Evaluating the Impact Adding Iron Supplementation to School-based Deworming Programs on Cognitive Development for School-age Children

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Abstract

School-age children bear the most burden of worm infection, and are therefore at highest risk for developing iron deficiency anemia. Routine deworming of school children in schools in areas that are endemic of soil-transmitted helminths (STH) is among the most safe and cost-effective way to deliver deworming pills regularly to children. Schools offer a readily available, extensive and sustained infrastructure with a skilled workforce that is in close contact with the community (The World Bank., 2009).

The impact of routine school-based deworming on nutrition status, hemoglobin, cognition, or school performance of school aged children has recently been questioned in two systemic reviews (Taylor-Robinson, Maayan, Soares-Weiser, Donegan, & Garner, 2015), (Hall, 2007). While experts agree that deworming is a necessary intervention to stop the spread of STH infections (Mascarini-Serra, 2011), (Taylor-Robinson et al., 2015), there is a question on the need to integrate interventions such as iron supplementation with nutrition supplementation programs that contributes to improving health status, productivity, economic development, and poverty reduction.

This systematic literature review analyzed and compared twenty-four studies (randomized control trials and program evaluations) of iron supplementation carried out on children aged 5-19 years in STH endemic areas. Although only a limited number of studies examined the effects of iron supplementation on school performance, at least 20 of the studies showed an improvement in hemoglobin status and anemia prevalence. Additionally, studies in the review shows that integrating iron supplementation if feasible and there have been no adverse events reported, with the exception of two studies that showed increased morbidity with supplementation in South Africa and Kenya.

Evaluating the impact of the addition of Iron Supplementation to school-based deworming programs on cognitive development for school-age children

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Evaluating the impact of the addition of Iron Supplementation to school-based deworming programs on cognitive development for school-age children

CHAPTER 1: INTRODUCTION

Soil transmitted helminth (STH) infections present a real danger to the economic development in low-income countries. Intestinal parasites impair physical and mental growth of children, therefore obstructing educational achievement, which ultimately hinders economic development. By the year 2009, of the one billion individuals worldwide who had Ascaris lumbricoides (roundworms), 400 million were school-age children (WHO, 2014). In that same year, 750 million people including 300 million children of school age were found to have Trichuris trichiura (whipworms). Hookworms (Ankylostomiasis) infections were also reported to have affected 750 million, of whom 170 million were children (WHO, 2014). Overall, approximately 2 billion people are infected with STH, majority of the cases occur more commonly and more intensely among school-aged children(WHO, 2014). Furthermore, in 2014, the World Health Organization (WHO) identified that over 600 million school-age children worldwide live in areas where STHs are intensively transmitted (WHO, 2014).

Based on the recognized burden, a workshop lead by McGill University and Pan American Health Organization (PAHO) held in the PAHO region in 2011, a call to action on the need for treatment of school age children (SAC) was made, in response to the cognitive deficits caused by STH infections, which include impairment of concentration and memory (PAHO; McGill University, 2011). School based deworming programs in the PAHO region aim to prevent and control anemia caused by STH infections in school children with an ultimate goal of improving children's health and improving their school performance (PAHO; McGill University, 2011).

WHO has termed the health consequences of iron deficiency anemia (IDA) resulting from STH infections, as stealthy but devastating, invisibly eroding the development potential of individuals, societies and national economies (WHO, 2014). Poor school performance is among the many devastating health consequences of IDA. An article by the Center for Global Development showed that in many poor countries, for each additional year of schooling missed, individuals lose up to about 10% of lifetime wages (Center for Global Development, 2002). These earnings, could potentially contribute to the country's economic growth. No country has ever achieved continuous and rapid growth without reaching an adult literacy rate of at least 40% (Center for Global Development, 2002). It is, therefore, very important that health and nutrition interventions that focus on improving school performance and ultimately a community's education status be made a priority in developing countries.

The global prevalence of anemia in school-age children is 25.4% (WHO, 2008). The current WHO guidelines on the use of supplements to prevent and treat iron deficiency anemia recommend school-based antihelminthic chemotherapy (deworming) for the prevention and treatment IDA resulting from helminth infections, particularly for populations with endemic helminthic parasites (WHO, 2005). However, the guidelines acknowledge that a most effective strategy for anemia control in these regions would be to combine anthelminthic therapy with iron and folate supplementation (WHO, 2005). This recommendation came a few years after United Nations Children's Fund (UNICEF) made a specific connection between deworming and the promotion of child development, which also acknowledged the simplicity, safety and cost-effectiveness of deworming (UNICEF, 2002). Moreover, the World Bank identified schools as a key platform through which to promote good health and provide nutrition interventions in communities.

Problem Statement

Previous reviews aiming to assess nutritional benefits following school-based and other population-based deworming programs have provided mixed results. While there are reviews that show the benefits of school-based deworming alone, other reviews reflect limitations in the ability to detect modest development gains, especially when a substantial proportion of the population is uninfected. Moreover, a lack of high quality longitudinal data has been a major impediment in this area of research.

Although there are several reviews of existing literature on the benefits of deworming in combination with micronutrient supplementation such as vitamin A, folate and iron, there is no systematic review that has focused on the impact of iron supplementation plus deworming on school age children. Specifically, no review has evaluated the feasibility and the impact of adding iron supplementation to deworming on school performance of school-age children. As such, an assessment of existing studies is needed to determine if there are any positive or negative impacts of including iron supplementation in school deworming programs.

Theoretical Framework

Protection Motivation Theory

This study will attempt to develop key questions for the scalability of adding iron supplementation to school-based deworming programs based on the protection motivation theory (PMT). The PMT framework may offer a theoretical basis to understanding why certain countries such as India already have policies for the integration of iron supplementation into school systems, , and why others have not. Table 1 below describes the four unifying key components of the PMT model: severity, vulnerability, response efficacy and response costs which will be used in this study to harmonize the diverse literature.

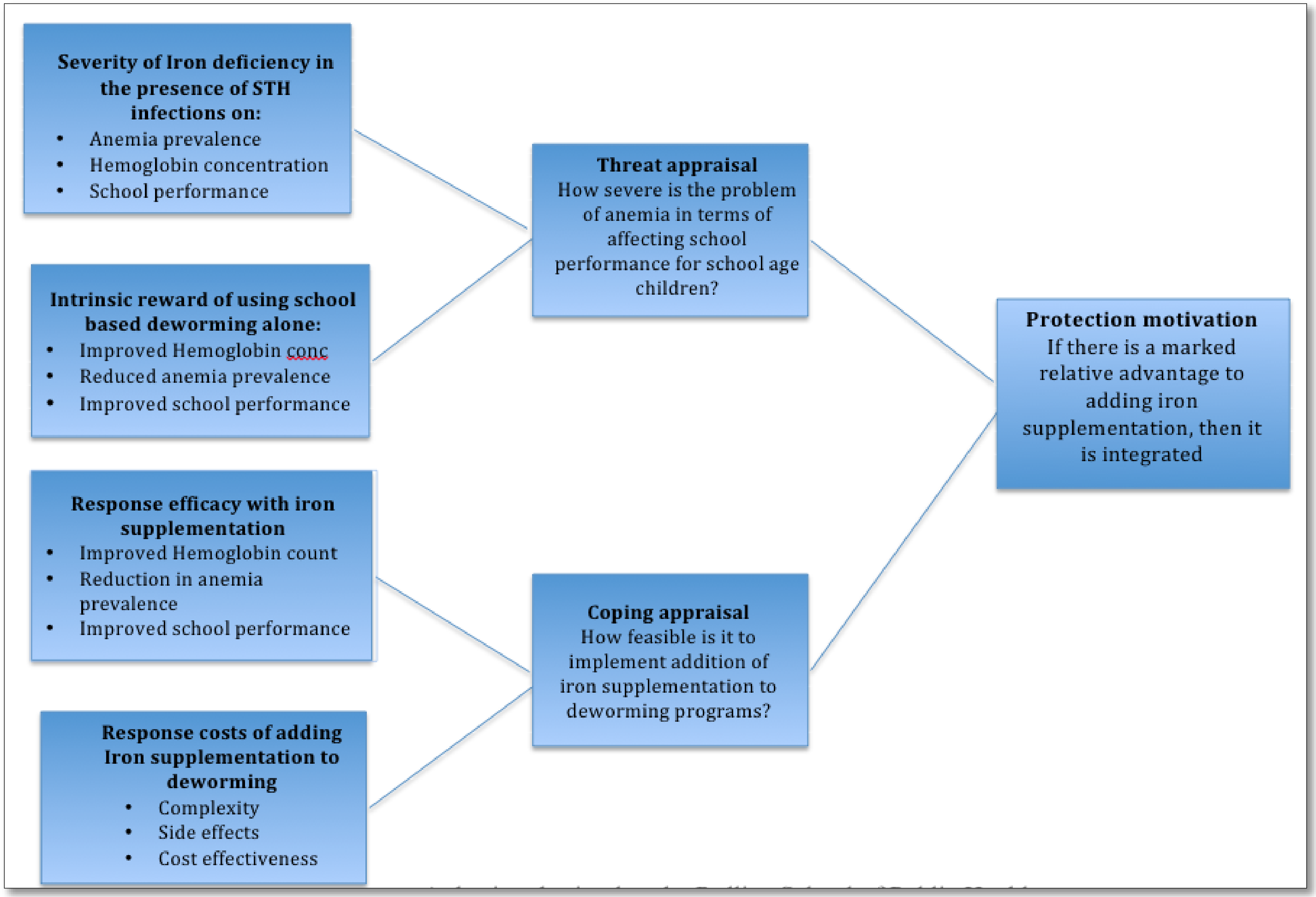
Table 1: Key Components of the Protection Motivation Theory

Severity	How severe are the consequences of the health threat?
Vulnerability	How probable is it that a negative health consequence will result from avoiding the recommended health behavior?
Response efficacy	How effective is the recommended health behavior in preventing the negative consequences?
Response costs	To what extent is it possible to perform the recommended health behavior successfully?

