The effect of zinc and/or multivitamin supplements on Early Childhood Development in Tanzania: Results from a Randomized Controlled Trial

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The effect of daily zinc and/or multivitamin supplements on early childhood development in Tanzania: results from a randomized controlled trial

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Trial Information

Location	Dar es Salaam, Tanzania
N	2400
Maternal HIV	Negative
Treatment	2x2 factorial: • Multivitamins (B, C & E) • Zinc • Multivitamins + Zinc • Placebo
Age at randomization + Follow-up	• Randomized at 6 weeks • Returned monthly until 18 months, death or LTF
Primary and Secondary Outcomes	• Morbidity (incidence of diarrhea and lower respiratory infection) • Growth

Background on Early Childhood Development (ECD)

- 250 million (43%) children <5 yrs fail to fulfill their developmental potential each year[1]
- The first years of life are particularly important for brain development - modest effects can have life-long effects on the brain's structure and capacity[2]
- Cognitive & socio-emotional development in early life are predictors of school progress [3]

1. Black, MM et al, Lancet 2016
2. Shonkoff & Phillips, 2000
3. Grantham-McGregor et al 2007, Stith et al 2003, Gorman & Pollitt 1996; Liddel & Rae 2001, Currie & Thomas, 2012; Feinstein 2003

BISD-III: Bayley Infant Scales of Development (3rd Ed.)

- A validated, standard series of measurements for infants and toddlers to assess:
  - motor (fine and gross) development
  - language (receptive and expressive) development
  - cognitive development
- Consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer.
- A Boston-based expert travelled to Dar es Salaam to train two nurses in the administration of the BSID-III (which was conducted in Swahili).

Supplement Details

- Infants under 6 months: 1 capsule of the following:
  - Zinc: 5 mg of zinc
  - Multivitamin arm: 60 mg Vitamin C, 8 mg vitamin E, 0.05mg bitamin B1, 0.6 mg vitamin B2, 4 mg niacin, 0.6 mg vitamin B6, 130 µg folate, and 1 vitamin B12
  - The above represents 150-600% of the AI
- Infants over 6 months received 2 capsules
  - Two capsules contains 200-400% of the AI for infants 7-12 months of age
  - Two capsules contain 133-800% of the RDA for 1-3 year olds

Why zinc?

- Required for >100 enzymes involved in DNA synthesis, protein synthesis and cell division → essential role in growth, immune function & development
- There is substantial heterogeneity in results from studies on the effect of preventative zinc supplementation on ECD[1]
- ***There have been few studies (particularly in sub-Saharan Africa) that have initiated high-dose zinc supplementation during early infancy and assessed the long-term impact on ECD.***

1. Black, 2003; Bhatnagar and Taneja, 2001; Gogia & Sachdev, 2012; Nissensohn, 2013; Warthon-Medina et al 2015

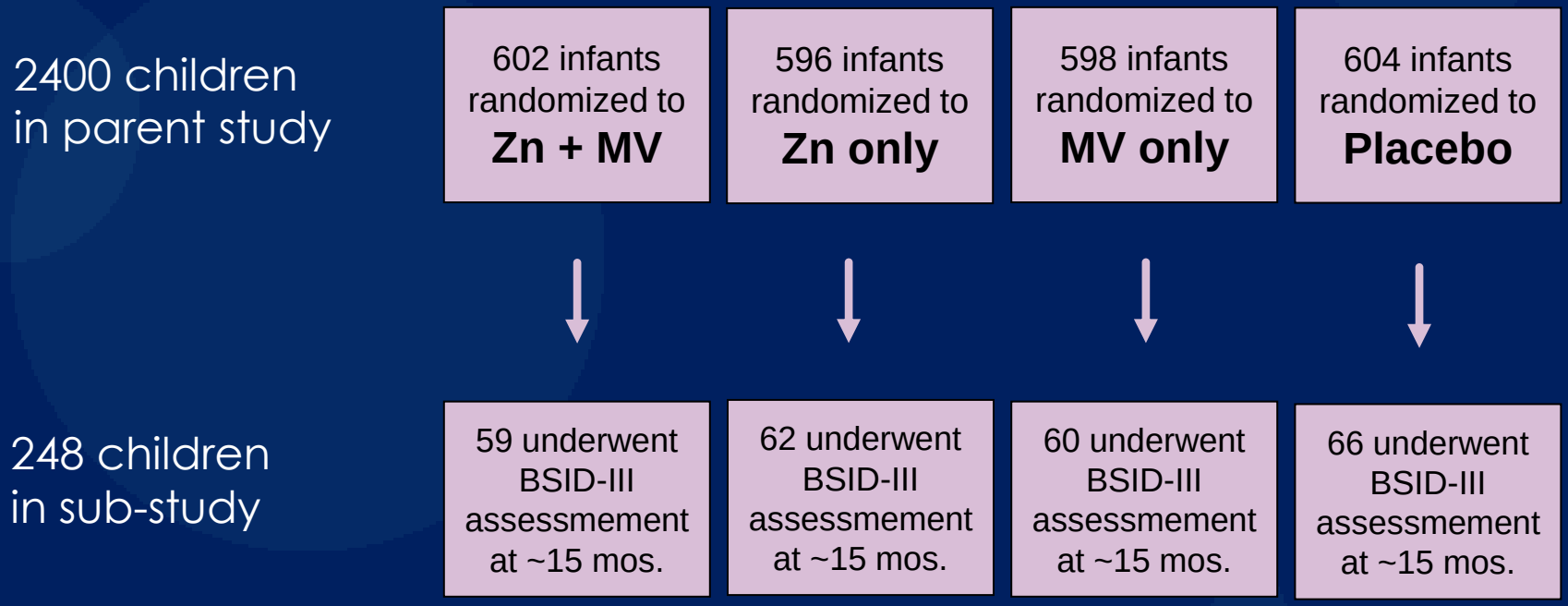
Why multivitamins?

