JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Iron Deficiency and Anemia
Causes, Consequences, and Solutions

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International Nutrition
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Outline

- Anemia, ID, IDA – Global burden
- Iron requirements
- Etiology of IDA
- Functional and health consequences of ID and anemia
- Iron-infection interaction
- Strategies for combating iron deficiency and anemia

Biologic Importance of Iron

- Iron is essential for almost all living organisms
  - Participates in oxidative and reductive processes as part of redox enzymes and thus plays an essential role in oxidative energy production
  - Involved in oxygen transport as part of the heme molecule

Iron deficiency

- Importance

  Iron deficiency is the most prevalent nutritional deficiency in the world, and probably the most important micronutrient deficiency in the US. Globally, it is estimated to affect 1.25 billion people

Iron deficiency vs. anemia

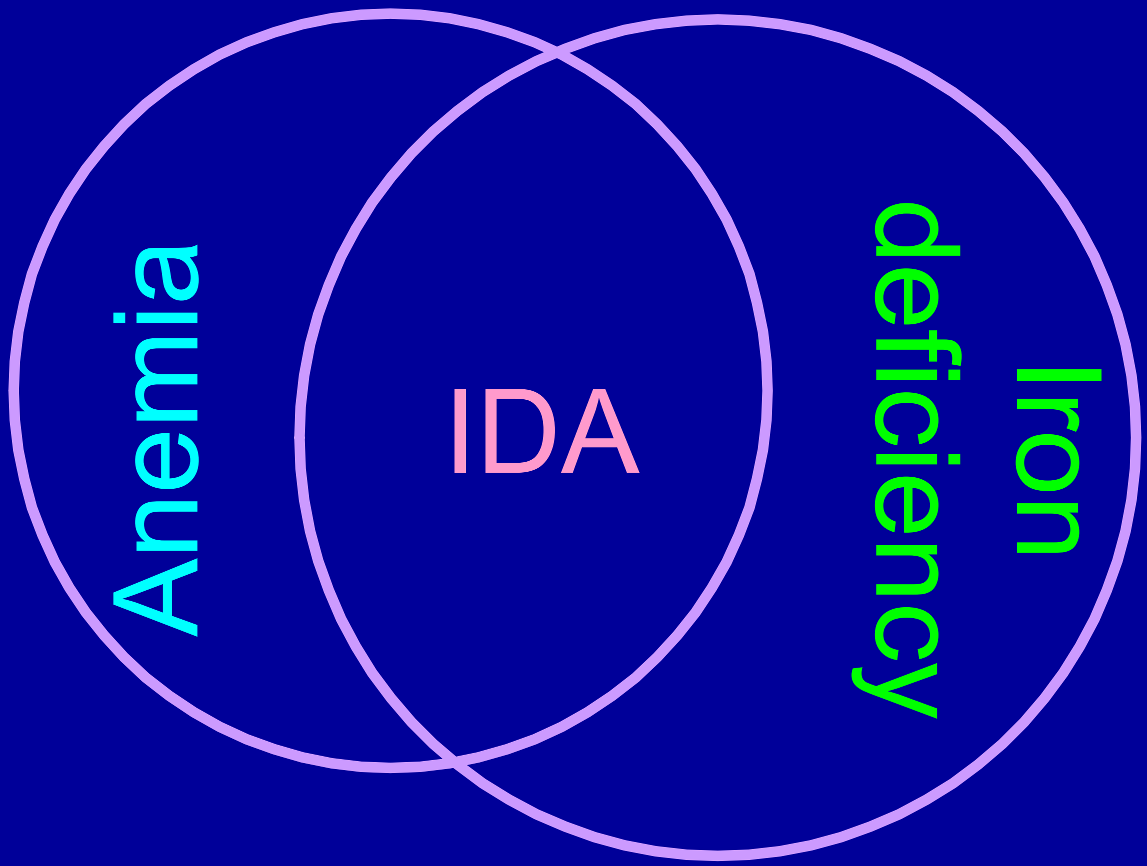
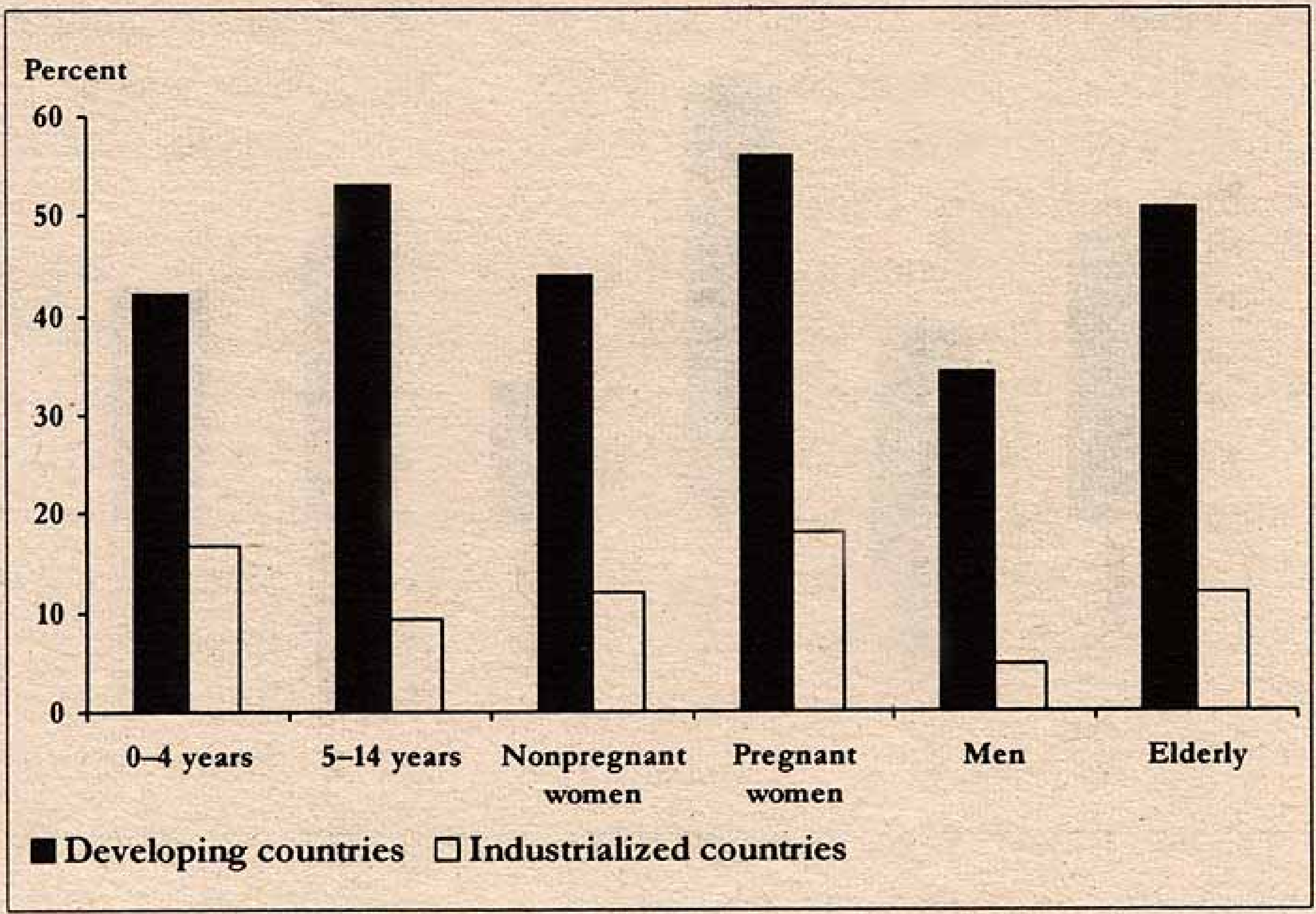
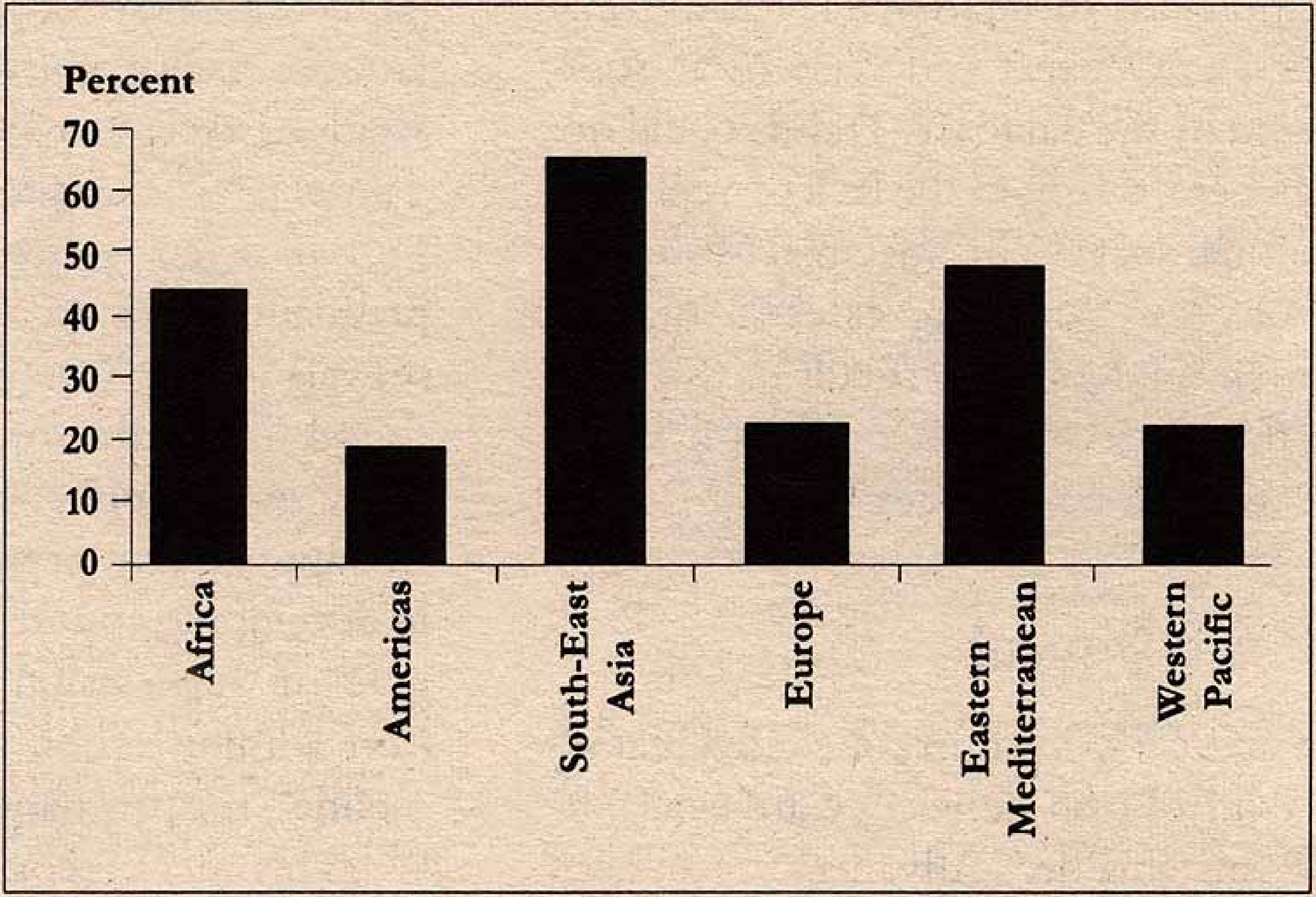


