# Zinc supplementation effects on child mortality in African setting

**Sunil Sazawal MD, MPH, PhD**

**Department of International Health**
**Johns Hopkins Bloomberg School of Public Health, Baltimore USA**

# Introduction

- **In spite of some success with interventions for child survival 10.6 million deaths/year in children under 5 years**
- **Pneumonia, diarrhea and malaria account for 45% of these**
- **Africa has 2.6 million deaths due to these causes**
- **90% of the global 0.8 million malaria deaths occur in high intensity transmission areas in middle Africa**

# Reported Impact of zinc supplementation on mortality in smaller studies from Asia

- Sazawal et al Pediatrics 2001;108:1280-86 Mortality In SGA children 1-12 months **0.32 (0.12, 0.89)**
- Morris et al. Am J Clin Nutr. 1998 ;68:418S-424S, Low Birth Weight children **0.40 (0.11-1.57)**
- Baquie et al BMJ. 2002;325(7372):1059. Diarrhea Treatment trial children 3-59 Months **0.49 (0.25 to 0.94)**
- Brooks et al Lancet. 2005;366(9490):999-1004. Children 2-12 months weekly zinc **0.15 (0.03 to 0.67)**

# Impact of Preventing Zinc deficiency – Malaria morbidity in Africa

- Bates CJ et al Br J Nutr 1993;69:243-55. Twice Weekly zinc supplementation 110 children, 15 months – 32% reduction in clinic visits
- Shankar AH et al Am J Trop Med Hyg 997; 57: 249. 274 children 10 months – 30-35% reduction health center attendance for malaria
- Muller O et al BMJ 2001; 322: 1-6. 709 children 6 months daily.
  - Malaria – RR 0.98 (95%CI 0.86-1.11)
  - Diarrhea – RR0.87 (95%CI 0.79-0.95)
  - Mortality – RR 0.41 (95%CI 0.15-1.19)

# Pemba ZINC Trial

## Primary Objectives

- To evaluate the efficacy of zinc supplementation as a daily supplement (dispersible tablet) to children 1-48 months old on reduction in mortality in comparison to control group children, when both intervention and control groups are given vitamin A

- [Hypo: zinc group mortality will be significantly lower than control group mortality]

- To evaluate the efficacy of Iron/F supplementation given with or without zinc as a daily supplement (dispersible tablets) to children 1-48 months old on reduction in mortality in comparison to control group children, when both intervention and control groups are given a vitamin A.

- [Hypo: Iron/F group mortality will not be significantly different from the control group]

## Design Overview

- 2x2 Factorial Design, four groups Zinc, iron/f, iron/f Zinc, Control all groups get Vitamin A
- Household based randomization covering all 53,000 households of Pemba Island
- 16 letter codes(4 for each of four treatment groups) but supplement strips labeled by child information
- Intervention – zinc 10mg, Iron 12.5 mg, foliate 50ug, children < 12 mo half the dose

