Links between malnutrition and intestinal “infections” in children in Lower Middle Income Countries

Mark Miller, MD
University of California, Berkeley on detail from US National Institutes of Health
March 20-22, 2018
Veyrier-du-Lac
WHO estimates of the causes of death in children

Jennifer Bryce, Cynthia Boschi-Pinto, Kenji Shibuya, Robert E Black, and the WHO Child Health Epidemiology Reference Group*

*The authors would like to acknowledge the contribution of the following individuals: Jane A. B. Miller, Per Gunnar Pedersen, and Scott Stennis. The authors would also like to thank the following organizations for their support: UNICEF, World Health Organization, and the World Bank.

Figure 3: Number of deaths in children younger than age 5 years and their distribution by cause for the six WHO regions (yearly average for 2000–03)

Lancet 2003;361
Figure 1.2 Proportional mortality in children younger than five years old


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Deaths associated with malnutrition

54%

ARI 18%

Diarrhoea 15%

Malaria 10%

Measles 5%

HIV 4%

Perinatal 23%

Other 25%

Global Health Diagnostics Forum

Reducing stunting among children: the potential contribution of diagnostics

Authors: Karen A. Ricci¹, Federico Girosi¹, Phillip I. Tarr², Yee-Wei Lim¹, Carl Mason³, Mark Miller⁴, James Hughes⁵, Lorenz von Seidlein⁶, Jan M. Agosti⁷ & Richard L. Guerrant⁸

**PREFACE**

Stunting is a major burden in developing countries, affecting ~147 million children. Repeated or prolonged episodes of diarrhoea during childhood increase the risk of stunting, which is believed to be associated with significant morbidity. Although the relationships between malnutrition, environment and diarrhoeal illnesses are complex, studies have suggested a connection between stunting and diarrhoeal diseases posed special challenges. Unlike the other diseases addressed at the forum, diarrhoea does not require a diagnostic test to determine its presence; rather, it is a symptom of an infection that can be caused by a variety of different bacterial, viral and parasitic pathogens. Regardless of aetiology, diarrhoea typically does not require a definitive diagnosis before initiating symptomatic interventions, and is usually managed primarily by oral rehydration therapy.
Systems Approach to Evaluate Health Outcomes Amenable to Public Health

What is the burden from diarrhea (enteric dysfunction?
  Mortality? Morbidity?
  Acute, Chronic?
  Simple extrapolations?

What is the distribution change over time?
What we know?
What we know that we don’t know?
What we don’t know about what we don’t know?

Evaluating a syndromic disease;
Qualitative and quantitative assessments regarding enteric disease and its impact on health and welfare
Global health inequity: scientific challenges remain but can be solved
Carol A. Dahl and Tadataka Yamada

Enteric infections, diarrhea, and their impact on function and development
William A. Petri, Jr., Mark Miller, Henry J. Binder, Myron M. Levine, Rebecca Dillingham and Richard L. Guerrant

New challenges in studying nutrition-disease interactions in the developing world
Andrew M. Prentice, M. Eric Gershwin, Ulrich E. Schaible, Gerald T. Keusch, Cesar G. Victora and Jeffrey I. Gordon
Longitudinal community-based studies of host, agent, and environmental factors responsible for disease

Studies are difficult and costly

Five classical nutrition oriented field studies, 1 Mexico, 3 Guatemala, 1 Haiti
Robert Fogel, Nobel Prize Economist  
BMI and Life Expectancy across time

Fogel R.  The Escape from Hunger and Premature Death, 1700-2100, 2004
Public health significance of growth

- 26% of children worldwide are stunted
- Stunting is an underlying cause of ~17% of child mortality
- Long-term associations:
  - Decreased economic activity?
  - Impaired cognitive development?
  - Chronic disease at older ages?
The MAL-ED Study

Platform to decipher relationships among enteric infection, gut physiology and malnutrition and their effects on child growth, development and vaccine response
Collaborating Institution
Longitudinal Cohort Site Institution
Case-Control Site
Hypotheses/Research Questions

**Longitudinal Measurements**
- Illness Symptoms
- Enteric Infections
- Social Environmental Factors
- Nutrient Intake

**Attributable effects**
- Genetic factors
- Gut Function
- Microbiome

**Outcome Measures**
- Growth
- Cognitive Development
- Vaccine Response
Environmental Enteropathy

Explorations of Gastrointestinal Physiology in Environmental Milieu
“The cause of many of our diseases is the condition of our lavatories and our bad habit of disposing of excreta anywhere and everywhere,” Gandhi wrote in 1925.