FIGURE 2.1 : Prevalence of anaemia by age group in industrialized and developing countries, 1998



ACC/SCN 4th Report on World Nutrition Situation, Jan 2000

FIGURE 2.2 : Prevalence of anaemia in children 0–5 years old by WHO region, 1998



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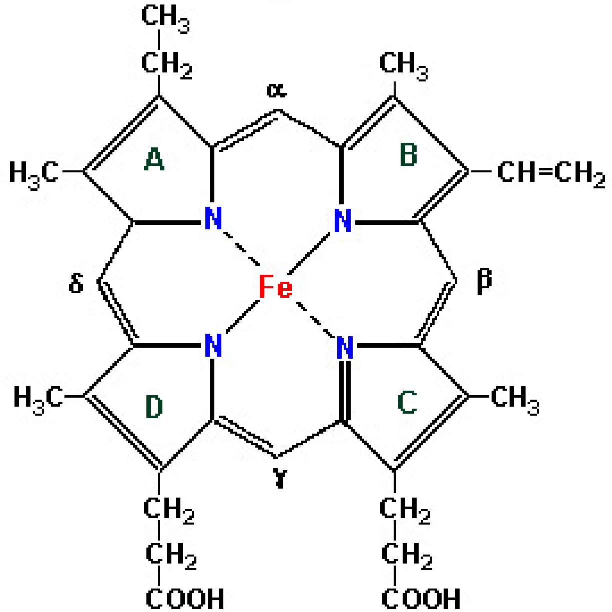


Heme Molecule

Iron compounds
(approx. values for a 55 kg woman)

Functional Compounds	Hemoglobin	1700 mg
	Myoglobin	222 mg
	Heme enzymes	50 mg
	Non-heme enzymes	55 mg
	Transferrin	3 mg
Storage Complexes	Ferritin	200 mg
	Hemosiderin	70 mg
Total		2300 mg

Comparison of screening and definitive measurements of iron status

Screening	Advantages	Limitations
1. Hemoglobin	Inexpensive, Universally available	Low sensitivity, Low specificity
2. Transferrin saturation	Inexpensive, Well established	Wide diurnal variation, Low specificity
3. Mean corpuscular Hb	Well available, established	Late indicator, low specificity
4. Zinc protoporphyrin	Portable assay, Inexpensive	Automation difficult, Affected by lead exposure
Definitive		
1. Serum ferritin	Quantitative (stores), well standardized	Affected by inflammation, liver disease
2. STfr	Quantitative (tissue deficiency) unaffected by inflammation	Affected by recombinant human erythropoietin
3. Bone-marrow iron	Well established, high specificity	Affected by EPO treatment, invasive, expensive, error-prone

Cook JD; Best Pract Res Clin Haematol 2005

Quantitative assessment of body iron

Body iron (mg/kg) =

-[log (R/F ratio) – 2.8229]/0.1207

R = transferrin receptor

F = ferritin

Cook JD; Blood 2003

Defining anemia at sea level

Age or Sex group	Hb below g/dL	Hematocrit below %
Children 6mo-5 y	11.0	33
Children 5-11 y	11.5	34
Children 12-13 y	12.0	36
Non-pregnant women	12.0	36
Pregnant women	11.0	33
Men	13.0	39

Stoltzfus & Dreyfuss; INACG/UNICEF/WHO 1998

Dietary Iron

- Two types of iron
  - Heme iron (animal sources)
  - Non-heme iron (plant sources)
- Absorption of heme iron is 20-30%
- Absorption of non-heme iron varies between 1-10% and is much more affected by iron status and intraluminal factors

Non-heme Iron Absorption

- Enhancers : ascorbic acid, meat
- Inhibitors : phytates, phosphates, tanins, oxalates, soy protein
- Other nutrients: zinc, calcium

Iron requirements for growth

Group	Age (y)	Wt gain (kg)	Mg iron/kg body wt	Mean iron for growth (mg/d)
Children	0.25-1	4.2	37	0.65
	1-2	2.4	37	0.24
	2-6	7.9	40	0.22
	6-12	20.2	41	0.38
Boys	12-16	26.2	46	0.66
Girls	12-16	15.2	43	0.36

Iron Losses
Men and Post-menopausal Women

Area of loss	Amount (mg/d)
Feces	0.2-0.5
Urine	0.2-0.3
Sweat, hair, nails	0.2-0.5
Total	0.8-1.0

Iron Losses

(Menstruating women - 55 kg)

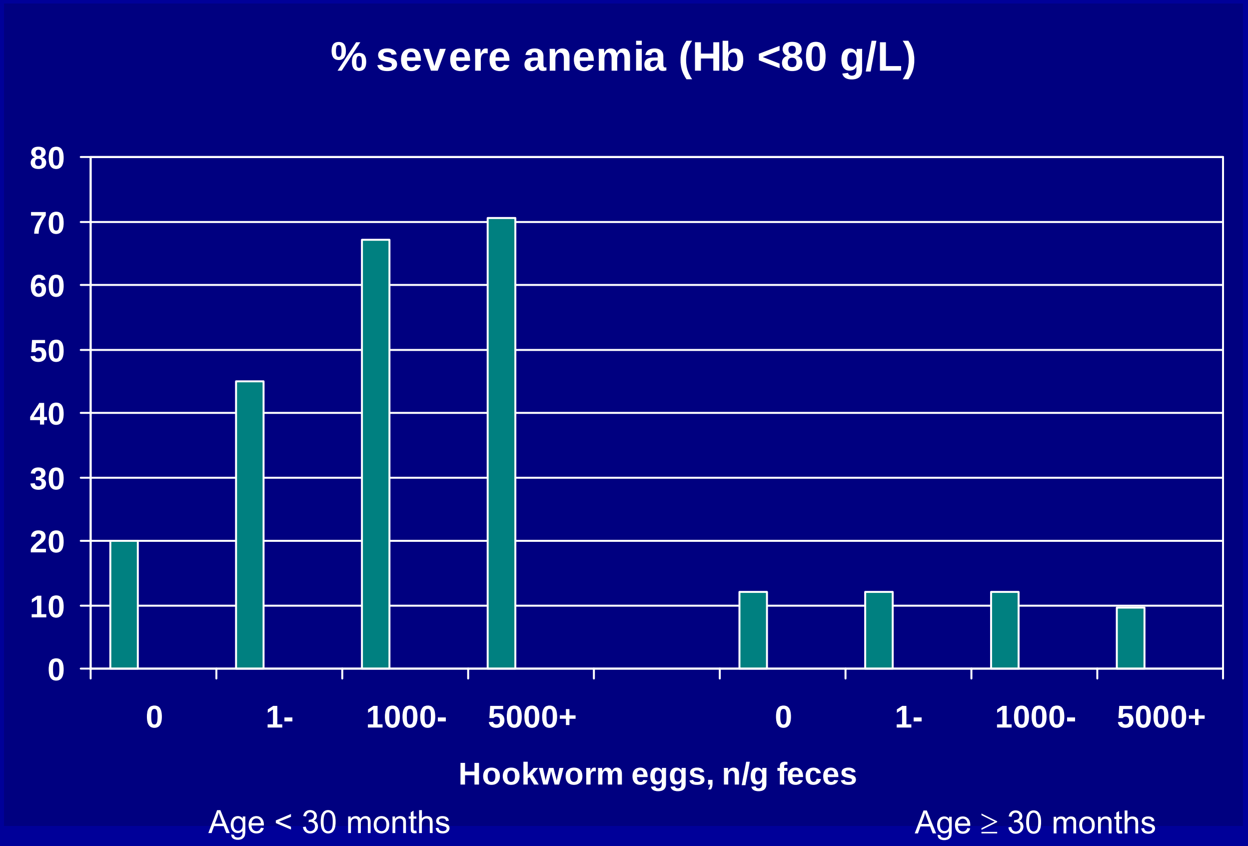
- Additional loss of 0.5 mg/d of Fe occurs due to menstruation; range is high

	Basal Fe loss	Menstrual Fe loss	Total Fe loss
		μg/kg/d	
No contraceptive	14	8	22
Oral contraceptive	14	4	18
IUD	14	16	30

Causes of anemia

- Major causes
  - Iron deficiency (1300-2200 m)
  - Hookworm (876 m)
  - Vitamin A deficiency (300 m)
  - Malaria infection (300 m)
- Other Important causes
  - Chronic infections: TB, HIV
  - Other vitamins
  - Genetic defects

Hookworm and Malaria in the Etiology of Iron Deficiency and Anemia



Proportion of Zanzibari children with severe anemia (hemoglobin <80 g/L) by malaria parasite density or hookworm fecal egg counts and age group. Chi-square tests for trends of association: malaria parasite density in age <30 months, P<0.00001, age ≥ 30 months, P>0.20. Hookworm fecal egg counts in age <30 months, P = 0.002, age ≥30, P = 0.005.

