BIOMARKERS OF GUT HEALTH FOR MATERNAL, NEONATAL AND CHILD HEALTH (MNCH)

WOMEN OF REPRODUCTIVE AGE, PREGNANT WOMEN, & LACTATING WOMEN

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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SEPTEMBER 2021

START CENTER

STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

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Introduction

Environmental enteric dysfunction (EED), also described as 'environmental enteropathy', 'tropical enteropathy', and in its most severe manifestations 'tropical sprue', is a syndrome characterized by intestinal and systemic inflammation, mucosal histological features including villous flattening and crypt hyperplasia, and weight and/or growth abnormalities in the absence of other gastrointestinal conditions (1). The etiologies of EED are varied and the condition is thought to result from some combination of micronutrient deficiencies (e.g., zinc deficiency), pathogenic diarrheal disease, and other chronic infections (e.g., HIV) (1,2). EED is most prevalent in low- and middle-income countries (LMICs) and appears to be often acquired in infancy and endures through adulthood (1).

Acting through mechanisms that include changes in chronic intestinal inflammation, malabsorption, hormonal disruption, intestinal permeability, and disruption of the gut microbiome, EED may be associated with stunting, chronic systemic inflammation, and inadequate response to oral polio and rotavirus vaccines (1–3). EED among pregnant women specifically may be associated with shorter gestation and shorter birth length (4). Given these associations between EED and infant and child growth, prevention and treatment of EED among women of reproductive age and children has the potential for cascading positive public health impacts. The sequelae of EED have additional implications for key health and economic outcomes such as decreased wages (5) and susceptibility to vaccine-preventable infections.

While great strides have been made toward reducing the incidence and mortality from diarrheal diseases worldwide (6), knowledge gaps and substantial opportunities for improving gastrointestinal health remain, including the lack of a consensus on the definition of EED (2,7). Biopsy via an upper gastrointestinal endoscopy is the established gold standard for diagnosis. However, given the impracticalities and invasiveness of endoscopy, other diagnostic methods have been used, such as dual sugar absorption tests and examination of a variety of biomarkers (1,2). Biomarkers for EED have been broadly categorized into domains by the origins and types of physiological alterations indicated by a given biomarker. Though there is some variation in conceptualization of domains across the literature, broadly these domains reflect markers of intestinal damage and repair, permeability, absorption, microbial translocation, intestinal inflammation, and systemic inflammation (7,8).

As a result of its substantial health impacts, EED is a key target for interventions that aim to improve the health of children. Therefore, the knowledge gaps surrounding practical, readily accessible, and clinically important biomarkers for identification and monitoring of EED must be addressed to support the design, evaluation, and implementation of interventions for its prevention and treatment. Within this context and building on a robust existing systematic review of EED (8), we searched for, and

reviewed the literature to identify key definitions of EED, and ii) describe EED biomarkers and associations between EED biomarkers and health outcomes among women of reproductive age, including pregnant and lactating women.

Objectives

The objectives of this project were as follows:

1) To identify the current definitions of EED
2) Delineate EED biomarkers and their distributions within the populations of interest, specifying key population characteristics when available (e.g., nutritional status)
3) Extract associations between EED biomarkers and health outcomes among women of reproductive age, including pregnant and lactating women

Methods

Search Strategy

Using a comprehensive two phased strategy, we searched electronic databases and grey literature for relevant studies.

PHASE I: SEARCHING THE DATABASE BY DONNA ET AL.

Our initial searches to gather a comprehensive list of key terms identified a report published by Donna et al. on biomarkers of gut health (8). We reviewed the 77 studies identified by Denno et al. in their systematic review of EED biomarkers/diagnostic tests to identify studies that met our inclusion criteria with the intent of identifying relevant studies published prior to 2010.

PHASE II: SEARCHES OF ELECTRONIC DATABASES AND OTHER SOURCES

We searched PubMed, Embase, Google Scholar, World Health Organization (WHO) Institutional Repository for Information Sharing (IRIS), and WHO International Clinical Trials Registry Platform (ICTRP) between June 23, 2021 and July 10, 2021. Our search strategy was informed by the terms

utilized by Denno et al. in their systematic review (8) and was developed in consultation with a University of Washington Health Sciences librarian with expertise in global health. In the absence of MESH headings, the EED terms in our search strategy included variations of “environmental enteric dysfunction”, “tropical sprue”, “idiopathic tropical malabsorption syndrome”, “tropical enteropathy”, and “environmental enteropathy”. Complete lists of the search terms used, dates of searches, and the corresponding number of records from each database are listed in Appendices 1-5.

Inclusion Criteria

The inclusion and exclusion criteria used to select studies were divided into two based on the project objectives. For Objective 1, we were less restrictive as the aim was to scope the literature for definitions of EED. Hence, we included any publication that defined EED.

For objectives 2 and 3, we included primary study designs that described EED biomarkers in the literature among women of reproductive age, pregnant women, lactating women, and children under 5 years of age. Women of reproductive age were defined as women between the ages of 15 to 49 years. Our geographical focus low- and middle-income countries in Sub-Saharan Africa, as defined by the World Bank (9), and Southeast Asia, as defined by the WHO Southeast Asia region (10). A more detailed breakdown of our inclusion and exclusion criteria can be found on Table 1 and Appendix 6.

Data Management and Extraction

Records from PubMed, Embase, and Google Scholar were uploaded into Covidence. The majority of duplicate records were automatically identified and removed using the Covidence deduplication feature. Additional duplicates identified during the review process were subsequently removed. The records were systematically screened for inclusion by title and abstract and then by full text. WHO IRIS records were reviewed using the same process in Excel. Single review by each team member was performed in parallel at each stage in accordance with the WHO Rapid Review Guidelines (11). A list of exclusion criteria was developed and used for the title and abstract screening as well as the full text screening (Appendix 6).

Due to the high number of results that qualified for extraction based on our screening criteria, we limited our focus to records detailing primary research including women of reproductive age, pregnant women, and lactating women that delineated descriptions and distributions of EED biomarkers (i.e., observed values of biomarkers in populations of interest) (objective 2) and/or associations between EED biomarkers and clinical outcomes (objective 3). Of note, we included records that assessed EED biomarkers among women of reproductive age and included outcomes of both women and their children (e.g., mother-infant dyads). However, in accordance with our

inclusion criteria, we did not extract data that was unstratified to the specific population of interest (e.g., result reported for men and women ages 16 to 80). Key definitions of EED (objective 1) were identified via focused review of relevant literature and are presented below.