- Multiple micronutrient (MMN) supplements have gained attention as a cost-effective intervention (several deficiencies often coexist in individuals & communities)[1]
- There is substantial heterogeneity in studies of MMN & ECD[2].
- Our group has shown that the daily provision of vitamins B-complex, C, and E to HIV-infected pregnant women can improve growth[3] and ECD[4] outcomes in their infants.
- ***To our knowledge, our study is the first study to assess the effect on ECD of zinc and/or multivitamin (B, C & E) supplementation in infants in Sub-Saharan Africa***

1. Allen, 2009; Ramakrishnan, 2009
2. Eilander, 2010; Ramakrishnan, Goldenberg & Allen, 2011
3. Villamor, 2005
4. McGrath et al., 2006

Study Sample

A sample of 248 children (from one clinic) from the previous described RCT underwent developmental assessment



Statistical Analyses

Linear Regressions

- To obtain estimates of mean difference across treatment groups controlling for infant sex, post-conceptual age and test administrator

Logistic Regressions

- To obtain odds ratios for odds of scoring in lowest quartile for each of the 5 domains
- Also controls for infant sex, post-conceptual age and test administrator


Results

Table 1. Characteristics of mothers and children enrolled in Early Childhood Development sub-study

	Zinc		Multivitamins	
	Yes (n=121)	No (n=126)	Yes (n=119)	No (n=128)
Maternal age (y) [1]	26.1 ± 4.5	25.8 ± 5.0	26.1 ± 4.7	25.8 ± 4.9
Maternal education ≤7 y [n (%)][2]	91 (75.2)	101 (80.8)	91 (77.1)	101 (78.9)
Daily food expenditure per person in household < 1000 TSh[3] [n (%)]	26 (22.2)	22 (19.5)	21 (19.3)	27 (22.3)
Child's age at randomization (wk)	5.9 ± 0.3	5.9 ± 0.3	5.9 ± 0.4	5.9 ± 0.3
Male sex [n (%)]	64 (52.9)	62 (49.2)	63 (52.9)	63 (49.2)
Low birth weight, <2500 g [n (%)]	6 (5.0)	2 (1.6)	3 (2.5)	5 (3.9)
Baseline length-for-age Z-score	-0.43 ± 1.23	-0.25 ± 1.16	-0.28 ± 1.30	-0.39 ± 1.09
Baseline weight-for-length Z-score	0.06 ± 1.21	0.07 ± 1.24	0.00 ± 1.32	0.13± 1.13
Baseline weight-for-age Z-score	-0.37 ± 1.13	-0.21 ± 0.97	-0.28 ± 1.18	-0.29 ± 0.93
Age in mos. at Bayley assessment	14.5 ± 0.4	14.5 ± 0.4	14.5 ± 0.4	14.5 ± 0.4

1. Mean ± SD (all such values unless otherwise indicated)
2. In Tanzania, 7 years is the duration of most primary schools.
3. At the time of the study, this was roughly equivalent to USD 0.75

Comparison of mean raw BSID-III[1] scores across four treatment groups

	ZN + MV	ZN only	MV only	Placebo	p-value for interaction[3]
	(n=59)	(n=62)	(n=60)	(n=66)	
Cognition	49.9 ± 3.5[2]	50.2 ± 3.2	50.2 ± 2.9	50.2 ± 3.7	0.508
Receptive Language	19.1 ± 2.1	19.1± 2.0	19.1 ± 2.1	18.8 ± 2.2	0.617
Expressive Language	20.3 ± 2.6	20.0 ± 2.7	19.9 ± 2.7	19.8 ± 2.9	0.838
Fine Motor	35.4 ± 2.8	35.0 ± 2.9	34.9 ± 3.0	34.8 ± 3.1	0.489
Gross Motor	48.4 ± 2.4	48.2 ± 2.4	48.3 ± 2.3	47.9 ± 2.4	0.894

