EFFECT OF IRON SUPPLEMENTATION ON THE INCIDENCE OF INFECTIONS IN CHILDREN: A SYSTEMATIC REVIEW

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Iron Deficiency

- Major public health problem
- Adverse effects on :
  - psychomotor development
  - work performance
- Early intervention recommendations
  - Supplementation: drug/fortification
- Establish safety

Iron and Infections

- Iron deficiency, a defense mechanism – 'Nutritional Immunity'
- Iron deficiency – impaired CMI
- Free radical injury due to iron
- Relation controversial
- Resolve issue by Systematic Review

Inclusion Criteria

i. Randomised placebo controlled except parenteral
ii. Iron supplementation - oral /parenteral/iron fortified formulas or cereals
iii. One or more infectious morbidity as an evaluated outcome measure.

Where other micronutrients/drugs administered- included if the only difference was iron only

Data Collection

- MEDLINE, COCHRANE controlled trials register, EMBASE, IBIDS and Healthstar database
- Reference lists of the identified articles, hand searches of reviews, bibliographies of books and abstracts and proceedings of international conferences or meetings
- Donor agencies, ‘experts’ and authors of recent iron supplementation trials

Data Collection (contd)

- Title and abstract scanned- irrelevant studies discarded
- Full text of rest retrieved for further scanning
- Publication bias avoided-both published and unpublished studies included

Methodologic Quality

- **Allocation Concealment**
  - A) adequate B) unclear C) inadequate D) not used.
- **Completeness of Follow-up**
  - A) < 3% B) 3-9.9% C) 10-19.9% D) >20%
- **Blinding**
  - A) double blinding B) single blinding
  - C) no blinding D) unclear

Data Abstraction

- Preformed questionnaires
- Derived from the published manuscript
- Morbidities and the outcomes included were as defined by the authors
- Wherever possible and required, the authors contacted for clarifications

Statistical Analysis

- STATA Statistical Software for funnel plot
- Statsdirect software
- *Incidence rate ratio* and i*ncidence rate difference* – pooled estimates calculated
- Both fixed and random model used
- Statistic Q computed to assess homogeneity

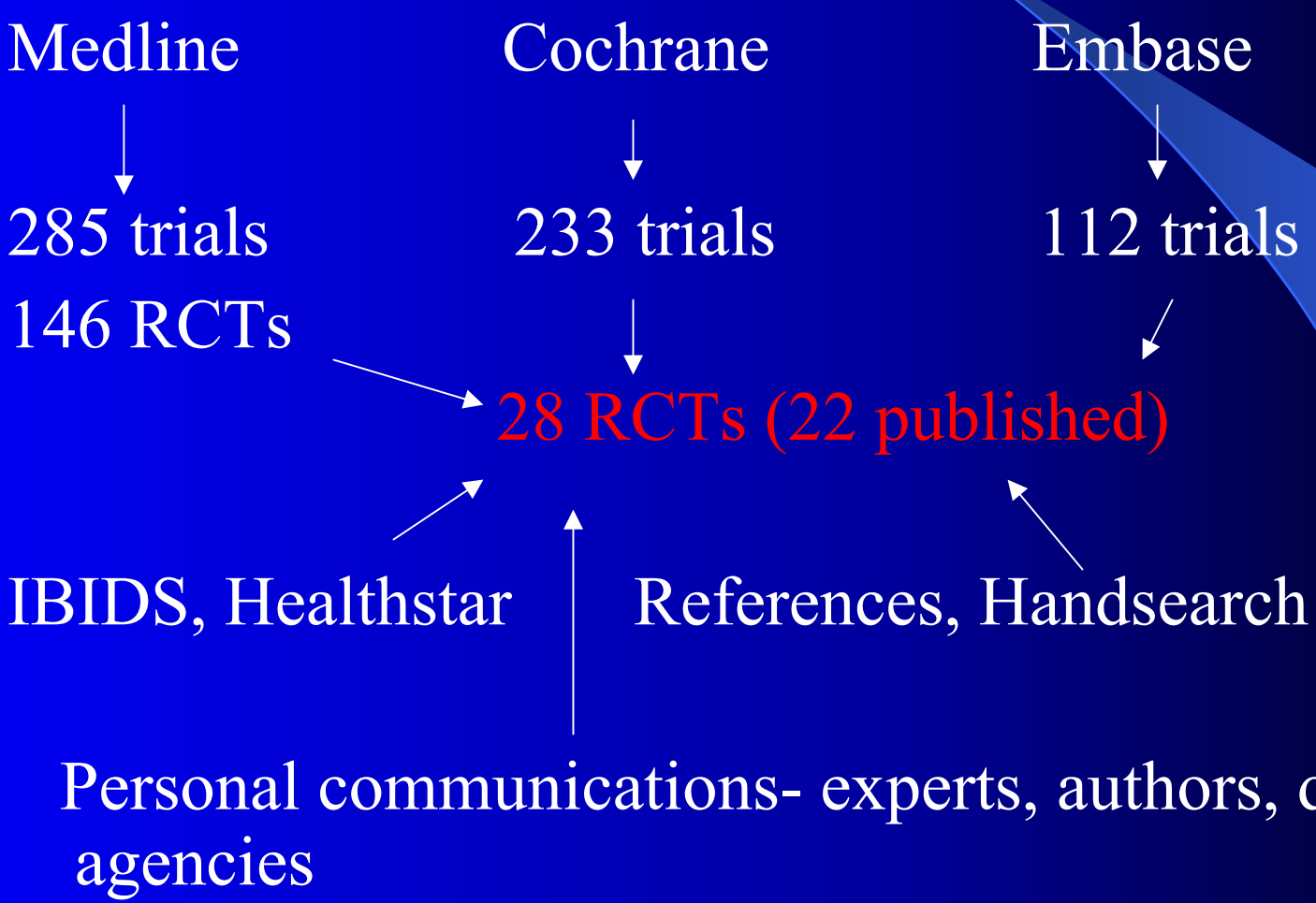
Statistical Analysis (contd)