A standardized data abstraction form was used to extract information from each study. Extracted information consisted of publication details (e.g., authors, year), study details (e.g., study design, population), and information relating to EED biomarkers (Table 2). Biomarker categories were reported as described by the framework proposed by Harper et al., with additional categorizations made for biomarkers not delineated in the Harper et al. framework categories (7). The full set of data elements are available in the extraction database that corresponds with this report.

Finally, we reviewed the records identified from ICTRRP. Cognizant of the fact that studies with negative and non-significant findings might not always publish their results, the ICTRP output was examined to facilitate the discovery of studies that have been conducted and not published. It also enabled us search for ongoing clinical trials whose findings are yet to be published.

We did not require ethics approval as the information collected during the current study are publicly available and were obtained by searching PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, WHO International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov.

Results

Key EED Definitions

Central definitions of EED were identified via focused review of relevant reports. Broadly, as described in a recent systematic review of the association between EED and child stunting, EED is "*an acquired subclinical disorder of the small intestine, characterized by villous atrophy and crypt hyperplasia*" (7). However, this accepted definition does not highlight the local and systematic pathophysiological implications of EED. Among children specifically, EED has been conceptualized to include three domains: (1) a syndrome of children age 2-36 months associated with linear growth faltering and negative screening for celiac disease; (2) confirmation via histopathology or two or more biomarkers; and (3) presence of other criteria, which may support EED diagnosis such as markers for systemic inflammatory and metabolic effects (12). Within the context that EED is often asymptomatic, the authors suggested that this definition be considered on a "sliding scale", such that there is opportunity to center definitions on biomarkers associated with worse pathophysiology or

using higher cutoffs depending on the specifics of a given intervention (e.g., potential adverse events of an intervention).

Among studies of adults, additional nuances in the definition have been proposed. Hossain et al. noted that EED presents as low body mass index (BMI) due to malabsorption-induced malnutrition, as opposed to stunting observed in children (13). Further, a study of biomarkers among pregnant women and their infants described EED, citing two other sources, as: "*a subclinical inflammatory disorder of the small intestine characterized by altered gut morphology, reduced absorptive capacity, and impaired barrier function*" (4). A 2019 study of maternal EED biomarkers and infant growth included discussion of EED that focused more on subclinical inflammation, permeability of the intestine, and systemic inflammation, likely in part due to the focus of the study on mechanisms for EED and stunting (14).

Screening Results

The searches of PubMed, Embase, Google Scholar, and WHO IRIS yielded 1,107 total records (Figure 1A). After deduplication (194 duplicates), 909 records were reviewed in the title and abstract screening phase. At the title and abstract phase, 479 (52.7%) records were excluded and 430 (47.3%) records were included for full text review. Next, the full texts of these 430 records were reviewed and a further 57 (13.3%) were excluded due to being published before 2010 (n = 3), not defining or delineating EED biomarker distributions or associations (n = 44), not including women of reproductive age, pregnant women, lactating women, and/or children under 5 years of age (n = 8), and not stratifying results to women of reproductive age, pregnant women, lactating women, and/or children under 5 years of age (n = 2). Due to the high number of included records (365 records after merging records from each database) and time limitations associated with the project, a shift in scope was made to extract data only from records of women of reproductive age (ages 15 to 49), pregnant women, and lactating women that delineated EED biomarkers and their distributions (objective 2) or reported associations between EED biomarkers and health outcomes (objective 3). After reviewing the reports from the Denno et al. review (8), no record described EED in women of reproductive age pregnant or breastfeeding women (Figure 1B).

Characteristics of Included Studies

After applying the inclusion and exclusion criteria, 9 studies were identified for inclusion (Table 3). Studies were published between 2015 and 2021 and included the following designs: cross-sectional (n = 5), case-control (n=1), interventional trial (n = 1), prospective cohort (n = 1), and case report (n = 1) (Table 4). These studies were conducted in India (n=4), Bangladesh (n = 2), Zambia (n = 2), and Uganda (n = 1). Studies most frequently included non-pregnant women of reproductive age (n = 8); only one study included pregnant women.

Further, 56% (n = 5) of reports were community-based and 33% (n = 3) were based in a clinical in setting. There was one study in which the samples were collected from healthy clinic employees. The sample sizes ranged from 1 to 220 and the ages of all included participants ranged from 15 years to 80. Of note, some reports presented the results of studies of both men and women and/or participants that were not within reproductive age. We excluded these reports from the analyses, with the exception of reports that presented results stratified by sex and age such that results applying only to women ages 15 to 49 were extractable.

EED Biomarkers

A variety of EED biomarkers were assessed, including intestinal mucosal morphometry as assessed by biopsy (e.g., villous height, crypt depth, villous height to crypt depth ratio) and measures of permeability and absorption (e.g., lactulose/mannitol ratio), damage and repair (e.g., glucagon-like peptide), and microbial translocation (e.g., anti-flagellin) (Table 4).

MORPHOMETRY

The results of morphometry, measured via biopsy to assess intestinal damage, were detailed in six reports. Broadly, it was suggested that women of reproductive age had diminished villous height (15,16) and/or villous height:crypt depth ratios below normal values which were defined as greater than 3:1 (17) and 3:1 or more (18). Ramya et al. stratified results by sex and age, as well as provided additional categorizations of villous height:crypt depth ratios of less than 3:1 to 2:1 being mild, less than 2:1 to 1:1 being moderate, and less than 1:1 to 0.1:1 being severe; among women in the 20-30 age group (n = 24), 3 (12.5%) had a mild villous height:crypt depth ratio and 21 (87.5%) had a moderate villous height:crypt depth ratio and among women in the 31-4 age group (n = 29), 3 (10.3%) had a mild villous height:crypt depth ratio, 25 (86.2%) had a moderate villous height:crypt depth ratio, and 1 (3.4%) had a severe villous height:crypt depth ratio (17). Finally, in a case-control study of malnourished adults with suspected EED and healthy adults in Bangladesh, 0% of malnourished adults had normal doudenums (versus specific duodenitis or non-specific duodenitis), indicating that all had inflammation or morphological alteration of duodenal mucosa (non-specific duodenitis) or presence of a disease process (specific duodenitis) (13). Similarly, as determined by the presence of neutrophilic infiltration or polymorphonuclear invasion, 0% of malnourished adults had normal duodenums, indicating that all had chronic active duodenitis or chronic duodenitis. In the same study, healthy control adults with dyspepsia were all found to have either normal villous height or a mild reduction in villous height, with 0% having subtotal villous atrophy (i.e., partial blunting or shortening) or total villous atrophy (i.e., villous to crypt ratio of 0:1 to 1:1 (13). This finding was echoed in a cross-sectional study including healthy adults in Bangladesh who underwent upper gastrointestinal endoscopy and biopsy, which found that no participants had evidence of alteration to

the villous to crypt ratio (19). Finally, malnourished adults in Bangladesh were all found to have some degree of cellular infiltrates, and 0% of healthy control adults had marked cellular infiltration, characterized by intense, diffuse inflammatory inflammation that was viewed by eye with a microscope (13).