1. BSID-III: Bayley Scales of Infant and Toddler Development 3rd Edition
2. Mean ± SD all such values.
3. P-value is for interaction term (ZN+MV) obtained from multiple linear regression models for BSID-III raw scores. Models compared four treatment groups (ZN+MV, ZN only, MV only vs. Placebo), adjusted for examiner (examiner 1 vs. examiner 2), post-conceptual age and sex of child.

Results for Zinc

Table 2: Comparison of mean raw BSID-III[1] scores across zinc treatment groups

	Mean Raw Score ± SD	Mean Raw Score ± SD	Crude difference[2] (95%CI)	P value	Adjusted difference[3] (95%CI)	P value
	Zn+	Zn-				
	(n=121)	(n=126)				
Cognition	50.03 ± 3.33	50.19 ± 3.35	-0.16 (-0.99, 0.68)	0.711	-0.19 (-1.04, 0.65)	0.652
Receptive Language	19.13 ± 2.03	18.94± 2.11	0.19 (-0.33, 0.71)	0.478	-0.01 (-0.40, 0.38)	0.956
Expressive Language	20.12 ± 2.63	19.84 ± 2.80	0.28 (-0.40, 0.96)	0.415	-0.02 (-0.52, 0.48)	0.947
Fine Motor	35.17 ± 2.84	34.89 ± 3.02	0.28 (-0.45, 1.02)	0.446	-0.09 (-0.53, 0.36)	0.698
Gross Motor	48.28 ± 2.41	48.06 ± 2.33	0.23 (-0.37, 0.82)	0.455	-0.06 (-0.43, 0.32)	0.767

1. BSID-III: Bayley Scales of Infant and Toddler Development 3rd Edition
2. Crude differences and CIs obtained from a linear regression model with only zinc supplementation as a predictor
3. Adjusted for examiner, post-conceptual age and sex of child

Table 4.
Effect of Zinc Supplementation on Odds of BSID-III[1] Score in the Lowest Quartile

	Zn+ (n=121)	Zn- (n=126)	Crude OR (95%CI)[2]	P value	Adjusted OR (95%CI)[3]	P value
	N (%)	N (%)				
Cognition	35 (28.9)	34 (27.0)	1.10 (0.63, 1.92)	0.734	1.14 (0.65, 2.00)	0.652
Receptive Language	27 (22.3)	37 (29.4)	0.69 (0.39, 1.23)	0.207	0.71 (0.37, 1.37)	0.304
Expressive Language	35 (28.9)	41 (32.5)	0.84 (0.49, 1.45)	0.539	1.10 (0.55, 2.24)	0.784
Fine Motor	28 (23.1)	41 (32.5)	0.62 (0.36, 1.10)	0.101	0.68 (0.31, 1.49)	0.334
Gross Motor	44 (36.4)	54 (42.9)	0.76 (0.46, 1.27)	0.298	1.03 (0.37, 2.89)	0.961
Either language category	39 (32.2)	49 (38.9)	0.75 (0.44, 1.26)	0.275	0.85 (0.43, 1.66)	0.627
Either motor category	45 (37.2)	56 (44.4)	0.74 (0.45, 1.23)	0.247	0.94 (0.30, 2.93)	0.915
Any of 5 categories	68 (56.2)	71 (56.4)	0.99 (0.60, 1.64)	0.981	1.55 (0.75, 3.22)	0.236

1. BSID-III Bayley Scales of Infant and Toddler Development 3rd Edition
2. Crude odds of scoring in the lowest quartile for those in Zn+ group compared to Zn-
3. Adjusted for examiner, post-conceptual age and sex of child

Results for Multivitamins

Table 3:
Comparison of mean raw BSID-III[1] scores across multivitamin treatment groups

	Mean Raw Score ± SD	Mean Raw Score ± SD	Crude difference[2] (95%CI)	P value	Adjusted difference[3] (95%CI)	P value
	MV+	MV-				
	(n=119)	(n=128)				
Cognition	50.04 ± 3.19	50.18 ± 3.47	-0.14 (-0.97, 0.69)	0.746	-0.19 (-1.04, 0.65)	0.649
Receptive Language	19.09 ± 2.09	18.98 ± 2.07	0.11 (-0.41, 0.63)	0.683	-0.11 (-0.50, 0.27)	0.562
Expressive Language	20.10 ± 2.65	19.87 ± 2.78	0.23 (-0.45, 0.92)	0.501	-0.05 (-0.55, 0.45)	0.831
Fine Motor	35.14 ± 2.87	34.92 ± 2.99	0.22 (-0.51, 0.96)	0.555	-0.13 (-0.58, 0.31)	0.555
Gross Motor	48.32 ± 2.33	48.02 ± 2.40	0.31 (-0.28, 0.91)	0.301	0.03 (-0.34, 0.41)	0.863

