Giving Iron Supplementation to Malaria exposed children: what is the way forward?

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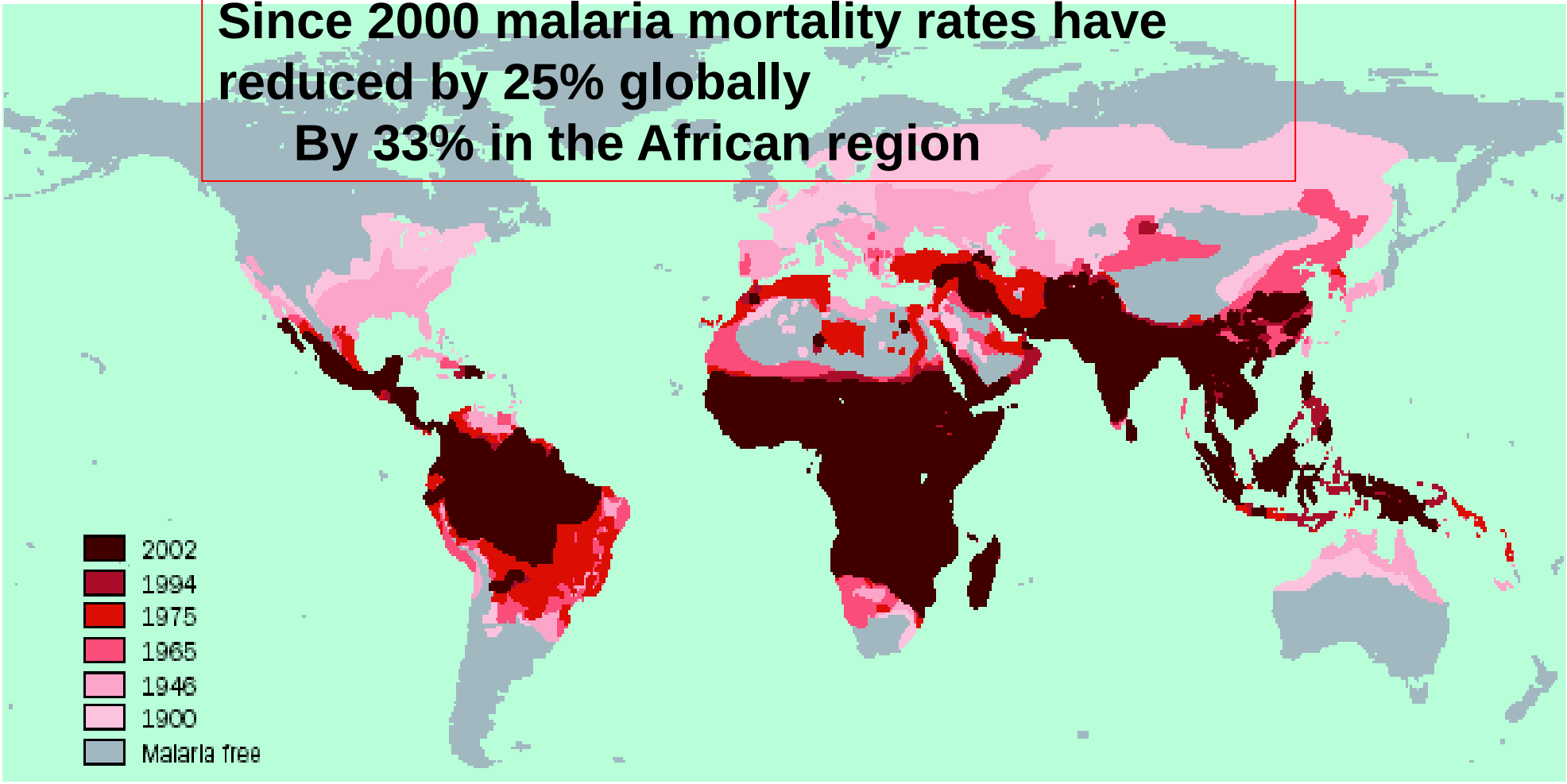
Malaria risk distribution

Since 2000 malaria mortality rates have reduced by 25% globally
By 33% in the African region



Hay et al. The global distribution and population at risk of malaria: past, present, and future. The Lancet Infectious Diseases 2004; 4:327-336.

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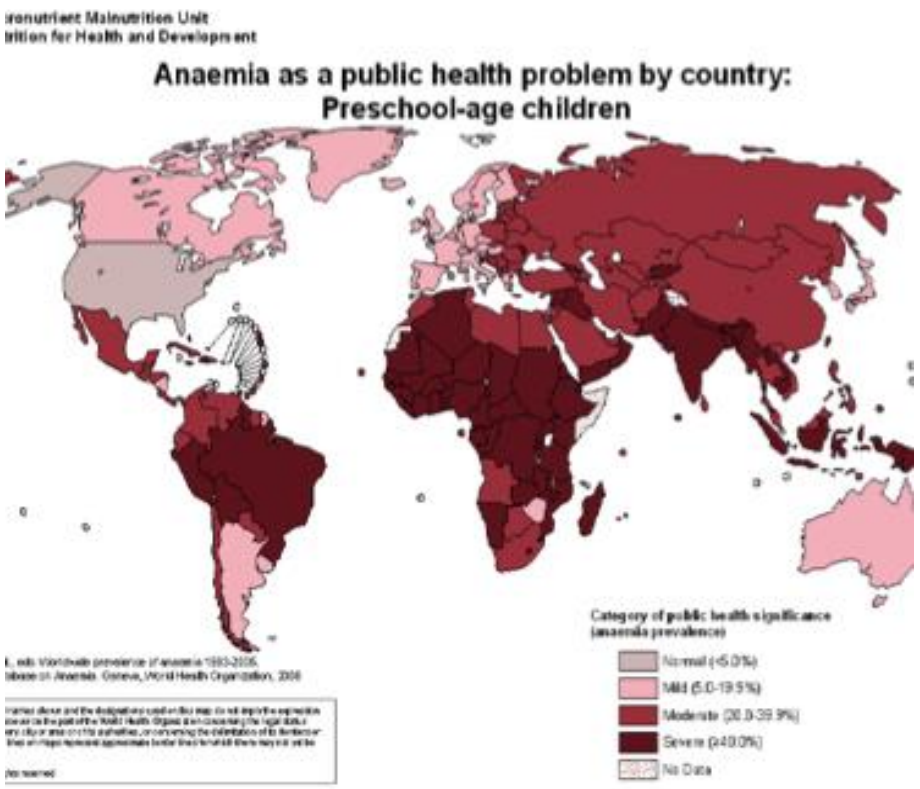
Burden of Iron Deficiency

