MMS: Biological and Impact Gaps

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MMS Impact and Biological Gaps

Nutritional Exposures Coexist

- Protein-energy deficits
- Energy Excess
- Micronutrient deficiencies
  - Vitamins A, E, D, B-complex, folate, zinc, iron, iodine, others
- Behavioral Causes
  - Breast/complementary feeding
  - SES, hygiene, education, etc
- Food Systems Causes
  - Agricultural/animal husbandry, seasonality, infrastructure, Markets
- Societal and Political Causes

Child and Maternal Health Problems

- Infant or Child
  - Infection
  - Inflammation
  - Poor growth
  - Impaired cognition, motor development
  - Mortality
- Adolescent or Maternal
  - Short stature
  - Thinness…. overweight
  - Infection/sepsis
  - Obstetric problems
  - Anemia
  - Mortality

Chronic disease, disability, mortality

Photos: Paul Joseph Brown
Micronutrients are Essential Throughout Pregnancy & Gestation

Vitamin A Deficiency, Iodine Deficiency and Iron Deficiency Anemia
### TABLE 1. POPULATIONS AT RISK OF AND AFFECTED BY MICRONUTRIENT MALNUTRITION, BY WHO REGION, 1991

(millions)

<table>
<thead>
<tr>
<th>Region</th>
<th>Iodine deficiency disorders</th>
<th>Vitamin A deficiency</th>
<th>Iron-deficient or anaemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At risk</td>
<td>Affected</td>
<td>At risk</td>
</tr>
<tr>
<td>Africa</td>
<td>150</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>Americas</td>
<td>55</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>280</td>
<td>100</td>
<td>138</td>
</tr>
<tr>
<td>Europe</td>
<td>82</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>33</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>405</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>1 005</td>
<td>225</td>
<td>190</td>
</tr>
</tbody>
</table>
Setting research priorities on multiple micronutrient supplementation in pregnancy

