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Community-Based Interventions: Implications for Childhood Anemia Prevention and Control in India

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Stockholm 2018

Published by Karolinska Institutet. Printed by Eprint AB 2018

ISBN 978-91-7676-242-4

Dedicated to the remarkable mothers in the study area and mothers worldwide.

"I have been impressed with the urgency of doing. Knowing is not enough; we must apply. Being willing is not enough; we must do. "

- Leonardo da Vinci

ABSTRACT

Background: Nutritional iron deficiency is the number one cause of anemia worldwide. Iron deficiency anemia has morbidity and mortality effects borne predominantly by premenopausal women and children living in South Asia and sub-Saharan Africa. Community-based interventions have successfully addressed several global health problems, although there is limited evidence of their effectiveness for childhood anemia. The overall aim of this thesis was to test the hypothesis that community-based education and counseling delivered to mothers of anemic children by health workers would improve anemia cure rates.

Methods: The thesis included 4 studies, two of which (Study I and II) were cross sectional studies constituting the background for intervention design. The social cognitive theory framework guided the development of the intervention, which consisted of five monthly education sessions delivered by a health worker covering: i) maternal anemia awareness, ii) adherence to iron treatment, iii) dietary modification, and iv) hygiene and sanitation. The intervention was evaluated in a pragmatic mixed methods trial conducted among 12-59 month old children from 55 villages of the Chamarajnagar district, Karnataka. Villages (and health workers therein) were randomly assigned 1:1 to provide anemic children either the usual iron treatment alone or the same treatment complemented by education and counseling of their mothers/caregivers. The primary trial outcome was the difference in anemia cure rates (return of hemoglobin to ≥11g/dL) at the end of six months. Thematic analysis with the framework method was utilized to understand health workers acceptance of the intervention and their perceptions of obstacles and opportunities connected to its implementation (Study III). A cluster randomized trial contrasting intervention to usual treatment condition was used to study the effects of the intervention (Study IV). The statistical analysis was conducted taking into account the cluster design, using multilevel regression.

Results: A high prevalence of childhood anemia was found in healthy rural toddlers (75%) mainly due to iron deficiency anemia (Study 1). Coverage of children with iron supplements from the national anemia control program was low (Study II). Health workers delivering the intervention found it acceptable and feasible to implement during routine work activities (Study III). After six months, anemic children in the intervention group had significantly higher anemia cure rates compared with anemic children in the usual treatment group (55.5% vs. 41.4%; relative risk ratio 1.33, confidence interval [CI], 1.04-1.69). The proportion of anemic children consuming >75% of prescribed iron was higher in the intervention group compared with the usual treatment group (61.7% vs. 48.4%; p=0.001). The results indicated that seven mothers needed to be counselled in order to cure one anemic child (Study IV).

Conclusions: The studies included in this thesis indicate that mother/caregiver education achieved a perceivable improvement to the cure rate of nutritional iron deficiency anemia in children from rural India, probably through improved adherence to iron treatment. High intervention acceptance at the health worker level suggests that wider implementation is possible. Scientific evaluations of community-based interventions are feasible even in rural disadvantaged environments.

Keywords: Childhood anemia, iron deficiency, lay health workers, iron supplements, India, cluster randomized controlled trial

LIST OF SCIENTIFIC PAPERS

1. *Pasricha SR, Black J, Muthayya S, Shet A, Bhat V, Biggs BA, Prashant NS, Sudarshan H,* ***Shet AS.*** Determinants of anemia among young children in rural India.

   Pediatrics 2010 Jul;126 (1):e140-9. Epub 2010 Jun 14.

2. *Sant-Rayn Pasricha, Jim Black, Beverley-Ann Biggs, Robert Moodie, H Sudarshan,* ***Shet AS.*** Factors Influencing Receipt of Iron Supplementation by Young Children and their Mothers in Rural India: Local and National Cross-Sectional studies.

   BMC Public Health 2011 Aug 3;11:617.

3. ***Shet AS,*** *Rao A, Jebaraj P, Mascarenhas M, Zwarenstein MA, Galanti RM, Atkins S* Lay health workers perceptions of an anemia control intervention in Karnataka, India: a qualitative study

   BMC Public Health. 2017 Sep 18;17(1):720. doi: 10.1186/s12889-017-4758-x.

4. ***Shet AS,*** *Zwarenstein MA, Jebaraj P, Rao A, Arumugam K, Atkins S, Mascarenhas M, Klar N, Galanti RM.* Community based education by lay health workers improves childhood anemia cure rates in rural India: a pragmatic cluster randomized trial. Manuscript

LIST OF RELATED PUBLICATIONS

1. *Pasricha, SR, Vijay Kumar, V, Sudarshan, H, Biggs, BA, Black, J, *Shet, AS.* Undertaking a community based field research project exploring nutrition and anemia amongst young children living in rural Karnataka, India.

   BMC Public Health 2009 Feb 17;9:59

2. *Pasricha, SR, Anita Shet, Sachdev HPS, *Shet, AS.* The risks of routine iron and folic acid supplementation for young children living in India – learning from new evidence.

   Indian Pediatrics 2009; 46(10):857-66

3. **Shet, AS, Pinto S, Mitra G, Subramanium P, Mandal AK.* Glutahionyl hemoglobin is elevated in iron deficiency anemia.

   Acta Haematol 2011 Oct 13;127(1):26-30

4. *Patel P, Shet A, Iyer A, Sen G.* Pregnant women with moderate to severe anemia: lacunae in screening and treatment efforts. FKILP Policy Brief 2012, Vol 4. *http://fkilp.iimb.ernet.in/policy_briefs.html*

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GLOSSARY OF TERMS

Childhood anemia: Hemoglobin less than 11 g/dL in children aged 6 mth-6 years.

Iron deficiency: Total body iron below the lower limits of normal with preservation of levels of erythroid iron.

Iron-deficiency anemia: Depressed levels of both total body iron and erythroid iron evidenced by the development of anemia.

Functional iron deficiency: Insufficient mobilization of erythroid iron in the presence of increased demand, as occurs after treatment with erythropoiesis-stimulating agents.

Iron-restricted erythropoiesis: A reduced supply of iron for the purpose of erythropoiesis, regardless of the level of iron stores, which are usually replete.

Anemia of inflammation: Multifactorial anemia associated with increased cytokine production, up-regulation of hepcidin, and abnormal iron homeostasis.

Pragmatic trial: Trials designed to show the real-world effectiveness of the interventions or health care innovations in broad patient groups.

Effectiveness: the degree of beneficial effect of a treatment or preventive measure in “real world” settings.

Efficacy: the degree of beneficial effect of a treatment or preventive measure in pure experimental conditions.

Lay health worker: A health worker performing health care delivery functions trained in some way in the context of an intervention, but not receiving formal professional training or a tertiary education degree.

Integrated Child Development Services (ICDS): A large national program for the promotion of the mother and child health and development. Beneficiaries are children below 6 years, pregnant and lactating mothers, and other women in the age group of 15 to 44 years. The scheme covers services including supplementary nutrition, immunization, health check-up, referral services, nutrition and health education, and pre-school education. The distribution of

iron and folic acid tablets and vitamin A is also undertaken to prevent iron deficiency anemia and vitamin A deficiency.

Anganwadi day care center (ADC): *Anganwadi* means courtyard and refers to the village child-care center. A typical rural ADC employs an ICDS-funded ADC lay health worker providing child-care and serving a village with a population of about 1000 (with 10-15% aged 1·0-6·0 years). Usually it is a simple single room or two roomed facility located in the village, made according to guidelines laid by ICDS.

National Nutritional and Anemia Control Program: A national program implemented through the Primary Health Centers aiming to decrease the prevalence and incidence of anemia in women of reproductive age and other vulnerable groups.

National Iron Plus Initiative (NIPI): A national program launched by the Ministry of Health and Family Welfare in 2013 as a comprehensive strategy to combat the public health challenge of iron deficiency anemia prevalent across the life cycle.

Iron and folic acid (IFA): Iron and folic acid tablets, each containing 20 mg of elemental iron and 0.5 mg of folic acid.

LIST OF ABBREVIATIONS

WHO	World Health Organization
ID	Iron deficiency
IDA	Iron deficiency anemia
IFA	Iron and Folic Acid
NRHM	National Rural Health Mission
NNACP	National Nutritional and Anemia Control Program
NIPI	National Iron Plus Initiative
ADR	Adverse Drug Reaction
CI	Confidence Interval
DSMB	Data and Safety Monitoring Board
Hb	Hemoglobin
HR	Hazard Ratio
RR	Relative Risk
OR	Odds Ratio
RCT	Randomized Controlled Trial
cRCT	Cluster Randomized Controlled Trial
SD	Standard Deviation

1 INTRODUCTION

1.1 ANEMIA: HISTORICAL BACKGROUND

Despite several prescient observations of anemia-associated maladies treatable with iron made by the medical community as early as in the 17th century (chlorosis, microcytic anemia with achlorhydria, post cricoid webs with anemia), an underlying nutritional problem was not recognized until two centuries later. In the late 1920's, Helen Mackay (Figure 1) observed that the late anemia of infancy (after the physiological post-natal hemoglobin fall) was preventable with iron[1]. Mackay noted that anemia diminished in iron-supplemented infants compared with infants not receiving supplementary iron, when iron was started 6 months after birth. These seminal observations clearly established a link between nutritional iron deficiency and anemia. Mackay's studies demonstrated the nutritional vulnerability of premature infants, drawing conclusions that the anemia of late infancy resulted from insufficient dietary iron and could be eliminated by supplementary iron. Her recommendation that iron should be given to non-breastfed infants from the first months of life because this can yield higher levels of hemoglobin later in infancy remains valid even today.

Almost 100 years after Mackay began her studies, nutritional iron deficiency anemia (IDA) is still the number one form of anemia worldwide. Unsurprisingly, the principal clinical concern with iron nutrition remains the same as it did before the role of iron was delineated, namely detection, treatment and prevention of anemia in vulnerable groups. Global inequalities in anemia prevalence reflect the stark differences between developing and developed countries and the differential exposure to the social determinants of anemia. It is in this context that the thesis should be read. Its focus is on childhood iron deficiency anemia, a condition successfully controlled by prevention programs in other settings, but still unchecked in India.

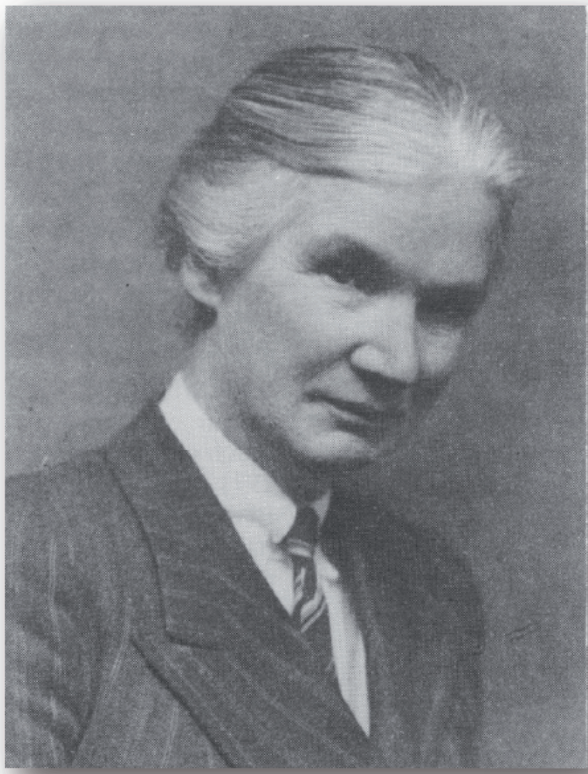

Figure 1. Helen Mackay. To generations of pediatricians, a British physician Helen Mackay is remembered for laying down the foundations of our current knowledge of iron deficiency anemia in infancy. Relevant to this thesis is her recognition of the impact of social conditions on child health. Dr. Mackay carried this conviction into her working life by setting up clinics for mothers and babies in the community.

1.2 ANEMIA IN CHILDREN: A GLOBAL HEALTH PROBLEM

1.2.1 Pathogenesis of iron deficiency anemia

Iron is the fourth most common ground element in nature and forms an essential component of hemoglobin, myoglobin, enzymes, and cytochromes necessary for oxygen transport and cellular respiration. Iron is also critical for optimal physical growth, neurogenesis and cognitive function[2,3]. Uptake, recycling and storage of iron in the body is a tightly regulated process controlled by a series of iron regulatory proteins (Figure 2)[4].

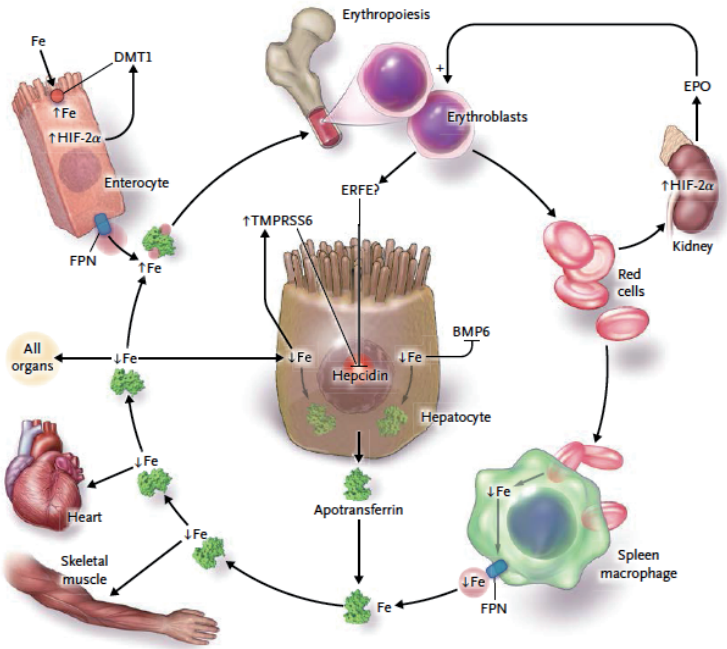

Figure 2. Hepcidin plays a central role in iron homeostasis. Suppression of the hepatic hormone hepcidin, permits iron absorption by reducing the degradation of ferroportin (FPN) on macrophages and enterocytes. Iron export from enterocytes and macrophages occurs through plasma transferrin to the bone marrow for erythropoiesis.

Cellular iron uptake (heme iron or non heme iron) occurs in the proximal duodenum via cellular transport proteins, the dimetal transporter (DMTP-1) and a yet to be identified heme transporter. Gut iron absorption, normally ~5% at steady state body iron stores can increase to 30% in the presence of iron deficiency anemia[4]. Since there is no bodily iron excretion mechanism, absorption of iron from the intestinal epithelium into the blood stream is tightly regulated by ferroportin, currently the only known cellular iron export protein. Hepcidin, the principal regulator of iron homeostasis, controls ferroportin expression on intestinal epithelium and reticuloendothelial cells by inducing its degradation[5].

Upstream signals triggering hepatic hepcidin release include hypoxia (HIF 2alfa), inflammation (IL-6)[6], and erythroferrone[7], a protein recently described in mice. In states of iron deficiency and iron deficiency anemia, hepcidin levels are extremely low permitting greater ferroportin expression and consequently increased iron import from intestinal epithelial cells into the blood stream. Iron thus absorbed, gets bound to transferrin and is utilized by erythrocytes produced in the bone marrow. Preexisting iron from senescent erythrocytes undergoing phagocytosis by reticuloendothelial macrophages is exported via macrophage ferroportin to developing marrow erythrocytes. During inflammation, hepcidin levels are high, ferroportin expression is low and iron is neither exported from the intestinal epithelium into the blood nor exported out from macrophages to newly synthesized developing erythrocytes, resulting in iron-restricted erythropoiesis. Under the influence of competing signals (anemia, iron deficiency, and infection) hepcidin controls cellular uptake of supplemental/therapeutic iron[8].

From a biological perspective, iron deficiency anemia occurs either due to decreased erythrocyte production e.g. in nutritional iron deficiency (ineffective erythropoiesis); or increased loss of erythrocytes through increased destruction (hemolysis) or blood loss (bleeding); or a combination of the two (Table 1)[4].

Table 1. The etiology of iron deficiency

Physiologic causes	Infancy, adolescence, pregnancy 2nd and 3rd trimester
Insufficient intake	Malnutrition, vegetarians, vegans, and iron poor food
Decreased iron absorption	Drugs e.g. proton pump inhibitors, dietary iron chelators, disease conditions e.g. Inflammatory bowel disease, tropical sprue, infections e.g. H. pylori, gastric surgery, and genetic causes e.g. iron refractory iron deficiency anemia
Increased iron loss	Gastrointestinal (e.g. worm infestations) and genitourinary bleeding (e.g. menstrual blood loss) bleeding from hereditary disorders and phlebotomy from routine blood donations
Chronic diseases	Chronic kidney disease, cancer related anemia, infections (e.g. tuberculosis) inflammatory disease related anemia, heart failure associated anemia, obesity related anemia, anemia of the elderly

It is important to recognize that not all cases of anemia are due to iron deficiency anemia, although much of the public health literature fails to make this distinction[9]. It has been estimated that about half of the anemia burden worldwide is due to nutritional iron deficiency[10], with and without other coexistent deficiencies (folate, vitamin B_{12} and vitamin A). Other factors contribute to the etiology of anemia, including mineral and essential element deficiencies, genetic hemoglobin disorders, and infectious diseases[11]. Inflammation, and chronic illness such as cancer and renal disease are also contributory causes although these are more prevalent in adults[11,12]. Accurately defining the proportion of anemia that results from nutritional iron deficiency would greatly clarify the beneficial effects of interventions designed to specifically target this process. In spite of its multifactorial etiology[13-19], iron deficiency anemia is the predominant form of anemia in Indian children[20,21].

1.2.2 Global burden of disease due to anemia

The World Health Organization (WHO) currently defines anemia based on thresholds set at the fifth percentile of hemoglobin in a normal population appropriately adjusted for age and sex[22]. According to this definition, it is estimated that 25% of the world's population (1.62 billion people) is anemic. Preschool children (47.4%) and pregnant women (41.8%) have the highest anemia prevalence overall[23]. In terms of geographic regions, Africa (67.6 and 57.1%)

and Southeast Asia (65.5 and 48.2%) have the highest burden of anemia in preschool children and pregnant women, respectively (Figure 3)[23,24].

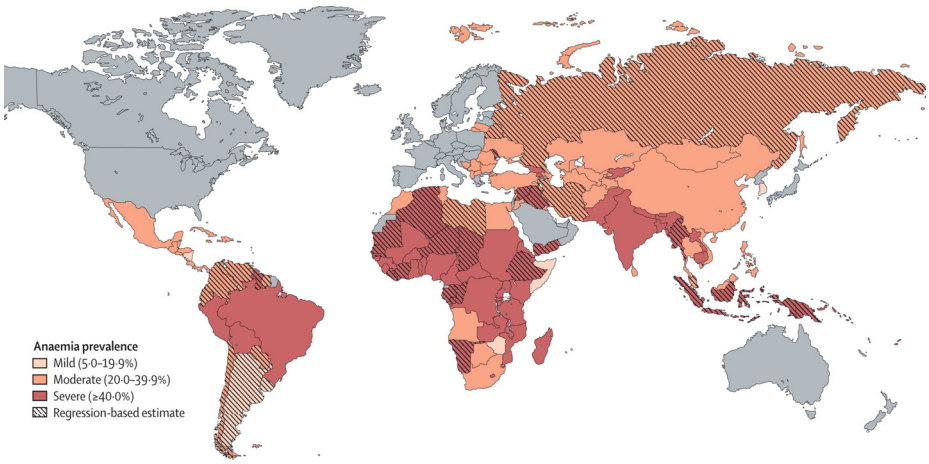

Figure 3. Global anemia prevalence in children aged 0 – 5 years. Data are adapted from Worldwide prevalence of anemia 1993–2005: WHO global database on anemia / Edited by Bruno de Benoist, Erin McLean, Ines Egli and Mary Cogswell.

Globally, anemia accounted for 68.4 million years of life lived with disability in 2010 i.e. for 8.8% of all disease related disability lived years[10]. In 2013, iron deficiency anemia was the leading cause of years lived with disability among children and adolescents, affecting 619 million individuals[25]. Notwithstanding this global picture, childhood anemia receives little attention in the public health domain.

Global anemia prevalence has remained unchanged over the past two decades according to trends in hemoglobin distribution between 1995-2011, emphasizing the scale and pernicious nature of this problem (Figure 4)[10,26]. During this period, preschool age children had the highest anemia prevalence in all geographic regions, the highest mean severity in all low and middle-income regions, and were the only age group to demonstrate an increase in anemia prevalence.

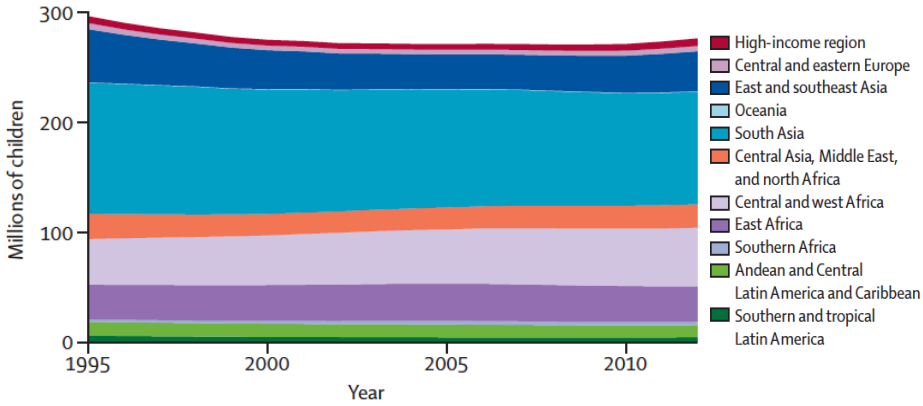

Figure 4. Number (millions) of children with anemia by region.

In absolute terms, India is home to one third of the worlds' anemic population, with over 70% affected women and children, which translates to over 100 million preschool children with IDA[10].

Several factors are associated with the development of iron deficiency anemia[11,27]. Inadequate iron intake particularly among people in low-income (especially rural) settings may be due to limited access to quality nutrition, iron fortified foods, knowledge, appropriate health care, hygiene and sanitation. Poor sanitation promotes bacterial and parasitic infections (malaria) and infestation with soil parasites (hookworms). At the family level, physiological vulnerability of women due to early onset pregnancy, multiparity and inadequate birth spacing result in maternal anemia and increase the risk of childhood nutritional iron deficiency anemia.

All the above are influenced at a more proximal sociopolitical and geopolitical level by factors affecting health care access (roads and transportation), cultural sanitation norms,

agricultural practices, anemia control policies, and ultimately, the prevailing economic, political, and environmental conditions (Figure 5).

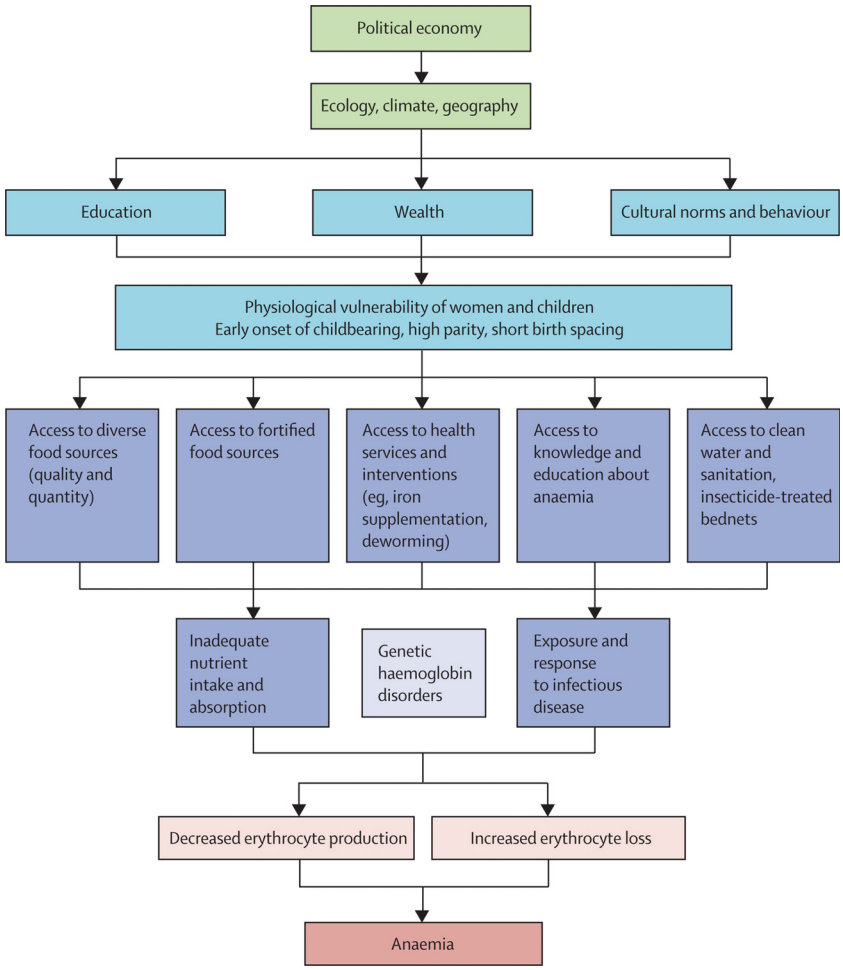

Figure 5. Factors associated with the development of anemia in low middle-income settings.
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1.2.3 Childhood anemia prevalence in India

The fifth percentile of plasma hemoglobin concentration in children 6–59 months is <11 g/dL and forms the basis for the WHO recommended diagnosis of anemia in children[22]. Using this definition, two population-wide National Family Health Surveys in 1999 (NFHS 2) and 2006

(NFHS 3) showed a rise in anemia prevalence from 75% to 79% in 6-35 month old children in 28 Indian states[28]. This increase was largely due to a rise in rural anemia prevalence (Figure 6)[28].

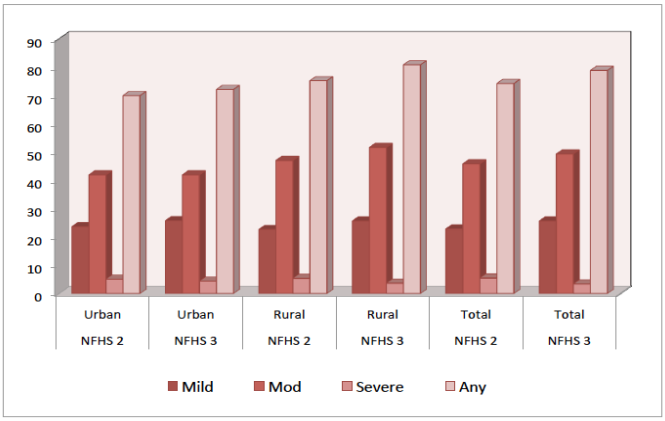


Figure 6. Childhood anemia prevalence data from the National Family Health Survey conducted in 1999 (NFHS 2) and 2006 (NFHS 3). Rising prevalence of anemia in rural preschool children compared to urban preschool children.

Anemia is also classified according to its population prevalence as a mild (0-20%), moderate (21-40%), or severe (>40%) public health problem[23]. With over 40% of its preschool children anemic, India and its South Asian neighbors have a severe public health problem (Table 2). Of note, community-based interventions in neighbouring Bangladesh have been shown to improve nutrition outcomes in women and children[29].

Country	Estimated proportion preschool children with anemia (Hb <11 g/dl)	Confidence intervals	*Category of public health significance
Bangladesh	47.0	42.9–51.1	Severe
Bhutan	80.6	67.3–89.3	Severe
India	74.3	73.4–75.1	Severe
Nepal	78.0	76.1–79.8	Severe
Pakistan	50.9	49.2–52.6	Severe
Sri Lanka	29.9	27.0–33.0	Moderate

Table 2. Prevalence of anemia in South Asian children

1.2.4 Factors influencing childhood iron status

Several antenatal and perinatal factors affect the accumulation and eventual body iron stores of the child setting the stage for adequate iron status at birth[30]. Soon after birth, infant iron status is determined by four factors: the iron the infant is born with, the infant's postnatal iron needs, the external sources of bioavailable iron, and iron losses (Figure 7).