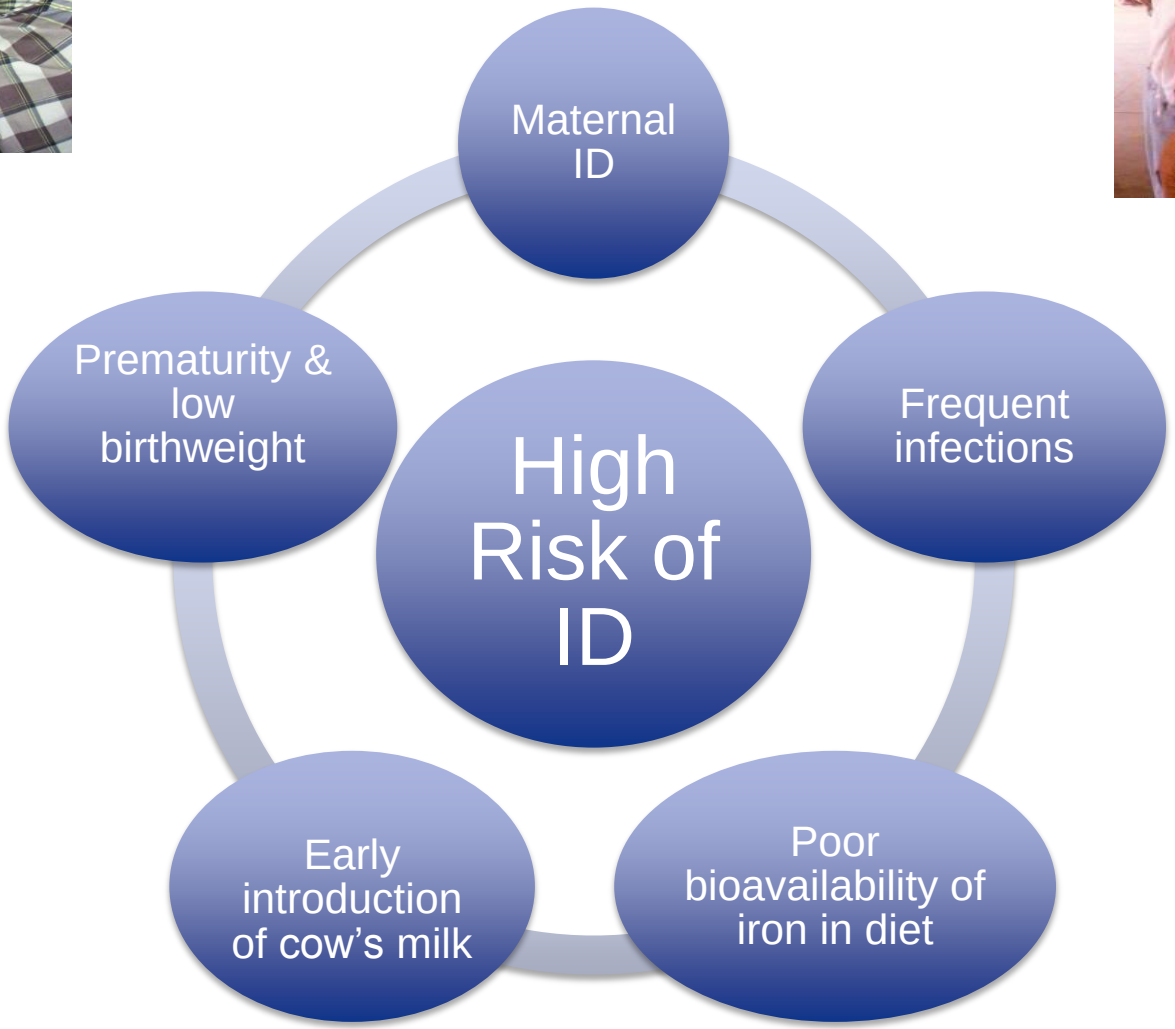
Estimates 1993-2005
WHO



- **In 2010**
  - **ID accounted for**
    - **0·1 million deaths**
    - **Nearly 2% (1·9% [1·4–2·6]) DALYS**
      - Vitamin A and zinc deficiencies amongst children accounted for less than 0·8% of the disease burden
  - **ID is the 13th risk factor for burden of disease globaly**
    - **The 4th factor in sub-saharan Africa**
      - Vit A and Zinc deficiency are in 29 and 31position respecitively and over 6th ranking for SSA but with larger uncertainty

Lim et al. The Lancet 2012

Children <2yr from developing countries at highest risk of IDA



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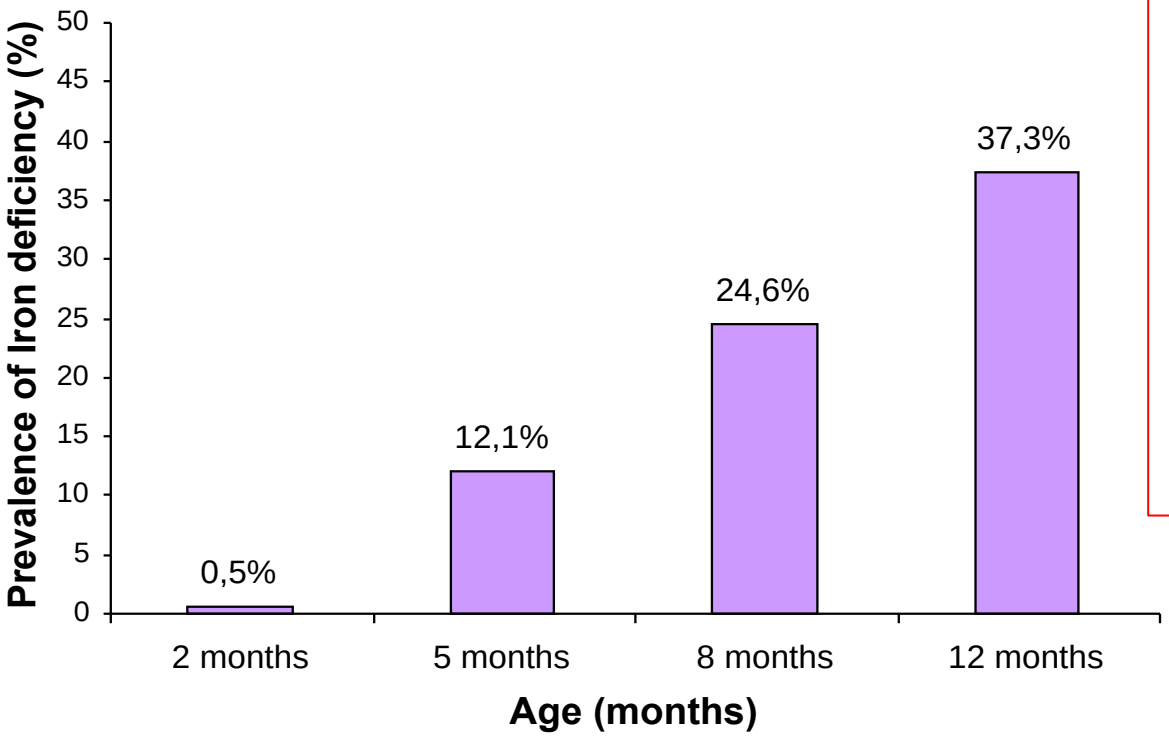
Prevalence of Iron Deficiency by age in (healthy) Tanzanian infants