Copied from: Protection Motivation Theory, Norman, Paul and Boer, Henk and Seydel, Erwin R. (1996)

Although PMT was originally proposed as a conceptual framework for understanding fear appeals, Rogers revised it in 1983 to extend it to a more general framework of persuasive communication, with an emphasis on the cognitive processes mediating change (National Cancer Institute, 2008). PMT has been recommended for use with preventive interventions for specific groups at risk such as, HIV prevention, tobacco control and breast cancer prevention. The framework offers a basis for assessing vulnerability and ultimately the efficacy and cost of response. The model has also been used to predict the likelihood of the occurrence of desired behavior change. As such, this study will use the PMT framework to assess the impact and feasibility of the addition of iron supplementation component into school deworming programs. Figure 1 below conceptualizes how this review will be conducted based on the PMT which sets a basis for two overarching questions: 1) how severe is the problem of anemia following the response given using deworming strategies; and 2) how feasible is it to implement an additional component to school based deworming such as that or iron supplementation. To describe the severity of the problem would require a review and analysis of the added benefits of iron supplementation to school-based deworming.

Figure 1: Protection Motivation Theory



Copied and modified from: http://www.biomedcentral.com/1471-2458/7/104

Research Questions

Based on the framework set by the PMT, this systematic literature review will address four critical questions on the integration of iron supplementation into deworming programs:

1. What is the severity of iron deficiency anemia in the presence of STH infections?
2. Does deworming alone without iron supplementation impact hemoglobin concentration, anemia prevalence and school performance?
3. Does the addition of iron supplementation to school-deworming programs have an added benefit in terms of hemoglobin concentration, anemia prevalence and school performance?
4. What are the associated costs of response? In other words, how feasible is it to integrate iron supplementation to school deworming programs? Is it a cost effective strategy?

In order to assess the effects of the integration of deworming and iron supplementation, an analysis of the several components of intervention studies including; the study design, the country and target population, the sample size, the -intervention, the duration of the study and the measurable outcomes used. The focus of this review is on iron or iron and folate supplementation plus deworming specifically for children of school going age. Additional consideration will be given to morbidity patterns emanating from iron supplementation such as malaria and other reported illness in the studies resulting in school absence.

Significance Statement

An emerging body of international literature suggests that investment on the overall wellbeing of children in developing countries plays an important role in contributing to a country's economic development by raising their educational performance (Nugent, 2008). Recent macroeconomic estimates suggest that the average impact of iron deficiency anemia resulting from STH infections could lead to a 4 percent drop in Gross Domestic product (GDP) through both physical capacity and cognitive losses in developing countries (Horton & Ross, 2003). Through its impact on school performance, iron deficiency anemia could also be central to understanding the cycle of poverty in the context of soil-transmitted helminthiasis.

Existing research makes a convincing case that there are nutrition and health interventions that improve school performance by improving cognitive abilities, concentration and regular school attendance (WHO, 1998). While there has been a large amount of literature linking treatment of IDA and improved school performance in school children, (Karande & Kulkarni, 2005) (Bobonis, Miguel, & Puri-Sharma, 2006) , there has been differing opinions over whether deworming schoolchildren in developing countries improves nutritional outcomes, school attendance or educational achievement.

The aim of this systematic review of literature is to assess the dynamics around integration of iron supplementation into school-based deworming programs. This study will review trials and program evaluations conducted in STH endemic and high anemia prevalence countries where iron supplementation has been conducted. This systematic review of literature proposes to add to the value of using findings from already conducted studies, in the hopes of assisting policy makers understand the impact of adding iron supplementation to school based deworming and how feasible it is to implement iron supplementation in countries as well as to identify research gaps.

Definition of terms

School based deworming programs are programs that provide medical treatment for soil-transmitted intestinal worms and schistosomiasis, as well as, preventive health education to children of school going age with an objective to reduce serious worm infections and reduce the detrimental effects resulting from these infections. Deworming is carried out in schools under the supervision of teachers following the receipt of signed permission slips from parents (Deworm the World, 2010).

Iron supplementation is the ingestion of an oral product (tablet or liquid) that contains dietary iron with an aim to treat existing IDA by adding further nutritional value to the diet. Supplements may be administered in the form of ferrous sulphate supplements, iron plus folic acid, or multivitamin tablets or liquid. Iron supplementation is a primary intervention for the prevention and control of IDA until either significant improvement are made in the diets of entire populations or food fortification is achieved (WHO, 2005).

<u>CHAPTER 2:</u> BACKGROUND

Introduction

The review of literature on soil transmitted helminthes (STH) and iron deficiency showed that iron deficiency anemia (IDA) is the most worrisome outcome of STH infections (WHO, 2014). IDA a result of helminthes infestation results in serious economic consequences and is therefore an obstacle to national development (WHO, 2015). According to WHO, the poorest and the least educated populations are disproportionately affected by IDA and would gain the most from the reduction of IDA (WHO, 2015).

A 2007 World Development report showed a number of countries offer iron supplementation to schoolchildren. However many countries such as Benin and Cameroon, where close to 50% or more of the young girls are anemic, do not offer school-based iron supplementation (World Bank, 2006). This is despite the fact that it has been estimated through cost ratio studies, that one dollar invested in iron supplementation will yield 26 to 45 dollars in return(World Bank, 2006).

Socio-economic Burden of Iron Deficiency anemia due to STH infections

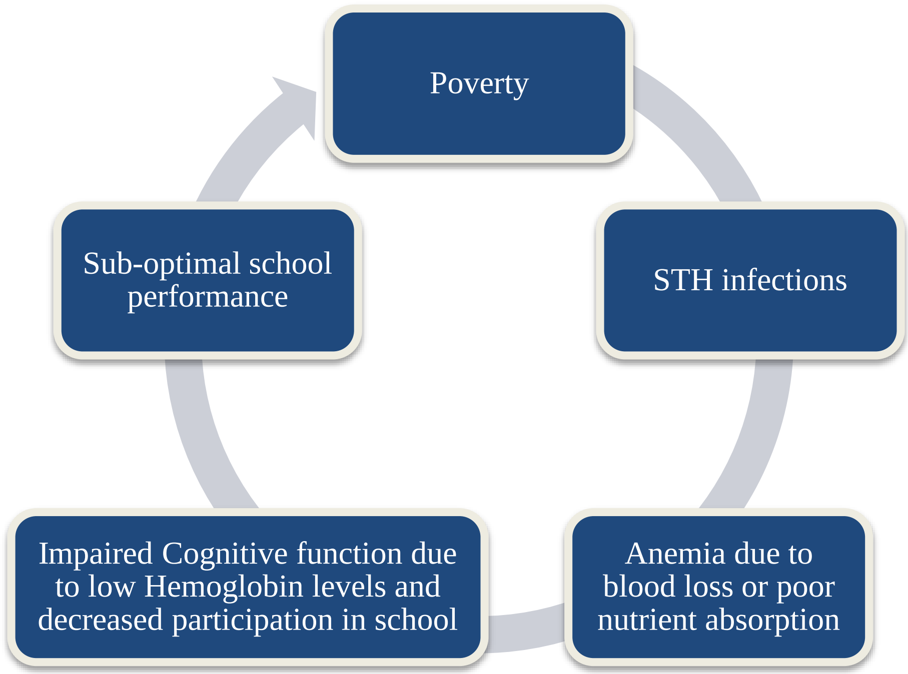
Widespread poverty resulting in chronic and persistent hunger is the single biggest scourge of the developing world today (Penney, Brown, Maguire, Kuhn, & Monsivais, 2015). With minimal analysis, it is apparent that schooling levels differ dramatically between developing and developed countries. As such, achieving education is a critical element of the Millennium Development Goals and therefore should naturally be integrated into productive development strategies, by raising school participation.

Although there are a myriad of uncertainties associated with improving school performance and subsequently economic development, it is certain that raising education attainment among other factors is correlated with more fundamental forces of economic development (Eric A. Hanushek, 2008). Poverty on its own limits the chances of educational attainment, while education is one of the prime mechanisms for escaping poverty (Brown & Pollitt, 1996).

From the WHO fact sheet on STH infections, impaired cognitive development results from micronutrient deficiencies, a consequence of parasitic infections in children (WHO, 2014). There is a strong co-relation between hemoglobin (Hb) level and cognitive achievements of individuals (Petranovic, Batinac, Petranovic, Ruzic, & Ruzic, 2008). Additionally, there is a significant negative correlation between worm burden and Hb level. Besides impairing cognitive development, helminth infections appear to constitute a very real barrier to children's progress in school due to high rates of absenteeism, under-enrollment and attrition. Although little evidence has linked helminth infections with intellectual development, the physical consequence of worm burdens, such as IDA significantly impacts cognitive development and educational achievement (Nga et al., 2011). A recent study on iron deficiency and cognitive achievement among school-aged children and adolescents in the United States showed that the impact of iron deficiency on cognition was best demonstrated among children that had the highest prevalence of iron deficiency (Halterman, Kaczorowski, Aligne, Auinger, & Szilagyi, 2001).

The heartbreaking fact is that children of school going age are the most affected by STH infections (GSK, 2012).The World Bank says STHs cause more ill health in school-age children (age 5–15 years) than any other infection in already economically deprived communities (Rajagopal, Hotez, & Bundy, 2014). Malnutrition secondary to STH infections has a significant impact on growth and physical development of children. Ultimately, economic development in poor communities continues to be hindered due to limitations in educational attainment as a result of impaired cognitive development caused by STH infections. This is one among many other plausible barriers to raising education status (GSK, 2012). Figure 2 below shows the continuous re-enactment of poverty makes individuals to be at increased risk of STH infections, which leads to under-nutrition. This compromised nutrition status manifests as micronutrient deficiencies, which includes anemia. Cognitive functions are subsequently impaired due to low hemoglobin and decreased participation in school. All these result in sub-optimal school performance, which reduces earning capacity, leading to further poverty, and the vicious cycle goes on.

