REVIEW PAPER

Guidelines for iron supplementation for Prophylaxis of Anemia in a National Programme - A Review

Ankita Mondal[1], Tinku Thomas[2], Sumathi Swaminathan[2], Sanjukta Rao[2], Jithin Sam Varghese[2], Bharati Kulkarni[1], Harsh Pal Singh Sachdev[3], [4]Umesh Kapil, Anura V Kurpad[2]

[1]National Institute of Nutrition, Hyderabad, [2]St John's Medical College, Bangalore [3]Sitaram Bhartia Institute of Science and Research, New Delhi, [4]All India Institute of Medical Sciences, New Delhi

Corresponding Author

Address for Correspondence: Dr. Anura V Kurpad, Department of Physiology, St. John's Medical College, Bangalore - 560034
E Mail ID: a.kurpad@sjri.res.in

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Abstract

Recent National Family Health Survey-4 data shows that anaemia continues to be a major public health problem in India. In India much of the anaemia is due to iron deficiency, and women and children are at the greatest risk of anaemia. TheMinistry of Health and Family Welfare took a policy decision, in 2013, to develop the National Iron+ Initiative (NIPI) to address the prevailing iron deficiency anaemia. This initiative covered pregnant and lactating women, children and adolescents. However, the guidelines do not match the current World Health Organization (WHO) guidelines for prevention of iron deficiency anaemia in these population groups. The background evidence for the WHO and NIPI is thus reviewed to come to a common consensus on the optimum recommendation of iron supplementation for the population, while taking into consideration the feasibility of the program, without burdening the groups with iron over-dose. However, from the present review, there is a need for increased number of trials in India that could qualify for a high grade of evidence to support the guidelines of NIPI.

Document Overview:This document was prepared to review the guidelines for the National Iron Prophylaxis Initiative (NIPI) program, in the context of the current WHO guidelines, as well as evidence that may have emerged subsequently.

The review was prepared for 4 population groups in 3 sections:

1. Infants and children
2. Adolescents and non-pregnant women in the reproductive age group
3. Pregnant women

The section on adolescents and non-pregnant women were combined as the guidelines are common for these categories. Lactating mothers were not included in this review. The review also includes a section on treatment of iron deficiency anaemia.

The structure within each section is as the follows

- A background section that included the physiological basis for supplementation;
- A summary of evidence leading to the current WHO guidelines;
- The current Indian recommendations for iron prophylaxis in that specific group;
- Evidence published after the WHO recommendation;
- Conclusion.

This is not a systematic review.

The focus was on reviewing evidence for a comparison of efficacy of doses, daily vs intermittent regimes, and the duration of intervention. The grade of evidence was not considered for the studies identified after the WHO recommendation was published, and special consideration was given to Indian studies.

PICOT (Population, Intervention, Control group, Outcome, Time) guidelines were followed to conduct the review. Appendixes are given at the end of the document. These highlight the methods used in the Cochrane reviews that were summarized here.

SECTION 1: PREVENTION OF ANAEMIA IN INFANTS AND CHILDREN

Background

Children are particularly at risk of iron deficiency, due to rapid growth with expanding erythroid mass and increased tissue requirements (1). Antenatal and perinatal factors often expose infants to iron deficiency, for example, inadequate iron stores are associated with low birth weight and premature birth (2), poor quantity and quality of iron available from complementary foods (3), and also prolonged feeding of human milk (4). The causes of iron deficiency differ among older children since the growth velocity decreases by the third year of age, with decreased iron requirement. However, inadequate quantity and quality of diet and poor hygiene and sanitation, leading to frequent bouts of infections can be a major cause of iron deficiency among this age group, especially in the developing countries owing to the inadequate health facilities (5). Iron deficiency among children may also lead to several functional consequences beyond anaemia, like impaired motor and cognitive function and physical growth (6).

Although there is consensus on iron supplementation to address iron deficiency anaemia among children, there is discrepancy between the international guideline (WHO) and the Indian recommendations of iron supplementation for children. The present document is an attempt to understand the background behind these guidelines to arrive at a common consensus to move ahead with the strategies to tackle anaemia among infants and children.

The Table below gives haemoglobin levels to diagnose anaemia in children

WHO RECOMMENDED HAEMOGLOBIN LEVELS TO DIAGNOSE ANAEMIA IN CHILDREN AT SEA LEVEL (G/L) (7)

Population	Non-anaemic	Anaemic		
		Mild	Moderate	Severe
Children (6-59 m)	110 or higher	100-109	70-99	lower than 70
Children (5-11 y)	115 or higher	110-114	80-109	lower than 80
Children (12-14 y)	120 or higher	110-119	80-109	lower than 80

Prevalence of Anaemia among Infants and Children

According to WHO 2011 Report, it is estimated that 43% of children, globally, have anaemia, that corresponds to 273 million children (WHO, 2011) (8). The prevalence of anaemia among children aged 6-59 months for the South East Asia Region is 53.8% and that of severe anaemia is 1.5%. Within this population group and region, the estimated percentage of anaemia amenable to iron supplementation is 41%, which is indicative of the refractoriness and depth of the problem. The Table below gives anaemia prevalence in different countries

REVALENCE OF ANAEMIA AMONG CHILDREN (6–59 MONTHS) (WHO) (8)

Country	Proportion of Anaemic Children aged 6–59 months (<110g/L)	
	2005 % (95% CI)	2011 % (95% CI)
Bangladesh	47 (43–51)	56 (40-70)
Bhutan	80 (67–89)	55 (24-78)
India	74 (73–75)	59 (40-72)
Nepal	78 (76–80)	51 (34-68)
Sri Lanka	29 (27–33)	36 (19-56)

As per the recent national health survey of India - National Family Health Survey-4 (NFHS-4) (9), the prevalence of anaemia (<11.0 g/dl) in children aged 6-59 months is 55.9% in urban and 59.4% in rural with an overall rate of 58.5%. On comparison with the NFHS-3 Report (10) (2005-2006), though the prevalence rate has decreased from 69.4% to 59.4%, anaemia continues to be a significant problem in India

Iron Prophylaxis

2.1 Infants and young children (6-60 months)

India follows one strategy to treat and prevent anaemia among both infants (6-23 months) and young children (24-59 months). According to the recommendation, a bi-weekly dose of 20 mg elemental iron is administered for 6-60 months old children along with 100 µg folic acid and bi-annual deworming throughout the period (11).

On the other hand, the current WHO guideline (2016) has separate recommendations for 6-23 months children and 24-59 months children with varying dosage. For children 6-23 months, in a

setting where the prevalence of anaemia among infants and children is 40% or higher, WHO recommends a daily administration of 10-12.5 mg elemental iron for three consecutive months (12).

According to WHO (2013), "iron supplementation has been traditionally given on a daily basis" (13). The WHO 2001 guideline on iron supplementation for infants had recommended a daily iron supplementation of 2 mg /kg body weight/ day iron supplement in settings with more than 40% anaemia prevalence (14). However, as stated in Lancet, Global Health 2013 (14), "these recommendations are not based on a systematic review of this specific intervention" and "intermittent doses once, twice or three times per week on nonconsecutive days may be an alternative to daily supplementation to improve iron stores and prevent anaemia" (13). However, according to Cochrane systematic review (15) that assessed the benefits and safety of intermittent iron supplementation with iron, or iron combined with other micronutrients for children up to the age of 12 years, children receiving intermittent iron supplementation were more likely to be anaemic at the end of their supplementation regimen than those supplemented daily. But adherence rates tended to be higher among children receiving intermittent compared to daily supplementation. The WHO (2011) (16) guidelines suggests an intermittent iron supplementation for preschool (24–59 months) or school-age (5–12 years) children for settings where anaemia rate is 20% or higher.

Problem Statement #1: Should India follow an intermittent iron supplementation strategy when the current WHO guideline suggests a daily iron supplementation for settings with prevalence of anaemia more than 40%?

Apart from the frequency of iron supplementation, the iron dosage provided by WHO and the Indian government is quite different. India is giving a much higher dose, annually, to the infants, compared to WHO. Recommended doses including those from India, are provided in the Table below for children 6-60 m

RECOMMENDED DOSES FOR IRON SUPPLEMENTATION

	WHO (2016)	NIPI (2013)
Dose	10-12.5 mg	20 mg
Frequency	Daily	Bi-weekly
Duration	3 consecutive months in a year	Throughout the year
Elemental iron provided in a year	900-1125 mg	2080 mg

Problem Statement #2: Is the dose to infants much higher than what is required? Should the efficacy of the iron dosage provided to the infants in India be evaluated?

2.1.1 Summary of Evidence leading to current WHO recommendation for Children aged 4–23 months (14)

A total of 35 randomized controlled trials including 42015 children, with 21175 randomised to iron supplementation and 21089 to control were included in the meta-analysis to review the evidence for benefit and safety of daily iron supplementation in children aged 4–23 months. The dosage ranged from 10 to 66 mg elemental iron per day and 1 mg/kg to 5 mg/kg elemental iron and the duration of administration ranged from 10 days to 11 months. Most studies were done in low-income or middle-income settings and included two Indian studies (Majumder 2003, Nagpal 2004). Participants of included studies were at high risk of anaemia (ie, 44% prevalence of anaemia at endpoint in the control group of the meta-analysis), iron deficiency (32% prevalence at endpoint in control group), and IDA (20% prevalence in control group).