- **ID definition**
  - (i) - ferritin <12 ng/mL (2- 5 mths) <10 ng/mL (8-12 mths)

or

  - (ii) - iron <11 μg/dL
    and
    - transferrin concentration >347 mg/dL

Menendez et al 2004

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Challenges in the Diagnosis of Iron Deficiency in Children Exposed to High Prevalence of Infections

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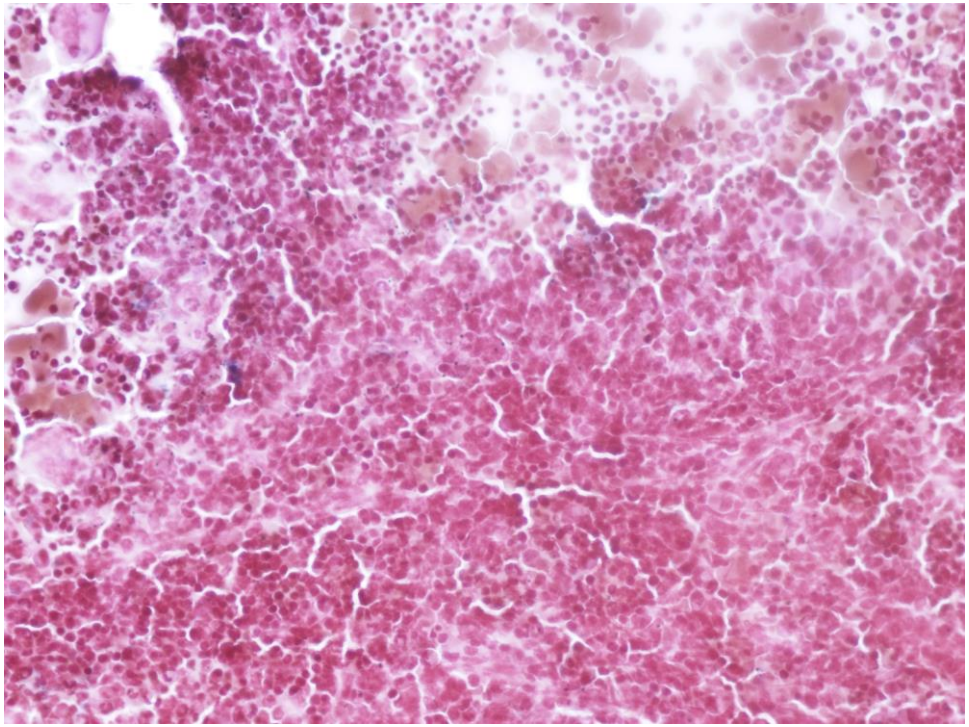
Abstract

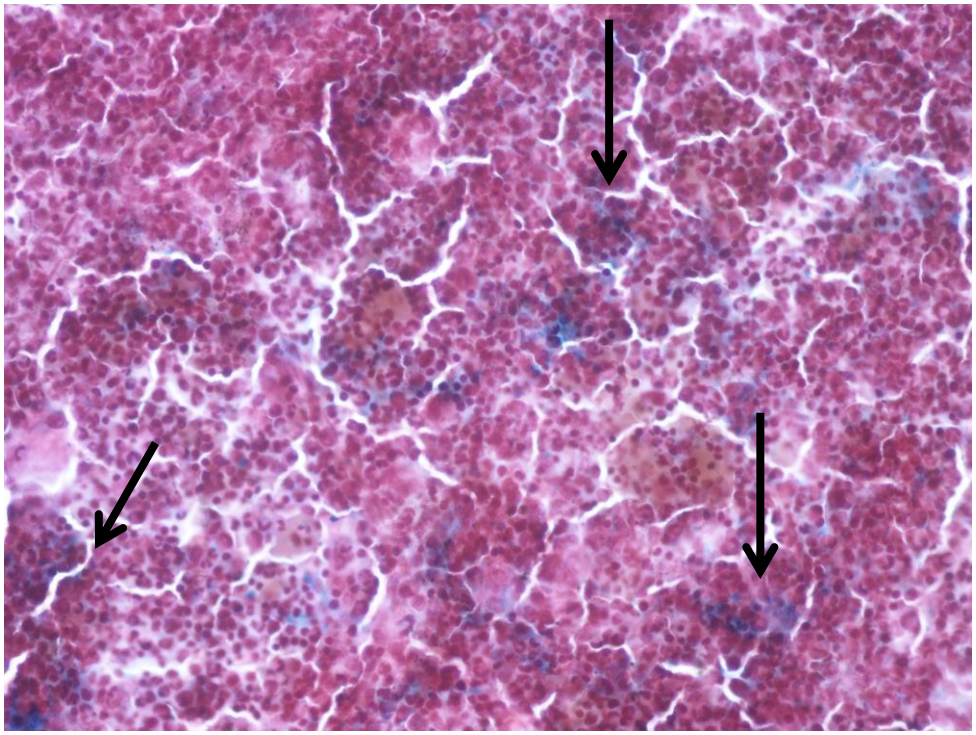
Background: While WHO guidelines recommend iron supplements to only iron-deficient children in high infection pressure areas, these are rarely implemented. One of the reasons for this is the commonly held view that iron supplementation increases the susceptibility to some infectious diseases including malaria. Secondly, currently used markers to diagnose iron deficiency are also modified by infections. With the objective of improving iron deficiency diagnosis and thus, its management, we evaluated the performance of iron markers in children exposed to high infection pressure.