PERMEABILITY AND ABSORPTION

Measures of permeability and absorption were included in four reports. One report detailed a chart review of adults diagnosed with tropical sprue and presented measures of permeability and absorption that were compared to a reference value, suggesting abnormal values of D-xylose excretion for all patients, with normal values defined as greater than 20% urinary excretion (20). In a report that presented results of claudin-4 expression in adults measured via immunostaining of biopsies, claudin-4 expression was described as “reduced” but no specific reference values were provided beyond two references to two articles providing further information on claudins (16). Another report of a interventional trial assessing goat milk protein digestibility of seven apparently healthy non-pregnant and non-lactating women in India presented measures of phenylalanine in plasma and allo-isoleucine in blood and, from a dual-sugar absorption test administered via oral solution, urinary concentration of lactulose and mannitol, percent recovery of lactulose and mannitol from urine, and lactulose/mannitol ratio; however, the authors did not compare these measures of permeability and absorption to reference values (21). In a study of pregnant women in Uganda, Lauer et al. also reported measures of urinary lactulose and mannitol excreted and lactulose:mannitol ratio, but do compare observed mean values to a reference value (4).

MICROBIAL TRANSLOCATION

Two reports described measures of microbial translocation. In a community-based study of Zambian adults, all participants were found to have detectable levels of plasma lipopolysaccharide (LPS), a measure of microbial translocation from the gut to the plasma (18). Among pregnant women in Uganda, mean values of 1.48 (SD: 0.55) and 1.81 (SD: 0.60) for anti-LPS IgA and anti-LPS IgG, respectively (4). However, these values were not compared with a reference value. A different measure of damage and repair was measured in the same study among pregnant women in Uganda; anti-flagellin IgA and anti-flagellin IgG were observed with mean values of 1.61 (SD: 0.68) and 1.15 (SD: 0.30) and were not compared to a standard value (4).

INTESTINAL DAMAGE AND REPAIR

Finally, one report provided findings for measures of intestinal damage and repair. Among adults from a community sample in Zambia who were not pregnant, had no concurrent illness, and no use of antibiotics or NSAIDs, serum GLP-2, a measure of intestinal damage and repair, was lower than

the pediatric reference range for all participants (16). In the pediatric study referenced, the median serum GLP-2 levels in healthy pediatric controls was 11.6 ng/mL (IQR: 7.0, 18.6) (22).

EED Biomarkers and Clinical Outomes

Only one report presented measures of effect. The report described the association between EED biomarkers and key clinical outcomes. In a community-based study of mother-infant pairs in Uganda, **log transformed concentrations of maternal anti-flagellin IgG and anti-LPS IgG were significantly associated with shorter gestation** (β: -0.89, 95% CI: -1.77, -0.01, p = 0.047; and, β: -1.01, 95% CI: -1.87, -0.17, p = 0.019, respectively) after adjusting for maternal age, height, diastolic blood pressure, years of education, first pregnancy, household food insecurity, access to safe water, and infant birth weight (4). Further, **higher concentrations of ln anti-flagellin IgG and ln anti-LPS IgG were significantly associated with reduced infant length** (β: -0.80, 95% CI: -1.55, -0.05, p = 0.036; and, β: -0.79, 95% CI: -1.54, -0.04, p = 0.039, respectively) **and length-for-age z score (LAZ)** (β: -0.44, 95% CI: -0.83, -0.05, p = 0.029; and, β: -0.40, 95% CI: -0.79, -0.01, p = 0.043, respectively) at birth in adjusted analyses.

In secondary analyses, the authors reported no significant unadjusted or adjusted associations between maternal EED biomarkers and infant weight, weight-for-age z score (WAZ), or head circumference at birth, but reported a significant association between higher concentrations of ln anti-flagellin IgG and ln anti-LPS IgG and higher weight-for-length z score (WLZ) at birth (β: 0.85 *z* score, 95% CI: 0.21, 1.49; and β: 0.65 *z* score, 95% CI: 0.10, 1.29, respectively) in unadjusted analyses. **ln anti-flagellin IgG remained statistically significantly associated with higher infant WLZ at birth in adjusted** models (0.79 *z* score; 95% CI: 0.14, 1.44).

When compared to mothers with term deliveries, mothers with preterm deliveries had higher lactulose:mannitol ratio values (0.16 ± 0.26 versus 0.08 ± 0.12, p < 0.05) **and anti-flagellin IgA concentrations** (1.93 ± 0.75 versus 1.58 ± 0.67, p < 0.05). In addition, **modest negative correlations were observed between log transformed lactulose:mannitol ratio values and ln anti-LPS IgA and ln anti-LPS IgG** (r = −0.15 and −0.19, respectively, p < 0.05 for both). **ln anti-flagellin and ln anti-LPS Ig concentrations pairs were also positively correlated** (all p < 0.001). **Finally, comparing infants who were born wasted to those who were not born wasted, maternal percent lactulose excretion was higher** (0.92 ± 1.16 compared with 0.49 ± 0.71, p < 0.05) **and anti-flagellin IgG was lower** (0.99 ± 0.35 versus 1.16 ± 0.29, p < 0.05).

Limitations of Included Studies

While the identified studies provide insight for EED biomarkers among women of reproductive age, the identified findings should be considered within the context of the limitations of the included studies. Most of the studies had small sample sizes. One included study was a case report of an adolescent girl with multiple comorbidities, a design which provides limited epidemiological evidence. Six included reports did not present results that were stratified to include only women of reproductive age, pregnant women, and/or lactating women. As such, it is not possible to infer the proportion of study participants who were in this population group; for these studies, only results that were indicated to be true of all participants (e.g. all participants of both sexes had abnormal villous height:crypt depth ratio, etc.) were extracted. Therefore, the findings reported from these studies may have limited applicability for the population of interest. Many reports (n = 5; 55.6%) described cross-sectional studies, which limits inferences regarding temporality of biomarkers. Finally, we identified few reports of EED biomarkers and the association between EED/EED biomarkers and health outcomes among women of reproductive age, pregnant women, and lactating women, suggesting a substantial knowledge gap. In order to aid in the design and implementation of future interventional trials to ultimately improve the health of women and their children, further study of EED biomarkers and associated health outcomes is necessary.

