Zinc Deficiency

Robert E. Black, M.D., M.P.H.
Edgar Berman Professor and Chair
Department of International Health
Johns Hopkins Bloomberg School of Public Health

Effects of Zinc Deficient Diets in Early Experiments in Rats

- **1922-27: Studies with equivocal effects**
- **1933 (Newell & McCollum): "Zinc is probably not an essential nutritional factor in the growth of the rat"**
- **1934 (Todd et al): Reduced the rate of growth**
- **1940 (Day & McCollum): Impaired growth and eczema**

Zinc Biology

- **Essential trace element**
- **Several hundred zinc metalloenzymes**
- **Zinc “fingers” in transcription proteins determine binding to DNA**
- **Intracellular regulation, e.g., cellular growth, differentiation and death**

Considerations Regarding Dietary Zinc

- **Breast milk, beef, oysters, crabmeat, poultry are good sources**
- **Phytates, fiber and lignin reduce bioavailability of zinc from cereals, legumes and tubers**
- **Calcium and casein may reduce bioavailability of zinc from cow's milk**

Causes of Excess Zinc Losses or Shifts

- **Fever/catabolism increases muscle breakdown and urinary zinc losses**
- **Diarrhea causes excess losses**
- **Proinflammatory cytokines induce metallothioneins, which binds zinc and results in shift to liver**

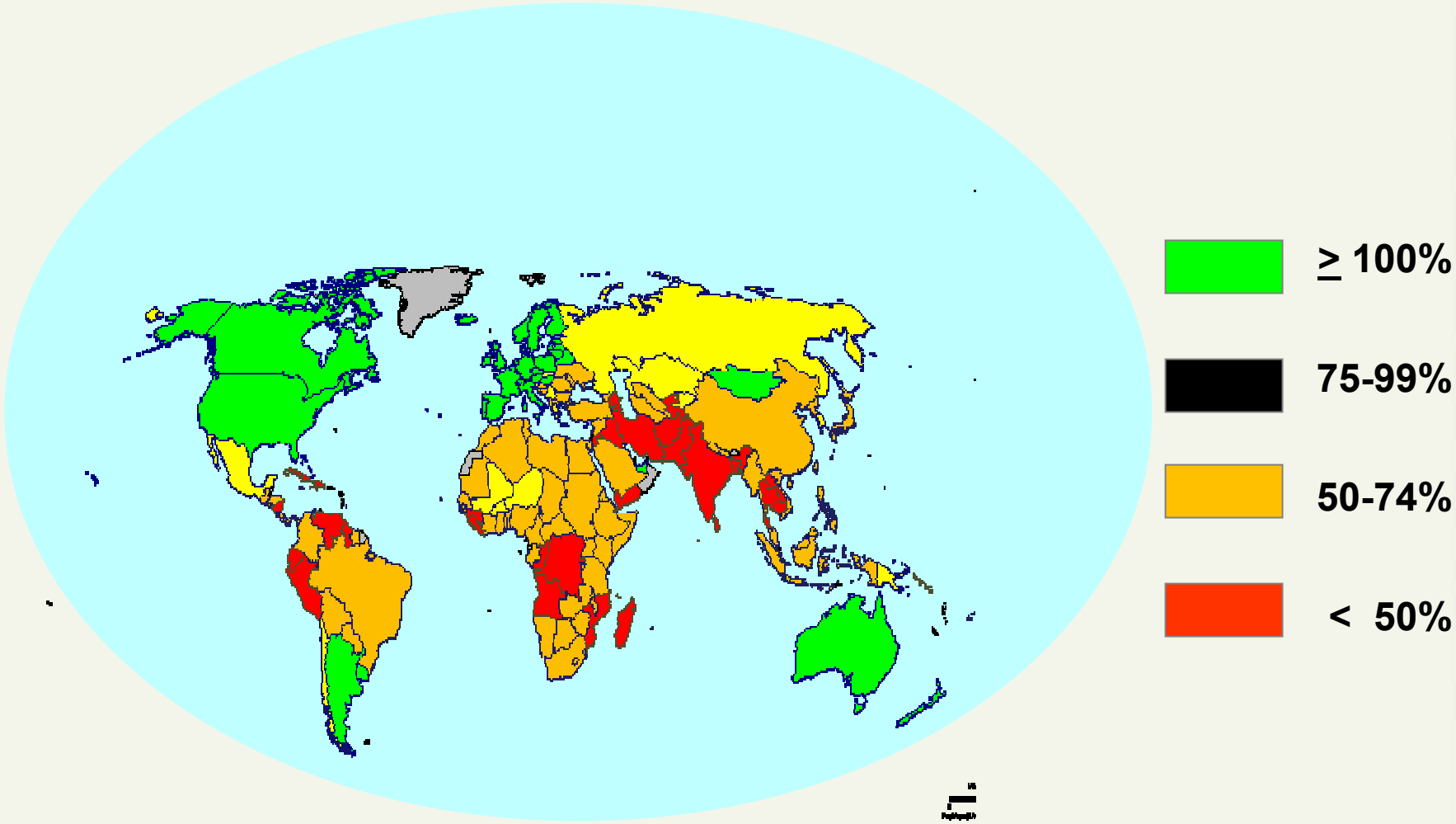
Factors Suggesting Zinc Deficiency in a Population