The meta-analysis suggested that iron supplementation increased haemoglobin (7.22g/L [4.87, 9.57], P<0.001, 26 studies) and ferritin (21.42 [17.25, 25.58], P<0.001), and reduced the risk of anaemia (Risk ratio (RR) 0.61 [0.50, 0.74], P<0.001); iron deficiency (RR:0.30 [0.15, 0.60], P<0.001), and iron deficiency anaemia(IDA) (RR:0.14 [0.10, 0.22], P<0.001) in children receiving daily iron supplementation compared to control.

Iron supplementation was more beneficial in iron deficient children. Longer duration (>3 months vs <1 month) of supplementation seemed to have a greater effect on ferritin and transferrin saturation but not on haematological indices. No significant change in psychomotor development was observed. Daily iron supplementation was found to impair length gain and weight gain. When growth was

reported as change from baseline, children who received iron supplementation had significantly reduced length gain and weight gain compared with control. Subgroup analysis showed that children receiving more than 3 months of iron supplementation had reduced weight gain (Mean difference, MD –2·39, 95% CI –4·37 to –0·41; p=0·02).

One potential cause could be the gastrointestinal symptoms (including vomiting as noted in the meta-analysis), impairing appetite and oral intake which is often associated with iron supplementation.

The meta-analysis confirmed the benefit of daily iron supplementation, but it also concluded that further trials are still needed to define the benefits and safety of iron supplementation in children of this age group.

2.2 Pre-school children and school-aged children (24-59 months and 5-12 years)

The Indian recommendation of iron supplementation for pre-school children (24-59 months) overlaps with that of infants, with a bi-weekly dose of 20 mg elemental iron along with 100 µg folic acid and bi-annual deworming throughout the period.

The current WHO (2016) recommendation for 24-59 months old children provides a daily iron supplement of 30 mg elemental iron for 3 consecutive months in a year for a setting with anaemia prevalence of more than 40%.

The WHO (2011) guideline had previously suggested a weekly dosage of 25 mg of elemental iron to be administered for 3 consecutive months in a year or if feasible, throughout the year. However, this recommendation is for a setting with 20% or higher prevalence of anaemia. Nevertheless, weekly iron supplementation may be an alternative to daily supplementation especially since compliance is a major concern for the supplementation program and may act as a possible alternative in the Indian context.

Focusing on the dosage, an understanding of the Cochrane review that formed the basis of the WHO intermittent iron supplementation guideline can be helpful.

For children aged 5 to 10 years, the Indian recommendation suggests a weekly dose of 45 mg elemental iron, along with 400 µg folic acid and bi-annual de-worming whereas WHO(2016) suggests a daily dose of 30-60 mg elemental iron for 3 consecutive months in a year (5-12 years).

The Table below summarizes the WHO and NIPI recommendations

COMPARATIVE SUMMARY OF RECOMMENDATIONS BY WHO AND NIPI

	WHO (2011)		WHO (2013)		WHO (2016)		NIPI, GOI (2013)	
Target Group	Preschool-age children (24–59 m)	School-age children (5-12 y)	Infants and young children (6-23 m)	Infants and young children (6-23 m)	Preschool-age children (24–59 m)	School-age children (5–12 y)	6–60 months	5–10 years
Supplement Composition	25 mg of elemental iron	45 mg of elemental iron	Iron 2 mg/kg body weight/ day	Elemental Iron 10–12.5 mg	Elemental Iron 30 mg	Elemental Iron 30–60 mg	Elemental Iron: 20 mg Folic Acid: 100 µg De-worming for Children 12 months and above	Elemental Iron: 45 mg Folic Acid: 400 µg Biannual de-worming
Supplement Form	Drops/syrups	Tablets/capsule		Drops/Syrups	Drops/syrups/tablet	Tablets or capsules	Syrup	Tablets
Frequency	1 supplement per week		Daily	Daily	Daily	Daily	Biweekly	Weekly
Duration	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart. If feasible, intermittent supplements could be given throughout the school or calendar year		From 6 to 23 months of age, for 3 months duration	Three consecutive months in a year	Three consecutive months in a year	Three consecutive months in a year	throughout the period 6–60 months of age	throughout the period 5–10 years of age
Setting	Where the prevalence of anaemia in preschool or school age children is 20% or higher		Where the diet does not include foods fortified with iron Or, where anaemia	Where prevalence of anaemia in infants and children is 40% or higher		Where the prevalence of anaemia in infants and young children is 40% or higher	India	India

			prevalence is above 40%					
Total supplemental iron intake/year	Total no. of months of administration: 6 months Total no. of times:26 650 mg elemental iron per year	Total no. of months of administration: 6 months Total no. of times:26 1170 mg elemental iron If feasible, 2340 mg elemental iron	Considering an average body weight 7 kg (NNMB 2011-12), Total no. of days: 90 1260 mg elemental iron	Total no. of days administered in a year: 90 900-1125 mg elemental iron	Total no. of days administered in a year: 90 2700 mg elemental iron	Total no. of days administered in a year: 90 2700 – 5400 mg elemental iron	Total no. of days administered in a year: 104 2080 mg elemental iron	Total no. of days administered in a year: 52 2340 mg elemental iron

However, the Indian recommendation is according to WHO 2011 guideline (15), for 5 to 12-year-old children in settings where rate of anaemia is 20% or higher

2.2.1 Summary of evidence for intermittent iron supplementation (NIPI) in pre-school and school children

(taken from WHO, 2011)

The Cochrane Systematic review (16) assessed the effects of intermittent iron supplementation, alone or in combination with other vitamins and minerals, on nutritional and developmental outcomes in children from birth to 12 years of age compared to placebo, no intervention or daily supplementation. The review was conducted at the backdrop that although daily iron supplements is a widely used strategy for improving iron status in children, its effectiveness has been limited due to its side-effects that include nausea, constipation or staining of the teeth. Thus, the review was an attempt to assess the effectiveness of intermittent iron supplementation (one, two, three times a week on non-consecutive days).

The review included 33 trials, involving 13,114 children from 20 countries in Latin America, Africa and Asia. Two Indian studies were included in the meta-analysis that has been quoted separately. The age of the participants ranged from new-born to 19 years. The total weekly iron dose ranged from 7.5 mg to 200 mg per week. For studies that reported the provision of 1 mg to 8 mg of elemental iron per kg per day, weekly dose was calculated by using the median or average age reported in the trial and the corresponding weight according to the WHO growth charts, percentile 50. In almost all the studies, ferrous sulphate was the source of supplemental iron. Other forms tested were ferrous polymaltose, ferrous dextran and ferrous fumarate. Most of the studies included in the meta-analysis supplemented only with iron while five studies, including the two Indian studies gave iron in combination with folic acid. Out of the 40 trials that were excluded in the meta-analysis, 8 were Indian studies, and these were excluded as they were out of scope of the review (5 studies), no daily regimen was available (1 study), and were not randomized (2 studies).

2.2.2 Comparison of intermittent iron supplementation versus daily iron supplementation (21 trials)

Primary Outcomes studied:

a) Anaemia (6 trials; 980 participants)

Children receiving intermittent iron supplementation had a higher risk of being anaemic at the end of the study period compared to those receiving daily iron supplementation (RR 1.23, 95% CI 1.04 to 1.47)

b) Haemoglobin concentrations (g/L) (19 trials; 2851 participants)

There was no significant difference in haemoglobin between the daily and intermittent doses. There were high levels of heterogeneity for this outcome ($T^2 = 2.26$, $I^2 = 56\%$, and Chi^2 test for heterogeneity P = 0.001). The difference between groups were not statistically significant when only those trials at lower risk of bias were retained in the analysis, (MD -0.87, 95% CI -2.77 to 1.02).

c) Iron deficiency

Only one trial reported on iron deficiency and found that at the end of the intervention the number of children with iron deficiency was higher among those who received iron supplements intermittently compared to daily (RR: 4.00, 95% CI: 1.23 to 13.05).

d) Iron status measured by ferritin (ng/L) (10 studies, 902 participants)

Ferritin values were not statistically different between those receiving iron intermittently and those receiving daily iron (MD -4.19, 95% CI -9.42 to 1.05).

e) All-cause morbidity (2 trials, 601 children)

There was no evidence of a difference between groups (RR 0.96, 95% CI 83 to 1.12).

f) Any other adverse effects (4 trials, 895 children)

Four trials reported side effects among 895 children. There was no evidence of differences between intermittent and daily iron supplementation (RR 0.60, 96% CI 0.19 to1.87)

g) Adherence (5 trials, 1130 participants)

Five trials, including an Indian study reported on this outcome. There was no statistically significant difference in adherence to the interventions between groups although it tended to be higher among those children receiving intermittent iron supplements (RR: 1.23, 95% CI: 0.98 to 1.54).

h) School performance

One study examined IQ, Thai language development and mathematics performance; there were no clear differences between groups receiving intermittent iron versus no supplementation.

i) Physical capacity

One trial from India (Sen 2009) (17) that provided weekly and twice-a-week supplementation did not find statistically significant differences in the increment of steps climbed by children receiving either intermittent or daily supplementation.

