acid interventions in India, and call for action to enhance and improve folic acid interventions.
4. Vijayaraghavan 2002, India [72]	Programmatic evaluation	N/A	Yes	This document evaluates the state of folic acid interventions in India. The evaluation concludes that there is even a lack of general micronutrient programs in India.

4.2.1 Folic acid intervention programs in India

NTDs in India has an incidence of 6.51 – 8.21 cases per 1000 live births [73, 75]. NTD incidences also differ between different regions of India; southern Indian states have lower incidence rates than northern states [75]. Results have indicated that this high overall incidence rate is due to a lack of folic acid in the reigning vegetarian diets of South Asians, and compounded by the fact that South Asians also do not customarily consume folic acid supplements [75]. At the same time, according to an article published in Nutrition Reviews, there is a lack of programs effectively addressing even general micronutrient deficiency in India [72]. It has also been acknowledged that folic acid interventions are weak in India [74]. Furthermore, there is no mandated folic acid fortification program in India [75].

4.2.2 Weak nutritional interventions in India

In India today, there are very few micronutrient interventions programs that focus on providing folic acid to women of reproductive age. The most well known program, the National Pilot Program on Control of Micronutrient Malnutrition, was commissioned by the federal government to be piloted in a few states in North India. While the main clearly documented flaw with the program was that the dosage disseminated to the women was between 75-168 micrograms, which is well below the recommended 400 micrograms in order to prevent birth defects [73]. Some of the other constraints and obstacles in adequately providing interventions are listed below:

- Inadequate supplies—quantities of micronutrient supplements often do not cover all the eligible recipients [72, 73];
- Poor outreach and irregular distribution—appropriate audiences are not reached [72, 73];

- Absence of community participation—communities are not prepared or informed about nutritional interventions and their benefits [72];
- Absence of nutrition education—lack of nutritional education did not incentivize beneficiaries to take part in nutritional interventions [72];
- Nonutilization of resources—due to high rates of illiteracy, the community did not make proper use of the resources, often leading to adverse health outcomes [72]; and
- Absence of monitoring and supervision—due to no effective monitoring system of the nutritional interventions programs, there was no ability to make corrections within the course of the interventions to ensure high utilization and adherence [72, 73].

One key fact has which results from the said obstacles should be highlighted: low community participation and high attrition to nutritional supplement programs alludes to the low adherence rate to supplementation regimen. According to a 2005-2006 National Family Health Survey, for 65% of births, mothers received micronutrient supplements but only 23% consumed them for the recommended 90 days [79]. Therefore, the positive and significant statistics reported in aforementioned sections of this paper may largely be due to the highly monitored and evaluated nature of many of the studies. Therefore, while those studies proved to be efficacious within their research capacities, when implemented at a large national scale, they proved to be less effective. Therefore, addressing these limitations would build upon government efforts.

5. Ethical considerations

This thesis research did not have direct affiliations with human subjects, thereby limiting the possibility of ethical malpractices. There may be some limitations with the information put-forth in this paper, as it has not been sourced all from the Indian subcontinent but rather from international databases. Therefore, it may be difficult to interpret the information presented in this paper and directly apply it into India. Generalizability from and external validity of sourced literature is limited.

One ethical consideration would be my limitation in understanding and interpreting the literature included in this paper. Literature sourced may have limitations within them. My generalizations are based on my best judgment and all errors are mine.

However, because this paper aims to examine the cost-effectiveness of folic acid supplementation trials and then make a recommendation for IIPH, there may actually be a beneficial ethical aspect to this study—to ensure efficient and effective utilization of resources that IIPH would include for the dissemination of folic acid interventions. This study would also contribute to literature in understanding the CEA of folic acid supplementations (and other modes of appropriate interventions) in India that may be able to be extrapolated into other similar spaces.