Methodology/Principal Findings: Iron markers were compared to bone marrow findings in 180 anaemic children attending a rural hospital in southern Mozambique. Eighty percent (144/180) of the children had iron deficiency by bone marrow examination, 88% (155/176) had an inflammatory process, 66% (119/180) had moderate anaemia, 25% (45/180) severe anaemia and 9% (16/180) very severe anaemia. Mean cell haemoglobin concentration had a sensitivity of 51% and specificity of 71% for detecting iron deficiency. Soluble transferrin receptor (sTfR) and soluble transferrin receptor/log ferritin (TfR-F) index (adjusted by C reactive protein) showed the highest areas under the ROC curve (AUC^{ROC}) (0.75 and 0.76, respectively), and were the most sensitive markers in detecting iron deficiency (83% and 75%, respectively), but with moderate specificities (50% and 56%, respectively).

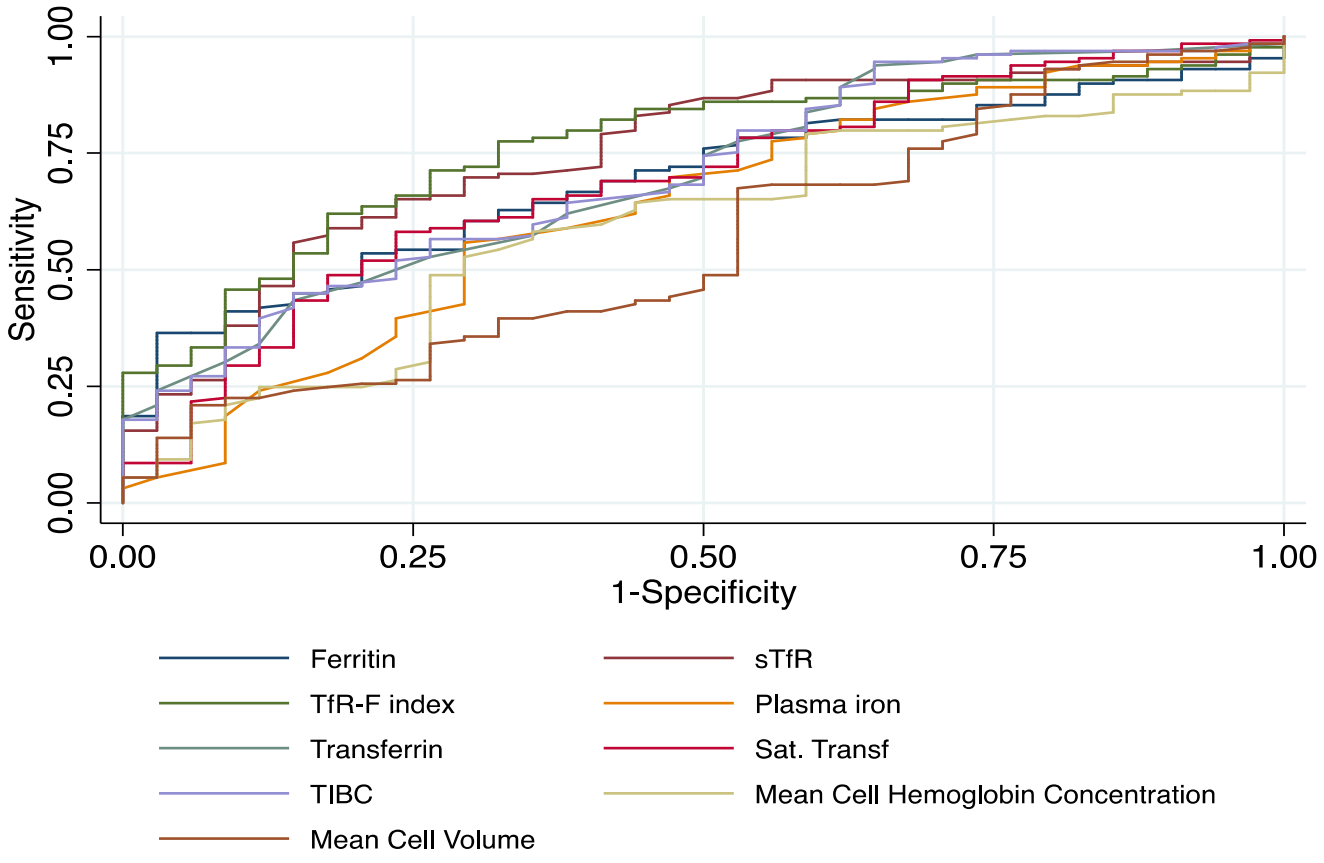
Conclusions/Significance: Iron deficiency by bone marrow examination was extremely frequent in these children exposed to high prevalence of infections. However, even the best markers of bone marrow iron deficiency did not identify around a quarter of iron-deficient children. Tough not directly extrapolated to the community, these findings urge for more reliable, affordable and easy to measure iron indicators to reduce the burden of iron deficiency anaemia in resource-poor settings where it is most prevalent.