2.2.3 Summary of Cochrane review

The review suggested that although daily iron supplementation has proven to be effective in increasing haemoglobin concentrations in children, especially in those who are anaemic in real world settings the long regimen duration, the low coverage rates and insufficient tablet distribution, and side effects associated with daily iron supplementation (for example, gastrointestinal discomfort, constipation and staining of teeth with drops or syrups) limit adherence, especially in young children.

Intermittent iron supplementation is efficacious to improve haemoglobin concentrations and reduce the risk of having anaemia or iron deficiency in children younger than 12 years of age when compared with a placebo or no intervention, but it is less effective than daily supplementation to prevent or control anaemia. Intermittent supplementation may be a viable public health intervention in settings where daily supplementation has failed or has not been implemented. Information on mortality, morbidity, developmental outcomes and side effects, however, is still lacking.

Evidence for recommendations on Iron Supplementation followed by India

There is only one India-specific study which is likely to be the evidence for the current NIPI recommendation for pre-school children (18). See Table below for a summary.

SUMMARY OF INDIAN STUDY LIKELY TO BE REFERRED FOR NIPI GUIDELINES FOR PRE-SCHOOL CHILDREN

Study	Intervention	Outcome (unit)	Groups	Initial	Final
Awasthi 2005 North India	Participants: Children, 3-6years Iron: 20mg Folic Acid: 100µg Duration: 1year	Haemoglobin (Mean + SD)	100 days Bi-weekly (n=403) Daily (n=400) 1 year Bi-weekly (n=403) Daily (n=400)	 9.78 + 1.5 10.26 + 1.8 9.78 + 1.5 10.26 + 1.8	 10.09 + 1.39 10.53 + 1.34 10.85 + 1.29 11.09 + 1.19
		Anaemia prevalence, n (%) Adherence n(%)	Bi-weekly Daily Bi-weekly 100 days 1 year Daily 100 days 1 year	231 (57.32) 201 (50.25) - - - -	92 (25.14) 58 (17.22) 309 (89.05) 398 (88.02) 236 (63.51) 235 (63.51)

This paper has been included in the meta-analysis that formed the basis of the WHO, 2011 guideline for intermittent iron supplementation. However, there was potential bias in the paper - some children received supervised intake of the supplement; it was not clear whether this varied depending on intervention group and the impact of the cluster-design effect was not clearly taken into account in the study.

Evidence post WHO recommendation

There are no studies that are available post WHO 2016 recommendation with comparison of daily and weekly programs that can throw more light into this issue.

Conclusions

Children are particularly at risk of iron deficiency due to demands of rapid growth. Iron supplementation in children has been identified as the strategy to address the burden of anaemia. However, there are differences in the regimes recommended by WHO and that followed in India under NIPI, in terms of frequency and dosage. The current Indian guidelines are more in accordance with the earlier WHO guideline of 2011. There is sufficient evidence on the efficacy of the weekly supplementation. The benefits of a daily vs weekly program is not conclusive. More studies comparing the two recommendations with clear documentation of risks and benefits in the Indian context would be helpful.

An important consideration is the possibility of iron overload with these regimens.

The Tolerable Upper Limit of intake of iron has been defined as 40 mg/day (2017 ICMR Committee to define the TUL for micronutrients, not yet published). With the current recommended dose of 20mg/day and average dietary iron intake of 8.9 mg/day (4-6 year) and 5.8 mg/day (1-3 year) (19), the intake is unlikely to cross the TUL.

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SECTION 2: PREVENTION OF ANAEMIA AMONG ADOLESCENTS AND WOMEN IN REPRODUCTIVE AGE

Background

Iron requirement is higher in girls who reach menarche, owing to menstrual blood loss and this need in women continues until menopause. Adolescence is a time of accelerated growth and development with higher nutritional demands. Iron is an important component of the growing process as it is required in both myoglobin and haemoglobin production due to rapid expansion in blood volume and red cell mass (1). It estimated that during the pubertal stage, haemoglobin concentration increases by 50-100 g/L per year, resulting in an increased demand for iron. The average iron requirement for an adolescent girl, after menarche, is around 455 mg/year while it is 350 mg/year for an adolescent boy (2).

Iron deficiency occurs when body iron stores are exhausted, the production of red blood cells is impaired, finally resulting in iron-deficiency anaemia. Since pregnancy also increases iron requirements due to the increased requirement of the growing foetus, pregnancy during the adolescent period bestows presumably an even higher strain on the requirement for iron (3).

Iron deficiency anaemia is further exacerbated by the habitual consumption of cereal based diets that contain inhibitory substances like phytate and lacks in bio-available sources of iron like meat and fish, particularly in developing countries (1). Added to this, poor hygiene and sanitation leading to infections that do not receive adequate treatment from often inefficient health system, further inhibits iron absorption or increases losses, and aggravates anaemia in these vulnerable groups. The Table below provides haemoglobin levels to diagnose anaemia in non-pregnant women and adolescent girls.

WHO RECOMMENDED HAEMOGLOBIN LEVELS TO DIAGNOSE ANAEMIA AT SEA LEVEL (G/L) (3)

Population	Non-anaemic	Anaemic		
		Mild	Moderate	Severe
Adolescent girls	120 or higher	110-119	80-109	lower than 80
Non-pregnant women	120 or higher	110-119	80-109	lower than 80

Prevalence of anaemia among adolescents and women of reproductive age.

WHO set a target in 2011 to "decrease the prevalence of anaemia by 50% among adolescent girls and boys (10-19 years group)" in five years. However, a global estimate of prevalence of anaemia among adolescents is not available. Looking at the South East Asian countries, adolescents constitute around 20% of the population (4). Although the reproductive age of a woman is considered to be from 15-49 years, adolescent pregnancy is a major issue in some of the South East Asian countries. For e.g, around 18.2 % of girls in India and 21% and 10.2% girls in Bangladesh and Nepal, respectively, are married by 15 years (5). Early marriage and pregnancy further depletes the already poor iron status among this population. According to National Family Health Survey 4 (2015-16) (6), 7.9% adolescent girls in India were pregnant and the prevalence of anaemia among adolescent girls is estimated to be 56% (7). The prevalence of anaemia in non-pregnant women in different countries is provided in the Table below.

PREVALENCE OF ANAEMIA AMONG NON-PREGNANT WOMEN (15-49 YEARS) (5)

Country	Anaemic non-pregnant (<12.0 g/dl) 2006 % (95% CI)	Level of Public Health Significance
Bangladesh	43(35–50)	Severe
Bhutan	44(21–63)	Severe
India	48(29–63)	Severe
Nepal	36(28–44)	Moderate
Sri Lanka	26(12-46)	Moderate

Anaemia affects around half a billion women of reproductive age (15-49 years) worldwide. In 2011, 29% (496 million) of non-pregnant women aged 15-49 years were anaemic, the prevalence being highest in South Asia. In India, 53% of women in reproductive age suffer from anaemia (NFHS 4). With a global nutrition target of a 50% reduction of anaemia in women of reproductive age, the current figures show that we are far from meeting the goals.

Iron Prophylaxis

Both the World Health Organization, and the National Iron Plus Initiative, India guidelines recommend iron supplementation for women of reproductive age (WRA) and adolescent girls aged 10 to 19 years of age.

Details of the WHO and Indian recommendations are provided in the Table below:

COMPARATIVE SUMMARY OF RECOMMENDATIONS BY WHO AND NIPI

	WHO		NIPI, 2013 GoI	
	Recommendation for a daily dose of Iron Folic Acid Supplementation (IFS) (2016)	Recommendation for an intermittent dose of IFS (2011)		
Target Group	Menstruating adult women and adolescent girls	All menstruating adolescent girls and adult women	Adolescent girls and boys (10-19 years)	Women of reproductive age (15-45 years)
Dose	Iron: 30–60 mg elemental iron	Iron: 60 mg of elemental iron and Folic acid: 2800 µg	Iron: 100 mg of elemental iron and Folic Acid: 500 µg	Iron: 100 mg of elemental iron and Folic Acid: 500 µg
Frequency & Duration	Daily For 3 consecutive months in a year	One supplement/week For 3 months. Followed by 3 months of no supplementation after which the provision of supplements should restart. If feasible, intermittent supplements could be given throughout the school or calendar year	One supplement/week Given throughout to ages of 10–19 years. Along with biannual de-worming	Weekly throu ghout the reproductive period
Setting	Where the prevalence of anaemia in menstruating adult women and adolescent girls is 40% or higher	Where the prevalence of anaemia among nonpregnant women of reproductive age is 20% or higher		
Total supplemental iron intake/year	Total no. of days: 90; 2700 mg – 5400 mg	Total no. of months in a year: 6 months Total no.of times administered: 24 i.e 1440 mg elemental iron	5200 mg elemental iron	5200 mg elemental iron

WHO has two sets of recommendations for iron supplementation in non-pregnant adult women and adolescent girls (8)

- "Daily iron supplementation is recommended as a public health intervention in menstruating adult women and adolescent girls living in settings where the prevalence of anaemia is 40% or higher in this age group, for the prevention of anaemia and iron deficiency." (WHO, 2016)
- "In populations where the prevalence of anaemia among non-pregnant women of reproductive age is 20% or higher, intermittent iron and folic acid supplementation is recommended as a public health intervention in menstruating women, to improve their haemoglobin concentrations and iron status and reduce the risk of anaemia." (WHO, 2011)

In contrast, India follows the National Iron+ Initiative (NIPI), under the Ministry of Health and Family Welfare, Government of India that gives two sets of recommendations for adolescents (10-19 years) and women in reproductive age (15-45 years) (9).

