

# **Zinc and Childhood Mortality**

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## **Comments on the results of Zinc Supplementation on Mortality from the Pemba and Nepal trials**

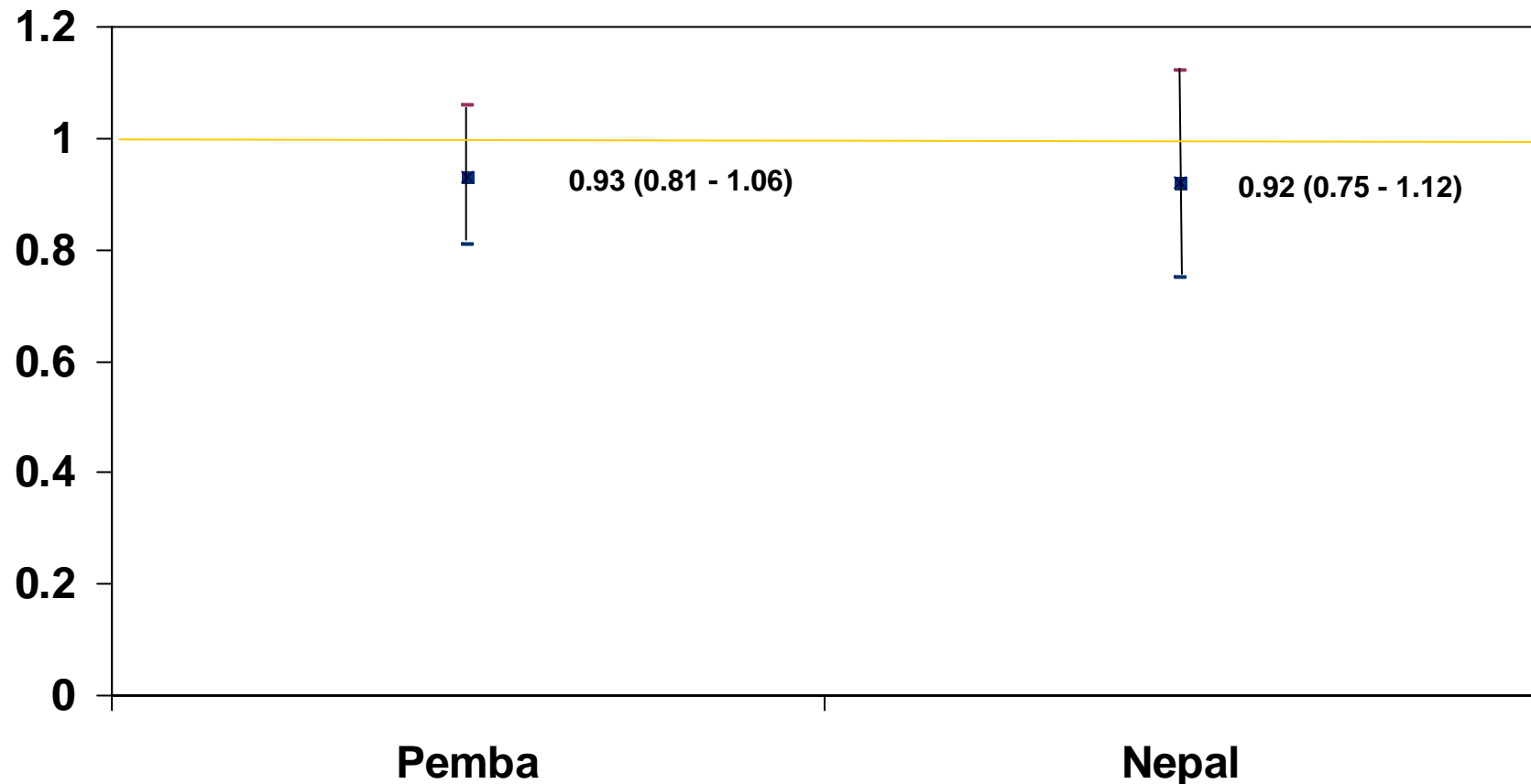
**Dr. Juan A. Rivera  
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National Public Health Institute (Mexico)**