High phytate staple foods
Low intake of “flesh” food
Prevalent stunting
High rate of diarrhea
Nutritional iron deficiency
Geophagia

Recommended Daily Intake of Zinc

Age Group	High Bioavailability (US)	Low Bioavailability (WHO)	Low Bioavailability (IZiNCG)
0-5 mo	2.2 mg	7.1 – 8.0 mg	--
6-11 mo	3.0 mg	7.0 – 8.0 mg	5.0 mg
12-59 mo	3.0 – 5.0 mg	7.9 – 9.2 mg	3.0 – 5.0 mg

Zinc in the national food supply, as % weighted mean per capita requirement (adjusting for estimated zinc absorption from food supply)



Clinical Spectrum of Human Zinc Deficiency

- **Adolescent nutritional dwarfism: hepatosplenomegaly, hypogonadism, dwarfism, described by Prasad in Iran and Egypt**
- **Severe zinc deficiency: hypogonadism, growth retardation, dermatitis, alopecia, mental disturbances, infections, death**
- **Mild-moderate zinc deficiency: hypogonadism, growth retardation, decreased immune function, infections**

Meta-analysis of Randomized Controlled Trials of Zinc Supplementation Effects on Growth in Prepubertal Children*

- **33 data sets**
- **10 from US/Canada, Europe, Japan**
- **23 from 16 low- and middle-income countries**
- **Zinc dose 1-20 mg/d for 2-15 mo**

***Brown KH et al., Am J Clin Nutr, 2002**

Effects of Zinc Supplementation on Growth

- **Overall highly significant effects of zinc on weight and height increments**
- **Effects greater in underweight or stunted children**
- **Absolute difference in height (for 25 studies with average initial age of 2.8 y and 6 mo. supplementation) was 0.72 cm (similar to food supplementation trials)**

Effects of Zinc Deficiency on Immune Function

- **Reduced nonspecific immunity, including PMN and NK function and complement activity**
- **Reduced T and B lymphocytes**
- **Multiple effects on function, including suppressed delayed hypersensitivity, cytotoxic activity and antibody production**

Randomized Controlled Trials of Zinc Supplements for Prevention or Therapy

Prevention – supplements of zinc given daily to all children in population where there is some indication of zinc deficiency to assess prospectively rates of infectious diseases

Therapy – supplements of zinc given to children who have an infectious disease to examine benefits for that episode and sometimes subsequent illness

Preventive Effects of Zinc Supplements for Diarrhea, Pneumonia and Malaria

- **Analysis of 9 trials with diarrhea outcomes**
- **Analysis of 5 trials with pneumonia outcomes**
- **Analysis of 2 trials with malaria outcomes**