2. Summary of Evidence for WHO Recommendations

2.1 Daily iron supplementation in adult women and adolescent girls (2016)

The present WHO guideline (10) are based on a Cochrane review (11) that assessed the effects of daily iron supplementation in menstruating adult women and adolescent girls. The review included 8506 women (menstruating) in the age group of 12 to 50 years from 67 trials across low-, middle- and high-income countries, covering different cultural and economic back ground. The review included two Indian studies, one looking at the efficacy of daily dose of 60 mg elemental iron on adolescent girls and the other assessing the efficacy of weekly vs. daily iron supplementation. The most frequently used oral iron formulations was ferrous sulphate. Doses of elemental iron varied from 1 mg of elemental iron to 300 mg of elemental iron a day and the duration of administration ranged from 1 week to 24 weeks.

Primary outcomes studied

a) Anaemia prevalence: Prevalence of anaemia was measured in 10 studies, comprising of 3273 women. Women receiving iron were significantly less likely to be anaemic at the end of intervention compared to women in the control group (RR: 0.39, 95% CI: 0.25 to 0.60, moderate quality evidence). Although non-linear with increasing dose, there were significant

differences in the effect size of risk of anaemia across different doses and durations of iron supplementation.

b) Haemoglobin: Haemoglobin levels at the end of the therapy was assessed for 6861 women from 51 trials. Women receiving iron had a higher haemoglobin concentration at the end of intervention compared with women receiving control (MD 5.30, 95% CI 4.14 to 6.45; heterogeneity: $Tau^2 = 11.74$; $Chi^2 = 356.76$, df = 50 ($P < 0.00001$); $I^2 = 86\%$; high quality evidence). Sub group analysis suggests that there was no difference in effect on haemoglobin with varying dosage of iron.

c) Iron Deficiency: Seven studies recruiting 1088 women measured iron deficiency at the end of the intervention. Women receiving iron had a reduced risk of iron deficiency compared with women in the control group (RR 00.62, 95% CI 0.50 to 0.76; heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.37$, df = 6 (P value = 0.21); $I^2 = 28\%$; moderate quality evidence). A sub group analysis to assess the effect of various doses was not possible due to few number of studies.

d) Side effects: Data on adverse effects were reported as proportions of participants experiencing side effects. The limited number of studies did not allow for a dose-responsive analysis of the side-effects. However, there was evidence of a trend towards an increase in risk of any adverse effects as dose of elemental iron was increased, from 30 mg to 60 mg (RR 1.01, 95% CI 0.93 to 1.10, 3 studies, 305 women), to 61 mg to 100 mg (RR 2.61, 95% 1.44 to 4.75, 2 studies, 157 women), to more than 100 mg (2.15, 95% CI 1.24 to 3.73, 3 studies, 439 women; test for subgroup differences: $Chi^2 = 16.30$, df = 2 (P value = 0.0003), $I^2 = 87.7\%$).

The Cochrane review only focused on the efficacy of daily dosage of elemental iron and did not consider weekly supplementation studies that compared daily and weekly administration of iron supplementation for this review. Since the Indian recommendation suggests a weekly dosage of 100 mg elemental iron (vs. 60 mg daily dosage by WHO), this background paper has specifically evaluated the weekly supplementation trials that compared daily and weekly administration of iron supplementation.

*2.2 Weekly Supplementation Wing of Trials included in the **Cochrane Review (2016)***

Out of the 67 trials considered in the review, 6 had a comparative group of weekly dosage of iron supplementation. The following table is a collation of the daily vs. weekly comparison of iron supplementation from the respective trials.

COMPARISON OF STUDIES OF DAILY VS WEEKLY IRON SUPPLEMENTATION

Study	Participants	Baseline Characteristics	Outcome	Groups	Initial	Final	Change	Author's Conclusion
Agarwal, 2003, India	n=2088 Age: 10-17 yrs Duration of supplementation: 100 days Measurement by 115 days and 230 days Intervention: Elemental iron:100 mg Control: No intervention	Girls 48% anaemic (Hb <12 g/dl) Baseline Hb >=7 g/dl	Hb (g/dl) Mean ± SD	115 days Control (n=691) Daily (n = 699) Weekly Treatment (n=695) 230 days Control (n= 579) Daily (n = 581) Weekly Treatment (n=695)	 11.8±1.3 11.7±1.3 11.7±1.3 11.8±1.3 11.7±1.3 11.7±1.3	 11.6±1.2 12.3±1.1 11.8±1.3 12.1±1.3 12.2±1.1 12.1±1.3		7 girls in the daily wing had dropped at 2nd week due to gastric side effects. "The weekly administration showed delayed response as prevalence of anemia was higher at 115 days compared to the daily group and at 230 days the response was comparable to the daily intervention group" "Regular weekly administration was effective and seems suitable for populations with mild to moderate anemia."
Jayatissa, 1999, Sri Lanka	n=690 Duration: 8 weeks Dose: 60 mg		Hb (g/dl) Mean ± SD	Weekly (n = 220) Daily (n = 222) Placebo (n =217	12.8 ± 1.3 12.9 ± 1.1 12.9 ± 1.1	13.1 ± 1.0 13.2 ± 0.9 13.1 ± 1.1	0.4±1.2 0.4±1.1 0.2±1.2	16 girls dropped out due to side-effects (constipation, sleepiness, abdominal pain, rash, and nausea): 11 in the daily supplementation group and 5 in the weekly group. "long-term weekly doses of iron are suitable for the prevention of iron deficiency anaemia in adolescents." The effects of weekly and daily supplementation were not distinguishable
	n=690		Anaemia	Anaemic				

	Duration: 8 weeks		no. (%)]	Weekly (n = 220)	55 (25.0)	21 (9.5)		Weekly supplementation is an economically advantageous and simple intervention to improve the haemoglobin status of adolescent girls.
	Dose: 60 mg		[Under 12 years of age, Hb <11.5 g/dl; 12 years of age or more, Hb <12.0 g/dl]	Daily (n = 222) Placebo (n = 217 Non-anaemic Weekly (n = 220) Daily (n = 222) Placebo (n = 217)	41 (18.5) 43 (19.8) 165 (75.0) 181 (81.5) 174 (80.2)	19 (8.6) 29 (13.4) 199 (90.5) 203 (91.4) 188 (86.6)		Weekly supplementation generated fewer complaints of side effects, and compliance was high. The greater rise in serum ferritin with daily administration of iron is of no practical significance as long as the preventive supplementation programme is continued
	n=690 Duration: 8 weeks Dose: 60 mg		Serum Ferritin (µg/L) Mean ± SD	Weekly (n = 9) Daily (n = 22) Placebo (n = 11)	66.6 ± 32.9 54.1 ± 26.7 59.1 ± 34.9	82.7 ± 34.8 92.3 ± 39.9 56.3 ± 30.4	16.1 ± 21.3 38.2 ± 41.1 –2.8 ± 31.2	
Shah, 2002	N=209 Median age:15 years Dose: 350 mg ferrous sulphate		Anaemia No. (%)	Daily (n=70) Weekly (n=67) Control (n=72)	(68.6) 47(70.1) (68.1)	14 (20) 9(13.4) 47 ((65.3)		2 withdrawn from daily supplementation for sideeffects. Supervised iron and folic acid therapy once a week is an effective alternative to daily administration and helps lower the prevalence of anaemia in adolescent girls.
Zavalate , 2000 Peru	N=296 Girls Age: 12-18 years	Hb > 8 g/dL	Hb (g/dL)	Anaemic Daily (n=20) Intermittent	11.3 11.4	12.4 12.1		Side-effects were not a problem in any of the groups probably since the girls were informed about the benefits of iron supplementation before and during the trial. Daily supplementation is more effective than intermittent supplementation in increasing Hb concentrations; however, the

	Duration:17 weeks Dose: 20 mg elemental iron			(n=18) Placebo (n=15) Non-anaemic Daily (n=81) Intermittent (n=80) Placebo (n=82)	10.9 13.5 13.4 13.1	11.4 13.1 12.9 12.8		intermittent supplementation dose was also effective and could be used if given over a longer period than in this study.
Kianfar, 2000 **[Full paper not availabl e]**	High school girls	N=260 Duration: 3 month Dose: 50 mg elemental iron	Hb	Daily Weekly Placebo	Increase in Hb concentration n was not significant between the supplemente d groups, but were different from control group			Over the study period a weekly iron dose was as effective as a daily dose in treating anaemia but the daily dose was more effective in improving iron stores than a weekly dose in the short run.