Adapted from: Stoltzfus et al, J Nutr 2000

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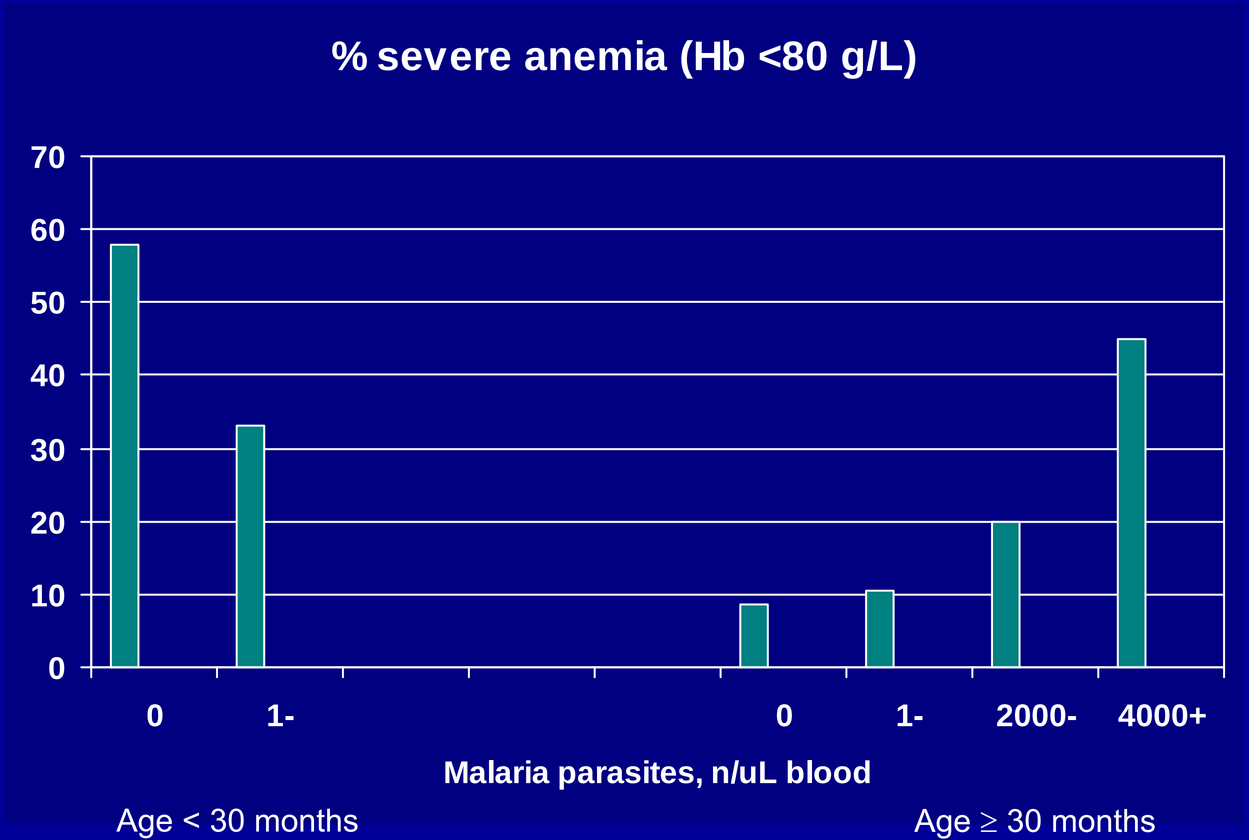

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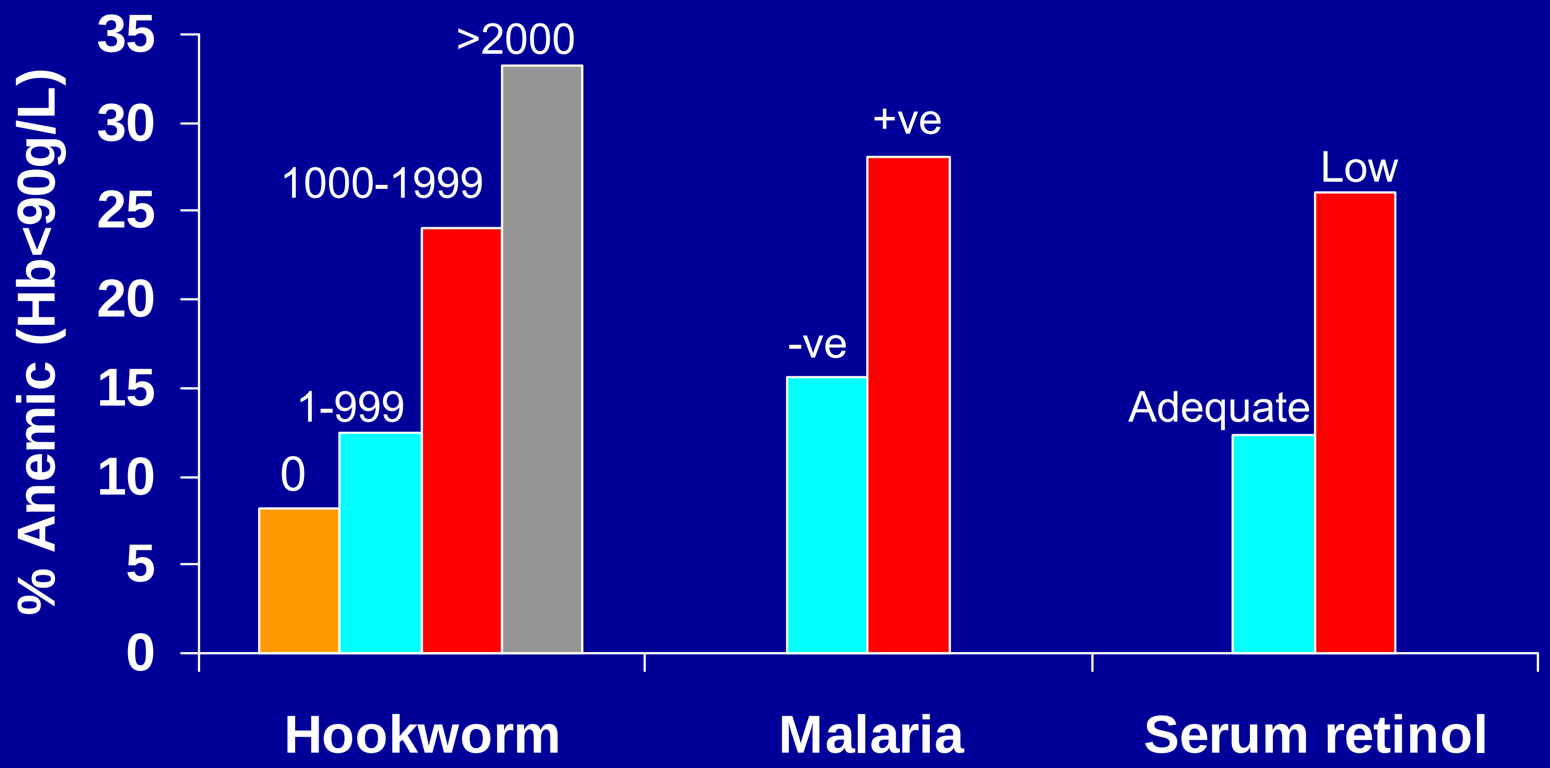
Etiologies of anemia in pregnant rural Nepali women



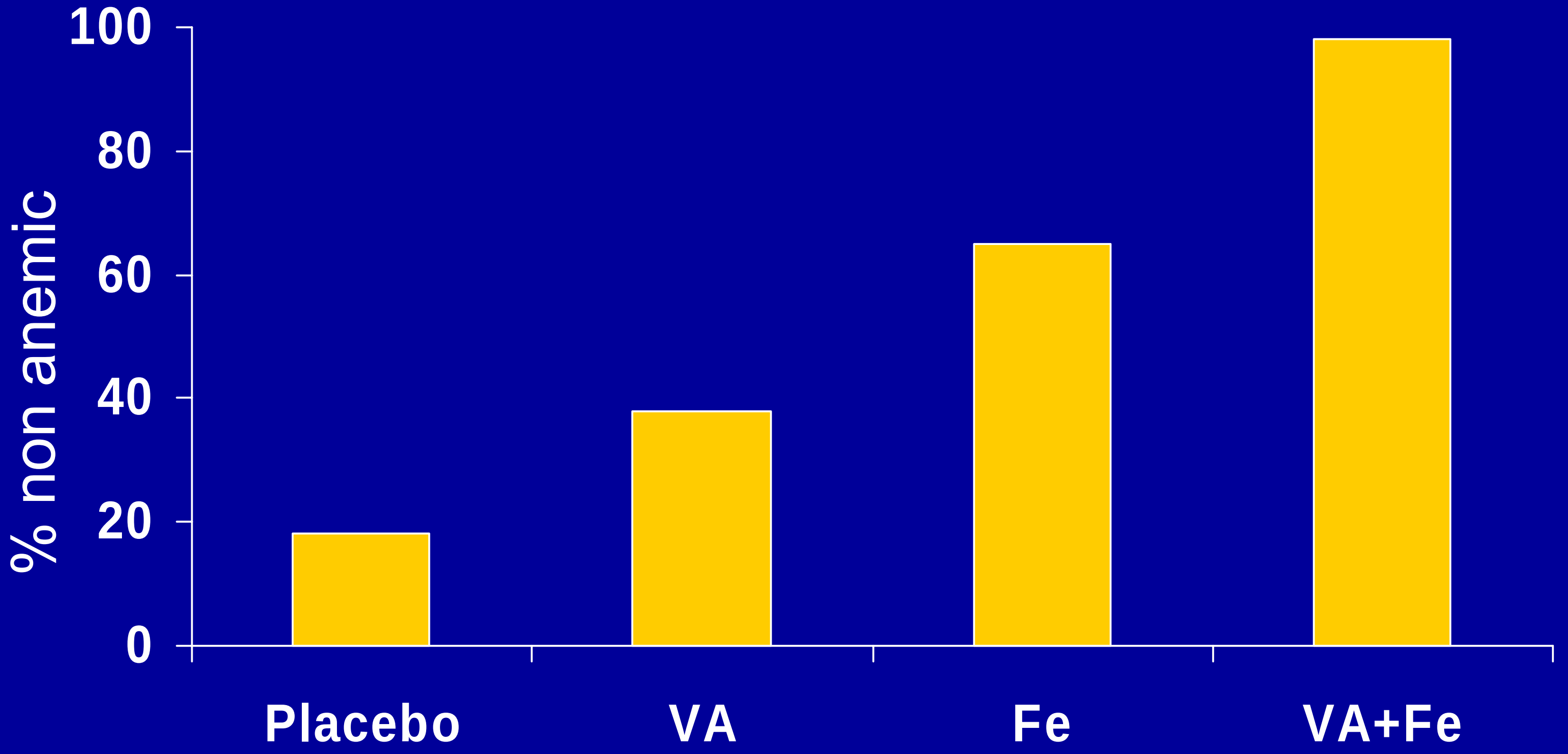
Dreyfuss et al, J Nutr 2000

Deficiency of vitamins may cause anemia

- RBC production (erythropoeisis)
  - VA, FA, B12, B6, riboflavin
- Protect mature RBC free radical oxidation
  - VC, VE
- Fe mobilization
  - VA, VC, riboflavin
- Fe absorption

