Food is Necessary …
But Not Sufficient

Biological Insights into Malnutrition

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NUTRITION LAB AFRICA STUDIES ARE A PLATFORM FOR STUDYING IMPLEMENTATION AND ALSO NOVEL ISSUES AND HYPOTHESES.

UGANDA, MALAWI, SOON EGYPT
Nutrition Interventions (listed below) only address a minor portion of stunting

- Adequate calories (proteins, fats, carbs) in all life stages
- Diversity of micronutrients, vitamins, high quality proteins
- Optimal breastfeeding, responsive feeding practices, stimulation
- Good complementary feeding 6-23 months, dietary diversity
- Wealth, education

Others.....

PREGNANCY

EARLY CHILDHOOD

FLEX THESE: 20-33% STUNTING AVOIDED

Lancet 2013
The Unsanitary World

- **Animals** get *antibiotics as growth hormones*. It’s because they live in unsanitary farms.

- **Lunn** et al 1991: infants in unsanitary world → develop inflamed, permeable gut enteropathy which can explain > 40% of stunting.

- **Spears**: Shows open defecation – living in an unsanitary environment – explains > half the difference in height (stunting) globally

- **Gordon** et al: abnormal intestinal microbiome *actively* promotes malnutrition.
High potential for animals and people to contaminate household environment and water with feces.

Photo: J K Griffiths  Ethiopia August 2012
# Agricultural Wastewater

<table>
<thead>
<tr>
<th>Organism</th>
<th>Typical Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>Humans; Perhaps Zoonotic</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Humans</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Humans, Swine</td>
</tr>
<tr>
<td><em>E. coli</em> (bacteria)</td>
<td>Cattle, Humans</td>
</tr>
<tr>
<td><em>Shigella</em> species</td>
<td>Humans</td>
</tr>
<tr>
<td><em>Salmonella enterica</em> (bacteria)</td>
<td>Cattle, Poultry, Swine, Humans</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em> (bacteria)</td>
<td>Poultry</td>
</tr>
<tr>
<td>Cryptosporidium* (protozoan)</td>
<td>Cattle, Humans, Other Farm Animals</td>
</tr>
<tr>
<td><em>Microsporidia</em> (fungus)</td>
<td>Farm and Domestic Animals, Humans</td>
</tr>
</tbody>
</table>

* Causes chronic diarrhea, wasting, malnutrition in people with HIV/AIDS

*Cryptosporidium* – a leading cause of diarrhea children < 24 months; known to cause stunting; and African children have x 4 risk of death in next year

Pathogens in Rural and Agricultural Water and Watersheds. USDA 2010
ENVIRONMENTAL ENTEROPATHY (EE)

- People in contaminated environments have leaky, chronically inflamed intestines.
- Lunn et al 1991: gut permeability, the hallmark of enteropathy, explained 43% of stunting and 39% of underweight in Gambian children.
- EE is associated with ↑ caloric, protein, carbohydrate needs.
Window of Opportunity to end stunting: Pregnancy, and first 24 months of age

Mean height for age z scores by age, relative to the WHO standard, according to region (1–59 months). Victora C G et al. Pediatrics 2010;125:e473-e480
Intestinal permeability and mucosal damage (left) and antibody to bacterial surface endotoxin (right) rise after weaning when exposure to pathogens increases and nutritional faltering accelerates.

Lunn et al *Lancet* 1991
### Table 4

Intestinal infections detected in 3,260 monthly samples from asymptomatic participants*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Frequency of isolation</th>
<th>Frequency of isolation one month before investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium parvum</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Microsporidia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Giardia intestinalis</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Blastocystis hominis</td>
<td>236</td>
<td>19</td>
</tr>
<tr>
<td>Ascaris lumbricoides</td>
<td>489</td>
<td>33</td>
</tr>
<tr>
<td>Hookworm</td>
<td>92</td>
<td>13</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Taenia saginata</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Iodamoeba butschlii</td>
<td>120</td>
<td>5</td>
</tr>
<tr>
<td>Entamoeba histolytica/dispar</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Entamoeba hartmannii</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>Chilomastix mesnili</td>
<td>208</td>
<td>25</td>
</tr>
<tr>
<td>Endolimax nana</td>
<td>259</td>
<td>12</td>
</tr>
<tr>
<td>Hymenolepis nana</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aeromonas hydrophila</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Citrobacter rodentium</td>
<td>608</td>
<td>42</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*The table shows which organisms were isolated from asymptomatic participants and which organisms were isolated from participants in the month prior to investigations carried out.
• 317 Malawian twins studied first 3 years of life
• 50% both well nourished; 43% discordant (one well, one malnourished); 7% both were malnourished.
• Both twins in discordant pairs received RUTF, a therapeutic food. Gut microbiomes (MB) studied: RUTF → transient MB improvement.
Gnotobiotic (sterile gut) mice – given **Normal** or **Kwashiorkor** Microbiomes from Malawian Children