ICTRP Review

As expected, review of the ICTRP search results indicated registration of studies resulting in one or more publications identified by our peer-reviewed literature searches. Further, one ongoing trial was identified entitled “Stunting and Bangladesh Environmental Enteric Dysfunction Study” (23). This trial will include both children and non-pregnant and non-lactating adults and endeavors to assess the impact of nutritional interventions on change in body mass index in adults, as well as a variety of EED biomarkers as secondary outcomes. The stated estimated completion date is December 31, 2021.

Conclusions

Broadly, our review identified substantial gaps in the existing published and gray literature concerning both delineation of known EED biomarkers and associations between EED biomarkers and health outcomes among women of reproductive age, pregnant women, and lactating women. While some studies reported distributions of EED biomarkers in the population of interest for our

review, few compared observed values to reference values in adult populations. Notably, only one study presented on the association between EED biomarkers and health outcomes, indicating a key knowledge gap in the impact of EED on both adult health and, in the case of pregnant and lactating women, children's health.

Furthermore, we did not find evidence of many EED biomarkers among children, such as citrulline, myeloperoxidase, and alpha-1 antitrypsin (7), being evaluated in women of reproductive age, pregnant women, and lactating women (Table 4). Two EED biomarker domains, systemic inflammation and intestinal inflammation, were also not evaluated in this population. Biomarkers that are only accessible via biopsy (e.g., villous height) were frequently evaluated among included reports. However, biopsy methods have limited scalability and concerns have been noted about the safety of biopsy methods (24). Further knowledge on the use of noninvasive biomarkers for EED among women of reproductive age, pregnant women, and lactating women would improve accessibility of and safety for EED diagnoses. Future studies of adults should endeavor to incorporate assessment of EED biomarkers observed in children. In addition to increasing the accessibility of assessment of EED biomarkers, characterization of reference adult values for EED biomarkers known in children would enable improved interpretation of these biomarkers in women of reproductive age, pregnant women, and lactating women.

Opportunities for further engagement with this work remain. Most notably, due to the high proportion of relevant studies identified while screening abstracts, studies containing women of reproductive age, pregnant women, and/or lactating women were prioritized for data extraction. Studies of infants and children for objectives 2 and 3 have not yet been extracted. Extraction of these studies would yield an up-to-date database of recent reports of EED in infants and children. Another opportunity is to consider the relevance of reports of adults that were unstratified (i.e., did not report results among women of reproductive age, pregnant women, or lactating women only) and/or to contact the report authors with a request for stratified results. Continued characterization of EED definitions utilized in the literature (objective 1) is also possible using the full set of included reports. Finally, target searches including terms for known EED biomarkers may identify further reports relevant for women of reproductive age, pregnant women, and lactating women, though these studies may not be designed to assess for EED.

While outside of the scope of the current project, additional areas that may contribute to building a greater understanding of EED biomarkers for maternal and child populations include expanding the geographic scope beyond Sub-Saharan Africa and the WHO Southeast Asia region and further examination of the relation between EED biomarkers and inflammatory mechanisms. To facilitate large clinical trials and diagnosis of EED in clinical settings, additional consideration of scalability of biopsies may be warranted.

