

Impact of Zinc Supplementation on Preschool Child Morbidity & Mortality in Nepal

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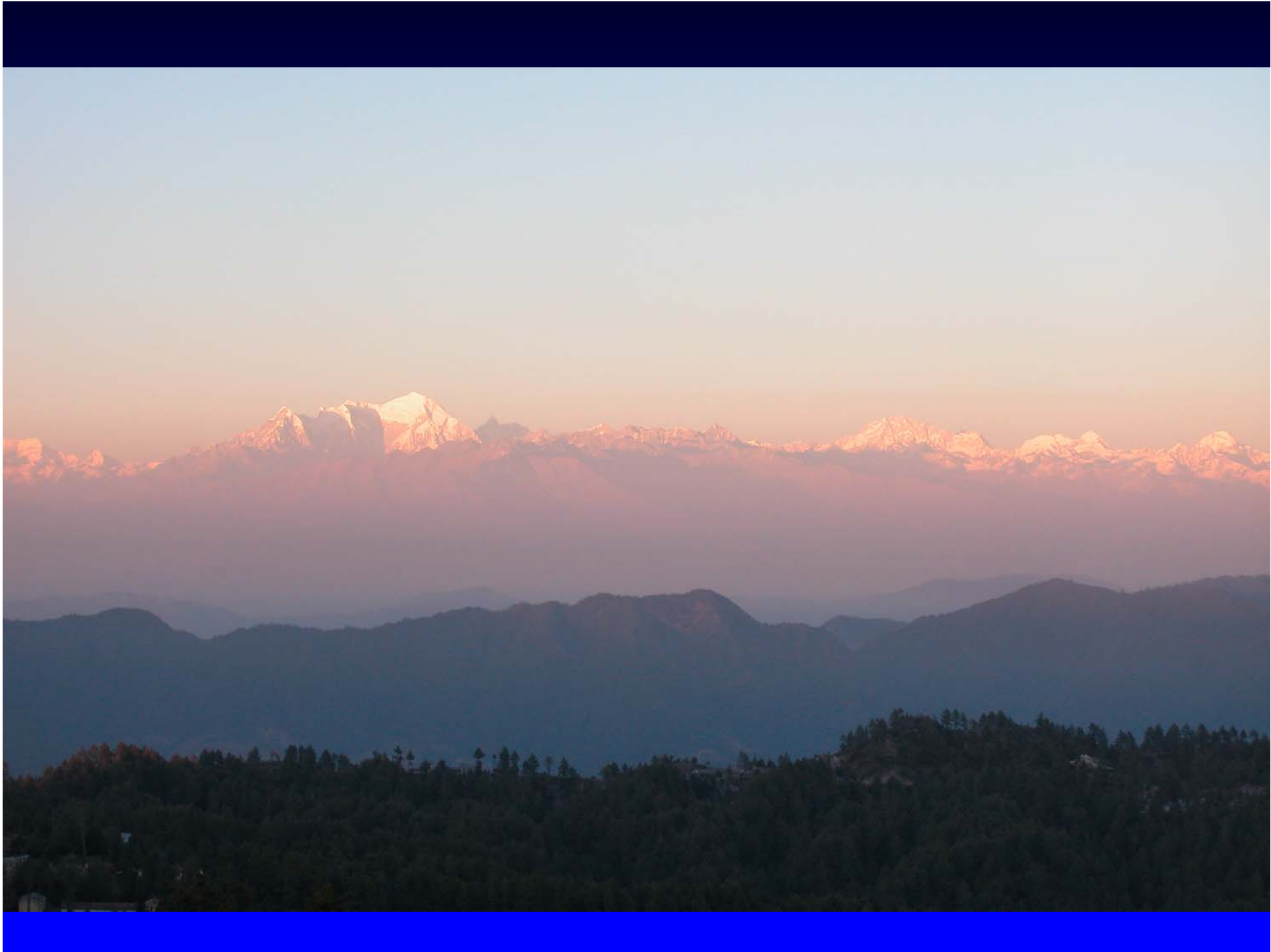
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Specific Aims

1. To assess impact of daily zinc and/or iron-folic acid supplementation on mortality among children 1-35 months.
2. To assess impact of these interventions on morbidity, growth, and motor and cognitive development.