Filomena Gomes, Megan W. Bourassa, Seth Adu-Afarwuah, Clayton Ajello, Zulfiqar A. Bhutta, Robert Black, Elisabete Catarino, Ranadip Chowdhury, Nita Dalmiya, Pratibha Dwarkanath, Reina Engle-Stone, Alison D. Gernand, Sophie Goudet, John Hoddinott, Pernille Kæstel, Mari S. Manger, Christine M. McDonald, Saurabh Mehta, Sophie E. Moore, Lynnette M. Neufeld, Saskia Osendarp, Prema Ramachandran, Kathleen M. Rasmussen, Christine Stewart, Christopher Sudfeld, Keith West, and Gilles Bergeron
<table>
<thead>
<tr>
<th>Research priority score, unweighted (%)</th>
<th>Rank</th>
<th>AEA score</th>
<th>Question</th>
<th>Domain</th>
<th>Subdomain</th>
</tr>
</thead>
<tbody>
<tr>
<td>83.2</td>
<td>1</td>
<td>0.47</td>
<td><strong>What strategies (cash transfers, easier ANC access, free MMS, pharmacy vouchers, quality service delivery, mass media, social and behavior change communication interventions, SMS text messages, etc.) can best increase ANC attendance and adherence to MMS, including in hard-to-reach populations?</strong></td>
<td>Delivery</td>
<td>Coverage</td>
</tr>
<tr>
<td>82.8</td>
<td>2</td>
<td>0.50</td>
<td><strong>What limited set of biomarkers of nutritional status (e.g., hemoglobin) and their cutoffs can be used to identify populations that will benefit from prenatal MMS?</strong></td>
<td>Description</td>
<td>Assessment</td>
</tr>
<tr>
<td>81.1</td>
<td>3</td>
<td>0.53</td>
<td><strong>If MMS were continued through lactation, are there additional benefits for the mother and child (e.g., reduced mortality, infection, improved development, etc.)?</strong></td>
<td>Discovery</td>
<td>Impact</td>
</tr>
<tr>
<td>80.8</td>
<td>4</td>
<td>0.49</td>
<td><strong>Can community workers help identify pregnancies in the first trimester and facilitate timely ANC attendance that leads to an earlier initiation of MMS?</strong></td>
<td>Delivery</td>
<td>Coverage</td>
</tr>
<tr>
<td>79.0</td>
<td>5</td>
<td>0.43</td>
<td><strong>What is the burden of micronutrient deficiencies among pregnant women?</strong></td>
<td>Description</td>
<td>Prevalence</td>
</tr>
<tr>
<td>Score</td>
<td>#</td>
<td>Rating</td>
<td>Question</td>
<td>Description</td>
<td>Assessment</td>
</tr>
<tr>
<td>-------</td>
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<td>---------------------------------------------------------------------------------------------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>78.5</td>
<td>6</td>
<td>0.46</td>
<td>What field-friendly methods can be used to assess multiple micronutrient deficiencies among pregnant women? (contrast all methods along cost-effectiveness, invasiveness, and training requirements)</td>
<td>Description</td>
<td>Assessment</td>
</tr>
<tr>
<td>76.0</td>
<td>7</td>
<td>0.42</td>
<td>Which essential micronutrients (e.g., biomarkers or intake) beyond iron should be routinely monitored for pregnant women?</td>
<td>Description</td>
<td>Assessment</td>
</tr>
<tr>
<td>75.2</td>
<td>8</td>
<td>0.39</td>
<td>Are MMS in pregnancy effective in women with low intakes of energy and protein?</td>
<td>Discovery</td>
<td>Impact</td>
</tr>
<tr>
<td>74.4</td>
<td>9</td>
<td>0.49</td>
<td>What are the most effective counseling strategies about the benefits of MMS in pregnancy that lead to increased adherence to the MMS regimen?</td>
<td>Delivery</td>
<td>Adherence</td>
</tr>
<tr>
<td>73.6</td>
<td>10</td>
<td>0.42</td>
<td>What MMS dosage (timing and duration) should be recommended in prepregnancy and pregnancy to achieve maximum adherence and benefits on outcomes?</td>
<td>Development</td>
<td>Implementation</td>
</tr>
<tr>
<td>73.0</td>
<td>11</td>
<td>0.50</td>
<td>Can human-centered design principles (focused on the needs, contexts, behaviors, and emotions of the people) be used to increase the effectiveness of behavior-change programs and increase adherence to prenatal MMS?</td>
<td>Delivery</td>
<td>Adherence</td>
</tr>
<tr>
<td>73.0</td>
<td>12</td>
<td>0.47</td>
<td>How can a policy framework be strengthened within a country to ensure the availability of MMS supplements?</td>
<td>Development</td>
<td>Implementation</td>
</tr>
<tr>
<td>72.7</td>
<td>13</td>
<td>0.40</td>
<td>To what extent do MMS benefit maternal health (not just anemia or pregnancy outcomes)?</td>
<td>Discovery</td>
<td>Impact</td>
</tr>
<tr>
<td>Score</td>
<td>Rank</td>
<td>Percentage</td>
<td>Question</td>
<td>Category</td>
<td>Subcategory</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>71.3</td>
<td>16</td>
<td>0.42</td>
<td>What is the most cost-effective packaging of MMS (i.e., blister packs or bulk packaging; 30-, 90-, or 180-count bottles, etc.) that will optimize both cost and adherence, without adversely affecting ANC attendance?</td>
<td>Delivery</td>
<td>Packaging</td>
</tr>
<tr>
<td>70.9</td>
<td>17</td>
<td>0.43</td>
<td>In pregnant women taking MMS who develop iron deficiency anemia, what is the ideal amount and duration of additional iron supplements?</td>
<td>Development</td>
<td>Dosage</td>
</tr>
<tr>
<td>70.2</td>
<td>18</td>
<td>0.49</td>
<td>What data commonly available in national surveys can be used to identify populations that will benefit from prenatal MMS?</td>
<td>Description</td>
<td>Prevalence</td>
</tr>
<tr>
<td>70.2</td>
<td>19</td>
<td>0.40</td>
<td>What indicators can be measured through routine health information systems to best monitor program performance in relation to MMS delivery during pregnancy (through ANC contacts)?</td>
<td>Delivery</td>
<td>Coverage</td>
</tr>
<tr>
<td>69.7</td>
<td>20</td>
<td>0.42</td>
<td>To what extent do infections blunt the impact of prenatal MMS in preventing anemia?</td>
<td>Discovery</td>
<td>Impact</td>
</tr>
<tr>
<td>69.3</td>
<td>21</td>
<td>0.51</td>
<td>What are the predictive risk factors of micronutrient deficiencies among pregnant women?</td>
<td>Description</td>
<td>Prevalence</td>
</tr>
<tr>
<td>68.3</td>
<td>22</td>
<td>0.40</td>
<td>Is fortification of food staples or ensuring intake of fortified foods (such as lipid-based nutrient supplements) better than providing MMS at scale, on maternal and birth outcomes?</td>
<td>Discovery</td>
<td>Formulation</td>
</tr>
<tr>
<td>68.0</td>
<td>23</td>
<td>0.48</td>
<td>Would pregnancy outcomes be further improved by the addition of calcium to MMS, given WHO recommendations for calcium supplementation during pregnancy to reduce the risk of preeclampsia? How would this affect adherence, costs, and stability (given iron and calcium interaction)?</td>
<td>Discovery</td>
<td>Formulation</td>
</tr>
<tr>
<td>67.9</td>
<td>24</td>
<td>0.47</td>
<td>Would outcomes be further improved by the addition of choline to MMS, especially with regard to child development? What would be the cost implications?</td>
<td>Discovery</td>
<td>Formulation</td>
</tr>
<tr>
<td>ID</td>
<td>Type</td>
<td>Question</td>
<td></td>
<td></td>
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<td>-----</td>
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<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.3</td>
<td>Disc.</td>
<td>Would birth outcomes be further improved by the addition of n-3 LC-PUFA to MMS, given a recent Cochrane meta-analysis showing reduction in preterm delivery with n-3 LC-PUFA supplementation? What would be the cost implications?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.2</td>
<td>Disc.</td>
<td>Are there subpopulations at risk of adverse outcomes with MMS, such as stillbirths or perinatal asphyxia?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.1</td>
<td>Disc.</td>
<td>Would outcomes be further improved by the addition of magnesium to MMS? What would be the implications on adherence and costs?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.8</td>
<td>Disc.</td>
<td>Is selenium deficiency independently associated with prematurity and small-for-gestational-age?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.3</td>
<td>Disc.</td>
<td>When compared with UNIMMAP, are there more cost-effective formulations?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.8</td>
<td>Disc.</td>
<td>What is the most appropriate dosage for each micronutrient, other than iron?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Micronutrient Deficiencies in 3rd Trimester by Supplement Group, JiVitA-3, Bangladesh

