The Malnutrition – Enteric Diseases Project

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The Foundation for the National Institutes of Health
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Foundation for the National Institutes of Health

http://www.fnih.org/
Building partnerships for discovery and innovation to improve health.

Purpose
• To support the NIH in its mission
• To advance collaboration with biomedical researchers from universities, industry and not-for-profit organizations.

Structure
• 501(c)(3) not-for-profit organization
• Independent Board of Directors; NIH Director and FDA Commissioner ex-officio board members

Highlights
• Raised >$750 million since 1996
• Supported >400 projects, ~100 currently active
  – research partnerships
  – scientific education/training
  – conferences/events
  – capital programs
• 94 cents of every dollar spent directly supports programs
• 4-star Charity Navigator rating for past seven years.
• Create innovative public-private biomedical partnerships that complement NIH priorities and advance the public health
• Partner with corporations, foundations, academia, federal agencies, and philanthropic individuals
• Serve as “honest broker”, providing a neutral forum able to engage all partners
• Enable efficient, effective collaboration
• Structure flexible donor relationships
• Manage grants, contracts, and projects efficiently
Building partnerships for discovery and innovation to improve health.

Discovery  Pre-clinical  Clinical

MAL-ED
MAL-ED NETWORK

A hypothesis generating and –testing platform for the relationships among enteric infection, gut function, and malnutrition and their effects on child physical growth, cognitive development and response to childhood vaccines

Distinguishing features of MAL-ED:

• Project scale and scope
• Breadth and depth of data types
• Mechanistic studies of gut function
• Administrative structure and constitutional framework

http://mal-ed.fnih.org/
The Problem in Resource Poor Communities:
Environmental exposures early in life have consequences

- Lack adequate access to clean water and good sanitation
- Early and frequent exposure to pathogens
- High disease and infection incidence
- Tropical (environmental) enteropathy develops which may affect digestion, nutrient absorption, and immune response to vaccines
- Inadequate food supply – amount and nutritional content
- Developing malnutrition leads to stunting, wasting
- Diarrheal disease and malnutrition are synergistic and have long term effects on cognition, development
Poor Sanitation in India May Afflict Well-Fed Children With Malnutrition

“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

Pathogen ingestion, Enteric infection (± Diarrhea)

Exacerbated infection severity and damage

Microbiome

Impaired innate and mucosal responses

Probiotic Microflora, food supplements

Malnutrition

Growth impairment
Cognitive impairment

Inadequate dietary intake

Repetitive and persistent infections

Genetic and epigenetic polymorphs.

Malabsorption or loss of nutrients

Repair micro-nutrients

Breastfeeding, antibiotics

Environment

Intestinal damage
Inflammation

Long term societal effects
MAL-ED Hypotheses/Research Questions

**Longitudinal Measurements**
- Illness Symptoms
- Enteric infections
- Social/Environmental
- Nutrient Intake

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

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

#P4C2014
MAL-ED Study Design

- Community-based observational study
- 8 field sites
- Standardized, harmonized protocol
- Phased enrollment
- Intensive, longitudinal follow-up of ~200 children/site to 24m of age
- Centralized database
- Centralized data QC/cleaning
- Centralized data sharing
MAL-ED Supplement

Clinical Infectious Diseases Journal supplement published on line Oct 13; print edition November 1, 2014

19 articles:
- Project background
- Methods
- Site descriptions

http://cid.oxfordjournals.org/content/59/suppl_4.cover.toc
MAL-ED Network Field Sites And Collaborating Institutions

- Collaborating Institution
- Longitudinal Cohort Site Institution
- Case-Control Site

Field Sites
- Iquitos, Peru
- Fortaleza, Brazil*
- Haydom, Tanzania
- Limpopo, S. Africa
- Dhaka, Bangladesh*
- Naushahro Feroze, Pakistan
- Vellore, India

- 2145 enrolled at birth
- 1875 followed to 12 months
- 1737 followed to 24 months
MAL-ED Organizational Chart