# Acknowledgements

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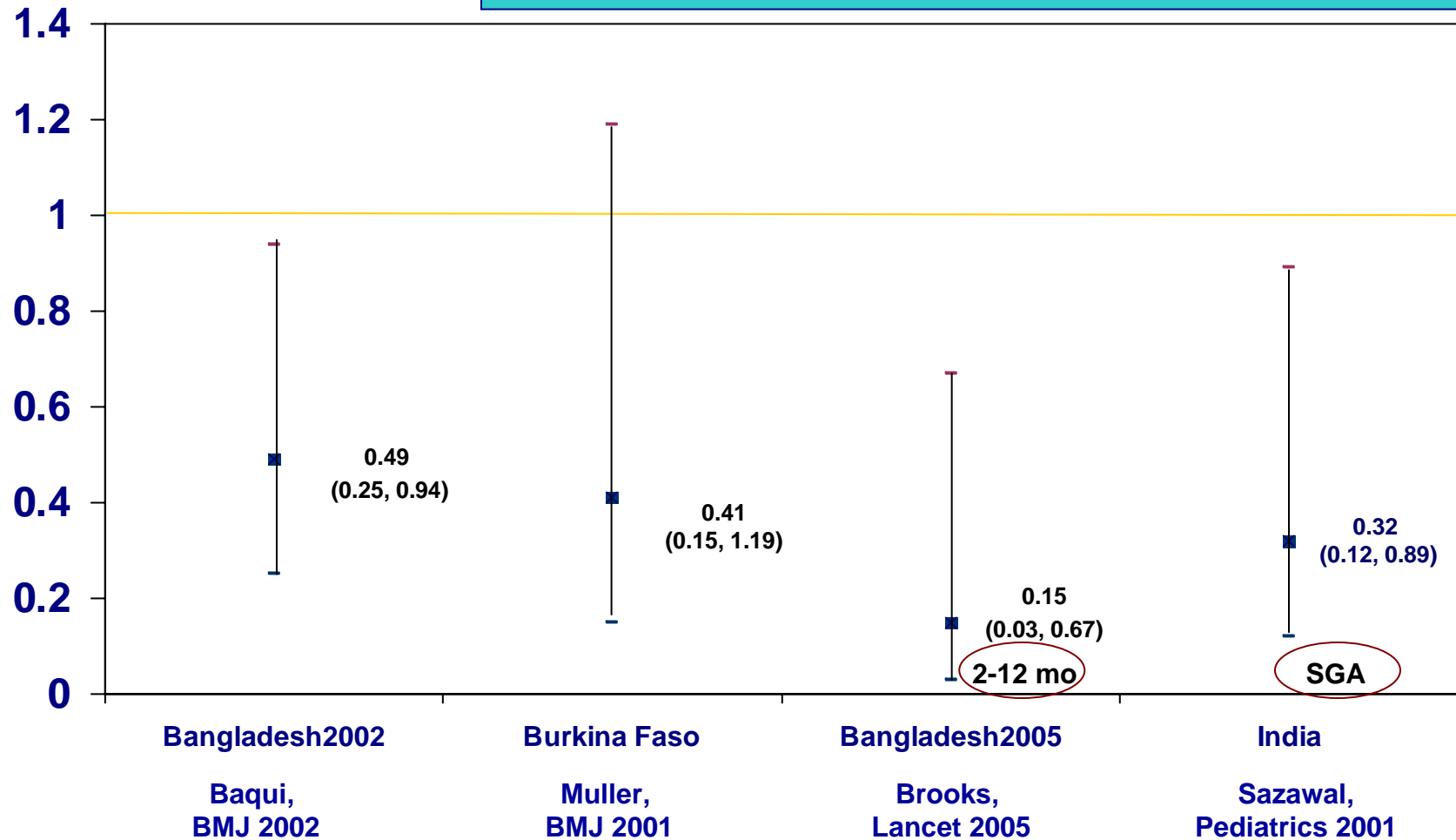
- Contribution of Ivonne Ramírez (INSP)
- K. Brown, S. Hess and J. Pearson (UC Davis) provided data and comments
- Authors
  - Pemba Trial: S Sazawal (Manuscript and Presentation)
  - Nepal Trial: JM Tielsch (Presentation)

# Effects of zinc supplementation on mortality in young children in the trials presented today

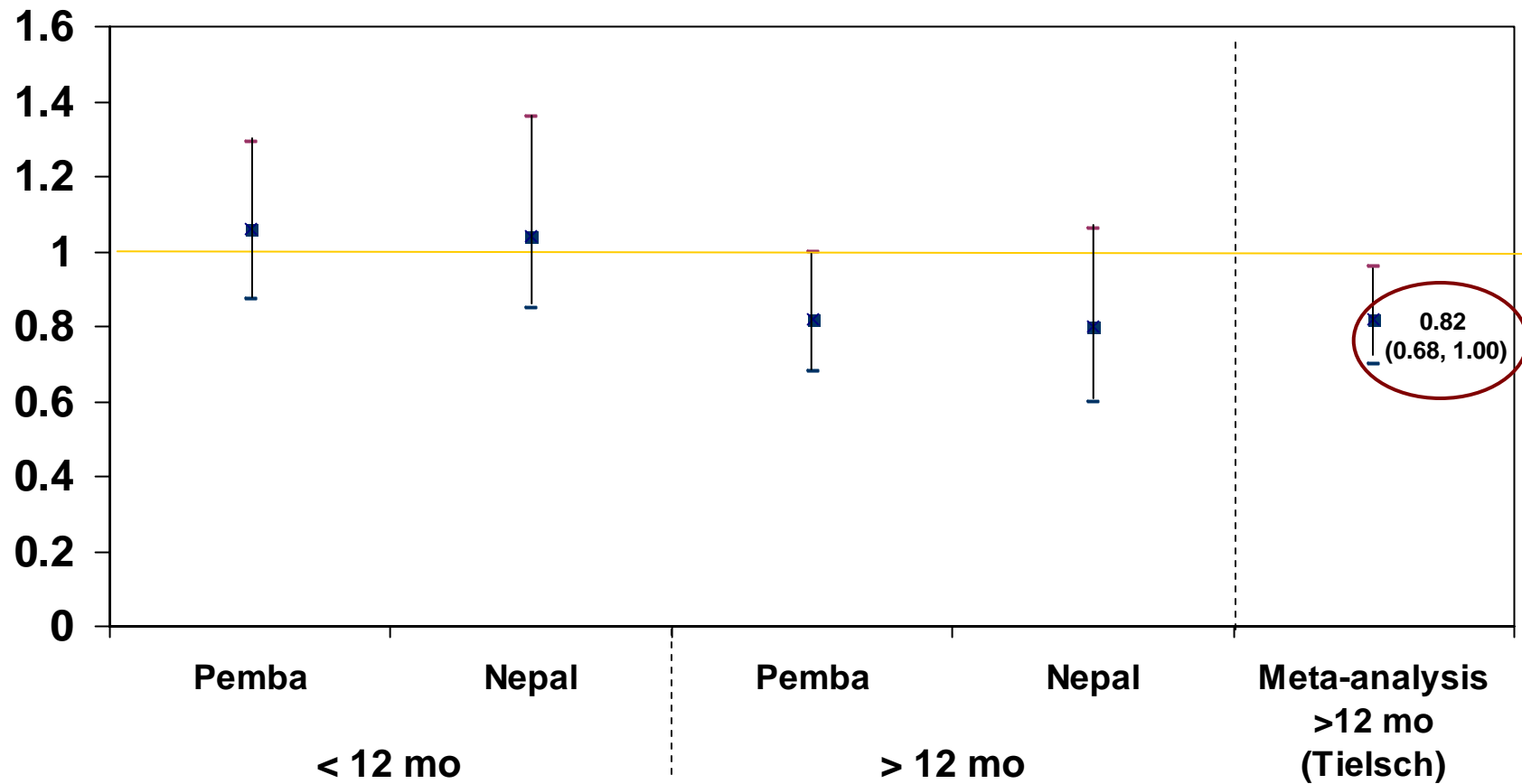


# Results of 4 smaller trials previously published

~50-85% reduction in young child mortality observed in 4 small-scale field trials