6. Discussion: recommendation of framework

As mentioned in the results and analysis section, there is a high incidence rate of NTDs in India, however there are very few nutritional interventions, and almost no folic acid interventions, in India. While this is the basis for IIPH's multifold study (as outlined in more detail in the Acknowledgement sections), a component of their study also aims to examine the cost-effectiveness of their proposed interventions. After having had assessed the results and analyzed them, this section will now outline a very detailed list of items (costs, impacts, benefits, etc. as highlighted in the results and analysis section) to consider and include when IIPH conducts its cost-effectiveness analysis for their folic acid interventions.

Beforehand, however, there needs to be a brief discussion on the overall limitations with the results reported and their implications towards the recommendation and future policy work for India. Many of the studies that reported encouraging statistics of the impact of folic-acid fortification on their respective populations were monitored and evaluated regularly, which is a recurring theme for any programmatic effort. Further, the academic and controlled nature of these studies hinder their external validity; while many of the studies demonstrated to be efficacious in their conclusions, when looking at statistics collected by the National Family Health Survey in India, such interventions had low adherence rates therefore implying suboptimal utilization of interventions. Therefore, something to consider when examining the recommendation below is that without high utilization and active participation into the folic acid intervention programs administered through policy, even a very cost-effective intervention will not have an optimal and positive effect on addressing the

burden at hand. In such cases cost-effective interventions' dissemination strategy, education campaigns, and implementation will have to be revisited.

After examining literature (as per the Current Literature section), looking at the cost-effectiveness of folic acid simply in relation to its impact on preventing NTDs may actually be quite limiting to the CEA. This is because of the known fact that folic acid and interventions providing it may actually have numerous additional benefits on the health statuses of mothers and newborns. Therefore, measuring a whole set of additional health outcomes that folic acid impacts along with NTDs may represent folic acid interventions more accurately as cost-effective. IIPH should study additional literature on health outcomes that are impacted by the consumption of folic acid and aim to collect data on these outcomes' incidence and prevalence.

Furthermore, in order for the federal government of India and IIPH to truly understand the burden of NTDs in their context, and with a lack of global DALY estimates in reference to folic acid interventions and NTDs, it is advisable that they utilize the information collected based on the frameworks below to construct and estimate their own DALY estimates. This will allow for a holistic assessment of the burden of NTDs in the Indian context.

It should also be noted that data collection on productivity and diminishing productivity due to caregivers and families caring for children with NTDs is not included in the framework below. This is largely due to a contextual understanding that caregivers for children in India are often mothers, who primarily are not active participants of the labor force. However, should it be feasible to collect this data, it may be interesting to examine to challenge the aforementioned claim. Moreover, including specific productivity costs may

double-count inputs and outputs that are already highlighted and accounted for in the Tables below.

The "framework", found below, has been broken into two separate tables: Tables 3 and 4. Table 3 will primarily highlight inputs that the government (and its agencies such as IIPH) will be anticipated to spend on administering and implementing the folic acid intervention. Table 4 will discuss the outputs that will result from IIPH's folic acid interventions. A part of the outputs highlighted in Table 4 will be the costs borne from NTDs, and these costs can be utilized to estimate cost-savings with implementing folic acid interventions.

The two Tables below will be cognizant to include those inputs and outputs that are specific to the context of the Indian subcontinent to address the constraints and barriers to implementing quality folic acid interventions. In terms of outputs, a CEA can take two different paths. First, it can compare the inputs against the number of children (and their mothers) it is able to reach. This approach would help determine if the interventions are cost-effective in terms of their inputs and outreach. Second, the inputs of the intervention can be compared to the overall consequences borne due to providing no folic acid intervention, where the output would be the costs associated with a case of NTDs. The framework encourages the collection of data on indirect costs mainly to allow for the evaluation of the intervention's implementation and appropriateness from a holistic and comprehensive standpoint. This information will allow IIPH, from a public health sector perspective, to construct and improve its intervention by taking into account the indirect costs that the intended beneficiaries of the intervention incur.