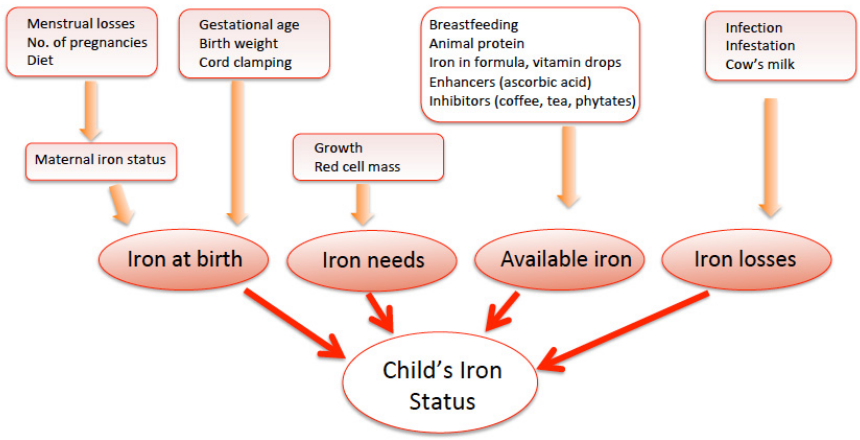


Figure 7. Factors determining infant iron status

Among contextual factors, maternal malnutrition and anemia during pregnancy play a key role in determining the child's iron status in this region. Maternal nutritional iron deficiency coupled with sociocultural factors (high anemia prevalence in adolescence, early marriage, and low birth spacing) affects the child's iron status in-utero. Rural Indian diets consist of predominantly non-heme proteins and high phytate containing cereals, both factors seriously limiting gastrointestinal iron absorption. In addition to dietary factors a high burden of infectious diseases also possibly explains the prevalence of iron deficiency anemia in rural Indian children. India's burden of childhood infectious disease is high[31,32], with a large number of under-five children reporting an acute infection in the 2 weeks preceding the NFHS 3 survey [acute respiratory infections (6%), diarrhea (9%) and fever (15%)][28].

Children with infections have high serum hepcidin level, which can limit absorption of dietary and supplemental iron from the duodenum (see Figure 2)[8,33].

1.2.5 Consequences of childhood iron deficiency anemia

Iron deficiency anemia results in protean clinical manifestations. Symptoms are usually mild most children and adults appear to disregard or seem minimally affected as they acclimatize to the resultant hypoxia. Young children are most affected in the long-term by the detrimental effects of iron deficiency anemia[3,34,35].

Clinical consequences

Symptoms of iron deficiency anemia in both children and adults are generally non-specific resulting from impaired tissue oxygen delivery and may include weakness, fatigue, difficulty concentrating, or decreased attention, lethargy, and irritability. However, iron deficiency anemia has also been associated with ischemic stroke in otherwise healthy children[36]. A case-control study found that among 15 cases of stroke in otherwise healthy children ages 12 to 38 months, eight had iron deficiency anemia (53%) compared with 13 of 143 (9%) matched healthy controls suggesting that children with iron deficiency anemia are at increased risk for stroke[37]. In adults, the clinical effects, especially when severe, are correlated with increased risk of preterm labor, low birth weight[38], and maternal mortality and may predispose to infection and cardiac morbidity[4]. Iron is important for immune function[39] and its deficiency may increase the frequency of infection[40] but whether iron deficiency and iron deficiency anemia are associated with an increased risk of infections due to compromised cellular or humoral immune responses has been harder to establish in human studies[33,41].

Cognitive effects

Iron deficiency anemia is thought to have profound effects on childhood cognitive and psychomotor development[34,35,42-46]. A review of 15 studies found that infants with iron deficiency anemia had cognitive test scores 6 to 15 points lower and motor test scores 9 to 15 points lower than iron-sufficient infants[3]. The effect of iron deficiency anemia in infancy and long-term developmental outcomes was evaluated in 114 healthy and relatively well-

nourished Costa Rican children from ages 12 to 23 months to age 19 years[34,45]. Cognitive delays and psychomotor retardation were significantly greater in children having iron deficiency anemia after adjusting for socioeconomic status[34]. There is inconsistent evidence suggesting reversibility of these cognitive and psychomotor changes in randomized trials of iron treatment[3,35,47-49].

Mortality

Longitudinal studies that report death seldom incorporate specific biomarkers of iron status, such as serum iron, ferritin or transferrin receptor. Therefore, it is difficult to determine the iron deficiency anemia (rather than anemia due to other causes) and child mortality is difficult to characterize. Consequently, the contribution of anemia to mortality is estimated assuming that low hemoglobin concentrations in children reflect an iron deficit in approximately half of the cases[10]. Making such assumptions, a recent meta-analysis of nearly 12,000 children aged 28 days to 12 years, from six African countries demonstrated a combined odds ratio of 0.76 (CI, 0.62-0.93), indicating that for every 1 g/dL rise in hemoglobin, the risk of mortality fell by 24%[50]. Although these studies were conducted in predominantly malaria endemic regions, mortality was similar in cases of anemia that were not attributable to malaria. Thus, indirect evidence suggests that anemia per se contributes to childhood mortality.

Morbidity, social and economic impact

Among health problems causing the greatest disability in India, nutritional iron deficiency anemia was ranked the top in 2016, leading to the loss of over 18% of all disability adjusted life years[51,52]. More recent economic estimates in a 6 and 59 month old Indian birth cohort affected by iron deficiency anemia amount to intangible costs of 8.3 million disability adjusted life years and production losses of 24,001 million USD in 2013[53]. Both intangible costs and production losses as a result of future losses due to cognitive delays arise in all socio-economic groups, but the largest share of these effects occurring in poor rural households. Iron deficiency anemia was the leading cause of years lived with disability among children and adolescents, affecting 619 million in the year 2013[25]. The combination of iron deficiency anemia with a health system unable to provide optimal anemia preventive care (see section 1.3.2) is a key obstacle to optimizing health in rural Indian children.

1.2.6 Treatment of iron deficiency anemia

Treatment of anemia follows the assessment of anemia severity and of the state of tissue oxygenation. In an emergency situation, blood transfusions can be indicated, but in all cases, identification of etiology of anemia and treatment of the underlying cause (nutritional deficiency, infectious disease, and infestation) are warranted. The scope of treatment is to replenish micronutrient stores to normal levels and prevent future recurrence of micronutrient loss or deficiency through targeted interventions delivered to affected individuals throughout the life cycle[54].

Iron deficiency anemia in children is typically treated with oral iron. For infants and young children, the recommended dose for treating iron deficiency anemia is 3-6 mg/kg elemental iron per day in three daily doses, although some studies have found that once-daily dose results in similar improvement as two to three doses daily and does not significantly increase adverse effects[55]. Recent studies of single dose and alternate day dosed iron show improved iron incorporation into erythrocytes and fewer associated adverse effects that could improve adherence[56]. Treatment for 4 weeks generally results in an increase in hemoglobin of at least 1 g/dL and generally lasts for several months; the duration of treatment depends on the severity of anemia[54]. Treatment includes an additional 3 months of oral iron after normalization of hemoglobin to adequately replenish body iron stores. In rare cases of intolerance or clinical unresponsiveness to oral iron (iron refractory iron deficiency anemia), intravenous iron may provide optimal therapeutic responses[4].

Adverse events are typically limited to gastrointestinal tract symptoms, such as constipation, which appear to be directly related to the dose of elemental iron. Increasing the dose over several days, reducing the amount of elemental iron taken daily, or taking the iron with food may improve these symptoms. Urine and stool may be darker in color when taking iron (usually black), and liquid formulations can cause temporary gray staining of teeth and gums. Iron can cause important interactions with several drugs and can be fatal in overdose in children warranting the use of child proof IFA dispensation containers.

The safety of childhood population wide iron supplementation was questioned by a large cluster randomized placebo controlled trial in a malaria endemic region of Africa[57] but the absence of similar finding from other studies conducted in both malaria endemic and nonendemic areas have been reassuring[58-61]. Due to high baseline iron deficiency prevalence and low malaria prevalence in the study area, these risks appear to be largely theoretical.

1.3 PUBLIC HEALTH INTERVENTIONS FOR ANEMIA CONTROL

1.3.1 Interventions for nutritional anemia: what works

The WHO recently prioritized reduction of global anemia prevalence in women by 2025 and the United Nations Development Programme sustainable development goal number two actively advocates better control of childhood malnutrition underscoring the notion that nutritional anemia is a high priority[52,62,63]. Yet, judging by trends in global anemia prevalence[26], the probability of achieving these goals is low, prompting an examination of successful anemia control efforts in countries other than India.

Broad based public policy interventions targeting nutrition

At the broad policy level, improving socioeconomic status, addressing food insecurity, and food fortification programs have decreased maternal and child undernutrition and anemia prevalence[52,64,65]. Integrated public health nutrition interventions aimed at improving nutritional status in vulnerable groups showed the greatest effect in populations with significant income, health and nutrition disparities[66-68]. Amongst these are interventions directed at nutrition education[69], dietary modification, food provision/supplementation[66,67,70], agricultural interventions including bio-fortification[71], multiple micronutrient supplementation[72] and food fortification[52,73-75]. Aside from the integrated child development scheme (ICDS)[70,76], there are remarkably few broad based policy efforts addressing anemia in India, where anemia prevention activities also include fortification of staple foods with iron. Unfortunately, limitations in rice fortification technology and low population level acceptance of fortified foods make such programs strategically less appealing. Furthermore, food fortification programs efforts are primarily aimed at the urban populations with limited reach to rural communities[75,77].

Policies addressing iron and multiple micronutrient deficiencies

Specific public health programs include population-wide iron supplementation targeting high risk groups, a strategy that has led to overall anemia risk reduction by 49% and iron deficiency risk reduction by 74%[12,78,79]. Use of multiple micronutrient supplementation has been shown to improve hemoglobin and reduce anemia risk in children by 57%[42]. However, when compared with iron alone, multiple micronutrient supplements add little benefit to hemoglobin responses[42,72]. Although overwhelming scientific evidence demonstrates the effectiveness of targeted iron supplementation in reducing childhood anemia prevalence worldwide[80,81], this strategy has yielded lower than expected results in India. The reasons are explored in greater detail in the next section.

Interventions aiming at improving hemoglobin levels

Periodic deworming has no obvious effect on hemoglobin response[82], but programs that screen and detect worm infestation followed by a single treatment of deworming show improvements of hemoglobin levels[83]. Currently, population-wide deworming on a biannual basis for children above 2 years is widely practiced in India and continues to have policy support[84]. Malaria is nonendemic in many areas of India and specific interventions tend to focus on vector control combined with effective diagnosis and treatment of individual cases[75]. The contribution of common infections to anemia burden appears to be largely ignored or underestimated. Effective implementation of ongoing community interventions directed at treatment and prevention of these diseases (IMNCI, RNTCP, and WASH)[1] could help address the overall burden of non-iron deficient anemia resulting from infectious diseases.

Genetic hemoglobin disorders affecting anemia prevalence are beyond the scope of the current work and strategies for their treatment and control, integral components of childhood anemia prevention are reviewed elsewhere[85,86]. Currently, there are ongoing efforts to integrate hemoglobinopathy screening in areas of high prevalence but these are few and require national efforts[87]. While important, these interventions do not specifically target the major cause of mild to moderate anemia in children: iron deficiency.

[1] IMNCI, Integrated Management of Neonatal and Childhood Illnesses; RNTCP, Revised National Tuberculosis Control Program; WASH, Water Sanitation and Hygiene.

1.3.2 Public health measures for anemia control in India

Public health anemia control activities in India began in 1970 with the nutritional anemia prophylaxis program and were re-designated as the National Nutritional and Anemia Control Program (NNACP) in 1991, when they incorporated both anemia prevention and treatment activities. However, decades of efforts with childhood iron supplementation and treatment of anemic children have yielded a reduction in anemia prevalence which is lower than expected reductions. Possible reasons for this include poor health infrastructure, inadequate funding of the program and other health system factors ultimately leading to insufficient coverage of children with IFA[77,88]. In fact, nationwide surveys demonstrate unacceptably low coverage of both women and children, important target beneficiaries of the program[28]. Anemia case detection is also limited by low sensitivity screening strategies (e.g. visual inspection of mucous membranes for anemia screening by community health workers) which also hamper program effectiveness[77].

To date, the anemia control program is implemented largely by the Accredited Social Health Activist (ASHA) from the primary health center, which serves a population of 30,000 individuals (approximately 20-30 villages). Among diverse health promotion activities, anemia control efforts include: (a) promoting the consumption of iron rich foods, (b) providing IFA tablets, and (c) identifying and treating severe anemia. Case detection is targeted to groups at high risk for anemia (women, pregnant women, adolescent girls and 1-5 year-old community dwelling children). Unfortunately, ASHA workers are non-salaried employees and do not receive financial incentives for anemia control work unlike the other health promotion work activities (e.g. providing primary health care services for pregnant and antenatal women). Thus, in addition to the limitations identified above, lack of financial incentives and low health worker motivation levels adversely affects childhood anemia control. IFA adherence in young beneficiaries, another important understudied aspect that affects program success will be explored in greater detail in the next two sections.

In 2013, the National Rural Health Mission and the Ministry of Health and Family Welfare consulted with domain experts and released new anemia control guidelines entitled National Iron Plus Initiative (NIPI; Appendix 1)[84]. These guidelines are a major step that begin to address several of the limitations described above. First, they recommend financial incentives for ASHA workers specifically for anemia control activities, simplification of iron

supplementation regimens, and provision of age appropriate iron formulations for children (liquid iron formulation that can facilitate adherence by small children). Second, they recognize the potential value of motivating behavior change (dietary habits and adherence), social marketing of IFA to improve adherence, and the utility of LHW education and counseling for anemia. Unfortunately, the guidelines fail to prioritize the detection/treatment of anemic cases and lack a statewide/national implementation strategy.

1.3.3 Community-based interventions delivered by lay health workers

Lay health workers are usually the point of first contact and deliver important health services to rural communities in India. In this thesis, the term lay health worker is used synonymously with the *anganwadi* day care center worker (a health worker that is quite distinct from the ASHA worker). The *anganwadi* day care center health worker is a salaried employee of the ICDS who is administratively responsible for the village *anganwadi* day care center and provides care for children in her own village. The *anganwadi* day care center worker is thus uniquely poised to provide health education for mothers during their routine consultations and to closely monitor nutritional health outcomes in the child. Previous studies have shown that lay heath workers optimize maternal and child health outcomes by facilitating nutrition education, immunization uptake, breast and complementary feeding practices, adherence to iron supplementation and reducing infectious disease mortality[68,82,89-96].

Studies from Bangladesh[97] and Indonesia[68] indicate that lay health workers play a key role in preventing childhood anemia. In rural Indonesia, lay health workers enhanced intervention uptake at the community level and better performing lay health workers achieved better childhood anemia reduction outcomes[68]. Community-based interventions led by lay health workers have effects that are moderated by social and environmental conditions acting at different levels, including interpersonal (family, peers, and social networks), community (day care center and school), and governmental (local, state, and national policies)[98]. These interventions have the advantage of achieving parental knowledge and practice changes that are usually affordable for the target audience, therefore potentially transmissible to the next generation and sustainable in the long term[99].

1.3.4 Improving adherence to IFA among children's caregivers

In medical sciences, there is an abundance of studies about adherence to prescribed treatment among patients with chronic diseases[100,101]. In contrast, factors motivating adherence behaviors of mothers/caregivers who receive "treatment" for their healthy children from a community health worker are less predictable[102-107]. Moreover, few studies have actually evaluated adherence to iron supplements in preschool children[107-109]. Most of the published studies evaluated adherence among women and adolescent girls[56,104,109-114] and have not investigated whether mothers adhered to instructions about giving iron to their children.

Knowledge and use of supplements

Large studies have evaluated perceptions of pregnant women about anemia and iron deficiency in limited resource settings including India[110,115]. Pregnant women recognized IFA tablets and took them as instructed but usually did not know why they were prescribed. Among pregnant women, improving knowledge about anemia and its treatment increases their adherence to iron supplements[116]. Contrary to common beliefs, relatively few mothers report decreased adherence due to side effects from iron supplements (~30%)[115]. Health system factors, such as inadequate or fluctuating supplies of iron tablets also diminish adherence[115]. Based on the above mentioned studies in women and adolescent girls, it can be hypothesized that interventions to educate mothers about childhood anemia may enhance adherence in administering iron supplements to their children.

Barriers and facilitators

Studies have showed that major barriers for pregnant women taking iron supplements were poor access to iron (inadequate supplies), side effects (mostly gastrointestinal), fear (large baby, difficult delivery, harm to the baby), recovery (feeling better so no longer needing the tablets) and resistance (forgetting or just not wanting to take tablets)[106,115,117]. Facilitators included alleviation of anemia symptoms, appreciation of benefits for the growing fetus, and a subsequent increased demand for prevention and treatment of anemia[106]. Literacy appears to influence IFA uptake with educated mothers in some cases actually demanding their share of iron from lay health workers[115].

Modifiers of adherence behaviors in community interventions

Combining micronutrient interventions with food supplementation, appears to facilitate adherence which is greater among less educated mothers than more educated mothers[103]. Involvement of lay health workers facilitates intervention uptake and plays an important role in influencing health-seeking behaviors of low socioeconomic status communities[68]. Contextual and health system factors also affect adherence behaviors[102,104,110,118] profoundly influencing intervention implementation and eventual health outcomes.

In summary:

In the Indian context there is a wide gap of knowledge concerning: estimates of community level anemia prevalence in children using accurate diagnostic tests; coverage of children with IFA by anemia control programs; development and scientific evaluation of novel community-based public health intervention specifically targeting mothers/caregivers of anemic children. The studies in this thesis address the gaps identified above and develop an intervention to improve the cure rate of anemic children.

2 AIMS

2.1 OVERALL RESEARCH QUESTIONS

- What are the determinants of childhood anemia in community dwelling children in rural provinces of South India (Study I)?

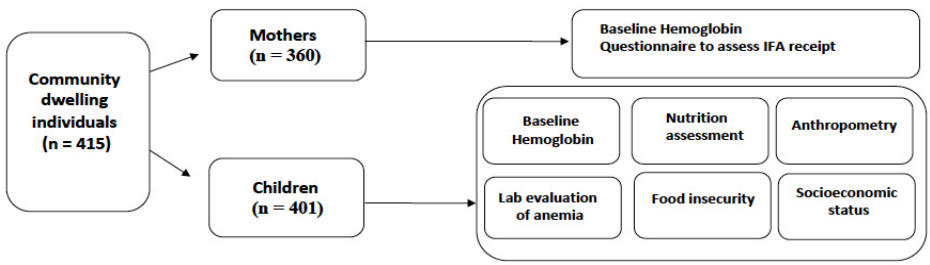
- What is the coverage of rural children with iron supplements by the national anemia control program (Study II)?

- What effect does a community-based parental educational intervention delivered by lay health workers have on anemia cure rate in rural children, when added to usual treatment (Study IV)?

- What are the experiences of community lay health workers delivering such an intervention (Study III)?

2.2 RATIONALE FOR THE THESIS AND CONCEPTUAL FRAMEWORK

Studies I and II provided the background for intervention development through the estimation of the prevalence and etiology of anemia in rural children as well as of the coverage of these children with iron supplements according to the national anemia control program (see overview of studies 1 and II shown below).



Childhood anemia control in India has had limited success for reasons including insufficient parental awareness of anemia, insufficient coverage of children with IFA, inadequate

program support by community health workers, and lack of adherence to iron supplementation by children's families. Lay health worker supported community-based interventions have previously improved maternal and child health outcomes[64,119] and anemia specific outcomes[68]. Remarkably few community-based interventions have used lay health workers as interventionist's to achieve health improvement in India and not a single one has examined childhood anemia programs[69,120]. We hypothesized that an educational and counseling intervention delivered by a lay health worker, with a strong parental component specifically directed at reducing knowledge gaps among mothers, at improving parental self-efficacy, and at enhancing adherence to IFA delivery to the anemic child would achieve better anemia cure rates than usual treatment (Figure 8).

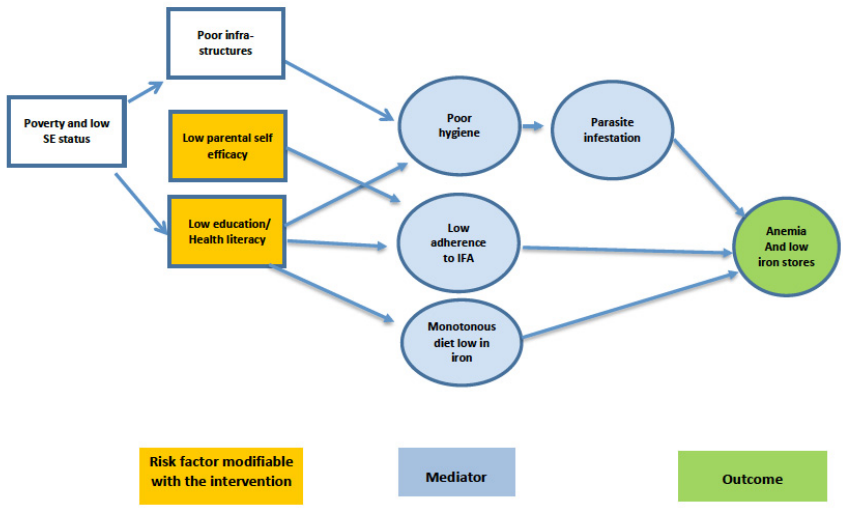


Figure 8. Directed acyclic graph of the anemia intervention

2.3 METHODS

2.3.1 Intervention theoretical basis and design

Theoretical frameworks in the planning stage of the intervention were developed according to Fraser et al and optimized in a stepwise manner[121,122]. In the Problem Theory, mother's knowledge, attitude, beliefs, care and control, role model, willingness to change, and parental self-efficacy were identified as malleable factors in order to influence the hygiene, dietary habits, and adherence to IFA supplements in their children[123]. The Social Cognitive Theory

framework largely guided the intervention design, wherein at least two principal sources of enhancement of self-efficacy were identified: verbal persuasion and performance accomplishment[124]. Education of mothers about anemia, nutrition, IFA supplementation, and hygiene could foster the perception that their actions would control anemia in their children. This would lead to positive expectations about their children's health outcomes, which, along with LHW facilitation of learning and positive reinforcement would improve IFA adherence in the child. Additional details about the intervention are provided in the methods section. Evaluating the effectiveness of the outcome of this intervention scientifically led to the production of the study protocol (Appendix 2).

2.3.2 Pragmatic trial design using mixed methods

The effectiveness of the intervention was evaluated in a pragmatic trial based on a cluster randomized design (Figure 9; Study IV) the protocol of which is shown in Appendix 2. By measuring the degree of beneficial effect under "real world" clinical settings pragmatic trials tend to emphasize effectiveness rather than "efficacy"[125].

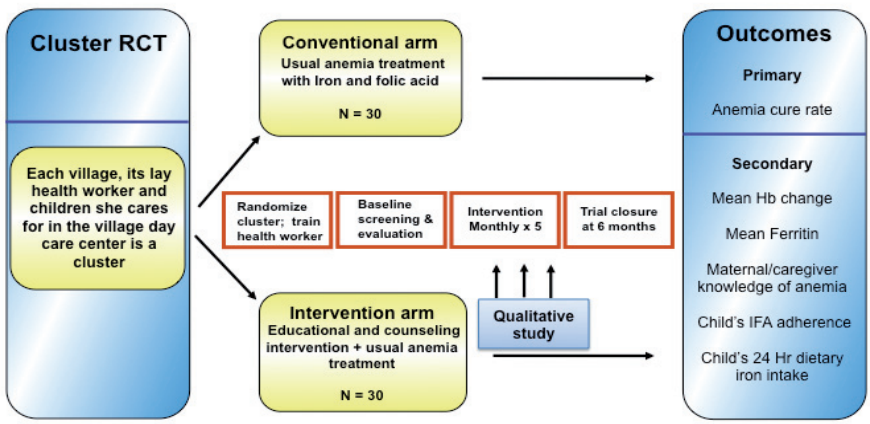
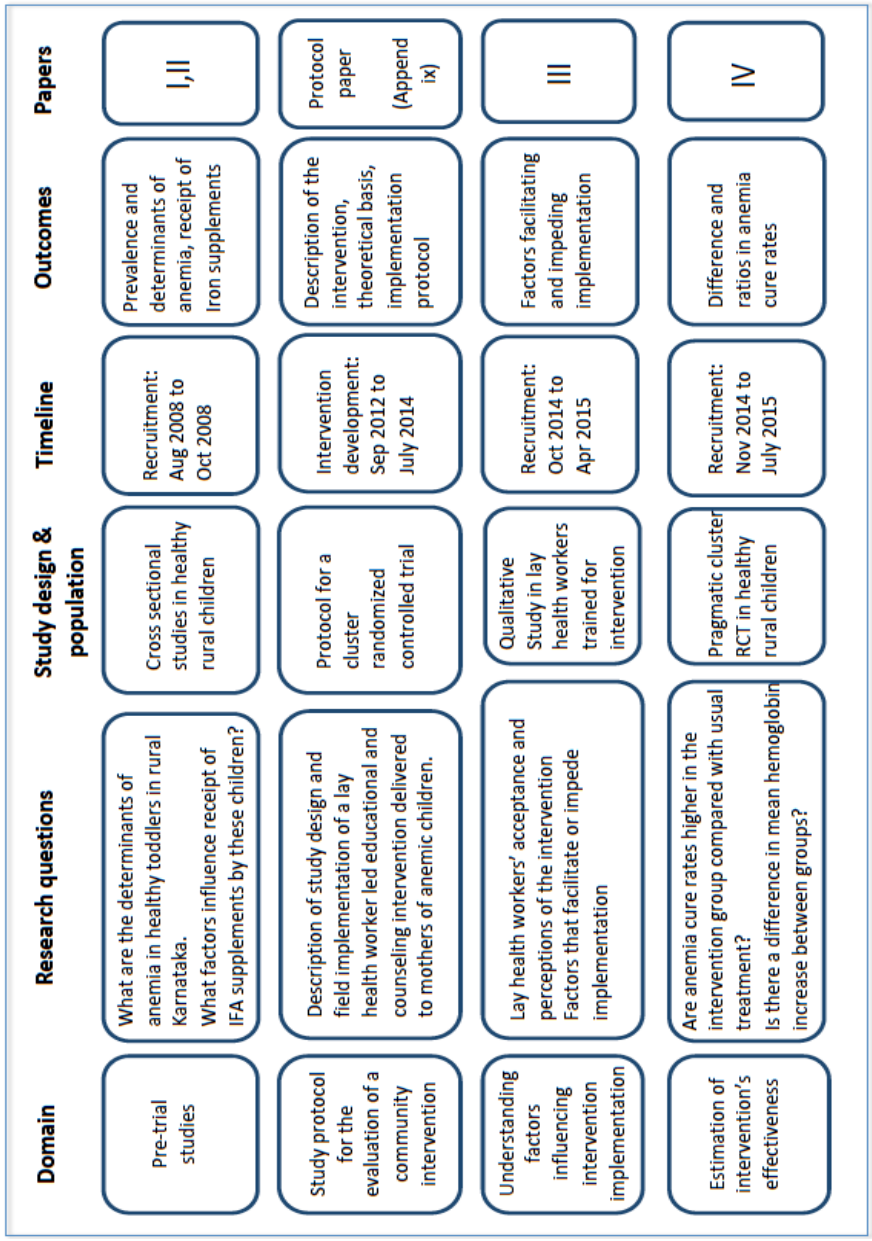


Figure 9. Trial design and outcomes measures

We believe that this approach would provide the most relevant information for decision makers. Since community sensitivities, intervention design aspects, contextual and health system factors profoundly influence lay health worker performance, we used qualitative methods to understand lay health worker perspectives regarding intervention acceptability and implementation (Study III)[126].

3 METHODS

3.1 THESIS OVERVIEW



3.2 STUDY SETTING

Studies I and II were conducted as situational analyses of childhood anemia in healthy rural community dwelling children from rural Karnataka, South India. Studies III and IV, were conducted in the Chamarajnagar district of South India (Figure 9). The study district is located in the south Indian state of Karnataka, which with a population of 61 million (7.1 million of which are children 0-6 years of age) is the ninth most populated state. The study areas are rural with a predominantly agrarian economy and an average annual household income of Indian rupees (INR) 22,006 (US $478), reflecting state and national income averages.

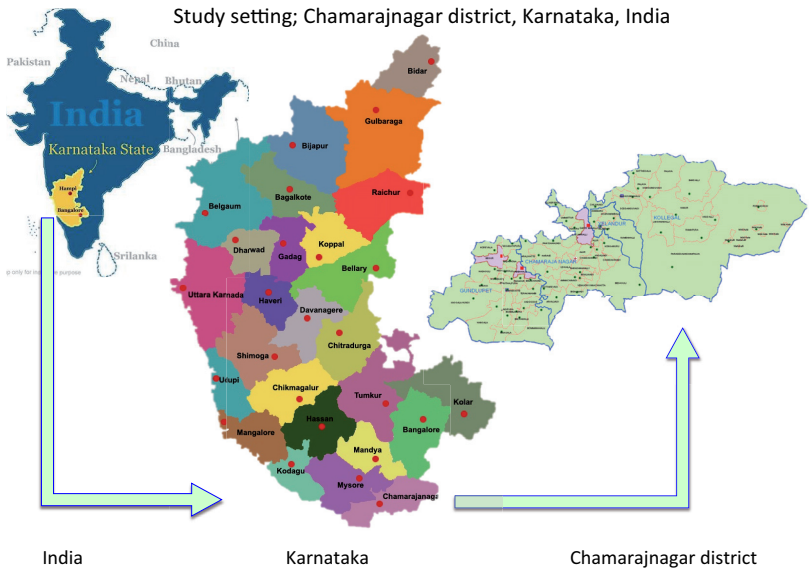


Figure 10. Map of the study area. Recruiting villages were situated in the Chamarajnagar district located in the southern state of Karnataka.

