ENVIRONMENTAL ENTERIC DYSFUNCTION: ADVANCING CURRENT KNOWLEDGE

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Acknowledgments

We would like to thank the Gates Foundation for their generous support of this project. We also thank Foundation program officers Dr. Debbie Burgess, Dr. Thomas Brewer, and Dr. Yiwu He, for sharing their valuable ideas.

We would also like to thank members of our research staff: Xeno Acharya, Nicole Basta, Kathryn Bergh, Jennifer Berthiaume, Tonya Cooksey, Teja Dyamenahalli, Diane Friedman, Marta Haftek, Christopher Kemp, Alastair Matheson, Jean McDougall, Majdi Osman, Anna Talman, Anjali Truitt, and Ngoc Wasson; as well as the members of our administrative staff: Cindy Bohse, Adrienne Genise, Alison Griffith, Ariana Jasarevic, Maida Redzic, and Jeanette Smith. We appreciate your dedication to the project.

We thank Tomas Allen of the World Health Organization for assistance in building the systematic search strategy. The project also benefitted from the database expertise of J. Kevan Essmyer of REDCap and Harry Stevens.

Many thanks to the Washington University librarians Cathy Sarli and Amy Suiter, who facilitated the e-publication process.

We would like to extend our thanks to those not named here who contributed to the project in various ways.
Abbreviations

∆HAZ  delta height-for-age Z-(score)
∆WAZ  delta weight-for-age Z-(score)
∆WHZ  delta weight-for-height Z-(score)
AGP   alpha-1-acid glycoprotein
ANOVA analysis of variance
CF    cystic fibrosis
CI    confidence interval
CMPA  cow’s milk protein allergy
CONSORT Consolidated Standards of Reporting Trials
CRP   C-reactive protein
ED    enteric dysfunction
EE    environmental enteropathy
EED   environmental enteric dysfunction
ESR   erythrocyte sedimentation rate
ETEC  enterotoxigenic E. coli
FA    fatty acid
GAG   glycosaminoglycan
GCA   glycocholate
HAZ   height-for-age Z-(score)
HBT   hydrogen breath test
HCT   hematocrit
HGB   hemoglobin
HLA-DR human leukocyte antigen DR-1
HPLC  high-performance liquid chromatography
HSPG  heparan sulfate proteoglycan
IEL   intraepithelial lymphocytes
IFN-γ interferon gamma
IL    interleukin
IBD   inflammatory bowel disease
L:Cr  lactose:creatinine ratio
L:M   lactulose:mannitol ratio
L:R   lactulose:rhamnose ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>low birth weight</td>
</tr>
<tr>
<td>MCV</td>
<td>mean corpuscular volume</td>
</tr>
<tr>
<td>MGA</td>
<td>maltase-glucoamylase</td>
</tr>
<tr>
<td>MN</td>
<td>micronutrient</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger RNA</td>
</tr>
<tr>
<td>NCD</td>
<td>non-communicable disease</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>ORT</td>
<td>oral rehydration therapy</td>
</tr>
<tr>
<td>PD</td>
<td>persistent diarrhea</td>
</tr>
<tr>
<td>PDF</td>
<td>portable document format files</td>
</tr>
<tr>
<td>PEM</td>
<td>protein energy malnutrition</td>
</tr>
<tr>
<td>PICO</td>
<td>population intervention comparison outcome</td>
</tr>
<tr>
<td>RA</td>
<td>research analyst</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SBBO</td>
<td>small bowel bacterial overgrowth</td>
</tr>
<tr>
<td>SBT</td>
<td>sucrose breath test</td>
</tr>
<tr>
<td>SCL:L</td>
<td>sucralose:lactulose ratio</td>
</tr>
<tr>
<td>SEM</td>
<td>scanning electron microscopy</td>
</tr>
<tr>
<td>SES</td>
<td>socioeconomic status</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>STARD</td>
<td>Standards for Reporting of Diagnostic Accuracy</td>
</tr>
<tr>
<td>SUC:L</td>
<td>sucrose:lactulose ratio</td>
</tr>
<tr>
<td>TE</td>
<td>tropical enteropathy</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>TGF-β</td>
<td>tumor growth factor-β</td>
</tr>
<tr>
<td>TMS</td>
<td>tropical malabsorption syndrome</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TNF-αRI</td>
<td>tumor necrosis factor-α receptor I</td>
</tr>
<tr>
<td>TS</td>
<td>tropical sprue</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WaSH</td>
<td>water, sanitation and hygiene</td>
</tr>
<tr>
<td>WAZ</td>
<td>weight-for-age Z-score</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHZ</td>
<td>weight-for-height Z-score</td>
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</tbody>
</table>
Synopsis

**Purpose of Project:** Gut dysfunction in children in resource-poor environments is well documented. The precipitant of this dysfunction is unknown. However, infections, nonspecific inflammation, malabsorption, and leakiness of mucosa are frequently incriminated as processes that underlie this dysfunction. Major consequences of this dysfunction have been postulated, the most critical of which is poor growth, especially stunting. The study of gut dysfunction in children would have as its ultimate goal the prevention of growth consequences. In this project, we have collated literature published between 2000 and 2010, with the purpose of guiding near-term research into the causes and pathophysiology of enteric dysfunction. In particular, we have attempted to identify biomarkers with which to detect this dysfunction.