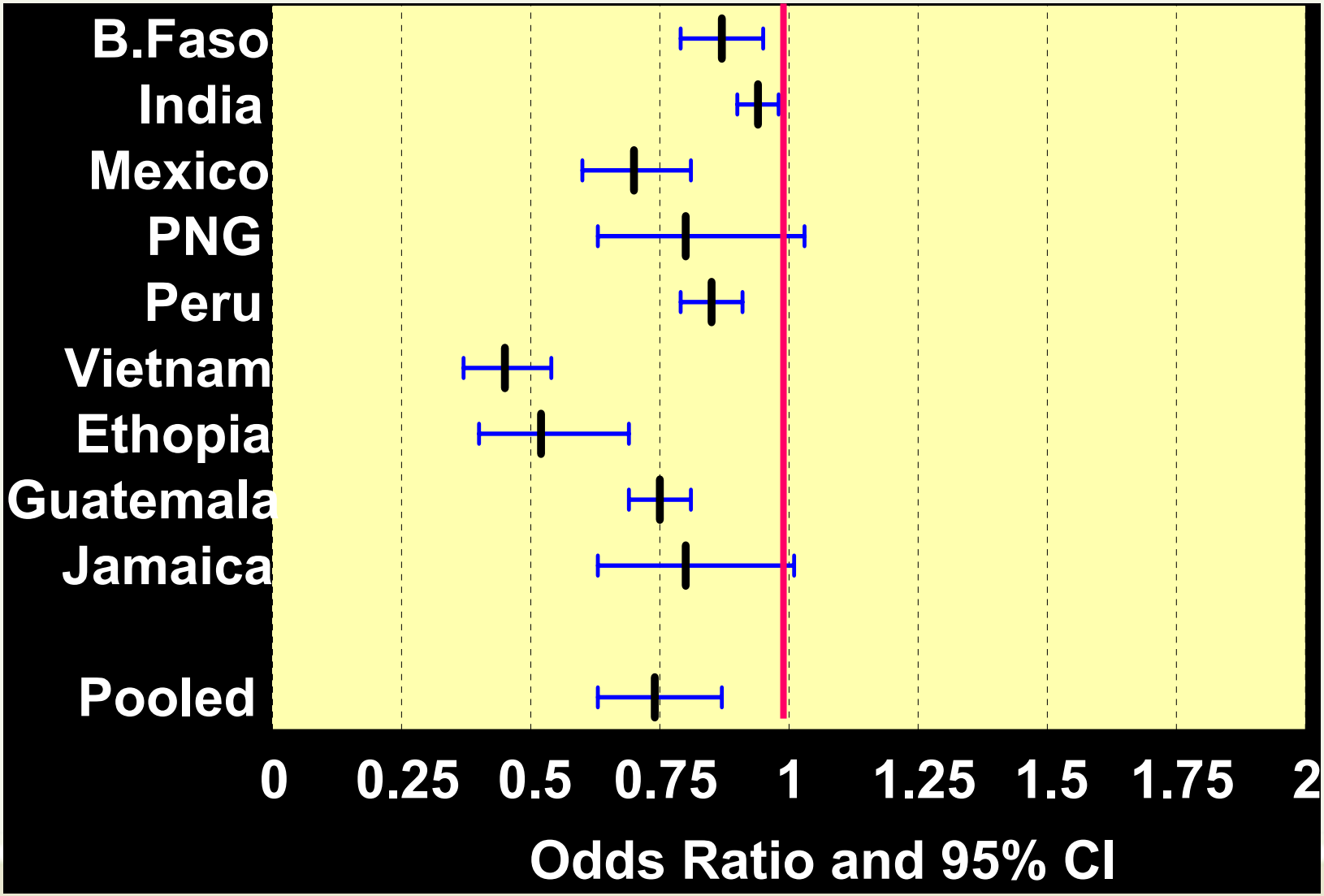
Trials Evaluating the Preventive Effects of Zinc Supplementation on Diarrhea and Pneumonia

- **Countries: Burkina Faso, Ethiopia, Guatemala, India (2), Jamaica, Mexico, PNG, Peru, Vietnam**
- **Age groups: 4-60 mo**
- **Dose of zinc: ≈10mg/d (range 5-20 mg/d)**

Provision of Vitamins and Minerals to Both Zinc and Control Groups in Preventive Trials of Zinc Supplementation

Trial	Vitamins/Minerals
India	Vit. A,B,D,E
India	Vit. A
Jamaica	Vit. A,B,C,D
Mexico	Half given iron
PNG, Peru, Vietnam, Guatemala, Ethiopia, Burkina Faso	None