The study provinces represent the typical religious and sociocultural diversity of rural Indian communities. Primary health care to residents of villages in these provinces is provided through a network of primary health centers, representative of the Indian rural health system. Staff members from these facilities deliver primary health services such as immunization, antenatal care, postnatal care, nutritional care and general health advice. Service delivery, including iron and folic acid supplements, vitamin A supplements, deworming activities, and

patient education, is ensured with logistic support from the National Rural Health Mission (NRHM), a program administered by the Ministry of Health, Government of India. The center operates under the NRHM program guidelines providing services that are free of cost.

In addition to primary health care, each village in this province is serviced by a network of *anganwadi* day care centers under the administrative support of the Integrated Child Development Services (ICDS), a program administered by the Maternal and Child Welfare Department, Ministry of Health, Government of India[76]. The *anganwadi* day care center is usually a simple single room or two roomed facility located in the village, made according to guidelines laid by ICDS. The lay health worker in charge of the *anganwadi* (*anganwadi* worker) is employed by the ICDS and administratively under the supervision of the ICDS scheme staff at the district headquarters. The ICDS provide supplementary nutrition, preschool non-formal education, nutrition and health education, immunization, health check-ups and referral services to children, as well as to pregnant and lactating mothers. In theory, these services are universal for all categories of beneficiaries and cover all village children below 6 years of age, pregnant women and lactating mothers[70,76]. The *anganwadi* day care center does not participate in primary health care delivery but aims to focus on the nutritional health of its beneficiaries. Therefore, very little coordination of activities happens between the primary health care center and the *anganwadi* day care center.

Health promotion by the primary health care center and the *anganwadi* day care center is supported by a network of non-governmental organizations (NGOs), partially addressing the needs of socially disadvantaged communities. These agencies complement efforts by providing services in remote areas poorly covered by government. The research team partnered with one such non-governmental organization, the Mysore Resettlement and Development Agency (MYRADA). Since 1968, MYRADA has worked with more than a million families in 18 districts of Karnataka, Andhra Pradesh and Tamil Nadu, improving health and education status of the community and building the community's capacity to raise and manage resources independently. The collaborative partnership between an academic institute and a local NGO was intended to be mutually beneficial to all stakeholders. A history of working with this community over several decades fostered community participation.

3.3 STUDY PARTICIPANTS

In study I and II, all healthy rural 12-23 month children living in the study provinces of rural Karnataka along with their mothers or caregivers were invited to participate. Invited participants were considered eligible if they were living in the village, were in their usual state of health, did not have a fever, had not received a blood transfusion in the previous three months or had a history of hemoglobin disorder. After obtaining informed consent, subjects were recruited between August 2008 and October 2008.

In study III, lay health workers delivering the intervention in the trial were approached to complete a questionnaire on anemia awareness after the training. Lay health workers were then purposively selected based on the results of this questionnaire (the top 5 best performing and the bottom 5 worst performing) and invited to participate in focus group discussions. After informed consent, focus group discussions and non-participant observations were conducted between October 2014 and April 2015.

In study IV, 60 villages were selected at random from 270 villages in the geographic study area and 55 eventually agreed to participate. All caregivers of children aged 12-59 months in these villages were invited to participate. Participants were considered eligible if they were resident in the village, were in their usual state of health, did not report a fever, and agreed to receive counseling and education by the lay health worker upon assignment to the intervention group. While obtaining informed consent participants were blinded as to village assignment to intervention or control. Participants were recruited between October 2014 and July 2015.

3.4 STUDY DESIGN AND INTERVENTION

3.4.1 Anemia determinants and anemia program coverage (Study I & II)

Studies I and II were cross sectional studies conducted in 12-23 month-old community dwelling children and their mothers in two rural provinces of Karnataka state (Figure 9). After recruitment and administration of a questionnaire, subjects and their mothers had a blood sample obtained by phlebotomy. Questionaires collecting sociodemographic

information, 24 Hr dietary intake, food insecurity, and receipt of primary health care services including IFA were administered in the local language in the format of an interview conducted by a research team member. Anthropometry was performed using standard methods. Anticoagulated blood was used to perform a complete blood count, hemoglobin electrophoresis, and measure serum Vitamin B12 and Folic acid levels.

3.4.2 Pragmatic cluster randomized controlled trial (Study IV)

3.4.2.1 Study definitions

Cluster was defined as a village in the Chamarajnagar district that was randomly allocated to one of the study arms together with the *anganwadi* day care center or (if the village had more than one center) the selected day care center belonging to that village, and its corresponding lay health worker.

Anemia was defined as hemoglobin (Hb) concentration below 11 g/dL.

Hypoferremia was defined as a serum ferritin concentration below 15 ng/dL.

Iron deficiency anemia was defined as a hemoglobin below 11 g/dL and a serum ferritin below 15 ng/dL.

Anemia cure was defined as a child with anemia at baseline whose hemoglobin level at follow-up was at or above the threshold of 11 g/dL.

Net hemoglobin change was measured as the difference in children's mean hemoglobin level between baseline and follow-up.

Adherence to IFA was defined as the percentage of the total pills consumed divided by the total pills dispensed in the previous 30 days obtained during month 6.

3.4.2.2 Study protocol

Population

The target population for enrolment to the trial included all children aged 12-59 months registered in the village day care centre. All children and their mothers that were resident in the village were potentially eligible. Children were excluded if they had fever (>101°F), severe anemia (Hb<8.0g/dL) or had a recent blood transfusion in the previous 3 months. Children absent from the village either due to vacation or travelling with parents for religious holidays were unable to fulfil eligibility criteria and were excluded. In keeping with the guidelines, all non-anemic participants irrespective of treatment group assignment (≥11 g/dL) received IFA supplements (8 tablets/month, each containing 20 mg elemental iron) and deworming every 6 months (albendazole 400mg, single dose).

Intervention

1) Lay health workers in the intervention group delivered *monthly education and counseling only to mothers of anemic children in addition to usual treatment for anemia*. These sessions were conducted in the participants' homes and were intended to change:

- Mothers' knowledge regarding anemia and its consequences
- Knowledge of treatment of iron deficiency anemia with IFA
- Adherence to IFA administration
- Awareness and use of iron-rich food and enhancers of iron absorption
- Diet diversification and minimization of dietary iron chelators
- Hygiene and sanitation

Non-anemic children in intervention villages received the usual prophylactic dose of oral iron (reported in section "Comparator")

2) Monitoring of adherence to IFA supplements and side effects

In the intervention group, lay health workers delivering IFA tablets recorded mothers' *monthly* adherence to the tablets in the previous 30 days *for anemic children* and

recorded side effects to the IFA tablets using a standardized adherence data collection form (appendix 4).

At the end of the trial, during the 6 month follow up visit, adherence to and side effects of IFA in the previous 30 days was retrospectively assessed in both the intervention and the control groups by the research team using a standardized adherence data collection form.

Training activities also included a module to enhance trial specific documentation skills by the intervention group lay health workers enabling measurement of intervention process outcomes.

Comparator

The control group received only received usual care for prevention and treatment of iron deficiency anemia according to international consensus statements and in line with National guidelines (National Iron Plus Initiative, Appendix 1). Since these guidelines were released just prior to trial initiation, specific efforts were made to train the control arm regarding changes in the guidelines. In addition, IFA was actively sourced by the research team and provided to the lay health worker and monthly telephone contact was maintained to confirm IFA delivery.

- All anemic participants (Hb≥8 and ≤11 gm/dL) received therapeutic IFA dosage to control iron deficiency anemia (20 tablets/month, each containing 20 mg elemental iron for a total period of 5 months) and deworming every 6 months (albendazole 400mg, single dose).

Outcomes

Primary outcome

The primary outcome was anemia cure rate, defined as the proportion of children who were diagnosed as anemic at enrollment being no longer anemic at follow up (6 months after the start of the intervention).

Secondary outcomes

The trial also assessed several secondary outcomes occurring along the hypothesized causal pathway of the interventions effect. These included:

1) Net change in individual hemoglobin values between baseline and 6 month follow-up among anemic children exposed and not exposed to the intervention.
2) Changes of knowledge and practice of mothers of anemic children from baseline to 6-months follow-up.
3) Estimated 24-hour dietary iron intake among anemic participants exposed and not exposed to the intervention.
4) Net improvements in mean ferritin values (indicating iron stores) among anemic participants exposed and not exposed to the intervention.
5) Changes in cluster-level anemia prevalence between baseline and follow up.

Measures of intervention effects were modeled as outcomes' ratios or differences between the trial groups, as defined further in the statistical methods.

Randomization

Randomization occurred at the village level. A third party independent of the research team performed the randomization prior to enrollment. From a total of 270 villages in Chamarajnagar, 60 villages were selected using a computer random number generator[127]. The villages were then stratified based on the number of <6 year-old children listed in the ADC registers as being resident in each village. There were 26 villages with <50 children and 34 villages with ≥50 children. After stratification, the villages were randomly allocated using a computer algorithm in a 1:1 ratio to the intervention or control groups, in blocks of 2 in order to ensure equal representation of each stratum in both groups. Random assignment was subsequently communicated to the lay health workers and after obtaining their informed consent, training for the intervention occurred followed by enrolment of children.

3.4.2.3 Lay health worker training

In the intervention group, lay health workers were trained to deliver the intervention in four separate hands-on workshops conducted over 6 months. Training techniques included the use

of peer group interaction, role-play, facilitation, and group discussions. The training workshops were supported with the use of supplementary education material (including flip charts provided for each health worker, Appendix 3) with which the lay health workers became familiar. Training occurred at a location different from the lay health workers habitual training/supervision sites, to minimize the risk of contamination. Each training session lasted for one to two days. During each training workshop, the research team organized food, accommodation and transportation to and from the training site.

3.4.2.4 Study procedures and field implementation

The trial was implemented in the field by the research team assisted by the village LHW during enrollment and trial closure activities. All education and counseling related intervention components were delivered solely by the LHW.

Recruitment of participants

The steps and the flow of recruitment of villages and individual participants are shown in Figure 11, in the results section. Participants were mobilized by the *anganwadi* day care center lay health worker. Recruitment occurred at the village *anganwadi* day care center, and lasted usually for 2 days. When <80% of eligible participant were recruited, the research team spent an extra day recruiting or returned to the village until 80% of the target population was reached. Home visits made on recruitment days helped identify reasons for nonattendance and mobilize those that had forgotten to attend. At study entry, a baseline questionnaire and other study instruments were used to record participant information and collect relevant data (Appendix 4).

Out of 60 randomly selected villages, LHWs agreed to participate in 56 (effects of cluster dropout N=4; n=155). Further, random selection of villages with lower numbers of children relevant to the study group and an overestimation of children in ADC registry information yielded less eligible children (n=1860 vs. 2500). This left 1625 possible children for screening.

Screening for enrolment of individual children aged 12-59 months and of theirs mothers/caregivers was conducted between October 2014 and July 2015. Physical absence of families during recruitment (traveling n=341; migrated/untraced n=80) resulted in non-participation (26%) but the characteristics of non-participants were similar to participants. During screening, few individuals either did not consent (n=9). Also in one case mothers/caregivers from an entire cluster withdrew consent *en masse* (N=1; n = 56). Of the remaining children screened (n=1219), 75 failed to meet the inclusion criteria and were excluded (severe anemia n=50, inability to provide a blood sample n=24 and withdrawal of consent during phlebotomy n=1). Lay health worker notified mothers of children with severe anemia (Hb<8.0g/dL) of their study ineligibility and referred the child to the primary health center for medical care. Thus, from 55 villages a baseline population of 1144 children was enrolled to the trial (control villages=27, n=536; intervention villages=28, n=608).

Anemia detection, list of anemic children, and IFA delivery

All children had venous blood sampled to determine hemoglobin and detect anemia and a report of the child's hemoglobin value was subsequently provided by the research team to the lay health worker who then delivered it to the child's mother. The research team also provided lay health workers with a list of anemic and non-anemic children. The research team made monthly telephone reminders to lay health workers in both study arms to ensure that IFA was delivered to mothers/caregivers.

Intervention delivery and adherence monitoring by the LHW

In the intervention group, lay health workers delivered the first of five educational and counseling sessions (IFA delivery, education and counseling, and adherence monitoring) to mothers of anemic children. A month later, during the second session, lay health workers delivered the second month's IFA supply, collected adherence data (obtaining the remaining IFA pills/empty strip from the first month) and performed the second education and counseling continuing this activity monthly for five months. At the end of the trial, adherence and side effects in the previous 30 days was monitored during the end of study visit (6 months after the start of the intervention) in all study participants in both study arms.

Six month follow up visit and end of study

Approximately 6 months from start of the intervention, all study participants received an end of study visit by the research team. At this time the research team obtained venous blood to estimate hemoglobin, collected 24-hour dietary recall information, adherence/side effect information, and performed anthropometry.

3.4.2.5 Quality control

Data collection instruments were tested for acceptability in pretrial pilot studies. After trial recruitment began, weekly review of recruitment and data collection was performed. All questionnaires underwent quality checks on the day of data collection to ensure accuracy and address missing values. A quality control manager ensured that data entered in the physical case report forms on a day-to-day basis was complete and accurate. Data entry was blinded and double entered into an Excel database under the supervision of a dedicated data manager. Intervention process outcomes were assessed during monthly checks by the research team for completion of the IFA adherence and monitoring forms.

3.4.3 Focus group discussions with lay health workers (Study III)

From 30 lay health workers allocated to the intervention group, 2 declined to participate prior to intervention training. Using performance during training as indicative of probably success during implementation, we sought to obtain views of both well and less well performing lay health workers. To achieve this goal we purposively sampled well performing (n=5) and less well performing (n=5) lay health workers based on a questionnaire used to evaluate training success. Since nine of the ten LHWs agreed to participate, after the first focus group discussion, two additional lay health workers (one well performing and one less well performing) were invited to participate (total invited to participate=12). Three focus group discussions were conducted in total, the first occurring immediately after intervention training and the subsequent two focus group discussions during intervention delivery (Figure 9). All focus group discussions were conducted with the same cohort of LHWs in the local language by experienced researchers working in the main trial. Focus group discussions were audio recorded, transcribed and translated into English using a professional translator, checked for accuracy, and then coded independently by two researchers.

In addition to the focus group discussions, we gained broader insights into implementation with non-participant observations and maintenance of detailed field notes. For non-participant observations, the research team based on their field experience purposively sampled two lay health workers that implemented the intervention easily and two that encountered difficulties implementing the intervention. Observations were conducted over multiple time points during intervention conduct. Detailed field notes were maintained by the research team during conduct of the intervention training, focus group discussions and the nonparticipant observations and were subsequently used to validate emerging themes from the focus group discussions. Data triangulation using multiple data sources was sought to enhance validity.

3.5 LABORATORY METHODS

3.5.1 Sample processing, storage and transport

All blood samples were collected and processed in the Chamarajnagar field laboratory within 6 hours of blood collection. Anticoagulated blood was used immediately to obtain complete blood counts, and then processed appropriately to obtain serum and plasma. Samples for ferritin assays were stored at -20°C in the field laboratory and transported weekly on dry ice to the hematology research laboratory at St. Johns National Academy of Health Sciences where they were stored at -80°C for batch analysis at a later date.

3.5.2 Complete blood counts

A complete blood count was measured using a three-part differential automated cell counter (Sysmex XP 300, Transasia Laboratories, Tokyo, Japan) located in the field laboratory at the Chamarajnagar district.

3.5.3 Iron stores

Ferritin was measured using an immunoassay detected by chemiluminescence (Access 2, Beckman Coulter, California, USA).

3.5.4 Quality control for laboratory

Trained laboratory personnel using standard operating protocols following principles of Good Laboratory Practice performed all tests described above. Research staff maintained daily quality control checks of the field automated cell counter instrument to ensure accurate hemoglobin measurements and verified these weekly in the Hematology Research Laboratory at St. Johns National Academy of Health Sciences. The sample processing, storage and assay conditions were field tested in pilot studies to confirmed that preanalytical variables did not affect hemoglobin and ferritin measurements. A bar coded sample management software ensured that samples were accurately labeled prior to storage to minimize errors during future batch analysis.

3.6 STATISTICAL METHODS

3.6.1 Study I and II

Linear and logistic regression analysis was performed to assess the cross-sectional associations between socio-demographic and behavioral characteristics of participants and hemoglobin (continuous variable) or receipt of iron supplementation (binary variable). The fit of each model was evaluated with likelihood ratio testing and confirmed using either the Shapiro-Wilk test or Hosmer-Lemeshow goodness-of-fit test.

3.6.2 Study III

The analysis of focus group discussions centered on lay health worker perceptions, acceptability and experiences with regard to the intervention particularly attempting to identify barriers and facilitators to its implementation. The data corpus was analyzed inductively using the framework method to ensure systematic analysis of themes identified across all the different sources of transcripts[128,129]. Analysis was conducted independently by two members of the research team. Each transcript was manually coded, and from these codes, abstractions were developed to form categories, followed by themes. Subsequently, a framework of these themes was developed, following which the transcripts were re-coded

into the framework. Non-participant observations and field notes were similarly manually coded and analyzed inductively.

3.6.3 Study IV

Sample size estimation

A 12% difference in 6-month anemia cure rates after 6 months was judged to be clinically meaningful, based on published trials of anemia treatment [96,130]. To detect this difference at an alpha level of 0.05 for a two-tailed test, with 80% power, a total unadjusted sample size of 500 children with anemia was required. After adjustment for clustering (design effect = 2.2; intracluster correlation coefficient (ICC) = 0.05 and cluster size = 25), a total sample size of 1,100 children with anemia was estimated. Allowing for a 10% loss to follow-up of children identified with anemia at baseline, led to a final sample size of 610 children with anemia per arm (1,220 in all)[131]. Assuming a 50% anemia prevalence[20], it was calculated that screening of 1,220 in each arm (total = 2440) would be required to achieve this desired sample.

Statistical analysis

The intervention's effect was expressed as Risk Ratio (RR) with the corresponding 95% Confidence Interval (CI) of being non-anemic at follow-up in the intervention group relative to usual treatment. The estimate of effects was derived through multilevel models based on Poisson distribution. We used linear regression to study the interventions effect concerning the secondary outcome, net hemoglobin change.

4 RESULTS

4.1 STUDY I: PRETRIAL ANEMIA ETIOLOGY AND DETERMINANTS

There were 405 children and corresponding 364 consenting mothers participating in the study and providing a venous blood sample. The mean age of children was 17.2 months, and 204 (50.3%) were boys.

Social and demographic characteristics

The mean age of mothers in the study was 23 years with a 70% literacy rate and a median of 7 years of schooling. The socioeconomic status determined by the demographic and health survey wealth index yielded a mean score of 18 (SD±1.2), similar to other national rural Indian populations estimated in the NFHS 3 survey.

Anemia prevalence and determinants

Anemia prevalence in children was high (75%). Iron deficiency anemia, defined as anemia (Hb<11g/dL) in the presence of either a ferritin of <15ng/dl or a ferritin of <30ng/dl when the CRP was >5mg/L, accounted for the majority of cases (62%). Children with anemia were more likely to have iron deficiency (OR 6.1; p <0.001) and a mother herself having anemia (OR 1.9; p <0.01) compared to children without anemia

Multiple regression analysis performed using children's hemoglobin as a continuous variable identified hemoglobin to be primarily associated with serum ferritin (an indicator of body iron stores) but also positively associated with maternal hemoglobin level, folate intake, the child's age, family wealth and food security. Children's hemoglobin was inversely associated with male gender, CRP levels, and the presence of beta thalassemia trait.

KEY FINDINGS (STUDY I)

- The prevalence of anemia was high among Indian children (75%) and the majority of anemia was due to iron deficiency (62%).

4.2 STUDY II: COVERAGE OF CHILDREN BY THE NATIONAL ANEMIA CONTROL PROGRAM

Study II was conducted contemporaneously with Study I and had the same source population. Eventually 403 children and 376 mothers were included in the analysis.

Coverage of children with IFA by national program

Less than half of the mothers (42%) reported receipt of IFA for their child in the preceding 12 months of the study and only a minority of those (30%) reported that the IFA they provided their child was obtained from the national anemia control program. Most mothers (70%) reported purchasing iron directly from a private pharmacy through a prescription obtained from a private physician. Primary health care service coverage i.e., antenatal and postnatal visits; receipt of vaccinations and immunization; Vitamin A supplements; and visits to the primary health center and *anganwadi* day care center was above 90%.

Factors associated with IFA coverage for children

Factors associated with greater odds of a child having received IFA included being male, belonging to a higher socioeconomic background, having a mother tested for anemia during pregnancy, and having a mother receiving IFA during pregnancy. Factors were associated with lower odds of a child receiving IFA tablets were: the mother's religion being identified as Muslim, and the child having received good primary care (being fully vaccinated, previously visiting the *anganwadi* day care center or having a mother that required more antenatal health worker visits).

KEY FINDINGS (STUDY II)

- The coverage of beneficiaries (children) with IFA was low with less than half (42%) of mother admitting to giving IFA to their child in the previous 12 months.
- Among those children receiving IFA, approximately one third (30%) were covered with IFA provided by the government national anemia control program. The rest (70%) received IFA purchased from private pharmaceutical stores.

4.3 STUDY III: LAY HEALTH WORKER PERCEPTIONS OF THE ANEMIA INTERVENTION

In this qualitative study, 10 out of a possible 28 lay health workers participating in the intervention were initially selected purposively to conduct focus group discussions and non-participant observations immediately after training for the intervention and during intervention delivery. Nine of the ten LHWs agreed to participate. Subsequently, one of the nine LHWs was unable to continue participating in the remaining focus group discussions resulting in the inclusion of two additional LHWs (one well performing and one less well performing). Thus, eleven lay health workers eventually participated.

Overall feasibility of the intervention

Analysis of the lay health worker focus group discussions using the framework method identified the following themes (Table 4): i) initial acceptance of the intervention changing over time; ii) ability to innovate and adapt the implementation protocol; iii) precarious relationships with mothers in participating communities; and iv) working conditions challenging intervention delivery.

Non-participant observations and field notes supported themes identified in the focus group discussions and provided explanations as to why supplementary educational materials were not used by the lay health worker during implementation. Some lay health workers explained this behaviour with the feeling that they had a good grasp of the materials and did not require prompts during intervention delivery.

Overall, lay health workers found the intervention feasible to deliver during routine activities, and appeared genuinely pleased to participate in a trial to improve children's health. Modifiable barriers to the successful implementation of this intervention were seen at two levels. At a broader contextual level, hindering factors included being overburdened, inadequately reimbursed, and receiving insufficient employer support. At the health system level, lack of streamlining of duties, inability to diagnose anemia in the village and temporary shortfalls in the availability of iron supplements were barriers.

Table 4. Summary of themes from focus group discussions with lay health workers

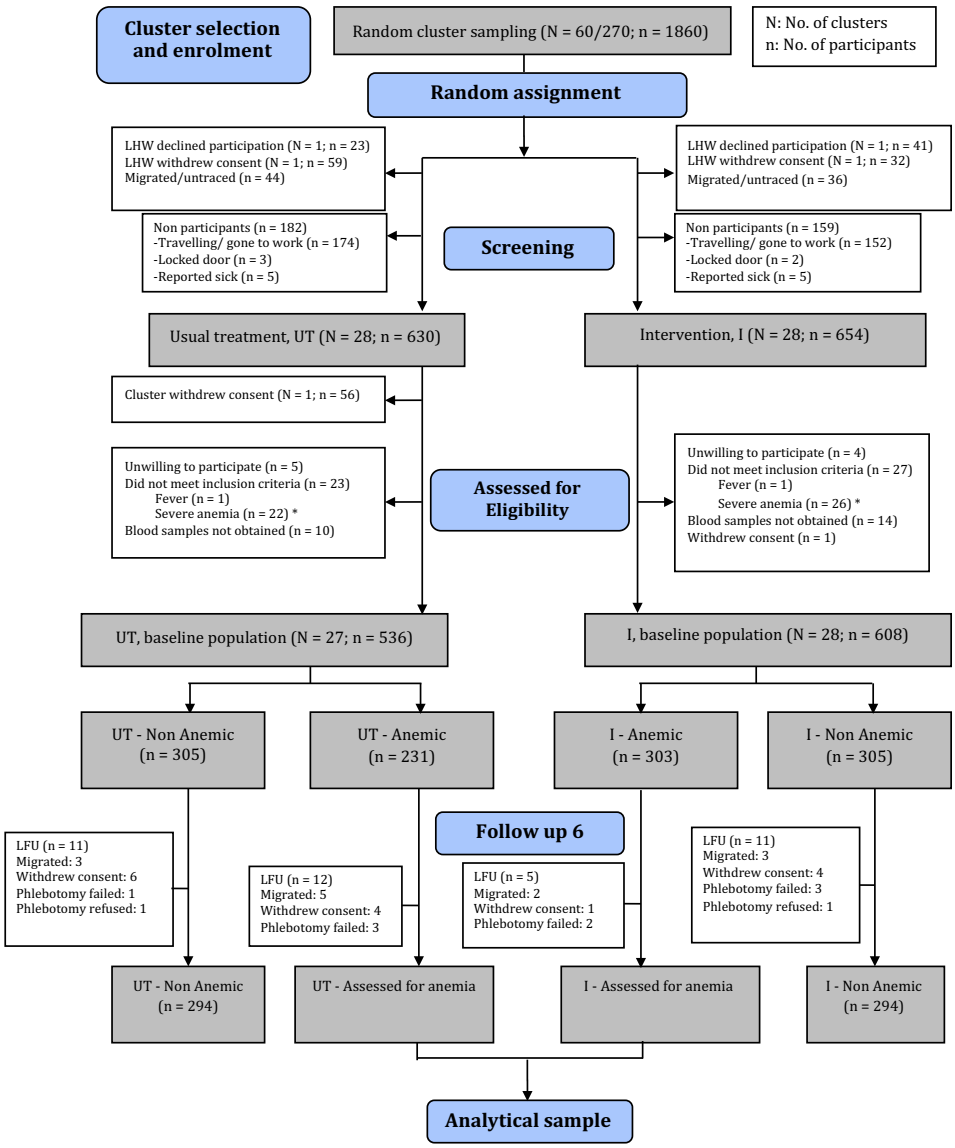
Theme #	
1.	**Lay health workers initial acceptance of the intervention changing over time** • Intervention found feasible to deliver during routine activities • Pleasure in trial participation, optimism, need to continue after trial completion • Waning of enthusiasm while performing activities • Forms burdensome, work not feasible long term, lack of health system support
2.	**Lay health workers innovating and adapting the implementation protocol** • Incorporating intervention activities in daily schedule • Delivering intervention at day care center • Inconsistent use of supplementary educational material
3.	**Lay health workers having a precarious relationships with mothers in participating communities** • Multiple roles complicating the relationship • Status in the community positively influencing the relationship
4.	**Lay health workers working conditions challenging intervention delivery** • Wide ranging services and high burden of work • Salary concerns • Job security concerns • Inadequate employer support and recognition

KEY FINDINGS (STUDY III)

- Results from qualitative study showed that the intervention was acceptable to lay health workers who found it easy to incorporate in their usual activities.
- Lay health worker workload, burdensome working conditions, and low job satisfaction were several important barriers to optimal implementation.

4.4 STUDY IV: INTERVENTIONS EFFECTS ON ANEMIA CURE RATE

In the recruited population, 534 children (43%; n=231 in the usual treatment group and 50%; n=303 in the intervention group) were anemic, constituting the comparison groups for the primary outcome of the intervention (Figure 11). At the end of six-month follow-up, 517 of these children were again assessed (usual treatment=219 and intervention=298).



LFU, loss to follow up

Figure 11. Flow diagram of recruitment, follow up and analysis

Characteristics of participants at baseline

No significant between-group differences in mean age, sex, maternal age, parity, breast-feeding patterns, 24-hour dietary iron intake and standard of living were apparent in the baseline population. However, modest between-group differences at baseline were detected in mean hemoglobin, mother/caregiver's education level and child's birth weight. The high overall prevalence of indicators of acute and chronic malnutrition suggested overall poor childhood nutritional status. Dietary iron intake was less than 50% of the recommended daily iron allowance and probably contributed to the low total body iron stores. Thus, non-anemic children had a high prevalence of nutritional iron deficiency (Hb>11g/dL and serum ferritin of <15ng/ml) and iron deficiency anemia (Hb<11g/dL combined with ferritin <15ng/ml) was detected in over 80% of the anemic children.

Anemia cure rate, net hemoglobin change and IFA adherence

In an intention-to-treat (ITT) analysis, anemia cure rate at the end of 6-month treatment follow-up was significantly higher in the intervention group compared with the usual treatment group (55.7%, 95% CI 50-61.3 vs. 41.1%, 95% CI 34.5-47.6) resulting in a 14.5% difference that was larger than the preplanned minimally important clinical difference of 12%. After taking clustering into account, the risk ratio of anemia cure for intervention vs. control was 1.33 (1.04-1.69). The analysis of Hb change between baseline and follow up among anemic children revealed a mean increase of 1.08, SD=0.10 g/dL in the intervention group and of 0.83, SD=0.11 g/dL in the usual treatment group, i.e. a between-group mean difference of 0.26 g/dL (95% CI 0.07-0.44; p=0.006). In a linear mixed effects model analysis adjusted for clustering, the mean hemoglobin difference was 0.24 g/dL. During study month six, anemic children in the intervention group consumed significantly more IFA tablets than anemic children in the usual treatment group (proportion of children with >75% adherence to IFA tablets, 61.7% vs. 48.4%).