Figure 2: The Cycle of Poverty in the context of STH infections



Copied and modified from: FAO Cycle of Poverty

http://www.fao.org/docrep/x0172e/x0172e05.htm

Given the high prevalence of STH infections among the children of school going age, this age group has the highest risk for IDA. WHO defines anemia as a condition in which the hemoglobin content of the blood is lower than normal (WHO, 2005). In developing countries, the prevalence of anemia among school age children is 40%, classified as a severe public health problem (Assefa, Mossie, & Hamza, 2014). Iron deficiency anemia (IDA) mostly results from parasitic infections, and is very common in the regions with severe cases of anemia such as Asia, Africa and South America (R.C. Mishra, 2009).

Anemia and malnutrition are as a result of the reduced absorption of nutrients in the body and intestinal bleeding caused by STH infections (Rajagopal et al., 2014). As a result, school aged children are often either too sick or too tired to attend school or concentrate in class (Rajagopal et al., 2014). Data from the WHO database on anemia from 2005 shown on Table 2 below indicates that, of the 1.62 billion people suffering from anemia, non-pregnant women are 468.4 million, making up the highest sub population.. The second highest burden occurs among school aged children (inside the red triangle) who make up 305 million of cases. .

Table 2: Anemia Prevalence Among School Aged Children compared to other Populations Globally

Population group	Prevalence of anemia		Population affected	
	Percent	**95% CI**	**Number (millions)**	**95% CI**
Preschool-age children	47.4	45.7-49.1	293	283-303
School-age children	25.4	19.9-30.9	305	238-371
Pregnant women	41.8	39.9-43.8	56	54-59
Non-pregnant women	30.2	28.7-31.6	468	446-491
Men	12.7	8.6-16.9	260	175-345
Elderly	23.9	18.3-29.4	164	126-202
Total population	**24.8**	**22.9-26.7**	**1620**	**1500-1740**

Copied from: http://www.who.int/vmnis/anaemia/prevalence/summary/anaemia_data_status_t2/en/

Risk Factors for Iron Deficiency Anemia in STH Endemic Countries

Understanding the risk factors for both STH infections and IDA has a public health significance. Several studies have shown that STH infection is a significant risk factor for anemia and IDA (Ngui, Lim, Chong Kin, Sek Chuen, & Jaffar, 2012). Additionally, a growing body of evidence shows that, besides helminth infections, malaria and malnutrition are also associated with anemia and IDA (Knopp et al., 2010).

Secondary to the morbidity risk factors there are the socio-economic and demographic factors that either contribute to or result from STH infections and IDA.

Poverty is the greatest risk factor for helminth infections (Battle, 2009). A poor economy is likely to result in poor sanitation, poor access to healthcare and little to no health education programs (Brown & Pollitt, 1996). Poor sanitation due to poverty increases a child's risk to getting STH infection. Secondly, poverty leads to insufficient access to iron rich foods. Some studies have also pointed to the seasonal occurrence of IDA which corresponds to the variation in the production of iron rich foods (Knopp et al., 2010).

Interventions

a) School Based Deworming

Compared with other education interventions, school-based mass deworming is a very cost-effective method of improving school performance. School-based deworming costs less than 50 US cents per child per year after taking into account: teacher training, drug procurement and distribution. **Table** 3 below summarizes the recommended dosage by age and the cost of procurement for each dose. The main drugs used to treat STH infections among children who are more than 12 months old are Albendazole 400 mg or Mebendazole 500 mg. Each of these therapies costs as little as 3 cents per tablet. Schistosomiasis on the other hand is treated using Praziquantel 600 mg, administered based on weight, and typically costs about 10 cents per tablet.

Table 3: Summary of Cost of Deworming in US ($)

Worm Infection	Drugs and Dosages	Notes	Cost (US)
STH	Albendazole 400mg (single dose) OR	• 1 – 2 years of age – ½ a tablet. • 2 years of age and above – 1 tablet.	3 cents per tablet
	Mebendazole 500mg (single dose)	• 12 months old and above – 1 tablet. • <12 months – do not treat children.	
Schistosomiasis (Urinary or Intestinal)	Praziquantel 600mg (Praziquantel 40mg/kg)	Where there are scales, doses can be based on weight otherwise it should be based on height using a praziquantel tablet pole.	10 cents per tablet

Copied from: School-based deworming: A planner's guide to proposal development for national school-based deworming programs, Deworming the World, 2010

Successful implementation and uptake of mass deworming interventions benefits the poorest individuals who are at the greatest risk of exposure to worms(e.g. due to poor sanitation) and the most vulnerable to infection (e.g. due to poor nutritional status) (Hall, Hewitt, Tuffrey, & de Silva, 2008) and may improve health equity . The WHO 2013 map in **Figure 3** shows the number of school age children and preschool age children requiring preventive chemotherapy for soil transmitted helminthiases. The list of countries listed with the number of children is shown in **Appendix 1:** India, Nigeria, Indonesia and Bangladesh are among the top four countries.

Micronutrient co-interventions suggested by some experts are expected to improve well-being, growth, cognitive development, and educational performance of those at risk. However, mediating factors, which affect the causal pathway, include poverty, under-nutrition, hygiene, sanitation, prevalence and intensity of infection and co-infections and should be taken into consideration (Hall et al., 2008).

b) Iron Supplementation for School Children

The current WHO guidelines recommend the intermittent administration of iron supplements as a public health intervention for school aged children in settings where the prevalence of anemia is 20% or higher (WHO, 2005). Table 4 below shows the WHO definitions of anemia as a public health problem, by ranking the four categories of public health significance. Where anemia is highly prevalent, a lot of literature shows that food fortification may not be sufficient and iron supplementation becomes necessary (Rohde, 1990).

Table 4: Hemoglobin Thresholds for Classifying Anemia as a Public Health Problem(WHO, 2008)

Prevalence of anemia (%) health	Category of public health significance
≤4.9	No public health problem
5.0–19.9	Mild public health problem
20.0–39.9	Moderate public health problem
≥40.0	Severe public health problem

Copied from: http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf

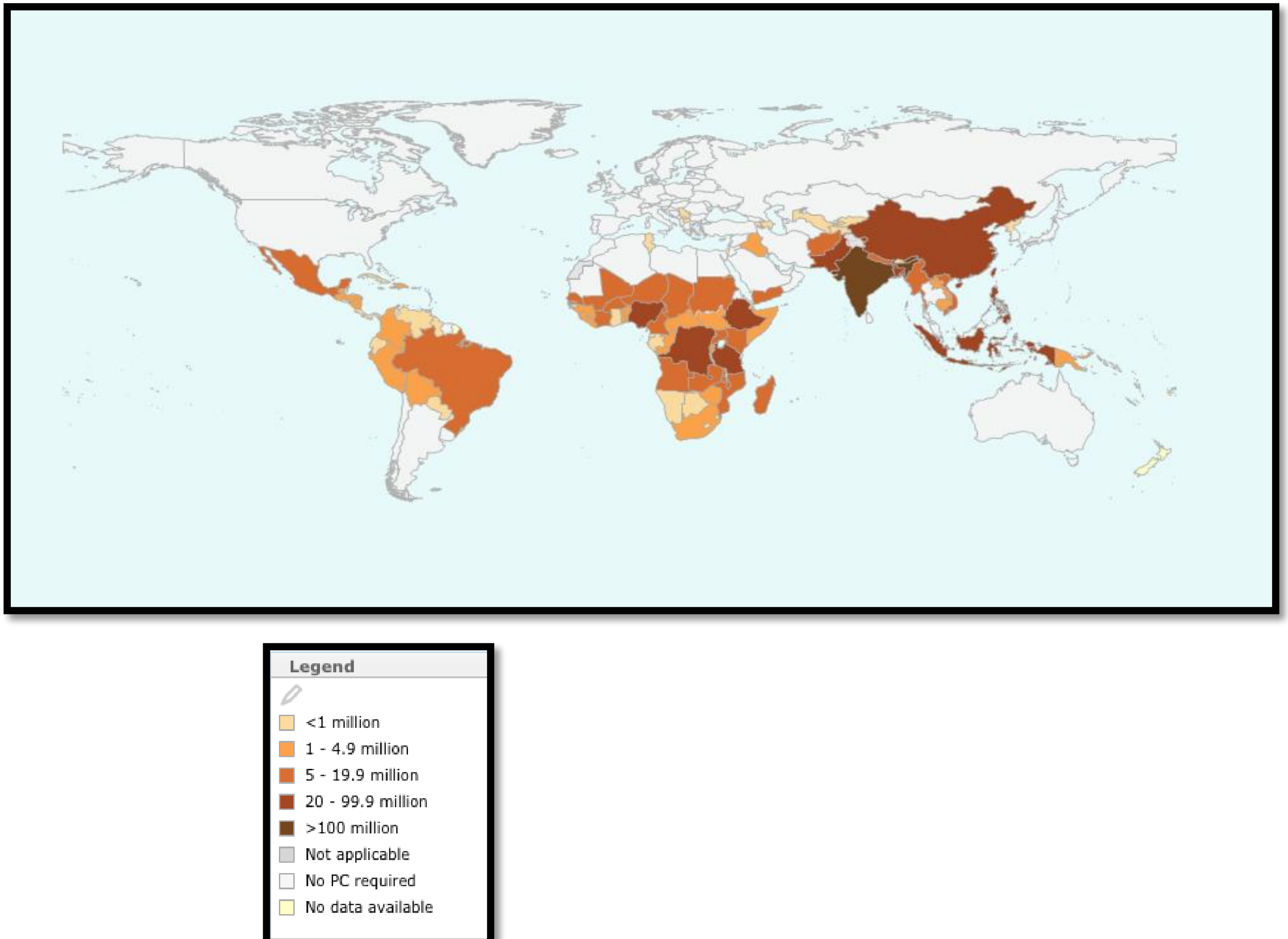
Table 5: WHO recommendation for School based Iron Supplementation

Indication for supplementation	Where prevalence is >40%
Dosage Schedule	Iron 30 mg/day Folic Acid: 250 µg/day
Duration	3 months

http://www.who.int/nutrition/publications/micronutrients/guidelines_for_Iron_supplementation.pdf

Table 5 above summarizes WHO's recommendation for school-based iron supplementation. Where prevalence of IDA is more than 40%, the recommendation is to supplement with no less than 30 mg/day of iron and 250 µg/day of Folate for a minimum of 3 months.