Preventive Effect of Zinc Supplementation on Diarrheal Prevalence in Continuous Supplementation Trials



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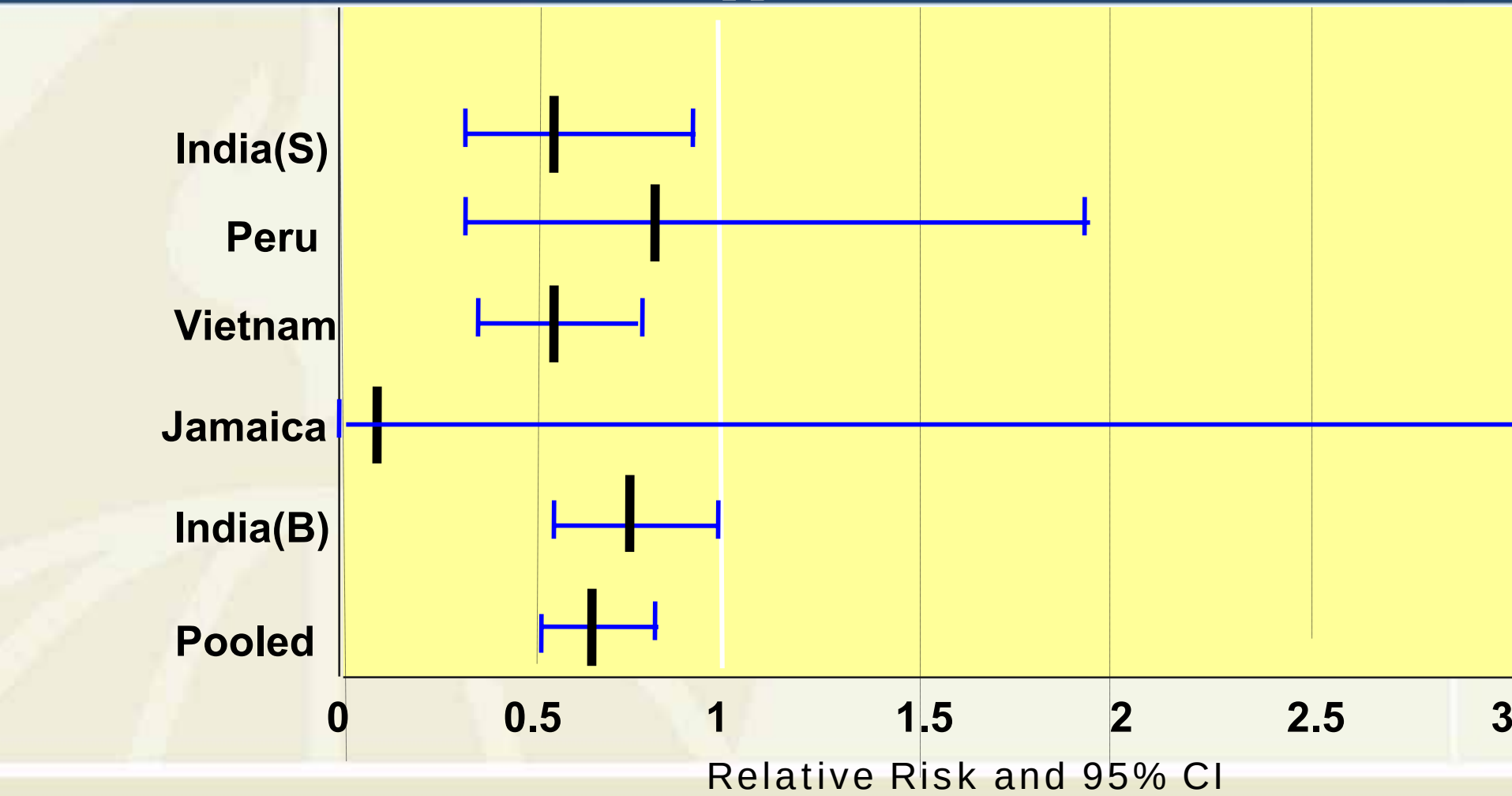
Preventive Effect of Zinc Supplementation on Pneumonia Incidence in Continuous Supplementation Trials