Design

- Cluster randomized 2 x 2 factorial community trial in Sarlahi District, Nepal (clusters=425).
- All children receive vitamin A 2x/year through the national program.
 - All missed during national campaign dosed by study team.
- Interventions:
 - Placebo
 - 10 mg zinc sulfate daily
 - 12.5 mg iron & 50 µg folic acid daily
 - Both zinc and iron-folic acid
½ if child less than 12 months
- Iron-Folic Acid arms stopped previously





Design-2

Field procedures:

- Baseline census.
- Enrollment conducted house-to-house; began October, 2001.
- All children 1-35 months eligible.
- Verbal informed consent at household with separate parental consent for each eligible child.

Design-3

Field procedures:

- Ward Distributors visit twice per week to directly dose and leave tablets for other days.
- Children born into study area enrolled as they become one month of age.
- Once enrolled, children followed and dosed until 36 months of age.
- Sample size = up to 66,000 person-years.

Design-4

Change in Design Following Iron-Folic Acid Stoppage:

- All sectors originally randomized to either iron-folic acid or iron-folic acid + zinc, re-randomized to either zinc or placebo.
- Children already enrolled re-consented and switched to new assignment.
- Children newly enrolled provided new assignment.

Design-5

Morbidity Substudy

- Four stratified random samples of approximately 1200 children, enrolled one year apart.
- Follow-up of each sample for one year.
- Weekly household visits to collect morbidity data and care-seeking on each day in the prior week.

Design-6

Zinc & Iron Status Substudy

- 12 month post supplementation assessments of serum zinc, copper, Hb, and ferritin post supplementation among children 24 months or older.

Questions for Analysis

1. Baseline comparability?
2. Compliance?
3. Impact on zinc status?
4. Difference in mortality?
5. Difference in morbidity?

Baseline Comparisons

- Groups were well balanced on a wide range of baseline characteristics including:
 - Demographic (age, sex, ethnicity, caste)
 - Socioeconomic (housing, family education, item & land ownership)
 - Health-related (water source, latrine)
 - Nutritional status (MUAC at enrollment)

Compliance

Percent Supplements Consumed*	Placebo	Zinc
<40%	1829 (9.0%)	2552 (12.2%)
40%-59%	1895 (9.3%)	2461 (11.7%)
60%-79%	4499 (22.2%)	5036 (24.0%)
≥ 80%	12,085 (59.5%)	10,920 (52.1%)
Mean	76.8%	72.9%

* Difference in compliance between groups: $p < 0.001$

Impact on Zn & Cu Status Following 12 Months of Supplementation

Indicator	Placebo N=149	Zn N=190
Serum Zn Mean (SD) ($\mu\text{g/dL}$)	72.4 (13.9)	76.0 (14.8)
Difference	-	3.9
<60	24 (16.1%)	18 (9.5%)
60-69	48 (32.2%)	56 (29.5%)
≥ 70	77 (51.7%)	116 (61.1%)
Serum Cu Mean (SD) ($\mu\text{g/dL}$)	130.4 (23.3)	131.3 (25.9)