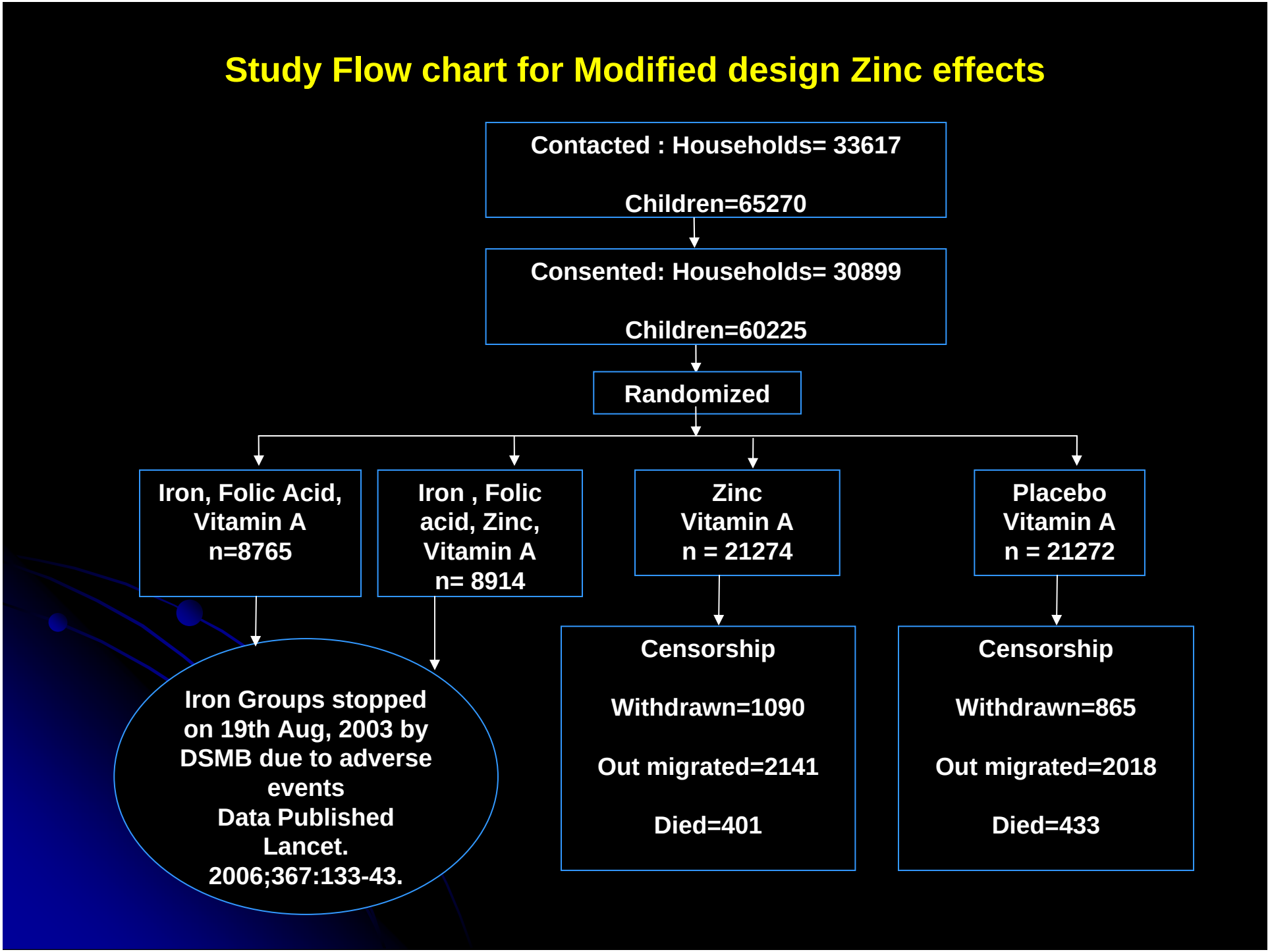
## Design Overview

- Unit of monitoring – monitor area
- Field Staff Levels – Monitor (community level-371), Supervisor L1(sub-center level-32), Supervisor L2 (district level-5)
- Weekly visitation, supplement delivery and collection of primary mortality info, compliance data, information on health care consultation, other hospitalizations
- Separate verbal autopsy team visitation
- Dedicated Laboratory Technicians (6) at PHL, malaria counts

## Design Hospital Surveillance

- 5 hospitals – all hospitals maintained under surveillance, study team within each hospital 2 shifts
- All admissions assessed – severity of morbidity, malaria and anemia evaluated – at admission, during hospitalization and at discharge
- All admissions blood sample, hematology (coulter), Malaria counts, iron status

# Study Flow chart for Modified design Zinc effects



# Analysis

- Intent to treat analysis, all children included irrespective of compliance.
- Out migration, withdrawals included till date of availability
- For Cause specific mortality – standard WHO VA used with translation and adoption to local language
- Cause of death, 2 MD physicians and 1 medical assistant independently
- VA team independent of investigators, blinded to allocation