Figure 3: Number of School Age and Preschool Age Children requiring Preventive Chemotherapy for Soil Transmitted Helminthiases in 2013



http://apps.who.int/neglected_diseases/ntddata/sth/sth.html

The current debate

While experts agree on the negative consequences of untreated STH infections including IDA, there have been conflicting views regarding the need for adding iron supplementation to school based deworming programs among experts. A 2014 article from PLoS Neglected Tropical Diseases, ‘Micronutrient supplementation and deworming in children with geohelminth infections’, resolved that integration of the two interventions does not have a significant added benefit over deworming alone. The authors concluded that evidence presented for the additional benefits of co-intervention of deworming and micronutrient supplementation is still unclear (Rajagopal et al., 2014). They, however, noted that there were two exceptions to this conclusion: first, for pregnant women in hookworm endemic areas and, second, for people with very intense infection and existing anemia (Rajagopal et al., 2014). Thus, integration of deworming with iron supplementation was not recommended based on the lack of evidence for sufficient benefits, and therefore does not justify the significant financial implications and complexity of integration (Rajagopal et al., 2014).

Conversely Andrew Hall in 2007 recommended integration of vertical disease control programs like deworming and vertical nutrition programs like iron supplementation (Hall, 2007). The objective of this approach in Hall’s view would be to comprehensively meet the needs of the school-aged children, who are often have the largest burden of disease due to infections and under nutrition. He criticized the assumption that treating soil-transmitted helminth infections would automatically and rapidly lead to improved nutritional status, and educational development (Hall, 2007). According to Hall, this assumption is flawed and could create overly optimistic expectations. From Hall’s viewpoint, identifying and treating concurrent nutritional deficits occurring due to helminth infections not only contributes to the Millennium Development Goals that combat poverty but also, ensures attainment of basic education for children in the STH endemic regions.

Summary

IDA and STH infections negatively impact the health and socio-economic wellbeing of millions of men, women, and children (Charles, 2012). School-based deworming has been identified as a cost-effective intervention in the prevention and treatment of STHs, while iron supplementation has been a widely used strategy for the prevention and treatment of iron deficiency anemia globally. These interventions are critical for school-aged children who are at a very critical stage in their intellectual development. Optimization of their school performance has long-term benefits to them and their communities.

<u>CHAPTER 3:</u> METHODOLOGY-A SYSTEMATIC REVIEW OF LITERATURE

Introduction:

The objectives of conducting this systematic review of literature is to identify studies that have assessed the impact of implementing iron supplementation together with school based deworming programs and to evaluate the nutritional outcomes, school performance and feasibility of these interventions. A search was conducted through the Emory Health Sciences Library Pub Med for any literature based on studies on these programs from 1990-2014.

Population:

Studies that included school aged children, 5 to 19 years residing in worm endemic areas in low and middle-income countries (LMICs) as defined by WHO (WHO, 2008) were reviewed. See Appendix 1 for a list of countries based on the number of children requiring anthelminthic chemotherapy. The studies include children receiving some form of iron supplementation; tablet or liquid preparations including ferrous sulphate, iron and folate (IFA) supplements, and multiple micronutrient supplements which contain iron of at least 50mg given daily, twice weekly or once weekly.

Research Design:

The objectives of the literature review were to identify and evaluate any studies carried out to: 1) show the severity of iron deficiency anemia in the presence of STH infections; 2) to make a comparison and determine the additional benefit of integrating iron supplementation to school based deworming programs; 3) to assess the level of complexity/simplicity in implementing iron supplementation in schools that are already carrying out antihelminthic chemotherapy.

To identify relevant published studies on iron supplementation in the context of deworming, we conducted a literature search using the Emory Health Sciences Library PubMed. Table 6 below lists key words that were used to identify relevant articles.

Table 6: Key words used in search terms

Worms	Target Population/Delivery Platform	Supplementation	Outcomes
intestinal worms Intestinal parasites soil-transmitted helminthiases geohelminth helminth ascaris ascaris-lumbricoides roundworms trichuris trichuris trichuria whipworm hookworm	school-based deworming school age children adolescent children of school going age	iron iron supplementation iron-folate supplementation micronutrient supplementation	cognition cognitive function school performance education attainment concentration intelligence quotient cognitive development hemoglobin iron status anemia cost effectiveness complexity test scores Serum ferritin Hemoglobin

Instruments:

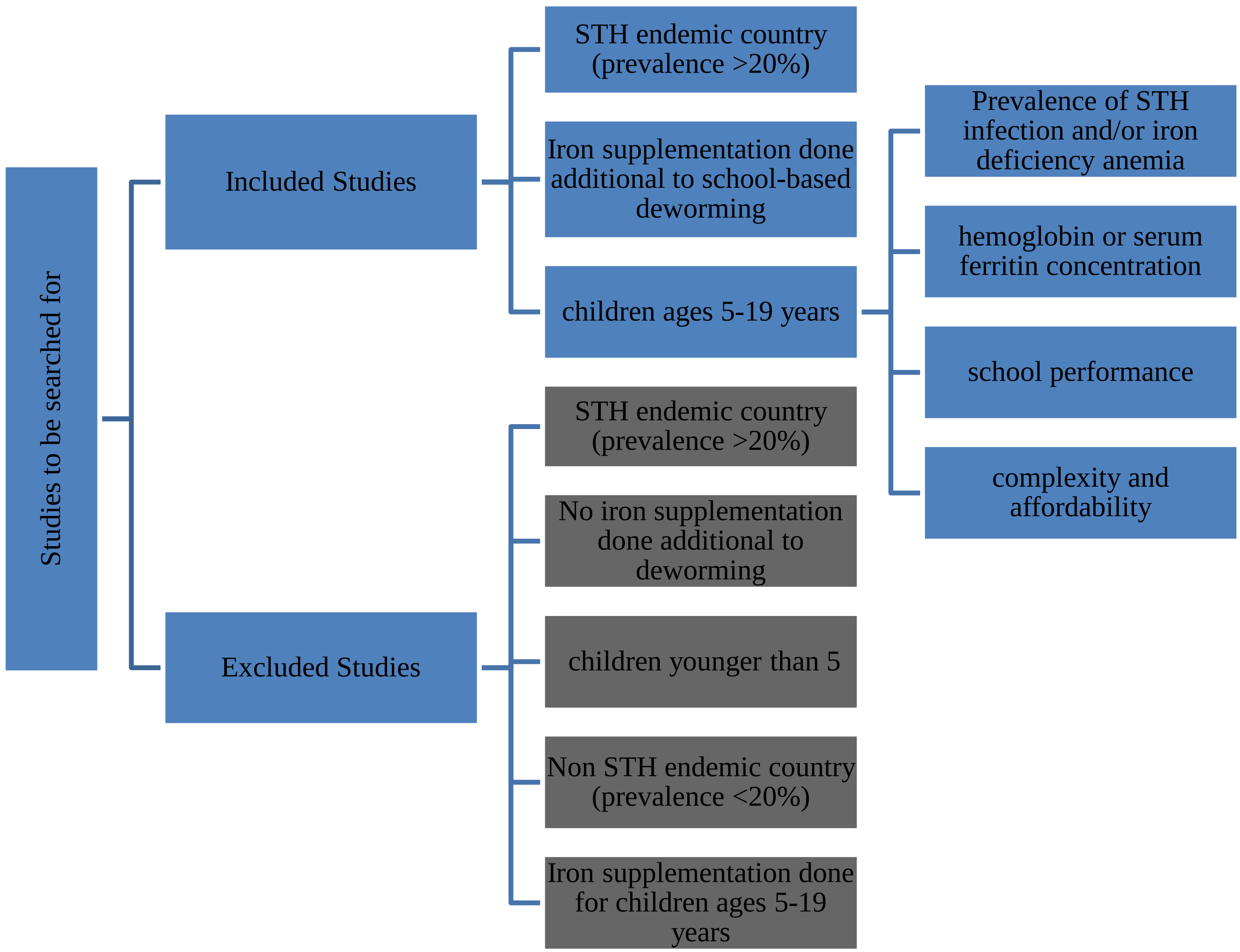
We used a framework (See Table 7 below) to determine studies to include for review and analysis based on based on extensive review and meta-analysis of the impact of intestinal worms on child growth and nutrition by Hall and colleagues in 2008. (Hall et al., 2008).

Table 7: Study Characteristics-Inclusion Criteria

Characteristic	Description
Prevalence of STH infection	Studies carried out in regions with high prevalence of and under-nourished children and worms. E.g. an STH infection prevalence of >20% and children are underweight or >40% are anemic.
Study design	Randomized controlled design with treatment and control groups; randomized clusters; and program evaluations of school-based deworming programs already carrying out iron supplementation.
Sample size	Although the Hall review notes that an ideal study should have no less than 250 participants, this review will not limit itself to this sample size, however, sample sizes for each study reviewed will be noted.
Treatment	Antihelminthic treatment should be given at least every 6months to a year.
Supplementation	Iron supplementation given either on its own or as a combination with other micronutrients, with a notable frequency, weekly, biweekly or monthly.
Key outcomes	Studies with measurable outcomes from baseline to demonstrate impact e.g. hemoglobin concentration, school performance, concentration, and overall education attainment. The gains in every parameter used should be related to growth of the children and standardized as mean gain per year.

The study's inclusion criterion is for randomized control trials (RCTs) and program evaluations both impact and process evaluations. Following the above framework, Figure 4 below demonstrates the inclusion criteria for studies that were reviewed in this study. It includes studies that were conducted in country's with; STH prevalence of >20%, where iron supplementation was carried out additional to school-based deworming in a population of children ages 5-19 years.