Mortality Analysis

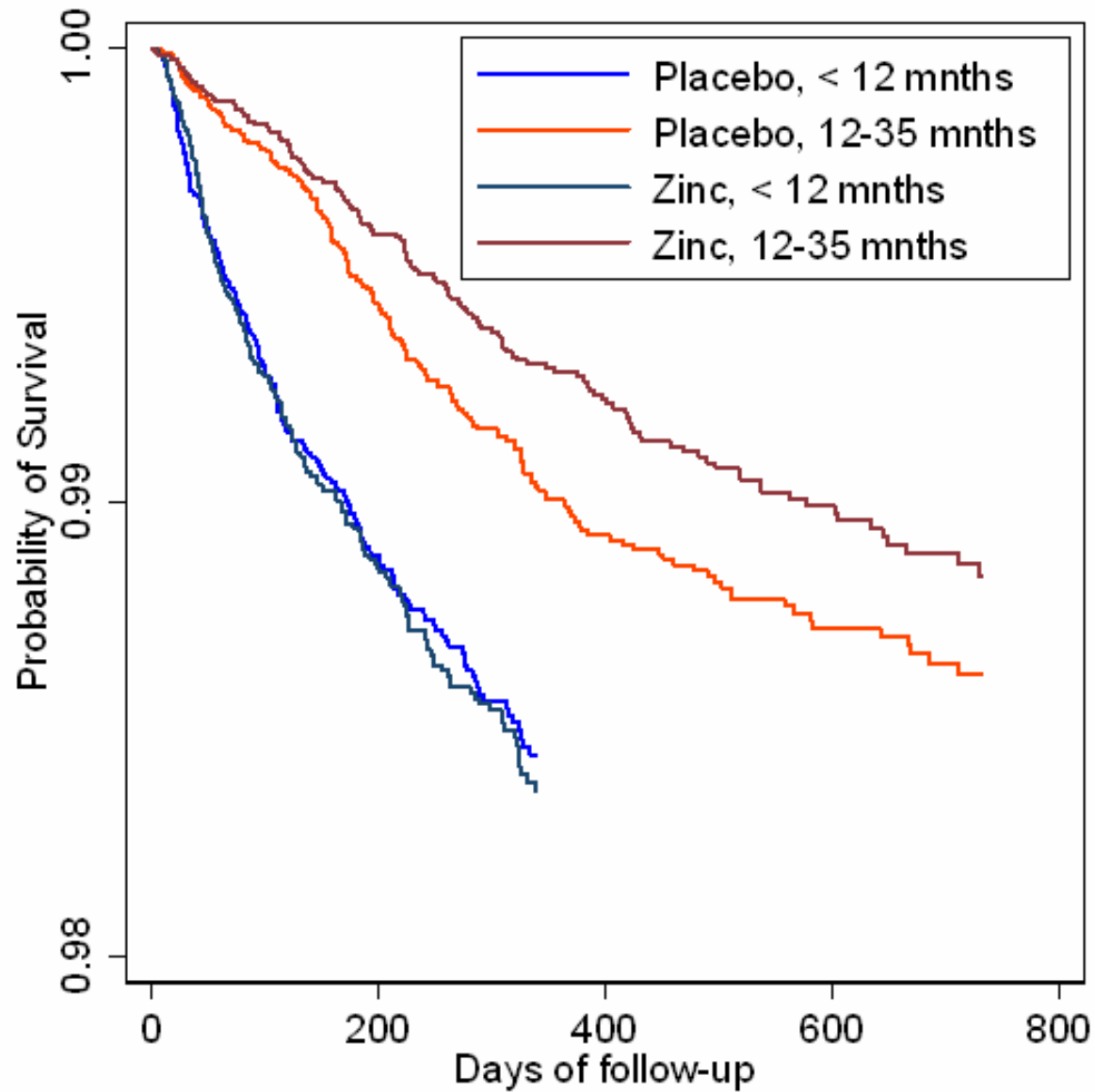
Two Approaches

1. Person-time.
2. Survival analysis.

Mortality by Age (months)

	Age (m)		
	1-11	12-36	Total
<u>Placebo</u>			
P-Y	9,237.1	20,607.2	29,844.6
Deaths	168	165	333
Rate	18.19	8.01	11.16
RR	1.00	1.00	1.00
<u>Zinc</u>			
P-Y	9,582.1	21,209.7	30,791.7
Deaths	181	135	316
Rate	18.89	6.37	10.26
RR	1.04	0.80	0.92
95% CI	(0.83, 1.41)	(0.60, 1.06)	(0.75, 1.12)

Mortality Analysis



Mortality by Sex & Age

	<u>Placebo</u>	<u>Zinc</u>	<u>RR</u>
<u>Males</u>			
1-11m	17.2	16.0	0.93 (0.68, 1.28)
12-35m	5.7	5.3	0.92 (0.60, 1.41)
<u>Females</u>			
1-11m	19.2	22.0	1.14 (0.85, 1.54)
12-35m	10.3	7.5	0.73 (0.52, 1.02)

Morbidity by Treatment Group

	Placebo Rate*	Zinc Rate*	RR	95% CI
Diarrhea	3.12	2.99	0.96	0.90,1.02
Persist. Diarrhea	0.06	0.07	1.06	0.77,1.46
Dysentery	0.3	0.3	1.06	0.87,1.28
ALRI	1.40	1.43	1.01	0.92,1.10

* Episodes/child/year.

