Micronutrient Supplementation to Improve Nutrition and Health Outcomes of Adolescent Girls, Pregnant Women and Infants

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Nutrition and Disease Prevention and Alleviation During the First 1000 Days of Life

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Important nutritional conditions

- Low or excessive protein-calorie intake
  - During pregnancy
  - During first 5 years of life
  - During adolescence

- Lack of exclusive breastfeeding and improper weaning

- Low micronutrient intake
  - Vitamin A
  - Iron
  - Zinc
  - Iodine
  - Others...
Global trends in overweight

Figure 2: Trends in thinness (BMI < 18.5 kg/m²), overweight (BMI ≥ 25 kg/m²), and obesity (BMI ≥ 30 kg/m²), using population weighted average prevalences for women aged 20–49 years UN regions and globally, 1980–2008. Error bars are 95% CIs. BMI = body-mass index.

Black RE, Lancet 2013; 382: 427–51
Leading to adverse nutritional outcomes

- Intra-uterine growth restriction
- Poor growth in infancy and adolescence
  - Underweight
  - Stunting
  - Wasting
- Risk of diabetes, hypertension, heart disease
- Mortality
Global deaths in children younger than 5-years attributed to nutritional disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Attributable deaths with UN prevalences*</th>
<th>Proportion of total deaths of children younger than 5 years</th>
<th>Attributable deaths with NIMS prevalences†</th>
<th>Proportion of total deaths of children younger than 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal growth restriction (&lt;1 month)</td>
<td>817 000</td>
<td>11.8%</td>
<td>817 000</td>
<td>11.8%</td>
</tr>
<tr>
<td>Stunting (1–59 months)</td>
<td>1017 000*</td>
<td>14.7%</td>
<td>1179 000†</td>
<td>17.0%</td>
</tr>
<tr>
<td>Underweight (1–59 months)</td>
<td>999 000*</td>
<td>14.4%</td>
<td>1180 000†</td>
<td>17.0%</td>
</tr>
<tr>
<td>Wasting (1–59 months)</td>
<td>875 000*</td>
<td>12.6%</td>
<td>800 000†</td>
<td>11.5%</td>
</tr>
<tr>
<td>Severe wasting (1–59 months)</td>
<td>516 000*</td>
<td>7.4%</td>
<td>540 000†</td>
<td>7.8%</td>
</tr>
<tr>
<td>Zinc deficiency (12–59 months)</td>
<td>116 000</td>
<td>1.7%</td>
<td>116 000</td>
<td>1.7%</td>
</tr>
<tr>
<td>Vitamin A deficiency (6–59 months)</td>
<td>157 000</td>
<td>2.3%</td>
<td>157 000</td>
<td>2.3%</td>
</tr>
<tr>
<td>Suboptimum breastfeeding (0–23 months)</td>
<td>804 000</td>
<td>11.6%</td>
<td>804 000</td>
<td>11.6%</td>
</tr>
<tr>
<td>Joint effects of fetal growth restriction and suboptimum breastfeeding in neonates</td>
<td>1348 000</td>
<td>19.4%</td>
<td>1348 000</td>
<td>19.4%</td>
</tr>
<tr>
<td>Joint effects of fetal growth restriction, suboptimum breastfeeding, stunting, wasting, and vitamin A and zinc deficiencies (&lt;5 years)</td>
<td>3 097 000</td>
<td>44.7%</td>
<td>3 149 000</td>
<td>45.4%</td>
</tr>
</tbody>
</table>

Data are to the nearest thousand. *Prevalence estimates from the UN. †Prevalence estimates from Nutrition Impact Model Study (NIMS).
Inequities in dietary diversity

Children aged 12–23 months who ate meat, fish, poultry, or eggs in the 24 h before the survey

Bars reflect range of dietary diversity from the least poor (blue) to most poor (red) quintile

Adapted from Black et al. Lancet 2008; 371: 243–60
Countries with vitamin A deficiency as a public health problem
Risk of zinc deficiency in children under 5 years
Global prevalence of anemia in preschool children

Balarajan Y et al. Lancet. 2011 Aug 1, ePub
Importance of maternal nutrition during pregnancy

- Needed for growth of the baby
- Needed for maternal support of pregnancy and lactation
- Overall increase in basal metabolic rate
- Fat deposition
- Health of the mother
The placenta integrates maternal signals with information from nutrient and growth sensing signaling pathways.
Pathways towards fetal growth restriction

Wu G et al 2012 Ped Perinatal Epi 26 Supp 1: 4-26
Government prenatal health programs currently provide iron and folic acid.
Iron Supplementation


- Increased need
  - Expanded blood volume
  - Fetal and placental requirements
  - Blood loss during delivery

- Recommended dose
  - Daily for pregnancy: 60 mg elemental iron + 400ug folic acid

- Meta-analysis of 44 trials, and 43,274 women compared the daily oral supplements with or without iron.
  - Preventive iron supplementation reduced maternal anemia at term by 70% (RR 0.30, 95% CI 0.19 to 0.46)
  - Reduced iron-deficiency anemia at term by 67% (RR 0.33; 95% CI 0.16 to 0.69)
Prevalence of micronutrient deficiencies during the first trimester among pregnant women in Nepal

Christian. Annu Rev Nutr 2010
Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial

The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group


- Randomized double-blind trial in 32,000 pregnant women in Lombok, Indonesia
- 18% reduction of infant mortality at 3-months after birth, with 38% reduction in children of women who were anemic during pregnancy
- Reduced low birth weight by 14%
SUMMIT: effects of MMN on maternal morbidity

Benefits from enrollment to 12 weeks post partum:

- Reduced night blindness by 24%
  (RR 0.76, 95% CI 0.63-0.91, p=0.002)

- Reduced heavy bleeding after birth by 18%
  (RR 0.82, 95% CI 0.73-0.92, p= 0.001)

- Reduced illness around birth by 15%
  (RR 0.85, 95% CI 0.76 -0.94 p=0.002)
MMN is associated with decreased mtDNA copy number

Change in mtDNA copy number from first to second blood draw

-20
-10
0
10
20
30
40
50

IFA
n=60

MMN
n=60
Mean cognitive z-scores for women receiving MMN or IFA

- Word list memory
- Digit span forward/backward
- Mental rotation
- Category fluency
- Speeded picture naming
- Reading efficiency
- Coin rotation
- Mood scale

Do maternal micronutrients affect brain development?