In the list above 4 out of the 5 trials, (Agarwal 2003, Jayatissa 1999, Shah 2002, Kianfar 2000) concluded that weekly iron supplementation would be a more effective strategy than a daily supplementation which is because a daily administration of IFS generates more side-effects compared to intermittent and thus compliance was high. Viteri 1999 also reported the same, but the complete paper could not be obtained for review. Intermittent supplementation had a delayed response compared to a daily administration, but the effect of daily and intermittent became comparable when intervention was continued for longer duration. The intermittent dosage was economically advantageous according to Jayatissa, 1999 (Sri Lanka).

2.3 Intermittent iron and folic acid supplementation in menstruating women (2011)

WHO (2011) (12) guideline was based on a Cochrane systematic review (13) that assessed the effects of intermittent oral iron supplementation on anaemia compared with: a. no intervention or placebo and b. daily iron supplementation. Overall, the study included 21 randomised controlled trials involving 10,258 women and the results consistently showed that in comparison to no intervention or placebo, intermittent iron supplementation reduces the risk of anaemia (RR 0.73; 95% CI 0.56 to 0.95, 10 trials) and improves the concentration of haemoglobin (MD 0.458 g/L; 95% CI 2.56 to 6.59, 13 trials) and ferritin (MD 8.32 µg/L; 95% CI 4.97 to 11.66, six trials). However, compared to daily supplementation, women who received supplements intermittently presented anaemia more frequently (RR 1.26; 95% CI 1.04 to 1.51, six trials), despite achieving similar haemoglobin concentrations on average (MD -0.15 g/L; 95% CI -2.20 to 1.91, eight trials). The review concluded that "intermittent regimens increase haemoglobin concentrations with fewer negative side effects and this may encourage women to adhere better to the intervention for a longer period." "Overall, whether the supplements were given once or twice weekly, for less or more than three months, contained less or more than 60 mg of elemental iron per week, or to populations with different degrees of anaemia at baseline did not seem to affect the findings."

NOTE: In the present document, we are focusing only on the excerpt on the comparison between intermittent iron supplementation versus daily iron supplementation from the systematic review.

For the comparison between intermittent iron supplementation versus daily iron supplementation, 11 trials involving 5742 women were included.

Primary Outcomes studied

a) Anaemia: Six trials with 1492 women reported on change in anaemia prevalence. Women receiving iron supplements daily were less likely to have anaemia at the end of the intervention than those receiving iron supplements intermittently (RR 1.26; 95% CI 1.04 to 1.51). There was no indication of heterogeneity (I^2 = 0% and Chi^2 test for heterogeneity P < 0.93).

b) Haemoglobin (g/L): Eight trials involving 1676 women reported on haemoglobin as an outcome. There was no statistical evidence that mean haemoglobin concentrations were different between those women receiving intermittent iron supplementation and those who received daily iron supplementation (MD -0.15; 95% CI -2.20 to 1.91). There was high heterogeneity in the size and direction of the effect (I^2 = 81% and Chi^2 test for heterogeneity P < 0.00001).

c) Iron deficiency: Change in iron deficiency as an outcome was reported only in one study (n=198) (Angeles Agdeppa et al) and found no evidence of differences between daily and intermittent groups (RR 4.30; 95% CI 0.56 to 33.20) (11).

d) Ferritin (µg/L): Three trials involving 657 women reported on ferritin levels as an outcome. Women receiving iron supplements daily had higher concentrations of ferritin at the end of the intervention than those women receiving iron supplements intermittently (MD -11.32 µg/L; 95% CI -22.61 to -0.02). The heterogeneity was high (I^2 = 90% and Chi^2 test for heterogeneity P < 0.0001).

e) Iron deficiency anaemia: None of the included trials reported on this outcome

f) All-cause morbidity: No trials reported on this outcome.

g) Side effects: Four trials involving 823 women compared adverse outcomes between the two treatments. There was no evidence that the incidence of adverse side effects was different between those women receiving iron supplements daily and those women receiving iron supplements intermittently (RR 0.36; 95% CI: 0.10 to 1.31). Only one study reported on diarrhoea and found no evidence of differences between daily and intermittent groups (RR 2.41; 95% CI 0.12 to 49.43).

h) Adherence: Four trials involving 507 women reported on this outcome. There was no evidence that the adherence to intermittent supplementation was different from that observed among women receiving daily supplements (RR 1.04; 95% CI 0.99 to 1.09).

i) Other secondary outcomes

No studies reported on other pre-specified outcomes: respiratory infections, work performance and economic productivity, school performance or malaria outcomes. There was no evidence that the effects of intermittent supplementation on these indicators were different from that produced by daily supplementation.

Subgroup comparisons

There was considerable variation among trials in terms of the populations examined and the way studies were conducted which very likely resulted in the high statistical heterogeneity observed in some outcomes. For primary outcomes, subgroups were examined to look for possible differences between studies in terms of the length of the intervention; women's anaemia and iron status at baseline; higher and lower weekly doses of iron; type of iron compound provided; supplementation regimen, and malaria endemicity. As very few studies contributed data for most of the outcomes, we limited the subgroup analysis to anaemia and haemoglobin and ferritin concentrations.

The meta-analysis has provided overall totals along with subtotals for subgroups and the statistics for subgroup differences.

a) Supplement nutrient composition (iron only, iron plus folic acid, iron plus other micronutrients) - There were no statistical differences between supplements containing iron only (9 trials, or iron plus folic acid (8 trials), or iron plus other micronutrients (2 trials) regarding their effect on anaemia, haemoglobin and ferritin.

b) Anaemia status at baseline (anaemic, non-anaemic, mixed/unknown) - Intermittent iron supplementation had similar effects on anaemia, haemoglobin and ferritin concentrations in populations with different degrees of anaemia. Anaemic women tended to have a stronger response; however, as only one or two trials contributed to this subgroup category the results should be cautiously interpreted.

c) Iron deficiency at baseline (iron deficient, non-iron deficient, mixed/unknown) - This subgroup analysis was not conducted as only two trials reported the baseline prevalence of iron deficiency.

d) Dose of elemental iron per week in the intermittent group (60 mg of iron or less, more than 60 mg of iron*)* **-** Almost an equal number of trials provided more than 60 mg of iron per week or 60 mg or less. In most of the studies there was no difference in haematological outcomes between the effects produced by 60 mg of iron or less per week and those observed with higher doses of iron per week other than one study where, women who received 60 mg or less intermittently showed higher haemoglobin concentrations in comparison to those women who received higher doses.

e) Duration of the intervention (three months or less, more than three months) - In most of the cases the duration of the intervention did not alter the effect of intermittent supplementation on haematological outcomes.

f) Malaria endemicity (yes, no/unknown) - The endemicity for malaria at the time where the trial was conducted did not alter the effect of intermittent supplementation on haematological outcomes.

Summary of WHO recommendations

The studies showed that daily supplementation had better response in terms of differences in anaemia prevalence and ferritin concentration but was comparable to weekly regime for haemoglobin and iron deficiency. Among the secondary outcomes, adherence to supplementation or side effects were not different between daily vs weekly regime. Evidence of better response of haemoglobin to doses >60 mg was also not consistent.

3. Recommendations on Iron Supplementation followed by India (14)

Anaemia among women of reproductive age, including adolescents, has been the concern of policy makers in India and with the recommendations of the National Consultation on Anaemia Control in 1997 that stated, "Adolescent girls on attaining menarche should consume one IFA tablet containing 100mg elemental iron and 500 µg folic acid once a week. This should be accompanied by appropriate dietary counselling. Considering the large size of the adolescent population as well as the financial and operational constraints, it is recommended that district-level pilot projects should be undertaken. The total duration of a weekly dose of iron supplements, its cost-effectiveness and operational feasibility should be examined."

India has been following the "Weekly iron and folic acid supplementation programmes for women of reproductive age" (WHO, 2011) (15) along with the other South East Asian Region countries. The WHO recommendation for weekly iron supplementation (2011) suggested 60 mg of iron in the form of ferrous sulphate (FeSO4.7H2O) and 2800 µg folic acid for adolescents (10-19 years) and women up to age 49 years. However, while the other South Asian Region countries followed a dosage of 60 mg elemental iron, in India, a higher dose of 100 mg elemental iron was provided to the adolescents through the National Rural Health Mission along with 500µg folic acid, considering that one third of adolescent girls in India began childbearing at the young age of 19 years. The folic acid supplement varied across countries that ranged from 0.3 mg to highest 3.45 mg per tablet. As per WHO 2008, "No rationale was presented for the variation in composition of the supplement."