Figure 4: Inclusion and Exclusion Criteria of Studies Based on Targeted Outcomes for this Study



Data Extraction and Analysis Methodology

A data extraction tool was used to extract data from the studies to address the following key questions:

1. The description of studies/Study design
2. Location: country in which study was conducted, urban or rural area
3. Population of focus: age, prevalence of STH and IDA
4. Type of intervention
5. Accompanying health promotion activities
6. Outcome measures: hemoglobin concentration, school performance and feasibility of the intervention program

Data Analysis was conducted using Microsoft Excel for data entry and analysis. A qualitative analysis was conducted to assess the impact of the interventions in these studies against the four criteria outlined in the methodology: prevalence of STH and IDA, impact of the intervention on Hemoglobin concentration and Serum Ferritin, impact of the intervention on school performance and lastly, the affordability or complexity of the intervention. The findings are presented using charts, graphs, and text.

Summary

This systematic literature review is focused on learning the impact and scalability of the addition of iron supplementation to school based deworming programs. Literature was collected and assessed for eligibility to be included in the review based on the study inclusion criteria. Analysis and dissemination will be done using text, graphs and tables to summarize the findings.

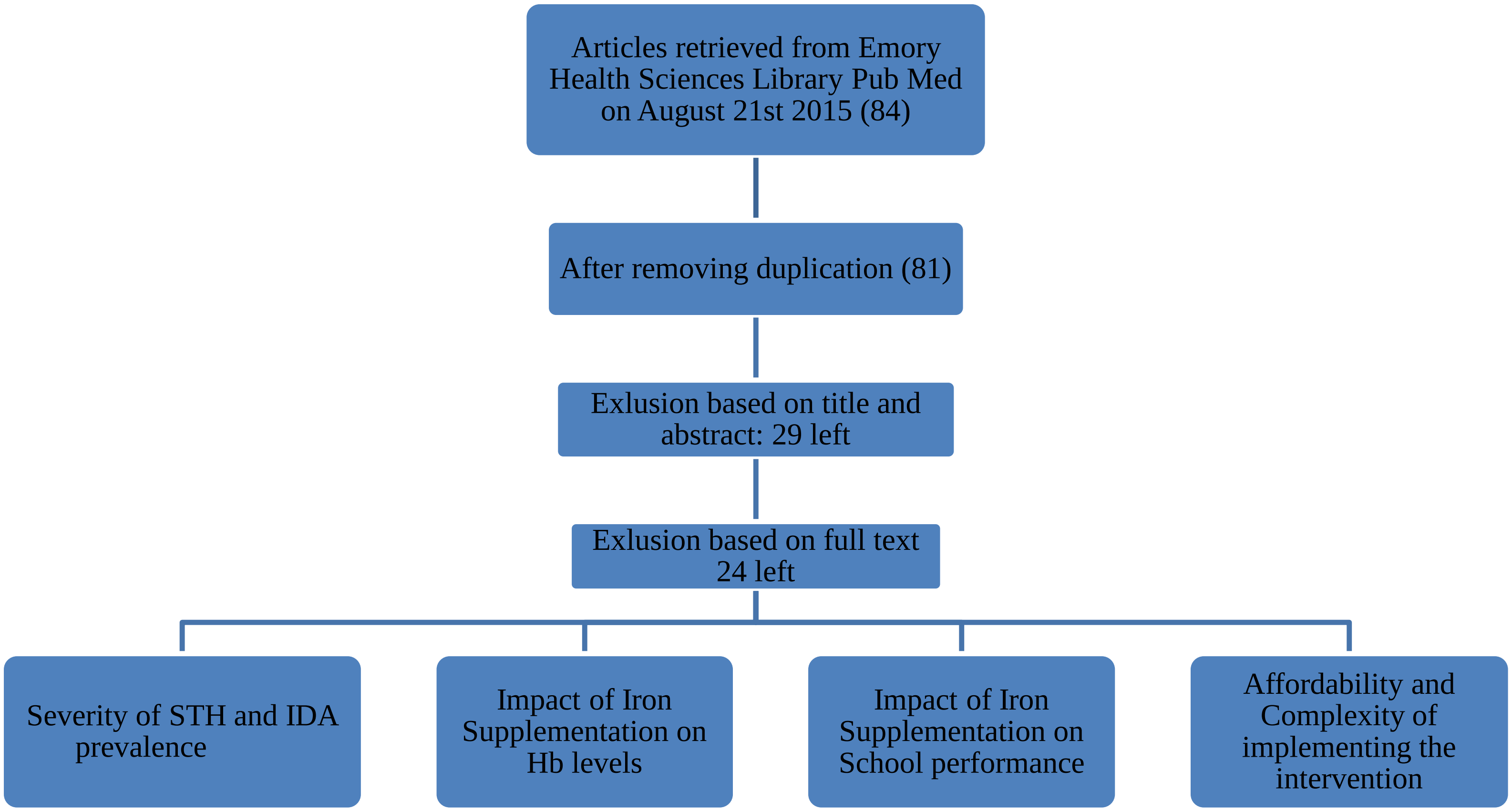
CHAPTER 4: RESULTS

Introduction

The literature search for studies of iron supplementation in schools identified 84 studies in PubMed on August 23rd 2015. Out of the 84 studies, 3 were duplicates and therefore excluded. Based on a review of titles and abstracts, an additional 51 studies were excluded because they did not meet the inclusion criteria. Studies were excluded if they did not include iron supplementation as an intervention, if the intervention was not involving supplementation (as some interventions might be fortification),or the study group ages were outside of the 5-19 year . Studies that address worms additional to the STH such as schistosomasis were included. 24 out of 84 studies met the inclusion criteria. **Figure 5** below summarizes the findings follow the inclusion and exclusion search for the literature search.

This review is by no means exhaustive, but aims to cover a number of studies in each of the major iron deficiency intervention strategies elements, severity of iron deficiency and STH infection, outcomes such as hemoglobin concentration and school performance following intervention and lastly the complexity and/or affordability of integrating the program.

Figure 5: Summary of Findings From PubMed Literature Search



Key Findings

Description of Studies:

On the basis of the inclusion criteria used for this review, the following is the approach we used to detail and harmonize key aspects of the studies in this systematic literature review using the below criteria

1. Location
2. Population
3. Study Design
4. Deworming
5. Accompanying health promotion activities

1. Location

This literature review found a total of 24 studies carried out in 14 different countries as summarized in **Table 8** below. The highest numbers of studies were conducted in the South-Eastern Asia region with 11 studies, followed by the African region with 6 studies. The Western Pacific region had 4 studies, and Americas and Eastern Mediterranean regions had 1 and 2 respectively.

Table 8: Summary of Study Locations in the Literature Review

Region	Country	Number of Studies
Africa (6)	South Africa	1
	Mali	2
	Kenya	2
	Mozambique	1
Americas (1)	Mexico	1
Eastern Mediterranean (2)	Iran	1
	Pakistan	1
South-Eastern Asia (11)	India	8

	Thailand	2
	Bangladesh	1
Western Pacific (4)	China	1
	Cambodia	1
	Philippines	1
	Malaysia	1

Figure 6 below summarizes the studies according to the year and region in which they were conducted. Majority of the studies as shown on the graph were conducted after the year 2005. More specifically, in the South-Eastern Asia region, 3 studies were conducted in the same year in 2009 in India and Bangladesh.

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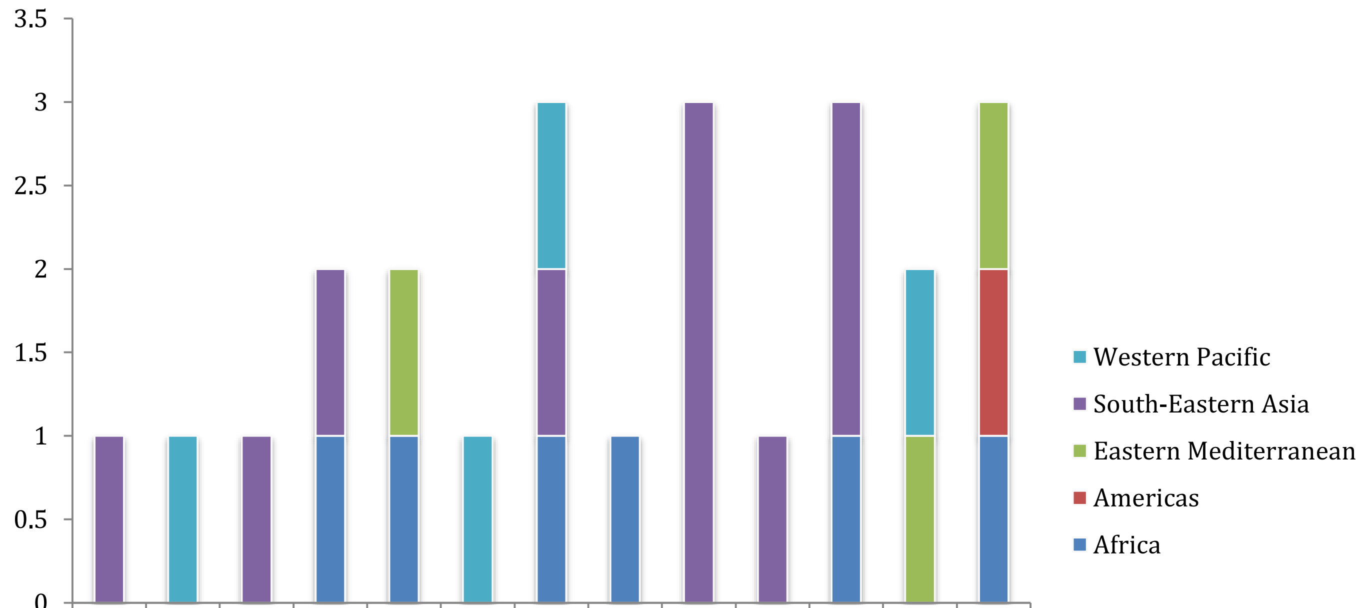
Figure 6: PubMed Studies meeting the inclusion criteria by Region and Year of Study



	1992	1999	2000	2002	2003	2004	2005	2007	2009	2010	2012	2013	2014
Western Pacific		1				1	1					1	
South-Eastern Asia	1		1	1			1		3	1	2		
Eastern Mediterranean					1							1	1
Americas													1
Africa				1	1		1	1			1		1

Year of Study

2. **Population:**

For all the 24 studies, children were recruited from schools. For 18 studies consent was obtained by teachers sending home consent forms where the parents signed for children to participate in the studies. The minimum age for children in these studies was 5 years for studies from Mexico, Pakistan and Cambodia and a maximum age of 19 years in studies from Mali and India. Mali had the biggest age bracket of 13 years in their study, with children as young as 6 years and as old as 19 years. China and Thailand had the smallest age bracket with, 10years to 12years and 9years to 11 years respectively.