1. BSID-III: Bayley Scales of Infant and Toddler Development 3rd Edition
2. Crude differences and CIs obtained from a linear regression model with only zinc supplementation as a predictor
3. Adjusted for examiner, post-conceptual age and sex of child

Table 5.
Effect of Multivitamin Supplementation on Odds of BSID-III[1] Score in the Lowest Quartile

	MV+ (n=119)	MV- (n=128)	Crude OR (95%CI)[2]	p-value	Adjusted OR (95%CI)[3]	p-value
	N (%)	N (%)				
Cognition	29 (24.4)	40 (31.3)	0.71 (0.40, 1.24)	0.229	0.74 (0.42, 1.31)	0.301
Receptive Language	30 (25.2)	34 (26.6)	0.93 (0.53, 1.65)	0.809	1.07 (0.56, 2.06)	0.829
Expressive Language	34 (28.6)	42 (32.8)	0.82 (0.48, 1.41)	0.471	1.01 (0.50, 2.04)	0.978
Fine Motor	29 (24.4)	40 (31.3)	0.71 (0.40, 1.24)	0.229	0.80 (0.36, 1.74)	0.565
Gross Motor	44 (37.0)	54 (42.2)	0.80 (0.48, 1.34)	0.403	1.15 (0.41, 3.23)	0.798
Either language category	39 (32.8)	49 (38.3)	0.79 (0.47, 1.33)	0.367	0.92 (0.47, 1.80)	0.797
Either motor category	46 (38.7)	55 (43.0)	0.84 (0.50, 1.39)	0.491	1.53 (0.48, 4.94)	0.474
Any of 5 categories	64 (53.8)	75 (58.6)	0.82 (0.50, 1.36)	0.446	1.11 (0.54, 2.29)	0.773

1. BSID-III Bayley Scales of Infant and Toddler Development 3rd Edition
2. Crude odds of scoring in the lowest quartile for those in Zn+ group compared to Zn-
3. Adjusted for examiner, post-conceptual age and sex of child

Limitations

- Single neurodevelopmental assessment
- Limited generalizability (peri-urban population, low prevalence of LBW)
- Limited power to assess effect in sub-groups (ie LBW infants)
- BSID-III may not be sensitive enough to detect small changes in developmental outcomes (Columbo et al. 2012, Columbo & Carlson, 2013)

Strengths

- 2x2 factorial, randomized, double-blind study design
- Large sample size
- Dosage multiple times the RDA or AI for infants & young children
- Early introduction of supplements in infancy
- Length of supplementation regime

Take-home messages

- Our findings do not support the hypothesis that zinc and/or multivitamin (vitamins B-complex, C and E) supplements improve early childhood development in peri-urban Dar es Salaam.

- Alternative approaches to improving ECD in vulnerable populations should be pursued such as interventions that:
  - **integrate** nutrition with responsive caretaking and stimulation activities[1]
  - multisectoral interventions to establish **nurturing care**[2].

1. Grantham-McGregeor el al, 2014; UNICEF & WHO 'Integrating early childhood development activities into nutrition programmes in emergencies' 2014.
2. Black, MM et al., the Lancet 2016 & Britto et al., the Lancet 2016

- The mothers and infants who participated in the study
- The field staff in Dar es Salaam (study nurses, physicians, data clerks)
- Co-authors on the study:
  - **Harvard Chan School of Public Health:** Christopher P. Duggan, Christine McDonald, Roland Kupka, Molin Wang, David C. Bellinger & Wafaie W. Fawzi
  - **Muhimbili University of Health and Allied Sciences:** Karim P. Manji, Rodrick Kisenge and Said Aboud
- National Institutes of Health (NICHD R01 HD048969-01 and K24 DK104676; Clinicaltrials.gov identified NCT00421668)
- The audience today for listening!

Other findings from the same trial…

Morbidity (McDonald et al, 2015):

- Zn supplementation resulted in lower rates of physician-diagnosed ARI and diarrhea
- No effect of MV on morbidity

Growth (Locks et al, 2016):

- No effect of zinc and/or multivitamin supplements on incidence of stunting, wasting or underweight
- Small, statistically significant differences in continuous variables (

Anemia (Carter et al. 2015):

- MV supplements reduced the risk of iron deficiency and severe microcytic anemia
- Zn was associated with increased risk of iron deficiency but not longer term increase in risk of anemia