KEY FINDINGS (STUDY IV)

- Anemic children exposed to the intervention were 1.33 times more likely to have their anemia cured and also had a higher mean hemoglobin difference from baseline to the 6 month follow up point.
- Anemic children exposed to the intervention also consumed more IFA tablets, strengthening the conclusion that anemia cure was related to better treatment adherence.

5 DISCUSSION

The studies included in this thesis demonstrated both high prevalence of childhood iron deficiency anemia and inadequate coverage of children by the national anemia control program in this district of Karnataka, South India. Based on this information a novel intervention was designed, as education and counseling specifically targeting anemic children's caregivers, thereby strengthening community-based anemia control. We evaluated the outcome and the potential population impact of this intervention using both qualitative and quantitative studies. In a pragmatic cluster randomized trial we estimated the effectiveness of this intervention when combined with usual anemia treatment, while the perspectives of lay health workers delivering the counseling were analyzed in a qualitative study using focus group interviews. This approach allowed the identification of individual and health system barriers to effective implementation.

Children exposed to the intervention were more likely to have their anemia cured compared with children exposed to usual treatment. Moreover, children exposed to the intervention achieved a higher net hemoglobin increase (equivalent to a quarter unit blood transfusion) compared to children exposed to usual treatment. These differences were consistent with greater adherence to medicinal iron in anemic children exposed to the intervention compared with anemic children exposed to usual treatment thus strengthening the plausibility of a causal effect. The advantages of the intervention were seemingly achieved through reasonable costs, as seven mothers/caregivers needed to be educated/counseled in order to cure one anemic child (NNT=7). The results can be used by state and national policy makers to make public health decisions regarding childhood anemia control based upon scientific evidence.

5.1 NEW ESTIMATES OF THE PREVALENCE AND DETERMINANTS OF CHILDHOOD ANEMIA IN RURAL AREAS

Compared with previous studies in this region, we used more accurate methods to estimate plasma hemoglobin (automated hemocytometry using the coulter principle) thus providing credible childhood anemia prevalence estimates in this province. The study also revealed a low prevalence of folate, B12, Vitamin A, worm infestation, thalassemia, and malaria) in healthy rural Indian children contrary to a small study in urban children[17]. Two recent studies

in children under age five from rural north and south India confirm this high iron deficiency anemia prevalence[19,21]. Thalassemia, sickle cell anemia and malaria infections are rare in this province[20] suggesting that population wide iron supplementation programs might be expanded without much risk for toxicity from IFA[132] or iron overload.

5.2 IRON AND FOLIC ACID COVERAGE OF CHILDREN BY THE NATIONAL ANEMIA CONTROL PROGRAM

In population-wide anemia control efforts, it is of paramount importance to assess the extent of the program's coverage regarding the intended target population. Despite this well-acknowledged need, prior studies did not assess whether children's caregivers had previously *ever* received iron supplements for their children. Instead, they asked whether mothers/caregivers were actively receiving IFA. Due to this methodological difference, coverage of beneficiaries from our study (41%) and data from a national survey (3%) are not directly comparable[28,133]. More recent data from a demographic survey in the north Indian state of Bihar yielded coverage estimates similar to ours (46%)[111], providing confirmation that the national iron supplementation program coverage remains suboptimal. Most mothers (70%) paid out of pocket for IFA prescribed by a health provider, possibly due to combination of lack of awareness and/or insufficiency of IFA due to an overburdened health system[75,134], emphasizing the importance of publicizing government led anemia control efforts in rural communities[135].

Our seemingly paradoxical observation that an *anganwadi* day care center visit by mothers/caregivers was associated with significantly lower IFA receipt is not easily explained[133]. A possible explanation for this discrepancy could be that the study population consisted only of 12-23 month old children that unlike 36-59 month old children are not targets of the ICDS program[136].

5.3 THE NOVEL APPROACH CONVEYED BY THE COMMUNITY-BASED INTERVENTION

The intervention evaluated in the frame of this research project was developed using the combined strengths of several disciplines including pediatrics, community health, nutrition, social science, hematology, biochemistry, epidemiology and biostatistics. Evaluating interventions in logistically challenging health systems is facilitated by mixed method approaches[90,137,138] with qualitative studies often providing explanations about implementation processes, mechanisms, and sometimes explaining trial results[126]. Moreover, targeting the intervention to mothers/caregivers of anemic children and facilitating its uptake by the *anganwadi* lay health worker overcame any potential encumbrances that may have limited the positive behavioral effects of this community intervention[90,139,140]. Specific contextual challenges discussed further below included: i) recruitment of participants, ii) procuring uninterrupted government issued iron supplements and iii) human resource challenges that challenged smooth intervention implementation.

i) Recruitment and participation: Although specific efforts were made to maximize participation, due to unavoidable reasons (travel away from the village) some mothers/caregivers were non-contactable. Among those that mothers/caregivers were contacted and screened, refusal rates were very low.

ii) IFA supply and procurement: Consistent with published data[134], our field experiences revealed interruptions to the state government procured IFA supply. When these occurred, the research team worked closely with state government officials to source IFA and avoided major implementation delays.

iii) Human resource challenges: A three-week strike by lay health workers mid-way through the study delayed trial implementation. Qualitative studies provided important insights into factors motivating community health worker performance and permitted a deeper understanding of the lay health worker condition[141-144]. Therefore, additional qualitative research of lay health worker led community-based interventions is required[145].

5.4 COMMUNITY-BASED INTERVENTIONS FOR ANEMIA

Large-scale community-based interventions with investment in community health workers have yielded impressive gains in maternal and childhood mortality in Bangladesh[29,97].

Moreover, the opportunity to deliver health-services with maximal reach is optimized by informal and contractual partnerships that capitalize on the ability of non-governmental organizations to generate community trust, and reach the most deprived populations to address service gaps[97]. Our experience in India supports this literature, reinforcing the notion that rigorous scientific experiments in resource-limited setting are feasible and yield important contextual information.

Community-based nutrition interventions, iron supplementation uptake, and adherence to iron have previously been shown to be enhanced by i) education and counseling, ii) provision of free medicinal iron, iii) directly observed therapy, iv) education seeking to promote behavior change, v) parental involvement, and vi) use of community facilitators[66-70,80,96,146-151]. Community-based education as a childhood anemia prevention strategy has been evaluated using less rigorous methods than experimental studies[80,148,149]. In addition, these studies did not include anemic children and did not specifically assess anemia cure rate as the primary endpoint. In the current trial, we evaluated for the very first time, the combined effects of lay health worker delivered mother/caregiver education combined with medicinal iron on children's anemia cure rate. We found that this intervention enhanced the effectiveness of the medicinal iron treatment, probably because of improved adherence. The simple and scalable nature of this intervention combined with its feasibility and acceptance by lay health workers imply that wider implementation could improve childhood anemia control.

The trial provides scientific evidence for the tangible benefits of mother/caregiver education and counseling in improving the effectiveness of prescribed iron for the treatment of anemia in children. Moreover, education and general awareness of anemia in the community matter to bringing about behavior change[152]. However, to further optimize such community-based anemia interventions, sociocultural and behavioral factors must be also considered[153]. On the one hand, anemia must be seen as an important health problem by people in the community. On the other hand, lay health workers must feel that the intervention they deliver is in line with their training and contributes positively to their performance as judged by their superiors, by the clients and by the whole community[112,141,152]. Several models of community-based interventions exist depending on the setting of the intervention, its target for health promotion, and its involvement of the community as an agent or resource[154]. Harnessing the community as an agent to strengthen its own health and building its capacity to address

health-related issues would better prepare mothers/caregivers to receive anemia treatment measures and optimize intervention success.

5.5 METHODOLOGICAL CONSIDERATIONS

5.5.1 Study limitations

Cross sectional study design

The studies evaluating anemia prevalence and receipt of iron supplements were cross sectional and therefore precluded conclusions about the direction of associations. The prevalence study also incompletely phenotyped anemia in 10% of the children with biochemical evidence of inflammation due to the inability to test for sTfR[21] or serum hepcidin[4].

Qualitative study

Qualitative studies conducted alongside randomized controlled trials may generate responses atypical of individuals that are unlikely to participate. Additionally, the number of focus group discussions in this study was small limiting transferability. Other important considerations in this setting are the hierarchical structure of health care in India and subtle power equations that may have unduly influenced lay health workers responses. Finally, the study was limited by the absence of focus group discussions with mothers/caregivers that may have provided a holistic perspective of the intervention.

Non-participation

Although considered a gold standard for evaluation of effectiveness because of their inherent control for known and unknown sources of confounding, randomized experiments are prone to selection bias with post-randomization events representing the major threats to validity[155,156]. In cluster randomized experiments this can happen at both the cluster and the individual levels.

Cluster level: After randomization, four lay health workers (2 from each group) elected not to participate in the trial. Additionally, while screening the baseline population, mothers/caregivers in one village withdrew consent *en masse*. However, no clusters were lost to follow up after enrolment of the baseline population. It may be hypothesized that these exclusions occurred amongst less motivated lay health workers/mothers with validity consequences and possible implications during wider implementation of the intervention.

Individual level: Despite efforts to maximize participation, some children and their mothers/caregivers could not participate because they were traveling raising some concerns regarding validity. Thus, it was reassuring to learn that the baseline characteristics available from these missing, not contactable and non-consenting participants were similar to those of participants (Appendix 5). Unfortunately, access to blood samples and consequently hemoglobin values leaves the anemia status of these children unknown.

Potential for contamination

Lay health worker training was conducted at a location distinct from the administrative headquarters to minimize the risk of contamination. Moreover, the geographic distance between villages precluded travel between intervention and control villages further limiting contamination. Even when lay health workers in the control group became aware of the intervention, they neither received training to deliver the intervention nor had access to training materials, factors severely limiting their ability to successfully deliver the intervention in control villages. Thus, misclassification of exposure due to contamination would be quite unlikely, and would in any case rather attenuate the estimate of effect, i.e. the anemia cure rate ratio and difference.

Effects of attrition

Individuals: Individual attrition among anemic children was extremely low (n=17; 3%), relatively balanced among the treatment groups and occurred for a variety of known reasons. In the control group (n=12) loss to follow up was due to migration (n=5), withdrawal of consent (n=4), failure to obtain blood during phlebotomy (n=3). In the intervention group (n=5) loss to follow up was lower occurring for similar reasons: migration (n=2), withdrawal

of consent (n=1) and failure to obtain blood during phlebotomy (n=2). Thus, efficient follow up of clusters and individuals in the study minimized attrition.

Sample size and power considerations

In cluster randomized trials, the total number of clusters affect power more than the total number of individuals within a cluster[157]. Post-randomization cluster attrition was very small and occurred prior to enrolment of the baseline population. Moreover, the eventual number of participating clusters (intervention=28 and control=27) was greater than the a priori minimum required per treatment group (cluster number=25/arm). Cluster loss therefore minimally impacted study power.

More importantly, the trial fell short of individual anemic subject recruitment by 50%, raising concerns of a threat to internal validity from a type II error. However, any reduction in power was counterbalanced by the larger than anticipated effect size (15%), the lower than expected standard deviation of mean hemoglobin values (0.68 vs. 1.2) and the lower than anticipated number of subjects lost to follow up[158].

The intraclass cluster correlation coefficient (ICC) results from the correlation between responses of individuals in the same cluster, providing an estimate of the proportion of the total variance explained by between clusters variance. Clustering accounted for 18% of the variability in anemia cure rate at the village level (ICC=0.18). However, the effect of clustering on net change in hemoglobin between baseline and follow up among anemic children in both treatment groups was less pronounced accounting for less than 9% of the variability in hemoglobin change (ICC=0.086).

High level of usual care

The control group received usual treatment at a level higher than usual. This was due to factors associated with trial participation such as training of the lay health workers, repeated blood testing of participants, and sharing of hemoglobin results i.e., trial activities themselves that may have prompted practice changes among lay health workers. Of note, anemia cure

rates of 41% in the usual treatment arm were similar to those observed in a previously published individual randomized controlled trial conducted in a contextually similar setting[159]. It is therefore possible that in a non-experimental setting with lower lay health worker and mother/caregiver awareness, the interventions' effect size would be larger.

5.5.2 Study strengths

Internal validity

The validity or trustworthiness of the qualitative study was enhanced by ensuring two independent data analysts as well as the use of data triangulation.

The intervention trial was conducted with methodological rigor and sought to ensure a high degree of internal validity by random selection of villages, random allocation to the intervention and blinded assessments of outcome. Over 80% of the "anemic cases" had iron deficiency anemia using rigorous criteria for case definition. Objective and reliable outcome measures such as hemoglobin, serum ferritin, pill count adherence and dietary iron intake measures also contributed towards maintaining internal validity. The definition of anemia cure rate (return of Hb to its normal value at or above 11g/dL) ensured clinical relevance to practitioners. Finally, the baseline characteristics between participants and non-participants were similar, providing reassurance of the success of randomization. In a sensitivity analysis, considering all children lost to follow-up as not having changed their anemic status (worst case scenario), the corresponding proportions were 54.8 and 39% in the intervention and usual treatment groups, respectively. Additional sensitivity analyses demonstrated that minor baseline imbalances in hemoglobin and maternal education that were most likely due to chance did not exert any confounding effect on the estimates.

External validity

Based on the pragmatic design and the setting in which this intervention was conducted, the cluster randomized trial results may be widely generalizable to anemic individuals (both adults and children) living in similar agrarian parts of India and possibly to other similar agrarian regions of the world.

5.6 ETHICAL CONSIDERATIONS

The studies were performed according to Good Clinical Practice Guidelines and the principles of Declaration of Helsinki and appropriate ethical approvals were obtained from the institutional ethical review board prior to study initiation. In addition the trial was registered with ISCRTN. An independent Data and Safety Monitoring Board (DSMB), including a statistician, pediatrician and an internist with clinical trials expertise, reviewed the data and performed a pre-specified blinded interim analysis mid-way thought the trial.

Written Informed Consent and Confidentiality

Participants in all the studies in this thesis provided written informed consent and confidentiality was maintained throughout the study by the use of a unique participant identification number on questionnaires, case report forms, laboratory results, stored samples, or in the database. Similar efforts to maintain the confidentiality of lay health workers participating in the focus group discussions were taken.

Cluster randomization

Cluster randomization at the level of the village minimized ethical concerns about the decision to allocate individual participants from the same village to different regimens. This strategy offered greater administrative flexibility during field implementation and provided lay health workers with greater parental credibility during study recruitment.

Involvement of the community and its health infrastructure

The community was actively involved in the design and implementation of the intervention with consultation of elders and use of community health workers from the local village for intervention delivery. The existing health infrastructure was utilized for referral and medical management of ineligible children with severe anemia. Active involvement of local government officials and the use of locally sourced IFA provide contextually relevant information to stakeholders and policy makers.

Promoting equity

As a direct benefit of this intervention, improving children's health and nutrition promoted equity in two ways. First, the poorest children, the ones benefiting most from health and nutrition programs, harbor the greatest burden of disease. Second, amongst those susceptible to poor health and nutrition, treating disease confers the greatest benefit on the most vulnerable children: on the poorest and on those suffering from other micronutrient deficiency related disease.

Cost effectiveness

Although the interventions' cost-effectiveness has not been formally assessed, nutrition education interventions are considerably low cost[99], making this a key priority for the Indian government. In conditions such as iron deficiency anemia that can be treated with a few pills, such as with iron and deworming, costs are typically lower than $5 per child per year.

Sustainability

The study team in collaboration with the NGO partner disseminated results of anemia prevalence rates and obtained feedback from lay health workers participating in the intervention. Several Karnataka state level officers from the district attended this meeting. Future dissemination workshops with stakeholders, academicians, researchers, public health nutritionists, social scientists, pediatricians, state and national government actors and policy makers are warranted.

WHAT DO THE STUDIES IN THIS THESIS ADD TO THE LITERATURE?

i) The prevalence of iron deficiency anemia was documented for the first time using valid biomarkers of iron status in a large sample of community dwelling rural toddlers from south India. Furthermore, the reach of anemia control activities to young children was clearly defined.

ii) Design and implementation of community-based education interventions demonstrated high feasibility. This points toward a great advantage of local practitioners delivering community based interventions, both in terms of performance and in terms of recognition of their roles

iii) Community-based experimental studies can be conducted with high methodologic standards even in a logistically challenging environment.

6 CONCLUSIONS

- Childhood iron deficiency anemia was highly prevalent in this district of Karnataka in rural South India.

- Coverage of children with iron supplements from the national anemia control program was suboptimal. Rather than obtain medicinal iron free of cost from the national program, over half the mothers in this study paid out of pocket to purchase medicinal iron from a private pharmacy.

- The development of a community-based intervention was facilitated by interdisciplinary collaboration, community engagement, involvement of field research agencies, and local government stakeholders.

- A pragmatic experiment provided scientific evidence that mother/caregiver education/counselling enhances the effects of nutritional programs based on iron supplements alone and adds to population level anemia control activities.

- Qualitative studies conducted alongside randomized trials in rural communities identified barriers and facilitators to trial implementation and provided insights on how to optimize intervention uptake.

- Performing rigorous scientific experiments in rural communities is feasible and provides an important evidence base to guide policy makers.

7 POLICY IMPLICATIONS

7.1 RESEARCH PRACTICE AND POLICY IMPLICATIONS

Childhood iron deficiency anemia is a major concern in this rural district and other similar rural agrarian parts of India. Overall, these studies suggest that childhood iron deficiency anemia should be prioritized in the Indian context. The National Iron Plus Initiative has made important modifications to anemia control policy in India yet several important issues remain unaddressed. Specifically, clear government issued directives for implementation and routine monitoring/evaluation procedures are required. Moreover, the guidelines must indicate how anemia control programs should screen, detect and treat anemic children.

The studies in this thesis clearly demonstrate the effectiveness of a public health intervention when used to specifically target anemic children. The pragmatic design of the study ensures that the resultant information is of direct relevance to support Indian policy makers when making choices regarding population anemia control in India.

Implementing this intervention in other geographic areas of high IDA prevalence may reduce the global burden of childhood anemia prevalence. However, additional studies are required to determine whether these findings are replicable in India and perhaps other low middle-income countries. Specifically, these include optimal screening to detect anemic children by lay health workers and methods to enhance training uptake by lay health workers from different regions of the country.

From a broader perspective, several factors apart from nutritional iron deficiency contribute to anemia prevalence. Characterizing the contribution of infectious diseases, functional iron deficiency and genetic factors to the overall burden of anemia would inform the design of future community-based interventions.

8 ACKNOWLEDGEMENTS

Many people have contributed towards making this work possible and I am deeply grateful to all of them.

I have had the most enriching experience in Stockholm working with Rosaria Galanti, my main supervisor and mentor. Rosaria, you are amazing! You helped shaping these studies into what I consider art form. You always asked the right question and facilitated my search for academic excellence. Thank you!

Merrick Zwarenstein, my co-supervisor and Canadian collaborator, you are a great mentor who got my studies started on a high note. Thank you for always making yourself available for quick input.

Salla Atkins, my co-supervisor and Finnish collaborator gave me a qualitative "immersion" experience. Salla, you opened my eyes to the value of qualitative studies and I am going to try and keep those eyes open.

Birger Forsberg, thank you for being a fantastic mentor. All the guidance, both solicited and unsolicited is much appreciated. More important were all those lunches, museum visits and art explorations!

Maya Mascarenhas, my community medicine buddy from St. Johns and fellow music lover. Thank you for your excellent collaborative spirit, your networking with the state government and for all those great times we had together in the field.

I am deeply grateful to Fr. Lawrence D'souza, Director of St. Johns National Academy of Health Sciences for being supportive of this work and enabling my search for further education and scholarship.

My earnest thanks to senior colleagues, Drs. Prem Pais and George D'souza, both deans at St. Johns and my mentors. You helped facilitate my work in many ways administrative and scientific.

I could not have survived without an excellent research team: Sant-Rayn Pasricha, Paul Jebaraj, Vidya Chellaswamy, and Jimmy Anthony were excellent field research coordinators. Abha Rao and Giridhar Kanuri my first two post-doctoral scholars did me proud. Karthika Arumugam my database manager, you are a great asset. All of the field team members and laboratory support staff contributed immensely, thank you.

My deepest appreciation for Lucie Laflamme, previously Head of the Public Health Sciences Department. Lucie, I valued the excellent advice that you provided. I am also grateful to Marie Hasselberg, currently Head of the Public Health Sciences Department. Thank you both for your unwavering support.

To the research group in Epidemiology and Public Health Intervention Research, a heart felt thank you. You adopted me with much grace and made me feel like I belonged in that fine research environment. Many thanks to Yvonne Forsell and Jette Möller for interesting discussions and support.

I am really grateful to Gunn Britt and Malin Pettersson who really have done so much for me. I appreciate your efforts and kindness. Thanks also to the other administrative staff at PHS, Marita, Maria, Andreas, Jacob, Bo, Maud and everyone else that eased my life at KI.

To my fellow researchers, Ashish, Senia, Sujith, Meena, Ulrika, Helle, Erica, Myra, Simon, Kristi, Kamila, Charisse, Bjorg and many many others. Thank you for the many shared experiences.

My fondest regards for Annika Johansson, whose warmth and generosity to our family has been incredible. Karrtorp is really a second home for us.

I acknowledge the State and National Anemia Control Program organizations for their support and facilitation of this research. I also acknowledge support from the Wellcome Trust/Department of Biotechnology India Alliance for their financial support of the Wellcome Trust/DBT Hematology Laboratory and the Karnataka Anemia Project 2; and the Erasmus Mundus scholarship for partial support of my travel to Sweden.

To my family, my closest friends:

My wife Anita, you convinced me of the benefits of doctoral education. You are my greatest friend and inspiration!

My sons, Roshan and Rishi; you are both terrific and amazing children who have traveled the globe on our crazy adventures through the United States, India, Sweden and then back again to the United States. Thank you for growing into human beings who will strive to make a difference.

My sister Kamini, and my brother Ajit, thank you for repeatedly testing the hypothesis that the youngest sibling is resilient; and for your inspirational late-life career changes.

My mother Rita, who raised me largely as a single parent after the early demise of my father. Thank you for believing that I would be a successful private medical practitioner in small town Chennai (like Big Uncle). Maybe I should consider that one day?

My aunt Celine, who always asked about where this thesis was going and hoped to see light at the end of the tunnel. The train is arriving!

My sister and brother in-law, my hyperexcitable nephews, cousins Arati, Victor and their kids, and aunt Louise who all visited Sweden and shared our experiences, thank you. Grona Lund at night is awesome.

9 REFERENCES

1. Mackay HM. Nutritional Anaemia in Infancy: Some Observations on a Common Deficiency Disease. *Proc R Soc Med* 1929; **22**(4): 385-91.
2. Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol* 2006; **13**(3): 158-65.
3. Lozoff B. Iron deficiency and child development. *Food Nutr Bull* 2007; **28**(4 Suppl): S560-71.
4. Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015; **372**(19): 1832-43.
5. Nemeth E, Preza GC, Jung CL, Kaplan J, Waring AJ, Ganz T. The N-terminus of hepcidin is essential for its interaction with ferroportin: structure-function study. *Blood* 2006; **107**(1): 328-33.
6. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 2004; **113**(9): 1271-6.
7. Kautz L, Jung G, Du X, et al. Erythroferrone contributes to hepcidin suppression and iron overload in a mouse model of beta-thalassemia. *Blood* 2015; **126**(17): 2031-7.
8. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. *Science* 2012; **338**(6108): 768-72.
9. Stoltzfus R. Defining iron-deficiency anemia in public health terms: a time for reflection. *J Nutr* 2001; **131**(2S-2): 565S-7S.
10. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014; **123**(5): 615-24.
11. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. *Lancet* 2012; **378**(9809): 2123-35.
12. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst Rev* 2011; (12): CD009085.
13. Sinha N, Deshmukh PR, Garg BS. Epidemiological correlates of nutritional anemia among children (6-35 months) in rural Wardha, Central India. *Indian J Med Sci* 2008; **62**(2): 45-54.
14. Shet A, Arumugam K, Rajagopalan N, et al. The prevalence and etiology of anemia among HIV-infected children in India. *Eur J Pediatr* 2011.
15. Semba RD, de Pee S, Sun K, Campbell AA, Bloem MW, Raju VK. Low intake of vitamin A-rich foods among children, aged 12-35 months, in India: association with malnutrition, anemia, and missed child survival interventions. *Nutrition* 2010; **26**(10): 958-62.
16. Kumar T, Taneja S, Yajnik CS, Bhandari N, Strand TA. Prevalence and predictors of anemia in a population of North Indian children. *Nutrition* 2014; **30**(5): 531-7.
17. Gomber S, Kumar S, Rusia U, Gupta P, Agarwal KN, Sharma S. Prevalence & etiology of nutritional anaemias in early childhood in an urban slum. *Indian J Med Res* 1998; **107**: 269-73.
18. Taneja S, Bhandari N, Strand TA, et al. Cobalamin and folate status in infants and young children in a low-to-middle income community in India. *Am J Clin Nutr* 2007; **86**(5): 1302-9.
19. Bains K, Kaur H, Bajwa N, Kaur G, Kapoor S, Singh A. Iron and Zinc Status of 6-Month to 5-Year-Old Children From Low-Income Rural Families of Punjab, India. *Food Nutr Bull* 2015; **36**(3): 254-63.

20. Pasricha SR, Black J, Muthayya S, et al. Determinants of anemia among young children in rural India. *Pediatrics* 2010; **126**(1): e140-9.
21. Nair KM, Fernandez-Rao S, Nagalla B, et al. Characterisation of anaemia and associated factors among infants and pre-schoolers from rural India. *Public Health Nutr* 2015: 1-11.
22. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1), 2011.
23. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. *Public Health Nutr* 2009; **12**(4): 444-54.
24. de Benoist B ME, Egli I, Cogswell M. http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf. Worldwide prevalence of anaemia 1993–2005. WHO global database on anaemia; 2008.
25. Global Burden of Disease Pediatrics C, Kyu HH, Pinho C, et al. Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013: Findings From the Global Burden of Disease 2013 Study. *JAMA Pediatr* 2016; **170**(3): 267-87.
26. Gretchen A Stevens DSc MMFP, Luz Maria De-Regil DrSc, Christopher J Paciorek PhD, Seth R Flaxman BA, Francesco Branca PhD, Juan Pablo Peña-Rosas MD, Prof Zulfiqar A Bhutta PhD, Prof Majid Ezzati PhD. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995—2011: a systematic analysis of population-representative data. *Lancet global health* 2013; **Volume 1**(Issue 1): Pages e16 - e25.
27. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; **370**(9586): 511-20.
28. National Family Health Survey (NFHS-3). Mumbai: International Institute for Population Sciences (IIPS) and Macro International 2005-06, 2007.
29. Adams AM, Rabbani A, Ahmed S, et al. Explaining equity gains in child survival in Bangladesh: scale, speed, and selectivity in health and development. *Lancet* 2013; **382**(9909): 2027-37.
30. Lozoff B, Kaciroti N, Walter T. Iron deficiency in infancy: applying a physiologic framework for prediction. *Am J Clin Nutr* 2006; **84**(6): 1412-21.
31. Deshmukh PR, Dongre AR, Sinha N, Garg BS. Acute childhood morbidities in rural Wardha: some epidemiological correlates and health care seeking. *Indian J Med Sci* 2009; **63**(8): 345-54.
32. Dhingra N, Jha P, Sharma VP, et al. Adult and child malaria mortality in India: a nationally representative mortality survey. *Lancet* 2012; **376**(9754): 1768-74.
33. Arezes J, Jung G, Gabayan V, et al. Hepcidin-induced hypoferremia is a critical host defense mechanism against the siderophilic bacterium Vibrio vulnificus. *Cell Host Microbe* 2015; **17**(1): 47-57.
34. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. *Arch Pediatr Adolesc Med* 2006; **160**(11): 1108-13.
35. Carter RC, Jacobson JL, Burden MJ, et al. Iron deficiency anemia and cognitive function in infancy. *Pediatrics* 2010; **126**(2): e427-34.
36. Munot P, De Vile C, Hemingway C, Gunny R, Ganesan V. Severe iron deficiency anaemia and ischaemic stroke in children. *Arch Dis Child* 2011; **96**(3): 276-9.
37. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. *Pediatrics* 2007; **120**(5): 1053-7.