**Rationale for seeking biomarkers:** Theoretically, tissue from the small bowel, the organ of greatest interest, could shed light on the underlying pathophysiology. However, analyzing this tissue poses challenges. These challenges include the practicalities of gaining access to this organ, incomplete confidence regarding sampling strategies to pursue, risk of sampling error, and the yet-to-be-determined value of the information that would be obtained. Thus, the more readily obtained and potentially more informative biomarkers found in stool or blood could feasibly advance the field.

**Methods:** A systematic literature review was performed by trained research analysts, two physicians, and two epidemiologists. Materials were collated in a master, highly inclusive database of publications relevant to environmental enteric dysfunction (EED) in children in resource-poor settings. This process was undertaken for two reasons. First, because search terms sensitive and specific for “enteropathy” and “enteric dysfunction” are not well indexed in literature databases (including PubMed), we had to create a resource with which to find data related to biomarkers. Second, the project was built to address multiple and different inquiries.
related to the topic. Development of an internal library was the most efficient preparation for multiple interrogations, including those seeking to identify publications relevant to the following systematic review question, which is a main focus of this book:

**What biomarkers or diagnostic tests have been used to identify, or have been shown to be associated with, mucosal dysfunction of the small intestine or host inflammation in children less than five years of age from developing-country settings?**

**Findings:** 67,903 unique references were obtained from PubMed, Embase, Global Health and World Health Organization (WHO) Regional Libraries (1980-2010). 9,675 of these publications met EED Library inclusion criteria and 374 between 2000 and 2010 were potentially relevant to the systematic review question. Of these, 77 met the review inclusion criteria.

Each relevant publication was thoroughly and systematically reviewed and summarized in evidence table format. Biomarkers were categorized as being relevant to one of eight processes that could underlie, be associated with, or reflect enteric function/dysfunction in children: (1) absorption; (2) porosity/permeability; (3) digestion; (4) intestinal inflammation and/or intestinal immune activation; (5) systemic inflammation and/or systemic immune activation; (6) microbial drivers; (7) nonspecific intestinal injury, and (8) non-small intestinal organ function. A meta-analysis of pooled data from these publications was not possible because of the heterogeneity of study populations and methods, non-standardized information portrayal, scant attempts to correlate biomarkers to intestinal pathology (and where this was attempted, correlation was lacking), small population sizes, and limited relation of biomarkers with outcomes of interest, i.e., stunting. However, the data do strongly suggest the presence of broad categories of intestinal dysfunction, and imply a high prevalence of poorly functioning guts, in children in resource-poor environments. It is quite likely that a panel of biomarkers reflecting multiple physiologic derangements might predict intestinal injury.
Conclusions: Our novel search and EED construction methodology effectively identified a diffusely defined and poorly indexed (in the literature)—but nevertheless important—public health problem. Our EED Library format permits efficient information retrieval for multiple EED-related inquiries and the methodology can be applied to other health issues that face similar definition and search/retrieval issues.

Using this comprehensive data collation and extraction system, we found no evidence of a globally applicable, simple, single-purpose biomarker that reliably correlates with intestinal dysfunction in children or to growth faltering mediated by such a lesion. The studies that are available were often not performed with this goal in mind. However, there is a large body of evidence that enteric dysfunction in children is highly prevalent in resource-poor settings, and that this dysfunction could be an important, and potentially remediable, cause of stunting. Therefore, we urge that future research on biomarkers in human populations be pursued. We also urge that future work adheres to the following principles:

1. Assess function-related candidate biomarkers.
2. Relate the biomarker data to consequential outcomes.
3. Rigorously describe the study design and methodology underlying the data produced.
4. Provide robust data repositories. Employ best practices publication guidelines, such as those endorsed by the Consolidated Standards of Reporting Trials (CONSORT) system including the Standards for Reporting of Diagnostic Accuracy (STARD) Initiative.
5. Consider indices of enteric dysfunction, incorporating “stacking” multiple biomarkers representing diverse pathophysiologic processes, potentially also including non-laboratory test derived clinical characteristics.
6. Explore invasive, field-adaptable, host assessments (e.g., saliva, transcutaneous), even if technology needs to be developed or adapted.