Conclusions

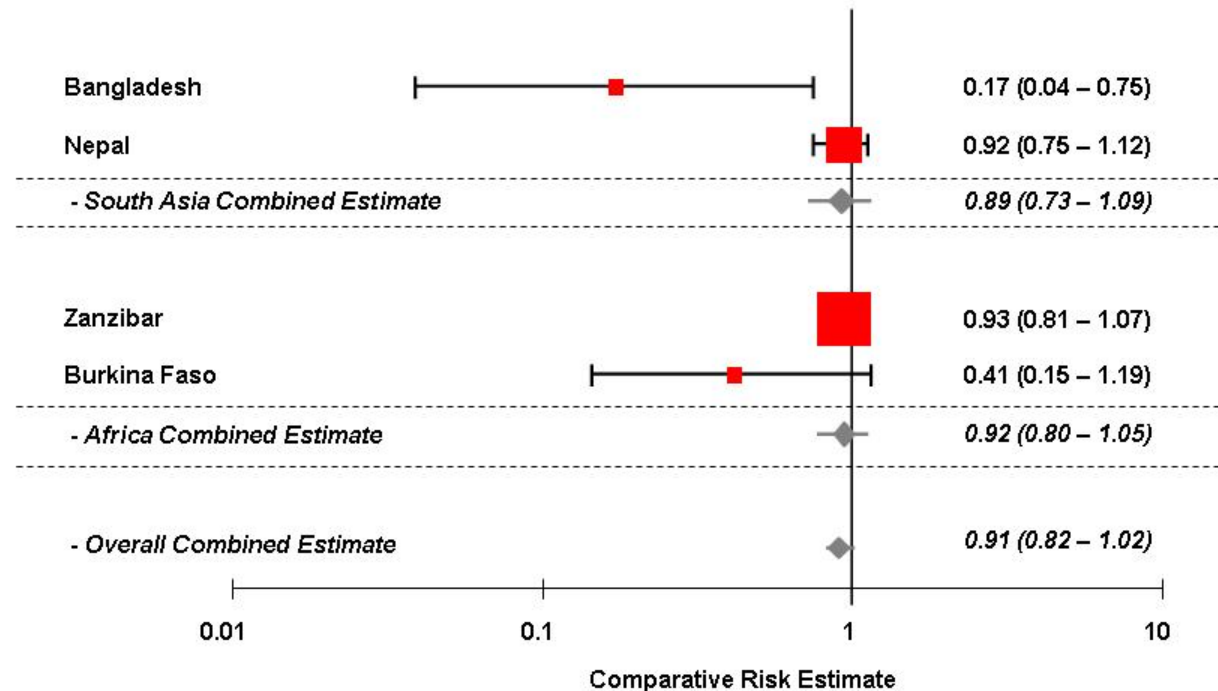
- Non-significant 8% reduction of daily zinc supplementation on total mortality.
- Effect modification by age:
 - <12 m, no effect.
 - ≥ 12 m, 20% reduction (NS).
- No impact of daily zinc supplementation on incidence of diarrhea, persistent diarrhea, dysentery, or ALRI.
- Cause-specific analyses suggest that treatment effect on gastroenteritis is focused on most severe cases and not on routine watery diarrhea or dysentery.