This framework considers the perspective of input costs from a public health systems standpoint and output costs and effectiveness from a social societal standpoint. Hence, the

framework's vantage point is in line with the mission of IIPH and should be comprehensive enough to give IIPH a good start in data collection for ultimately completing a CEA on their folic acid interventions.

Table 3: Descriptions of inputs to consider when evaluating IIPH's folic acid interventions' cost-effectiveness from the public perspective of the government

Input	Rationale for including this item
Costs and **quantities** of medical supplies (supplements, fortification powders, etc.) including: • packaging costs	Ensuring that the appropriate quantities of supplies/supplements are available for the interventions will directly impact the number of mothers being outreached to, which will ultimately determine the effectiveness of the intervention.
Cost of distributing and storing supplements and other components of the folic acid interventions including: • transportation costs • personnel (income) costs	These inputs are needed to effectively estimate the costs in actually disseminating the supplements and various intervention components for the successful implementation of the interventions.
Cost of outreach (promotional, educational, marketing, etc.) strategies including: • personnel (income) costs • training costs • transportation costs • media advertisement costs • print costs (i.e. posters, etc.) • incentive costs (i.e. free antenatal care visits, etc.) • other logistical and material costs	For the intervention to be successful it has to include, serve and cater towards the right audiences and beneficiaries. This also goes in line with addressing the problem of lack of community participation in India. If proper promotional tools are utilized to advertise the interventions, then communities would be more educated about the nutritional interventions and also be more inclined and convinced to take part in them. Furthermore, with appropriate outreach strategies, the issue of nonutilization of resources could also be addressed.
Cost of monitoring and supervising of interventions including: • personnel (income) costs • training costs • transportation costs • technology costs	Without close monitoring and supervision, nutritional programs that may be proceeding ineffectively may not be amended in time to regain their effectiveness. Furthermore, in order to accurately track the costs and effectiveness of the folic acid interventions to conduct a CEA, monitoring and supervision will also have to be in place. Rigorous training will have to be provided to ensure that the right data are collected and reported to the right individuals in a reliable and prompt fashion.

• other logistical costs	
Costs of institutional administrative costs in running the interventions including: • personnel (income) costs • training costs	These costs include the actual staff that are running and implementing the interventions at the various levels – national, districts, and village. Staff that should be included are: doctors, nurses, health workers, research assistants, principle investigators, etc.

Table 4: Descriptions of outputs to consider when evaluating IIPH's folic acid interventions' cost-effectiveness from a social (societal) perspective

Output	Rationale for including this item
Number of women outreached to (to be categorized as an outreached women, she would have to be actively consuming folic acid supplements or other products of folic acid interventions)	This output is essential in understanding whether the efforts and inputs associated with the folic acid interventions are being delivered to a sizable and large enough audience making the folic acid intervention cost-effective. This would help address whether this output (the number of women outreached to) outweighs the inputs. Furthermore, it would be extremely important to ensure that for women to be classified under this measure, they would have to be active participants of the folic acid interventions and consuming the products of their respective intervention.
Number of NTD cases for all pregnancies provided with the folic acid interventions (to compare the number of children born without NTDs to the number of children born with NTDs)	First, this measure would be crucial in understanding whether the folic acid interventions are even being effective at an intervention level. Second, this output would clearly address whether certain aspects of the interventions are being cost-effective or not (in terms of ensuring that the appropriate populations are being outreached to, etc.). Clearly including data on this would help identify where the intervention needs more development, where the interventions' strengths are, etc.
Costs of living with NTDs including: • hospitalization after birth costs • surgery costs (cleft palette, neural tube closure, etc.) including all necessary costs associated with surgery • outpatient follow-up costs • travel and transportation costs for follow-up or regular hospital visits • costs of comorbidities	These costs will estimate what the realistic costs are for every case of NTDs. These costs will highlight whether the costs of inputs are more or less than the costs associated with being born with NTDs and having to suffer the lifelong costs associated with NTDs. These costs will be direct costs for the child with NTDs for the rest of his or her life.