38. Watson-Jones D, Weiss HA, Changalucha JM, et al. Adverse birth outcomes in United Republic of Tanzania--impact and prevention of maternal risk factors. *Bull World Health Organ* 2007; **85**(1): 9-18.
39. Weiss G. Iron and immunity: a double-edged sword. *Eur J Clin Invest* 2002; **32 Suppl 1**: 70-8.
40. Kumar V, Choudhry VP. Iron deficiency and infection. *Indian J Pediatr* 2010; **77**(7): 789-93.
41. Collins HL. Withholding iron as a cellular defence mechanism--friend or foe? *Eur J Immunol* 2008; **38**(7): 1803-6.
42. Gera T, Sachdev HP. Iron supplementation for improving mental development. *Indian Pediatr* 2009; **46**(2): 125-6.
43. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials. *Public Health Nutr* 2005; **8**(2): 117-32.
44. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med* 1991; **325**(10): 687-94.
45. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000; **105**(4): E51.
46. Lozoff B, Corapci F, Burden MJ, et al. Preschool-aged children with iron deficiency anemia show altered affect and behavior. *J Nutr* 2007; **137**(3): 683-9.
47. Lozoff B, Smith JB, Clark KM, Perales CG, Rivera F, Castillo M. Home intervention improves cognitive and social-emotional scores in iron-deficient anemic infants. *Pediatrics* 2010; **126**(4): e884-94.
48. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. *Pediatrics* 2003; **112**(4): 846-54.
49. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks. *Am J Clin Nutr* 2006; **84**(6): 1261-76.
50. Scott SP, Chen-Edinboro LP, Caulfield LE, Murray-Kolb LE. The impact of anemia on child mortality: an updated review. *Nutrients* 2014; **6**(12): 5915-32.
51. Institute for Health Metrics and Evaluation; GBD profile: India 2013. Available from:http://www.healthdata.org/results/country-profiles. Accessed Jan 2016.
52. Bailey RL, West KP, Jr., Black RE. The epidemiology of global micronutrient deficiencies. *Ann Nutr Metab* 2015; **66 Suppl 2**: 22-33.
53. Plessow R, Arora NK, Brunner B, et al. Social Costs of Iron Deficiency Anemia in 6-59-Month-Old Children in India. *PLoS One* 2015; **10**(8): e0136581.
54. Cook JD. Diagnosis and management of iron-deficiency anaemia. *Best Pract Res Clin Haematol* 2005; **18**(2): 319-32.
55. Zlotkin S, Arthur P, Antwi KY, Yeung G. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. *Pediatrics* 2001; **108**(3): 613-6.
56. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol* 2017; **4**(11): e524-e33.
57. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006; **367**(9505): 133-43.
58. World Health Organization. Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent

WHO statement, 2006.
59. Raiten DJ, Namaste S, Brabin B. Considerations for the safe and effective use of iron interventions in areas of malaria burden - executive summary. *Int J Vitam Nutr Res* 2012; **81**(1): 57-71.
60. Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. *Cochrane Database Syst Rev* 2009; (3): CD006589.
61. Okebe JU, Yahav D, Shbita R, Paul M. Oral iron supplements for children in malaria-endemic areas. *Cochrane Database Syst Rev* 2011; (10): CD006589.
62. Alderman H, Linnemayr S. Anemia in low-income countries is unlikely to be addressed by economic development without additional programs. *Food Nutr Bull* 2009; **30**(3): 265-9.
63. Global Nutrition Targets 2025: Anaemia policy brief, 2014.
64. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013; **382**(9890): 427-51.
65. Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA. Control of iron deficiency anemia in low- and middle-income countries. *Blood* 2013; **121**(14): 2607-17.
66. Rivera JA, Sotres-Alvarez D, Habicht JP, Shamah T, Villalpando S. Impact of the Mexican program for education, health, and nutrition (Progresa) on rates of growth and anemia in infants and young children: a randomized effectiveness study. *Jama* 2004; **291**(21): 2563-70.
67. Black MM, Cutts DB, Frank DA, et al. Special Supplemental Nutrition Program for Women, Infants, and Children participation and infants' growth and health: a multisite surveillance study. *Pediatrics* 2004; **114**(1): 169-76.
68. Shankar AV, Asrilla Z, Kadha JK, et al. Programmatic effects of a large-scale multiple-micronutrient supplementation trial in Indonesia: using community facilitators as intermediaries for behavior change. *Food Nutr Bull* 2009; **30**(2 Suppl): S207-14.
69. Fernandez-Rao S, Hurley KM, Nair KM, et al. Integrating nutrition and early child-development interventions among infants and preschoolers in rural India. *Ann N Y Acad Sci* 2014; **1308**: 218-31.
70. Tandon BN. Nutritional interventions through primary health care: impact of the ICDS projects in India. *Bull World Health Organ* 1989; **67**(1): 77-80.
71. Masset E, Haddad L, Cornelius A, Isaza-Castro J. Effectiveness of agricultural interventions that aim to improve nutritional status of children: systematic review. *BMJ* 2012; **344**: d8222.
72. Persson LA, Arifeen S, Ekstrom EC, et al. Effects of prenatal micronutrient and early food supplementation on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat randomized trial. *JAMA* 2012; **307**(19): 2050-9.
73. Deb S. Emplementation of National Iron Plus Initiative for child health: challanges ahead. *Indian J Public Health* 2015; **59**(1): 1-2.
74. Vinodkumar M, Rajagopalan S. Efficacy of fortification of school meals with ferrous glycine phosphate and riboflavin against anemia and angular stomatitis in schoolchildren. *Food Nutr Bull* 2009; **30**(3): 260-4.
75. Sachdev HP, Gera T. Preventing childhood anemia in India: iron supplementation and beyond. *Eur J Clin Nutr* 2013; **67**(5): 475-80.
76. Kapil U. Integrated Child Development Services (ICDS) scheme: a program for holistic development of children in India. *Indian J Pediatr* 2002; **69**(7): 597-601.
77. Vijayaraghavan K. Control of micronutrient deficiencies in India: obstacles and strategies. *Nutr Rev* 2002; **60**(5 Pt 2): S73-6.

78. Gera T, Sachdev HP, Nestel P, Sachdev SS. Effect of iron supplementation on haemoglobin response in children: systematic review of randomised controlled trials. *J Pediatr Gastroenterol Nutr* 2007; **44**(4): 468-86.
79. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on physical growth in children: systematic review of randomised controlled trials. *Public Health Nutr* 2006; **9**(7): 904-20.
80. Dongre AR, Deshmukh PR, Garg BS. Community-led initiative for control of anemia among children 6 to 35 months of age and unmarried adolescent girls in rural Wardha, India. *Food Nutr Bull* 2011; **32**(4): 315-23.
81. Awasthi S, Verma T, Vir S. Effectiveness of biweekly versus daily iron-folic acid administration on anaemia status in preschool children. *J Trop Pediatr* 2005; **51**(2): 67-71.
82. Awasthi S, Peto R, Read S, Richards SM, Pande V, Bundy D. Population deworming every 6 months with albendazole in 1 million pre-school children in North India: DEVTA, a cluster-randomised trial. *Lancet* 2013; **381**(9876): 1478-86.
83. Taylor-Robinson DC, Maayan N, Soares-Weiser K, Donegan S, Garner P. Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin and school performance. *Cochrane Database Syst Rev* 2012; **11**: CD000371.
84. National Iron + Initiative: Ministry of Health and Family Welfare, Government of India, 2013, http://www.pbnrhm.org/docs/iron_plus_guidelines.pdf (accessed March 26, 2015).
85. Colah RB, Mukherjee MB, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. *Indian J Med Res* 2015; **141**(5): 509-15.
86. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**(9963): 117-71.
87. Piel FB. The Present and Future Global Burden of the Inherited Disorders of Hemoglobin. *Hematol Oncol Clin North Am* 2016; **30**(2): 327-41.
88. Kotecha PV. Nutritional anemia in young children with focus on Asia and India. *Indian J Community Med* 2011; **36**(1): 8-16.
89. Lewin SA, Dick J, Pond P, et al. Lay health workers in primary and community health care. *Cochrane Database Syst Rev* 2005; (1): CD004015.
90. Lewin S, Munabi-Babigumira S, Glenton C, et al. Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases. *Cochrane Database Syst Rev* 2012; (3): CD004015.
91. Bhutta ZA, Soofi S, Cousens S, et al. Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. *Lancet* 2012; **377**(9763): 403-12.
92. Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *Lancet* 2013; **381**(9876): 1469-77.
93. Bang AT, Bang RA, Sontakke PG. Management of childhood pneumonia by traditional birth attendants. The SEARCH Team. *Bull World Health Organ* 1994; **72**(6): 897-905.
94. Bhandari N, Bahl R, Mazumdar S, Martines J, Black RE, Bhan MK. Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth: a cluster randomised controlled trial. *Lancet* 2003; **361**(9367): 1418-23.
95. Bhandari N, Mazumder S, Bahl R, Martines J, Black RE, Bhan MK. An educational intervention to promote appropriate complementary feeding practices and physical growth in infants and young children in rural Haryana, India. *J Nutr* 2004; **134**(9): 2342-8.

96. Bharti S, Bharti B, Naseem S, Attri SV. A community-based cluster randomized controlled trial of "directly observed home-based daily iron therapy" in lowering prevalence of anemia in rural women and adolescent girls. *Asia Pac J Public Health* 2015; **27**(2): NP1333-44.
97. El Arifeen S, Christou A, Reichenbach L, et al. Community-based approaches and partnerships: innovations in health-service delivery in Bangladesh. *Lancet* 2013; **382**(9909): 2012-26.
98. Achterberg C, Miller C. Is one theory better than another in nutrition education? A viewpoint: more is better. *J Nutr Educ Behav* 2004; **36**(1): 40-2.
99. Contento IR, Randell JS, Basch CE. Review and analysis of evaluation measures used in nutrition education intervention research. *J Nutr Educ Behav* 2002; **34**(1): 2-25.
100. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353**(5): 487-97.
101. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *Lancet Infect Dis* 2011; **11**(12): 942-51.
102. Nagata JM, Gatti LR, Barg FK. Social determinants of iron supplementation among women of reproductive age: a systematic review of qualitative data. *Matern Child Nutr* 2012; **8**(1): 1-18.
103. Shaheen R, Streatfield PK, Naved RT, Lindholm L, Persson LA. Equity in adherence to and effect of prenatal food and micronutrient supplementation on child mortality: results from the MINIMat randomized trial, Bangladesh. *BMC Public Health* 2014; **14**: 5.
104. Seck BC, Jackson RT. Providing iron/folic acid tablets free of charge improves compliance in pregnant women in Senegal. *Trans R Soc Trop Med Hyg* 2009; **103**(5): 485-92.
105. Lopez-Flores F, Neufeld LM, Sotres-Alvarez D, Garcia-Guerra A, Ramakrishnan U. Compliance to micronutrient supplementation in children 3 to 24 months of age from a semi-rural community in Mexico. *Salud Publica Mex* 2012; **54**(5): 470-8.
106. Kwon HJ, Ramasamy R, Morgan A. "How often? How much? Where from?" knowledge, attitudes, and practices of mothers and health workers to iron supplementation program for children under five in rural Tamil Nadu, south India. *Asia Pac J Public Health* 2014; **26**(4): 378-89.
107. Geltman PL, Hironaka LK, Mehta SD, et al. Iron supplementation of low-income infants: a randomized clinical trial of adherence with ferrous fumarate sprinkles versus ferrous sulfate drops. *J Pediatr* 2009; **154**(5): 738-43.
108. Christensen L, Sguassero Y, Cuesta CB. Anemia and compliance to oral iron supplementation in a sample of children attending the public health network of Rosario, Santa Fe. *Arch Argent Pediatr* 2013; **111**(4): 288-94.
109. Omotayo MO, Dickin KL, Chapleau GM, et al. Cluster-Randomized Non-Inferiority Trial to Compare Supplement Consumption and Adherence to Different Dosing Regimens for Antenatal Calcium and Iron-Folic Acid Supplementation to Prevent Preeclampsia and Anaemia: Rationale and Design of the Micronutrient Initiative Study. *J Public Health Res* 2015; **4**(3): 582.
110. Sununtnasuk C, D'Agostino A, Fiedler JL. Iron+folic acid distribution and consumption through antenatal care: identifying barriers across countries. *Public Health Nutr* 2015: 1-11.
111. Wendt A, Stephenson R, Young M, et al. Individual and facility-level determinants of iron and folic acid receipt and adequate consumption among pregnant women in rural Bihar, India. *PLoS One* 2015; **10**(3): e0120404.

112. Winichagoon P. Prevention and control of anemia: Thailand experiences. *J Nutr* 2002; **132**(4 Suppl): 862S-6S.
113. Chaturvedi S, Ranadive B. Are we really making motherhood safe? A study of provision of iron supplements and emergency obstetric care in rural Maharashtra. *Natl Med J India* 2007; **20**(6): 294-6.
114. Seshadri S, Gopaldas T. Impact of iron supplementation on cognitive functions in preschool and school-aged children: the Indian experience. *Am J Clin Nutr* 1989; **50**(3 Suppl): 675-84; discussion 85-6.
115. Galloway R, Dusch E, Elder L, et al. Women's perceptions of iron deficiency and anemia prevention and control in eight developing countries. *Soc Sci Med* 2002; **55**(4): 529-44.
116. Bilenko N, Yehiel M, Inbar Y, Gazala E. The association between anemia in infants, and maternal knowledge and adherence to iron supplementation in southern Israel. *Isr Med Assoc J* 2007; **9**(7): 521-4.
117. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? *Soc Sci Med* 1994; **39**(3): 381-90.
118. Nwaru BI, Salome G, Abacassamo F, et al. Adherence in a pragmatic randomized controlled trial on prophylactic iron supplementation during pregnancy in Maputo, Mozambique. *Public Health Nutr* 2015; **18**(6): 1127-34.
119. Lassi ZS, Bhutta ZA. Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. *Cochrane Database Syst Rev* 2015; **3**: CD007754.
120. Vazir S, Engle P, Balakrishna N, et al. Cluster-randomized trial on complementary and responsive feeding education to caregivers found improved dietary intake, growth and development among rural Indian toddlers. *Matern Child Nutr* 2013.
121. Fraser WM, Richman MJ, Galinsky MJ, Day SH. Intervention research. New York: Oxford University Press; 2009.
122. Wight D, Wimbush E, Jepson R, Doi L. Six steps in quality intervention development (6SQuID). *J Epidemiol Community Health* 2015.
123. Fraser MWaG, M.J. Steps in Intervention Research: Designing and Developing Social Programs. *Research on Social Work Practice* 2010; **20**(5): 459-66.
124. Bandura A. Health promotion by social cognitive means. *Health Educ Behav* 2004; **31**(2): 143-64.
125. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med* 2016; **375**(5): 454-63.
126. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ* 2009; **339**: b3496.
127. Urbaniak GC, & Plous, S.,. Research Randomizer v4.0. 2013. http://www.randomizer.org/form.htm.
128. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013; **13**: 117.
129. Ritchie J SL. Qualitative data analysis for applied policy research. London: Routledge; 1994.
130. Jack SJ, Ou K, Chea M, et al. Effect of micronutrient sprinkles on reducing anemia: a cluster-randomized effectiveness trial. *Arch Pediatr Adolesc Med* 2012; **166**(9): 842-50.
131. Shet AS, Zwarenstein M, Mascarenhas M, et al. The Karnataka Anemia Project 2--design and evaluation of a community-based parental intervention to improve childhood anemia cure rates: study protocol for a cluster randomized controlled trial. *Trials* 2015; **16**: 599.

132. Pasricha S, Shet A, Sachdev HP, Shet AS. Risks of routine iron and folic acid supplementation for young children. *Indian Pediatr* 2009; **46**(10): 857-66.
133. Pasricha SR, Biggs BA, Prashanth NS, et al. Factors influencing receipt of iron supplementation by young children and their mothers in rural India: local and national cross-sectional studies. *BMC Public Health* 2011; **11**: 617.
134. Vijayaraghavan K, Brahmam GN, Nair KM, Akbar D, Rao NP. Evaluation of national nutritional anemia prophylaxis programme. *Indian J Pediatr* 1990; **57**(2): 183-90.
135. Pandey P, Sehgal AR, Riboud M, Levine D, Goyal M. Informing resource-poor populations and the delivery of entitled health and social services in rural India: a cluster randomized controlled trial. *JAMA* 2007; **298**(16): 1867-75.
136. Lahariya C, Khandekar J. How the findings of national family health survey-3 can act as a trigger for improving the status of anemic mothers and undernourished children in India: a review. *Indian J Med Sci* 2007; **61**(9): 535-44.
137. Glenton C, Lewin S, Scheel IB. Still too little qualitative research to shed light on results from reviews of effectiveness trials: A case study of a Cochrane review on the use of lay health workers. *Implement Sci* 2011; **6**: 53.
138. Glenton C, Colvin CJ, Carlsen B, et al. Barriers and facilitators to the implementation of lay health worker programmes to improve access to maternal and child health: qualitative evidence synthesis. *Cochrane Database Syst Rev* 2013; **10**: CD010414.
139. Bonell C, Fletcher A, Morton M, Lorenc T, Moore L. Realist randomised controlled trials: a new approach to evaluating complex public health interventions. *Soc Sci Med* 2012; **75**(12): 2299-306.
140. Sanson-Fisher RW, Bonevski B, Green LW, D'Este C. Limitations of the randomized controlled trial in evaluating population-based health interventions. *Am J Prev Med* 2007; **33**(2): 155-61.
141. Saprii L, Richards E, Kokho P, Theobald S. Community health workers in rural India: analysing the opportunities and challenges Accredited Social Health Activists (ASHAs) face in realising their multiple roles. *Hum Resour Health* 2015; **13**(1): 95.
142. Fathima FN, Raju M, Varadharajan KS, Krishnamurthy A, Ananthkumar SR, Mony PK. Assessment of 'accredited social health activists'-a national community health volunteer scheme in Karnataka State, India. *J Health Popul Nutr* 2015; **33**(1): 137-45.
143. Singh D, Negin J, Otim M, Orach CG, Cumming R. The effect of payment and incentives on motivation and focus of community health workers: five case studies from low- and middle-income countries. *Hum Resour Health* 2015; **13**: 58.
144. B. M. Prasad VRM, Community health workers: a review of concepts, practice and policy concerns, http://www.crehs.lshtm.ac.uk. Community health workers: a review of concepts, practice and policy concerns. London: LSHTM, March 2008.
145. Balaji M, Chatterjee S, Koschorke M, et al. The development of a lay health worker delivered collaborative community based intervention for people with schizophrenia in India. *BMC Health Serv Res* 2012; **12**: 42.
146. Vir SC, Singh N, Nigam AK, Jain R. Weekly iron and folic acid supplementation with counseling reduces anemia in adolescent girls: a large-scale effectiveness study in Uttar Pradesh, India. *Food Nutr Bull* 2008; **29**(3): 186-94.
147. Shi L, Zhang J. Recent evidence of the effectiveness of educational interventions for improving complementary feeding practices in developing countries. *J Trop Pediatr* 2012; **57**(2): 91-8.
148. Kapur D, Sharma S, Agarwal KN. Effectiveness of nutrition education, iron supplementation or both on iron status in children. *Indian Pediatr* 2003; **40**(12): 1131-44.
149. Haldar D, Chatterjee T, Sarkar AP, Das SK, Mallik S. A study on the role of parental involvement in control of nutritional anemia among children of free primary schools in a rural area of West Bengal. *Indian J Public Health* 2011; **55**(4): 332-5.

150. Palupi L, Schultink W, Achadi E, Gross R. Effective community intervention to improve hemoglobin status in preschoolers receiving once-weekly iron supplementation. *Am J Clin Nutr* 1997; **65**(4): 1057-61.
151. Osei A, Pandey P, Nielsen J, et al. Combining Home Garden, Poultry, and Nutrition Education Program Targeted to Families With Young Children Improved Anemia Among Children and Anemia and Underweight Among Nonpregnant Women in Nepal. *Food Nutr Bull* 2016.
152. Berman P, Kendall C, Bhattacharyya K. The household production of health: integrating social science perspectives on micro-level health determinants. *Soc Sci Med* 1994; **38**(2): 205-15.
153. Fiese BH, Jones BL. Food and family: a socio-ecological perspective for child development. *Adv Child Dev Behav* 2012; **42**: 307-37.
154. McLeroy KR, Norton BL, Kegler MC, Burdine JN, Sumaya CV. Community-based interventions. *Am J Public Health* 2003; **93**(4): 529-33.
155. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005; **365**(9453): 82-93.
156. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol* 2003; **3**: 28.
157. Donner A, Klar N. Design and Analysis of Cluster Randomization Trials in Health Research. London: Arnold; 2000.
158. Zwarenstein M. Peer review of statistics in medical research. Journal reviewers are even more baffled by sample size issues than grant proposal reviewers. *BMJ* 2002; **325**(7362): 491; author reply
159. Bhutta Z, Klemm R, Shahid F, Rizvi A, Rah JH, Christian P. Treatment response to iron and folic acid alone is the same as with multivitamins and/or anthelminthics in severely anemic 6- to 24-month-old children. *J Nutr* 2009; **139**(8): 1568-74.

10 APPENDICES

APPENDIX 1

Guidelines for Control of Iron Deficiency Anaemia

National Iron+ Initiative

Towards infinite potential in an anaemia free India

6

Supplementation through the Life Cycle

An anaemia supplementation programme across the life cycle is proposed in which beneficiaries will receive iron and folic acid supplementation irrespective of their iron/Hb status. The age-specific interventions are based on WHO recommendations, synthesis of global evidence on IFA supplementation and the recommendations of national experts (Table 6.1 and Figure 6.1).

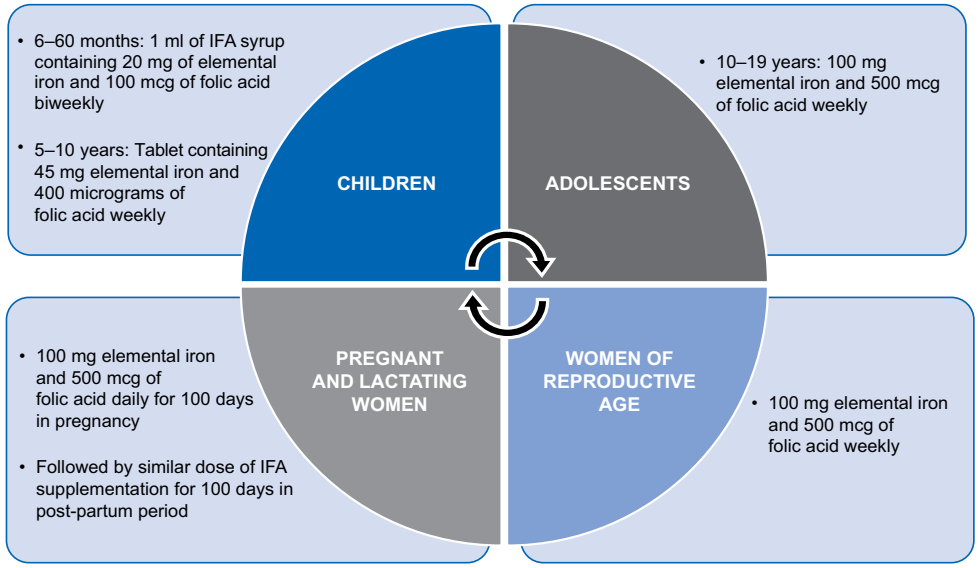
Table 6.1: IFA supplementation programme and service delivery

Age group	Intervention/Dose	Regime	Service delivery
6–60 months	1ml of IFA syrup containing 20 mg of elemental iron and 100 mcg of folic acid	Biweekly throughout the period 6–60 months of age and de-worming for children 12 months and above.	Through ASHA Inclusion in MCP card
5–10 years	Tablets of 45 mg elemental iron and 400 mcg of folic acid	Weekly throughout the period 5–10 years of age and biannual de-worming	In school through teachers and for out-of-school children through Anganwadi centre (AWC) Mobilization by ASHA
10–19 years	100 mg elemental iron and 500 mcg of folic acid	Weekly throughout the period 10–19 years of age and biannual de-worming	In school through teachers and for those out-of-school through AWC Mobilization by ASHA
Pregnant and lactating women	100 mg elemental iron and 500 mcg of folic acid	1 tablet daily for 100 days, starting after the first trimester, at 14–16 weeks of gestation. To be repeated for 100 days post-partum.	ANC/ ANM /ASHA Inclusion in MCP card
Women in reproductive age (WRA) group	100 mg elemental iron and 500 mcg of folic acid	Weekly throughout the reproductive period	Through ASHA during house visit for contraceptive distribution

ASHA to be suitably incentivized for provision IFA supplements to beneficiary

Note: The IFA supplementation programme is a preventive public health measure and should not be confused with treatment of IDA which is dealt with in the subsequent section.

Fig. 6.1: IFA supplementation programme



Overview of Implementation Modalities for IFA Supplementation for Each Target Segment

6.1. Supplementation for Children 6–60 months

The onset of anaemia in young children is generally after 6 months of age. Before this, iron in breast milk is sufficient to meet the needs of a breastfed child. Iron from breast milk is also in a form that is more easily bio-available to the young child. Thereafter the incidence of anaemia increases from 6–8 months till the child is 1 year old. In India, diets for children in the age group 6–23 months are predominantly plant-based and provide insufficient amounts of micronutrients to meet the recommended nutrient intakes.

The following intervention is proposed for this target segment.

Dose and Regime

One ml of IFA syrup containing 20 mg of elemental iron and 100 mcg of folic acid biweekly for 100 doses in a year. Iron folic acid supplements will be supplied in bottles of 100 ml each and composition, preparation, dose and duration of IFA supplementation will remain same as the existing guidelines. The bottles should have an auto-dispenser so that only 1 ml of syrup will be dispensed at a time.

Albendazole tablets will be provided to children for biannual de-worming as per Table 6.2.

Table 6.2: Dosage of Albendazole tablets for biannual de-worming

Age	Dose (Albendazole 400 mg tablet)	Appropriate administration of tablets to children between the ages of 1 and 3 years is important. The tablet should be broken and crushed between two spoons, then safe water added to help administer the drug
1–2 years	Half tablet	
2 years upwards	One tablet	

Note: **Prophylaxis with iron should be withheld in case of acute illness (fever, acute diarrhoea, pneumonia etc.), Severe Acute Malnutrition (SAM) and in a known case of haemoglobinopathy/ history of repeated blood transfusion.**

Implementation

For all children aged 6 to 60 months it is proposed that IFA supplement will be administered under the direct supervision of an Accredited Social Health Activist (ASHA) on fixed days on a biweekly basis. The micro plan for reaching out to these children can be worked out at village level. It is recommended that a particular child should receive the supplement on the fixed day (Monday and Thursday), though it can vary for the groups of children depending on the home visits schedule prepared at block/district level. The nutritional status of children should be assessed by MUAC (Mid Upper Arm Circumference less than 11.5 cm) to ensure that IFA syrup is not given to children with Severe Acute Malnutrition (SAM).

ASHA would give IFA syrup bottles to mothers for safe storage and to lessen the logistic hurdle of carrying bottles around, but the IFA syrup will be administered under her direct supervision only. During the visits, the ASHA will also advise/inform the caregiver about the following issues:

- Time of administration – half an hour after food if the child has been breastfed (in LBW infants)/fed semisolid/solid food
- Benefits of regular intake of IFA syrup in physical and cognitive development of the child e.g. improvement in well-being, attentiveness in studies and intelligence etc.
- Minor side effects associated with IFA administration such as black discolouration of stools.
- Preservation of IFA bottle – in a cool and dark place, away from reach of children, keeping the lid of the bottle tightly closed each time after administration, etc.

Note: ASHAs/frontline workers/caregivers should be specifically instructed to administer IFA supplement half an hour after the child has been breastfed (in LBW infants)/fed semisolid/solid food.

Details of IFA supplementation will be included in the Mother and Child Protection (MCP) Card.

ASHAs will be suitably incentivised for undertaking this activity.

6.2. Supplementation for Children 5 (61 months onward)–10 years

Iron deficiency during childhood is often caused by inadequate dietary intake, absorption or utilisation of iron, increased iron requirements during the growth period, or blood loss due to parasitic infections such as malaria and soil-transmitted worm infestations.

7

Therapeutic Approach through the Life Cycle

7.1. Six Months – 60 Months

ASHAs and ANMs will screen children from 6 months up to 5 years of age for signs of anaemia as per Integrated Management of Neonatal and Childhood Illness (IMNCI) Guidelines through opportunistic screening at

- VHNDs
- Immunisation sessions
- House-to-house visits by ASHAs for biweekly IFA supplementation
- Sick child coming to health facility (Sub-centre/PHC)

Screening through assessment of palmar pallor (as per IMNCI guidelines)
If the skin of child's palm is paler than that of others, the child will be referred to the appropriate health facility (PHC)/Mobile Medical Teams for Hb estimation and treatment of anaemia.

Facility level management

- Any child reporting to any facility (PHC level and above) with any illness will be assessed clinically by the attending Medical Officer for anaemia **routinely** and should undergo Hb estimation if found to be anaemic clinically
- All children referred from field (community, outreach, sub-centre) to PHC due to palmar pallor will undergo Hb level estimation before initiating treatment

Children will be categorised as having mild, moderate and severe anaemia on the basis of Hb levels and will be managed as per Table 7.1.