No effects on iron or folate status

Reductions in, but not elimination of, multiple micronutrient deficiencies

Hb <110 g/L
Ferritin <12 ug/L
TfR > 8.3 mg/L
FA < 6.8 nmol/L
Retinol < 0.7 umol/L
a-Toco < 12.0 umol/L
25(OH)D < 50 nmol/L
PLP < 19 nmol/L
B12 < 150 pmol/L
Zinc < 8.6 umol/L
Tg > 55 ug/L
AGP > 1 g/L

Schulze et a J Nutr 2019
Preconception vitamin E deficiency occurs in LMICs

Ninety-six years ago… Factor “X” was found to restore fertility in rats fed purified diets.

Animals suffering from sterility do not differ so profoundly from normal in their ovarian function as they do in placental behavior. … the placentas are abnormal… Resorption invariably overtakes the products of conception.

Hypothesis: Multiple sourced, variably processed, mutli-vendored, environmentally exposed, over-cooked vegetable oils may lack vitamin E
Omics Innovations and Applications for Public Health Nutrition: An integrated view

Su Eun Lee
Center for Human Nutrition, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Key messages

- Omics technologies comprise sets of molecular mapping tools that can help us understand and navigate to or from states of health, including nutrition.
- Single-omics studies explore sets of genes, epigenetic marks, transcripts, proteins, or metabolites, as well as microbial communities, in an isolated manner.
- Trans-omics studies offer opportunities to connect, integrate, and map a group of molecules across multiple omics layers to identify pathways, interactions and feedback loops that may more fully reveal the biology and likely suites of diagnostic markers, therapeutic targets and pathways to and from disease states.
- Omics approaches are transitioning from the chemical level to the level of practical application to benefit vulnerable populations.

Introduction

Let’s assume that you have been taken to a place you have never been before, and are not sure how you got there. The first thing you might do is look at a Google map, which may reveal several roads leading to the place, each with its own intersections and roads from other towns. Different areas may reveal varying terrain, weather or road conditions throughout the region leading to your destination. Now, imagine a health problem affecting a population as your destination, and the plethora of pathways (tissues), biochemical networks (tissues, function (traffic flow) and other influential conditions (sensitivity, road upklop, weather, etc.) that may lead to the health problem, overlaid on the map. Omics technologies comprise sets of molecular mapping tools for each overlay that can help us understand and navigate to or from states of health, including nutrition. This breakthrough approach has become possible due to advances in the development and application of high-throughput technologies, which allow us to analyze large-scale biological data to form new molecular maps to health and disease.