3. **Study Designs**

Twenty studies were randomized control trials, which included, two double-blinded trials and one longitudinal assessment with a control group. Additionally, two studies were evaluations of ongoing programs, one in Iran and the other evaluation conducted in India. Two other studies were impact evaluations of ongoing programs in India and Cambodia.

4. **Deworming**

Although only 17 out of the 24 studies mentioned deworming interventions prior to or during the supplementation program (See Table 9), all of these studies were conducted in the countries listed in Appendix 1 as countries that still have children requiring deworming. Therefore, it is assumed that the prevalence of STH infections for each of these countries is equal or more than the 20% threshold recommended for deworming by WHO(WHO, 2014)

Table 9: Summary of Study Interventions Components

Intervention Component	Deworming	Accompanying health promotion component
Administered	17	5
Not Administered	-	-
Not Reported	7	19

5. **Accompanying Health promotion activities**

Out of the twenty-four studies, five had a health promotion component additional to the iron supplementation. Four studies had health education activities on nutrition and sanitation, while a Pakistan study in 2013 (Rousham et al., 2013), gave hygiene kits to study participants at the beginning of the intervention as part of a sanitation intervention in reducing STH infections. Seasonal variations were monitored in 3 studies (Horjus, Aguayo, Roley, Pene, & Meershoek, 2005), (Rousham et al., 2013) (Roschnik, Parawan, Baylon, Chua, & Hall, 2004), while 6 studies monitored and accounted for compliance (Kheirouri & Alizadeh, 2014) (Bhoite & Iyer, 2012) (Longfils, Heang, Soeng, & Sinuon, 2005) (Roschnik et al., 2004) (Olsen et al., 2003) (Tee et al., 1999) respectively. The compliance and seasonality variables were used in the studies to account for either positive or negative outcomes as well as assessing feasibility of iron supplementation.

Outcome Measures

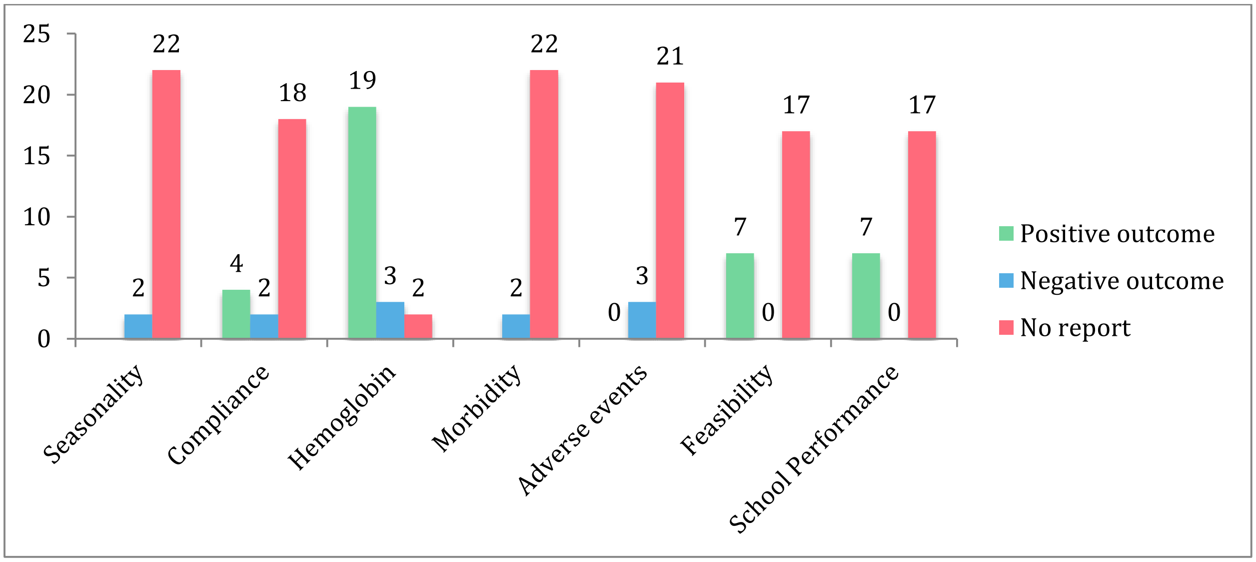
The study outcomes were grouped according to the three research questions that were the basis for this this review:

1. Iron Status
2. School Performance

3. Feasibility

4. Adverse events

Figure 7: Summary of Study Outcome measures



1. Iron Status

The studies used various measures to determine the impact of iron supplementation on the nutritional status of the study participants:

- Anemia prevalence
- Hemoglobin status
- Serrum Ferritin levels
- Plasma Ferritin levels

Figure 7 above summarizes the hematologic and iron status outcomes as follows: Out of the 24 studies, 19 reported hematologic and iron indices, three of which reported no significant change in iron status. Two out of the twenty-four studies did not demonstrate explicitly the nutritional impacts of iron supplementation. Although Hemoglobin measures were taken at baseline, the changes were not mentioned in the

South Africa 2014 study (Malan, Baumgartner, Calder, Zimmermann, & Smuts, 2015). The Iran program process evaluation was heavily focused on compliance and therefore placed more emphasis on the education component of the intervention, the study was conducted to gain insight into the reasons why expected effects (improved iron status and school performance) were or were not achieved (Kheirouri & Alizadeh, 2014).

Out of the twenty-two studies that measured Hb levels following the intervention, only three reported no significant improvement in Hb. The Mexico study for instance did not show any significant improvement in Hb concentration, but the ferritin concentration increased in schoolchildren with low iron stores (Duque et al., 2014). The second study conducted in the Philippines showed no significant improvement with Hb concentration, owing this to two factors: 1) some children in the study were already receiving iron fortified rice and 2) the relatively short duration for supplementation of ten weeks (Roschnik et al., 2004). Nevertheless, the study was able to demonstrate that relatively small amounts of iron administered to children may have quite significant long-term effects where anemia is only a mild public health problem. Lastly, the study in Pakistan (Rousham et al., 2013) also showed no improvement in Hb concentration which may have been due to the moderate baseline prevalence of anemia at 33%; or other present micronutrient deficiencies; or compliance; or due to seasonal changes in dietary iron and other nutrients.

2. School Performance

Seven studies (Figure 7 above) measured the impact of iron supplementation on school performance using the following measures:

a) General performance (A Sen & Kanani, 2009) (Ayoya, Spiekermann-Brouwer, Traore, & Garza, 2012)

b) Reduction of anxiety (Zhang et al., 2013)

c) Improved cognition (Bruner, Joffe, Duggan, Casella, & Brandt, 1996; Rico et al., 2006; Aditi Sen & Kanani, 2009; Taras, 2005) (Duque et al., 2014)

d) Improved attendance (Kheirouri & Alizadeh, 2014) (Malan et al., 2015) (Sungthong, Mo-Suwan, Chongsuvivatwong, & Geater, 2002) (Olsen et al., 2003)

All of the studies showed marked improvement in school performance either resulting from reduced anxiety, improved cognitive functions or reduced absenteeism due to illness. However, the South Africa study demonstrated increased absenteeism due to increased respiratory illness resulting from increased iron concentration, for which they recommend a combination docosahexaenoic acid and eicosapentaenoic acid (DHA/EPA) (Malan et al., 2015).

3. Feasibility of the Intervention

Overall from all the studies reviewed, iron supplementation was an integrated intervention in addition to deworming, and was safe, well tolerated, and inexpensive. Seven studies (see Figure 7) specifically assessed feasibility based on cost and complexity. The Iran study proved that the distribution of iron supplements to at-risk groups is a feasible and well-practiced strategy based on their process evaluation (Kheirouri & Alizadeh, 2014). A Malaysia study showed that it cost ≈$0.04 per person per school year to implement such a program which would be more cost-effective than periodic screening and selective therapy or than the proposed supplementation schedule (3 mo/y) of the WHO (Ngui et al., 2012). Lastly a Mozambique study found that weekly school-based iron and folic acid supplementation was feasible and cost effective, and would beneficial to prevent seasonal drops in Hb concentration and reduce anemia prevalence (Horjus et al., 2005). None of the studies addressed challenges in implementation of this intervention, however, two studies discussed a need for improving compliance among the study participants such as the Kenya study (Olsen et al., 2003) and the Thailand study (Sungthong et al., 2002).

4. **Adverse Events**

There were no adverse events noted in any of the studies. However, there was increased morbidity noted in the South Africa study which found increased school absenteeism due to respiratory illness among the study participants (Malan et al., 2015). Additionally, one study in Kenya found an positive correlation between improved hemoglobin concentrations with increased incidence of malarial infections, for which they argue, the benefits outweigh the risks, particularly for iron deficient or menstruating girls (Leenstra et al., 2009).