Conclusions: Program Implications

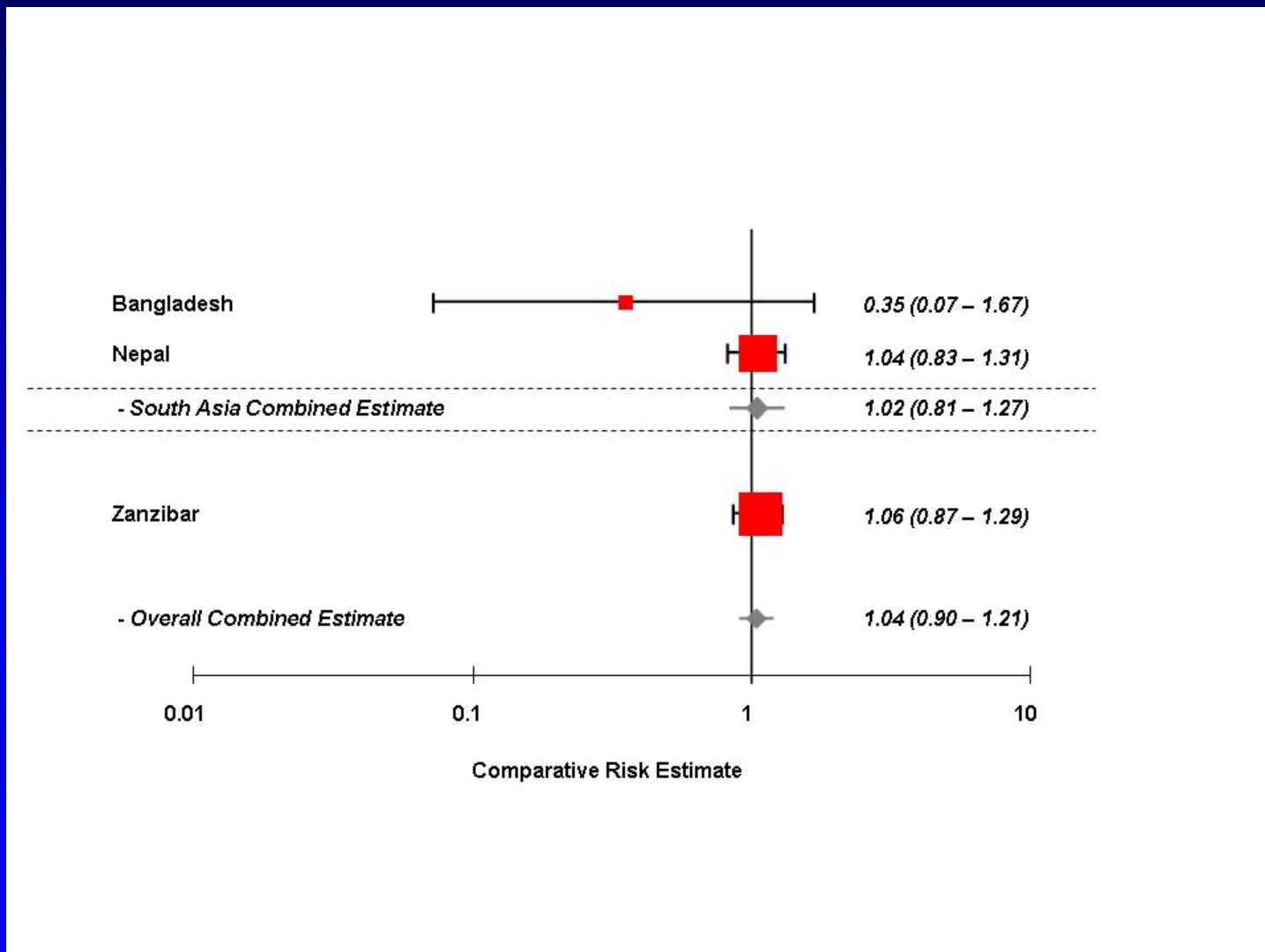
Daily Supplementation

- Universal supplementation (all <5) not likely to be cost-effective relative to other child survival interventions.
- Targeted approaches (≥ 12 m) may be cost-effective, but mortality rates lower in this age group and evidence for impact is weak.
- Adjuvant for treatment of diarrhea already proven.

Meta-Analysis of Zinc Mortality Trials All Preschool Ages



Meta-Analysis of Zinc Mortality Trials <12 months



Meta-Analysis of Zinc Mortality Trials ≥12 months