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Tables and Figures

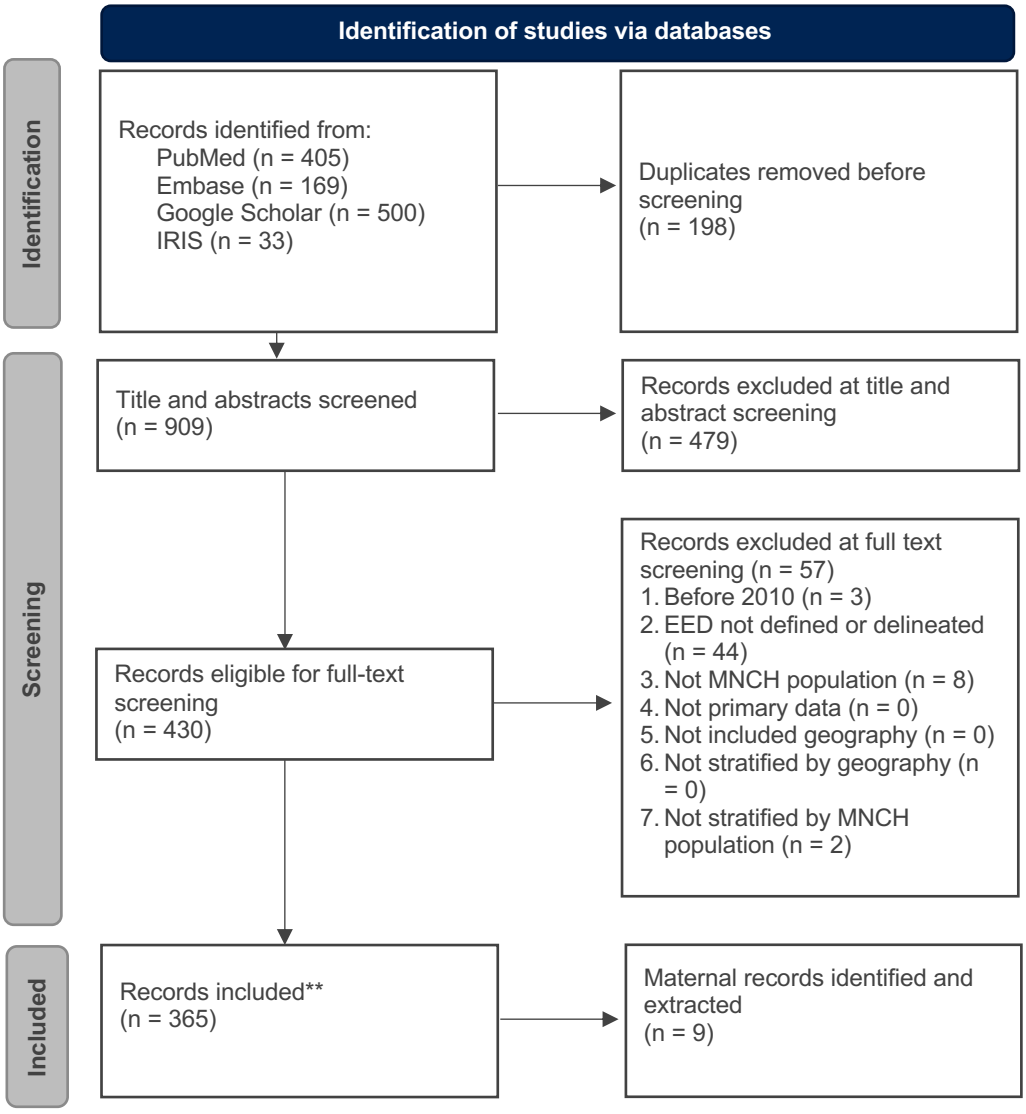
Table 1: Inclusion Criteria

Domain	Inclusion Criteria	Reasons to Exclude at Title/Abstract Stage
Study design	Studies reporting primary data collection (RCT, quasi-experimental designs, cohort, case controls, cross sectional studies, case studies, case reports)	Textbooks Systematic reviews Animal studies
Population	Includes women of reproductive age, pregnant women, lactating women, children under 5 years (< 61 months) of age (even if not results presented in abstract are not stratified to only the MNCH population(s) of interest)	Does not include women of reproductive age, pregnant women, lactating women, children under 5 years of age
Exposure	EED with biomarkers described	Intestinal function/microbiome studies describing relevant biomarkers but not specifically stating that these biomarkers were examined within the context of EED
Outcome	Clinical outcomes including but not limited to Infant characteristics (live birth, date and time of delivery, sex, weight, length, and head circumference)	None
Setting	Low- and middle-income countries in Sub-Saharan Africa, as defined by the World Bank, and Southeast Asia, as defined by the WHO Southeast Asia region	Other countries not included within our settings of interest

Table 2: Extraction Database Fields

Extraction Domain	Data Extracted
Publication Details	Author first and last name Year of publication Study title Abstract Publication URL Study design Study aim Primary study Primary study URL Language
Study Details	Country of data Setting Primary population of interest Target age for enrollment Number enrolled Population II Population III Main inclusion criteria Existing medical conditions (e.g. HIV, diabetes) Nutritional status of population at enrollment EED at enrollment Interventions Outcome Brief description of methods Time points of data collection Other comments Data availability statement Key limitations
Biomarker Details	Non-biomarker tests relevant to EED Biomarker Category Cutoffs for biomarker Findings for biomarker Effect size

Figure 1A: PRISMA Diagram for 2010 to Present



*Note: some records merged in extraction stage (e.g. conference abstract and corresponding article).

Figure 1B: PRISMA Diagram for Denno et al. Records

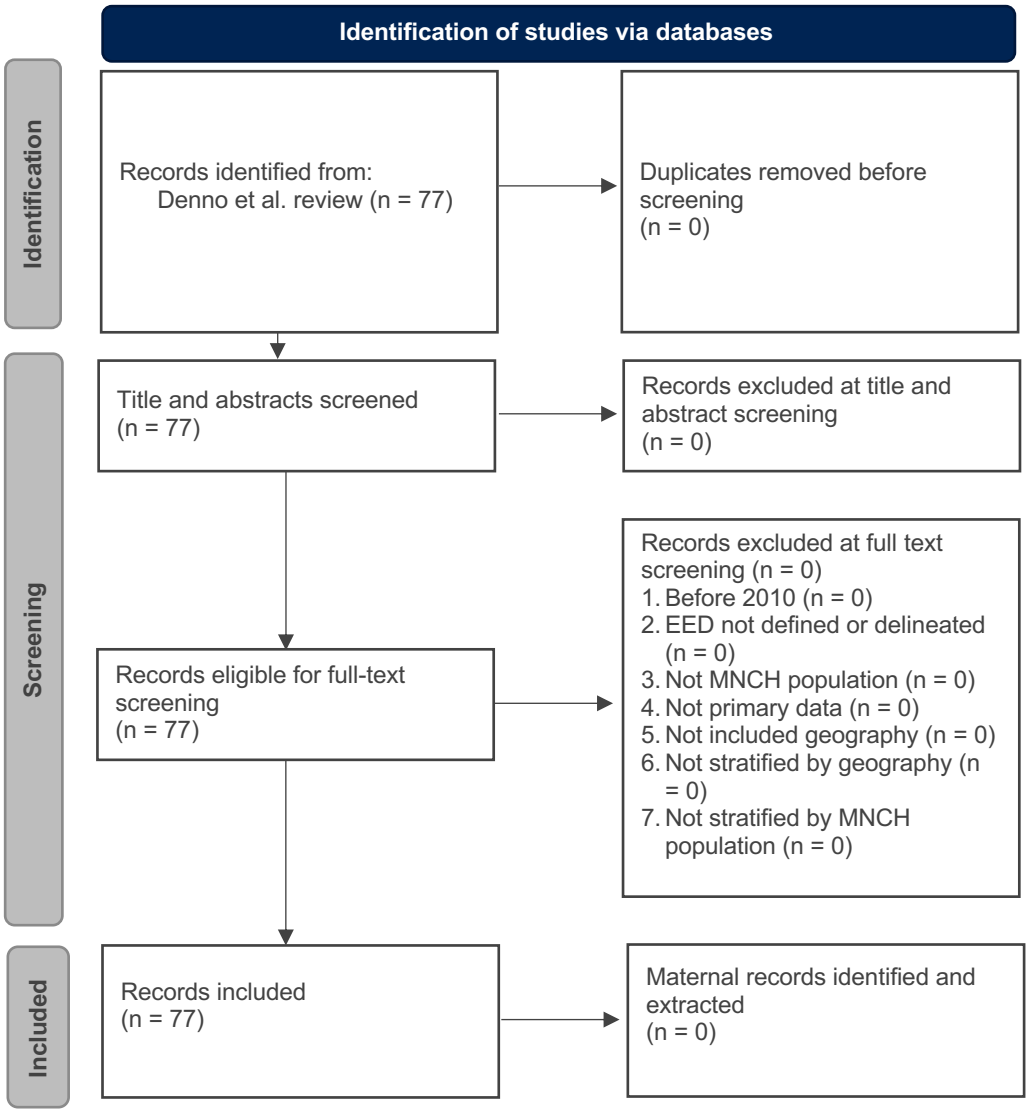


Table 3: Included Studies

Author and Year	Study Design	Country of Data Collection	Age Range (Years)	Sample Size
Amadi 2017	Cross-sectional study	Zambia	Not specified	61 (43 women)
Hossain 2021	Case-control study	Bangladesh	18 - 45	64 (39 women)
Karim 2015	Cross-sectional study	Bangladesh	18 - 60	116 (32 women)
Kashyap 2021	Interventional trial	India	20 - 35	7
Kelly 2016	Cross-sectional study	Zambia	18 - 55	49
Lauer 2018	Prospective cohort	Uganda	18 - 45	220
Patnayak 2016	Case study	India	15	1
Ramya 2020	Cross-sectional study	India	Above age 18	485 (181 women)
Shetty 2016	Case series	India	16 - 80	50 (18 women)