Fishman, Christian and West et al, PHN 2000

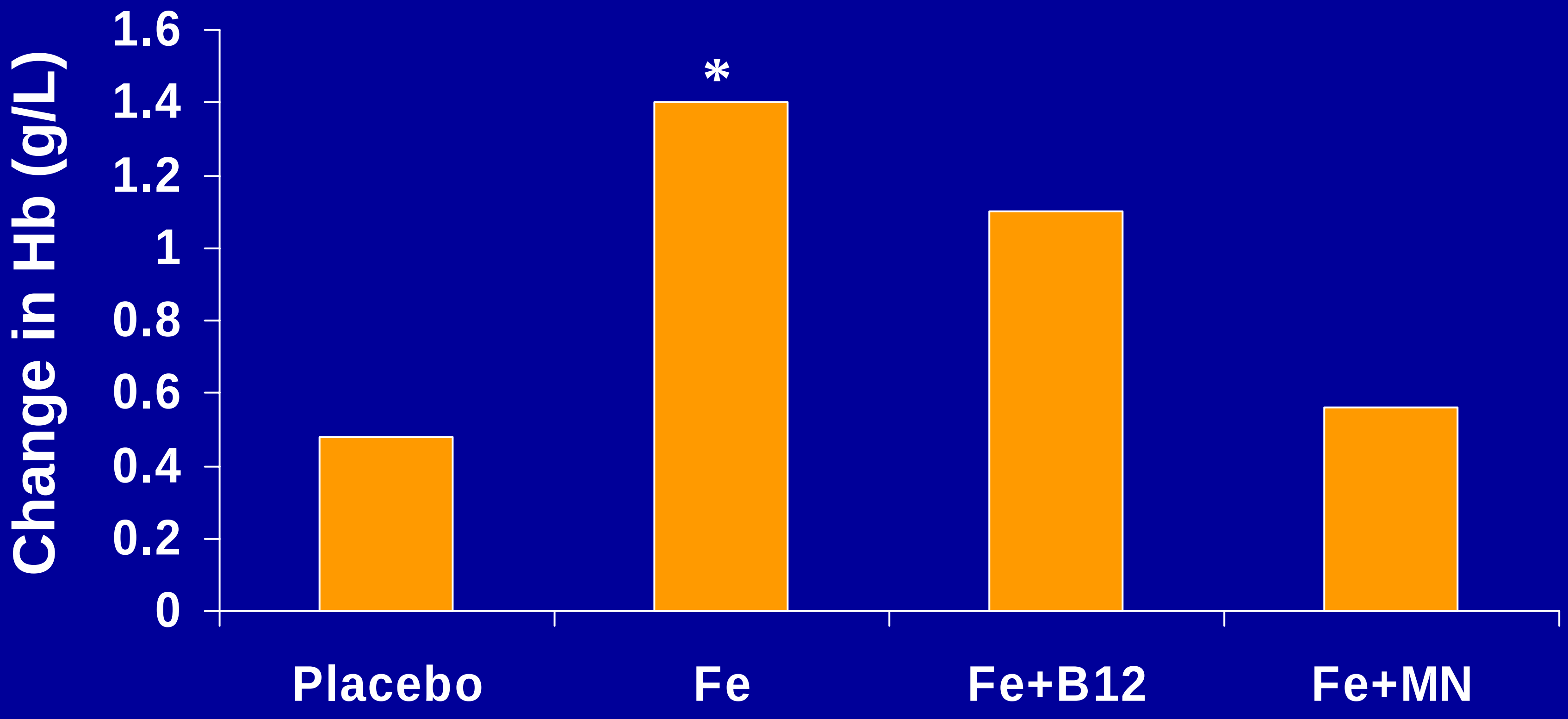
Vitamin A and iron interaction in Indonesian pregnant women



Suharno et al, AJCN 1993

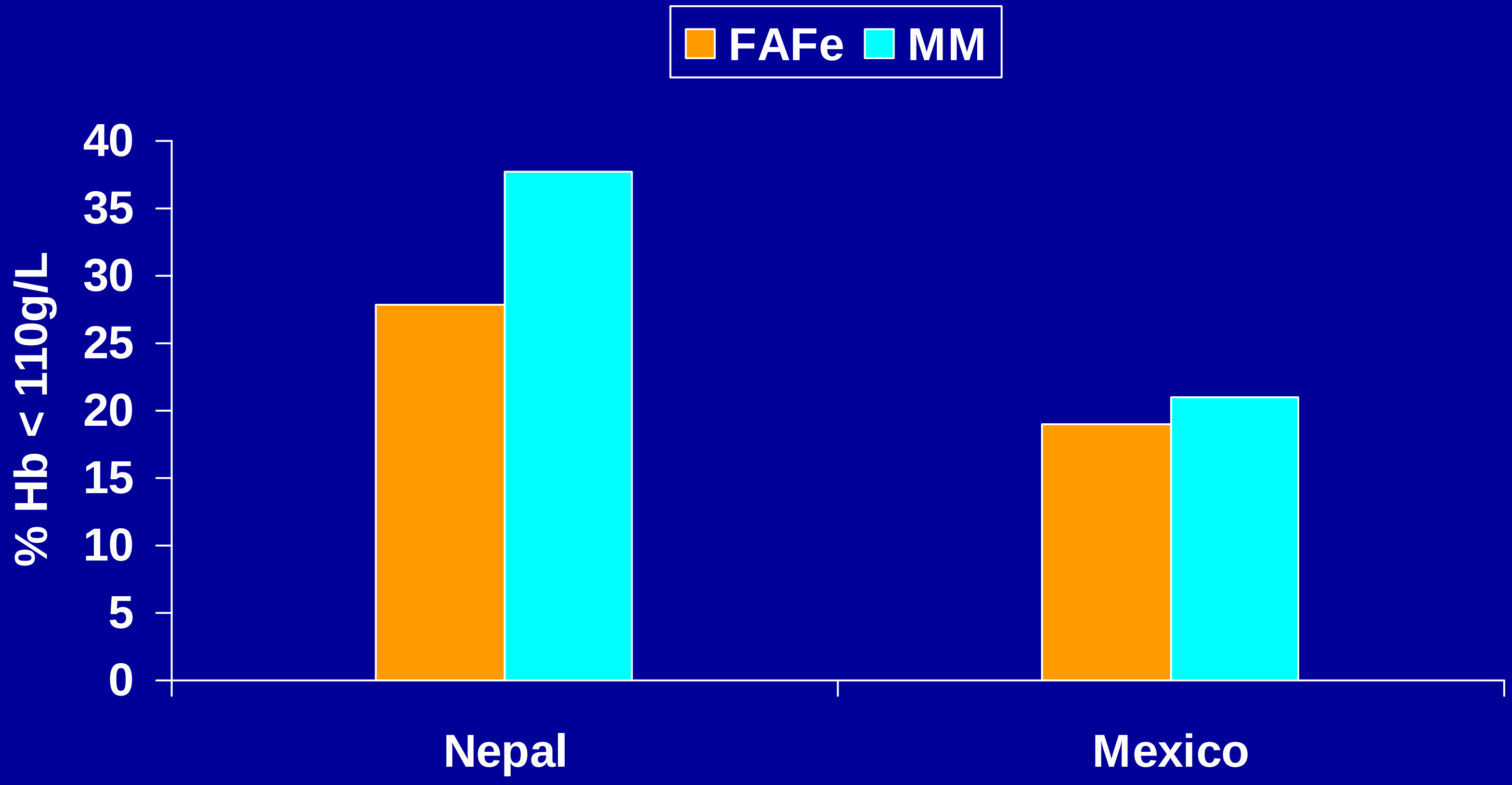
Iron and micronutrients supplementation in anemic Mexican children - RCT

(Lopez et al, J Nutr 2001)



B2, B12, A, B6, E, folic acid, zinc, copper

Impact of antenatal multiple micronutrient supplementation on anemia in the third trimester

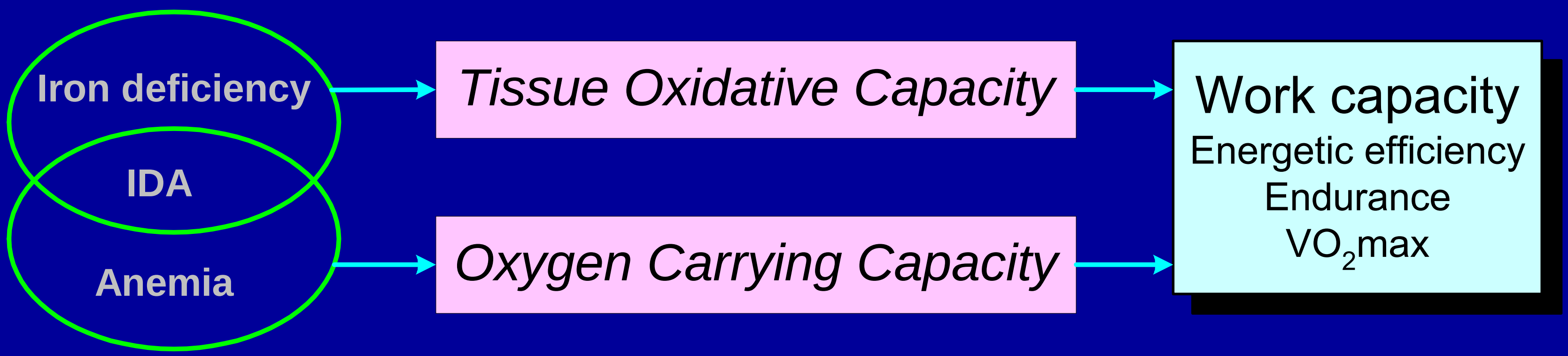


Christian et al, J Nutr 2003; Ramakrishnan et al, J Nutr 2004

Consequences of Iron Deficiency and Anemia

- Decreased work capacity
- Prematurity and LBW
- Perinatal mortality
- Maternal mortality
- Child mortality
- Impaired neurocognitive function in children