associated and resulting from NTDs including further hospitalization, treatment, accommodation, etc.	
Indirect costs such as: • costs associated with production losses by caregivers (including parents) • costs associated with production losses by child (and adults) with NTDs • costs associated with premature loss of life • special education costs to society	While these indirect costs do not necessarily need to be factored into IIPH's CEA, it is instrumental to consider and understand them to really understand all the costs associated with the lack of folic acid interventions (which may result in more births affected by NTDs). Assessing indirect costs will also allow IIPH to review its intervention more holistically and implement a more comprehensive and appropriate intervention.

7. Conclusion

The framework highlighted in the previous section aims to provide a comprehensive list of elements or items to consider when IIPH conducts its CEA. Writing this paper also led to the understanding of a multitude of additional lessons and nuances that exist when attempting to conduct a CEA, which IIPH can refer to in the literature review and results sections of this paper. Although traditionally CEA only consider direct costs, understanding the indirect costs that beneficiaries would encounter in India would be extremely important as these costs may impact utilization, uptake and adherence to IIPH's folic acid intervention. Focusing on addressing participation into the interventions will ensure that the intervention's impact is optimal on beneficiaries.

Finally, it will be key that IIPH employs careful and aggressive monitoring and evaluation as conducting a CEA requires data that is thorough and comprehensive. The benefits of extensive monitoring and evaluation would also provide other insightful data and lessons that can be extrapolated as best practices.

Understanding costs-effectiveness from the two perspectives of Tables 3 and 4, through the government's perspective (inputs) and society's perspective (outputs), will lead to a comprehensive understanding of the role IIPH's folic acid interventions will play. Should the interventions be found to be cost-effective, this would contribute towards the evidence base advocating for further understanding the public cost of preventing illnesses and adverse health conditions. Hence, such interventions will shift the paradigm of funding; ensuring that more funding is appropriated towards prevention instead of treatment. If the cost-savings are high and overwhelm the costs of providing specific interventions, in the

future, the federal government would be able to foster more programmatic efforts on preventive interventions.

8. Appendix 1 – Tables (methods)

Table 5: Folic acid supplementation and cost-effectiveness analysis; the goal was to identify articles focusing on pre-, peri-, and postconception supplementation.

SEARCH DATE and DATABASE	SEARCH TERMS	TOTAL ARTICLES YIELDED	TOTAL RELEVANT ARTICLES
September 18, 2012 on PubMed	((("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields]) AND ("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields] OR "supplementation"[All Fields])) OR (("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields]) AND ("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields] OR "supplementation"[All Fields]))) AND (("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]) AND ("analysis"[Subheading] OR "analysis"[All Fields]))	30	7
September 21, 2012 on The Cochrane Library	folic acid supplementation in All Fields AND cost effectiveness analysis in All Fields	79	1

Table 6: Variations of folic acid supplementation/micronutrient supplementation/iron supplementation, pregnancy/pregnant women/preconception/periconception/postconception, NTDs/neural tube defects/anencephaly/encephaloceles/spina bifida/hydranencephaly/iniencephaly/schizencephaly/oro-facial cleft/cleft lip, and cost-effectiveness analysis.