Table 4: Characteristics of Included Studies

Publication Characteristic	Number of Publications (%) or Range
Country	
India	4 (44.4)
Zambia	2 (22.2)
Bangladesh	2 (22.2)
Uganda	1 (11.1)
Study Type	
Cross-sectional study	5 (55.6)
Case-control study	1 (11.1)
Case report	1 (11.1)
Interventional trial	1 (11.1)
Prospective cohort	1 (11.1)
Population Type	
Women of reproductive age	8 (88.9)
Pregnant women	1 (11.1)
Setting	
Community-based	5 (55.6)
Clinical	3 (33.3)
Clinic employees	1 (11.1)
Sample Size	1 to 220
Adult Participant Age Range (Years)	15 to 80

Figure 2: Map of Included Countries

Table 5: Identified EED Biomarkers

EED Biomarker Domains*	EED Biomarkers Delineated by Harper et al. (7)	Identified Biomarkers	Definitions of Identified Biomarkers (7,8,21,24)
Intestinal damage and repair	• Citrulline • Intestinal fatty acid binding protein (I-FABP) • Regenerating (REG) family proteins [fecal REG] • Glucagon-like peptide 2 (GLP-2)	Glucagon-like peptide (GLP)	Gut trophic factor that is released by enteroendocrine L-cells in ileum that aids in mucosal regeneration
Permeability and absorption	• Dual-sugar absorption test: lactulose-mannitol (LM) or lactulose-rhamnose (LR) ratio • Alpha-1-antitrypsin (AAT) • Claudin: claudin-2, -15, -4 • Zonulin	Lactulose	Sugar that is able to permeate pores in epithelial cells that result from intestinal inflammation
		D-xylose	Sugar that is a measure of small bowel absorptive capacity
		LR ratio	Rhamnose is a sugar that, in the presence of villous atrophy, has reduced absorption; higher LR ratio is indicative of EED
		LM ratio	Mannitol is a sugar that, in the presence of villous atrophy, has reduced absorption; higher LM ratio is indicative of EED
		Claudins	Protein that modulates tight junctions that make up barriers between epithelial cells; higher claudin-2 and -15 indicate decreased absorption while higher claudin-4 indicates higher cell shedding
		Phenylalanine	Amino acid that approximates intestinal absorption
		Allo-isoleucine	An isotopically labeled nonprotein isotopologue of an L-amino acid that can be used to measure intestinal amino acid absorption
Microbial translocation	• Lipopolysaccharide (LPS) • Flagellin • Elevated plasma endotoxin core antibody (EndoCAb) titers	Anti-flagellin	Component of bacterial structure that is used to indicate microbial translocation
		Anti-Lipopolysaccharide	Component of bacterial structure that is used to indicate microbial translocation; anti-LPS IgA and IgG are indicative of systemic LPS

	• Anti-LPS immunoglobulin G (IgG) and A (IgA)		
Intestinal inflammation	• Translocated LPS neutrophils, macrophages, and dendritic cells • Myeloperoxidase (MPO) • Neopterin (NEO) • EED Composite score: comprised of three fecal biomarkers - AAT, MPO, and NEO • Calprotectin (calcium- and zinc-binding protein)	None	None
Systemic inflammation	• Interferon gamma (IFN-gamma) • Tumor necrosis factor (TNF) • Interleukins (e.g., IL-6, IL-10) • Alpha-1-acid glycoprotein • C-reactive protein • Ferritin • Soluble CD14 (sCD14) • Total IgG and IgM • Kynurenine-tryptophan ratio (KTR)	None	None
Morphometry	• Villous height • Crypt depth • Other morphological characteristics	Villous height	Measurement of the height of villi, with shortening and blunting being indicative of damage to intestinal structure
		Villous height:crypt depth ratio	Measurement of the ratio of villous height to crypt depth, with a lower ratio being indicative of damage to intestinal structure

* Additional categorizations made for biomarkers not delineated in the Harper et al. 2018 framework categories. Morphometry was added as an additional domain for this report.

Appendix

Appendix 1: PubMed Search Terms

Search run on July 7, 2021 (n = 405)

All boxes connected with AND

EED	("environmental enteric dysfunction"[Tiab] OR "EED"[Tiab] OR "tropical sprue"[Tiab] OR "sprue, tropical"[MeSH Terms] OR "idiopathic tropical malabsorption syndrome"[Tiab] OR "idiopathic tropical malabsorption syndromes"[Tiab] OR (("environment"[MeSH Terms] OR "environment*"[Tiab] OR "tropic*"[Tiab]) AND ("enteropath*"[Tiab] OR "enteric"[Tiab]))z
MNCH Population	("women"[MeSH Terms] OR "women*"[TIAB] OR "woman*"[TIAB] OR "mother"[TIAB] OR "maternal"[TIAB] OR "pregnant"[TIAB] OR "infant"[MeSH Terms] OR "infant*"[TIAB] OR "newborn"[TIAB] OR "child"[MeSH Terms] OR "child*"[TIAB] OR "kid"[TIAB] OR "kids"[TIAB] OR "baby"[TIAB] or "babies"[TIAB])
Sub-Saharan Africa and Southeast Asia Geography	(((Deprived Countries[tw] OR Deprived Population[tw] OR Deprived Populations[tw] OR Developing Countries[tw] OR Developing Country[tw] OR Developing Economies[tw] OR Developing Economy[tw] OR Developing Nation[tw] OR Developing Nations[tw] OR Developing Population[tw] OR Developing Populations[tw] OR Developing World[tw] OR LAMI Countries[tw] OR LAMI Country[tw] OR Less Developed Countries[tw] OR Less Developed Country[tw] OR Less Developed Economies [tw] OR Less Developed Nation[tw] OR Less Developed Nations[tw] OR Less Developed World[tw] OR Lesser Developed Countries[tw] OR Lesser Developed Nations[tw] OR LMIC[tw] OR LMICS[tw] OR Low GDP[tw] OR Low GNP[tw] OR Low Gross Domestic[tw] OR Low Gross National[tw] OR Low Income Countries[tw] OR Low Income Country[tw] OR Low Income Economies [tw] OR Low Income Economy[tw] OR Low Income Nations[tw] OR Low Income Population[tw] OR Low Income Populations[tw] OR Lower GDP[tw] OR lower gross domestic[tw] OR Lower Income Countries[tw] OR Lower Income Country[tw] OR Lower Income Nations[tw] OR Lower Income Population[tw] OR Lower Income Populations[tw] OR Middle Income Countries[tw] OR Middle Income Country[tw] OR Middle Income Economies [tw] OR Middle Income Nation[tw] OR Middle Income Nations[tw] OR Middle Income Population[tw] OR Middle Income Populations[tw] OR Poor Countries[tw] OR Poor Country[tw] OR Poor Economies