Limitations

This review was limited by the lack standardization in the determination of specific measures for the studies for example: the reporting of hematologic and iron indices were either reported as Hb concentration, serum ferritin concentration, and iron concentration or anemia prevalence. Baseline measures of STH infection and anemia were not explicitly reported for the majority of the studies; therefore, the assumption was a more than 20% prevalence of STH infections based on the WHO recommendation for school based deworming when the prevalence is at or above this threshold. Additionally, many studies did not report their methods of randomization or blinding. Unfortunately, major outcomes for this study (school performance) were only reported for 7 studies, more trials are needed to evaluate the non-hematinic benefits of iron supplementation as an additional component to school based deworming programs in STH endemic countries.

Summary

Overall, the studies analyzed in this review, were selected based on: 1) location (STH endemic countries, mostly poor communities or rural); 2) population (school aged children); 3) study designs (RCTs or program evaluations); 4) deworming; and 5) accompanying health promotion activities which include iron supplementation. Although iron deficiency and STH parasitic infections rarely cause mortality or other acute effects, there are measurements that have been used to demonstrate their impact on quality of life in children (e.g. hemoglobin concentration, prevalence of iron deficiency anemia, school performance and absenteeism among others). The 24 studies analyzed in this review, collectively demonstrated that there are potential benefits of integrating iron supplementation and deworming.

School-based iron supplementation combined with deworming is an inexpensive intervention especially when considered on a per-person-treated basis (in the range of less than $0.50). Although the focus of the studies in this review was not on school performance specifically, a few studies that assessed school performance found a positive correlation between the intervention and school performance. By far, the most significant improvement was noted in Hb concentration and/or reduction in anemia prevalence. Although the studies in this review did not adequately attribute improved cognitive function to the addition of iron supplementation to deworming programs, there may be literature beyond the scope of this review that demonstrates the positive impact of improved iron status on school performance.

CHAPTER 5: DISCUSSION

Introduction:

While it is concerning that about 600 million school aged children are at risk for STH infections, the estimation that about 25 per cent of school aged-children are anemic (Low, Farrell, Biggs, & Pasricha, 2013) is even more worrisome. Childhood anemia has been negatively correlated with educational outcomes such as grades, attendance, and test scores. A New York times article on IDA and children in 2012, identified that low levels of iron are a cause of decreased attention span, reduced alertness, and learning difficulties, both in young children and adolescents (NY Times Health Information, 2012).

An initial review of literature revealed that there are not enough trials testing the efficacy, feasibility and long term benefits of integration of deworming and iron supplementation programs. Besides reduction in the cost with using a singular platform for delivery of both interventions, there is a potential to combat poverty particularly in developing countries by mitigating chronic losses resulting from STH infections.

Summary of Study

The twenty-four studies that were assessed in this review reported various effects associated with iron supplementation in combination with deworming in children aged 5-19 years. This study focused on the outcomes of iron status, school performance, feasibility and adverse events. By understanding whether or not the integration of iron supplementation to school offers a relative advantage for STH endemic countries, policies makers will be better informed as they develop strategies to reduce poverty in their National Development Plans.

Conclusion:

Based on the present review, it can be concluded that the school is an appropriate platform for the delivery of iron tablets to children, and that the effectiveness of the intervention depends on supervision for compliance. The evidence shows that iron supplementation programs are feasible and cost-effective enough to be integrated into school-deworming programs. Secondly, iron supplementation can be integrated to significantly reduce prevalence of iron deficiency anemia is STH and IDA endemic countries.

In this review, it was evident that school performance was markedly improved for the studies that measured it as an outcome. However, it is worth mentioning that similar to a Cochrane review on intermittent iron supplementation, this study found insufficient studies (7) reporting school performance or cognitive outcomes, or adverse effects (3). Unlike previous reviews, this study focused on children ages 5years to 19 years who are already receiving deworming and iron supplementation treatments in their schools.

Finally, routine daily iron supplementation is likely to improve school performance, either by reducing absenteeism, or by improving school performance. While daily supplementation is likely to provide the highest dose of iron and showed potential to reduce prevalence of anemia by as much as 50%, intermittent weekly iron supplementation is more feasible and comparable to daily supplementation in terms of benefits in reducing anemia prevalence and improving school performance.

Recommendations:

From the conclusions drawn from this systematic review, it is evident that iron supplementation delivered through school deworming programs is feasible, safe and effective. As such reduction of iron deficiency and iron deficiency anemia is attainable and therefore must continue to be a priority for governments, non-governmental organizations and international aid agencies alike. The ideal approach to addressing iron deficiency is a nutritious and well balanced diet that naturally provides adequate iron intake. However, this reality in many developing countries, may be out of reach in the immediate future especially countries where subsistence comes from cereals with low iron bioavailability. There is a need for a cost-effective, simple and easy to administer solution that may be in the form of supplementation. Other reviews are also currently being undertaken to better understand the benefits and feasibility of iron fortification in countries with moderate to high anemia prevalence among school children (Lauren C. Ramsay and Christopher V. Charles, 2015).

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Appendix 1: Number of Children School Age Children and Preschool Age Children requiring Preventive Chemotherapy for Soil Transmitted Helminthiases in 2013

	Country	Number of Children		Country	Number of Children
1	India	220,619,029	54	Liberia	1,697,428
2	Nigeria	70,313,956	55	Central African Republic	1,691,530
3	Indonesia	67,699,700	56	Nicaragua	1,178,283
4	Bangladesh	43,944,119	57	Dominican Republic	1,147,740
5	Ethiopia	37,190,665	58	Democratic People's Republic of Korea	908,349
6	Philippines	31,267,582	59	El Salvador	849,969
7	Pakistan	30,292,389	60	Namibia	772,065
8	Democratic Republic of the Congo	27,763,317	61	Guinea-Bissau	647,940
9	China	25,822,218	62	Gabon	591,291
10	United Republic of Tanzania	20,266,223	63	Lesotho	517,058
11	Kenya	17,274,325	64	Timor-Leste	478,730
12	Uganda	16,658,677	65	Ghana	471,670
13	Sudan	14,440,734	66	Paraguay	454,727
14	Afghanistan	13,291,651	67	Swaziland	436,424
15	Myanmar	12,367,829	68	Panama	419,689
16	Brazil	11,758,272	69	Jamaica	417,491
17	Mozambique	10,802,876	70	Uzbekistan	394,207
18	Mexico	10,282,283	71	Azerbaijan	345,495
19	Angola	9,333,297	72	Gambia	247,536
20	Nepal	9,101,969	73	Fiji	236,426
21	Yemen	9,086,016	74	Botswana	227,132
22	Madagascar	8,949,008	75	Venezuela	212,000
23	Cameroon	8,784,539	76	Solomon Islands	208,643
24	Vietnam	8,608,402	77	Guyana	205,184
25	Niger	8,101,168	78	Tunisia	200,856
26	Cote d'Ivore	7,688,619	79	Ecuador	193,708
27	Burkina Faso	7,064,479	80	Comoros	182,463
28	Malawi	6,815,793	81	Carbo Verde	136,960
29	Mali	6,589,495	82	Equatorial Guinea	131,943
30	Zambia	6,193,898	83	Tajikistan	117,046
31	Chad	5,668,533	84	Bhutan	108,115
32	Senegal	5,638,104	85	Kyrgyzstan	107,534
33	Colombia	4,772,564	86	Djibouti	105,768

34	Rwanda	4,626,207	87	Vanuatu	86,866
35	Guinea	4,563,197	88	Cuba	55,804
36	Somalia	4,528,586	89	Sao Tome and Principe	48,905
37	South Sudan	4,365,862	90	Armenia	38,698
38	Cambodia	4,347,927	91	Tonga	36,604
39	Burundi	4,100,902	92	Saint Lucia	36,090
40	Benin	4,061,209	93	Costa Rica	29,473
41	South Africa	3,773,640	94	Serbia	25,618
42	Haiti	3,351,768	95	The Former Yugoslav Republic	22,983
43	Guatemala	3,205,688	96	Mauritius	20,861
44	Zimbabwe	3,111,242	97	Trinidad and Tobago	17,829
45	Peru	3,008,028	98	Kiribati	17,311
46	Honduras	2,646,769	99	Micronesia	15,351
47	Togo	2,617,472	100	Marshal Islands	14,594
48	Papua New Guinea	2,579,260	101	Dominica	7,949
49	Sierra Leone	2,330,179	102	Belize	7,565
50	Leo People's Democratic Republic	2,200,386	103	Montenegro	5,267
51	Bolivia	2,124,918	104	Tuvalu	2,788
52	Iraq	2,003,182	105	Nauru	2,787
53	Congo	1,730,106	106	Antigua and Barbuda	1,360

Copied from: http://apps.who.int/neglected_diseases/ntddata/sth/sth.html

Appendix 2: Summary of Studies from PubMed

PubMed Studies (Search terms: Iron Supplementation, Schools, Deworming)						
Country/Year/Source	**Aim**	**Ages/Sample size**	**Study Design/Sample**	**Outcomes**	**Deworming treatment**	**Other outcome**
South Africa (2014) (Malan et al., 2015)	Respiratory morbidity caused by iron supplementation	6-11 years (321 children)	A randomized, placebo-controlled, double-blind, 2-by-2 factorial design	Iron Status (+) Hemoglobin concentration (+) Morbidity (-)	Mebendazole at baseline and after 4 mo.	Iron supplementation increased general morbidity by 139% and respiratory morbidity by 325%
Iran (2014) (Kheirouri & Alizadeh, 2014)	Process evaluation of school based Fe Supp	Adolescent high school girls (658 students/8 schools)	Process evaluation of the integrated Iron Deficiency Control Program (IDCP)	Compliance rates were significantly higher for one school out of the 8 schools		
Mexico (2014) (Duque et al., 2014)	Ferrous Sulphate effects on ferritin concentration in children (30 mg/day of elemental iron)	5–13 years	A randomized control trial	Significantly increased serum ferritin concentration	400 mg albendazol dose at the beginning of the study as anti-helminthic prophylaxis	Negligible side effects (adverse events)
Pakistan (2013) (Rousham et al., 2013)	Hemoglobin concentration	5-17 years (1110/370 in each group)	Assessment of longitudinal school health intervention	No significant increase in Hb or decrease in anemia prevalence from baseline	Low prevalence of STH infections	Seasonal variation in anemia prevalence corresponding with increased availability of dietary carotenoids
China (2013) (Zhang et al., 2013)	To examine if MMS reduces both anemia and anxiety	10-12 years (2730)	Randomized controlled trial	5 months of treatment lead to increased Hb concentrations and reduced anemia and significantly reduced anxiety	Not mentioned, though prevalence is >20%	Intervention was biologically efficacious in improving anemia and mental health scores