- **80% of the children had iron deficiency by bone marrow examination**





ROC curves

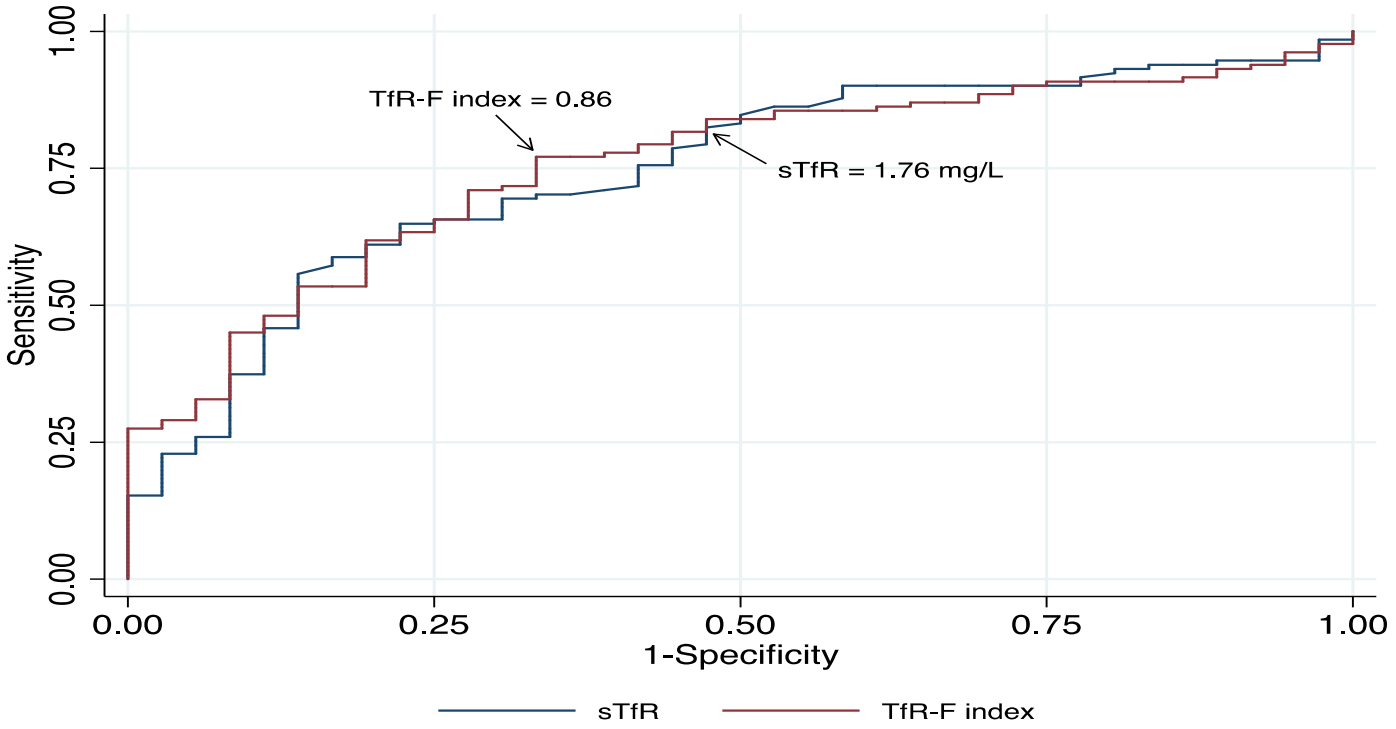

Sensitivity
0.00
0.25
0.50
0.75
1.00
1-Specificity
0.00
0.25
0.50
0.75
1.00
Ferritin
TfR-F index
Transferrin
TIBC
Mean Cell Volume
sTfR
Plasma iron
Sat. Transf
Mean Cell Hemoglobin Concentration

AUCROC values for iron markers to identify children with iron stores deficiency

Iron marker	Area under ROC curve	(95% Conf. Interval)	p-value *
TfR-F index	0.76	(0.68, 0.85)	0.0024
sTfR	0.75	(0.66, 0.84)	0.0059
TIBC	0.71	(0.61, 0.81)	0.0280
Transferrin	0.71	(0.61, 0.81)	0.0298
Ferritin	0.70	(0.61, 0.79)	0.0268
Sat. Transf	0.70	(0.60, 0.80)	0.0326
Plasma iron	0.64	(0.53, 0.75)	0.1584
Mean Cell Hemoglobin Concentration	0.59	(0.49, 0.70)	0.3382
Mean Cell Volume	0.55	(0.43, 0.66)	0.6311

* Comparison of each area under ROC curve with 0.5 which is the random classification corresponding to an ineffective test.

ROC curves



- The sensitivity and specificity to detect ID were
  - TfR-F: 78% and 65%
  - sTfR: 83% and 50%

- The best indirect indicators of ID failed to detect an important proportion of iron-deficient cases
- Their assessment is not feasible in most developing settings

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Attributable fractions of risk factors independently associated with anemia (Hb<11g/dl) in Mozambican children 1-59 months of age case-control study

Number of Cases for model estimation: 303

Risk Factor	Proportion of cases with factor (%)	Adjusted Association		Adjusted Attributable Fraction		Attributable cases
		Odds Ratio	(95% CI)	Estimate (%)	(95% CI)	
Plasmodium falciparum infection	90.1	7.11	(3.55; 14.24)	77.42	(68.62; 86.23)	235
Iron deficiency	**70.0**	**4.05**	**(2.16; 7.61)**	**52.71**	**(41.85; 63.57)**	**160**
Vitamin A deficiency	49.2	8.10	(3.82; 17.18)	43.10	(38.54; 47.67)	131
Plasmodium falciparum infection	42.2	8.39	(3.82; 18.40)	37.21	(33.25; 41.16)	113
Albumin deficiency	39.6	4.29	(1.78; 10.35)	30.37	(22.24; 38.51)	92
Iron deficiency	21.5	5.73	(1.65; 19.92)	17.71	(13.05; 22.37)	54
ALL RISK FACTORS IN MODEL				*97.51*	*(96.16; 98.87)*	*295*

Moraleda et al submitted

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207 infants -Placebo-Placebo