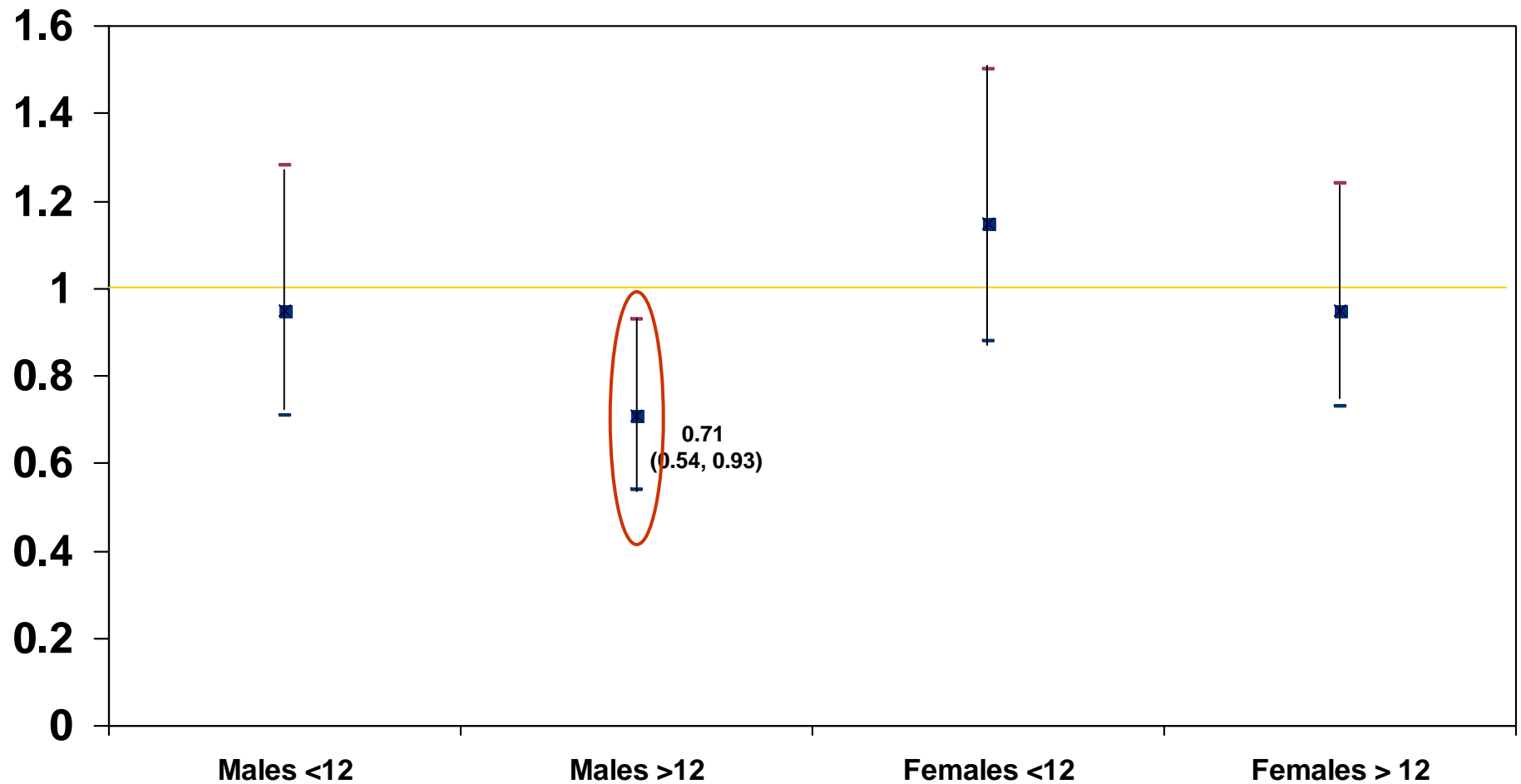
# Effects of zinc supplementation on mortality in infants vs young children in the Tanzania and Nepal trials