- Data in the form of the total episodes of illnesses and the person-time exposed (in child years).
- Individual morbidities: Diarrhea, RTI, Malaria, Other Infections
- Malarial parasitemia: Pooled OR calculated and metaregression to adjust for baseline prevalence

Metaregression for Heterogeneity

1. Methodologic quality
2. Case detection (active or passive)
3. Case definition specificity
4. Route of iron administration
5. Duration of supplementation
6. Baseline haemoglobin

Results

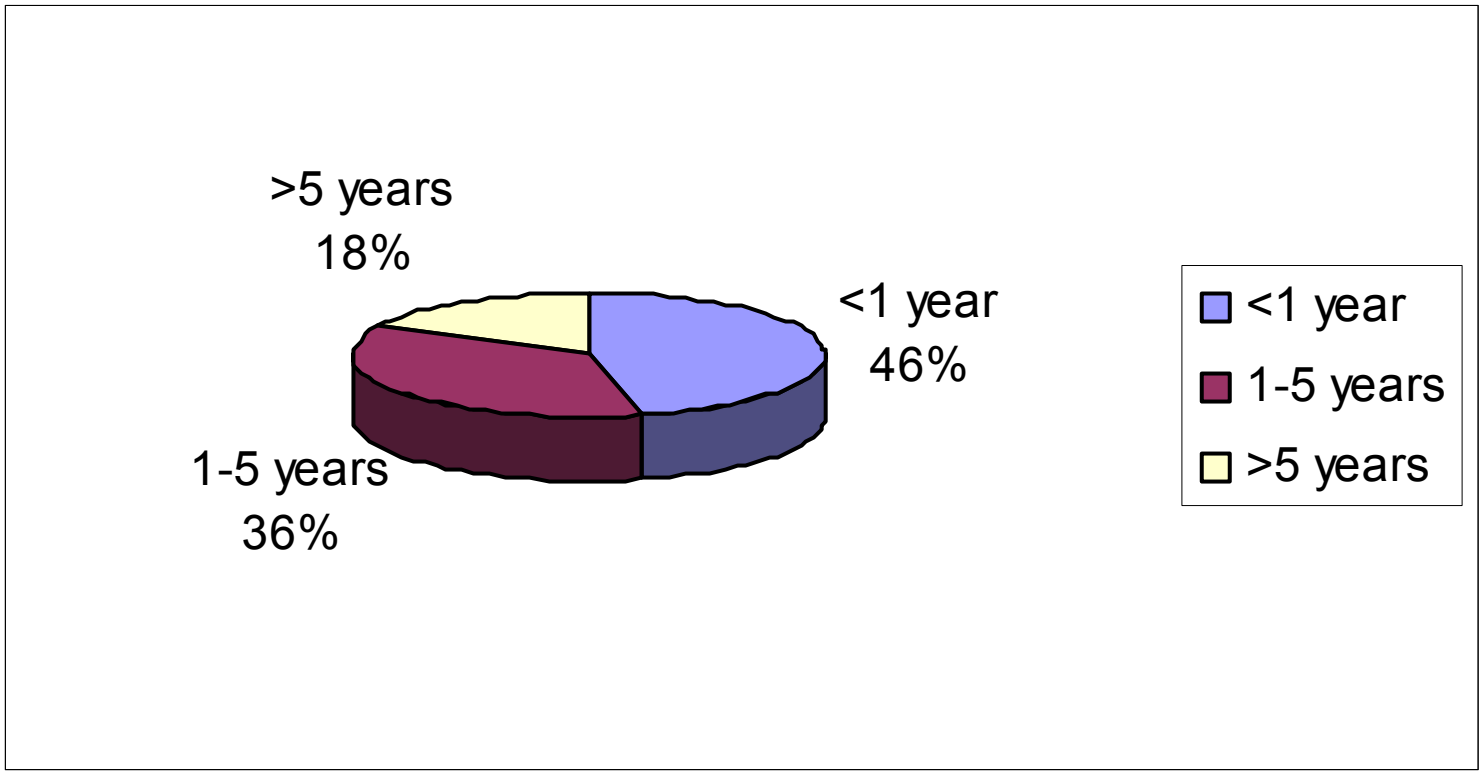

Medline
Cochrane
Embase
285 trials
146 RCTs
233 trials
112 trials
28 RCTs (22 published)
IBIDS, Healthstar
References, Handsearch
Personal communications- experts, authors, donor agencies