Effect of Zinc Supplementation on Malaria in Children

Location	Reduction in Clinic Visits for Malaria
The Gambia	32% (p=0.09)
Papua New Guinea	38% (p<0.05)
Combined	36% (CI 9-55%, p<0.05)

Trial of Zinc or Vitamin/Iron Supplementation in Term, SGA Infants in India

- **Term, below 10th percentile W/A**
- **4 Groups supplemented 1-9 mo. of age**
  - **Riboflavin**
  - **Riboflavin, zinc**
  - **Riboflavin, folate, iron, calcium, phosphorus**
  - **Riboflavin, zinc, folate, iron, calcium, phosphorus**
- **68% lower mortality in zinc-supplemented groups (5 vs 15 deaths, p=0.028)**

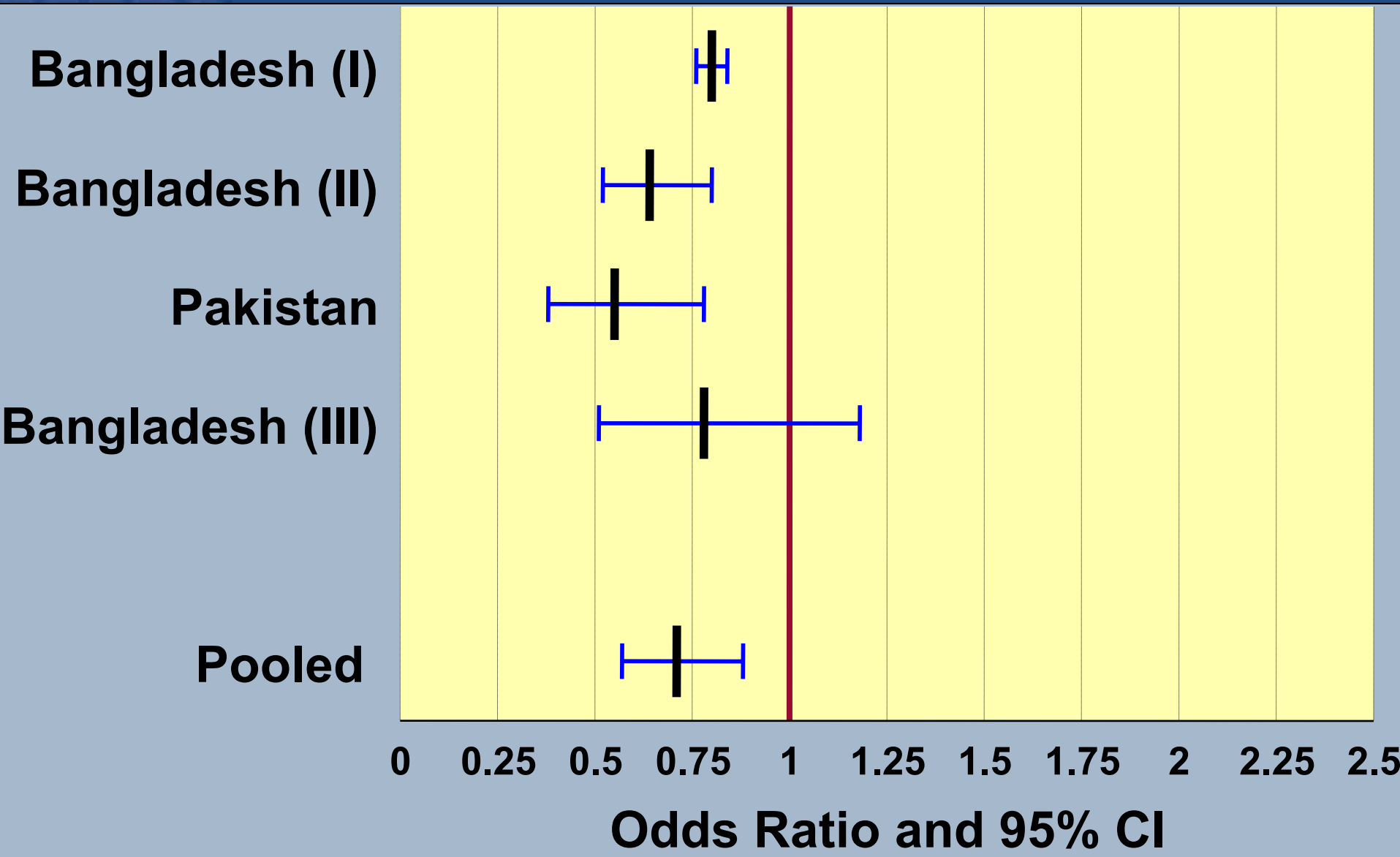
Sazawal, Black, Menon et al, Pediatr, 2001