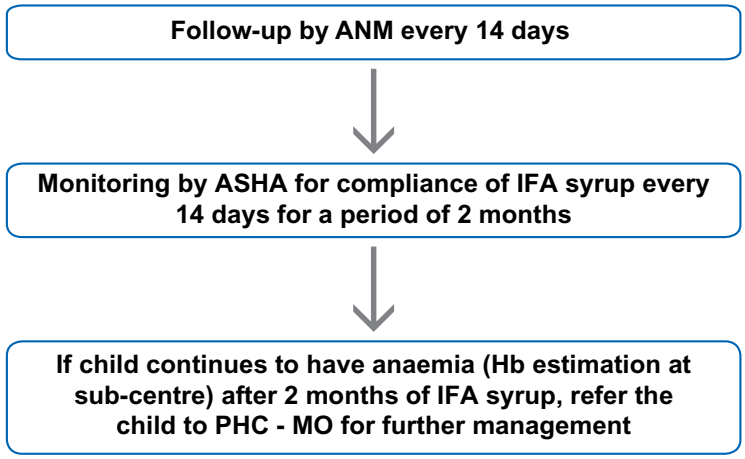
Table 7.1: Management of anaemia on the basis of haemoglobin levels in children 6 months–5 years

Level of Hb	Treatment	Follow-up	Referral
No Anaemia (>11 gm/dl)	20 mg of elemental iron and 100 mcg of folic acid in biweekly regimen		
Mild Anaemia (10–10.9 gm/dl)	3 mg of iron/ Kg/ day for 2 months	Follow-up every 14 days by ANM Hb estimation after completing 2 months of treatment to document Hb>11 gm/dl	In case the child has not responded to the treatment of anaemia with daily dose of iron for 2 months, refer the child to the FRU/DH with F-IMNCI trained MO/ Paediatrician/Physician for further investigation
Moderate Anaemia (7–9.9 gm/dl)	3 mg of iron/ Kg/ day for 2 months	Follow-up every 14 days by ANM Hb estimation after completing 2 months of treatment to document Hb >11 gm/dl	In case the child has not responded to the treatment of anaemia with daily dose of iron for 2 months, refer the child to the FRU/DH with F-IMNCI trained MO/ Paediatrician/Physician for further investigations
Severe Anaemia (<7 gm/dl)	Refer urgently to DH/FRU		

Table 7.2: Dose of IFA syrup for anaemic children 6 months–5 years

Age of child	Dose	Frequency
6 months–12 months (6–10 kg)	1 ml of IFA syrup	Once a day
1 year–3 years (10–14 kg)	1.5 ml of IFA syrup	Once a day
3 years–5 years (14–19 kg)	2 ml of IFA syrup	Once a day

Follow-up of children undergoing treatment of anaemia to be done by ANM



- After completion of treatment of anaemia and documenting Hb level >11 gm/dl, the IFA supplementation to be resumed.
- Treatment of anaemia with iron should be withheld in case of acute illness, Severe Acute Malnutrition and in a known case of haemoglobinopathy. Anaemia in these cases should be treated as per the standard treatment guidelines, by the attending physician, as per the merit of the individual case.

Management of severe anaemia at FRU/DH (as per F-IMNCI) in children 6 months–5 years

History to be taken for	Examination for
• Duration of symptoms • Usual diet (before the current illness) • Family circumstances (to understand the child's social background) • Prolonged fever • Worm infestation • Bleeding from any site • Any lumps in the body • Previous blood transfusions • Similar illness in the family (siblings)	• Severe palmar pallor • Skin bleeds (petechial and/or purpuric spots) • Lymphadenopathy • Hepato-splenomegaly • Signs of heart failure (gallop rhythm, raised JVP, respiratory distress, basal crepitations)

Investigations	Indication for blood transfusion	Blood transfusion
• Full blood count and examination of a thin film for cell morphology • Blood films for malaria parasites • Stool examination for ova, cyst and occult blood	• All children with Hb ≤4 gm/dl • Children with Hb 4–6 gm/dl with any of the following: – Dehydration – Shock – Impaired consciousness – Heart failure – Deep and laboured breathing – Very high parasitaemia (>10% of RBC)	• If packed cells are available, give 10 ml/kg over 3–4 hours preferably. If not, give whole blood 20 ml/kg over 3–4 hours.

Indications for further investigations and referral for management:

- Cases of anaemia and Hepato-splenomegaly/Splenomegaly, if malaria has been excluded or not strongly suspected
- Children with similar history in the family (siblings)
- Cases of anaemia with significant lymphadenopathy, bleeding manifestations
- Cases of anaemia with abnormal/immature cells or marked leucocytosis or bicytopenia or pancytopenia on smear examination
- Children who are not responding to adequate dose of iron/folate given for 2 weeks

Trials

STUDY PROTOCOL Open Access

The Karnataka Anemia Project 2 — design and evaluation of a community-based parental intervention to improve childhood anemia cure rates: study protocol for a cluster randomized controlled trial

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Abstract

Background: Childhood anemia is highly prevalent worldwide. Improving the hemoglobin level of preschool age children could yield substantial benefits in cognitive and psychosocial development and overall health. While evidence-based recommendations for reducing childhood anemia in high anemia prevalence countries are available, there is no experimental evidence of community centered education and counseling programs, as a route to improved acceptance of iron supplements, demonstrating beneficial effects on anemia outcomes. We report on the evaluation protocol of a complex educational intervention led by the community lay health worker (LHW) and delivered to mothers of 12–59-month-old anemic children living in and visiting village day care centers in a large district of southern India.

Methods and design: The study is designed as a cluster randomized controlled trial. The intervention is based on the social cognitive theory and aims to promote among mothers, anemia awareness, dietary modifications to increase iron intake in the child, and recognition of the need for enhanced adherence to supplemental iron in the anemic child. From 270 eligible villages in the study area, a sample of 60 villages will be randomized to intervention [$n = 30$] or to treatment as usual [$n = 30$] of the study. LHWs in the intervention arm will be trained to administer the following intervention components to mothers of anemic children: 1] monthly distribution of Iron and folic acid (IFA) supplements to mothers of anemic children, and 2] five monthly counseling sessions of mothers of anemic children covering: a] anemia awareness education b] IFA adherence counseling and assessment, c] dietary modification to improve iron intake, and d] hygiene and sanitation. LHWs in the control arm will distribute IFA to mothers of anemic children as in the intervention arm but will not provide monthly education and counseling support. The primary outcome is the difference between the two experimental groups in anemia cure rates of children found to be anemic at baseline. Secondary outcomes, assessed as differences between all participants in both experimental groups, are: change in mothers' knowledge regarding anemia; 24 hour dietary iron intake; net improvement in individual hemoglobin values; serum ferritin; and the difference in overall cluster level childhood anemia prevalence. All outcomes will be measured 6 months after the start of the intervention. Multilevel linear and logistic regression models will be used to analyze differences between intervention and control groups in outcome variables.

(Continued on next page)

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Discussion: This trial is designed to evaluate the effectiveness of an intervention intended to improve anemia cure rates in anemic children living in villages of Chamarajnagar, Karnataka a large district in south India. The extensive study of secondary endpoints will be used to identify possible weak points in the compliance to intervention delivery and uptake. This evaluation is one of the few large randomized trials evaluating the impact of an education and counseling intervention to reduce childhood anemia prevalence.

Trial registration: This trial was registered with ISRCTN.com (identifier: ISRCTN68413407) on 17 September 2013.

Keywords: Iron deficiency anemia, Hemoglobin, Cluster randomization, Controlled trial, Counseling, Evaluation

Background

Over 1.6 billion people worldwide suffer from anemia and approximately 80 % of the burden of this disorder is borne by individuals living in South Asia and Africa [1–3]. Anemia is associated with a significant economic burden [4], accounts for 68.4 million years lived with disability (8.8 % of total for all conditions), increased maternal and perinatal mortality, and contributes to global mortality [5–7]. The prevalence of anemia in India is particularly high, where 50 % of reproductive age women, 59 % of pregnant women, 25 % of men, 40 % of adolescent girls, and 70 % of children under five years are anemic [8, 9]. The etiology of childhood anemia in limited resource settings is multifactorial [10–12], but in India it is mainly attributable to iron and other micronutrient deficiencies [6, 9, 13–15]. Iron deficiency anemia (IDA) is associated with cognitive and psychomotor retardation in children [16, 17], and trials of iron supplements in iron deficient children demonstrate improved outcomes [18]. The major cause of IDA in India is inadequate iron intake due to both low dietary iron content of food [19] and inadequate dietary animal protein [20]. In this context, childhood anemia appears to be mostly influenced by maternal anemia during pregnancy [8], poor nutritional and dietary iron intake [9, 19], and a combination of adverse socioeconomic factors [9].

Public health strategies addressing IDA have concentrated efforts on improving dietary iron intake by promoting population-based iron supplementation and diversification of diets, and by improving the iron content of food by fortification [21, 22]. These efforts have successfully reduced anemia prevalence in other Asian settings [20], but such benefits have not accrued in India [23, 24]. In line with WHO recommendations, the Indian government iterated the National Nutritional Anemia Control Programme (NNACP), which featured the use of iron supplements [21, 24]. More recently, launching of the national Iron + initiative by the Indian government has made anemia control more comprehensive by including an emphasis on nutrition [25]. Globally, however, challenges to childhood anemia control remain [26]. In India, inadequate procurement and distribution of iron and folic acid (IFA)[27], a perceived lack of adequate lay health worker (LHW) support in the village [27–29], and unfounded beliefs and psychological issues among individuals [9, 27] appear to hamper effective childhood anemia control. Previous research has shown that LHW-led education interventions are effective at promoting dietary modification, complementary feeding, and immunization uptake among rural communities [30–35]. We hypothesized that an educational and counseling intervention with a strong parental component specifically to reduce knowledge gaps among mothers, improve parental self-efficacy, and enhance adherence of the anemic child to (IFA would achieve better anemia cure rates than treatment as usual. This paper describes the study protocol for the Karnataka Anemia Project 2, which evaluates the effectiveness of a community LHW-led educational and counseling intervention delivered to mothers of anemic children residing in villages located in a province of southern India. We follow the CONSORT statement for reporting of cluster randomized trials [36, 37].

Design and Methods

Study design and setting

The study is designed as a cluster randomized controlled trial (CRCT) set in the Chamarajnagar taluk, Chamarajnagar district of Karnataka state, India. Karnataka, a south western state with a population of 61 million (7.1 million of which are children 0–6 years of age) is the ninth most populated state in India (2011 census) [38]. The study area, Chamarajnagar district, is located in a rural setting with a predominantly agrarian economy and an average annual household income of Indian rupees (INR) 22 006 (US $478) reflecting state and national averages. The Karnataka average annual household income is INR 26 123 (US $567), and the Indian overall average annual household income is INR 25 825 (US $561). Literacy rates are slightly higher (total = 75 % M = 82 %; F = 66 %) than the national average.

In India, the Integrated Child Development Service (ICDS) runs a network of village-based child care centers (ADCs), caring for children up to age 6 years and potentially offering the setting in which to deliver health

interventions to mothers of registered children [35]. The LHW in charge of the ADC is an integral component of the health system whose routine work includes the maintenance of childhood immunization records, health education for mothers, as well as kindergarten education for all village children. From the age of 36 months, children attend the ADC and receive day care services, education, and nutritional supplements under a government funded ICDS scheme. Although children younger than 36 months are registered in the ADC, for practical reasons they are not encouraged to attend. Typically the ADC LHW lives in the village, has a good relationship with mothers of children below 6 years of age, and an overall good standing in the community.

In this trial, a cluster (randomization unit) will be defined as a village in the Chamarajnagar subprovince that is randomly allocated to one of the study arms together with the ADC or (if the village has more than one ADC) the selected ADCs belonging to that village, and the corresponding LHW in charge of the ADC. Using a computerized random number generator [39], 60 villages from a total of 270 eligible villages will be randomly selected. The villages will be stratified based on the number of <6 year-old children listed in the ADC registers as resident in each village. After stratification, the selected villages will be assigned to intervention and control arms of the trial using a 1:1 ratio, in order to ensure equal representation of both strata to both arms. The observational units consist of children aged 12–59 months registered in the randomized villages and their mothers/caregivers, eligible for the study. We plan to recruit all eligible children (Fig. 1).

Participants

All children aged 12–59 months, residing in the village and registered in the village ADC, will be eligible to participate in the trial.

Inclusion criteria

For enrollment, children should be accompanied by their mother or caregiver. Mothers/caregivers of participants in the intervention arm should consent to receive LHW-led intervention and intend to reside in the village for at least 6 months after enrollment in the trial.

Exclusion criteria

Children with severe anemia defined as Hb ≤ 7.9 gm/dl for the purpose of this trial [40] will be excluded and referred to the primary health center/first referral unit for assessment and medical management. Children with a reported history of an active infection or fever >101 °F will also be excluded from participation and referred to the primary health center/first referral unit for management as usual.

Intervention

Rationale for the intervention and its development

In the planning stage of the intervention, theoretical frameworks were developed according to Fraser et al [41]. In the Problem Theory, the mother's knowledge, attitude, beliefs, care and control, role model, willingness to change, and parental self-efficacy were identified as malleable factors in order to influence the hygiene, dietary habits, and adherence to IFA supplements in their children. The design of the intervention is guided by the Social Cognitive Theory (SCT) [42], based on evidence in the published literature [23, 29, 31, 33, 34, 43, 44], and modulated based on discussions with stakeholders and policymakers in the Karnataka. According to the SCT, at least two principal sources of self-efficacy: verbal persuasion and performance accomplishment, are intended to mediate the effect of this intervention. The education of mothers about anemia, nutrition, IFA supplementation, and hygiene could foster the perception that their actions can control anemia in their children. This would lead to positive expectations about their children's health outcomes, which, along with LHW facilitation of learning and positive reinforcement, could improve IFA adherence (Fig. 2).

Furthermore, the intervention benefits are hypothesized to spill over to the entire community. Following a socio-ecological framework [45, 46], the child's immediate environment affected by the intervention would be the microsystem (the family) and the mesosystem (for example, parent-teacher meetings, the neighborhood, and social gatherings at the village level). At both these levels, one could expect counseled mothers of anemic children to modify the behaviors of mothers of non-anemic children, with respect to IFA consumption and dietary iron intake, thereby reducing the overall prevalence of anemia at the cluster level. Thus, the intervention is evidence based, contextually relevant, uses locally relevant resources, and has the potential to influence national policy.

Lay health worker training

LHWs in the intervention villages [$n = 30$] will receive training under four separate hands-on workshops over a period of 6 months. Training will occur with the use of role play, facilitation, and flip charts to help develop counseling and education skills of the LHWs. Training will take place at a location different from the LHWs' habitual training/supervision sites, to minimize the risk of contamination. LHWs will be trained to deliver five monthly education and counseling sessions to mothers/caregivers of anemic children. Specifically, these sessions will aim to improve mothers' knowledge regarding anemia and its consequences, the treatment of iron deficiency anemia with IFA, the importance of adherence to IFA treatments, sources of iron-rich food, diet modification behaviors, and

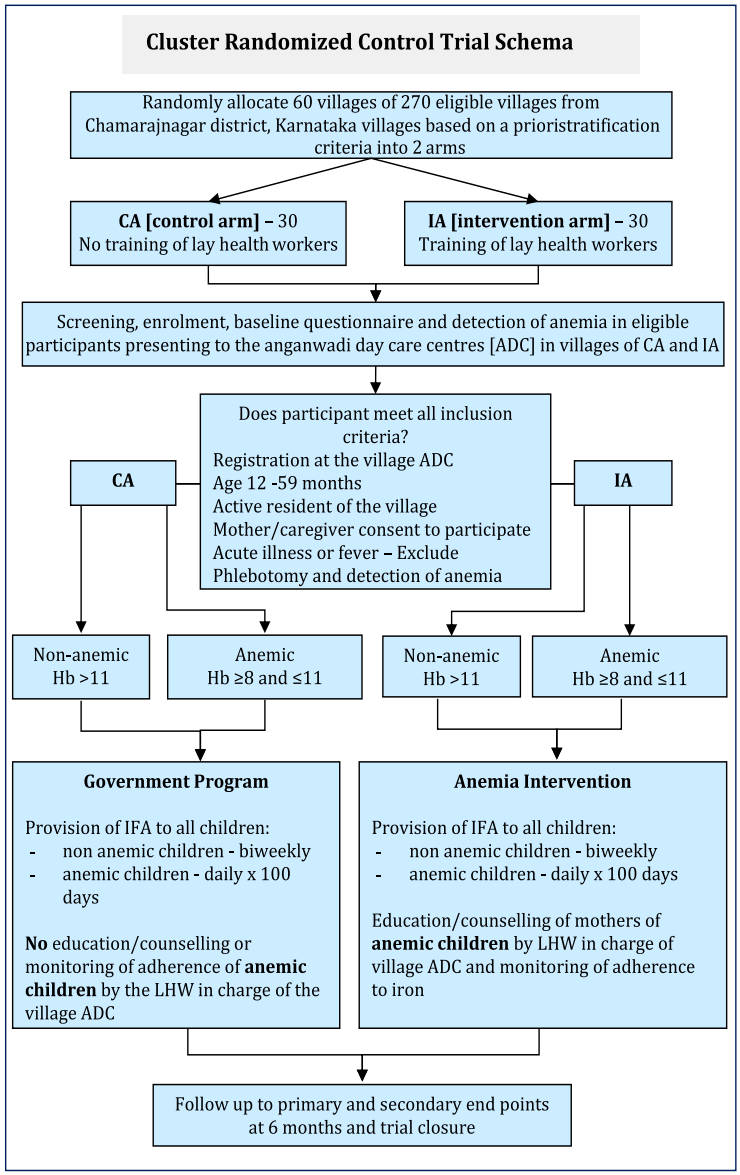

Fig. 1 Study schematic of the Karnataka Anemia Project 2 study to evaluate a community-based parental intervention to improve childhood anemia cure rate

hygiene. The possibility of contamination during LHW-supervisor monthly meetings, due to interaction between control group and intervention group LHWs, is minimal. LHWs in the control group neither receive training nor have access to training and intervention materials and will therefore be unable to replicate the intervention in their villages.

Components of the Intervention

i) *Enrollment and screening for anemia*
All eligible participants providing informed consent will be enrolled in the trial, provide information for a baseline questionnaire, have anthropometric measurements, and venous blood obtained by

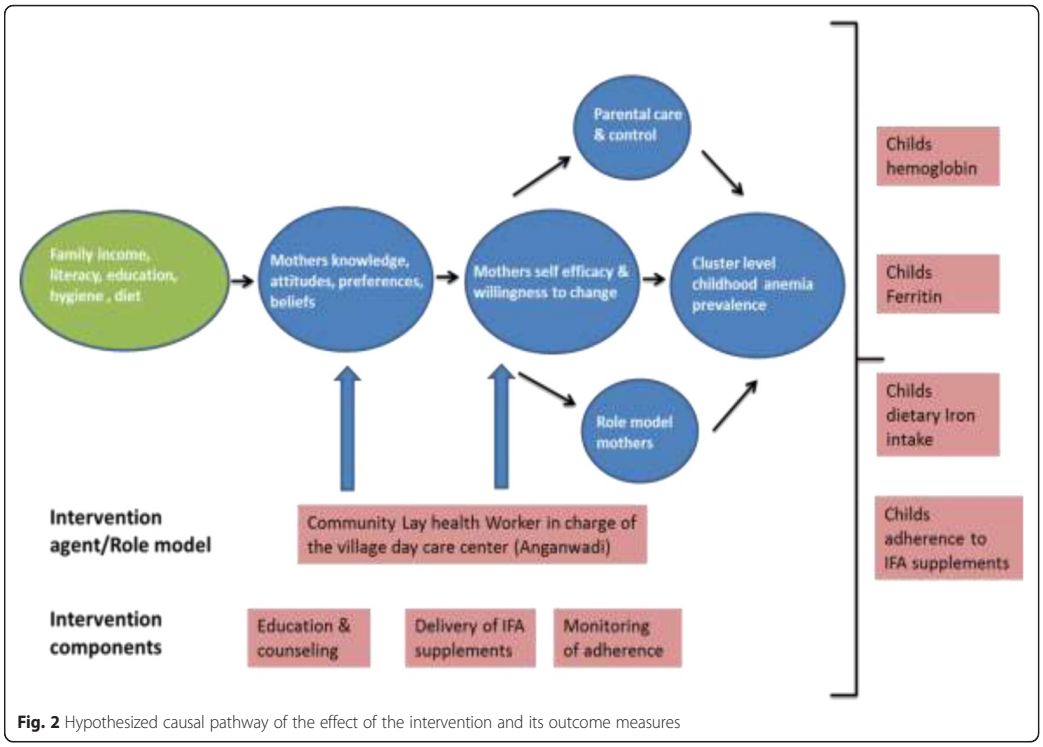

Fig. 2 Hypothesized causal pathway of the effect of the intervention and its outcome measures

phlebotomy to screen for anemia by the research team.

ii) *Iron supplementation*
A core preventive measure common to both trial arms is the delivery of iron supplements. All enrolled non-anemic participants are eligible for IFA supplements (tablets containing 20 mg elemental iron, 8 tablets/month) in line with National Iron + guidelines [25]. The guidelines recommend 20 mg IFA dispensed as syrup biweekly throughout the period 6–60 months and deworming for children 12 months and older. Since IFA syrup was not available in Karnataka, for the purpose of this trial, IFA is provided as 20 mg tablets. All enrolled participants detected with anemia (Hb ≥ 8 and ≤ 11 gm/dL) [40] in both arms of the trial are eligible for the therapeutic IFA dosage to control iron deficiency anemia (tablets containing 20 mg elemental iron, 20 tablets/month for 5 months). All subjects with acute infections or fever will be excluded during enrollment to the trial. Furthermore, during dispensation of IFA tablets, LHWs will advise mothers to withhold these during periods of fever or acute infections.

iii) *Education and counseling*
Only mothers/caregivers of anemic children (Hb ≥ 8 and ≤ 11 gm/dL) in the intervention arm will receive five monthly education and counseling sessions delivered by the LHW over the 6-month intervention period (Fig. 1).

iv) *Monitoring of adherence to IFA*
From the second counseling visit onward, LHWs in the intervention arm perform monthly pill counts to assess adherence to IFA dispensed only to mothers/caregivers of anemic children in the previous month and document the side effects of IFA, if any. In accordance with precautions in the guidelines, LHWs will advise mothers to withhold supplemental and treatment IFA during periods of fever or acute infections. A similar monthly assessment of adherence for mothers of anemic children in the control arm will not be performed. However, at the end of the 6 months of intervention, an assessment adherence to IFA in the previous 30 days will be performed for all participants in both arms of the trial.

Outcomes

The primary outcome will be the difference in anemia cure rate between the experimental arms at the end of

6 months from the intervention's start, in children found to be anemic at baseline. In addition, we will assess several secondary outcomes occurring along the hypothesized causal pathway of the intervention effect (Fig. 2), including: 1) difference in changes of knowledge and practice of mothers of anemic children from baseline to follow-up, 2) differences in the estimated 24-hour dietary iron intake among anemic participants exposed and not exposed to the intervention, 3) difference in net improvements in individual hemoglobin values between baseline and 6 month follow-up among anemic children exposed and not exposed to the intervention, 4) net improvements in mean ferritin values among anemic participants exposed and not exposed to the intervention, and, 5) difference in the cluster level anemia prevalence between experimental arms. Additional process indicator data include evaluation of the proportion of expected IFA doses delivered to children in the study (adherence to iron treatment), maintenance of LHW records of delivery of the intervention and IFA, and recording of the incidence of side effects of IFA supplements in children. Qualitative research on the acceptability, perceptions, and experiences of the LHWs regarding the training for and the actual delivery of the intervention will be conducted using focus group discussions. These data will help identify key assumptions and limitations of underlying intervention feasibility and sustainability and scaling-up, particularly when involving LHWs at the national level.

Protocol of recruitment

From the list of all children < 6 years registered in each village by the LHW in charge of the ADC, the research team will generate an eligible 12–59 month child list. Using this list, the LHW will mobilize participants and their mothers to the village ADC for study enrollment. Recruitment will occur at the village ADC and last for approximately 2 days. Additional house visits will be made on recruitment days to identify reasons for non-attendance of participants on the list (for example, those who are too sick, traveling, or migrating] and to help mobilize those who forgot to visit the ADC. Mothers/caregivers of all eligible children, who after being provided information about the trial indicate willingness to participate and an intention to live in the village for at least 6 months after enrollment, and those in the intervention arm indicating a willingness to receive LHW-led counseling will be enrolled after providing written informed consent (Fig. 1). Where recruitment is <80 % of the eligible list, an additional recruitment day will be allocated. Children who do not fulfill the inclusion criteria during recruitment sessions are not eligible for future recruitment.

Protocol of data collection

At study entry, a baseline questionnaire will record participant information. An additional file shows this in more detail [see Additional file 1]. Participants will also have a baseline sample of anticoagulated venous blood obtained to detect anemia and measure serum ferritin. All recruited participants will have a hemoglobin value estimated using an automated cell counter (Sysmex 405, Transasia laboratory systems, Japan). Within a few days the research team will provide mothers/caregivers with results of the hemoglobin values and anthropometry, and cluster LHWs with a list of anemic and non-anemic children. The list will permit LHWs in each cluster to organize the delivery of dose appropriate IFA to anemic and non-anemic children and to identify mothers of anemic children for delivery of monthly education and counseling.

The date of delivery of the first month's supply of IFA to the mothers of children in a cluster will herald the start of the intervention in that cluster. LHWs will deliver IFA to mothers of non-anemic children at the ADC during routine monthly visits. LHWs will typically deliver IFA together with education and counseling to mothers of anemic children at their homes. From the second visit onward, adherence data will be collected by the LHW, and the remaining IFA pills/empty strip will be obtained from the mother. In the control arm, LHWs will deliver IFA as usual in the setting of the ADC and will not deliver education and counseling to mothers of anemic children or collect monthly IFA adherence data. Approximately 6 months from the day of delivery of the first IFA supplement, the research team will perform a follow-up visit to collect 24-hour dietary recall data, anthropometry, and information on adherence to IFA in the previous month from all enrolled participants. During this time, a repeat phlebotomy to estimate hemoglobin is performed for all participants in the cluster, and the trial is completed.

Questionnaires prior to and after the intervention from mothers of anemic children provide information about the impact of LHW-delivered education and counseling on the mother's knowledge regarding anemia and its effects on the child. The mother's knowledge and practice questionnaire was explored by pilot testing it in the field for ease of administration and understanding. Assessment of 24-hour dietary iron intake at baseline and at the end of the intervention will provide information to estimate the effect of this intervention on promoting dietary diversification and improving dietary iron content. Finally, assessments of ferritin, a serum marker of iron stores, will provide information on whether actual improvements have been made in the total body iron stores of anemic children.

Statistical methods

Statistical power and sample size calculation

Primary analyses are limited to children with anemia at enrollment. At the end of 6 months, a difference of at least 12 % in the cure rate of anemic children is required if the intervention is considered to have sufficient public health utility to warrant its cost and effort [47–49]. We estimate that the 12 % reduction in proportion of anemic children at 6 months would occur due to a cure rate of 30 % in the control group (IFA alone) and 42 % in the experimental arm where children receive IFA plus the community-based parental intervention. To detect a 12 % difference in 6-month anemia cure rates at an alpha level of 0.05 for a two-tailed test, with 80 % power, a total unadjusted sample size of 500 children with anemia is required, which after adjustment for clustering (design effect = 2.2) results in a sample size of 1,100 children with anemia. The design effect assumes an intracluster correlation coefficient (ICC) of 0.05 and 25 participating children with anemia per village. The anticipated degree of intracluster correlation was selected based on results from several recent trials of interventions on anemia [47–49]. We further allow for a 10 % loss to follow-up of children identified with anemia at baseline, yielding a final sample size of 610 children with anemia per arm (1,220 in all). We will recruit 30 clusters per trial arm to accommodate potential losses of clusters if LHWs should stop working, resulting in loss of an entire cluster. Thus, power will be greater than 80 %. Analyses will also consider prevalence of anemia at 6 months among all participating children regardless of their baseline anemia status. Based on an estimated prevalence of 50 % anemia at baseline in each village, the number of children required will be 1,220 in each trial arm.

Statistical analysis

The primary analysis will follow the intention-to-treat principle, whereby all children regardless of whether they received the full intervention or not will be included in the analysis of the group to which they were randomized. Data will be analyzed at the individual level adjusting for clustering using generalized estimating equation (GEE) extensions of logistic regression for presence or absence of anemia while similar extensions of linear regression will be used to model individual hemoglobin levels [50]. All models will adjust for the stratification factor (the number of children per village). The effects of explanatory variables such as age, sex, socioeconomic status, literacy, nutritional parameters, and maternal anemia status will also be explored. Secondary analyses will consider the effect of adjustment for these potential explanatory variables on the estimated intervention effect using multivariable regression models. All tests will be declared statistically significant at the 0.05 level (two-tailed).

Ethical issues

Ethical approval

The study was approved by the St. Johns National Academy of Health Sciences Institutional Ethical Committee (IEC 115/2012).

Information and informed consent

Information about the trial is provided to community leaders and mothers through the LHW. Written and verbal information about the trial is provided in English and Kannada (the local language). Documents translated into Kannada are validated through back translation. All participant mothers/care providers are provided with study information prior to enrollment for review. Individual informed consent is obtained from mothers/care providers of selected children, and is recorded by signature or thumbprint. Mothers/care givers will also be informed that participation of their child in the study is completely voluntary and that they may withdraw from the study at any time.