Age

Below 1 year: 13

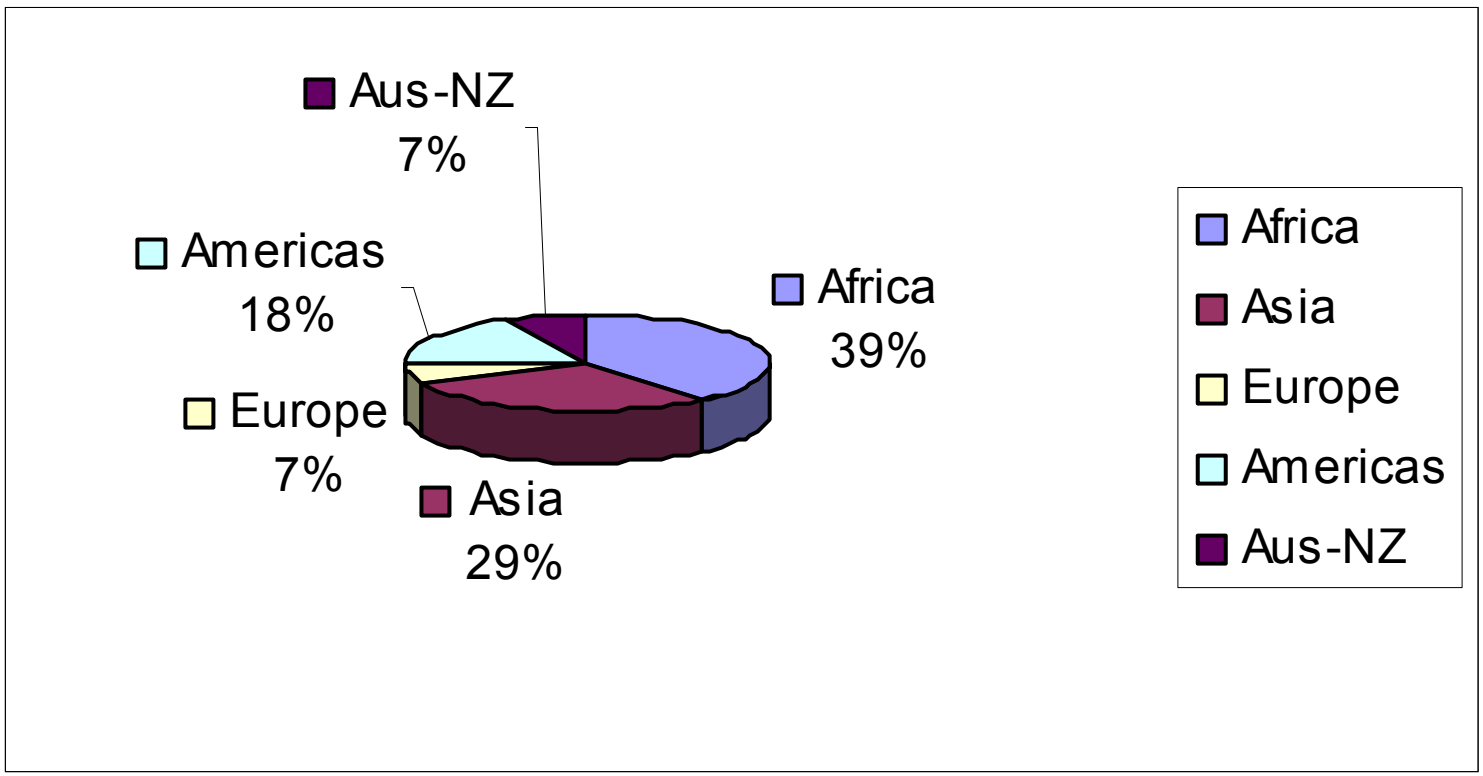
1-5 years: 10

>5 years: 5



Place of Study

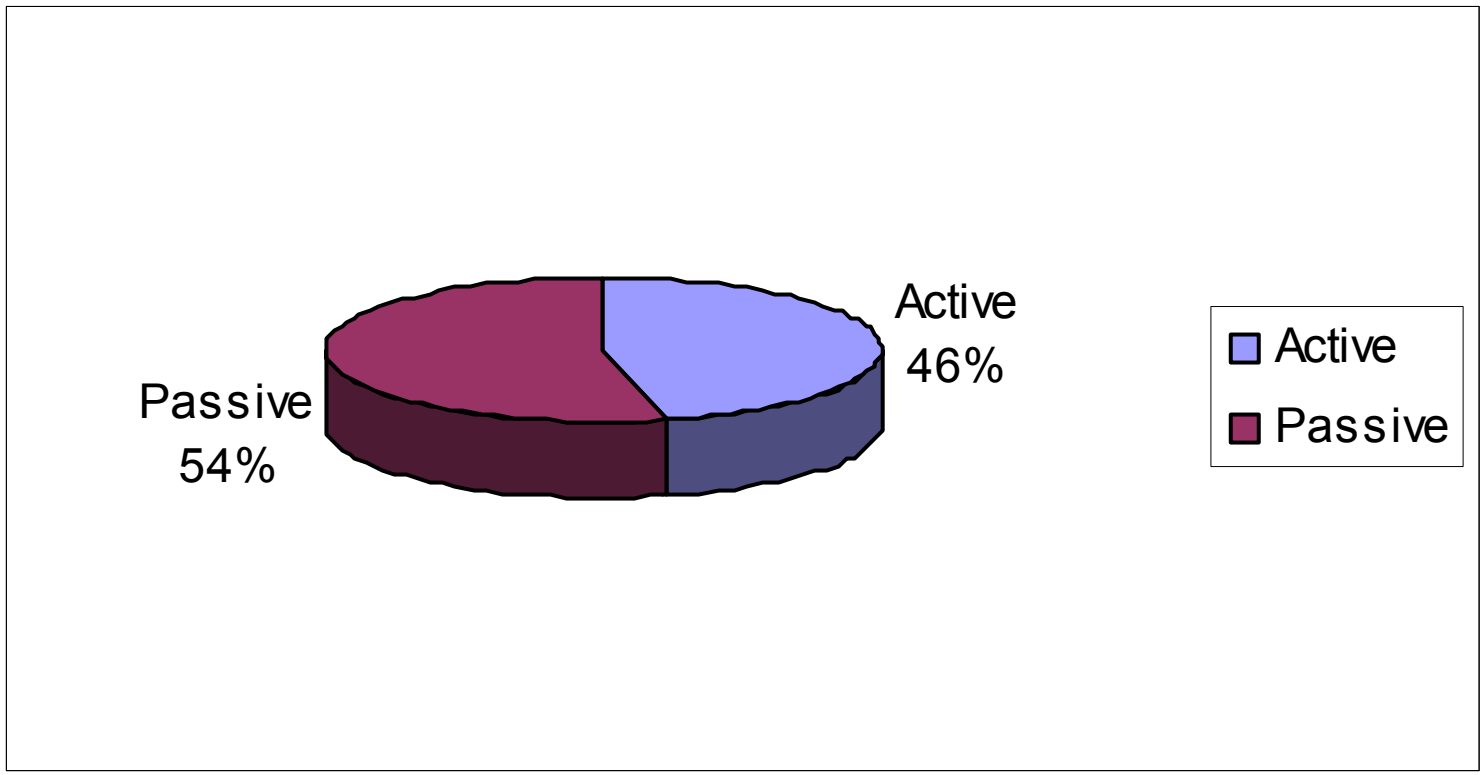
Africa: 11
Asia: 8
Americas: 5
Europe: 2
Aus-NZ: 2