- **Mice given normal bacteria** — maintained their weight
- **The bacteria found in children with kwashiorkor malnutrition actively promoted weight loss in these mice** – IF “BAD” MB AND MALAWIAN DIET BUT NOT OF THEY GOT “GOOD” DIET
- **Mice given Kwashiorkor bacteria** – lost 1/3 of their body weight in 18 Days
Major adverse changes in amino acid and other gut metabolites

Decoupled TCA cycle intermediates (↑ succinate) – mitochondrial metabolites – ↓ energy metabolism

Kwashiorkor microbiota + Malawi diet = abnormal sulfur metabolism (methionine, cysteine; protein metabolism)
Antibiotics as Part of the Management of Severe Acute Malnutrition


CONCLUSIONS

The addition of antibiotics to therapeutic regimens for uncomplicated severe acute malnutrition was associated with a significant improvement in recovery and mortality rates. (Funded by the Hickey Family Foundation and others; ClinicalTrials.gov number, NCT01000298.)
EE goes away when a contaminated environment is removed. US Peace Corps volunteers develop EE when they live in rural African villages. When they return to the US, their EE goes away. The absence of fecal material – be it human or animal – in the environment both prevents and “treats” EE. Water/sanitation is critical to this separation.

- Dean Spears has looked at open defecation as a marker of sanitation using 140 DHS data sets from 60 countries.

**How much stunting is due to poor sanitation?**
Going from > 80% without sanitation (far right) to 0% without sanitation moves the HAZ score from under -2 to just under -1. **Point: India would need to quadruple GDP to achieve same benefits Nigeria enjoys because of less open defecation.**

You want to live here .... and not here.

Figure 1: Open defecation predicts child height, across DHS survey round country-years
Solid OLS regression lines weight by country population; dashed lines are unweighted.
Aflatoxins and other mycotoxins
Cassava being dried on the ground: note green/yellow fungal discoloration

Photo: J K Griffiths  Kamwenge, Uganda December 2012
Gong et al (BMJ, 2002) showed that **stunting** and weight for age was inversely related to blood **aflatoxin levels** in Gambia ($p < 0.001$, $R^2 0.37$).
In Collaboration With Peanut & Mycotoxin Innovation Lab group – We will measure Aflatoxins in Pregnant Women and Infants enrolled in Birth Cohort

Post-Harvest Handling Can Decrease Aflatoxins in the Consuming Population

(Lancet 2005)
Poor populations:
- Will likely eat aflatoxins in foods
- Many will have environmental enteropathy and live without good water or sanitation
- Will have a microbiome that may be detrimental to growth and to health
Observational Birth Cohort study

• Enroll pregnant women; follow infants to 24 months of age
  Assess effectiveness of CC implementation on nutrition and health outcomes. Look at broader environment, not just the UCC interventions.

• Continuous perspective on impact outcomes
  – Maternal, infant and young child nutrition
  – Pregnancy and birth outcomes
  – Aflatoxin exposure and relationship to stunting
  – Will measure water contamination

• Continuous perspective of program exposure, uptake and utilization (process outcomes; already described by Patrick Webb for Nepal)
Prenatal Interventions
Antenatal Services
Diet during Pregnancy

Lancet 2013: Food is ~ 20% of Stunting

More Exclusive Breastfeeding
Better Maternal Nutrition
WASH, higher Incomes,
Less Aflatoxin

Improved Diet
Less stunting and underweight since
nutrition better, less illness
Gender Influences

Periodic biochemical sampling to complement anthropometric data
Baseline Survey

Enumerate agricultural, livelihood, food security, nutritional, health, and gender outcomes in vulnerable households and populations

> 3,600 households in 6 districts
> 2,700 variables
~ 10 million bits of data
Child Stunting and Animal Food Consumption

- Children who had consumed animal foods in the preceding day were 27% less likely to be stunted (p=0.0411). ASF = animal source food. (Baseline Survey)

A= severe anemia  
B=moderate anemia  
C=mild anemia

Kernel = epanechnikov, bandwidth = 0.5000
Maize, groundnuts
Key staple crops

Aspergillus spp. + moisture + warm temperature = Aflatoxin formation

Aflatoxin ingestion, Metabolites bind to DNA, proteins – Immunosuppression Growth Retardation

Enteropathy – permeable gut with high nutrient needs, chronic Inflammation

Microbiome – abnormal nutrient utilization by flora

Agricultural interventions

Leaky Inflamed Intestine (EE)

WASH interventions

Clinical Manifestations:
Cycle of repeated infections
Worsening nutritional status – stunting, underweight, IUGR

Diet, Societal Conditions
Diet: poor diversity, inadequate caloric & micronutrient intake, leading to immunosuppression

Pathogen exposure: Widespread food, water, environment contamination

Chicken Poop

Nutrition interventions
Research to address policy needs and innovative science

• Assessing major Ugandan integrated package – does it work, how well, and why? [Real pathways for which empiric evidence exists?]

• Holistic assessment of agriculture, nutrition, health interventions and influences

• Structured so that new hypotheses, influence of new technologies can be researched as well
Many collaborators (Asia and Africa):
Thanks!

Questions: jeffrey.griffiths @ tufts.edu

Photo: JK Griffiths Tanzania 2008