Trials in Bangladesh Evaluating the Preventive Effect of Weekly Zinc Supplementation

- **6-11 mo. old infants <-1z W/A, weekly zinc (20mg) had non sig. reduction in diarrhea and ALRI, but zinc plus iron (20 mg) had sig. 30% less diarrhea and 40% less ALRI[1]**
- **1-23 mo. old children, weekly zinc (70 mg) had sig. 6% less diarrhea, 17% less pneumonia, 49% less severe pneumonia and 42% less otitis media, as well as sig. 85% less mortality[2]**

[1]Baqui et al, J Nutr, 2004, [2]Brooks et al, submitted

Preventive Effect of Zinc Supplementation on Diarrheal Incidence in Short - Course Supplementation Trials



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Efficacy Trials of Zinc Supplementation on Child Mortality

- **Zanzibar and Nepal**
- **Children 1-35 mo. old (>60,000 child-years)**
- **Randomized, controlled trials**
- **Daily 10 mg zinc (5 mg if <12 mo old)**
- **All children receive vitamin A**
- **Trial to be completed in Zanzibar in September, 2005 and Nepal in January, 2006**

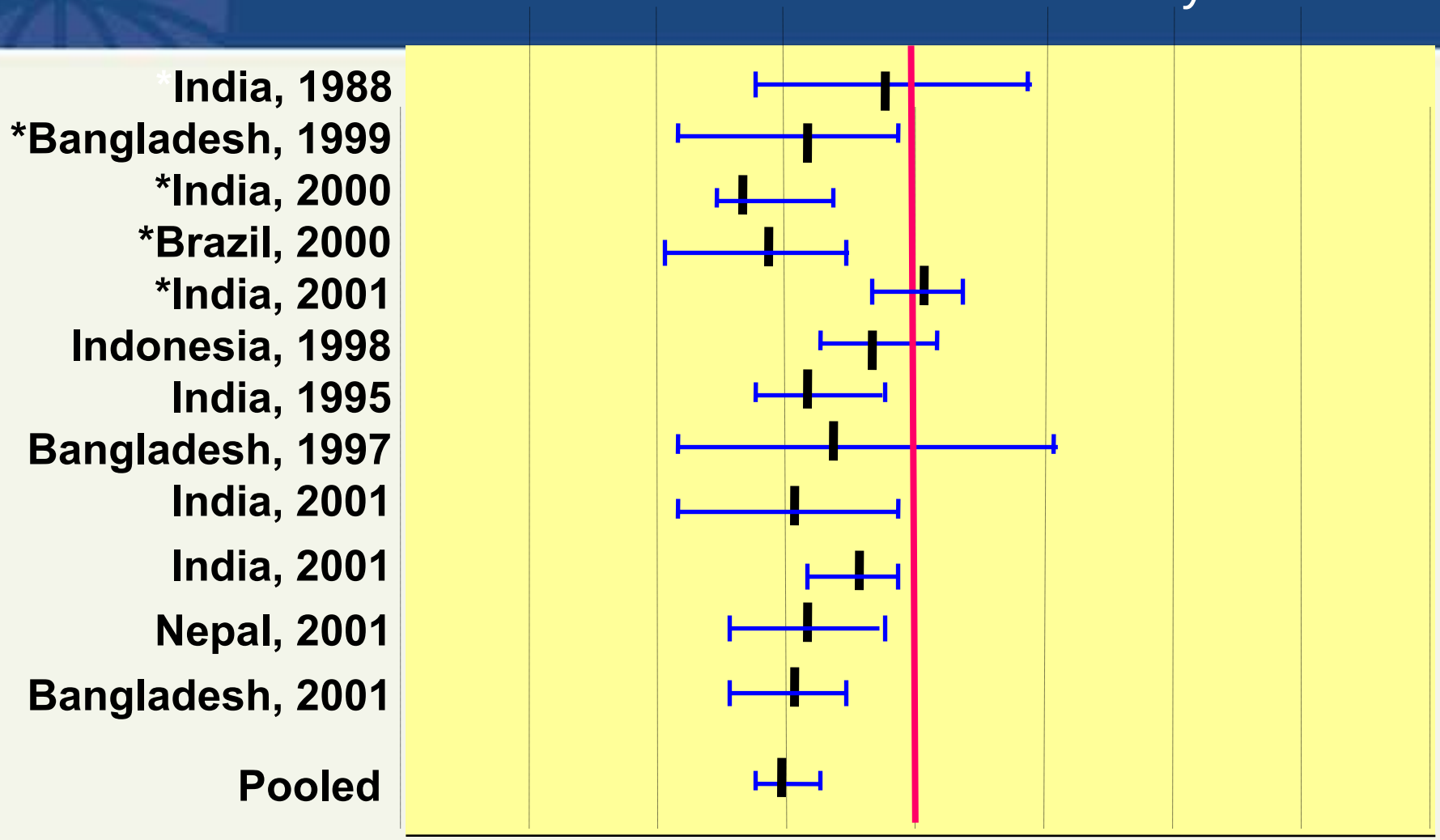
Therapeutic Effects of Zinc Supplements in Diarrhea, Pneumonia, and Malaria