Surveillance Methodology

Passive/ Facility based – 15

Active – 13



Iron Supplementation

- **Route of Supplementation**

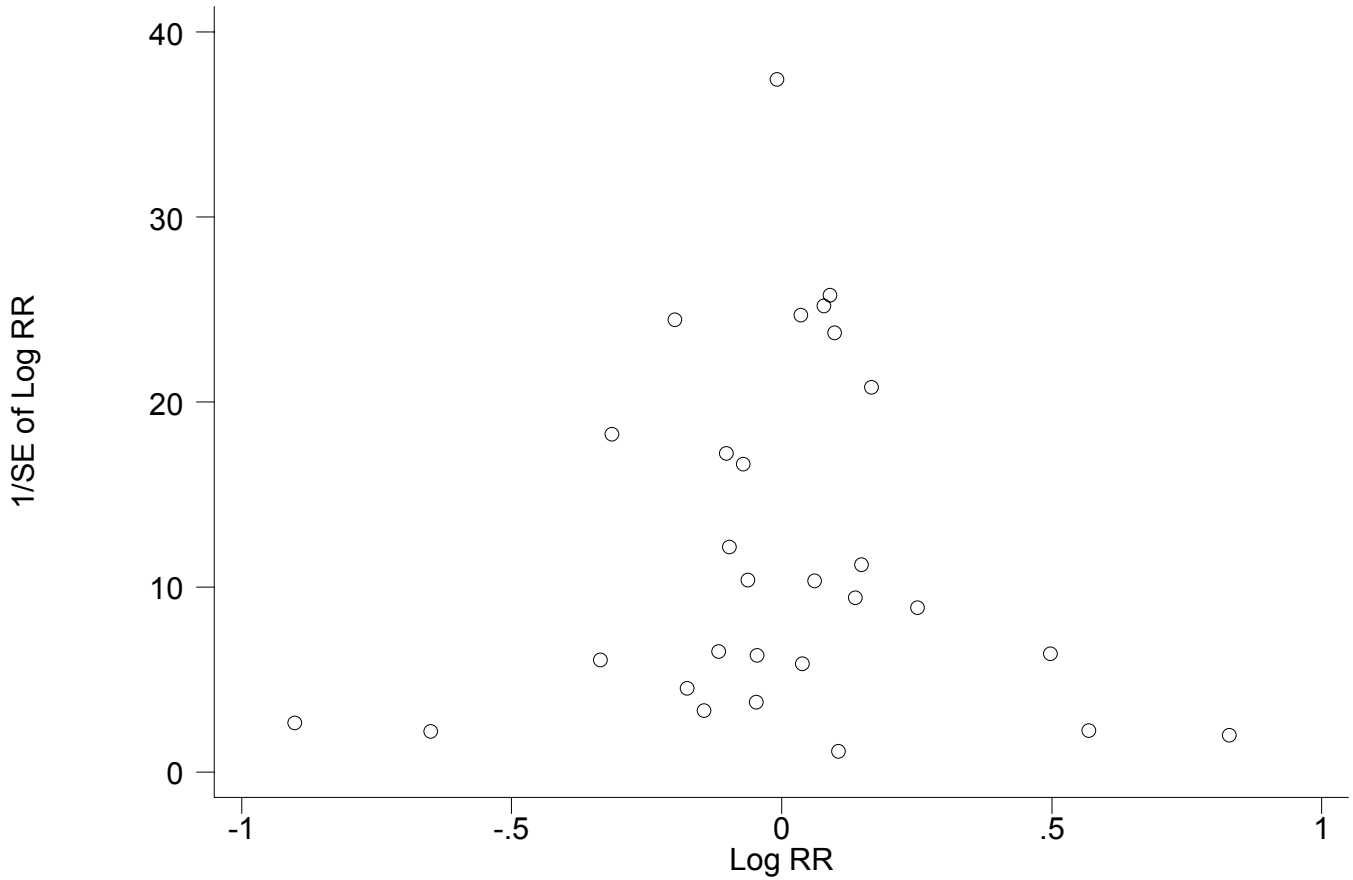
- Oral iron – 20
- Fortified feeds/ cereals - 5
- Parenteral iron – 3

Crude assessment of effect of dosage- Parenteral: max; Fortification: minimum

- **Duration**

- varied from 2-30 months

Bias Detection-Funnel Plot



Bias Detection

- Egger (weighted regression) method (p for bias=0.663)
- Begg (rank correlation) method (continuity corrected p = 0.488).