Iron and work capacity



Iron deficiency and anemia and work capacity

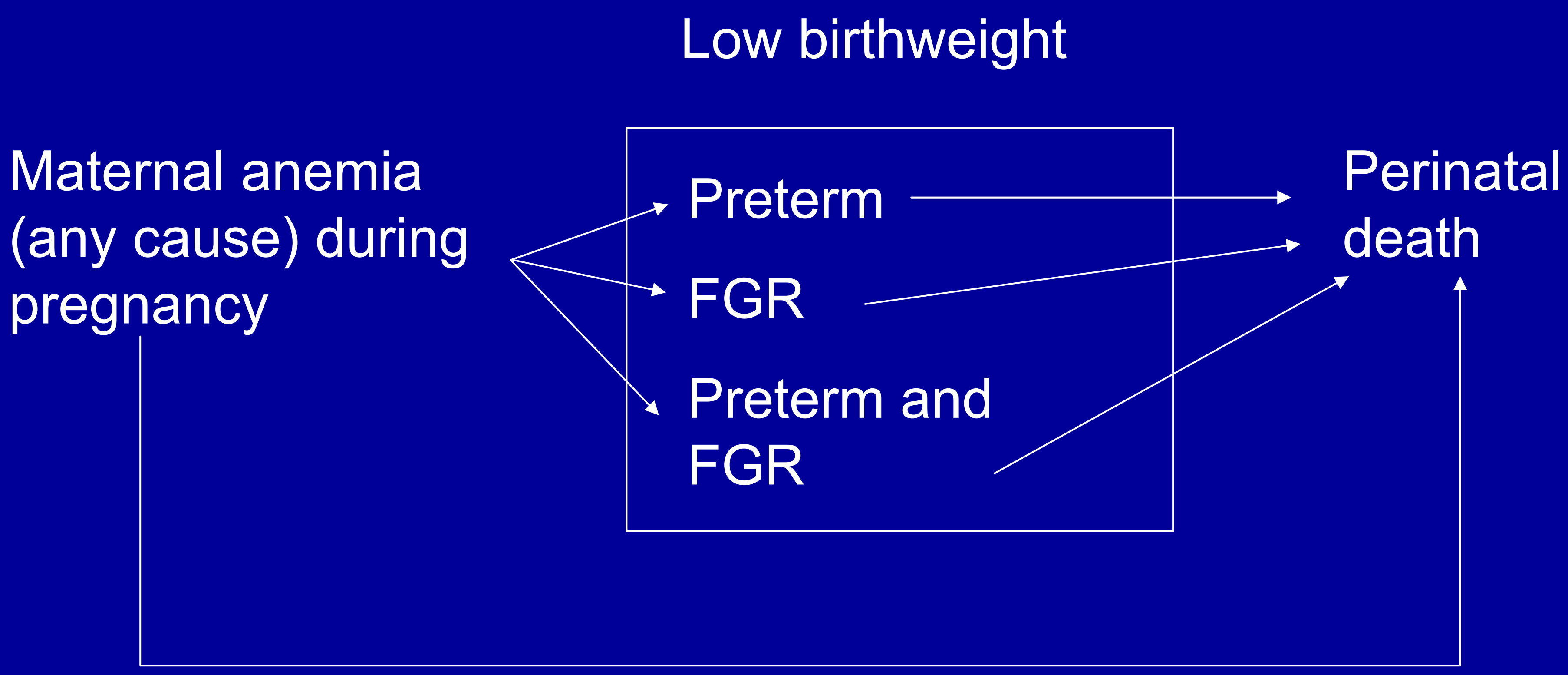
- *Laboratory studies*
- IDA causally associated with 10-50% reduction in VO_2 max
- No clear association between IDA and endurance capacity
- ID may impair energetic efficiency

- *Field studies*
- Provide further causal evidence
- ID and IDA may affect productivity
- Institutional and technological factors may constrain ability or motivation of subjects

What does this mean?

- Productivity losses due to iron deficiency
- Losses to GNP estimated from 6 countries range from 0.85% to 1.27%
- South Asia, where ID is high, loses $ 5 billion annually

Consequences of Pregnancy Anemia

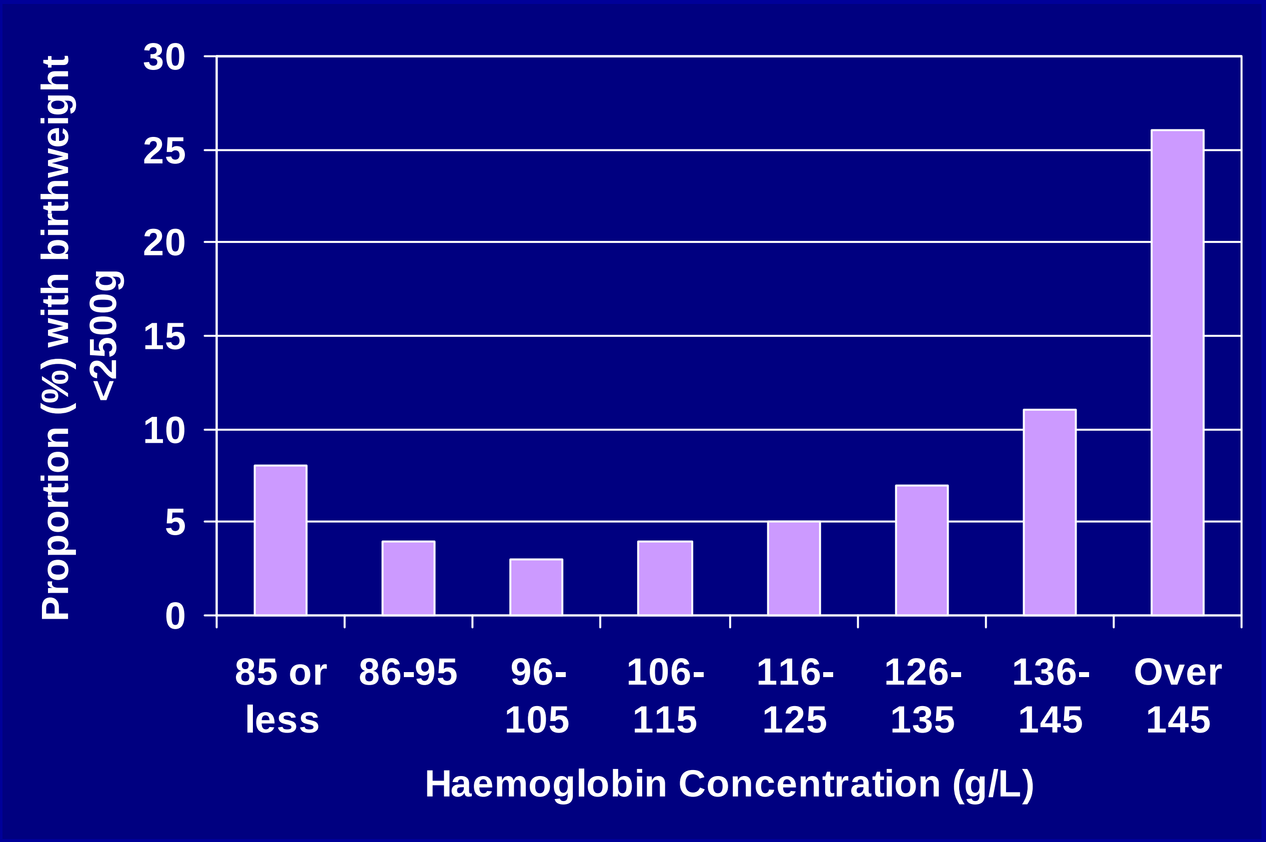


Adapted from Rasmussen, J Nutr 2001

Fetal/Placental development

- Maternal hematocrit determines O_2 tension in amniotic fluid (Nigeria)
- Maternal anemia/iron status influences placental size, morphology
- ID may be associated with increases in maternal ACTH and cortisol

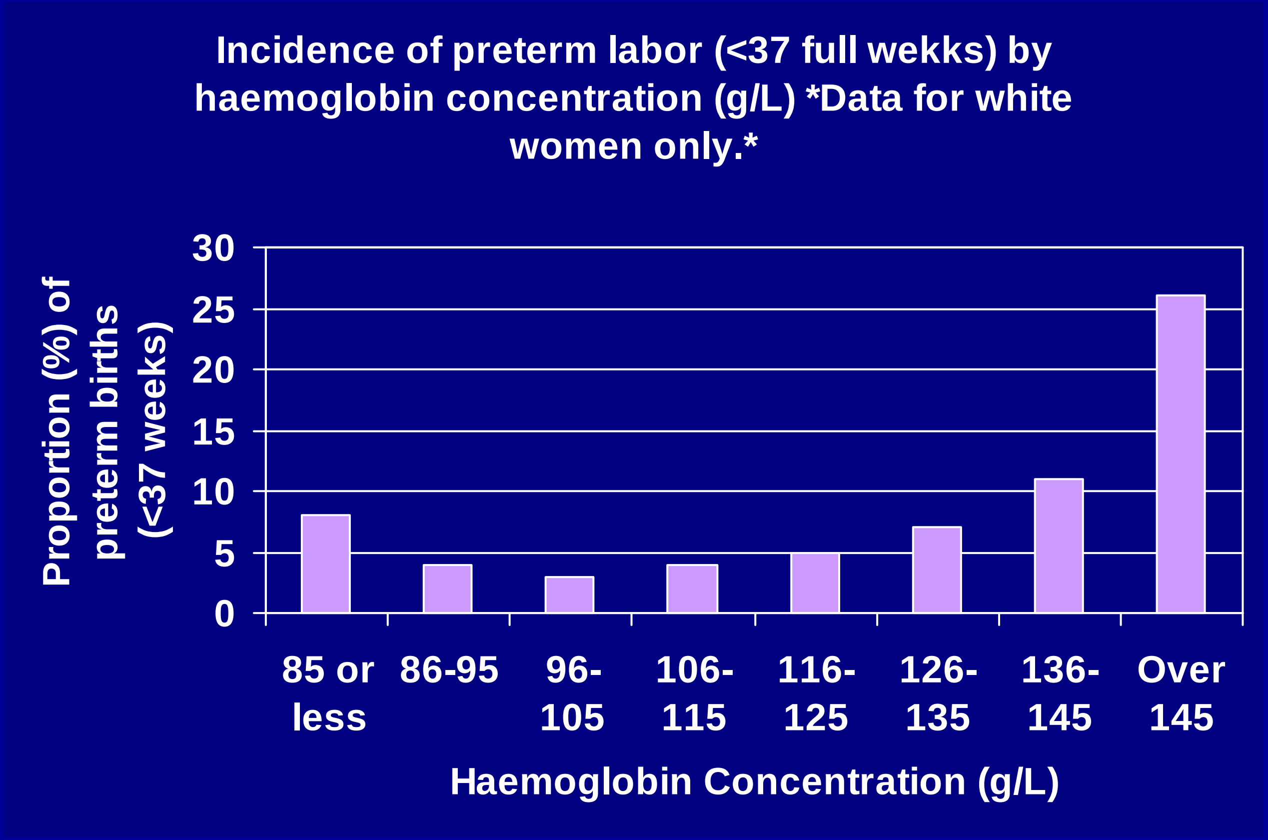
Child Development



Incidence of low birth weight (<2500 g) by haemoglobin concentration (g/L).
Data for white women only.