Mali (2012) (Ayoya et al., 2012)	Examine the effect on school attendance and performance of iron and multiple micronutrient	7-12 years of age (n=406)	A prospective randomized controlled efficacy supplementation trial	Hb concentration of treated children rose on average by 1.8 g l (-1) and the prevalence of anemia fell by 8.2%	praziquantel for S. haematobium,	iron supplements given by teachers are a potential health intervention for children in non-formal schools in Mali after they have been dewormed and given vitamin A, especially for girl
India (2012) (Aditi Sen & Kanani, 2012)	to investigate the relative impact of daily, once-weekly, and twice-weekly IFA supplementation on Hb levels and BMI of school girls	9 to 13 years	experimental-control semi-longitudinal study; an efficacy trial	all three dose regimens of iron folic acid supplementation (daily, once and twice weekly) significantly improved Hb levels, but growth (BMI gain) was significant only in daily- and twice-weekly IFA supplementation	Not mentioned, though prevalence is >20%	twice-weekly IFA showed a significant and comparable impact as did the daily IFA on cognition and physical work capacity versus the controls; while once-weekly IFA did not
India (2012) (Bhoite & Iyer, 2012)	Effects of on growth, hemoglobin level, and physical work capacity of schoolchildren	8-12 years (30 week trial) (n=144)	A randomized control trial	Hb concentration and growth using BMI	one group was given 400 mg Albendazole once in six months, the second got Albendazole with their weekly IFA tablets (60 mg Iron and 0.5mg folic acid)	Both the intervention did not make significant improvement in the prevalence of stunting. IFA+ deworming supplementation was more effective in increasing the hemoglobin levels
Bangladesh (2010) (Ahmed et al., 2010)	effects of long-term once- or twice-weekly supplementation of MMN in improving Hb and micronutrient status	11-17 year old girls (n=324)	a randomized double-blind trial	There was significant increase in Hb which did not differ among the groups at wk. 26 or 52	Albendazole 400 mg given before the study began, 26 weeks and at 52 weeks	Serum Ferritin increase in the MMN-1 group was significantly less than in the IFA-2 group at both time points and significantly less than in the MMN-2 group only after 52 wk.

India(2009) (Kotecha, Nirupam, & Karkar, 2009)	To evaluate the impact of iron and folic acid supplementation to school girls under the supervision of school teachers and nutrition education to the girls and their teachers	12-19 year old girls (n=2860)	Impact Evaluation on the Adolescent Anemia Control program in Gujarat	Reduction in anemia prevalence, reduction in proportion of girls with low Serum Ferritin, increase HB concentrations District wide	IFA tablet contained 100 mg elemental iron and 0.5 mg folie acid	Regional differences were noted between urban and rural households which coincided with literacy levels of parents
India (2009) (A Sen & Kanani, 2009)	assess impact of daily and intermittent iron-folate (IFA) supplementation on physical work capacity of underprivileged schoolgirls in Vadodara.	9-13 years (n=163)	randomized control trial (experimental-control semi-longitudinal study; an efficacy trial)	Hemoglobin, modified Harvard's Step test for physical work capacity	No deworming done on subjects, but prevalence is >20%	while once-weekly IFA may not suffice; twice weekly IFA has the potential to lead to significant improvement in physical work capacity at less cost and greater feasibility as compared to daily IFA supplements
India (2009) (Aditi Sen & Kanani, 2009)	Impact of iron-folic acid supplementation on cognitive abilities of school girls	9-13 years (n=161)	randomized control trial (experimental-control semi-longitudinal study; an efficacy trial)	daily and twice weekly iron folate supplementation are comparable as regards significant impact on hemoglobin levels as well as cognitive functions of girls in the pubertal phase	No deworming done on subjects, but prevalence is >20%	IFA supplementation given daily and twice weekly significantly improved cognition in most tests; the effect was not seen in once-weekly or control groups
Kenya (2007) (Andang'o et al., 2007)	Weekly Fe supplementation on Iron Status of adolescent girls	12–18 years (n=279)	Double-blind randomized placebo-controlled trial	Hb concentration, Serum Ferritin concentration, Malaria parasitemia and Height and Weight	Not mentioned, though prevalence is >20%	Weekly iron supplementation results in substantial increases in hemoglobin concentration in adolescent schoolgirls in western Kenya, which may outweigh possible risks caused by malaria
Cambodia(2005) (Longfils et al., 2005)	Weekly Fe supplementation on Iron Status of school-aged children	5-15 years	program impact evaluation	in 12 to 15year old children, success was less marked Hb concentration, anthropometric measures, and stool samples	Mebendazole twice per year	such an intervention is very cost-effective, since iron-folic acid tablets cost around 5 cents US per child per year.

India(2006) (Sivakumar et al., 2006)	Impact of multiple micronutrient supplements on biochemical status		double-blind, placebo-controlled, matched-pair, cluster, randomization study	Measurements related to hemopoiesis: hemoglobin, ferritin		
Mozambique(2005) (Horjus et al., 2005)	Impact of IFA on Hb concentration for girls 10-18 years	10-18 years	Randomized experimental	an 8-month weekly supplementation period was not more effective than shorter supplementation periods in maintaining girls' hemoglobin concentration at seasonal heights	Mebendazole 500mg was given at the beginning of the study and once six months later	
India (2005) (Gopaldas, 2005)	Impact of micronutrient supplementation with deworming in schools	6-15 years	Program process evaluation-Cross sectional (children were their own control)	Hemoglobin concentrations increased mainly due to Iron supplementation significantly for younger children	Deworming treatment given along with supplementation	Notable improved physical fitness as self reported by the program participants, reduced illness, and better appetite
Philippines (2004) (Roschnik et al., 2004)	Impact of weekly supplementation on school children	7-12years	Randomized experimental	net difference in the hemoglobin concentrations between the two study groups was three times higher in the younger age group (7–8 years) compared with the older age group (9–11 years) (5.9 g/l *vs.* 1.8 g/l)	400 mg albendazole dose at the beginning of the study as anti-helminthic prophylaxis	Hb conc did not change significantly for children on weekly supplementation. Weekly iron supplementation helped to prevent a fall inHb conc
Kenya (2003) (Olsen et al., 2003)	Effects of MMS on helminth infections in school children.	8.4-18years (mean age 13) (n=977)	randomized, placebo-controlled, double-blind, two-by-two factorial trial	significantly increased Hb and retinol concentration and, lowered S. mansoni reinfection intensity after 11 months	multihelminth chemotherapy (albendazole 600 mg in a single dose and/or praziquantel 40 mg/kg in a single dose)	imply that using schools for delivery of micronutrients could be useful even in a situation with relatively high school absenteeism

India (2003) (Agarwal, Gomber, Bisht, & Som, 2003)	Anemia prophylaxis in adolescent girls by weekly or daily IFA supplemetation	10-17 years (n=2210)	Prospective Study	Plasma Ferritin was significantly increased for all the groups, Hb levels was raised in the daily intake of supplements compared to weekly administration which showed delayed response as prevalence of anemia in the first 115 days	Not mentioned, though prevalence is >20%	Weekly administration, during the school session, seems more practical and Menstruating girls need more iron-folate supplements than pre-menarcheal girls
Mali (2002) (Hall et al., 2002)	Impact of weekly iron supplementation for school children	6-19 years of age (11.4)	Randomized experimental	Deworming done prior to study	400 mg Albendazole done prior to the study	There was an increase in Hb concentration following weekly Iron supplementation, anemia prevalence declined
Thailand (2002) (Sungthong et al., 2002)	Weekly versus Daily iron supplementation impact on growth and Hb	6 to 13 y (n=397)	A randomized control trial	Hb change in the daily and weekly supplemented groups were similar but both were greater than that in the placebo group	400 mg Albendazole done prior to the study	Hb, Ferritin, cognitive scores
Iran (2000) (Kianfar, Kimiagar, & Ghaffarpour, 2000)	Assess effectiveness of 50mg as $FeSO_4$ 7d/w vs. placebo	Average age 16.3	Randomized experimental			

India (2000) (Sharma, Prasad, & Rao, 2000)	Efficacy of IFA in adolescent girls in poor communities	n=705	Randomized experimental		The response of Hb levels to daily iron/folate supplementation was better in comparison to once-weekly supplementation.	The increment in Hb levels of subjects due to addition of vitamin C to iron/folate supplementation was more than that with supplementation of iron/folate alone
Malaysia(1999) (Tee et al., 1999)	To assess: effectiveness, safety, feasibility of weekly supplementation	12-17 year old school girls (n=624)	Randomized clinical trial	significant improvement in their iron nutrition and hemoglobin concentrations, supplementation was safe, no side effects stopped	Prevalence of STH infections in Malaysia in 1999 was >20% https://hal.archives-ouvertes.fr/file/index/docid/993505/filename/Review._Epidemiology_of_soil-transmitted_helminthiases_in_Malaysia.pdf	
Thailand (1992) (Hathirat, Valyasevi, Kotchabhakdi, Rojroongwasinkul, & Pollitt, 1992)	To assess the effects of an iron supplementation trial on the Fe status of Thai schoolchildren, assess, side effects and feasibility of using school devlivery platforms	9-11	A double blind clinical trial (Iron supplements administered daily (5days/week)	No side effects noted for iron supplementation or deworming, Hb significantly improved from baseline compared to deworming alone	Albendazole 200mg	Malaria areas exluded from this study