Pooled Estimates

- Data on 7892 subjects followed up for 5651 child years
- 4027 children and 2802 child years- iron supplemented group
- 3865 children and 2849 child years in the placebo group.

Total Morbidity

- **Incidence rate ratio**

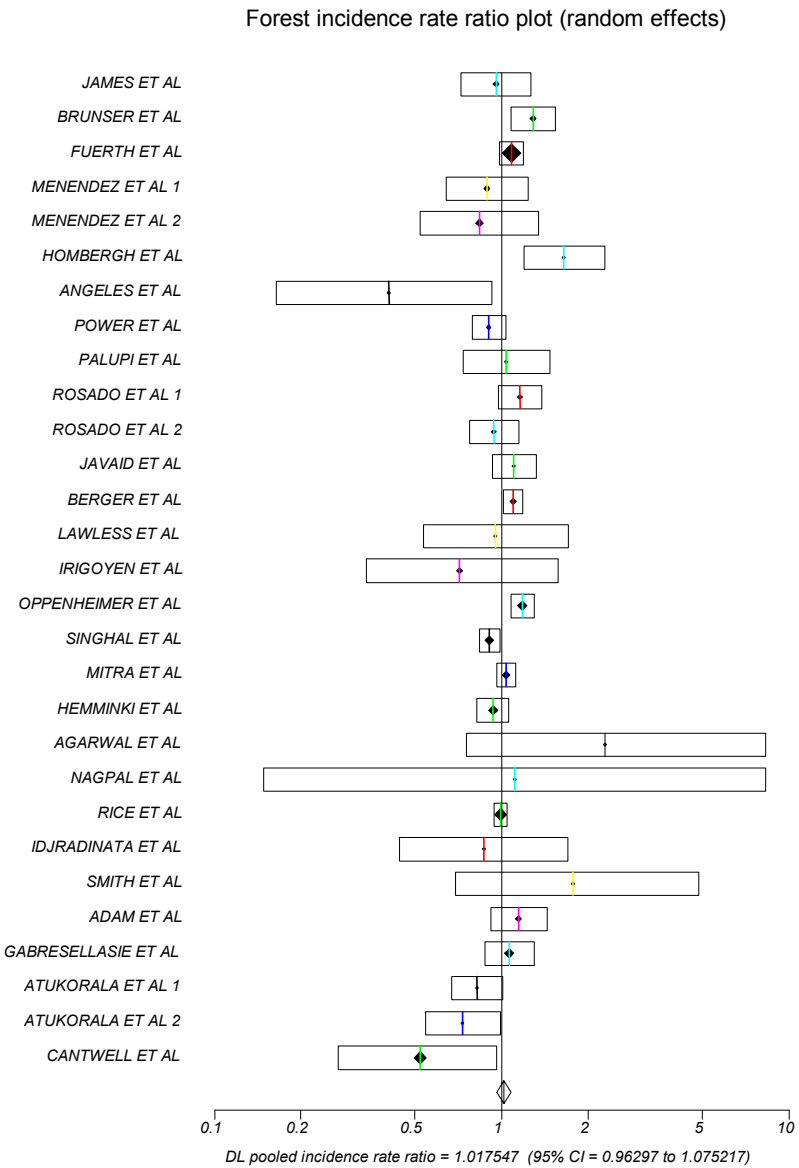
  IRR (iron versus placebo) for all the recorded morbidities = 1.02 (95% CI 0.96, 1.08); p=0.54

- **Incidence Rate Difference**

  IRD (iron minus placebo) for all the recorded morbidities = 0.06 episodes/child-year (95% CI –0.06, 0.18); p=0.34