# Interaction of age and sex with zinc supplementation in the Pemba study

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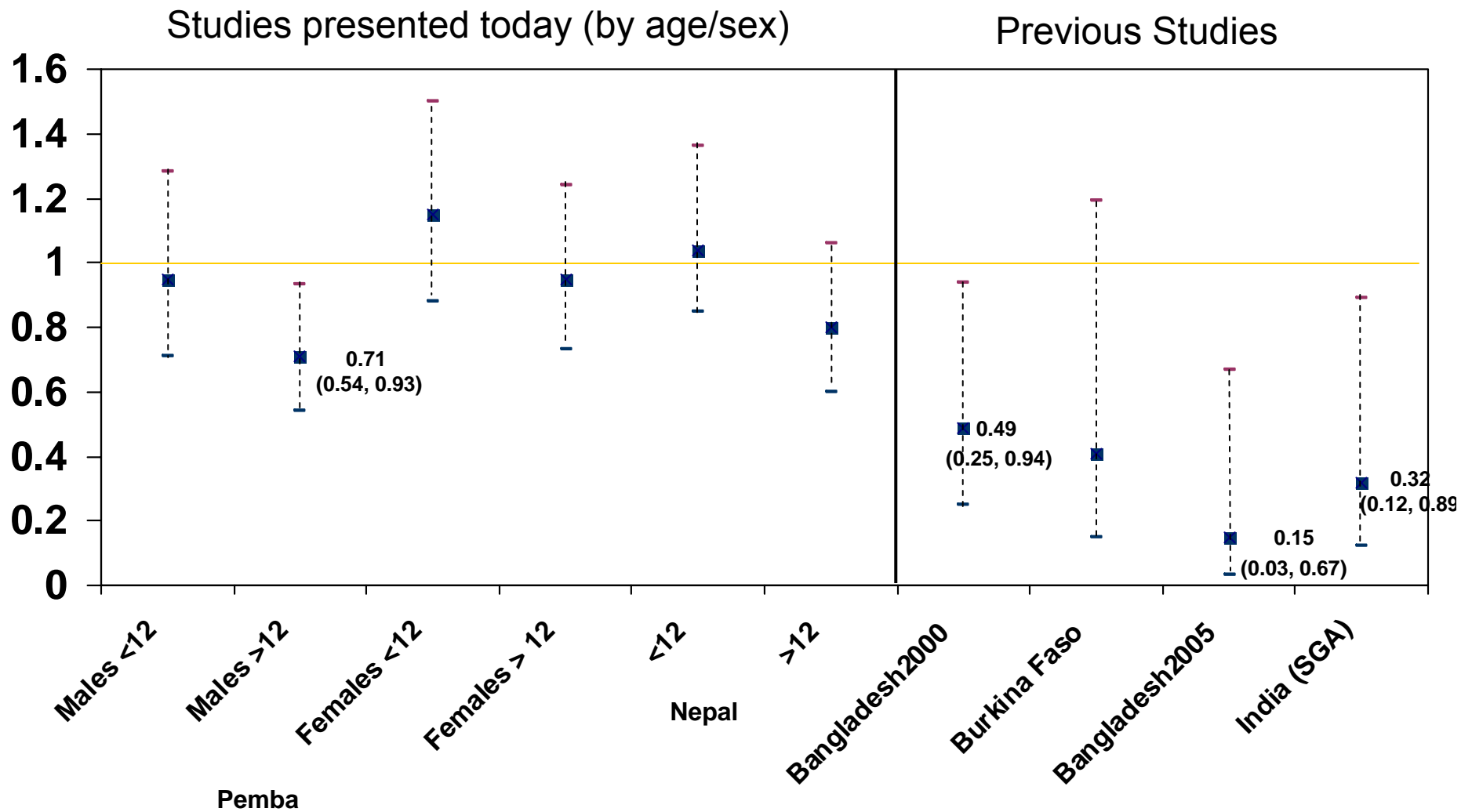


# Implications of results of new studies

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- Even if we were to ignore previous results...
  - Clear impact of zinc supplementation on mortality:
    - Children > 12 months (overall:18% reduction), although restricted to males in the Pemba study
- However, we should consider previous trials

# Comparison with previous studies studies



# Possible Reasons for differences in results

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- Design issues
- Differences in mortality related issues?
  - Lower mortality rates in populations in new trials?
  - Causes of death less likely to be reduced by zinc supplementation in populations in new trials ?
  - Differences between new and former trials in other factors affecting mortality?
- Is zinc status not deficient in populations in new trials?
- Was supplementation efficacious in improving zinc status as measured by serum zinc concentrations (delivery Issues) in new trials?
- Previous larger effects were due to chance

# Possible Reasons for differences in results

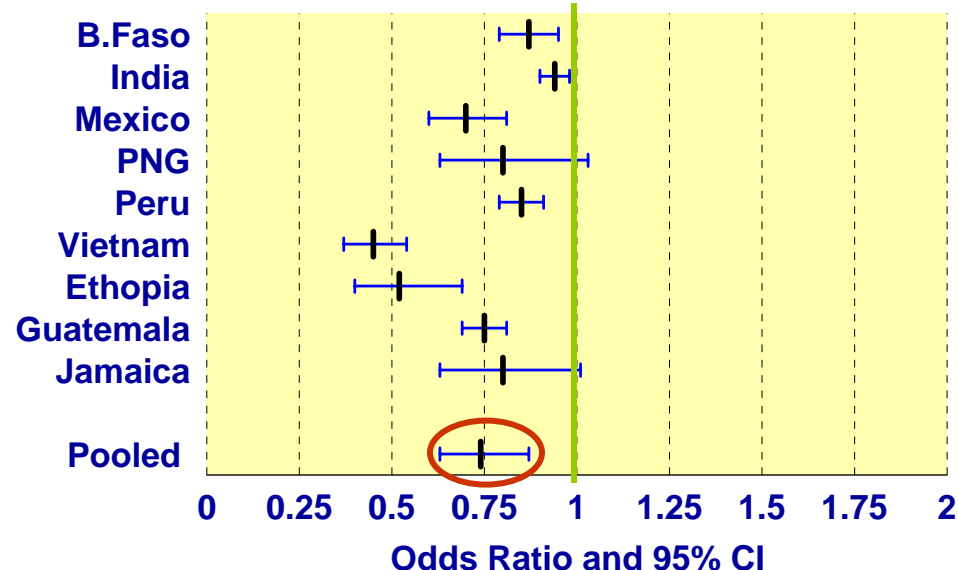
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- Design issues → Both studies well designed
- Differences in mortality related issues?
  - Lower mortality rates in populations in new trials?
  - Causes of death less likely to be reduced by zinc supplementation in populations in new trials ?
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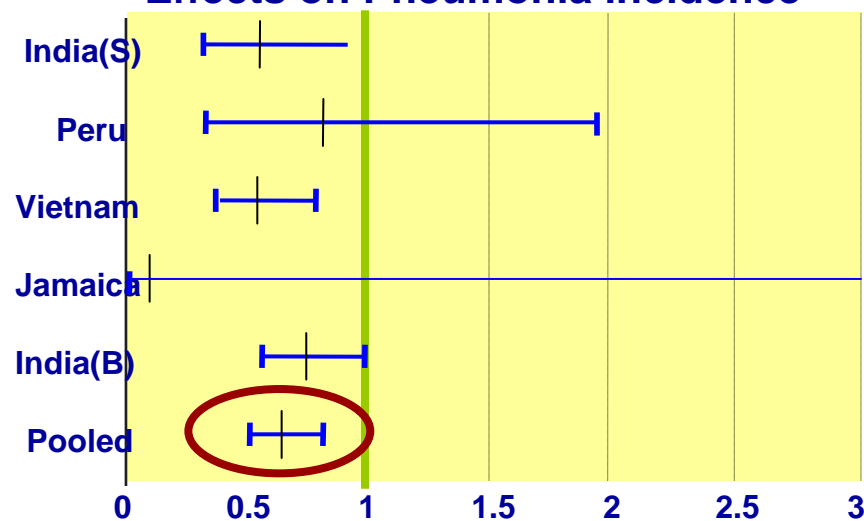
# Mortality Issues