Monitoring of side effects and trial supervision

Details regarding side effects to IFA supplements will be collected by the LHW and notified to the research team. In the event of side effects that are deemed related to IFA (either by the LHW or the research team), participants are advised by the LHW to discontinue IFA and report to the primary health center for evaluation. Since the intervention under comparison is non-invasive, the IFA supplements in the protocol follow national recommendations, and the setting is not a malaria endemic region, the occurrence of serious adverse events (SAEs) is unlikely. An interim analysis of the trial will take place when all subjects have been recruited and all 30 clusters have completed 3 months of delivery of the intervention. This analysis will be conducted in a blinded manner by an independent data safety and monitoring board (DSMB) consisting of experts in clinical medicine, epidemiology, and statistics. The primary aim of the interim analysis is to assess if the intervention arm shows a clearly better, or worse, outcome than the control arm as well as to evaluate SAEs.

Discussion

This is the first cluster randomized control trial (CRCT) designed to evaluate an intervention that includes both lay health workers and parents to complement India's existing national health policy for combating anemia in children, one of the most

pernicious and common nutritional health burdens among individuals in resource-limited settings [3, 6, 10, 51]. The present evaluation adopts a theory-based approach to investigate the causal chain through which the proposed intervention is expected to have its impact (Fig. 2). We employ qualitative methods to understand the perceptions and experiences of LHWs actually delivering the intervention and the context and process of the interventions delivery [52]. Results from this contextually relevant intervention will be used to establish whether it is possible to improve anemia cure rates in anemic children in India with relatively limited efforts targeted to the mothers of such children.

The CRCT design, whereby groups of individuals are randomly allocated to different interventions, has the potential to provide unbiased estimates of the impact of interventions delivered at the community level (in this case children in a village eligible to attend the village day care). A major strength of this trial is that it attempts to maximize participation at both the cluster and individual levels. For instance, LHWs in both arms of the study will be provided with training, support, and resources to achieve intervention goals, and will encourage cluster-level participation to minimize drop-out rates. Furthermore, randomization will be an inclusive process with active involvement and participation of the LHWs. During recruitment, the research team will actively support LHWs during periods of stress (wage-related agitations, unscheduled ADC closures for local holidays, and breaks during which LHWs perform other tasks such as immunization). The research team will perform door-to-door visits for eligible children who failed to attend the ADC after mobilization by the LHW to identify reasons for the mothers' lack of attendance. Analysis of all this data will provide clarity regarding participation in this trial and could address concerns related to selection bias.

Anemia has been a public health problem for several decades [3, 6] and is in great need of effective control programs. India bears a large portion of the burden of anemia in Asia, with close to 100 million anemic children [2, 6]. The need for effective intervention studies addressing anemia is particularly relevant to rural Indian communities, where the prevalence of anemia is highest. However, there is an increasing appreciation that such studies should not only evaluate if interventions work, but also how they work, thereby enhancing the policy implications of such evaluations [52, 53]. In order to maximize policy relevance, it is essential to understand the context of the research, the related policymaking processes and to engage key stakeholders. To achieve this, we intend to continuously engage with the health authorities at state, provincial, and district levels. Inadequate IFA supplies have been previously noted to be a major limitation to the success of anemia control in low-middle income settings [28]. Thus, instead of procuring IFA commercially, the Karnataka state health officials will be involved and the state infra-structure will be utilized to ensure that IFA is made available for the trial. These efforts could eventually lead to greater sensitization of the health department regarding IFA availability and recognition of the need for enhanced LHW capacity to screen and manage anemia in Karnataka. Conducting research in rural communities, especially in an Indian context, raises a number of practical and logistic issues. The research team has partnered with an experienced field research agency that has an established track record of development research in the Chamarajnagar district. This team will work collaboratively, coordinate with the government, involve community leaders from villages in the study area, and make participants stakeholders in their healthcare, all of which will contribute to the successful conduct of the trial.

Indeed, the novelty of this cluster RCT consists of its real-life setting evaluation of education and counseling combined with monitoring of parental compliance in connection with the delivery of IFA supplements to attenuate the public health problem of childhood anemia. All intervention components will be delivered by a community LHW, therefore relying on local human resources. Furthermore, the intervention will use healthy local dietary practices to positively influence the nutritional behaviors of children and parents. If successful, such an approach could profoundly shift the attention of anemia control policy towards a diet-focused rather than a supplementation-focused approach. Once effectiveness in real-life conditions is ascertained, all the above features of the intervention will collectively ensure high potential for sustainability and scaling-up of the intervention. The intervention may lead to improved hemoglobin values and reduced anemia prevalence among 12–59-month children in the short term [18, 26] and could result in better cognitive outcomes in these children over the long term [18, 54–56]. If effective, the intervention could be implemented on a larger scale to determine if such local effects may have a wider positive health effect nationally. Final results from this intervention trial are expected in mid-2016.

Trial status

The trial commenced recruitment in November 2014 and intends to complete recruitment in July 2015.

Additional file

Additional file 1: Baseline questionnaire. (PDF 287 kb)

Abbreviations

ADC: Anganwadi day care center; CHW: community health worker; Hb: hemoglobin; IDA: iron deficiency anemia; IFA: iron and folic acid; Iron +

Initiative: National Iron plus initiative; LHW: lay health worker; NNACP: National Nutritional Anemia Control Programme.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
AS secured the funding, is responsible for the overall study design and project management, and drafted the manuscript. AS, MZ, and RG designed the evaluation, wrote the protocol, and planned the analysis and assessment. AS, MM, and AR designed the intervention. AS and MM developed the training modules for LHWs and supervised the LHW training and data collection. NK planned the statistical analysis. AS and SA designed the qualitative studies. All authors read and approved the final version of the manuscript. All authors declare that they have no financial conflict of interest.

Acknowledgements
Special thanks are due to the research team, the lay health workers participating in the study, and the community that supported the project. We are also grateful to the mothers, children, and family members who participated in this project. We acknowledge the Ministry of Health and Family Welfare, Government of Karnataka, the Chamarajnagar district health administrative section, MYRADA staff, and the ICDS administrative section, Child Development Project Officer, Chamarajnagar district for their help and support in the project. We acknowledge contributions from the Karnataka state health officers who helped and facilitated the procurement of IFA supplements for the trial. We acknowledge the efforts of doctor, nursing, and paramedical staff from the primary health care system who were involved in the care of subjects referred from this trial. We especially acknowledge Dr. Abha Rao and Paul Jebaraj. We acknowledge Drs. Prem Pais (SJRI) and Irwin Nazareth (UCL) for helpful comments on the protocol.

Funding
Funding for the study is provided by the Wellcome Trust/DBT India Alliance through a research career development senior fellowship award (IA/SF/2013/AS/1) to Dr. Arun Shet.

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Received: 8 July 2015 Accepted: 18 December 2015
Published online: 30 December 2015

References
1. de Benoist B, McLean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993–2005. WHO global database on anaemia; 2008. http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf.
2. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr. 2009;12(4):444–54.
3. Stevens GA, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, Peña-Rosas JP, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Global Health. 2013;1:e16–25.
4. Horton SRJ. The economics of iron deficiency. Food Policy. 2003;28:51–75.
5. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
6. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615–24.
7. Watson-Jones D, Weiss HA, Changalucha JM, Todd J, Gumodoka B, Bulmer J, et al. Adverse birth outcomes in United Republic of Tanzania–impact and prevention of maternal risk factors. Bull World Health Organ. 2007;85(1):9–18.
8. IIPS. National Family Health Survey [NFHS-3]. Mumbai: International Institute for Population Sciences [IIPS] and Macro International 2005-06; 2007.
9. Pasricha SR, Black J, Muthayya S, Shet A, Bhat V, Nagaraj S, et al. Determinants of anemia among young children in rural India. Pediatrics. 2010;126(1):e140–9.
10. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. Lancet. 2012; 378(9809):2123–35.
11. Calis JC, Phiri KS, Faragher EB, Brabin BJ, Bates I, Cuevas LE, et al. Severe anemia in Malawian children. N Engl J Med. 2008;358(9):888–99.
12. Gomber S, Kumar S, Rusia U, Gupta P, Agarwal KN, Sharma S. Prevalence & etiology of nutritional anaemias in early childhood in an urban slum. Indian J Med Res. 1998;107:269–73.
13. Kumar T, Taneja S, Yajnik CS, Bhandari N, Strand TA. Prevalence and predictors of anemia in a population of North Indian children. Nutrition. 2014;30(5):531–7.
14. Pasricha SR, Shet AS, Black JF, Sudarshan H, Prashanth NS, Biggs BA. Vitamin B-12, folate, iron, and vitamin A concentrations in rural Indian children are associated with continued breastfeeding, complementary diet, and maternal nutrition. Am J Clin Nutr. 2011;94(5):1358–70.
15. Semba RD, de Pee S, Sun K, Campbell AA, Bloem MW, Raju VK. Low intake of vitamin A-rich foods among children, aged 12-35 months, in India: association with malnutrition, anemia, and missed child survival interventions. Nutrition. 2010;26(10):958–62.
16. Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, et al. Iron deficiency anemia and cognitive function in infancy. Pediatrics. 2010;126(2):e427–34.
17. Lozoff B, Corapci F, Burden MJ, Kaciroti N, Angulo-Barroso R, Sazawal S, et al. Preschool-aged children with iron deficiency anemia show altered affect and behavior. J Nutr. 2007;137(3):683–9.
18. Iannotti LL, Tielsch JM, Black MM, Black RE. Iron supplementation in early childhood: health benefits and risks. Am J Clin Nutr. 2006;84(6):1261–76.
19. Nair KM, Iyengar V. Iron content, bioavailability & factors affecting iron status of Indians. Indian J Med Res. 2009;130(5):634–45.
20. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007; 370(9586):511–20.
21. Stoltzfus R, Dreyfuss. ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington, D. C.: WHO: ILSI Press; 1998. Report No.: 1-57881-020-5.
22. Stoltzfus RJ. Research needed to strengthen science and programs for the control of iron deficiency and its consequences in young children. J Nutr. 2008;138(12):2542–6.
23. Kapil U. Prevention and control of iron deficiency anemia amongst young children. Indian Pediatr. 2003;40(4):293–5.
24. Kumar A. National nutritional anaemia control programme in India. Indian J Public Health. 1999;43(1):3–5. 16.
25. India Go. National Iron + Initiative. In: Welfare MoHaF, editor.; 2013. http://www.pbnrhm.org/docs/iron_plus_guidelines.pdf. Accessed 26 March 2015.
26. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database Syst Rev. 2011;12:CD009085. doi:10.1002/14651858.CD009085.pub2.
27. Pasricha SR, Biggs BA, Prashanth NS, Sudarshan H, Moodie R, Black J, et al. Factors influencing receipt of iron supplementation by young children and their mothers in rural India: local and national cross-sectional studies. BMC Public Health. 2011;11:617.
28. Galloway R, Dusch E, Elder L, Achadi E, Grajeda R, Hurtado E, et al. Women's perceptions of iron deficiency and anemia prevention and control in eight developing countries. Soc Sci Med. 2002;55(4):529–44.
29. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? Soc Sci Med. 1994; 39(3):381–90.

30. Bhandari N, Bahl R, Mazumdar S, Martines J, Black RE, Bhan MK. Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth: a cluster randomised controlled trial. Lancet. 2003;361(9367):1418–23.
31. Bhandari N, Mazumder S, Bahl R, Martines J, Black RE, Bhan MK. An educational intervention to promote appropriate complementary feeding practices and physical growth in infants and young children in rural Haryana, India. J Nutr. 2004;134(9):2342–8.
32. Bhutta ZA, Soofi S, Cousens S, Mohammad S, Memon ZA, Ali I, et al. Improvement of perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. Lancet. 2012;377(9763):403–12.
33. Lewin S, Munabi-Babigumira S, Glenton C, Daniels K, Bosch-Capblanch X, van Wyk BE, et al. Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases. Cochrane Database Syst Rev. 2012;3, CD004015.
34. Shi L, Zhang J. Recent evidence of the effectiveness of educational interventions for improving complementary feeding practices in developing countries. J Trop Pediatr. 2012;57(2):91–8.
35. Vazir S, Engle P, Balakrishna N, Griffiths PL, Johnson SL, Creed-Kanashiro H, et al. Cluster-randomized trial on complementary and responsive feeding education to caregivers found improved dietary intake, growth and development among rural Indian toddlers. Matern Child Nutr. 2013; 9(1):99–117.
36. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2010;345, e5661.
37. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
38. Census report 2011. In: Government of India; 2011.
39. Urbaniak GC, Plous S. Research Randomizer v4.0. 2013. http://www.randomizer.org/form.htm
40. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011 [WHO/NMH/NHD/MNM/11.1].
41. Fraser WM, Richman MJ, Galinsky MJ, Day SH. Intervention research. New York: Oxford University Press; 2009.
42. Bandura A. Health promotion by social cognitive means. Health Educ Behav. 2004;31(2):143–64.
43. Raiten DJ, Namaste S, Brabin B. Considerations for the safe and effective use of iron interventions in areas of malaria burden - executive summary. Int J Vitam Nutr Res. 2012;81(1):57–71.
44. Vijayaraghavan K, Brahmam GN, Nair KM, Akbar D, Rao NP. Evaluation of national nutritional anemia prophylaxis programme. Indian J Pediatr. 1990; 57(2):183–90.
45. Bronfenbrenner U, Ceci SJ. Nature-nurture reconceptualized in developmental perspective: a bioecological model. Psychol Rev. 1994; 101(4):568–86.
46. Fiese BH, Jones BL. Food and family: a socio-ecological perspective for child development. Adv Child Dev Behav. 2012;42:307–37.
47. Bharti S, Bharti B, Naseem S, Attri SV. A community-based cluster randomized controlled trial of "directly observed home-based daily iron therapy" in lowering prevalence of anemia in rural women and adolescent girls. Asia Pac J Public Health. 2015;27(2):NP1333–44.
48. Jack SJ, Ou K, Chea M, Chhin L, Devenish R, Dunbar M, et al. Effect of micronutrient sprinkles on reducing anemia: a cluster-randomized effectiveness trial. Arch Pediatr Adolesc Med. 2012;166(9):842–50.
49. Rivera JA, Sotres-Alvarez D, Habicht JP, Shamah T, Villalpando S. Impact of the Mexican program for education, health, and nutrition (Progresa) on rates of growth and anemia in infants and young children: a randomized effectiveness study. JAMA. 2004;291(21):2563–70.
50. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold; 2000.
51. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832–43.
52. Glenton C, Lewin S, Scheel IB. Still too little qualitative research to shed light on results from reviews of effectiveness trials: a case study of a Cochrane review on the use of lay health workers. Implement Sci. 2011;6:53.
53. Peterson S. Assessing the scale-up of child survival interventions. Lancet. 2010;375(9714):530–1.
54. Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. Cochrane Database Syst Rev. 2001; [2]: CD001444.
55. Lozoff B. Iron deficiency and child development. Food Nutr Bull. 2007; 28(4 Suppl):S560–71.
56. Stoltzfus RJ, Heidkamp R, Kenkel D, Habicht JP. Iron supplementation of young children: learning from the new evidence. Food Nutr Bull. 2007; 28(4 Suppl):S572–84.

APPENDIX 3

Karnataka Anemia Project 2

Counselling Resource for Anganwadi Workers

Flipchart

Counselling messages: Basic Facts of Anemia

MESSAGE *(SHOW PICTURES)*:
Below normal levels of haemoglobin in red blood cells results in anemia.

Pictures 1, 2: Fewer red blood cells in anemic children, visibly less reddish colour of red blood cells due to lack of haemoglobin. Inadequate amounts of iron in food commonly cause anemia. Sufficient iron in food usually results in production of haemoglobin.

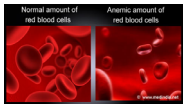
Pictures 3, 4: Normal iron intake and hemoglobin levels will lead to normal growth and brain development. Anemic children will not grow as strong or as be as smart as children without anemia.

CHECKING QUESTIONS:
- What is anemia?
- How can anemia effect the growth of the child ?

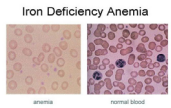
MOTIVATION:
- Children without anemia will be stronger and smarter.

REMINDERS: If you think your child has anemia, tell the anganwadi worker and she will test your child.

What is Anemia ?

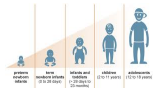


1



2


3


4

Counselling messages: Consequences of anemia

MESSAGE: *(SHOW PICTURES)*
Picture 1: If anemia is not corrected, the blood becomes weak. Many parts of the body (especially the brain) will not develop properly. Children may feel easily tired and may not play well. They may look pale and sometimes eat unusual things like mud, paint, and chalk.
- **Baby:** low birth weight, more prone to infections
- **Children:** slow body growth, low intelligence, poor school performance
- **Pregnant women:** maternal deaths, problems in pregnancy and delivery, longer time to recover after delivery

Picture 2: Anemia is correctable and you can identify and treat anemia if you know the signs and symptoms.

CHECKING QUESTIONS:
- What can happen if the child has anemia ?

MOTIVATION:
- Children without anemia fall sick less often and are stronger and smarter in school.

REMINDERS: Ask your anganwadi worker to test your child for anemia

Consequences of anemia

Anemic children can :
- Have low birth weight
- Fall sick easily
- Grow slowly
- Slow thinking
- Be less brainy

BUT! Anemia is correctable!!

Correcting anemia helps children become healthy, strong, and smart!!

These children can then become smart and brainy and do well in school

Counselling messages: Common signs of anemia

MESSAGE: *(SHOW PICTURES)*:

The signs of anemia are:

- Pictures 1, 2 and 3: Pallor, i.e., decreased pinkness, of skin of the palms, nail beds, lips, and lining of the eyelids.
- Picture 4: Tiredness all the time, weakness, irritability
- Picture 5: Poor performance in school
- Loss of concentration and attention, developmental delays, behavioural disturbances
- Breathlessness, rapid heartbeat, giddiness, lightheadedness

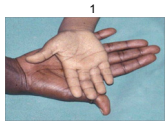
CHECKING QUESTIONS:
- What are the signs of anemia ?

MOTIVATION:
- Looking for the signs of anemia in yourself and your child can help you to ask your anganwadi worker for help before you or your child becomes very sick.

REMINDERS: Your anganwadi worker can test if you or your child has anemia.

Common Signs of Anemia

1 2 3



Pallor of the palms, nail beds and conjunctiva

Fatigue 4

Poor school performance 5

Counselling messages: Iron nutriture and diet

MESSAGE *(SHOW PICTURES)*:
Give foods rich in iron daily or as often as possible. If possible, sprout or germinate lentils and grams so that the iron is easily used by the child's body.

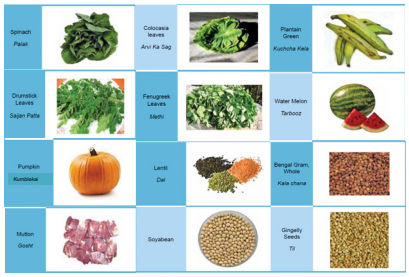
FLIP CHART ACTIVITY: Ask mother to point to iron rich foods dark green vegetables, fruits and other foods that her family commonly eats.

CHECKING QUESTIONS:
- What iron containing vegetables/meat/gram have you been giving to [child]?
- How have you been preparing these foods for [child]?

MOTIVATION:
- Eating food with more iron will helps a child have stronger blood, keeps them healthier and makes them smarter.

REMINDERS:
- Before and when preparing food and feeding your child, think of what iron-rich foods you can add to the meal.

Iron nutriture and Diet



Counselling messages: Anemia and hygiene

MESSAGE (SHOW PICTURES):
Pictures 1, 2: Hookworms and malaria (due to mosquitoes) can also lead to anemia. Regular deworming and maintaining proper hygiene can reduce the possibility of anemia.

FLIP CHART ACTIVITY (SHOW PICTURES): Pictures 3, 4, 5: Ask mother to point to steps she takes to maintain hygiene.

CHECKING QUESTIONS:
•What instructions regarding foot wear and hand washing have you given to [Child]?
• Do you wash your hands before preparing food for the [Child] and family?

MOTIVATION:
• When [child] wears foot wear outside of the house and washes their hands with soap and water before they eat, they are less likely to have worms and less likely to become anemic.

REMINDERS:
•Wash your hands with soap and water before preparing food and feeding your child. Washing gets rid of germs that can make children sick.

Anemia and hygiene


1


2


3


4

Counselling messages: Iron supplement adherence

MESSAGE (SHOW PICTURES):
Give iron tablets 5 days a week. Side effects are less if you give iron tablets after dinner, with a glass of water. Side effects of the iron tablets are mild and only temporary. Stomach pain and black stool. DO NOT give iron tablets with or after milk or tea. Lemon or orange juice helps iron tablets get absorbed better.

FLIP CHART ACTIVITY:
Ask mother to point to IFA supplement that the anganwadi worker has given her.

CHECKING QUESTIONS:
•How have you been giving Iron supplements to your child?
•How often have you been giving Iron supplements to your child? (number of days in the week)
•Show me how many pills you have left from my last visit (document).

MOTIVATION:
•Children that take iron regularly will have higher hemoglobin levels and stronger blood.
•Children with stronger blood will stay healthier and become smarter and do well in school.

REMINDERS:
•Because your child is anemic remember to give your child iron supplements 5 days/week
•Taking iron regularly will prevent weak blood in your child.

Iron supplement adherence

1 

2 

3 

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Contents

- Basic Facts of anemia
- Consequences of anemia
- Common signs of anemia
- Iron nutriture and diet
- Anemia and hygiene
- Iron supplement adherence
- **Remember**:
  - If the mother has done something correctly, PRAISE her! Try always to ENCOURAGE the mother!
  - Try not to scold the mother if she has not followed your instructions.

APPENDIX 4A **KAP2**

BASELINE ASSESSMENT FORM

(Completed by research team at baseline for all participants)

Village ID ಹಳ್ಳಿಯ ಸಂಖ್ಯೆ	PID ಸಂಖ್ಯೆ	Date: ದಿನಾಂಕ: (dd) (mm) (yyyy)
☐☐☐	☐☐☐☐	☐☐ ☐☐ ☐☐☐☐

Village name: _____	Activity done	Interview/Labs		QC	Data Entry 1	Data Entry 2
	Person's Initials					
	Date					

A. Participant details: ಭಾಗವಹಿಸಿದವರ ಮಾಹಿತಿ:

A1	Child's name: ಮಗುವಿನ ಹೆಸರು:	A2	Sex: ಲಿಂಗ: ☐1.Male ☐2.Female
A3	Date of birth: ಹುಟ್ಟಿದ ದಿನಾಂಕ ____ / ____ / _____ dd mm yyyy	A4	Age: ವಯಸ್ಸು: _____yrs _____months (eg:"2yr 3mon")
A5	Name of care-giver: ಪೋಷಕರ ಹೆಸರು	A6	Relationship of care-giver to child: ಪೋಷಕರ ಜೊತೆಗಿನ ಸಂಬಂಧ: ☐1. Mother (ತಾಯಿ) ☐2. Others, specify: _____ ಇತರೆ: ನಮೂದಿಸಿ:

B. Socio-demographic questions (mother): ಸಾಮಾನ್ಯ ಮಾಹಿತಿ (ಜನಸಂಖ್ಯೆಗೆ ಸಂಬಂಧಿಸಿದಂತೆ)

B1	Mother's age : ತಾಯಿಯ ವಯಸ್ಸು: _____(e.g. "25 yr") ☐ Deceased (ಮರಣವೊಂದ್ದಿದರೆ)	B2	Mother's religion: ತಾಯಿಯ ಧರ್ಮ: ☐ 1.Hindu ☐ 2.Muslim ☐3.Christian 1. ಹಿಂದೂ 2. ಮುಸ್ಲಿಂ 3. ಕ್ರಿಶ್ಚಿಯನ್ 4. ಇತರೆ: ನಮೂದಿಸಿ: ☐ 4. Other, specify: _____
B3	No. of years of schooling: _____ years ನೀವು ಎಷ್ಟು ವರ್ಷ ಶಾಲೆಗೆ ಹೋಗಿದ್ದೀರಾ?	B4	Can you read: ☐ 1. Yes ☐ 2.No ನಿಮಗೆ ಓದಲು ಬರುತ್ತದೆಯೆ: ೧. ಹೌದು ೨. ಇಲ್ಲ Can you write: ☐ 1.Yes ☐ 2.No ನಿಮಗೆ ಬರೆಯಲು ಬರುತ್ತದೆಯೆ: 1. ಹೌದು 2. ಇಲ್ಲ

C. Anemia risk factors (mother):

C1	How many pregnancies have you had so far? ನೀವು ಇಲ್ಲಿಯ ವರೆಗೆ ಎಷ್ಟು ಭಾರಿ ಗರ್ಭಿಣಿಯಾಗಿದ್ದೀರ? Number of pregnancies: _____ No. of abortions/still birth: _____ (if any)	C2	Could you tell me the birth order of this child among live births? ಜೀವಂತವಾಗಿ ಹುಟ್ಟಿದ ಮಕ್ಕಳಲ್ಲಿ ಈ ಮಗು ಎಷ್ಟನೆಯದು? Number of live births: _____ Birth order: _____

D. Anemia risk factors (child) ರಕ್ತಹೀನತೆಯ ಲಕ್ಷಣಗಳು (ಮಗು)

D1	Did you breast feed this child? ನಿಮ್ಮ ಈ ಮಗುವಿಗೆ ಎದೆ ಹಾಲು ಕುಡಿಸಿದ್ದೀರಾ? ☐ 1. Yes ☐ 2. No *(If 'No' goto D7)* 1. ಹೌದು 2. ಇಲ್ಲ *(ಇಲ್ಲ ಎಂದರೆ D7 ಕ್ಕೆ ಹೋಗಿ)*		
D2	For how many months did you give the child breast milk alone, with no other foods (exclusive breastfeeding)? _____ months ನಿಮ್ಮ ಮಗುವಿಗೆ ಬೇರ ಯಾವುದೆ ರೀತಿಯ ಆಹಾರವನ್ನು ನೀಡದೆ ಬರಿ ಎದೆ ಹಾಲನ್ನು ಎಷ್ಟು ತಿಂಗಳವರೆಗೆ ನೀಡಿದ್ದೀರಾ?	D3	Are you still breastfeeding this child? ಈಗಲು ನೀವು ಈ ಮಗುವಿಗೆ ಎದೆ ಹಾಲು ಕುಡಿಸುತ್ತಿದ್ದೀರಾ? ☐ 1. Yes ☐ 2. No *(If 'No', goto D7)* 1. ಹೌದು *(ಇಲ್ಲ ಎಂದರೆ D7 ಕ್ಕೆ ಹೋಗಿ)* 2. ಇಲ್ಲ
D4	How many times do you breast feed the child in a day? ಒಂದು ದಿನದಲ್ಲಿ ಸುಮಾರು ಎಷ್ಟು ಬಾರಿ ಈ ಮಗುವಿಗೆ ಎದೆಹಾಲು ಕುಡಿಸುತ್ತಿರೀ? ☐ 1. 2 times ☐ 2. 2-4 times ☐ 3. >4 times	D5	How long do you feed the baby on an average in a day? ಒಂದು ದಿನದಲ್ಲಿ ಸಮಾನ್ಯವಾಗಿ ಎಷ್ಟು ಸಮಯ ಈ ಮಗುವಿಗೆ ಎದೆಹಾಲು ಕುಡಿಸುತ್ತಿರೀ? ☐ 1. 5-10 min ☐ 2. 10-20 min ☐ 3. >20 min