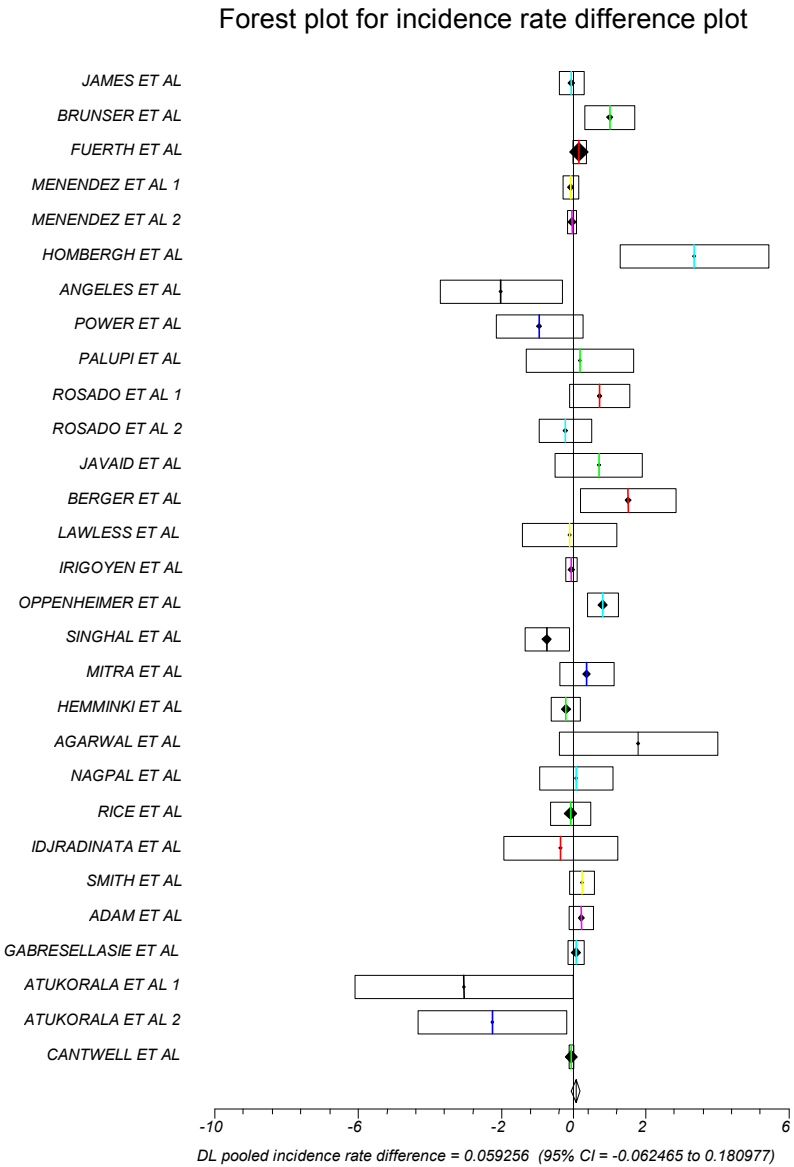
Incidence Rate Ratio

IRR=1.02 (95% CI 0.96, 1.08); p=0.54



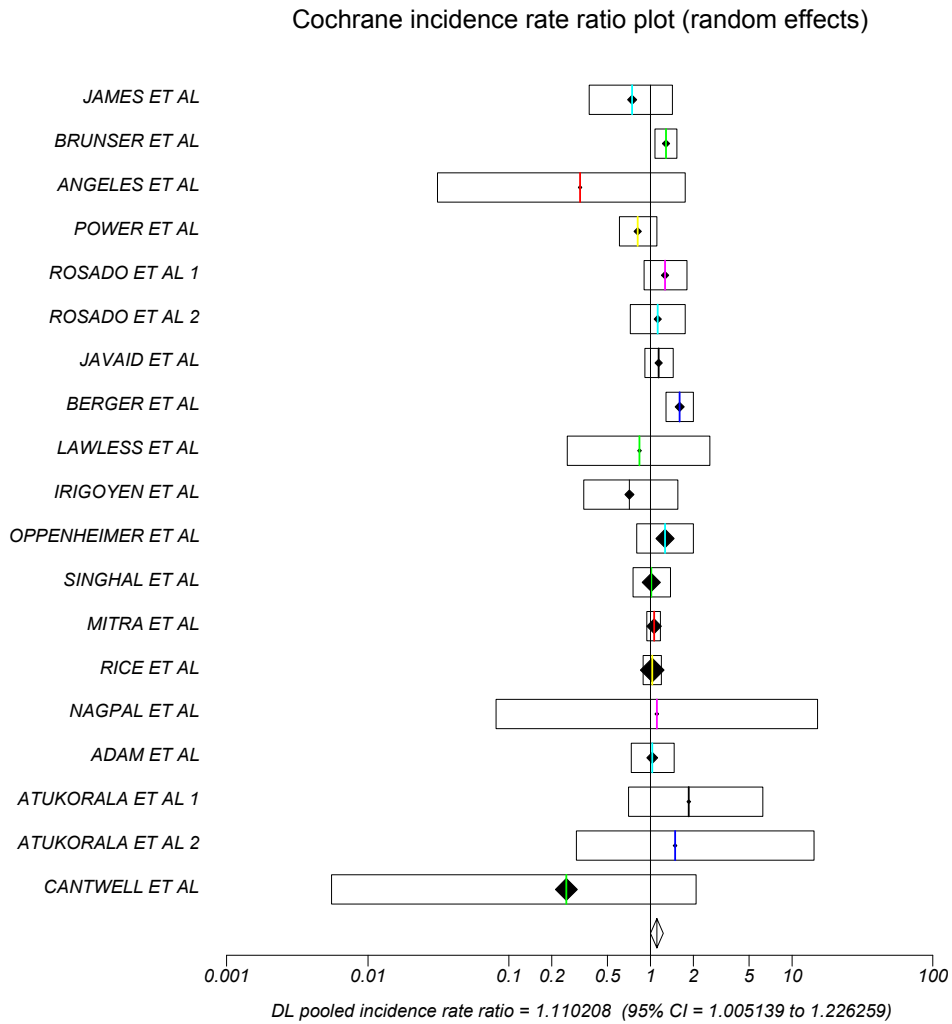
Incidence Rate Difference

IRD= 0.06 episodes/child-year (95% CI –0.06, 0.18); p=0.34



Diarrhea – IRR

1.11 (1.01, 1.23), p= 0.04

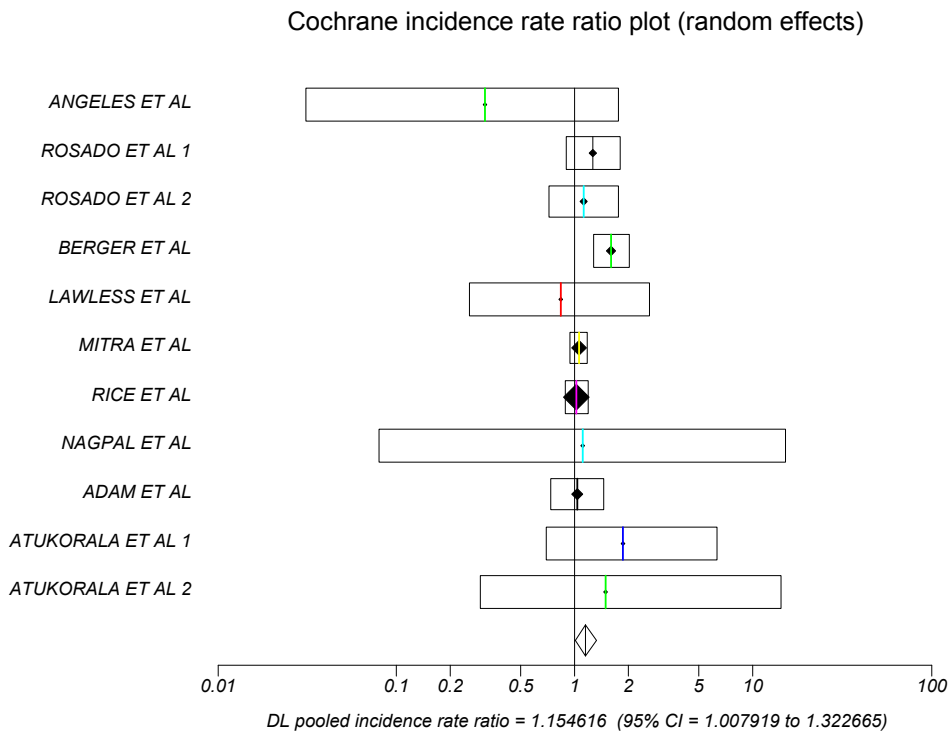


Individual morbidities-Diarrhea and Dysentery

Stratification feature	Trial	IRR (95% CI)	p	IRD (95% CI)	p
