The Risks of Giving Young Children Iron on Growth and Infectious Diseases and Possible Mechanisms

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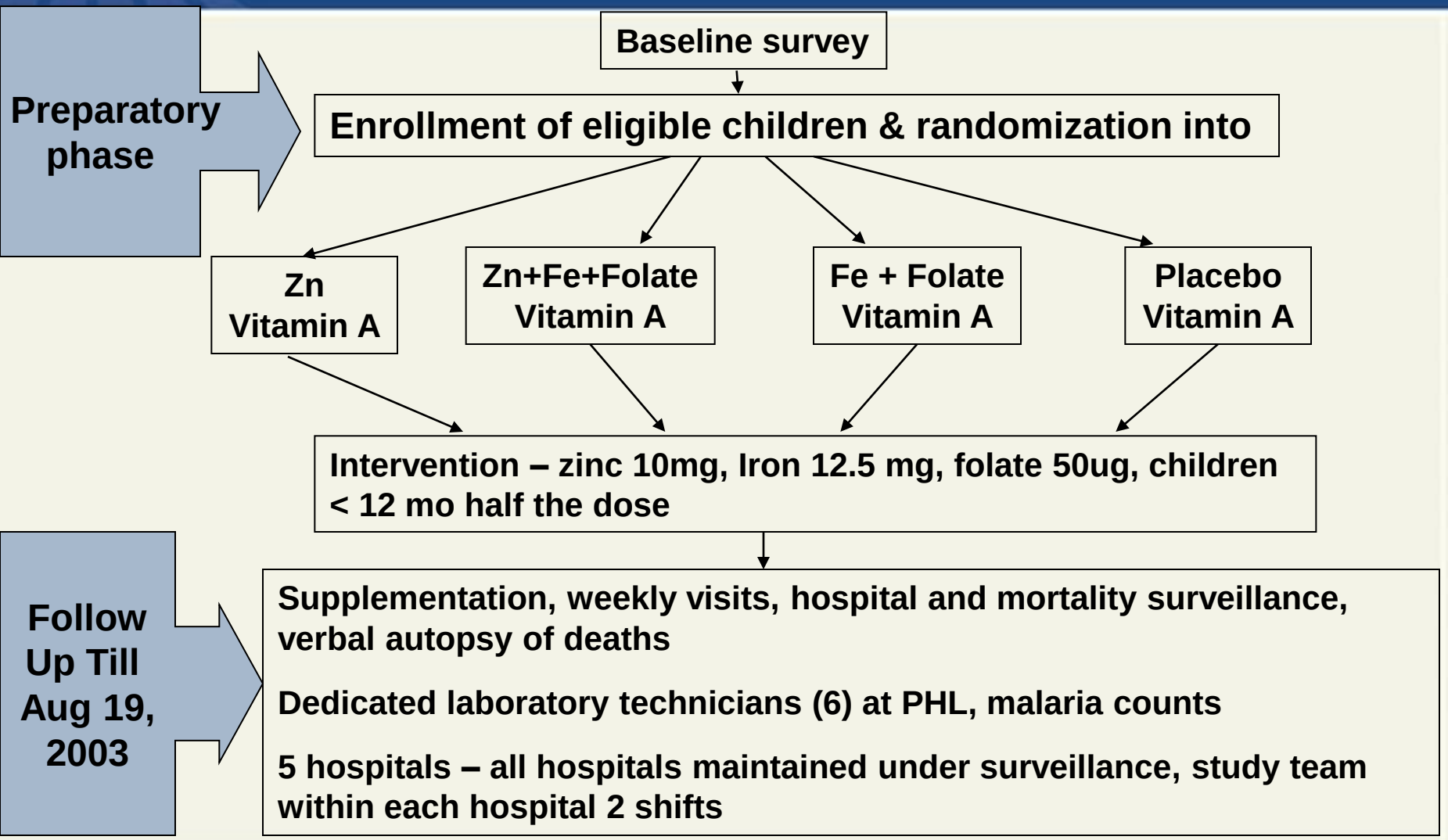
Outline of Presentation

- **Risks of oral iron supplements in young children**
  - **Infectious diseases in malaria areas**
  - **Infectious diseases in non malaria areas**
  - **Growth**
- **Possible mechanisms of adverse effects**
- **Balance of risks and functional benefits of iron supplements in young children**

Pemba Study Design



Source: Sazawal, et al, Lancet 2006

Effect of Iron/Folic Acid Supplementation on Adverse Events in Pemba

	Events	Child-Years of Follow-up	RR	95%CI	P Values
Combined Iron/F Groups	2135	16950	1.12	1.02-1.23	0.02
Control	965	8574			