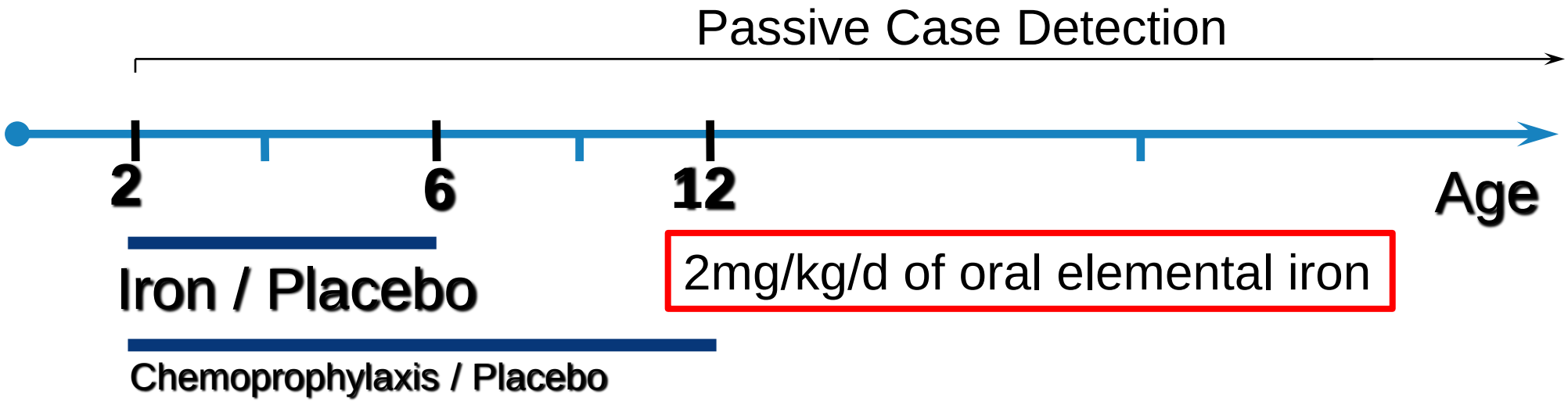
204 infants -Iron-Placebo

988
Two months old infants

213 infants- Chem-Iron

208 infants- Chem-Placebo

Supplementation periods



Menendez et al 1998

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Iron Deficiency

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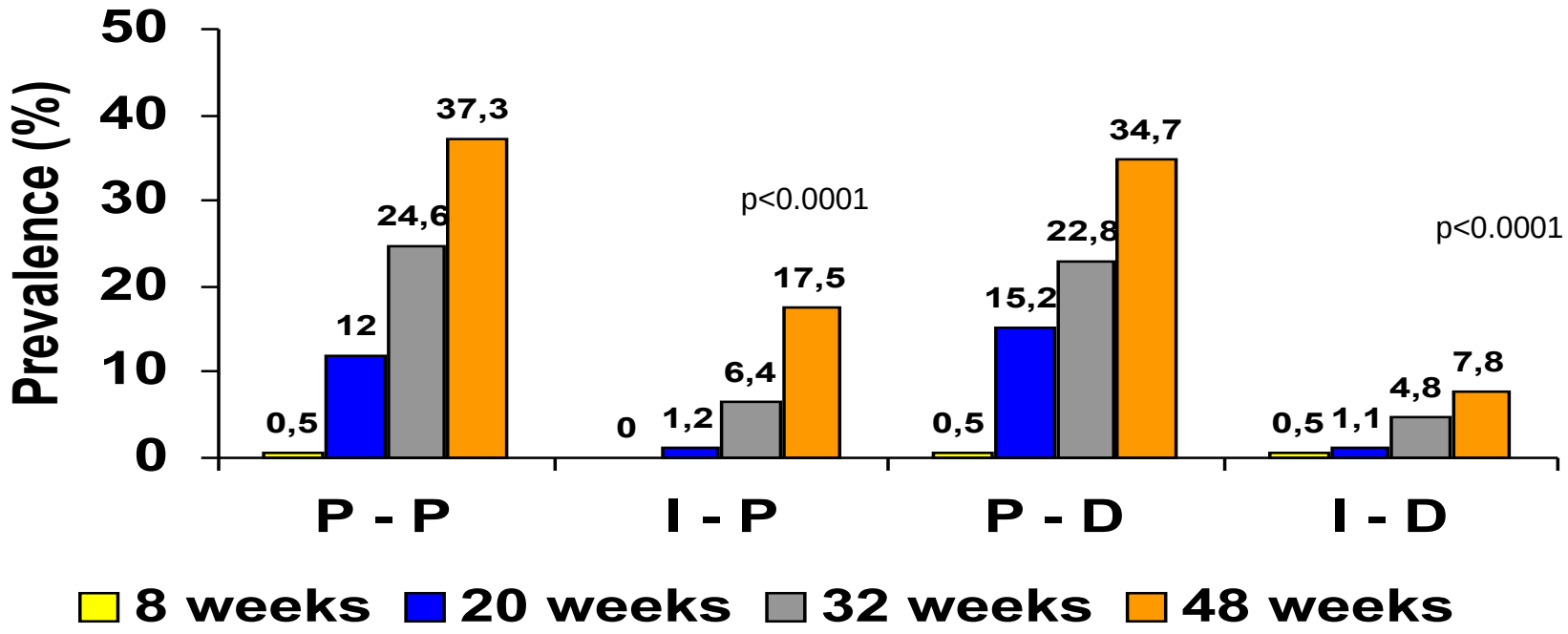


- **The effect of iron supplementation lasted for 6 months after the intervention was finished**

Table 2. Efficacy of iron supplementation from 2 to 6 months of age on anaemia prevention during different periods of follow-up

Outcome	Placebo group			Iron Supplementation group			RR	(95% CI)	p
	episodes	pyar	incidence	episodes	pyar	incidence			
During Iron supplementation (2 to 6 months of age)									
Severe Anaemia*	36	57,1	0,631	19	57,7	0,329	0,52	(0.30, 0.91)	0,019
Severe Anaemia - Multiple episodes	45	58,9	0,765	20	58,8	0,340	0,42	(0.23, 0.77)	0,004
During 6 months after iron supplementation (6 to 12 months of age)									
Severe Anaemia	64	83,8	0,764	44	87,4	0,503	0,66	(0.45, 0.97)	0,032
Severe Anaemia - Multiple episodes	75	96,1	0,781	49	95,8	0,512	0,65	(0.44, 0.95)	0,024
Extended follow-up (from 12 to 48 months of age)									
Severe Anaemia	53	381,4	0,139	53	370,7	0,143	1,03	(0.70, 1.51)	0,883
Severe Anaemia - Multiple episodes	74	488,5	0,151	85	466,8	0,182	1,24	(0.83, 1.86)	0,285

* Severe anaemia= Packed Cell Volume <25%

Outcome	Placebo group			Iron Supplementation group			RR	(95% CI)	p
	episodes	pyar	incidence	episodes	pyar	incidence			
During Iron supplementation (2 to 6 months of age)									
Clinical Malaria (fever * and *P. falciparum* > 0)	43	55,1	0,781	37	56	0,661	0,85	(0.55, 1.31)	0,455
Clinical Malaria (fever * and *P. falciparum* > 20000)	30	57,0	0,526	24	57,6	0,417	0,79	(0.46, 1.36)	0,394
Severe Malaria	22	59,2	0,371	11	59,2	0,186	0,50	(0.24, 1.03)	0,054
Clinical Malaria - multiple episodes	58	57,9	1,003	46	57,3	0,803	0,77	(0.46, 1.29)	0,320
Hospital admissions	73	61,5	1,186	48	59,9	0,801	0,67	(0.44, 1.03)	**0,069**
Fever - multiple episodes	159	51,1	3,114	139	51,3	2,712	0,86	(0.67, 1.11)	0,240
Pneumonia	25	60,4	0,414	10	59,5	0,168	0,40	(0.19, 0.86)	**0,014**
Respiratory distress	25	60,4	0,414	11	59,6	0,184	0,45	(0.22, 0.91)	**0,020**
Diarrhoea	77	56,4	1,364	65	55,4	1,174	0,86	(0.61, 1.21)	0,385