Diarrhea	17	1.11 (1.01,1.23)	0.04	0.05 (-0.03, 0.13)	0.21
Dysentery	2	1.00 (0.87,1.15)	0.99	0.00 (-0.05, 0.06)	0.90

Diarrhea and Oral iron

IRR=1.15 (1.01, 1.32), p=0.04

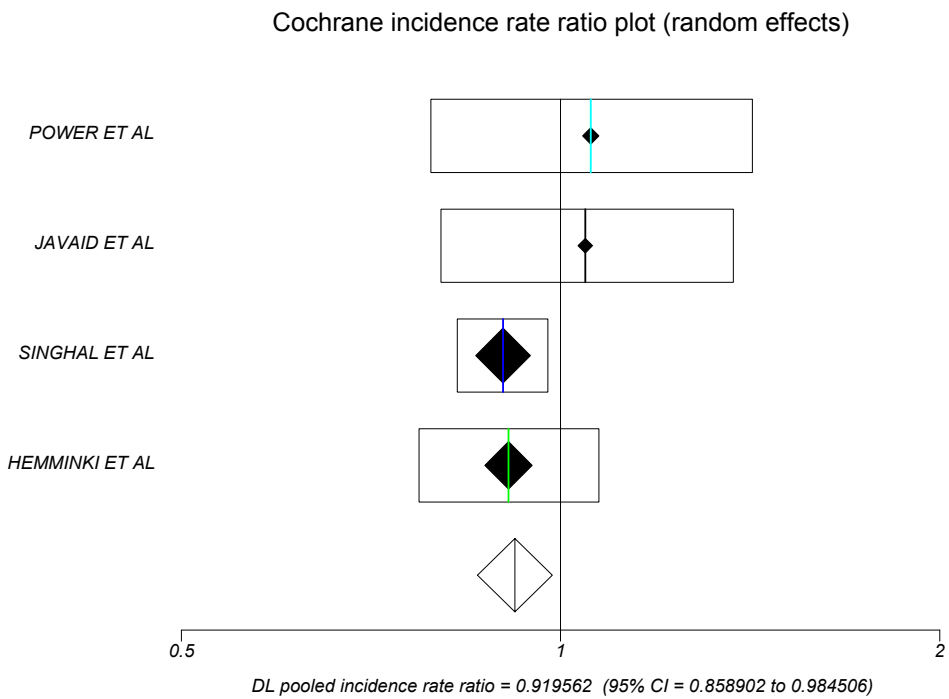


RTI and LRTI

Stratification feature	Trial	IRR (95% CI)	p	IRD (95% CI)	p
RTI	17	0.98 (0.90, 1.06)	0.54	0.02 (-0.13, 0.18)	0.79
LRTI	8	0.97 (0.83, 1.23)	0.93	0.01 (-0.11, 0.13)	0.84

RTI and Fortified Iron

IRR=0.92; 95% CI 0.86, 0.98 (p=0.02)