- High MR both in Nepal and Pemba (IMR=89/1000)
- Main causes of death likely to be affected by Zinc status
  - Effects of zinc supplementation documented on **diarrhea and pneumonia**
  - Effects on malaria morbidity less clear
- Both studies provided Vitamin A supplements very effectively
  - **Is zinc less efficacious in the presence of Vitamin A supplementation?**

### Effects on Diarrheal prevalence

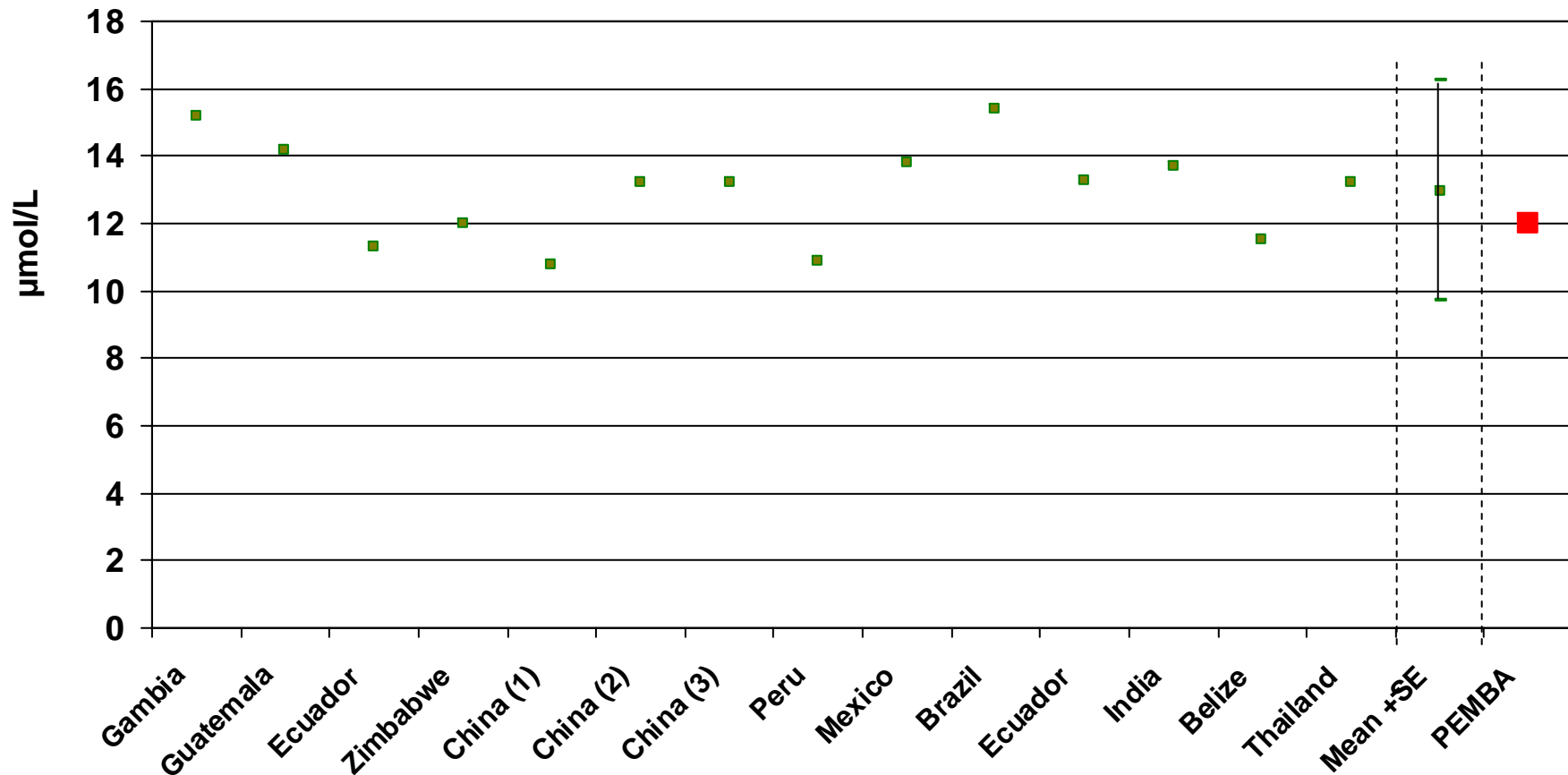