“In the meantime, I think we can all agree that it’s not a good idea to raise children surrounded by poop.”
Cycle of Malnutrition and Enteric Infection and Possible Interventions

- Diarrhea
- Entero-pathogens
- Enteropathy
- Behaviors
  - Feeding
  - Nutrition
  - WASH
- Growth
- Cognition
- Immunity
### Sample

<table>
<thead>
<tr>
<th>Blood</th>
<th>Measured</th>
<th>When</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hemoglobin, Ferritin, Zinc, Vitamin A, Lead, a-1 acid glycoprotein, transferrin receptor, amino acids</td>
<td>7, 15 months</td>
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<tr>
<td></td>
<td>Immune response to pertussis, tetanus, polio, measles, rotavirus</td>
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<table>
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<td>Gut integrity: Lactulose-Mannitol permeability test</td>
<td>3, 6, 9, 15 months</td>
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<td></td>
<td>Iodine</td>
<td>6, 15 months</td>
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<table>
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<th>Stool</th>
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<th>When</th>
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<tr>
<td></td>
<td>Myeloperoxidase, Neopterin, alpha-1-antitrypsin</td>
<td>Monthly 0-24m, AND one time during each diarrhea episode</td>
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<td></td>
<td>Enteric pathogens</td>
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### Survey and Measurement

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<th>Frequency</th>
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<td>Height, weight, head circumference</td>
<td>Monthly 0-24months</td>
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<td></td>
<td>Comprehensive diet</td>
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<td></td>
<td>Cognitive Function</td>
<td>6, 15 months</td>
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<td>Household / Maternal Assessment</td>
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<td>Diarrhea / Other Illness incidence</td>
<td>2X per week until 2 years</td>
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<td>Breastfeeding, supplemental diet</td>
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Levels of Analysis

- Individual
- Site
- Entire Cohort
Exclusive Breast Feeding Practices by Day

Growth trajectory and illness indicators of one MAL-ED child
Growth trajectory and pathogen isolation experience of one child
### Individual Analysis
**Pathogen Detection in one MAL-ED child**

<table>
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<tr>
<th>Stool Type</th>
<th>Age (months)</th>
<th>Pathogen(s) Isolated</th>
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<td>Aeromonas, Giardia, ETEC</td>
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<td>Diarrhea</td>
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<td>Campy</td>
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<td>EPEC, Giardia</td>
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<tr>
<td>Diarrhea</td>
<td>4.2</td>
<td>Campy, Giardia</td>
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<td>Giardia</td>
</tr>
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<td>Diarrhea</td>
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<td>6.9</td>
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<tr>
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<td>9.0</td>
<td>Campy</td>
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<tr>
<td>Monthly</td>
<td>9.9</td>
<td>Campy, Giardia</td>
</tr>
<tr>
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<td>Aeromonas, Campy, EPEC, Giardia</td>
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<td>Diarrhea</td>
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<td>Campy (?)</td>
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<tr>
<td>Monthly</td>
<td>11.9</td>
<td>Campy</td>
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Prevalence of stunting by severity by 0-24 months

**Z-scores**

- >2 No stunting
- <2 to <3 Moderate stunting
- <3 Severe
Pathogen: Diarrhea vs Monthly Stools

0-6 months
- Campylobacter
- EAEC
- Giardia
- ETEC
- aEPEC
- Cryptosporidium
- EPEC
- Astrovirus
- Adenovirus
- Rotavirus
- Aeromonas
- EIEC
- STEC
- Shigella
- A.lumb
- E.histolytica

Diarrhea (2161)  
Monthly (8701)

6-12 months
- Campylobacter
- EAEC
- Giardia
- ETEC
- aEPEC
- Cryptosporidium
- EPEC
- Astrovirus
- Adenovirus
- Rotavirus
- Aeromonas
- EIEC
- STEC
- Shigella
- A.lumb
- E.histolytica

Diarrhea (2229)  
Monthly (8280)

12-24 months
- Campylobacter
- EAEC
- Giardia
- ETEC
- aEPEC
- Cryptosporidium
- EPEC
- Astrovirus
- Adenovirus
- Rotavirus
- Aeromonas
- EIEC
- STEC
- Shigella
- A.lumb
- E.histolytica

Diarrhea (1708)  
Monthly (3741)
Pathogen Detection Monthly Stools by Age, Site

Average # of pathogens per stool

Age (months)
All MALED children, each a dot, complete data, # of pathogens in first 6 months
Relationship between Growth and Specific Enteropathogens