- **12 trials in acute diarrhea**
- **5 trials in persistent diarrhea**
- **2 trials in pneumonia**
- **1 trial in measles**
- **Multi-center trial in malaria**

Trials on the Therapeutic Effect of Zinc on Acute Diarrhea

- **Countries: Bangladesh (3), Brazil, India (6), Indonesia, Nepal**
- **Age groups: 3-60 mo**
- **Dose of zinc: ≈20 mg/d (range 5-45 mg/d)**

Effect of Zinc Supplementation on Duration of Acute Diarrhoea/Time to Recovery



*Difference in mean and 95% CI
Relative Hazards and 95% CI

Therapeutic Effects of Zinc Supplementation on Acute Diarrheal Severity

Country	Diarrhea Outcome	Percent Reduction
India	Frequency	18
India	Frequency	39
Bangladesh	Output	28
India	Output	38
Brazil	Frequency	59

Trials on the Therapeutic Effect of Zinc on Persistent Diarrhea

- **Countries: Bangladesh (2), India, Pakistan, Peru**
- **Age Groups: 3-36 mo**
- **Dose of zinc: 20 mg/d**

Effect of Zinc Supplementation on Duration of Persistent Diarrhea Episode

Analysis	Effect Measure	Effect Size (95% CI)
Pooled Analysis (n=4)	Lower probability of continuing diarrhea	24% (9%, 38%)
Meta-Analysis (n=5)	Reduction in mean duration	29% (6%, 52%)

Community-based Trial of Zinc Supplementation During Diarrhea

- **In rural Bangladesh, 30 health worker areas randomized**
- **8,070 3-59 mo. old children, 11,880 child-years**
- **ORT alone vs. ORT and 20 mg/d zinc**
- **Duration of episodes: RH 0.77 (0.69, 0.86)**
- **Diarrhea hospitalization: RR 0.81 (0.65, 1.00)**
- **Mortality: RR 0.49 (0.25, 0.94)**

Baqui, Black, Arifeen, et al., BMJ, 2002

Effects of Zinc Supplementation Started During Acute Diarrhea in Bangladesh*

Outcome	Zinc (%)	Control (%)
Treated with ORS	75	50†
Antibiotic use	13	34†
Other drug use	15	45†
Care from pharmacy	16	33†
Care from village "doctors"	12	27†
Care from homeopaths	6	13†

*Baqui, Black, Arifeen et al, J Health Pop Nutr, 2004

†All comparisons $p<0.01$

Zinc and/or Vitamin A in the Treatment of Acute Lower Respiratory Infection*

- **Indian children 2-24 mo old**
- **153 randomized to 10 mg zinc/d, 10,000 ug RE vitamin A, both or placebo**
- **Zinc supplemented boys had faster recovery (Recovery rate ratio from "very ill status" (2.6; 1.4, 5.1); no effect in girls**
- **Vitamin A supplementation had no benefit on recovery**