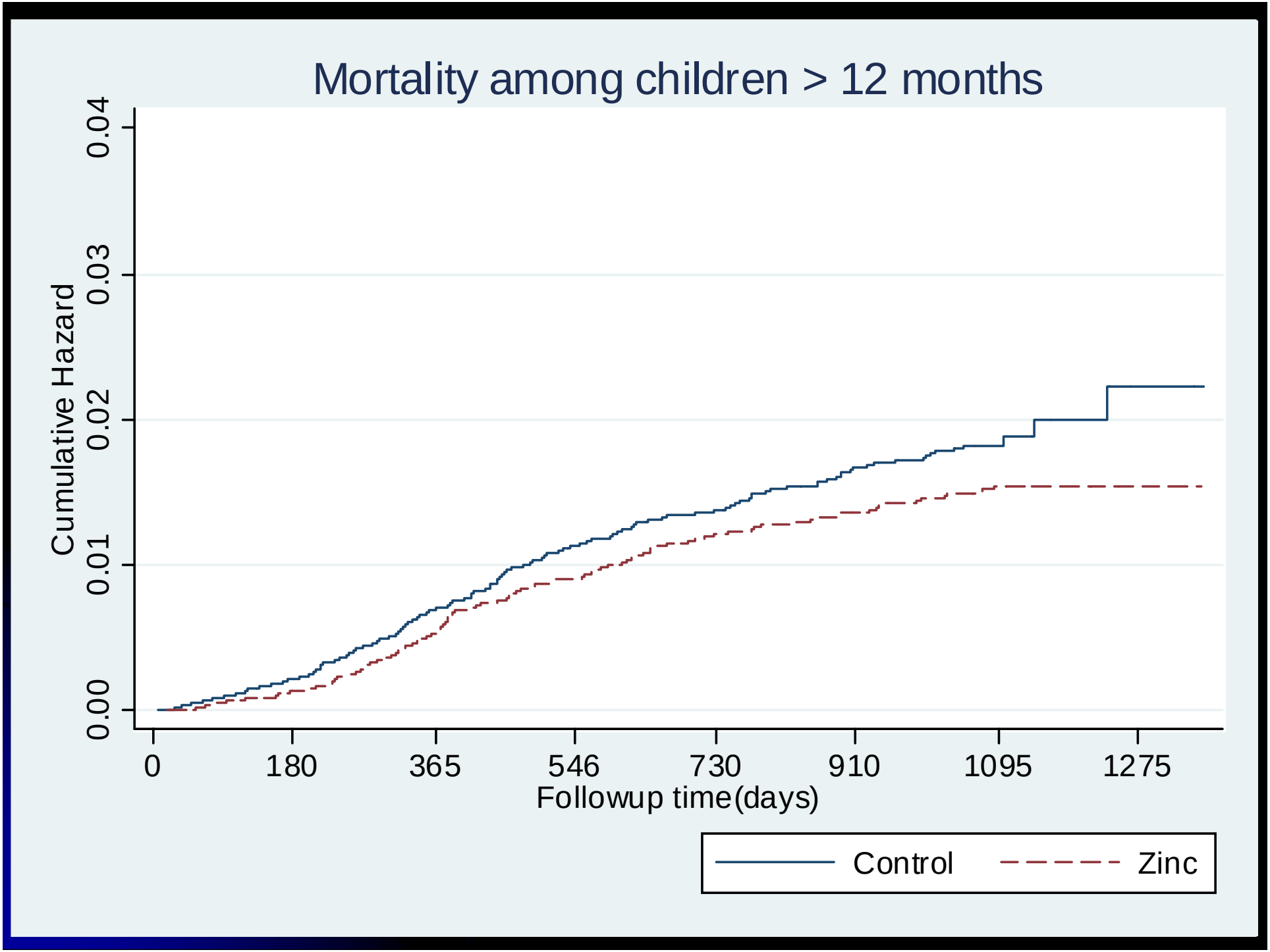
# Analysis

- Effect on mortality – Survival methods, with robust estimation of standard error (SAS 9.0, STATA 9.0)

- To prevent double counting in final analysis cause specific analysis used exclusive categories, event classified not eligible for next category

## Effect of Zinc Supplementation on Mortality Overall, by Gender and Age Group

| | Zinc Group | Placebo Group | RR | 95% CI | p |
|---|---|---|---|---|---|
| | Rate + | Rate + | | | |
| Overall | 1.42 | 1.53 | 0.93 | (0.81-1.06) | 0.29 |
| **By Age Group** | | | | | |
| 0-12 m | 3.55 | 3.36 | 1.06 | (0.87-1.29) | 0.57 |
| >12 m | 0.88 | 1.06 | **0.82** | **(0.68-1.00)** | **0.045*** |
| **By Gender** | | | | | |
| Male | 1.23 | 1.52 | **0.81** | **(0.66-0.99)** | **0.04*** |
| Female | 1.62 | 1.54 | 1.05 | (0.87-1.26) | 0.61 |


Mortality among children > 12 months
Cumulative Hazard
0.00
0.01
0.02
0.03
0.04
0
180
365
546
730
910
1095
1275
Followup time(days)
Control
Zinc

# Effects on Cause Specific Mortality

# Effect of supplementation with Zinc on Malaria and Infection Mortality

| | Zinc Group | | | Control Group |
|---|---|---|---|---|
| Cause of Death | Deaths | RR (95 % CI) | P | Deaths |
| **Malaria-related** | **272** | **0.90(0.77-1.06)** | **0.23** | **302** |
| Age > 12 m | 142 | 0.87 (0.70-1.09) | 0.24 | 164 |
| **Infection related** | **35** | **0.72 (0.46-1.11)** | **0.13** | **49** |
| Age > 12 m | 11 | 0.48 (0.23-0.99) | 0.05 | 23 |
| **Diarrhea** | **16** | **0.89 (0.45-1.74)** | **0.74** | **18** |
| Age >12 m | 5 | 0.50 (0.17-1.47) | 0.21 | 10 |
| **Other Causes** | **27** | **1.36 (0.76-2.42)** | **0.30** | **20** |
| Age >12 m | 14 | 1.01 (0.48-2.12) | 0.98 | 14 |

# Conclusion

- Effect of zinc supplementation on mortality showed a significant interaction with age and gender rendering overall impact less meaningful
- There was no effect in children below 12 months
- There was a significant 18% reduction in mortality among children greater than 12 months with higher reduction among boys
- The mortality reduction was contributed was not limited to a single cause and was contributed by reduction in malaria, infections including pneumonia and sepsis and diarrhea.

*Acknowledgements*

**Contributions of all members of the ZINC team, Participating parents and children of Pemba, and Ministry of Health Zanzibar**
**and**

**Funding support of US-AID, WHO, Gates Foundation, and UNF**

**Collaborative Investigators:**

**Robert E. Black, Olivier Fontaine, Mahdi Ramsaan, Hababu M. Chwaya, Rebecca J. Stoltzfus, Usha Dhingra, Arup Dutta, Saiket Deb, Fatma Mohd Kabole, Mashavu Othman**