Relationship between Growth and Other Factors by Site

Depressive symptoms
Socioeconomic status
Environment
Home

Child’s early experience at ages 0-9 months

Reasoning skills
Depressive symptoms
Mother’s

Repeated enteric infections
HAZ scores
Growth velocity
Nutrient intake
Iron status
Micronutrient intake
Breastfeeding status
Infant temperament

Child’s skills at age 15-24 months

Language development
Cognitive development
Motor development

Child’s early experience at ages 0-9 months
Major outcomes to date from MAL-ED:

<5% of the children at 6 of 8 sites are fed according to the WHO recommendation for exclusively breastfeeding to 6m.

At several sites, it is common practice to expose neonates to solid foods.

The quality of the early complementary food diet is low in diversity, in access to vitamin A and iron source foods.
Major outcomes to date from MAL-ED:

~50% of children had a mean length-for-age Z-score <-1 during the first month of life

Despite intense follow, 23-70% were stunted; Z score <-2 at 24 months in 7 of the 8 sites; Brazil site, linear growth is normalized (WHO standard)
Major outcomes to date from MAL-ED:

• Differences in the patterns of diarrhea illness and specific pathogens
  – Common: rotavirus, ST-producing ETEC, Shigella, Cryptosporidium
  – Unexpected: campylobacter, astrovirus and norovirus

• High incidence of the carriage without diarrhea

• Diarrhea, does not appear to be associated with linear growth in children, but pathogen load does

• Nutritional factors may have synergistic effects.
Major outcomes to date from MAL-ED:

Gut permeability, immunology and physiology demonstrated that lactulose-mannitol the “gold standard” of gut permeability was not consistently associated with growth faltering

Other measures of gut function with 3 other biomarkers, alpha-1- antitrypsin, neopterin, and myeloperoxidase were associated with growth faltering

Summary

• MAL-ED study designed to advance biomedical knowledge for public health action/intervention related to nutrition
  Elucidate attributable causes of under <5 morbidity
  Define further gaps of knowledge

• Develop datasets that could be utilized for additional add-on future studies

• Increase capacity and development of field sites in resource poor settings for harmonious multi-discipline studies of <5 morbidity

• Develop tools to evaluate disease burden distributions and therefore interventions for public health policy
Gut function biomarkers

Do enteric infections lead to growth shortfall?

Contribution of diarrhea to growth shortfall

Etiology of diarrhea

Factors in cognitive development

Contribution of micronutrients to growth patterns

Aim: Learning through Experience

Progress: dotted, on-going

Target Product: solid, completed

Clinical utility of biomarker of gut dysfunction

Reliability & Reproducibility of biomarkers

Utility of combined biomarkers

Prevalence & Role of Asymptomatic enteric pathogen detections

Diagnostic tools

Prevalence of acute diarrhea in a community setting

Non-diarrheal, pathogen positive stools

Pathogens ranked by attributable fraction

Recurrent infections

Co-infection

Need to control for other factors

Stability & Reliability of psychometrics in LMICs

Diversity of meal preparations

Diversity & adherence to feeding behaviors

Multivariate model of growth in first 24 months of life

Multivariate model of for first 6 months of life

Contribution of diarrhea to growth shortfall

Prevalence & Role of Asymptomatic enteric pathogen detections

Diagnostic tools

Stability & Reliability of psychometrics in LMICs

Diversity of meal preparations

Diversity & adherence to feeding behaviors

Utility of combined biomarkers

Multivariate model of growth in first 24 months of life

Aim: Learning through Experience

Progress: dotted, on-going

Target Product: solid, completed
Objectives
Introduce the purpose of the study, general framework and timelines and objectives of health outcomes

introduction to the study participants in the sites and network

understand the strengths and limitations of the data to form conclusions,
review the processes of quality assurance quality control

demonstrate the ability to make conclusions and studies based on the individual the site in the overall network type data

provided a description of all the sites and descriptive review of the data
demonstrates improve preliminary analyses that have been conducted in the field of microbiology diarrhea growth gut physiology.
present also data in the fields of cognitive development as well as the vaccine response
Overview of primary/secondary endpoints
central hypotheses (re: growth, cognitive
development, and immune response);
use of a harmonized protocol
analytical methods (single site, pooled, multisite comparative);
point out differences between GEMS and MAL-ED companion projects
Summary

• Neonatal and maternal factors were found to play a more influential role than postnatal factors during early childhood, and their contributions remained significant throughout the first 24 months.