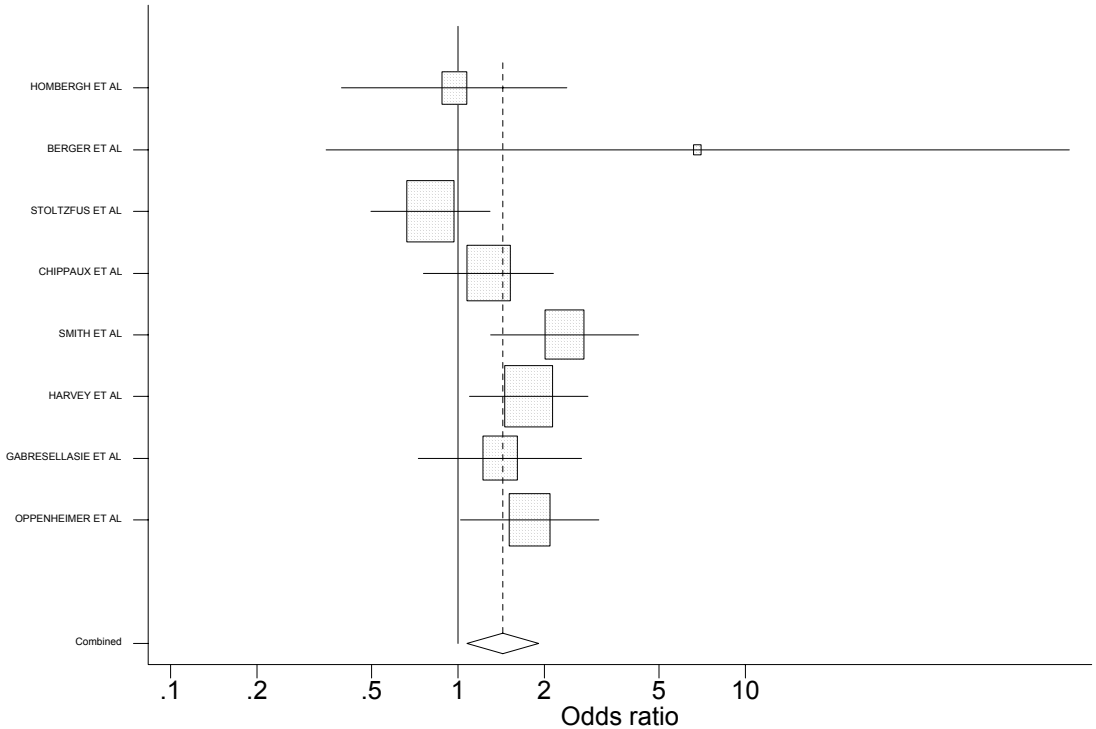


Malaria and Other Infections

Stratification feature	Trial	IRR (95% CI)	p	IRD (95% CI)	p
Malaria	5	1.07 (0.94, 1.24)	0.35	0.04 (-0.04, 0.11)	0.32
Other Infections	13	1.04 (0.98, 1.11)	0.20	0.05 (-0.02, 0.12)	0.15

Prevalence of Malarial Parasitemia

OR=1.43 (95% CI 1.08 to 1.91), p=0.014



Prevalence of Smear Positive Malarial Parasitemia

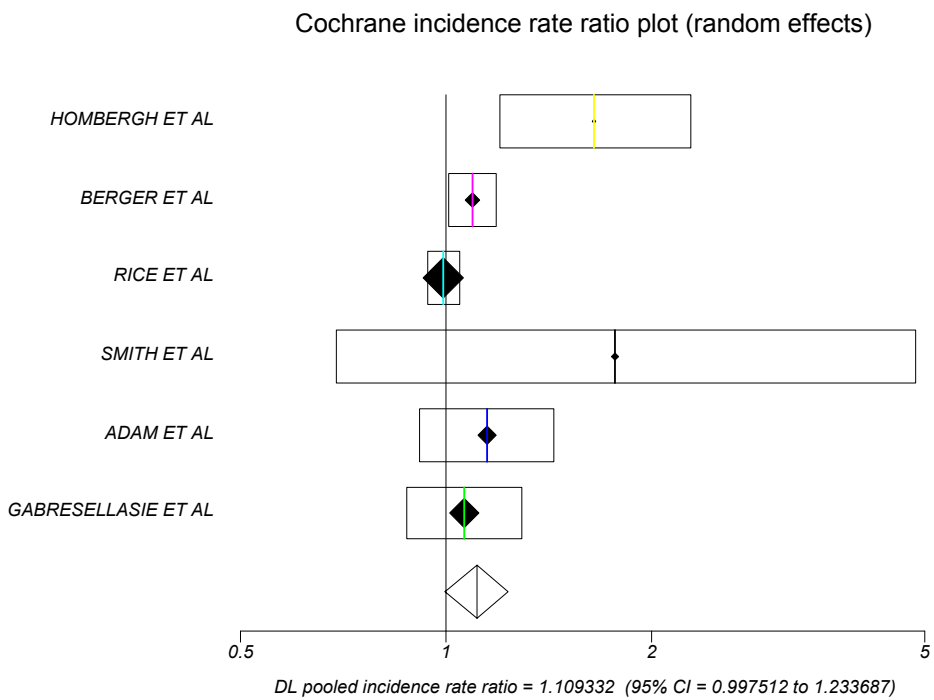
- Pooled log OR of acquiring malaria with iron supplementation = 1.13 (95% CI 0.91, 1.40; p=0.28)
- Significantly (p=0.004) related to the baseline log OR of malaria smear positivity

Metaregression for Heterogeneity

Study Characteristic	Univariable Analysis IRR (95%CI), p	Control all variables IRR(95% CI), p
Morbidity Surveillance (Passive versus active)	0.94 (0.84, 1.05), 0.266	1.03 (0.83, 1.27), 0.809
Route of Iron Supplementation (Oral or parenteral versus fortified	1.04 (0.92, 1.17), 0.555	1.03 (0.82, 1.30), 0.815
Geographic Location (Developed versus Asian or African)	0.98 (0.87, 1.11), 0.759	1.05 (0.81, 1.36), 0.723
Unit increase in baseline hemoglobin status of iron supplemented group (g/dL)	0.97 (0.94, 1.01), 0.151	0.95 (0.90, 1.00), 0.059
Unit increase in duration of supplementation (months)	1.00 (0.99, 1.02), 0.864	0.99 (0.97, 1.03), 0.921

Basal Hemoglobin<10g/dl

IRR=1.11(1.00, 1.23; p=0.06); n=6



Caveats

- Lack of uniform definitions for morbidities
- Not all studies of highest quality
- Wide heterogeneity of study population and study design

Conclusions

- No significant increase in the risk of infection with iron supplementation
- Slight (11%; 95% CI 1-23%) increase in the risk of developing diarrhea, more so in the group supplemented oral supplements; public health significance ??

Future Research

- Effect of iron supplementation on incidence of diarrhea with micro profile
- Fortification as the ‘safest’ and ? beneficial
- Risk in anemia: ? ethical

Thank you