Outcome	Placebo group			Iron Supplementation group			RR	(95% CI)	p
	episodes	pyar	incidence	episodes	pyar	incidence			
During 6 months after iron supplementation (6 to 12 months of age)									
Clinical Malaria (fever * and *P. falciparum* > 0)	70	81,0	0,864	64	81,1	0,789	0,91	(0.65, 1.28)	0,601
Clinical Malaria (fever * and *P. falciparum* > 20000)	46	87,7	0,524	42	87	0,483	0,92	(0.61, 1.40)	0,698
Severe Malaria	27	92,4	0,292	17	93,7	0,181	0,62	(0.34, 1.14)	0,119
Clinical Malaria - multiple episodes	93	94,8	0,981	85	92,9	0,915	0,94	(0.66, 1.34)	0,725
Hospital admissions	134	101,4	1,321	103	98,8	1,043	0,79	(0.59, 1.06)	0,115
Fever - multiple episodes	301	79,2	3,800	275	78	3,525	0,93	(0.78, 1.09)	0,368
Pneumonia	44	98,7	0,446	28	97	0,289	0,65	(0.38, 1.10)	0,111
Respiratory distress	38	99,0	0,384	27	97,3	0,277	0,74	(0.41, 1.31)	0,298
Diarrhoea	156	90,2	1,730	150	87,8	1,709	0,99	(0.76, 1.29)	0,926
Extended follow-up (from 12 to 48 months of age)									
Clinical Malaria (fever * and *P. falciparum* > 0)	117	253,0	0,463	120	228,5	0,525	1,14	(0.88, 1.46)	0,328
Clinical Malaria (fever * and *P. falciparum* > 20000)	90	314,2	0,286	94	296,2	0,317	1,11	(0.83, 1.48)	0,486
Severe Malaria	36	428,0	0,084	32	413,9	0,077	0,92	(0.57, 1.48)	0,728
Clinical Malaria - multiple episodes	335	468,6	0,715	311	448,1	0,694	0,97	(0.75, 1.25)	0,821
Hospital admissions	371	494,7	0,750	349	472,3	0,739	1,00	(0.78, 1.26)	0,971
Fever - multiple episodes	769	433,3	1,775	743	412,9	1,800	1,01	(0.87, 1.18)	0,909
Pneumonia	97	487,9	0,199	87	466,2	0,187	0,93	(0.63, 1.38)	0,729
Respiratory distress	65	490,5	0,133	52	469,1	0,111	0,82	(0.50, 1.35)	0,436
Diarrhoea	244	475,7	0,513	239	453,9	0,527	1,06	(0.83, 1.35)	0,658

Figure 2.b. Cumulative Hazard of clinical malaria

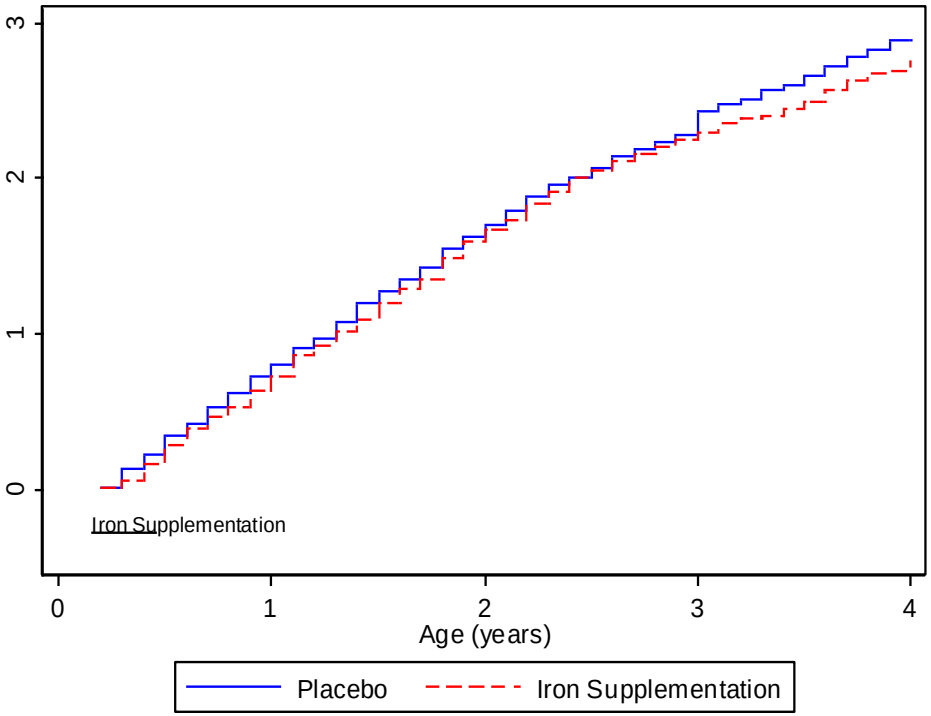
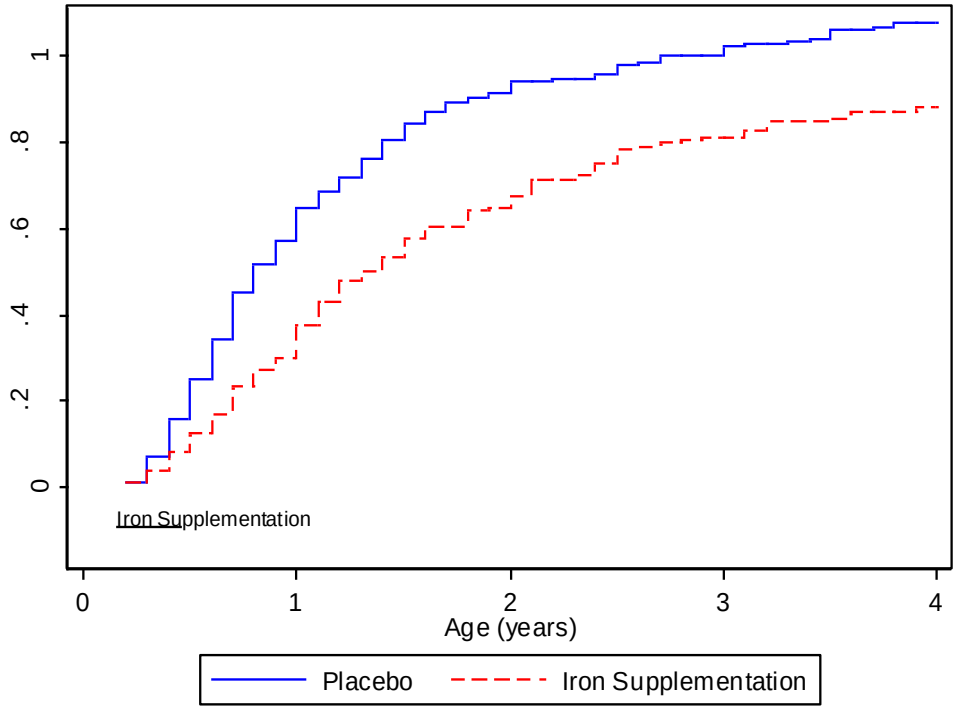