### Effects on Pneumonia incidence



# Evidence that zinc status was deficient

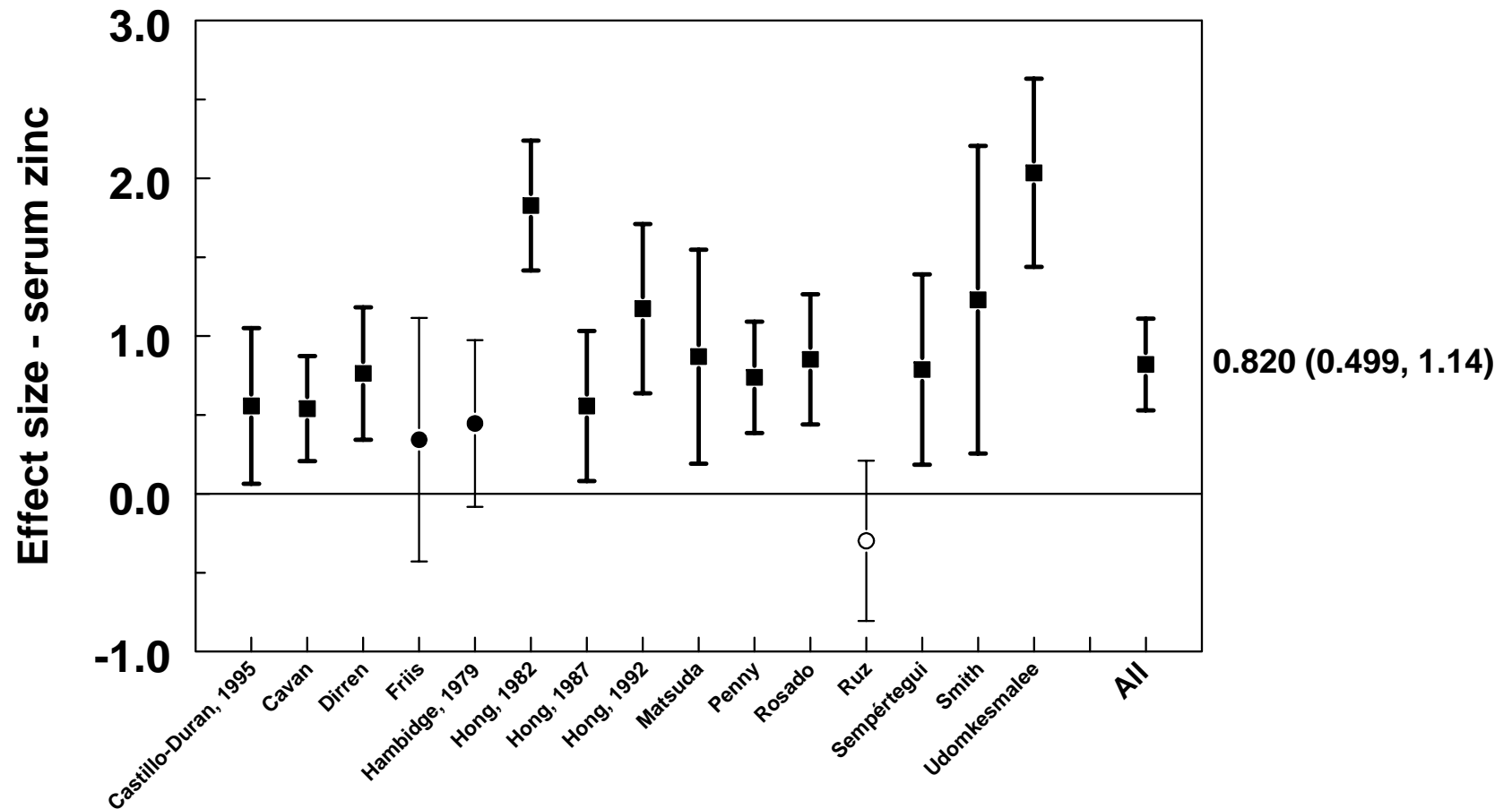
Baseline serum zinc concentrations in zinc supplementation trials where responses on growth were documented (Brown et al, AJCN, 2002) and in the PEMBA trial



- High stunting rates in both Nepal and Pemba
- Baseline Stunting rate in Pemba: 25% (half children < 12 mo age)

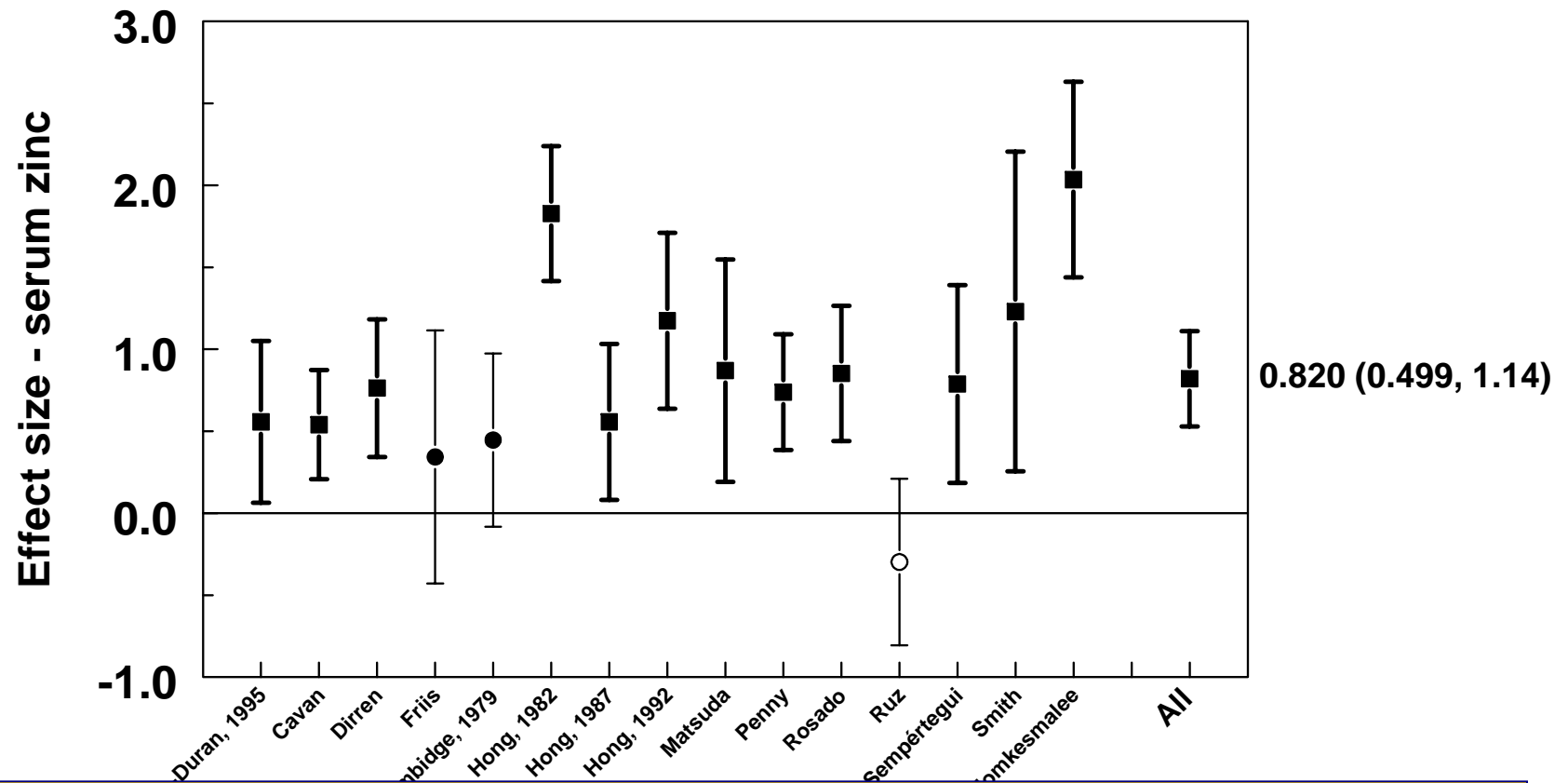
# Was supplementation efficacious in improving zinc status?