Adverse events = hospitalizations and deaths

Effect of Iron/Folic Acid Supplementation on Mortality in Pemba

	Deaths	Child-Years of Follow-up	RR	95%CI	P Values
Combined Iron/F Groups	295	16950	1.15	0.93-1.41	0.19
Control	130	8574			

Adverse Events by Malaria Diagnoses

Combined Iron/F Groups					Control
Malaria Diagnosis	N	RR	95%CI	P	N
MRC	943	1.16	1.02-1.32	0.02	411
CMA	430	1.22	1.02-1.46	0.03	182
NCM	496	1.12	0.95-1.32	0.20	225

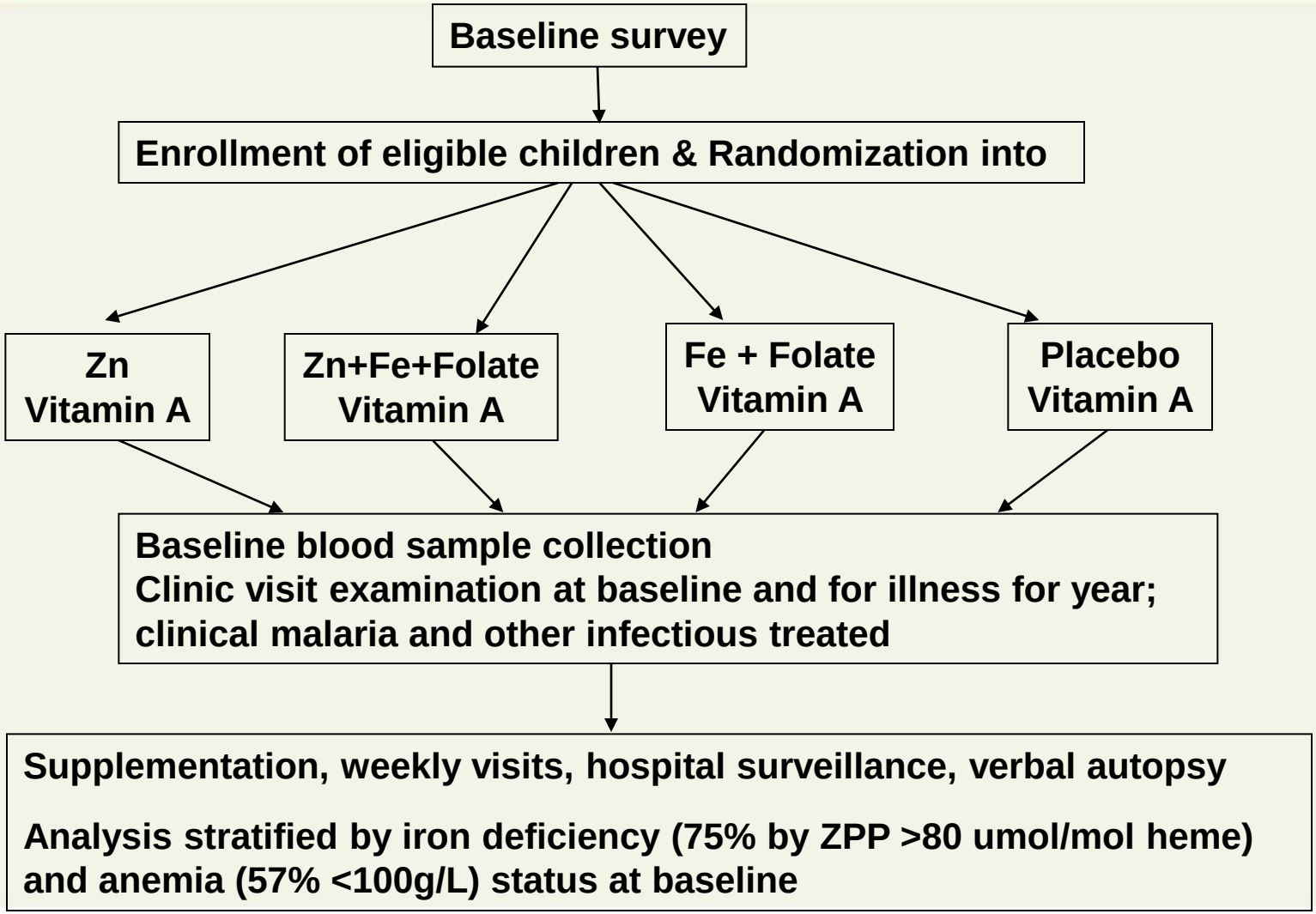
MRC = Malaria Related Causes, CMA= Cerebral Malaria, All NCM= Non Cerebral Malaria