• Postnatal exposures, including a higher burden of non-diarrheal enteropathogens, lower socioeconomic status, and lower protein content of the diet became increasingly important contributors with age relative to neonatal and maternal factors.

• Maternal interventions, especially during pregnancy, are likely to have intergenerational effects and a lasting impact on birthweight and child growth outcomes.

• Neonatal and maternal factors were early determinants of lower length-for-age, and their contribution remained important throughout the first 24 months of life, whereas the average number of enteropathogens in non-diarrheal stools, socioeconomic status, and dietary intake became increasingly important contributors by 24 months relative to neonatal and maternal factors.
Links between malnutrition and intestinal "infections" in children in Lower Middle Income Countries: The MAL-ED Study
## MAL-ED cohort completeness of surveillance and testing

<table>
<thead>
<tr>
<th>Site</th>
<th>Children enrolled</th>
<th>Diarrhea episodes collected</th>
<th>Diarrheal stools completely tested (%)</th>
<th>Surveillance stools collected</th>
<th>Monthly stools completely tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGD</td>
<td>265</td>
<td>1591</td>
<td>1526 (95.9)</td>
<td>2937</td>
<td>2910 (99.1)</td>
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<tr>
<td>INV</td>
<td>251</td>
<td>749</td>
<td>698 (93.2)</td>
<td>3215</td>
<td>3181 (98.9)</td>
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<tr>
<td>NEB</td>
<td>240</td>
<td>976</td>
<td>925 (94.8)</td>
<td>3105</td>
<td>3071 (98.9)</td>
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<tr>
<td>PKN</td>
<td>277</td>
<td>2272</td>
<td>1836 (80.8)</td>
<td>2820</td>
<td>2777 (98.5)</td>
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<tr>
<td>SAV</td>
<td>314</td>
<td>200</td>
<td>157 (78.5)</td>
<td>3720</td>
<td>3617 (97.2)</td>
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<td>TZH</td>
<td>262</td>
<td>206</td>
<td>171 (83.0)</td>
<td>3295</td>
<td>3252 (98.7)</td>
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<tr>
<td>BRF</td>
<td>233</td>
<td>129</td>
<td>117 (90.7)</td>
<td>2519</td>
<td>2425 (96.3)</td>
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<td>PEL</td>
<td>303</td>
<td>2047</td>
<td>1888 (92.2)</td>
<td>3185</td>
<td>3077 (96.6)</td>
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<td>TOTAL</td>
<td>2145</td>
<td>8170</td>
<td>7318 (89.6)</td>
<td>24796</td>
<td>24310 (98.0)</td>
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</table>
Pathogen detection and diarrheal episodes per child by age
Pathogen testing results by year of life

Year 1

Pathogen prevalence

Diarrheal stools
Non-diarrheal surveillance stools

Year 2

Pathogen prevalence

Diarrheal stools
Non-diarrheal surveillance stools
Adjusted AF of diarrhea for the **first** year of life

<table>
<thead>
<tr>
<th></th>
<th>BGD</th>
<th>INV</th>
<th>NEB</th>
<th>PKN</th>
<th>SAV</th>
<th>TZH</th>
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<tr>
<td># diarrhea</td>
<td>819</td>
<td>419</td>
<td>524</td>
<td>1230</td>
<td>84</td>
<td>145</td>
<td>38</td>
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### Adjusted AF of diarrhea for the second year of life

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Prevalence and adjusted AF of diarrhea for 3-month intervals
### Adjusted AF for specific diarrheal syndromes (1-2 years)

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<th>Prolonged (≥7 days)</th>
<th>Mild (score 1-3)</th>
<th>Moderate (score 4-6)</th>
<th>Severe (score &gt;6)</th>
<th>Blood in stool</th>
<th>Associated fever</th>
<th>Associated vomiting</th>
<th>Overall</th>
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Adjusted AFs associated with hospitalization, dehydration or dysentery

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Seasonal pathogen-specific attributability of diarrhea
Seasonal pathogen-specific attributability of diarrhea

SAV

BRF

TZH

PEL
Conclusions

Detection of enteropathogens in the absence of diarrheal symptoms was common

There was substantial heterogeneity in pathogen-specific burdens of diarrhea, with important determinants including age, geography, season, and symptomatology

We observed an unexpectedly high burden of disease due to *Campylobacter*, norovirus GII, and astrovirus

A preliminary association with linear growth shortfalls is seen for *Campylobacter*, EAEC, *Giardia*, and *Cryptosporidium*