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D6	For this child at what age did you stop breastfeeding altogether? Age : _____ months ನಿಮ್ಮ ಈ ಮಗುವಿಗೆ ಯಾವ ವಯಸ್ಸಿಗೆ ಎದೆ ಹಾಲು ಕುಡಿಸುವುದನ್ನು ನಿಲ್ಲಿಸಿದ್ದೀರಾ? ವಯಸ್ಸು_____ತಿಂಗಳುಗಳಲ್ಲಿ.	D7	At what age did you first give other foods for this child? Age : _____ months ನಿಮ್ಮ ಈ ಮಗುವಿಗೆ ಯಾವ ವಯಸ್ಸಿನಲ್ಲಿ ಪೂರಕ ಆಹಾರವನ್ನು ಕೊಡಲು ಪ್ರಾರಂಭಿಸಿದ್ದೀರಿ? ವಯಸ್ಸು_____ತಿಂಗಳುಗಳಲ್ಲಿ. ☐ Not yet started (ಇನ್ನೂ ಪ್ರಾರಂಭಿಸಿಲ್ಲ)
D8	Has the child ever tested for anemia(weakness) before? ☐1.Yes ☐ 2. No ☐3. Unsure ನಿಮ್ಮ ಮಗುವಿಗೆ ಇಲ್ಲಿಯವರೆಗೆ ಯಾವುದಾದರೀತಿಯ ರಕ್ತಹೀನತೆಯ (ಸುಸ್ತು, ಆಯಾಸ) ಪರೀಕ್ಷೆಯನ್ನು ಮಾಡಿಸಿದ್ದೀರಾ? 1. ಹೌದು 2. ಇಲ್ಲ 3. ನೆನಪಿಲ್ಲ	D9	Has the child ever received iron/ folic acid tablets or syrup? (*Interviewer prompt* : visual cue) ☐1. Yes ☐ 2. No ☐ 3. Unsure *(If 'Unsure/No', goto D13)* ನಿಮ್ಮ ಮಗುವಿಗೆ ಕಬ್ಬಿಣಾಂಶದ ಮಾತ್ರೆ/ಸಿರಪ್‌ನ್ನು ನೀಡಿದ್ದೀರಾ? 1. ಹೌದು 2. ಇಲ್ಲ 3. ನೆನಪಿಲ್ಲ *(ಇಲ್ಲ/ ಗೊತ್ತಿಲ್ಲ ಎಂದರೆ D13ಕ್ಕೆ ಹೋಗಿ)*
D10	If yes, from whom? ಹೌದಾದರೆ ಯಾರಿಂದ ಮಾತ್ರೆಗಳನ್ನು ತೆಗೆದುಕೊಂಡಿದ್ದೀರಿ? ☐ 1. Auxiliary nurse midwife (ಆರೋಗ್ಯ ಕಾರ್ಯಕರ್ತೆ) ☐ 2. Anganwadi worker (ಆಂಗನವಾಡಿ ಕಾರ್ಯಕರ್ತೆ) ☐ 3. Health worker at sub centre (ಪ್ರಾಥಮಿಕ ಆರೋಗ್ಯ ಕೇಂದ್ರದ ಆರೋಗ್ಯ ಕಾರ್ಯಕರ್ತೆ) ☐ 4. PHC (ಪ್ರಾಥಮಿಕ ಆರೋಗ್ಯ ಕೇಂದ್ರ) ☐ 5. From private shop, non-health worker initiated (ಖಾಸಗಿ ಔಷಧಾಲಯ, ಬೇರೆಯವರ ಬಳಿ ತೆಗೆದುಕೋಡಿರುವುದು) ☐ 6. Private doctor (ಖಾಸಗಿ ವೈದ್ಯರು) ☐ 7. Can't remember / Don't know (ನೆನಪಿಲ್ಲ / ಗೊತ್ತಿಲ್ಲ)		
D11	How many tablets were given in last one year? ಮಾತ್ರೆಗಳನ್ನು ನೀಡಿದ್ದರೆ ಕಳೆದ ಒಂದು ವರ್ಷದಲ್ಲಿ ಎಷ್ಟು ಮಾತ್ರೆಗಳನ್ನು ನೀಡಿದ್ದೀರಾ? ☐ 1. < 30 (<3 strips) ☐ 2. 30-60 (3-6 strips) ☐ 3. 60-90 (6-9 strips) ☐ 4. > 90 (>=9 strips) ☐ 5. No. of bottles:_____ ☐ 6. None (ಯಾವೂದು ಇಲ್ಲ) ☐ 7. Don't know (ಗೊತ್ತಿಲ್ಲ)	D12	How many tablets did your child actually take? ನೀವು ಮಾತ್ರೆಗನ್ನು ನೀಡಿದ್ದರೆ ನಿಮ್ಮ ಮಗು ಎಷ್ಟು ಮಾತ್ರೆಗಳನ್ನು ನುಂಗಿದೆ. ☐ 1. < 30 (<3 strips) ☐ 2. 30-60 (3-6 strips) ☐ 3. 60-90 (6-9 strips) ☐ 4. > 90 (>=9 strips) ☐ 5. No. of bottles:_____ ☐ 6. None (ಯಾವೂದು ಇಲ್ಲ) ☐ 7. Don't know (ಗೊತ್ತಿಲ್ಲ)

D13	Has your child ever received Vitamin A liquid or capsules? (*Interviewer prompt* : visual cue) ☐ 1. Yes ☐ 2. No ☐ 3. Unsure *(If 'Unsure/No', goto D15)* ನಿಮ್ಮ ಮಗುವಿಗೆ ಯಾವಾಗಲಾದರೂ ವಿಟಮಿನ್ – ಎ (ಇರುಳುಗುಡುತನ)ಮಾತ್ರೆ/ಸಿರಪ್ ಅನ್ನು ನೀಡಿದ್ದೀರಾ? 1. ಹೌದು 2. ಇಲ್ಲ 3. ನೆನಪಿಲ್ಲ *(ಇಲ್ಲ, ಗೊತ್ತಿಲ್ಲ ಎಂದರೆ D15 ಹೋಗಿ)*	D14	If yes, how many times in the last year? ಹೌದಾದರೆ ಕಳೆದ ವರ್ಷದಲ್ಲಿ ಎಷ್ಟು ಬಾರಿ ನೀಡಿದ್ದೀರಿ? ☐ Don't know (ಗೊತ್ತಿಲ್ಲ)
D15	Has your child ever received Albendazole tablets? (*Interviewer prompt* : visual cue) ☐ 1. Yes ☐ 2. No ☐ 3. Unsure *(If 'No/Unsure', goto D17)* ನಿಮ್ಮ ಮಗುವಿಗೆ ಯಾವಾಗಲಾದರೂ ಜಂತುಹುಳು ನಿವಾರಕ ಮಾತ್ರೆಗಳನ್ನು ನೀಡಿದ್ದೀರಾ? 1. ಹೌದು 2. ಇಲ್ಲ 3. ನೆನಪಿಲ್ಲ *(ಇಲ್ಲ/ಗೊತ್ತಿಲ್ಲ ಎಂದರೆ D17ಗೆ ಹೋಗಿ)*	D16	If yes, how many times in the last year? ಹೌದಾದರೆ ಕಳೆದ ವರ್ಷದಲ್ಲಿ ಎಷ್ಟು ಬಾರಿ ನೀಡಿದ್ದೀರಿ? ☐ Don't know (ಗೊತ್ತಿಲ್ಲ)

Immunization History (ಚುಚ್ಚುಮದ್ದಿನ ಮಾಹಿತಿ) 1. Card 2. PHC/Anganwadi register				
D17	Which vaccinations has your child received (tick those which have been received): ಯಾವ ಯಾವ ಚುಚ್ಚುಮದ್ದುಗಳನ್ನು ನಿಮ್ಮ ಮಗುವಿಗೆ ಕೊಡಿಸಿದ್ದೀರಾ? (ಕೊಟ್ಟಿರುವ ಚುಚ್ಚುಮದ್ದುಗಳ ಬಾಕ್ಸನಲ್ಲಿ ಟಿಕ್ ಮಾಡಿ).			
	0 (birth)	BCG ☐	Hepatitis B – 0 ☐	OPV – 0 ☐
	6 weeks(1.5 mo)	DPT – 1 ☐	Hepatitis B – 1 ☐	OPV – 1 ☐
	10 weeks (2.5 mo)	DPT – 2 ☐	Hepatitis B – 2 ☐	OPV – 2 ☐
	14 weeks (3.5 mo)	DPT – 3 ☐	Hepatitis B – 3 ☐	OPV – 3 ☐
	9 months	Measles ☐	Vit A 1st Dose ☐	
	18 months	DPT Booster 1 ☐	OPV Booster 1 ☐	
	Vit A 2nd- 9th Dose (upto 5 years)	☐ 1 1/2y ☐ 2y ☐ 2 1/2y ☐ 3y ☐ 3 1/2y ☐ 4y ☐ 4 1/2y ☐ 5y		
	4-5 years	DPT Booster 2 ☐	OPV Booster 2 ☐	Others, Specify:
	Other vaccinations:	Hib ☐	Specify age/s at vaccination:	
	Other vaccinations:	Jap E ☐	Specify age/s at vaccination:	
	Other vaccinations:	_____	Specify age/s at vaccination:	

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E. 24 hour dietary recall (child): ೨೪ ಗಂಟೆಗಳಲ್ಲಿ ಸೇವಿಸಿದ ಆಹಾರದ ಮಾಹಿತಿ

E1. Was yesterday a typical day in terms of what your child had to eat? ☐ 1.Yes ☐ 2. No
If 'Yes': recall yesterday's.
ನೆನ್ನೆ ನಿಮ್ಮ ಮಗು ಸಾಮನ್ಯತರಹದ ಆಹಾರವನ್ನು ತಿಂದ್ದಿತ್ತಾ?
1. ಹೌದು 2. ಇಲ್ಲ
ಹೌದಾದರೆ: ಹಿಂದಿನ ದಿನ ನೆನಪಿಸಿಕೊಳ್ಳೀ

If 'No': recall most recent typical day (write how many days ago: _____)
ಇಲ್ಲಾವಾದಲ್ಲಿ ಸಾಮನ್ಯತರಹದ ಆಹಾರವನ್ನು ಎಷ್ಟು ದಿನಗಳ ಹಿಂದೆ ತಿಂದ್ದಿತ್ತು?

E2. Date of recall: ____/____/_____ (dd/mm/yyyy)
ನೆನೆಪು ಮಾಡಿಕೊಂಡ ದಿನಾಂಕ:

Time period of recall: From _____AM to _____AM Oil used: _____
(ಸಮಯ) (ಎಲ್ಲಿಂದ) (ಎಲ್ಲಿವರೆಗೆ) (ಉಪಯೋಗಿಸಿದ ಎಣ್ಣೆ)

Are you vegetarian/non-vegetarian? ☐ 1.Veg ☐ 2. Non-veg ☐ 3. Veg + Egg

ನೀವು ಸಸ್ಯಹಾರಿಗಳೆ ಆಥವಾ ಮಾಂಸಹಾರಿಗಳೆ? 1. ಸಸ್ಯಹಾರಿ 2. ಮಾಂಸಹಾರಿ 3. ಸಸ್ಯ ಮತ್ತು ಮಾಂಸಹಾರಿ.

Period of consumption ಆಹಾರ ತಿಂದ ಸಮಯ	Food consumed ಸೇವಿಸಿದ ಆಹಾರ	Amount (gms/ml) ಪ್ರಮಾಣ (ಗ್ರಾಂ/ಮಿಲಿ)
Early morning (before breakfast)/ ಮುಂಜಾನೆ/ತಿಂಡಿಗೆ ಮುಂಚೆ		
Breakfast/ತಿಂಡಿ		
Mid-morning / ತಿಂಡಿಯ ನಂತರ		

Period of consumption ಆಹಾರ ತಿಂದ ಸಮಯ	Food consumed ಸೇವಿಸಿದ ಆಹಾರ	Amount (gms/ml) ಪ್ರಮಾಣ (ಗ್ರಾಂ/ಮಿಲಿ)
Lunch/ ಊಟ		
Evening/ಸಾಯಂಕಾಲ		
Dinner/ *ಊಟ*		
Bed time food / ರಾತ್ರಿಯ *ಸಮಯದಲ್ಲಿ* ಏನಾದರು ಆಹಾರವನ್ನು ತಿಂದ್ದಿತ್ತಾ?		
Any other food items during the day/ ದಿನದಲ್ಲಿ ಬೇರೆ ಏನಾದರು ಆಹಾರವನ್ನು ತಿಂದ್ದಿತ್ತಾ?		

F. Standard of Living Index Questionnaire/ *ಜೀವನಮಟ್ಟ ಸೂಚ್ಯಂಕಕ್ಕೆ ಸಂಬಂಧಿಸಿದ ಪ್ರಶ್ನೆಗಳು:*

G. Hygiene and Sanitation / ಸ್ವಚ್ಚತೆ :

	Question	Choose the appropriate answer
F1	Type of house *ಯಾವ ರೀತಿಯ ಮನೆ*	☐ 1. Pucca / ಪಕ್ಕಮನೆ, ಮೊಲ್ಡ್ ಮನೆ ☐ 2. Semi-pucca / ಹೆಂಚಿನ ಮನೆ ☐ 3. Katcha / ಗುಡಿಸಲು
F2	Does this household own this house or any other house? ಎಲ್ಲದರೂ *ಸ್ವಂತ* ಮನೆ ಇದೆಯೇ *?*	☐ 1. Yes / ಹೌದು ☐ 2. No / ಇಲ್ಲ

(1) **Pucca:** One which is built with a foundation, using stone or bricks with and cement, having concrete or a stone laid roof

(2) **Semi-pucca:** One house in which some cement or mortar plastering or flooring or roofing is used.

(3) **Kutcha:** A construction with more than one room and using mud walls and a thatched roof.

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	Question	Choose the appropriate answer
F3	Do you have a separate room for kitchen?/ ನಿಮ್ಮ ಮನೆಯಲ್ಲಿ ಅಡುಗೆ ಕೋಣೆ ಬೇರೆಯಾಗಿ ಇದೆಯೇ?	☐ 1. Yes/ ಹೌದು ☐ 2. No/ ಇಲ್ಲ
F4	What type of fuel does your household mainly use for cooking? ನಿಮ್ಮ ಮನೆಯಲ್ಲಿಅಡುಗೆ ಮಾಡಲು ಯಾವ ಇಂಧನವನ್ನು ಬಳಸುತ್ತೀರಾ?	☐ 1. Wood/ಕಟ್ಟಿಗೆ ☐ 2. Crop residues/ಬೆಳೆಯಿಂದಬಂದ ಕಡ್ಡಿಗಳು ☐ 3. Dung cakes/ಬಿರಣಿ ☐ 4. Coal/ coke/ lignite/ ಕಲ್ಲಿದ್ದಲು, ಕೋಕ್, ಲಿಗ್ನೇಟ್ ☐ 5. Charcoal/ ಕಲ್ಲಿದ್ದಲು ☐ 6. Kerosene/ಸೀಮೆಎಣ್ಣೆ ☐ 7. Electricity/ವಿದ್ಯುತ್ ☐ 8. LPG/ ಗ್ಯಾಸ್ ☐ 9. Bio-gas/ ಜೈವಿಕ ಇಂಧನ

G1. Do you wash your hands before preparing a meal? ನೀವು ಅಡುಗೆ ಮಾಡುವ ಮುಂಚೆ ನಿಮ್ಮ ಕೈಗಳನ್ನು ತೊಳೆಯುತ್ತೀರಾ ☐ 1. Yes/ ಹೌದು ☐ 2. No/ ಇಲ
G2. Does your child wash hands before eating? ನಿಮ್ಮ ಮಗು ಊಟ ತಿನ್ನುವ ಮೊದಲು ಕೈ ತೊಳೆಯುತ್ತದ? ☐ 1. Yes/ ಹೌದು ☐ 2. No/ ಇಲ

	Question	Choose the appropriate answer
F5	How much agriculture land does this household own? *ನಿಮಗೆ ಕೃಷಿ ಜಮೀನು ಎಷ್ಟಿದೆ?*	☐ 1. 5acres or more/*೫ ಎಕರೆಗಿಂತ ಹೆಚ್ಚು* ☐ 2. 2 to 4.9 acres/ *೨ರಿಂದ ೫ ಎಕರೆ* ☐ 3. < 2 acres /unknown acreage (*2 ಎಕರೆಗಿಂತಕಡಿಮೆ / ಗೊತ್ತಿಲ್ಲ*) ☐ 4. No land/ *ಜಮೀನು ಇಲ್ಲ (If 'No land' goto F7)*
F6	Out of this land, how much is irrigated?/ *ಇಷ್ಟು ಜಮೀನಿನಲ್ಲಿ ಎಷ್ಟು ನೀರಾವರಿ ಜಮೀನು ಇದೆ*	☐ 1. All / Some ಎಲ್ಲಾ/*ಸ್ವಲ್ಪ* ☐ 2. None/Don't know *ಯಾವುದು ಇಲ್ಲ*/ ಗೊತ್ತಿಲ್ಲ
F7	Does this household own any livestock? ನಿಮ್ಮ ಮನೆಯಲ್ಲಿ ಯವುದಾದರು ಜಾನುವಾರುಗಳು ಇದೆಯೇ?	☐ 1. Yes/ ಹೌದು ☐ 2. No/ ಇಲ್ಲ

	Question	Choose the appropriate answer
F8	What is the main source of lighting for your household? ನಿಮ್ಮ ಮನೆಯಲ್ಲಿ ಬೆಳಕಿಗಾಗಿ ಯಾವುದನ್ನು ಉಪಯೋಗಿಸುತ್ತೀರಾ?	☐ 1. Electricity/ವಿದ್ಯುತ್ ☐ 2. Kerosene /ಸೀಮೆಎಣ್ಣೆ ☐ 3. Gas/ಗ್ಯಾಸ್ ☐ **4.** Candle/oil ಮುಂಬತ್ತಿ /ಎಣ್ಣೆ

	Question	Choose the appropriate answer
F9	What is the main source of drinking water for members of your household?/ ನಿಮ್ಮ ಮನೆಯಲ್ಲಿರುವವರಿಗೆ ಕುಡಿಯುವ ನೀರಿಗಾಗಿ ಯಾವ ವ್ಯವಸ್ಥೆ ಇದೆ?	• Piped water (ನಲ್ಲಿಯ ಮುಖಾಂತರ) ☐ 1. Residence/ yard/ Plot (ಮನೆ, ಹೊರಗೆ, ಮನೆಯ ಅಗತ್ಯವಿರುವ ಕಡೆ) ☐ 2. Public tank (ಸಾರ್ವಜನಿಕ ನಲ್ಲಿ) • Ground water/ ಅಂತರ್ಜಲ ☐ 3. Hand pump at residence/yard/plot (ಹ್ಯಾಂಡ್ ಪಂಪ್) ☐ 4. Public hand pump (ಸಾರ್ವಜನಿಕ ಹ್ಯಾಂಡ್ ಪಂಪ್) • Well water (ಬಾವಿ ನೀರು) ☐ 5. Residence, yard, plot (ಮನೆಯ ಒಳಗೆ) ☐ 6. Covered well (ಮುಚ್ಚಿದ ಬಾವಿ) ☐ 7. Open well (ತೆರೆದ ಬಾವಿ) ☐ 8. Public well (ಸಾರ್ವಜನಿಕ ಬಾವಿ) • Surface water ☐ 9. Spring (ಜಿಗಿ/ಚಿಮ್ಮು) ☐ 10. River/Stream (ಹರಿಯುವ ನೀರು) ☐ 11. Pond/Lake (ಕೆರೆ) ☐ 12. Dam (ಸಂಗ್ರಹವಾಗಿರುವ ಕೆರೆ) • ☐ 13. Rain water (ಮಳೆಯ ನೀರು) • ☐ 14. Tanker truck (ಹೊರಗಡೆಯಿಂದ ನೀರು ತರಿಸುವುದು)
F10	What kind of toilet facility does your household have? ನಿಮ್ಮ ಮನೆಯಲ್ಲಿ ಯಾವ ರೀತಿಯ ಶೌಚಾಲಯ ವ್ಯವಸ್ಥೆ ಯಿದೆ?	• Flush toilet/ Latrine (ಫ್ಲಶ್/ನೀರಿನ ವ್ಯವಸ್ಥೆ ಇರುವ ಶೌಚಾಲಯ) ☐ 1. Own flush toilet (ಸ್ವಂತ) ☐ 2. Shared flush toilet (ಹಂಚಿಕೆಯ) ☐ 3. Public flush toilet (ಸಾರ್ವಜನಿಕ) • Pit toilet/ Latrine (ಇಂಗು ಗುಂಡಿ) ☐ 4. Own pit toilet (ಸ್ವಂತ) ☐ 5. Shared toilet (ಹಂಚಿಕೆಯ) ☐ 6. Public toilet (ಸಾರ್ವಜನಿಕ) • ☐ 7. No facility available *(Goto to G6)* (ಶೌಚಾಲಯ ಇಲ್ಲ)

PID | | | | |

G3	Does this child use the toilet routinely? ನಿಮ್ಮ ಮಕ್ಕಳು ನಿರಂತರವಾಗಿ ಶೌಚಾಲಯ ಬಳಕೆ ಮಾಡುತ್ತಾರೆಯೆ? ☐ 1.Yes ☐ 2. No 1. ಹೌದು 2. ಇಲ್ಲ	G4	Does your child wear footwear when going out? ನಿಮ್ಮ ಮಗು ಹೊರಗೆ ಹೋಗುವಾಗ ಚಪ್ಪಲಿಗಳನ್ನು ಧರಿಸುತ್ತದೇಯೇ? ☐ 1.Yes ☐ 2. No 1. ಹೌದು 2. ಇಲ್ಲ

F11	Does the household own any one of the following: ನಿಮ್ಮ ಮನೆಯಲ್ಲಿ ಈ ಕೆಳಕಂಡ ವಸ್ತುಗಳು ಇವೆಯೇ?	Yes / No ಹೌದು/ ಇಲ್ಲ (Circle if owned)
1.	A Bed / ಹಾಸಿಗೆ	Yes / No
2.	A Pressure cooker / ಕುಕ್ಕರ್	Yes / No
3.	A Chair / ಕುರ್ಚಿ	Yes / No
4.	A Cot / ಮಂಚ	Yes / No
5.	A Table /ಬೆಂಚು	Yes / No
6.	A Clock / ಗೋಡೆ ಗಡಿಯಾರ	Yes / No
7.	A Wrist watch / ಕೈಗಡಿಯಾರ	Yes / No
8.	A Cycle / ಬೈಸಿಕಲ್	Yes / No
9.	A Radio/transistor / ರೇಡಿಯೋ	Yes / No
10.	A Tailoring machine / ಹೊಲಿಗೆ ಯಂತ್ರ	Yes / No
11.	A landline/mobile phone / ದೂರವಾಣಿ	Yes / No
12.	A Fridge / ರೆಫ್ರಿಜರೇಟರ್	Yes / No
13.	A Black & white TV / ಕಪ್ಪು ಬಿಳುಪು ಟಿ.ವಿ	Yes / No
14.	A Colour TV / ಬಣ್ಣದ ಟಿ.ವಿ	Yes / No
15.	A Two wheeler / ಸ್ಕೂಟರ್, ಮೋಟಾರ್	Yes / No
16.	A Car / ಕಾರ್	Yes / No
17.	A Water pump/ ನೀರಿನ ಬಾವಿ	Yes / No
18.	A Bullock cart / ಎತ್ತಿನ ಗಾಡಿ	Yes / No
19.	A Tractor / ಟ್ರ್ಯಾಕ್ಟರ್	Yes / No

H. Anthropometric details:

Child	Birth Weight (kg) :	
	Weight (kg):	
	Height/Length (cm):	
	Mid upper arm circumference (cm):	
	Head circumference (cm):	

I. Laboratory investigations: sample collection checklists

I1. Child:

Sl.no.	Sample	Sample collected		Sample volume
1.	Blood : 2 ml EDTA vacutainer (purple top)	☐ 1.Yes	☐ 2. No	ml
2.	Blood :1 ml Serum vacutainer (yellow top)	☐ 1.Yes	☐ 2. No	ml
3.	Urine:10 ml urine in sterile urine container	☐ 1.Yes	☐ 2. No	ml

I2. Mother:

Sl.no.	Sample	Sample collected		Sample volume
1.	Blood : 2 ml EDTA vacutainer (purple top)	☐ 1.Yes	☐ 2. No	ml
2.	Blood :1 ml Serum vacutainer (yellow top)	☐ 1.Yes	☐ 2. No	ml
3.	Urine: 10 ml urine in sterile urine container	☐ 1.Yes	☐ 2. No	ml

APPENDIX 4B KAP2

BASELINE INVESTIGATION REPORT

(Completed by research team at baseline and given to mothers)

							Date:			
Village ID ಹಳ್ಳಿಯ ಸಂಖ್ಯೆ			PID ಸಂಖ್ಯೆ					(dd)	(mm)	(yyyy) ದಿನಾಂಕ:

Village name: _____	Activity done	Interview/Labs		QC	Data Entry 1	Data Entry 2
	Personnel Initials					
	Date					

Name of the Child : _____

Age : _____ Weight (kg): _____ Height (cm):_____

Anganwadi Roll No.: _____

Name of the Mother: _____

CHILD (ಮಗು):

Haematology	Results	Haematology	Results
Hemoglobin (g/dl)		MCV (fl)	
Total RBC count($x10^6/\mu L$)		MCH (pg)	
Total WBC count ($x10^3/\mu L$)		MCHC (g/dl)	
Platelets ($x10^3/\mu L$)		RDW (%)	

Child referred to PHC for further care: 1. Yes 2. No

MOTHER (ತಾಯಿ):

Haematology	Results	Haematology	Results
Hemoglobin (g/dl)		MCV (fl)	
Total RBC count($x10^6/\mu L$)		MCH (pg)	
Total WBC count ($x10^3/\mu L$)		MCHC (g/dl)	
Platelets ($x10^3/\mu L$)		RDW (%)	

Mother referred to PHC for further care: 1. Yes 2. No

_____

Signature of the Project Co-ordinator

Dr.Vidya Chellaswamy

APPENDIX 4C *KAP2*

ADHERENCE FORM - ANEMIC

(Completed by LHW for anemic children in intervention arm in the end of every month)

						Date:			
Village ID ಹಳ್ಳಿಯ ಸಂಖ್ಯೆ			PID ಸಂಖ್ಯೆ				(dd) ದಿನಾಂಕ:	(mm)	(yyyy)

Village name: _____	Activity done	Interview	QC	Data Entry 1	Data Entry 2
	Personnel Initials				
	Date				

This questionnaire is filled up in the follow-up month: ☐

A. Is the child receiving IFA? ☐ 1. Yes ☐ 2. No (if 'No', go to C)

Details of IFA tablets dispensed for last month:

Number of IFA tablets dispensed	Date of dispensation	Dispensed to	Number of IFA tablets remaining with mother
		1. Mother 2. Others : _____	

B. If the child has missed IFA doses, what may be the reasons for doing so? (do not probe)

Q.No.	Questions	Tick the boxes
1.	Child had side effects /wanted to avoid side effects	☐
2.	Did not get the tablets from the LHW /ran out of pills	☐
3.	Did not know why IFA tablets were important	☐
4.	Forgot to give the child the tablets	☐
5.	Religious dietary restrictions/community beliefs	☐

Q.No.	Questions	Tick the boxes
6.	Went away from home for holidays	☐
7.	Suspected the quality of government supplied tablets	☐
8.	Child refused /difficult to get the child to take IFA tablets.	☐
9.	Tablets were lost/misplaced	☐
10.	Others, specify: _____	☐

C. Check list:

Sl.No.	Counselling topics	Tick if counselled
1.	Symptoms and signs of anemia	☐
2.	Treatment with IFA, its side effects, monitoring of compliance	☐
3.	Sources of local iron rich foods and dietary diversification	☐
4.	Personal hygiene and value of deworming	☐
5.	Repeat testing to see effect of treatment of anemia	☐

ADHERENCE FORM – NON ANEMIC & CONTROL

(*Completed by LHW for all non-anemic participant in intervention arm & all children in control arm at trial closure*)

Village ID ಹಳ್ಳಿಯ ಸಂಖ್ಯೆ | PID ಸಂಖ್ಯೆ | Date: (dd) (mm) (yyyy) ದಿನಾಂಕ:

Village name: _____	Activity done	Interview	QC	Data Entry 1	Data Entry 2
	Personnel Initials				
	Date				

A. Is the Child receiving IFA? ☐ 1. Yes ☐ 2. No (if 'Yes' fill the details below)

Details of IFA tablets dispensed during the previous month:

Number of IFA tablets dispensed	Date of dispensation	Dispensed to	Number of IFA tablets remaining with mother (Instruct the mothers to bring the remaining pills along with them)
< 8 per month ☐ >8 per month ☐		1. Mother 2. Others : _____	

B. If the child has missed IFA doses, what may be the reasons for doing so? (do not probe)

Q.No.	Questions	Tick the boxes
1.	Child had side effects /wanted to avoid side effects	☐
2.	Did not get the tablets from the LHW /ran out of pills	☐
3.	Did not know why IFA tablets were important	☐
4.	Forgot to give the child the tablets	☐
5.	Religious dietary restrictions/community beliefs	☐
6.	Went away from home for holidays	☐
7.	Suspected the quality of government supplied tablets	☐
8.	Child refused /difficult to get the child to take IFA tablets.	☐
9.	Tablets were lost/misplaced	☐
10.	Others, specify: _____	☐

APPENDIX 5

Characteristics of non-participants compared with recruited baseline participants enrolled in the KAP 2 study, Chamarajnagar district, Karnataka.

Baseline characteristics	Non-participants (Control) n=226	Participants (Control) n=536	Non-participants (Intervention) n=195	Participants (Intervention) n=608
Reason for not participating (%)				
Travelling/work	174 (76.9)		152 (77.9)	
Migrated	44 (19.5)		36 (18.5)	
Reported sick	5 (2.2)		5 (2.6)	
Other	3 (1.3)		2 (1.0)	
Child's age months, mean (SD)	32.0 (12.8)	34.8 (12.0)	33.1 (13.4)	35.3 (12.8)
Sex				
Female (%)	53	52	54	53
Male (%)	47	48	46	47
Maternal age, mean (SD)	26.0 (3.8)	25.0 (3.5)	26.0 (3.9)	24.7 (3.4)
Maternal education, mean (SD)	8.4 (3.5)	8.1 (3.9)	7.4 (4.1)	7.3 (3.9)

SD - standard deviation