***Mahalanabis et al, AJCN, 2004**

Efficacy of Zinc in Therapy of Severe Pneumonia*

- **Bangladeshi children <2y old with severe pneumonia**
- **270 randomized to 20mg zinc/d or placebo along with standard antibiotics (amp./gent.)**
- **Zinc group had shorter duration of severe pneumonia (RH 0.81; 0.67, 0.99) and of chest indrawing, elevated RR and hypoxia**

*** Brooks et al, Lancet, 2004**

Efficacy of Zinc in Therapy of Measles and Malaria

- **Indian study found no effect of 20mg zinc/d in therapy of measles[1]**
- **Multi-center study (Ecuador, Ghana, Tanzania, Uganda, Zambia) found no effect of 20/40 mg zinc/d in therapy of malaria[2]**

[1]Mahalanabis et al, AJCN, 2002
[2]Zinc Against Plasmodium Study Group, AJCN, 2002

Summary of Prevention and Therapy Beneficial Effects of Zinc

- **Prevention**
  - **Consistent effects on diarrhea and pneumonia morbidity; possible effects on malaria and otitis**
  - **Two trials show mortality reduction**
- **Therapy**
  - **Consistent effects with diarrhea; possible effects with pneumonia**
  - **One trial shows mortality reduction**

Zinc Supplementation in Pregnancy

- **Countries: Bangladesh, Chile, Ecuador, Indonesia (3), Peru (2)**
- **Initiation: generally from 2nd trimester**
- **Dose: ≈25 mg/d (range 15 – 30 mg/d)**

From: Osendarp, West, Black, J Nutr, 2003

Results of Zinc Supplementation in Pregnancy

- **Intrauterine growth – evidence negative**
- **Labor and delivery complications, gestational age at birth, fetal neurobehavioral development – evidence conflicting or limited**
- **Neonatal immune status, early neonatal morbidity-evidence positive**

From: Osendarp, West, Black, J. Nutr, 2003

Supplementation to Improve Zinc Nutriture in Developing Countries

- **Dose**
  - **Approximately one RDA**
  - **Range of safety and benefit unknown**
    - **probably ½ - 2 RDA daily**
    - **unknown for weekly**

Supplementation to Improve Zinc Nutriture in Developing Countries

- **Form of zinc**
  - **most trials done with sulfate, then gluconate and acetate**
- **Combination with other micronutrients**
  - **some adverse interaction in both directions when given with iron in a supplement**

Supplementation to Improve Zinc Nutriture in Developing Countries

- **Frequency**
  - **Clear effects of daily**
  - **Similar change in plasma zinc with daily or weekly**
  - **Benefits with two weeks of supplement for 2 - 6 months**
  - **Benefits of weekly supplements of 20 mg or 70 mg**
  - **Benefits of 2 weeks of supplement for 2-6 months**

Supplementation to Improve Zinc Nutriture in Developing Countries

- **Presentation of supplement for children**

  Syrup - acceptability good, but expensive and difficult logistics

  Dispersible tablets- acceptability good

  Tablets/ capsules - only for school age children

Fortification to Improve Zinc Nutriture in Developing Countries

- **Addition of nutrient to maintain or improve quality of food**
- **Can improve zinc intakes in population**
- **Low cost**
- **Must assure that target population consumes enough**

Alternative Fortification Approaches for Zinc

- **Commercial foods e.g., “baby cereal”**
- **Special foods, e.g., sachet of powdered food or fat-based food with micronutrients added**
- **Staple foods, e.g., wheat flour in Indonesia or maize flour in Mexico**
- **Addition of micronutrients to home-prepared foods, e.g., a “sprinkle” being evaluated**

Implication for Global Burden of Disease

- **Burden attributable to zinc deficiency includes 779,000 child deaths and 27 million DALYs annually, about 2% of global DALYs**
- **Either preventive or therapeutic use of zinc supplements has the potential to reduce infectious disease illness and death if effective delivery systems can be deployed**