SEARCH DATE and DATABASE	SEARCH TERMS	TOTAL ARTICLES YIELDED	TOTAL RELEVANT ARTICLES
September 21, 2012 on PubMed	(((((“folic acid”[MeSH Terms] OR (“folic”[All Fields] AND “acid”[All Fields]) OR “folic acid”[All Fields]) AND (“dietary supplements”[MeSH Terms] OR (“dietary”[All Fields] AND “supplements”[All Fields]) OR “dietary supplements”[All Fields] OR “supplementation”[All Fields])) OR ((“trace elements”[MeSH Terms] OR (“trace”[All Fields] AND “elements”[All Fields]) OR “trace elements”[All Fields] OR “micronutrient”[All Fields] OR “trace elements”[Pharmacological Action] OR “micronutrients”[MeSH Terms] OR “micronutrients”[All Fields] OR “micronutrients”[Pharmacological Action]) AND (“dietary supplements”[MeSH Terms] OR (“dietary”[All Fields] AND “supplements”[All Fields]) OR “dietary supplements”[All Fields] OR “supplementation”[All Fields])) OR ((“iron”[MeSH Terms] OR “iron”[All Fields]) AND (“dietary supplements”[MeSH Terms] OR (“dietary”[All Fields] AND “supplements”[All Fields]) OR “dietary supplements”[All Fields] OR “supplementation”[All Fields]))) AND (“pregnancy”[MeSH Terms] OR “pregnancy”[All Fields]) OR (“pregnant women”[MeSH Terms] OR (“pregnant”[All Fields] AND “women”[All Fields]) OR “pregnant women”[All Fields]) OR preconception[All Fields] OR periconception[All Fields] OR postconception[All Fields]) AND NTDs[All Fields] OR (“neural tube defects”[MeSH Terms] OR (“neural”[All Fields] AND “tube”[All Fields] AND “defects”[All Fields]) OR “neural tube defects”[All Fields]) OR (“anencephaly”[MeSH Terms] OR “anencephaly”[All Fields]) OR encephalocoeles[All Fields] OR (spina[All Fields] AND finda[All Fields]) OR (“hydranencephaly”[MeSH Terms] OR “hydranencephaly”[All Fields]) OR (“neural tube defects”[MeSH Terms] OR (“neural”[All Fields] AND “tube”[All Fields] AND “defects”[All Fields]) OR “neural tube defects”[All Fields] OR “iniencephaly”[All Fields]) OR (“malformations of cortical development”[MeSH Terms] OR (“malformations”[All Fields] AND “cortical”[All Fields] AND “development”[All Fields]) OR “malformations of cortical development”[All Fields] OR “schizencephaly”[All Fields]) OR (oro-facial[All Fields] AND cleft[All Fields]) OR (“cleft palate”[MeSH Terms] OR (“cleft”[All Fields] AND “palate”[All Fields]) OR “cleft palate”[All Fields]) OR (“cleft lip”[MeSH Terms] OR (“cleft”[All Fields] AND “lip”[All Fields]) OR “cleft lip”[All Fields])) AND ((“cost-benefit analysis”[MeSH Terms] OR (“cost-benefit”[All Fields] AND “analysis”[All Fields]) OR “cost-benefit analysis”[All Fields] OR (“cost”[All Fields] AND “effectiveness”[All Fields]) OR “cost effectiveness”[All Fields]) AND (“analysis”[Subheading] OR “analysis”[All Fields]))	125	13
September 21, 2012 on The Cochrane Library	folic acid supplementation OR micronutrient supplementation OR iron supplementation in All Fields AND pregnancy OR pregnant women OR preconception OR periconception OR postconception in All Fields AND NTDs OR neural tube defects OR anencephaly OR encephalocoeles OR spina finda OR hydranencephaly OR iniencephaly OR schizencephaly OR oro-facial cleft OR cleft palate OR cleft lip in All Fields AND Cost effectiveness analysis in All Fields	20	2

Table 7: Search conducted to understand the landscape of folic acid interventions in India using variations of the following search terms: folic acid supplementation and India.

SEARCH DATE and DATABASE	SEARCH TERMS	TOTAL ARTICLE YIELDED	TOTAL RELEVANT ARTICLES
September 14, 2012 on PubMed	("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields]) AND ("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields] OR "supplementation"[All Fields]) AND ("india"[MeSH Terms] OR "india"[All Fields])	147	4
September 21, 2012 on The Cochrane Library	folic acid supplementation in All Fields AND india in All Fields	55	0

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