Adapted from: Steer et al; BMJ 1995

Child Development

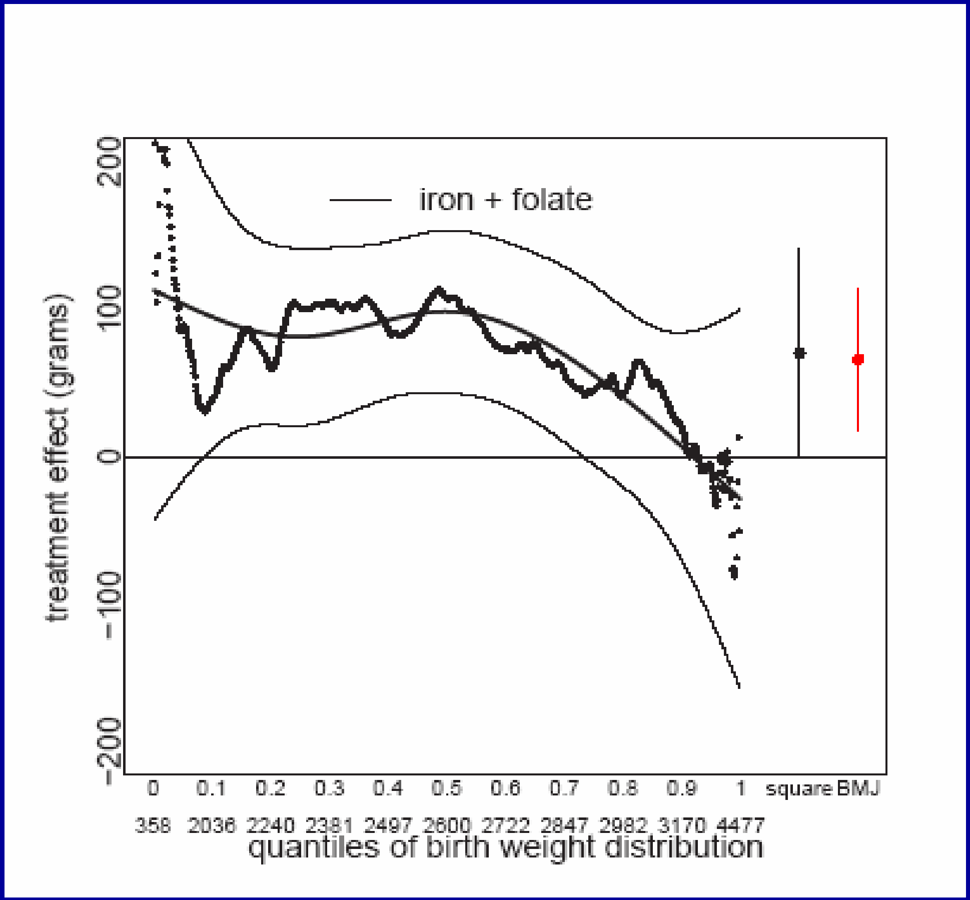


Adapted from: Steer et al; BMJ 1995

Antenatal iron and low birth weight

- All systematic reviews of RCTs have found evidence to be inconclusive (Rasmussen 2000)
  - Mainly because of poorly conducted studies, inadequate design, low sample size, biases
- Recent trials in Nepal and the US found that antenatal iron supplementation increased birth weight

Effect of antenatal iron supplementation on birth weight in rural Nepal



- Iron folate improved birth weight by about 80g for weights below 2800 g

Christian et al; unpublished

Anemia and maternal mortality

- No clinical trials, but strong clinical impression
- “At 6.0g/dL evidence of circulatory decompensation becomes apparent. Women experience breathlessness and increased cardiac output at rest. At this stage, added stress of labor can result in maternal death. Without effective treatment, maternal death from anemic heart failure is likely with Hb concentration of 4.0g/dL. Even a blood loss of 100 ml can cause circulatory shock and death.” (INACG Statement)

Child Mortality

- Relationship through infectious disease incidence is unlikely
- Relationship through anemia is possible, and probably severe anemia of any cause

Nepal Trial

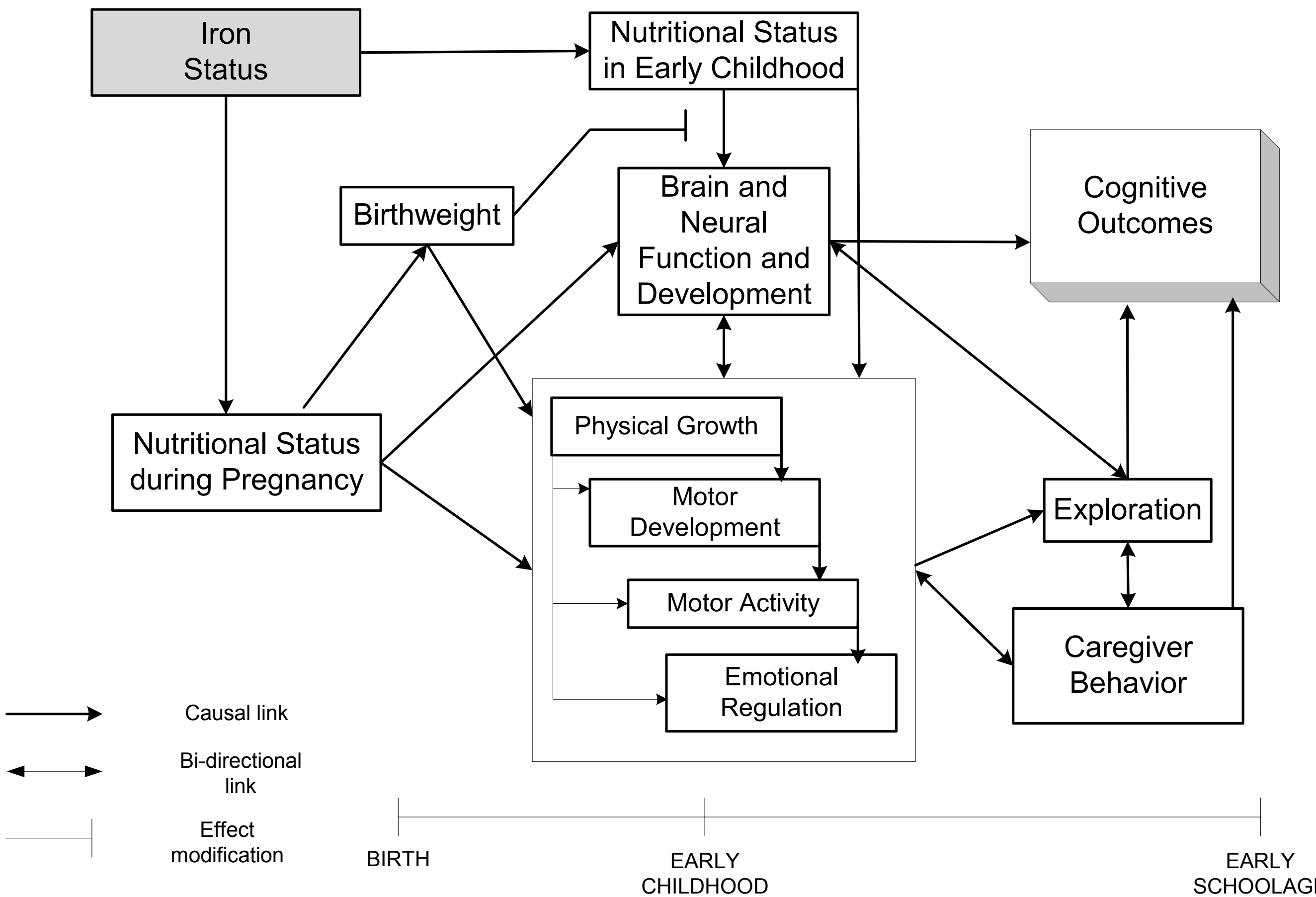
- RCT, 2x2 factorial design
- Placebo, Fe+FA, Zn, Fe+FA+Zn
- Children ages 2-35 mo
- Outcome: Infant/Child survival
- Iron arms of the trial stopped because of a lack of any impact on infant/child survival

Tielsch et al; unpublished

Child Development

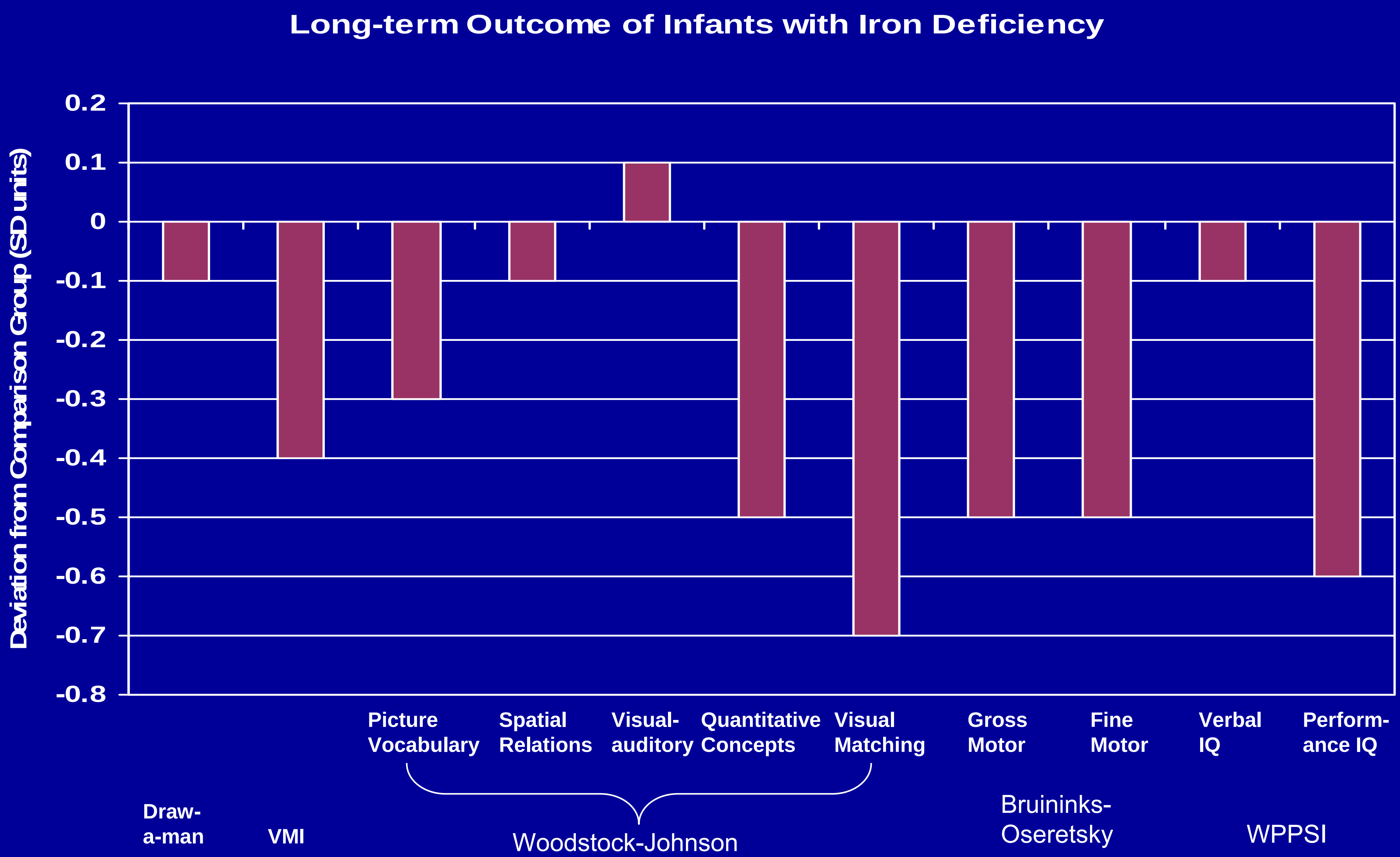
- <u>Iron</u> may affect brain development through decreased brain iron which affects
  - Myelination
  - Neural transmission systems (both neuronal metabolism and dopaminergic functioning)
- Functions affected
  - Delays in maturation of visual, auditory, motor functions and other aspects of neurofunctional development (e.g. recognition memory)
  - Child-caregiver interaction
  - Child “functional isolation” through lack of exploratory movement