IZiNCG meta-analysis on the response of serum zinc concentration to zinc supplementation in pre-pubertal children



# Was supplementation efficacious in improving zinc status?

Meta-analysis on the response of serum zinc concentration to zinc supplementation in pre-pubertal children from 15 efficacy trials

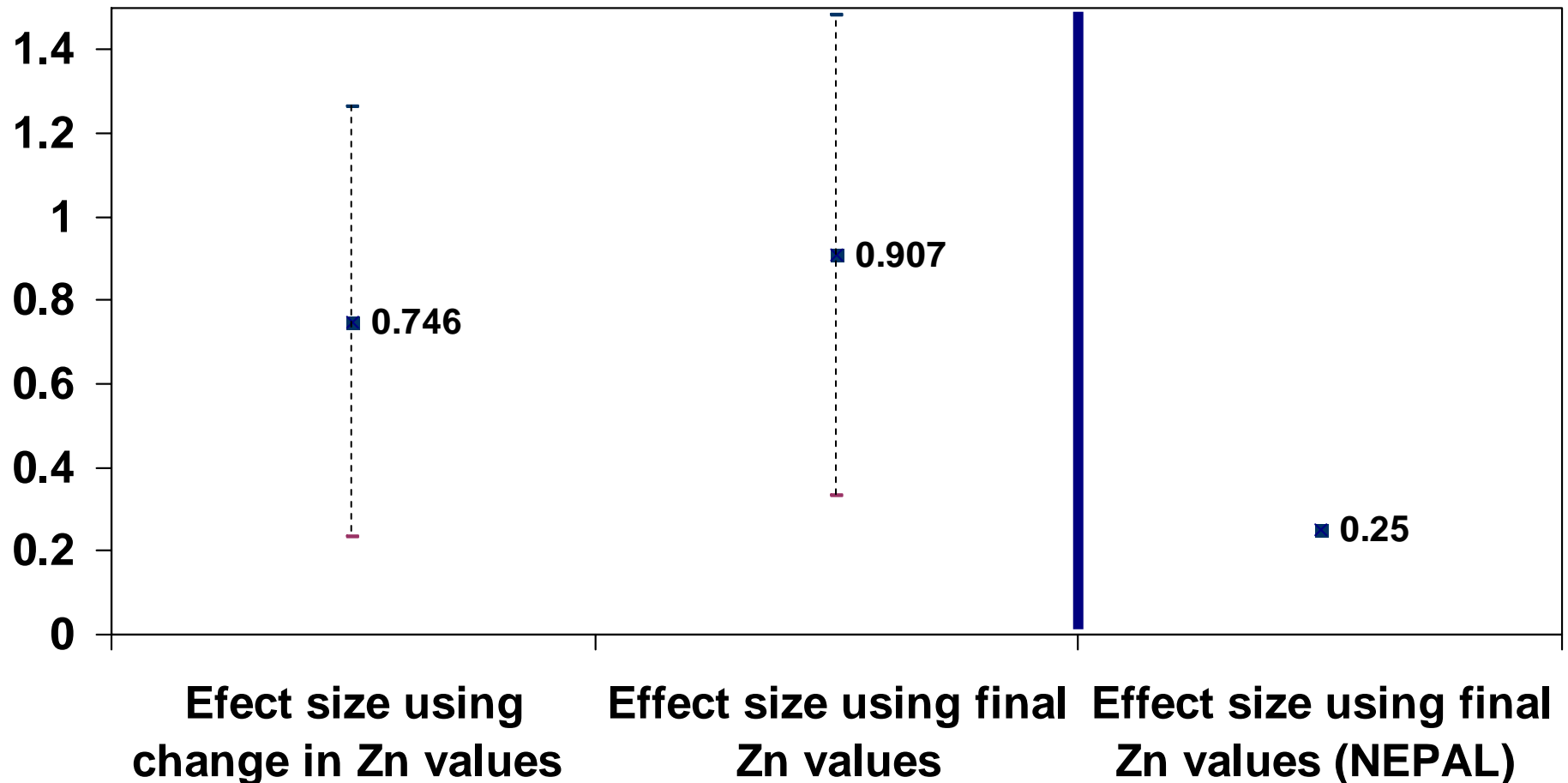


In the Pemba trial no significant differences in  $\Delta$  serum zinc between Zn and Control groups documented