	[tw] OR Poor Economy[tw] OR Poor Nation[tw] OR Poor Nations[tw] OR Poor Population[tw] OR Poor Populations[tw] OR poor world[tw] OR Poorer Countries[tw] OR Poorer Economies [tw] OR Poorer Economy[tw] OR Poorer Nations[tw] OR Poorer Population[tw] OR Poorer Populations[tw] OR Third World[tw] OR Transitional Countries[tw] OR Transitional Country[tw] OR Transitional Economies[tw] OR Transitional Economy[tw] OR Under Developed Countries[tw] OR Under Developed Country[tw] OR under developed nations[tw] OR Under Developed World[tw] OR Under Served Population[tw] OR Under Served Populations[tw] OR Underdeveloped Countries[tw] OR Underdeveloped Country[tw] OR underdeveloped economies[tw] OR underdeveloped nations[tw] OR underdeveloped population[tw] OR Underdeveloped World[tw] OR Underserved Countries[tw] OR Underserved Nations[tw] OR Underserved Population[tw] OR Underserved Populations[tw]) OR (Angola[tw] OR Bangladesh[tw] OR Benin[tw] OR Bhutan[tw] OR Botswana[tw] OR "Burkina Faso"[tw] OR Burma[tw] OR Burundi[tw] OR "Cabo Verde"[tw] OR "Cape verde"[tw] OR Cameroon[tw] OR "Central African Republic"[tw] OR Chad[tw] OR Comoros[tw] OR Comores[tw] OR Comoro[tw] OR Congo[tw] OR "Côte d'Ivoire"[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR "Guinea Bissau"[tw] OR "Guinea-Bissau"[tw] OR India[tw] OR Indonesia[tw] OR Kenya[tw] OR Korea[tw] OR Lesotho[tw] OR Liberia[tw] OR Madagascar[tw] OR Malawi[tw] OR Maldives[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mozambique[tw] OR Myanmar[tw] OR Namibia[tw] OR Nepal[tw] OR Niger[tw] OR Nigeria [tw] OR Principe[tw] OR Rwanda[tw] OR Ruanda[tw] OR "Sao Tome"[tw] OR Senegal[tw] OR Seychelles[tw] OR "Sierra Leone"[tw] OR Somalia[tw] OR "South Africa"[tw] OR "South Sudan"[tw] OR "Sri Lanka"[tw] OR Sudan[tw] OR Swaziland[tw] OR "Eswatini"[tw] OR Tanzania[tw] OR Thailand[tw] OR Timor[tw] OR "Timor-Leste"[tw] OR Togo[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw])))

Appendix 2: Embase Search Terms

Search run on July 7, 2021 (n = 169)

All boxes connected with AND; excluding results indexed in MEDLINE

EED	('environmental enteric dysfunction':ti,ab OR 'eed':ti,ab OR 'tropical sprue':ti,ab OR 'idiopathic tropical malabsorption syndrome':ti,ab OR 'idiopathic tropical malabsorption syndromes':ti,ab OR (('enteric*':ti,ab OR 'enteropath*':ti,ab) AND ('environ*':ti,ab OR 'tropic*':ti,ab)))
MNCH Population	('female'/exp OR 'female':ti,ab OR 'infant'/exp OR 'infant':ti,ab OR 'newborn'/exp OR 'newborn':ti,ab OR 'child'/exp OR 'child*':ti,ab)
Sub-Saharan Africa and Southeast Asia Geography	'deprived countries':de,ti,ab OR 'deprived country':de,ti,ab OR 'deprived nation':de,ti,ab OR 'deprived nations':de,ti,ab OR 'deprived population':de,ti,ab OR 'deprived populations':de,ti,ab OR 'deprived world':de,ti,ab OR 'developing countries':de,ti,ab OR 'developing country':de,ti,ab OR 'developing economies':de,ti,ab OR 'developing economy':de,ti,ab OR 'developing nation':de,ti,ab OR 'developing nations':de,ti,ab OR 'developing population':de,ti,ab OR 'developing populations':de,ti,ab OR 'developing world':de,ti,ab OR 'lami countries':de,ti,ab OR 'lami country':de,ti,ab OR 'less developed countries':de,ti,ab OR 'less developed country':de,ti,ab OR 'less developed economies':de,ti,ab OR 'less developed economy':de,ti,ab OR 'less developed nation':de,ti,ab OR 'less developed nations':de,ti,ab OR 'less developed population':de,ti,ab OR 'less developed populations':de,ti,ab OR 'less developed world':de,ti,ab OR 'lesser developed countries':de,ti,ab OR 'lesser developed country':de,ti,ab OR 'lesser developed economies':de,ti,ab OR 'lesser developed economy':de,ti,ab OR 'lesser developed nation':de,ti,ab OR 'lesser developed nations':de,ti,ab OR 'lesser developed population':de,ti,ab OR 'lesser developed populations':de,ti,ab OR 'lesser developed world':de,ti,ab OR 'lmic':de,ti,ab OR 'lmics':de,ti,ab OR 'low gdp':de,ti,ab OR 'low gnp':de,ti,ab OR 'low gross domestic':de,ti,ab OR 'low gross national':de,ti,ab OR 'low income countries':de,ti,ab OR 'low income country':de,ti,ab OR 'low income economies':de,ti,ab OR 'low income economy':de,ti,ab OR 'low income nation':de,ti,ab OR 'low income nations':de,ti,ab OR 'low income population':de,ti,ab OR 'low income populations':de,ti,ab OR 'lower gdp':de,ti,ab OR 'lower gnp':de,ti,ab OR 'lower gross domestic':de,ti,ab OR 'lower gross national':de,ti,ab OR 'lower income countries':de,ti,ab OR 'lower income country':de,ti,ab OR 'lower income economies':de,ti,ab OR 'lower income