However, country case report (WHO, 2011) has collated pilot trials in India from the States of Bihar, Gujarat, Madhya Pradesh and Uttar Pradesh that suggested improvement in the prevalence of anaemia among adolescent girls (10-19 years) with the higher dose (100 mg) of elemental iron. The design of these studies is given in the section below.

Evidence on Weekly Iron-Folic Acid Supplementation in India (15)

In India, WIFS programme findings in nine states revealed that with one year's intervention, there was a substantial decrease in anaemia prevalence and the decrease varied from 5% in Jharkhand to 43% in Andhra Pradesh and 50% in Uttar Pradesh. In Uttar Pradesh, adolescent girls were reached in school and out of school setting in an entire district with an intervention package comprising WIFS, six monthly deworming and family life education (7). In a period of four years, anaemia prevalence decreased from 73.3% to 25.4% and no significant difference in impact was observed between girls who were intervened in school (supervised) and out of school intervention (unsupervised WIFS intake). Following this reduction in anaemia prevalence, the WIFS programme was being scaled in the entire state as a part of the Adolescent Health Programme. Similar large scale WIFS programme implemented in other states of India, Bihar, Gujarat and Madhya Pradesh, have demonstrated a significant decrease in anaemia prevalence in adolescent school girls and those out of school (Table below).

The programmes had a strong component of education and social mobilization activities and a monitoring system. For improving management and compliance, a "fixed WIFS day" approach was used. The project was expanded to cover 11 entire states by the end of 2011. In 2013, the Government of India introduced national implementation of weekly iron and folic acid supplementation to approximately 120 million adolescent girls.

REDUCTION IN ANAEMIA PREVALENCE WITH WIFS IN DIFFERENT STATES OF INDIA (16)

States	Age	Coverage		IFS	Anaemia prevalence (baseline) (%)	% Reduction in anaemia prevalence (12 months)	WIFS Compliance (%)
		School going children	Non School Going Children				
Bihar, India (17)	10-18	79,590	1,91,070	Iron: 100 mg elemental iron Folic Acid: 0.5 µg	93.0	8.8	70-72
Gujarat, India (18)	12-19	65,000	9536	Iron: 100 mg elemental iron Folic Acid: 0.5 µg	74.7	20.5	89-94
Madhya Pradesh, India (19)	10-18	-	25,000	Iron: 100 mg elemental iron Folic Acid: 0.5 µg	87.8	7.8	>90
Uttar Pradesh, India (20)	10-19	77,000	73,700	Iron: 100 mg elemental iron Folic Acid: 0.5 µg	73.3	34.3	86-90

*SGG-School going girls (supervised), NSGG-Non-school going girls (unsupervised) + taken from a WHO document (13) on weekly iron folic acid supplementation.

Evidence after-WHO Guidelines (2015 - present)

There were no additional studies with low risk of bias other than the ones referred to by the WHO guidelines and NIPI on a separate search of databases, for evidence of interventions among adolescent girls and women.

Conclusions

The latest WHO (2016) guideline suggests a daily iron supplementation (60 mg elemental iron) for 3 months throughout the reproductive age including adolescence for settings where prevalence of anaemia is more than 40%.

However, India has been practicing WHO (2008) recommendation on weekly iron-folic supplementation with a higher dose. While WHO suggested 60 mg elemental iron per day, the Indian recommendation has been a higher dose of 100 mg elemental iron per week. There is no clear evidence that one dose is better than the other.

A recent study on efficacy of iron supplementation in India among adolescents, a weekly IFS was better adhered to (15) and was as efficacious to daily IFS which supports the national program by government of India in 2013.

Another point to note is that, the total dosage of iron supplementation for WRA is similar across the WHO and Indian Recommendation. Currently, with a weekly dosage of 100 mg elemental iron across 52 weeks, the Indian recommendation provides 5200 mg elemental iron in a year whereas, WHO, with a recommendation of daily iron supplementation of 60 mg elemental iron for 3 consecutive months in a year provides 5400 mg elemental iron per year to WRA. This converts to a daily supplement intake of 15 mg/day. Considering 10 mg/day intake from dietary sources, the total intake will not exceed the TUL (45 mg/day) for women in reproductive age group.
However, several questions remain unanswered and need to be explored:

- In 2011, WHO recommendations (15) suggested an intermittent IFS for WRA (women in reproductive age) in setting with more than 20% prevalence of anemia. The systematic review which was the basis of this guideline, suggested that weekly IFS had a better efficacy due to better compliance and comparable increase in haemoglobin overtime.

- The WHO guideline (2016) (10) recommends a daily IFS among WRA for settings where the prevalence of anaemia is more than 40%.

However, the efficacy and compliance of weekly IFS over daily IFS was missing in the review that formed the basis of the 2016 recommendation. The review stated that "This review will complement the findings of other Cochrane systematic reviews assessing the use of iron supplements in different female populations: intermittent iron supplementation in menstruating women", which leaves the question of why the efficacy of weekly IFS versus daily, was not considered in the formulation of recommendations for a setting with more than 40% anaemia prevalence among WRA. This is of further importance when compliance, (which is likely to be less in case of daily IFS, according to previous reviews comparing weekly versus daily IFS) is a major issue in adhering to a supplementation program.

- Should India, with a prevalence of more than 40% anaemia among WRA, follow a daily iron supplementation as recommended by WHO (2016) for the given setting or retain the current guidelines of weekly IFS with a higher dose of 100 mg elemental iron that meets the total dosage of iron (recommended by WHO) administered over a year?

- Does a higher dose of 100 mg elemental iron administered weekly across a year, compare with the physiological effect of providing a daily dose of 60 mg elemental iron for 3 months among this age group?

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SECTION 3: PREVENTION OF ANAEMIA IN PREGNANCY

Background and physiological basis for iron prophylaxis

Iron deficiency is one of the most common nutrient deficiencies during pregnancy as the body tries to meet the additional requirements of iron for the growing foetus. Pregnant women require around 1000 mg elemental iron to suffice for the foetal and placental growth (300 mg), maternal haemoglobin expansion (500 mg) and to replenish loss through gut, urine and skin (200 mg) (1). This iron is mostly used during the latter half of pregnancy, as the iron requirement increases from a 0.8 mg/day in the first trimester, to 6-7 mg/day in the second half of pregnancy. Overall, a pregnant woman needs about 2-4.8 mg of absorbable iron per day, for which she must consume 20-48 mg of dietary iron per day (1). An average vegetarian Indian diet does not provide more than 10 to 15 mg of iron per day.

Thus, the amount of iron absorbed from diet, coupled with that mobilized from body iron stores, is usually insufficient to meet the demands imposed by pregnancy in case of Indian women. This is true even though the bioavailability of iron from the gastrointestinal (GI) tract is moderately increased during pregnancy and menstrual iron loss ceases. Therefore, iron supplementation during pregnancy is recommended universally even in nonanemic women (1). The Table below provides the diagnostic cut off for haemoglobin.

WHO RECOMMENDED HAEMOGLOBIN LEVELS TO DIAGNOSE ANAEMIA AT SEA LEVEL (G/L) (2)

Population	Non-anaemic	Anaemic		
		Mild	Moderate	Severe
Pregnant Woman	110 or higher	100-109	70-99	lower than 70

Note: Currently, there are no WHO recommendations on the use of different haemoglobin cut-off points for anaemia by trimester, but it is recognized that during the second trimester of pregnancy, haemoglobin concentrations diminish approximately by 5 g/l (2).

Prevalence of anaemia in pregnant women

About 47% of anaemia during pregnancy is attributed to iron deficiency (3) Anaemia during pregnancy is associated with several adverse outcomes including low birth weight and an increased risk of maternal and perinatal mortality (4). In developing countries, maternal and neonatal mortality are responsible for 3.0 million deaths (5).Considering these factors, it is necessary to institute preventive measures to reduce the burden of anaemia.

Preventable morbidity and mortality due to pregnancy-related anaemia remains unacceptably high with the target of attaining the Sustainable Development Goals by 2030 being bleak. Although the overall global prevalence of anaemia has reduced from 41.8% in 2005 to 38.2% in 2011, the prevalence has remained consistently high for the South East Asia

Region (WHO), with 48.2% of pregnant women suffering from anaemia in 2005 and 48.7% in 2011 (Table below, taken from WHO 2011 (3); later statistics for India are available, but not presented here for ease of comparison).