“Omics technologies can help us understand and navigate to or from states of health”

Conventional hypothesis-driven studies typically focus on a few specific molecules of interest based on prior knowledge; a nutritional deficiency or success may sit into motion a geneti-ic alteration or epigenetic change that affects RNA expression, protein synthesis, metabolite production, or certain bacterial growth (Figure 1A). Single omics studies explore sets (individual omics) of genes, epigenetic marks, transcripts, proteins, or metabolites, or microbial communities, in an isolated manner. They are data-driven and provide opportunities to discover an...
Plasma Proteomics

A Future Approach to Assess Micronutrient Status and Health for Public Health Application
Plasma Nutriproteome in Nepalese Children

Lee SE, Schulze KJ, West KP Jr Food Nutr Bull 2019
Plasma Alpha-Tocopherome (n=119 proteins; q <0.10) in 500 Nepalese Children, 6-8 Yr of Age

Lipid/VE transport/metabolism
- APOA1
- APOA2
- APOB
- APOC1
- APOC2
- APOC3
- APOC4
- APOD
- APOE
- RBP4
- TTR
- LCN2
- AFM

Cell Adhesion/Cell-Cell Interactions
- CDH1
- CD44
- ICAM2
- VCAM1
- TGFB1
- DSG2
- ADAMTS

Cell Adhesion/Cell-Cell Interactions
- CF1
- C2
- C9
- sCD14
- TNFAIP-IP1
- ORM1 (AGP)
- ORM2 (AGP)
- FCGR3A

Host Defense
- QSOX1
- PKM
- GSTO1
- PRDX2
- TXN
- CAT
- PON1
- PON3
- SEPP1

Antioxidant
- RGS8
- UNC5C
- FOXO4
- PKM

Vitamin E (71%*)

Growth Regulation
- QSOX1
- IGFBP2
- IGFBP3
- IGFALS

Coagulation
- PROC
- vWF
- F2
- F11
- F13A1

Transcription
- KLF17
- FOXO4
- TMF1

* Percent of variance in plasma α-tocopherol

West KP et al J Nutr 2015 doi: 10.3945/jn.115.210682
Plasma Proteins Predict Selenium Status

Original Communication

Plasma Selenium Protein P.
Isoform 1 (SEPP1):
A Predictor of Selenium Status in Nepalese Children Detected by Plasma Proteomics

SEPP1 predicts 63% of plasma selenium concentration

Maternal Multiple Micronutrient Supplementation Stabilizes Mitochondrial DNA Copy Number in Pregnant Women in Lombok, Indonesia

Lidwina Priliani,1,2 Elizabeth L Prado,3,4 Restuadi Restuadi,1,5 Diana E Waturangi,2 Anuraj H Shankar,3,6 and Safarina G Malik1

TABLE 3 The Δ mtDNA-CN proportions of 108 pregnant women enrolled in the Supplementation with Multiple Micronutrients Intervention Trial study by supplementation group

<table>
<thead>
<tr>
<th>MtDNA-CN change</th>
<th>MMN (n = 54)</th>
<th>IFA (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10% decrease</td>
<td>14 (25.9)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>No change</td>
<td>12 (22.2)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>&gt; 10% increase</td>
<td>27 (51.9)</td>
<td>38 (70.4)</td>
</tr>
</tbody>
</table>

\( p^2 = 0.021 \)

Antenatal Micronutrients and the Mitochondrial Genome: A Glimpse of Future Nutritional Investigation

Sun Eun Lee,1 Michael F Fenech,2 and Keith P West, Jr1

MMS may improve health of materno-placental mitochondria and, thus, bioenergetics of pregnancy
Distillation of Biological & Impact Gaps

- Reveal Hidden Hunger: before, during after pregnancy; children, leading to accurate and timely estimates of extent
- Preconceptional MMS impact
- Optimization of dosage for health: eg 1 or more RDA?
- Contextualization: diet, status, dominant diseases, resources
- Additional nutrient frontiers: Calcium, magnesium, redox agents
- Micronutrient-inflammation interactions/implications
- Extended postnatal, life stage effects of MMS
- Effects of MMS in nutrition transition societies
- Implications of anemia – by cause
- Plausible biological mechanisms/pathways of MMS
Biology – Nutriture - Disease

Public Health Concern

Prevention