- The neural tube begins to form 16 days after conception
- Within 7 months, the brain resembles the brain of an adult, with 6 layers of cortex
- Brain development continues rapidly during the rest of pregnancy and infancy
42-month follow-up of SUMMIT children: MMN affects child cognitive and motor performance

Re-enrollment study at 10-years

- Re-enrolled 72% (19,800/27,300) of 9-12 years-old children from SUMMIT who were last reported alive at 3-months of age:
  - Growth
  - Morbidity and mortality
  - School performance

- Examined a subgroup of 3,400 for detailed cognitive and developmental status

- Venous blood draw
Maternal MMN has long term effects on child cognition at 9-12 years of age

Socio-Environmental Factors are more important than Bio-Medical Factors for child cognitive development

JiVita large-scale trial of MMN in Bangladesh

West et al. JAMA. 2014; 312: 2649-2658.

Figure 2. Kaplan-Meier Curves for Infants Through Age 6 Months (180 Days) by Maternal Supplement Allocation

<table>
<thead>
<tr>
<th>Mortality Rate per 1000 Live Births</th>
<th>Follow-up, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
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<tr>
<td>20</td>
<td>60</td>
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<td>30</td>
<td>90</td>
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<td>40</td>
<td>120</td>
</tr>
<tr>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>60</td>
<td>180</td>
</tr>
</tbody>
</table>

No. of infants at risk

Iron-folic acid: 14142, 13512, 13463, 13432, 13408, 13392, 13375
Multiple micronutrients: 14374, 13743, 13697, 13673, 13662, 13647, 13631
Three large scale trials assess mortality

  - Reduced infant mortality (18%), low birthweight (14%), fetal loss (10%)

- **China**: n=18,775 (Liu JM et al. *JAMA Intern Med* 2013 173:276-82)
  - No significant effects, although relative risks tended toward <1.0

- **Bangladesh**: JiVita-3 n=34,441 (West KP Jr et al. *JAMA* 2014 312:2649-58)
  - Reduced stillbirth (11%), preterm birth (15%), low birthweight (12%)
**Long term effect of maternal MMN on children at 4.5 years in Bangladesh**

Ekstrom E et al. 2016 Int J Epi 1656–1667

- MMN supplementation resulted in:
  - lower high density lipoprotein (HDL)
    - difference -0.028 mmol/l, 95% CL -0.053; -0.002
  - lower glucose
    - difference -0.099 mmol/l, 95% CL -0.179; -0.019
  - lower insulin-like growth factor 1 (IGF-1)
    - difference on log scale -0.141 mg/l, 95% CL -0.254; -0.028
Current status of the evidence and policy
(Haider and Bhutta Cochrane Review 2015)

- MMN performs better than iron and folic acid alone
  - Low birth weight reduced by 13%
  - Stillbirths reduced by 9%
  - Similar or greater impact on anemia
  - Large scale trials show no evidence of adverse effects

- Recommendations:
  - WHO Supports MMN in addition to iron-folic acid, and MMN in disaster situations and for women suffering from tuberculosis
  - Lancet Nutrition Series 2013 recommends transition to maternal MMN
  - Countries can decide their own national policy
MMN supplementation of adolescents and young adults

- Reduction in “depression-dejection” subscale of the Profile of Mood Assessment (White DJ et al 2015 Nutrients 7:9005–9017)

MMN supplementation of infants has inconsistent benefits

- Improved WAZ score by 0.14 ($p = 0.020$) in Tanzanian infants 6 weeks to 18 months (Locks L et al. 2016 AJCN 103:910-8)

MMN supplementation during the pre-conceptional period

  - mean uterine-artery resistance index
  - placental active transport capacity at delivery (fetal to maternal measles antibody (MMA) ratio).

Overall summary of MMN supplementation

- **Maternal supplementation has clear benefits**
  - Birth weight
  - Still birth
  - Cognition in women and children
  - Maternal health benefits
  - Long term effects

- **Infant supplementation has inconsistent benefits**
  - Some reported improvements in growth
  - IMPORTANT AREA FOR ADDITIONAL RESEARCH

- **Adolescent and peri-conceptional supplementation may have important effects**
  - Some evidence of psychological attitude
  - Improved placental function
  - IMPORTANT AREA FOR ADDITIONAL RESEARCH
Effect of scale up of interventions on deaths in children younger than 5 years

Bhutta ZA et al Lancet 2013 382: 452–77
Thanks to all collaborators

- **Summit design and implementation**: Mandri Apriatni, Susy Sebayang, Aditiawarman, Benjamin Harefa, Josephine Kadha, Abas Jahari, Husni Muadz

- **Cognitive studies**: Beth Prado, Michael Ullman, Katie Alcock

- **Biological specimen analysis**: Safarina Malik, Lidwina Prilian, Prionggo Mondrowinduro, Badru Kamal, Clarissa Febinia

- **Anatomical complexity**: Daniel Chamberlain, Varsha Raghavan, Richard Fletcher

- And many more...
Alone we can do so little, together we can do so much

Terima Kasih
Thank You