Iron status and neurocognitive development



Modified from Pollit E; EJCN 2000

Child Development



Adapted from Lozoff et al; NEJM 1991

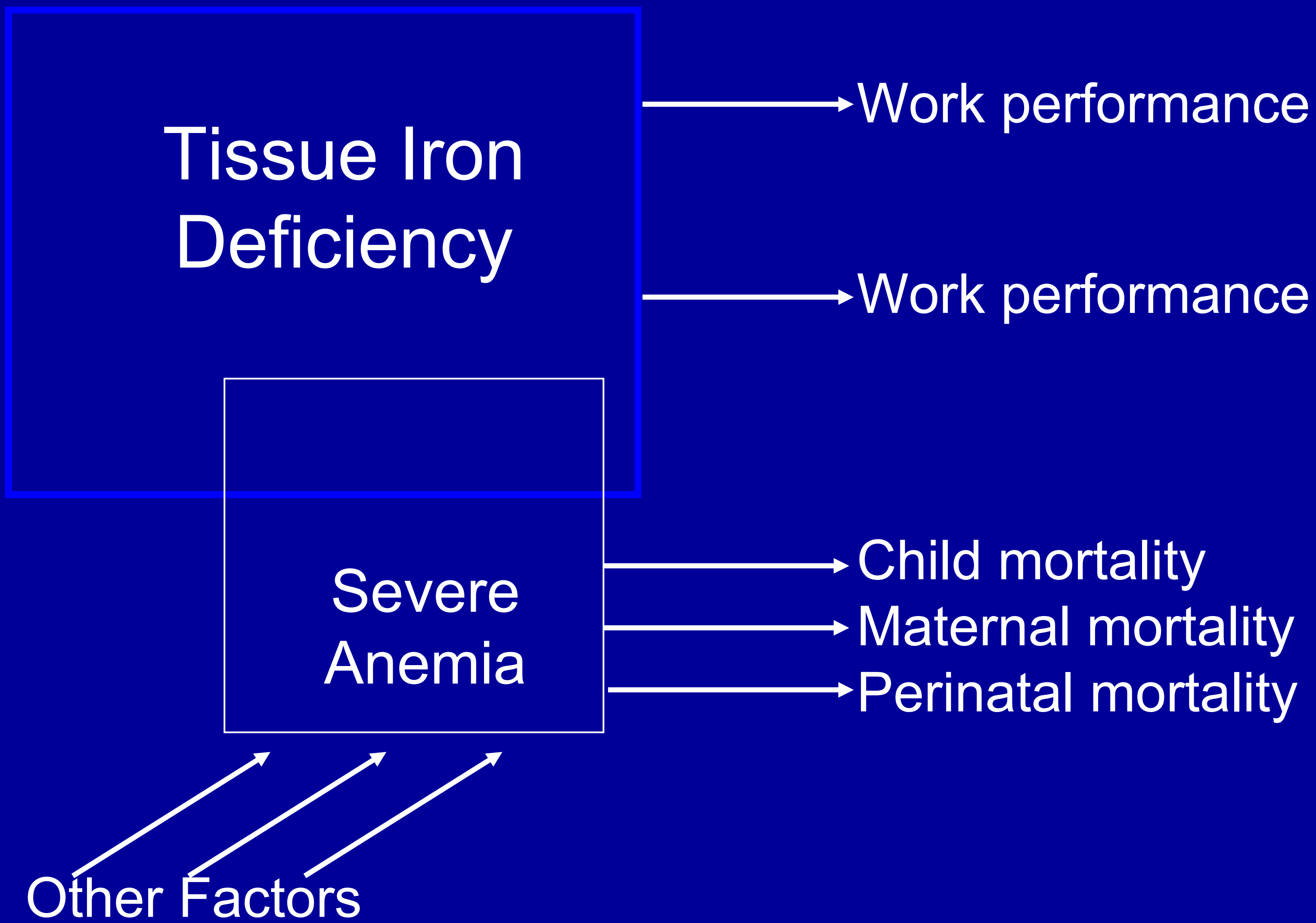
Language scores in four treatment groups with differences in scores showing effects of treatment

Treatment	Final language score*	Difference in score†
Placebo (n=85)	13.1 (12.7 to 13.9)	
Mebendazole (n=85)	13.5 (12.6 to 14.4)	
Iron (n=94)	14.0 (13.2 to 14.8)	
Mb + iron (n=85)	14.2 (13.4 to 15.0)	
Effect of iron *v* no iron		0.8 (0.2 to 1.4)
Effect of Mb vs no Mb		0.3 (−0.3 to 0.9)

Stoltzfus et al; BMJ 2001

Child Development - Summary

- Evidence favors a true relationship, but not conclusive; data from RCTs are not consistent
- Issues of timing, reversibility and optimal intervention remain unresolved
- Predictive and construct validity of Bayley's scales is questionable



Adapted from: Stoltzfus RJ; J Nutr 2001

Iron Supplementation and Infectious Disease

- 3 Systematic reviews:
  - Shankar et al (iron supplementation and malaria)
  - Oppenheimer (all interventions, all ages, all outcomes)
  - Gera and Sachdev (iron supplementation and incidence of infections in children)

INACG Consensus Statement-1999
(based on Shankar et al.)

- "Known benefits of iron supplementation are likely to outweigh the risk of adverse effects caused by malaria…Oral iron supplementation should continue to be recommended in malarious areas where IDA is prevalent".

Belmont meeting* conclusion (based on Oppenheimer)

- Evidence not convincing for or against a relationship of public health significance

* WHO/INACG convened meeting

Oppenheimer SJ; J Nutr 2001

Iron supplementation in young children in Pemba, Zanzibar

- 2x2 factorial study of iron-folic acid and zinc in malaria endemic Pemba island
- The iron arms of the trial were discontinued due to evidence of increased hospitalization and mortality
- In a subsample, where children received treatment for malaria and other infections, iron reduced mortality in iron deficient children

Sazawal, Black, Unpublished

Infectious disease and iron supplementation - summary

- IF an adverse relationship exists, it probably derives from risks of iron intervention, not protective effect of iron
- THUS, question is NOT : Is it better for children to be iron deficient
- BUT RATHER: How can we safely correct iron deficiency?
- Pemba study suggests screening and treatment of malaria and other infections may be required

Prevention and treatment guidelines for iron supplementation (WHO/UNICEF/INACG)

- Pregnant women:
  - Prevention: 60 mg iron + 400 μg folic acid daily for 6 mo in pregnancy
  - Treatment of severe anemia: 120 mg iron + 400 μg folic acid daily for 3 mo
- Children 6-24 mo:
  - Prevention: 12.5 mg iron + 50 μg folic acid daily from 6-12 mo of age or from 2-24 mo of age if lbw
  - Treatment of severe anemia: 25 mg iron + 100-400 μg of folic acid daily for 3 mo
- Children 2-5 yr : 20-30 mg iron
- Where hookworm is endemic, give anthelminthics

Prevention Strategies

- Supplementation of target populations – little success in pregnancy
- Dietary diversification/modification – can it work?
- Fortification –Potential vehicles: cereals, flour, condiments, infant formula. Issues regarding the appropriate vehicle, type of fortificant, organoleptic properties, bioavailability, efficacy and effectiveness

Table 8.1 Different Options for Aims of Iron Supplementation Activities in Terms of Hemoglobin Concentration (Hb)

Aim	Whom to Supplement	Programmatic Implications	How to Evaluate Aim	Advantages	Disadvantages
Reach full Hb potential (prevent and treat)	All	Routine supplementation of all women		All who may benefit receive supplement	Low effectiveness
Prevent low Hb level	Those at risk for low Hb level	Routine or screening	% above low Hb level	Moderate effectiveness	Uncertainty of cut-off levels, difficulties in screening?
Treat low Hb level	Those below low Hb level	Screening low level	% above low Hb level	High effectiveness	Uncertainty of cut-off levels, difficulties in screening?

Adapted from: Ekstrom EC; In: Nutritional anemias (ed Ramakrishnan U). CRC Press 2001

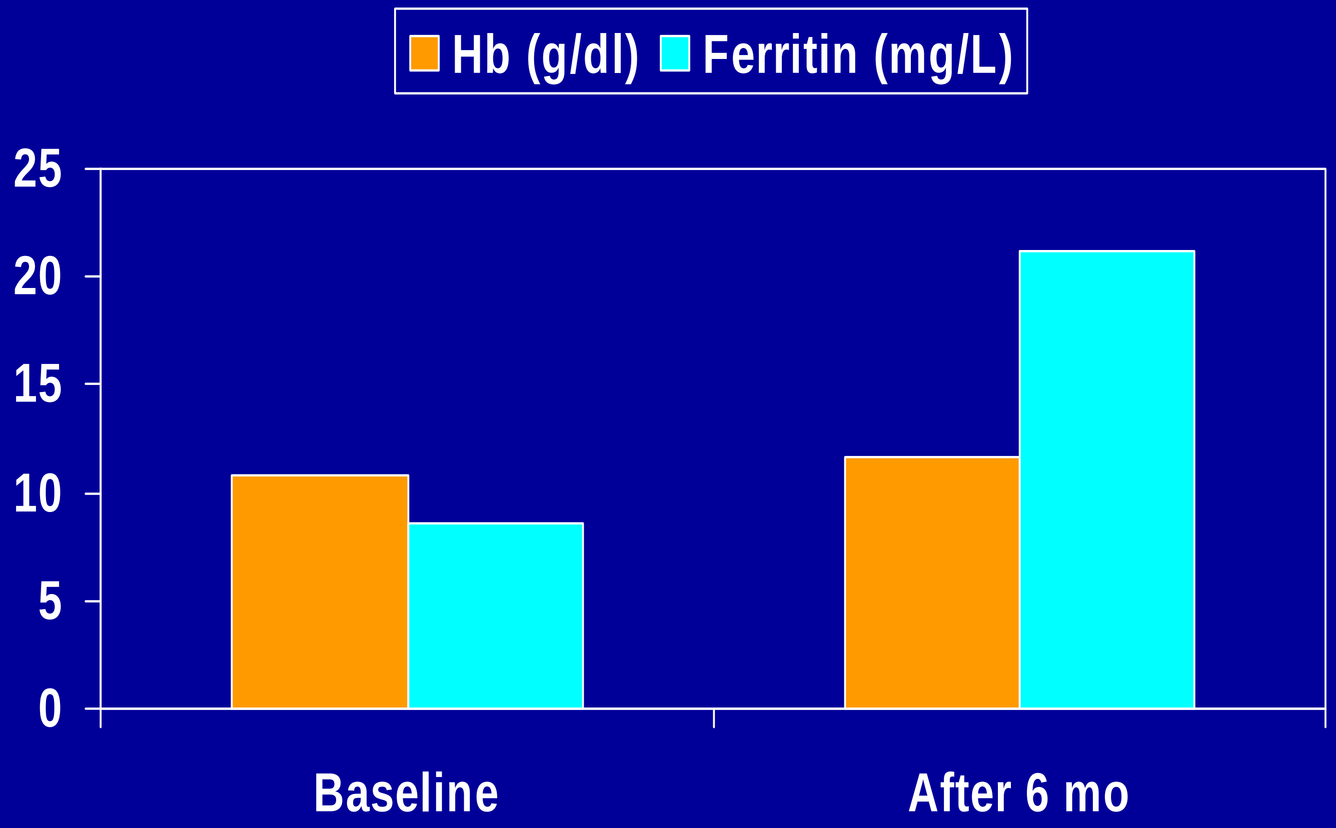
Difficulties in Iron Supplementation

	Thailand	India	Indonesia	Myanmar	Caribbean
Service Utilization	***	****	**	***	*
Tablet supply	***	***	**	**	**
Within-facility factors	**	**	*	*	*
Individual compliance	*	*	*	*	*