PREVALENCE OF ANAEMIA AMONG PREGNANT WOMEN (15-49 YEARS) (3)

Country	Anaemic pregnant (<11.0 g/dl)		Level of Public Health Significance
	2006 (95% CI)	2011 (95% CI)	
Bangladesh	47(34–60)	48(37-58)	Severe
Bhutan	50(20–79)	46(25-67)	Severe
India	50(48–52)	54(37-67)	Severe
Nepal	75(68–80)	44(33-56)	Severe
Sri Lanka	29(26-33)	25(15-45)	Moderate

The South East Region (WHO) includes Bangladesh, Bhutan, Democratic People's

Republic (DPR) of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste, with India, being the greatest contributor to prevalence of anaemia in this region. While for countries like DPR Korea, Thailand, Sri Lanka, anaemia is a moderate public health problem, for countries including India, Bangladesh, Nepal and Bhutan, anaemia remains a severe public health problem. However, while Nepal and Bhutan have made some progress in reducing the prevalence, in India, the burden of anaemia among pregnant women has increased from 49.7% (2005) to 54% (2011), demanding serious attention.

Iron Prophylaxis

International agencies have been advocating direct iron supplementation in most low and middle–income countries to meet the additional iron requirements during pregnancy and replenish iron reserves. Currently, WHO (2012) recommends a standard daily dose of 30 to 60 mg of elemental iron

and 400 µg (0.4 mg) of folic acid to all pregnant adolescents and adult women starting as soon as possible after gestation begins and continuing for the rest of pregnancy (5). In regions where anaemia among pregnant women is a severe public health problem (>40%), a higher dose of 60 mg is recommended over the lower dose. The dose of 60 mg is based on the estimated iron requirements for women during pregnancy and the gastro-intestinal side-effects associated with administration of large doses of iron supplementation, including nausea, vomiting, diarrhoea and constipation, depending upon the frequency and amount of elemental iron consumed (5).

Recommended doses are provided in the Table below, including those from India.

COMPARATIVE SUMMARY OF RECOMMENDATIONS BY WHO AND NIPI

	WHO, 2016	NIPI, 2013, GOI
Supplement composition	Iron: 30–60 mg of elemental iron Folic acid: 400 µg (0.4 mg)	Iron:100 mg elemental iron Folic acid: 500 µg (0.5 mg)
Frequency	One supplement daily	One supplement daily
Duration	Throughout pregnancy. Iron and folic acid supplementation should begin as early as possible	Starting at 14–16 weeks of gestation. To be repeated for 100 days post-partum.
Target group	All pregnant adolescents and adult women	All pregnant & lactating mothers
Total supplemental iron intake/year	1560 – 3120 mg elemental iron	5200 mg elemental iron

In settings where daily iron is not acceptable due to side-effects, and in populations with anaemia prevalence among pregnant women of less than 20%, WHO (2016) recommends an intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 µg (2.8 mg) of folic acid once weekly for non-anaemic women (6).

While most of the countries in the South East Asia Region including Bangladesh, Nepal, Sri Lanka, Thailand etc, follow the WHO recommendation of 30-60 mg elemental iron (7), India provides a much higher dosage of 100 mg elemental iron to the pregnant women (8). About 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate (WHO guideline 2016).

2.Summary of evidence leading to current WHO recommendations

At a juncture where excess iron dosage in the form of iron supplement is being criticised for its adverse effects, the present report explores the background for WHO recommendations of 60 mg of elemental iron during pregnancy and the scientific evidence, if any, behind the need to provide a higher dose (100 mg) as per the Indian Recommendations.

WHO Recommendation

The daily dose of 60 mg recommended by WHO, as a preventive dose for pregnant women was first established in 1959, based on the estimated iron requirements for women during pregnancy and was endorsed thereafter by subsequent expert consultants (9).

Summary of Evidence

The evidence on the effects of daily oral iron supplements for pregnant women was derived from a Cochrane review (9) that included 61 randomized, cluster-randomized and quasirandomized trials conducted in low-, middle- and high-income countries. Overall, 44 trials, involving 43274 women, contributed data to the review's meta-analyses. Among the studies included, a total of eight trials were conducted in Asia including Myanmar, Thailand, Nepal, Vietnam, Philippines, South Korea and Turkey. No Indian study was included for the metaanalysis; among the 136 studies excluded, 19 were from India. The Indian studies covered a period from 1979 to 2011 and were excluded due to low grade of evidence, arising mostly due to lack of comparability between intervention and control group, or lack of randomization.

Twenty-three trials were conducted in countries with some risk of malaria, of which two reported malaria outcomes after iron supplementation. The trials compared daily oral iron supplementation, with or without folic acid or other vitamin and mineral supplements, with various control groups (folic acid alone, placebo, no intervention, other vitamin and mineral supplements without iron or folic acid). Most of the evidence was derived from studies comparing iron supplementation with no iron supplementation. The dose of iron supplement ranged from 9 mg to 900 mg of elemental iron. The most commonly (18 trials) used dose of elemental iron was 60 mg daily followed by 100 mg (8 trials) and 30 mg (6 trials).

The effectiveness of iron supplementation for pregnant women was evaluated in terms of maternal and infant outcome. Most of the trials focused primarily on changes in maternal haemoglobin level and on some other haematological outcomes. A daily iron supplementation reduced the risk of maternal anaemia at term by 70% (RR 0.30, 95% CI 0.19 – 0.46, 14 trials) and iron deficiency at term by 57% (RR 0.43,

95% CI 0.27 – 0.66, 7 studies). In most of the trials, women began taking supplements before 20 weeks of gestation and continued taking supplements until delivery. The results consistently suggested that iron supplementation in pregnancy improves maternal haemoglobin and other haematological outcomes and that these benefits can be observed at lower iron doses than usual, with less side effects.

The evidence from the meta-analysis (Cochrane review) (9) was graded according to predefined quality (Appendix 2):

Maternal outcomes studied:

a) Maternal anaemia at term (Hb less than 110 g/L at 37 weeks' gestation or more)

Data from 14 trials among 2199 women suggest that women who receive daily iron supplements during pregnancy are less likely to have anaemia at term than those who do not consume (13.06% versus 35.71%, average RR 0.30; 95% CI 0.19 to 0.46, low quality evidence). A sub group analysis to assess the effect of different dose of iron supplementation (30mg or less elemental iron vs. more than 30 mg and less than 60 mg elemental iron vs. 60 mg elemental iron or more) did not show any difference (Chi^2 = 2.34, df = 2 (P = 0.31), I^2 =14%).

b) Maternal iron deficiency at term (based on any indicator of iron status at 37 weeks' gestation or more)

Seven studies (1256 women) reported data for this outcome, with women in groups receiving iron as part of supplements being less likely to have iron deficiency at term (average RR 0.43; 95% CI 0.27 to 0.66, low quality evidence). Subgroup analyses (30mg or less elemental iron vs. more than 30 mg and less than 60 mg elemental iron vs. 60 mg elemental iron or more) suggested that higher doses of iron were associated with more pronounced treatment effects (Chi^2 = 19.52, df = 2 (P = 0.0001), I^2 = 89%, respectively).

c) Maternal iron-deficiency anaemia at term (Hb below 110 g/L and at least one additional laboratory indicator at 37 weeks' gestation or more)

Data from six trials involving 1088 women showed that 4.4% of women who received daily iron supplements and 13.2% of those who did not have iron-deficiency anaemia at term (average RR 0.33; 95% CI 0.16 to 0.69). Sub group analysis (30mg or less elemental iron vs. more than 30 mg and less than 60 mg elemental iron vs. 60 mg elemental iron or more) did not suggest any significant difference in outcome with consumption of different amounts of iron by the pregnant women (Chi^2 = 2.07, df = 2 (P = 0.36), I^2 =3%).

Side effects

Data from 11 trials involving 2423 women indicated that daily iron supplementation probably has little or no effect on the risk of experiencing any side-effect (25.3% versus 9.91% reporting side effects respectively; average RR 1.29; 95% CI 0.83 to 2.02) and that it may have little or no effect on constipation (4 trials, 1495 women; RR: 0.95, 95% CI: 0.62–1.43), heartburn (3 trials, 1323 women; RR: 1.19, 95% CI:0.86–1.66) and vomiting (4 trials, 1392 women; RR:0.88, 95% CI: 0.59–1.30). Evidence that daily iron has little or no effect on nausea is of low certainty (4 trials, 1377 women; RR: 1.21, 95% CI: 0.72–2.03). Evidence shows that diarrhoea is less common with non-intervention vs daily iron supplements (3 trials, 1088 women; RR: 0.55, 95% CI: 0.32–0.93). However, the heterogeneity between the treatment effects is substantial and the results need to be interpreted with caution (heterogeneity:I^2 = 81%, Chi^2 test for heterogeneity P < 0.00001).

Summary of WHO recommendations

The results consistently showed that iron supplementation in pregnancy improved maternal haematological outcomes independent of the dosage. Regarding the maternal outcomes, women receiving iron compared with those receiving no treatment or placebo were less likely to be anaemic at term (13.06% versus 35.71%) and were less likely to have iron deficiency (28.50% versus 51.33%) and iron-deficiency anaemia at term (4.37% versus 13.18%). Based on the evidence, WHO recommends a standard daily dose of 30-60 mg elemental iron starting as soon as possible after gestation begins and continuing for the rest of pregnancy. However, in settings with anaemia prevalence 40% or higher, the higher dose of 60 mg of elemental iron is preferred.