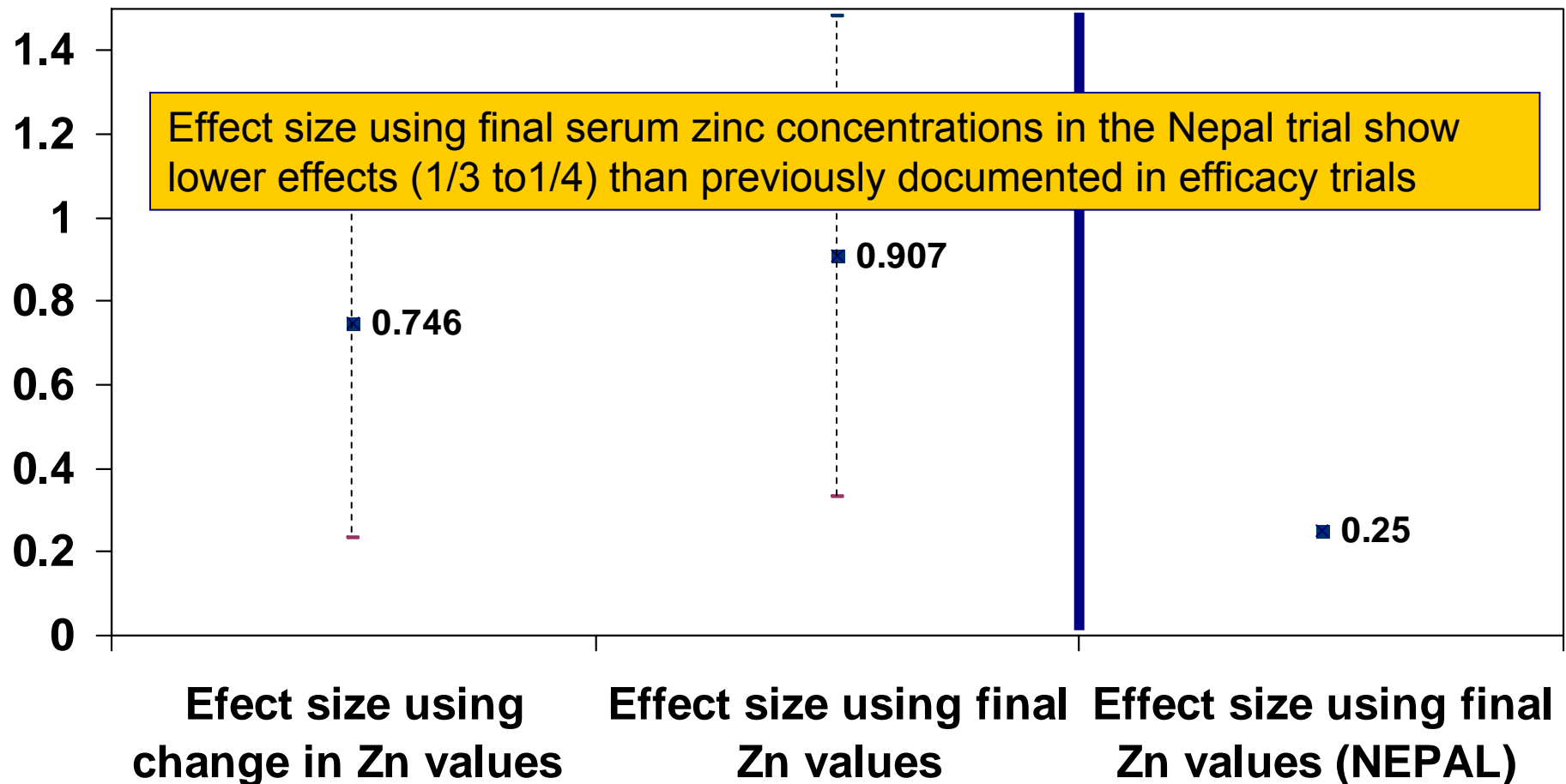
# Effect sizes in serum zinc concentrations using either final zinc values or changes in zinc values in 8 supplementation trials and only final values in the Nepal trial

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# Effect sizes in serum zinc concentrations using either final zinc values or changes in zinc values in 8 supplementation trials and only final values in the Nepal trial



## Some characteristics of zinc supplementation trials which assessed mortality

	Recent trials		Previous Trials			
Country	Pemba	Nepal	Bangladesh	Burkina-Faso	Bangladesh	India
Effect on Mortality	0.93 (0.81 - 1.06)	0.92 (0.75 - 1.12)	0.49 (0.25 - 0.94)	0.41 (0.15 - 1.19)	0.15 (0.03 - 0.67)	0.32 (0.12 - 0.89)
Age at recruitment	1 -35 mo	1-35 mo	3-59 mo	6-31 mo	2-12 mo	1 mo (SGA)
Type of zinc compound	Sulphate (Nutriset Tablets*)	Sulphate (Nutriset Tablets*)	Acetate (Syrup)	Sulphate (Tablets)	Acetate (Syrup)	Sulfate (Syrup)
Dose/day	10 mg (5mg)	10 mg (5mg)	20 mg /14 d (Diarrhea)	12 mg/ d	35 mg/ wk (5 mg/day)	5 mg/d
Duration (mo)	13	15	24	6	12	10
Adherence (%)	81.6%	72.9%				
Sample size	42,546	41,276	8. 070	709	1,655	1,154

# Was supplementation efficacious in improving zinc status?

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- No effects on changes in serum zinc concentrations documented in the Pemba trial
- Evidence from final values in Nepal suggests low efficacy of supplementation
- Can a study of > 40,000 children assure supplement intake? Were this efficacy or effectiveness studies?
  - Reported adherence in 2 studies lower than in previous efficacy trials (Pemba=80%, Nepal=73%)
  - Adherence evaluated through weekly visits in Pemba and method not reported in Nepal

## Was supplementation efficacious in improving zinc status?

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- It is possible that the amount of zinc delivered in both trials was lower than in previous trials and insufficient to produce effects in infants and larger effects in young children

# Previous larger effects due to chance?

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- Unlikely because effect sizes were systematically much larger in all 3 previous trials
- Assuming that differences due to chance
  - Why effects observed on SGA but not in infants?
    - SGA babies born with zinc depletion
  - Why effects on children  $\geq 12$  mo but not infants?
    - Evidence of lower effect on diarrhea morbidity  $< 12$  mo
    - Acquired adequate zinc during pregnancy
    - Receive adequate zinc through breastmilk
    - Zn results Optimal Th1/Th2 balance after 12 mo

# Conclusions

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- Evidence of effects of zinc supplementation on mortality reduction in:
  - SGA babies (1 study)
  - Children > 12 months of age
- Consistent with clear evidence of effects of zinc supplementation on morbidity reduction in Diarrhea and Pneumonia
- Why are results not found in infants (<12 mo) in studies presented?
  - It is possible that supplementation was less efficacious than in previous smaller efficacy trials
  - I have discussed credible biological reasons for true lack of effect

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**Tesekkür ederim!**

**Thank you!**

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