**** major constraint   * minor constraint

Effectiveness of iron-fortification

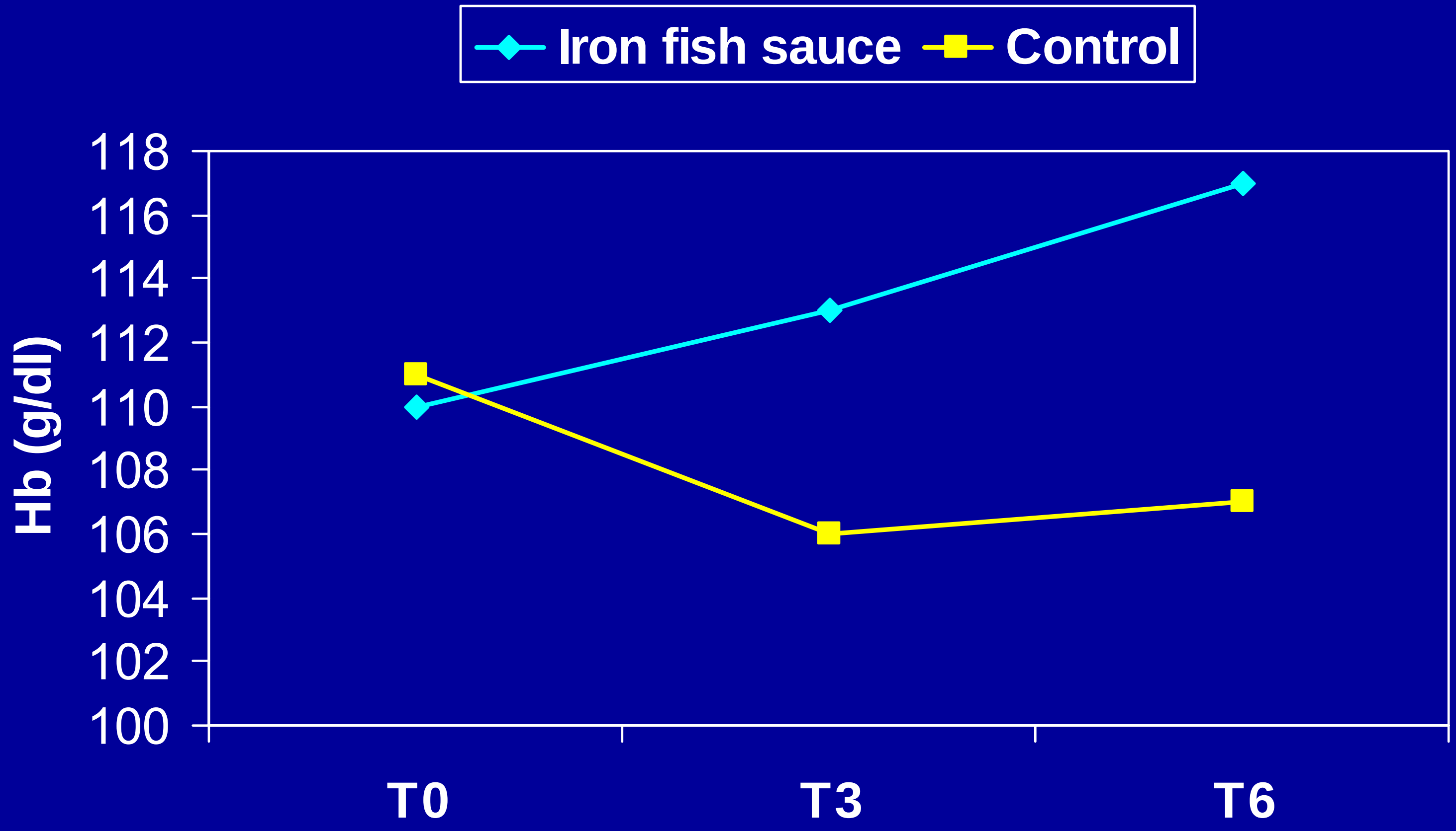
Iron coated-rice among Philippino children



Mannar & Gallego, J Nutr 2002

Effectiveness of iron-fortification

Iron-fortified fish sauce in Vietnam

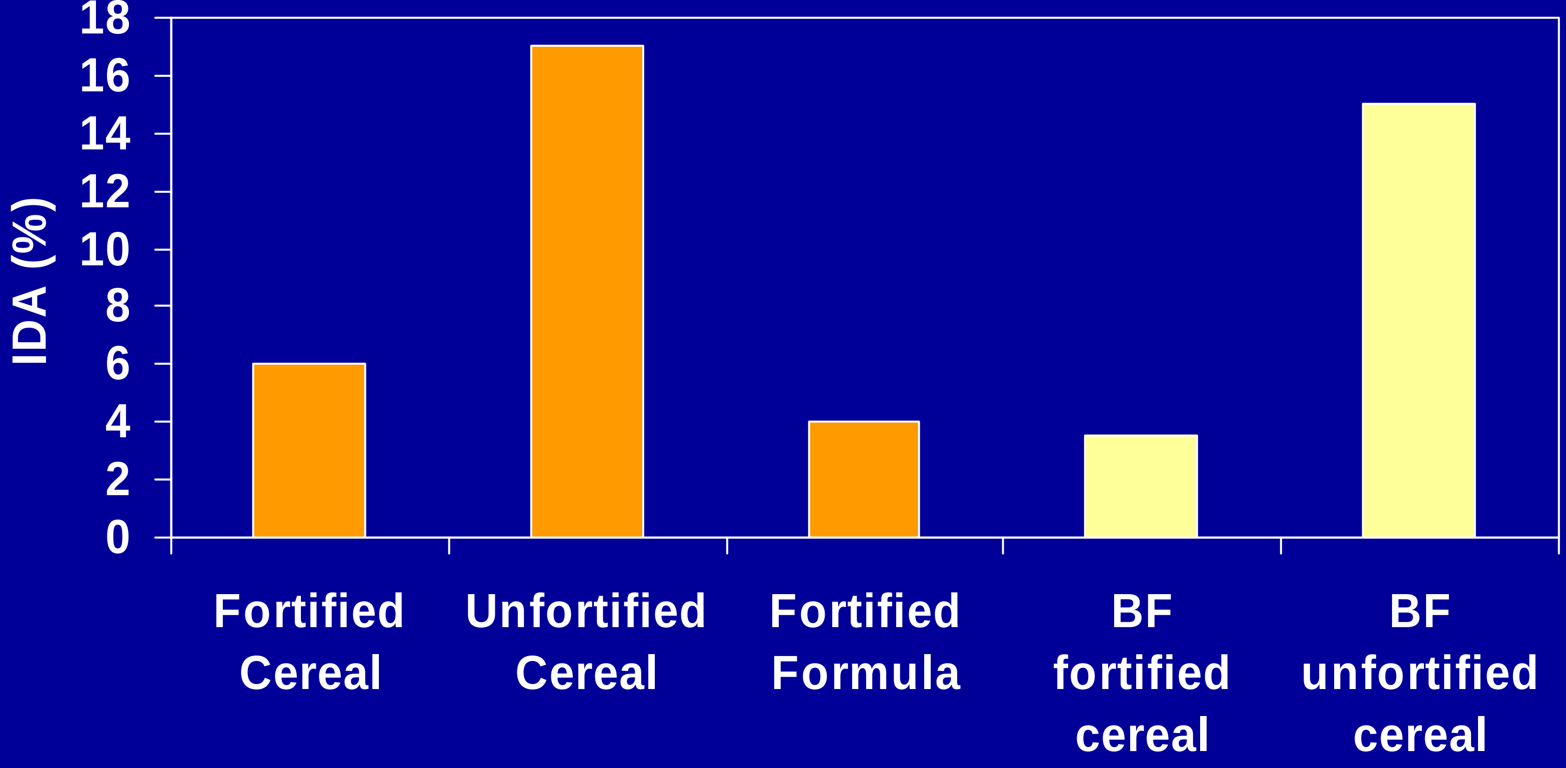


Mannar & Gallego, J Nutr 2002

Special case - Infants

- Infants are born with high iron stores
- Human milk has low iron content but bioavailability is high
- First 2-3 mo of life: exclusively BF infant is in positive iron balance
- During 3-6 mo of life infants are in negative balance
- Foods with bioavailable iron, fortified foods or a low-dose iron supplement should be provided at 6 mo (IOM recommendation)

Prevalence of IDA among 8-mo old infants



Walter et al, Pediatrics 1993

Home-fortification or Sprinkles

- "Sprinkles" are single-dose sachets containing micronutrients in a powdered form, which are easily sprinkled onto any foods prepared in the household
- Great for adding to complementary foods for young children
- Any homemade food can be fortified with the single-dose sachets, hence the term "home fortification".
- Sprinkles Nutritional Anemia Formulation has been tested in infants

Effective control of anemia through combination of strategies

- Increased iron intake
  - Iron supplementation
  - Fortification of foods with iron (especially weaning foods)
- Control of parasitic infections (diagnosis and treatment, chemoprophylaxis, preventing transmission)
- Increased intake of other vitamins such as vitamin A, folic acid through
  - Supplementation, Fortification, Nutrition Education

Summary

- Causes of iron deficiency and anemia are multifactorial
- The strength of causal evidence that ID or anemia affects functional outcomes is variable
- Control of iron deficiency and anemia may require multiple strategies and is context specific