	economy':de,ti,ab OR 'lower income nation':de,ti,ab OR 'lower income nations':de,ti,ab OR 'lower income population':de,ti,ab OR 'lower income populations':de,ti,ab OR 'middle income countries':de,ti,ab OR 'middle income country':de,ti,ab OR 'middle income economies':de,ti,ab OR 'middle income economy':de,ti,ab OR 'middle income nation':de,ti,ab OR 'middle income nations':de,ti,ab OR 'middle income population':de,ti,ab OR 'middle income populations':de,ti,ab OR 'poor countries':de,ti,ab OR 'poor country':de,ti,ab OR 'poor economies':de,ti,ab OR 'poor economy':de,ti,ab OR 'poor nation':de,ti,ab OR 'poor nations':de,ti,ab OR 'poor population':de,ti,ab OR 'poor populations':de,ti,ab OR 'poor world':de,ti,ab OR 'poorer countries':de,ti,ab OR 'poorer country':de,ti,ab OR 'poorer economies':de,ti,ab OR 'poorer economy':de,ti,ab OR 'poorer nation':de,ti,ab OR 'poorer nations':de,ti,ab OR 'poorer population':de,ti,ab OR 'poorer populations':de,ti,ab OR 'poorer world':de,ti,ab OR 'third world':de,ti,ab OR 'transitional countries':de,ti,ab OR 'transitional country':de,ti,ab OR 'transitional economies':de,ti,ab OR 'transitional economy':de,ti,ab OR 'under developed countries':de,ti,ab OR 'under developed country':de,ti,ab OR 'under developed economies':de,ti,ab OR 'under developed economy':de,ti,ab OR 'under developed nation':de,ti,ab OR 'under developed nations':de,ti,ab OR 'under developed population':de,ti,ab OR 'under developed populations':de,ti,ab OR 'under developed world':de,ti,ab OR 'under served countries':de,ti,ab OR 'under served country':de,ti,ab OR 'under served nation':de,ti,ab OR 'under served nations':de,ti,ab OR 'under served population':de,ti,ab OR 'under served populations':de,ti,ab OR 'under served world':de,ti,ab OR 'underdeveloped countries':de,ti,ab OR 'underdeveloped country':de,ti,ab OR 'underdeveloped economies':de,ti,ab OR 'underdeveloped economy':de,ti,ab OR 'underdeveloped nation':de,ti,ab OR 'underdeveloped nations':de,ti,ab OR 'underdeveloped population':de,ti,ab OR 'underdeveloped populations':de,ti,ab OR 'underdeveloped world':de,ti,ab OR 'underserved countries':de,ti,ab OR 'underserved country':de,ti,ab OR 'underserved nation':de,ti,ab OR 'underserved nations':de,ti,ab OR 'underserved population':de,ti,ab OR 'underserved populations':de,ti,ab OR 'underserved world':de,ti,ab OR angola:de,ti,ab OR bangladesh:de,ti,ab OR benin:de,ti,ab OR bhutan:de,ti,ab OR botswana:de,ti,ab OR 'burkina faso':de,ti,ab OR burma:de,ti,ab OR burundi:de,ti,ab OR 'cabo verde':de,ti,ab OR 'cape verde':de,ti,ab OR cameroon:de,ti,ab OR 'central african republic':de,ti,ab OR chad:de,ti,ab OR comoros:de,ti,ab OR comores:de,ti,ab OR comoro:de,ti,ab OR congo:de,ti,ab OR 'côte d ivoire':de,ti,ab OR eritrea:de,ti,ab OR ethiopia:de,ti,ab OR gabon:de,ti,ab OR gambia:de,ti,ab OR ghana:de,ti,ab OR guinea:de,ti,ab OR

	'guinea bissau':de,ti,ab OR 'guinea-bissau':de,ti,ab OR india:de,ti,ab OR indonesia:de,ti,ab OR kenya:de,ti,ab OR korea:de,ti,ab OR lesotho:de,ti,ab OR liberia:de,ti,ab OR madagascar:de,ti,ab OR malawi:de,ti,ab OR maldives:de,ti,ab OR mali:de,ti,ab OR mauritania:de,ti,ab OR mauritius:de,ti,ab OR mozambique:de,ti,ab OR myanmar:de,ti,ab OR namibia:de,ti,ab OR nepal:de,ti,ab OR niger:de,ti,ab OR nigeria:de,ti,ab OR principe:de,ti,ab OR rwanda:de,ti,ab OR ruanda:de,ti,ab OR 'sao tome':de,ti,ab OR senegal:de,ti,ab OR seychelles:de,ti,ab OR 'sierra leone':de,ti,ab OR somalia:de,ti,ab OR 'south africa':de,ti,ab OR 'south sudan':de,ti,ab OR 'sri lanka':de,ti,ab OR sudan:de,ti,ab OR swaziland:de,ti,ab OR 'eswatini':de,ti,ab OR tanzania:de,ti,ab OR thailand:de,ti,ab OR timor:de,ti,ab OR 'timor-leste':de,ti,ab OR togo:de,ti,ab OR uganda:de,ti,ab OR zambia:de,ti,ab OR zimbabwe:de,ti,ab

Appendix 3: Google Scholar Search Terms and Strategy

Search run on July 10, 2021 (n = 500)

Screen the first 500 records returned with the following search terms:

- “Tropical sprue” OR “Environmental enteric dysfunction” OR “Tropical enteropathy” OR “Environmental enteropathy” OR “Idiopathic Tropical Malabsorption Syndrome”

Appendix 4: WHO IRIS Search Terms

Search run on June 23, 2021 (n = 33)

Search each of the following terms independently:

- “Tropical sprue”
- “Environmental enteric dysfunction”
- “Tropical enteropathy”
- “Environmental enteropathy”
- “Idiopathic tropical malabsorption syndrome”

Appendix 5: WHO ICTRP Search Terms

Search run on July 2, 2021 (n = 15)

Search each of the following terms independently:

- “Tropical sprue”
- “Environmental enteric dysfunction”
- “Tropical enteropathy”
- “Environmental enteropathy”
- “Idiopathic tropical malabsorption syndrome”

Appendix 6: Exclusion Criteria

Reasons 1-3 apply to all objectives; reasons 4-7 apply only to studies that could be relevant for objectives 2 and 3. If a record is not relevant for objective 1, it will not be relevant for objectives 2 and 3.

1. Record was published before 2010 (with the exception of Denno et al. systematic review records).
2. Record does not define EED, delineate distributions of EED biomarkers, or describe associations between EED/EED biomarkers and clinical outcomes in humans.
3. Record does not include any of the following populations: women of reproductive age (ages 15 to 49), pregnant women, lactating women, children under 5 years (< 61 months) of age.
4. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, record does not present research that presents the analysis of primary data (i.e. exclude meta-analyses, commentaries, textbooks, etc.).
5. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, geographic location is not Sub-Saharan Africa or Southeast Asia.
6. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, geographic location is not stratified to Sub-Saharan Africa or Southeast Asia (e.g. results are aggregated across Brazil and Kenya, etc.).
7. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, distributions and/or associations are not stratified to include only the populations of interest (e.g. record presents distribution of a biomarker for children 10+, record presents association between biomarker and clinical outcome for female and male adults, etc.) OR age not specified (as seen in conference abstracts, etc.).