Recommendations on Iron Supplementation followed by India

India was one of the earliest countries to address anaemia among the population through the launch of the National Nutrition Anemia Prophylaxis Programme in 1970. Under the scheme, pregnant and lactating mothers received 60 mg elemental iron, which was later upgraded to 100 mg elemental iron along with 0.5 mg folic acid tablet daily.

In 2013, the Ministry of Health and Family Welfare, Government of India, launched the National Iron Plus Initiative (NIPI) as a comprehensive strategy to address the high prevalence of anaemia in the country and consequently an elemental iron dose of 100 mg was disseminated for the pregnant women in India. However, one would presume that the high prevalence of anaemia (more than 50%) was the driving force for the increased dose (100 mg) of elemental iron which probably overlooks the efficacy as well as the cost-effectiveness of a lower dose of 60 mg, as recommended by WHO. Several efficacy studies from India were reported across the year 1979 and 2011, that were in favour of 100 mg elemental iron (which could be the evidence base for NIPI) for pregnant women in India. However, these were excluded from the meta-analysis in Cochrane Systematic Review (2015) referred by WHO for the current recommendations. Available evidence suggests that a higher dose is also likely to be associated with increased episode of gastro-intestinal side-effects that effects the overall compliance of the program.

Evidence after-WHO Guidelines (2015 - present)

In this section, the studies that explore the various iron supplementation doses carried on after the Cochrane Systematic Review (2015) are summarized. A total of 4 trials were obtained from three data bases (none from India), of which 3 trials showed improvement in haemoglobin level with a daily dose of 60 mg (Table below).

EFFECT OF IRON SUPPLEMENTATION ON HAEMOGLOBIN

Reference	Type of Study	Study Sample	Dosage	Duration	Haemoglobin			
					Group	Before (g/dL)	After (g/dL)	Difference in Change
Etheredge et.al 2015 (10) (Tanzania)	Randomized Double-Blind Placebo-Controlled trial iron replete women	Intervention:731 Placebo:738	60 mg elemental iron Vs placebo	15th week to Delivery	Intervention	Mean:11.7 SD:1.4	Mean:11.8 SD:2.0	0.83
					Control	Mean:11.7 SD:1.3	Mean:10.9 SD:1.9	
Gengli et.al 2015 (11) (China)	Randomized Controlled Trial	Intervention:814 Control FA:802	60 mg elemental iron+0.4 mg FA Vs 0.4 mg FA	<=20 week gestation to Delivery	Intervention	Mean:12.3 95% CI: 12.2,12.3	Mean:12.2 95% CI: 12.2, 12.3	0.66
					Control	Mean: 12.3 95% CI: 11.6,11.7	Mean:11.7 95% CI: 12.1, 12.3	
Phuong H. Nguyen et al 2016 (12) (Vietnam)*	Double blind Randomized Controlled	Intervention:671 Control:672	60 mg elemental iron + 2800 µg FA Vs 2800 µg FA	Entire pregnancy	Intervention	Mean:12.91 SD:1.38	Mean: 11.48 S.D: 1.30	-0.07
					Control	Mean:13.04 SD:1.26	Mean:11.53 S.D: 1.31	

FA: Folic acid; ***:** Not significant

One trial looking at the effect of 30 mg elemental iron on anaemia, showed a trend, although not a significant change, in anaemia prevalence (Table below).

EFFECT OF IRON SUPPLEMENTATION ON ANAEMIA

Reference	Type of Study	Study Sample	Dosage	Duration	Baseline	Prevalence of Anaemia (Hb<11g/dl)		
						Intervention (%)	Control (%)	Change
Gunaratna et al 2015 (13) (Tanzania)	Randomized Controlled Trial	Intervention (Iron+FA):267 Control(FA):267	30 mg elemental iron	6 months	Intervention: Median: 10.9 Q1-Q3: 9.9,12.4	46	50	R.R: 0.91 95% C.I: 0.74,1.13
					Control: Median: 11.1 Q1-Q3: 10,12.4			

A daily dosage of 60 mg was effective in increasing serum ferritin levels significantly, while a weekly dosage of 60 mg was unable to increase prenatal serum ferritin levels (Table below).

EFFECT OF IRON SUPPLEMENTATION ON SERUM FERRITIN CONCENTRATION

Reference	Country	Study characteristics	Dosage	Freq.	Duration	Before (mg/L)	After (mg/L)
Etheredge et.al 2015 (10)	Tanzania	738 Intervention 741 Control	60 mg	Daily	Till Delivery	40.9 (33.3) 40.7 (31.4)	92.5 (171.1) 54.1 (90.3)
Phuong H. Nguyen et al 2016 (12)	Vietnam	5011	60 mg	Weekly	Until delivery	97.79 (90.96, 105.14)	90.92 (85.03, 97.21)

Finally, the search did not result in any study that showed significant adverse effects on maternal or infant outcome post the Cochrane review, 2015 (Table below).

ADVERSE EFFECTS DUE TO IRON SUPPLEMENTATION

Reference	Country		Study characteristics	Dosage	Freq.	Duration	Adverse Event	Intervention % (sd%)	Control % (sd%)
Etheredge et.al 2015 (10)*	Tanzania		738 Intervention 741 Control	60 mg	Daily	Till Delivery	Foetal Loss	56 (7.7)	45 (6.1)
							Infant Mortality at 6 weeks	20 (3)	16 (2.3)
							Birthweight < 2500g	45 (6.7)	51 (7.4)
							Birthweight <2000g	15 (2.2)	14 (2)
							Gestational age at delivery (weeks)	39.3 (2.5)	39.2 (2.7)
							Pre-term births (no) <37 weeks]	100 (15)	113 (16.5)
							<34 weeks	21 (3.2)	27 (3.9)
Gengli et.al 2015 (11)*	China (rural)	<=20 week gestation	1632	60 mg Elemental iron	Daily	Till Delivery	nausea, vomiting, diarrhoea, or constipation	68.2	68.4

***Not significant**

Conclusions

Pregnancy demands an additional requirement of around 1 mg iron per day. Considering a low iron absorption rate of 5%, an iron supplement dose of 60 mg per day would provide 5-6 times the additional iron need in early pregnancy and 3 times the additional iron need during late pregnancy. Dose-dependent studies have found smaller dose of oral iron to be as effective as higher dose to prevent anaemia. Further, a higher dose of iron did not provide any additional benefit to correct anaemia among pregnant women

Nevertheless, WHO recommends 120 mg/day iron for treatment of anemia in pregnancy. With about 60% anemia prevalence and women seeking ANC at around 20 weeks, a large number of women would need therapeutic dose of iron.

One consideration is where the recommended intake of iron during pregnancy lies in relation to the Tolerable Upper Limit (TUL) of intake. The TUL for iron has been set based on the gastrointestinal side effects associated with high levels of iron consumed on an empty stomach. High-dose iron supplements are commonly associated with constipation and other gastrointestinal effects including nausea, vomiting and diarrhoea, with frequency and severity varying according to the amount of elemental iron released in the stomach. The Institute of Medicine has established the tolerable upper limit for iron during pregnancy as 45 mg/day of iron, a daily dose much lower than international recommendations (14) .The results of this review suggest that women who consume daily supplements containing 60 mg of elemental iron or more may be more likely to report side effects, particularly diarrhoea, than those who consume lower doses per day that further concurs with the Institute of Medicine's approach which set 45 mg of elemental iron as the upper tolerable limit per day based on the likelihood of having side effects. WHO has set the tolerable upper intake of iron (30-60 mg elemental iron) based on the gastro-intestinal side-effects associated with consumption of high levels of iron on an empty stomach. These include gastrointestinal upset, constipation and nausea. Results from the systematic review suggest that women who consume daily supplements containing 60 mg of elemental iron or more may be more likely to report side effects, particularly diarrhoea, than those who consume lower doses per day or no iron supplements. Beside symptomatic effects, high single doses of iron as a fortificant or as a dietary supplement during pregnancy may be associated with increased oxidative stress with potential deleterious effect on the birth outcome (15,16). In one Indian study on non-anaemic pregnant women who were prescribed iron as part

of routine antenatal care, pregnant women in the highest tertile of supplemental iron intake had an increased risk of LBW compared with the lowest tertile (adjusted risk ratio: 1.89; 95% confidence interval: 1.26, 2.83) (17).

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APPENDIXES

Appendix 1: SEARCH STRATEGY

Search criteria:

Population: Pregnant women / Infant OR Child OR Preschool OR girl OR boy OR child OR toddler OR pre-school OR under 5 year OR young person OR young people / adolescent

Intervention: Iron supplements or iron or ferric or ferrous or Fe

Control: Placebo or None

Outcome: Improving haemoglobin levels, reducing anaemia and improving serum ferritin

Databases: MEDLINE, EMBASE, COCHRANE

Period: After the Cochrane review leading to WHO recommendation to February 2018

Appendix 2: GRADE OF EVIDENCE

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

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