Adverse Events by Other Infection Diagnoses

	Combined Iron/F				Control
Infection Diagnoses	N	RR	95%CI	P	N
IRC	497	1.32	1.10-1.59	0.002	190
Ac Inf	30	2.17	0.95-4.94	0.07	7
Pneu	346	1.33	1.07-1.65	0.01	132
Feb ill	121	1.20	0.80-1.68	0.29	51

IRC=Infection related causes, Ac inf = Acute infections, Pneu = Pneumonia, Feb ill = Febrile Illness

Subsample Study Design



Adverse Events by Iron Status and Anemia in Sub-Study Children

Combined Iron/F Groups					Control
	N	RR	95%CI	P	N
Iron Deficient and Anemic	42	0.51	0.31-0.83	0.006	38
Iron Deficient and Non Anemic	26	0.91	0.42-1.98	0.82	18
Iron Replete and Anemic	10	2.00	0.46-8.75	0.36	2
Iron Replete and Non Anemic	19	1.51	0.57-3.98	0.41	7

Trials of Multiple Micronutrients Containing Iron in Malaria Areas

- **Tanzania: MMN without zinc, iron 1-2mg/kg in 6-67 mo olds, total n about 300, BL and later Rx[1]**
  - **For all malaria episodes aHR 1.04 (0.87-1.23)**
  - **For first malaria episodes aHR 1.29 (1.08-1.54)**
  - **All malaria in iron deficient children given iron HR 1.41 (1.09-1.82)**

- **Ghana: MMN powders, microencap. iron 12.5mg, 6-40 mo olds, total n 1904 for 5 months, BL and later Rx, ITNs[2]**
  - **For all malaria episodes aRR 0.87 (0.75-1.01)**
  - **For hospitalizations RR 1.23 (1.02-1.49)**

Source: 1) Veenemanns et al, PLoS Med 2011; 2) Zlotkin et al, JAMA 2013

Summary of Results for Serious Adverse Events (AE) from Three Trials with Iron in Malaria Areas

	Child-Years	Hosp. & Deaths (AE)	Deaths	Stat. Sig Findings Re AE
Pemba	25, 524	3100	425	12% increase in AE in iron groups
Tanzania	291	68	3	Not reported
Ghana	751	389	5	23% increase in hospital admissions in iron group

Meta-analyses of the Effects on Morbidity and Growth of Oral Iron Supplements

- Children <12 y old, individual RCTs[1]
  - Increased diarrhea IRR 1.11 (1.01-1.23)
  - Increased malaria parasitemia OR 1.43 (1.08-1.91)
- Children 4-23 mo old, individual RCTs[2]
  - Increased vomiting RR 1.38 (1.10-1.73)
  - Increased fever prevalence RR 1.16 (1.02-1.31)
  - Reduced weight gain and length growth
  - No effect on mental or psychomotor development, diarrhea or malaria
- Children 2-5 years old, individual RCTs[3]
  - No effect on morbidity or growth; small benefit on development suggested but evidence very limited

Source: 1) Gera et al, BMJ 2002; 2) Pasricha et al, Lancet Global Health 2013; 3) Thompson et al, Pediatrics 2013

Possible Mechanisms for the Adverse Effects 0f Oral Iron Supplements

- Malarial parasites and pathogenic bacteria need iron to survive and multiply
- Humans have evolved mechanisms via hepcidin and ferroportin to reduce iron availability to pathogens as part of innate immune defenses
- Increased iron absorption may overwhelm these controls and provide iron for pathogen growth
- In children with anemia iron stimulates production of reticulocites which are preferred by malaria merozoites

Additional Considerations Regarding Possible Mechanisms for Adverse Effects of Oral Iron

- An iron load can exceed the capacity of available ferritin and non bound plasma iron results in formation of reactive oxygen species that cause damage to many tissues
- Iron deficiency limits the severity of the inflammatory response and provision of iron may shift the balance to be more pro-inflammatory
- Iron supplementation increased intestinal permeability in Zambian schoolchildren (oxidative damage?)[1]
- Iron fortified biscuits (unabsorbed iron?) resulted in a more pathogenic gut microbiota and in inflammation (by calprotectin) in Ivory Coast children[2]

Source: 1) Nchito et al, Trans RSTM&H 2006; 2) Zimmerman et al, AJCN 2010

Conclusions

- **Oral iron supplements in preschool children increase the risk of adverse events, including hospitalizations and deaths, in settings with and without malaria and negatively affect growth in children less that 2 years old**

- **Possible mechanisms for these effects need more study which may lead to improved interventions**

- **The risk of oral iron along with its lack of demonstrated functional benefits in preschool children should mitigate against universal iron supplementation or high-dose "fortification", i.e. micronutrient powders, even in areas with a high prevalence of anemia**