Figure 3.b. Cumulative Hazard of severe anemia



Menendez unpublished

Assuming administration through EPI Scheme

- Cost-effectiveness analysis estimates are favourable:
  - Costs 20.9$ per DALY averted

- Increased cost-effectiveness if the duration of effect is considered in the economic estimation

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Summary of Results

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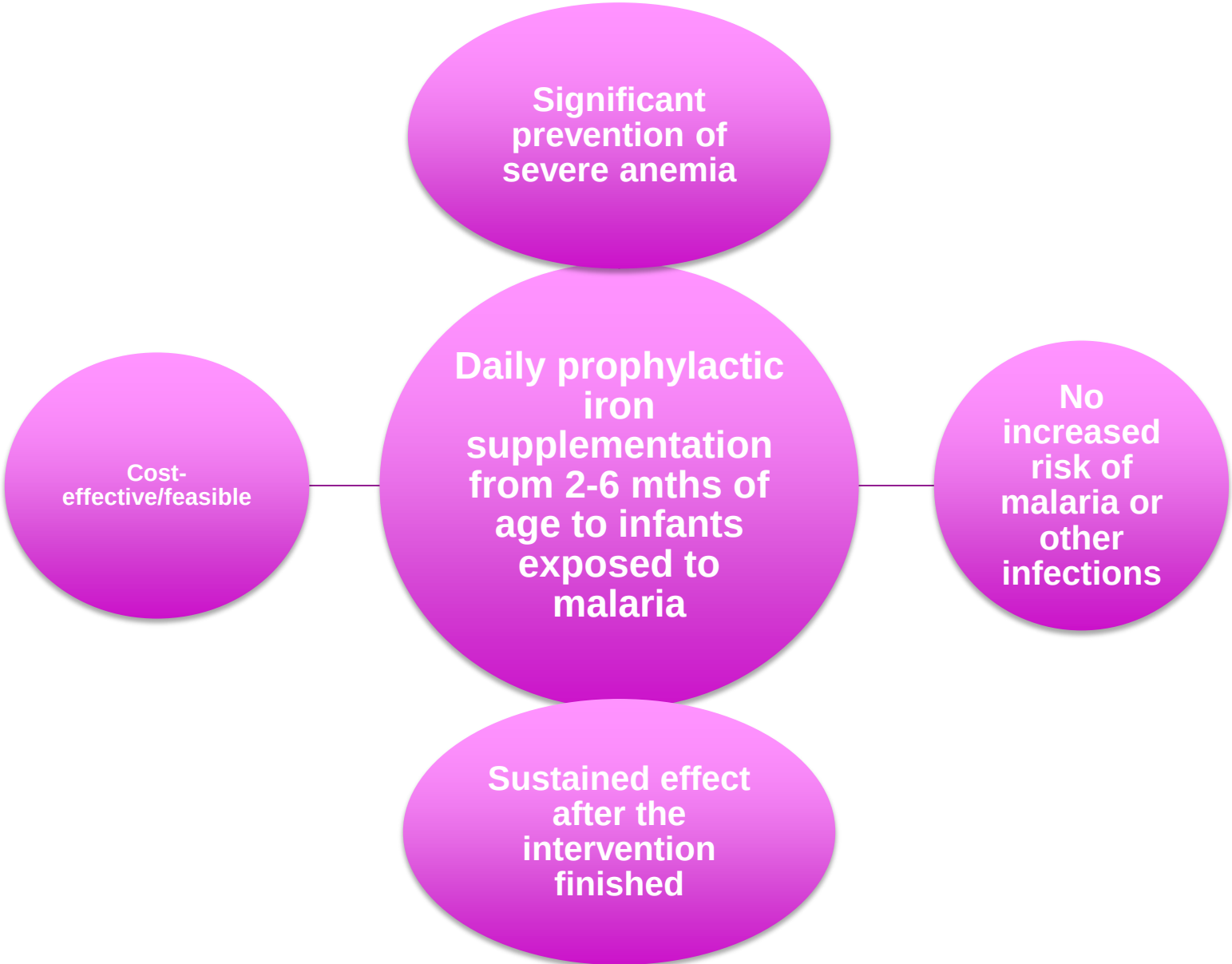

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Conclusions and Recommendations

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- **Iron deficiency is very frequent in children living in high infectious pressure settings**
- **Difficult to diagnose in those areas**
- **More reliable, affordable, and easy to measure iron markers are urgently needed**
- **Research on improved formulations and delivery mechanisms of iron supplementation**
- **To solve the controversy of the safety of iron supplementation in malaria exposed children**
  - **Adequately designed randomised placebo controlled trial is needed**
  - **Iron “only” group vs placebo group**

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Conclusions and Recommendations

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IN THE MEANTIME……

- **ID prevention programs should start targetting the age group at risk to maximise impact -> infants < 6 months of age**
- **Short duration to maximise compliance**
- **Using available health infrastructures- EPI- to ensure compliance and cost-effectiveness**

Ambigous recommendations, ….

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World Health Organisation 2006
WHO Statement

Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent

"Until the WHO recommendations are revised it is advised that iron and folic acid supplementation be targeted to **those who are anaemic and at risk of iron deficiency".**

Cochrane review concluded :"iron supplementation does not adversely affect children living in malaria-endemic areas and should not be withheld from them". Okebe JU, et al (2011) Cochrane Database Syst Rev: CD006589.

Different interpretations by policy makers and a lack of implementation of preventive policies

Many children continue at risk of IDA without prevention

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Thank You!