FIC
Mark Miller, Co-PI
Data Coordinating Center

FNIH
Michael Gottlieb, Co-PI

BMGF

MAL-ED Scientific/Administrative Core

Scientist & Bioethics
Advisory Committees

Steering Committee

University of Virginia
Johns Hopkins University
Henry M. Jackson Foundation
Christian Medical College
Aga Khan University

BMGF

Funding stream
Subaward from FNIH
Field Site

Brazil
Peru
Nepal
India
Pakistan

South Africa
Bangladesh
Tanzania
MAL-ED Research Consortium Agreement

Provides a constitutional framework of principles, policies and practices to bind together the participating institutions and investigators

• Management and corporate structure supports a sum greater than its parts
• Scientific and Bioethical Advisory Committees
• Data and sample sharing agreements and insurance of global access
• Distinction between site ownership of samples and data and centralized stewardship
• Data access to participating investigators and the broader community
• Publication and presentation policy
• All companion institutions must join in order to have access to MAL-ED data and clinical specimens
MAL-ED Data Flow: Site → DCC*

Site Data Collection (field and lab data)
- Anthropometry
- Breastfeeding
- Cognitive assessments
- Dietary diversity
- Food security
- Gut function biomarkers
- Illness surveillance
- Micronutrients
- SES
- Stool microbiology
- Quantitative dietary intake
- Vaccination record

Site Data Processing
- Verification
- 1st Entry
- 2nd Entry
- Audit
- Final data

Data Upload to MAL-ED DCC Central Database

*DCC: Data Coordinating Center
MAL-ED Data Flow: Site ↔ DCC*

**DCC data activities**

- **Individual site data**
  - Cleaned
  - QC’d
  - Processed
  - Delivered to site

- **Monthly reports**
  - Data Summary
  - Data Quality/Completeness reports

*DCC: Data Coordinating Center*
MAL-ED Prevalence of stunting by severity and age among children 0-24 months

Moderate stunting (orange) and severe (blue)
### Mal-ED Antibiotic Use from 0-24 Months of Age

<table>
<thead>
<tr>
<th>Site Country</th>
<th>Total days with antibiotics</th>
<th>Total days followed</th>
<th>Days with antibiotics per child year of follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>25,945</td>
<td>171,897</td>
<td>55</td>
</tr>
<tr>
<td>Pakistan</td>
<td>32,752</td>
<td>193,456</td>
<td>62</td>
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<tr>
<td>India</td>
<td>7,750</td>
<td>172,140</td>
<td>16</td>
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<tr>
<td>Nepal</td>
<td>6,341</td>
<td>171,847</td>
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<tr>
<td>Brazil</td>
<td>1,842</td>
<td>142,509</td>
<td>5</td>
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<tr>
<td>Peru</td>
<td>11,788</td>
<td>181,233</td>
<td>24</td>
</tr>
<tr>
<td>South Africa</td>
<td>3,581</td>
<td>186,764</td>
<td>7</td>
</tr>
<tr>
<td>Tanzania</td>
<td>11,571</td>
<td>174,169</td>
<td>24</td>
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</tbody>
</table>
MAL-ED Data Quantity

- 1,300,000 child days of follow-up
- 50,500 monthly stool samples
- 11,000 diarrheal stool samples
- 8,000 urine samples
- 6,000 blood samples
- 1.53 Gigabytes of data
MAL-ED Accomplishments and initial findings

- Establishment of infrastructure and expertise to address important public health problems in LMICs
- Development of mechanisms to share and analyze data across sites and platforms
- Recognition of importance of enteric pathogenic infection even in the absence of diarrheal symptoms
- Assessment of non-invasive gut function biomarkers as predictors of growth and development shortfalls
MAL-ED Opportunities and next steps

• Prioritize risk factors and identify causal pathways for development of new and improved interventions
• Provide access to data and samples for “companion” projects to address additional hypothesis driven and mechanism oriented questions
• Utilize sites and resources for assessing interventions
• Follow-up children to school age and beyond to assess impact of early life environmental factors
MAL-ED Acknowledgements

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