

# Environmental enteric dysfunction: An overview

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## Abstract

**Background.** Environmental enteric dysfunction (EED) refers to an incompletely defined syndrome of inflammation, reduced absorptive capacity, and reduced barrier function in the small intestine. It is widespread among children and adults in low- and middle-income countries. Understanding of EED and its possible consequences for health is currently limited.

**Objective.** A narrative review of the current understanding of EED: epidemiology, pathogenesis, therapies, and relevance to child health.

**Methods.** Searches for key papers and ongoing trials were conducted using PUBMED 1966–June 2014; ClinicalTrials.gov; the WHO Clinical Trials Registry; the Cochrane Library; hand searches of the references of retrieved literature; discussions with experts; and personal experience from the field.

**Results.** EED is established during infancy and is associated with poor sanitation, certain gut infections, and micronutrient deficiencies. *Helicobacter pylori* infection, small intestinal bacterial overgrowth (SIBO), abnormal gut microbiota, undernutrition, and toxins may all play a role. EED is usually asymptomatic, but it is important due to its association with stunting. Diagnosis is frequently by the dual sugar absorption test, although other biomarkers are emerging. EED may partly explain the reduced efficacy of oral vaccines in low- and middle-income countries and the increased risk of serious infection seen in children with undernutrition.

**Conclusions.** Despite its potentially significant

impacts, it is currently unclear exactly what causes EED and how it can be treated or prevented. Ongoing trials involve nutritional supplements, water and sanitation interventions, and immunomodulators. Further research is needed to better understand this condition, which is of likely crucial importance for child health and development in low- and middle-income settings.

**Key words:** Environmental enteric dysfunction, environmental enteropathy, malnutrition, stunting

## Introduction

Environmental enteric dysfunction (EED) is a poorly understood condition that may have far-reaching impacts on child growth, health, and development in low- and middle-income country settings. Characterized by small intestinal inflammation and strongly associated with stunting (low height-for-age), it is now the subject of significant research interest as investigators seek to define its causes, pathogenesis, consequences, and possible preventive or curative approaches.

The earliest descriptions of EED, previously known as “tropical enteropathy,” date back to the 1960s, when an abnormal microscopic appearance of the small bowel was observed in adults from low- and middle-income countries [1]. It was observed that the villi were blunted and shortened, leading to a decreased surface area for nutrient absorption. Tropical enteropathy was renamed “environmental enteropathy” in the late 2000s in recognition of emerging evidence that the quality of the environment was more important than climate or latitude; EED is not limited to tropical areas, nor does it affect all residents in the tropics. Over the past year, it has been further renamed “environmental enteric dysfunction.”

There is no universally accepted case definition or specific diagnostic criteria for EED, and it does not have immediately apparent clinical symptoms. The key

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demonstrable histological features (villous flattening, crypt hyperplasia, and lymphocytic infiltration of the lamina propria [2–5]) are not unique to EED. Tropical sprue (a syndrome of chronic diarrhea, malabsorption, and malnutrition seen in residents of tropical countries) and EED were initially thought to be the same process, with symptomatic tropical sprue the most severe pathology but representing the “tip of the iceberg” of largely unrecognized EED, although this distinction remains unclear [6]. There are also some similarities with other chronic gut inflammatory conditions, such as celiac disease and inflammatory bowel disease (Crohn’s disease and ulcerative colitis) [7].

## Impact of EED on health and nutrition

### Impact on nutrition and development

Childhood EED has been associated with stunting (low height-for-age) for as long as it has been a recognized entity [8–12] although it is not entirely clear which of these two is the primary instigator and which the consequence. A 2008 systematic review of the effectiveness of existing complementary feeding interventions for malnutrition among 6- to 24-month-olds suggested that they had only moderate benefits and that EED may be a key factor limiting effectiveness [13]. Nutritional intervention alone may not be fully addressing the problem of stunting among infants and children in low- and middle-income country settings—with EED possibly explaining this shortfall [14].

There are many ways, other than malabsorption, in which chronic intestinal inflammation could impact growth. One proposed mechanism is appetite suppression, since this—rather than food availability—is often a key factor restricting children’s food intake [15]. Proinflammatory cytokines are known to act on appetite centers in the brain [16]. Another proposed mechanism is via negative regulation of systemic inflammatory activation on signaling through the growth hormone–insulin-like growth factor 1 (IGF-1) axis, which has been clearly demonstrated in pediatric Crohn’s disease [16, 17]. A similar situation may occur in EED: indeed, higher blood inflammatory markers in Zimbabwean infants were associated with lower levels of IGF-1 and with stunting [18].

Stunting has devastating consequences for child health. Difficult to reverse beyond 2 years of age, it has long-lasting effects on health and development [19, 20]. A meta-analysis in 2007 suggested that each year 200 million children do not reach their developmental potential due to stunting [21]. Certain noncommunicable diseases in adulthood are associated with stunting in childhood, perhaps through epigenetic regulation (which refers to long-term alteration in gene expression) or via chronic inflammation [22].

### Impact on immunity

The gut is the site of a highly sophisticated immune surveillance operation, the purpose of which is to detect and destroy potential pathogens and maintain the integrity of host tissues while at the same time avoiding unhelpful immune responses against foods, nonpathogenic microorganisms, and other harmless contents of the gut lumen. The presence of abnormally large numbers of white blood cells in the gut wall of children and adults with EED suggests that this surveillance operation is being stressed. Impaired barrier function (a hallmark of EED) results in luminal contents (including both harmless and potentially pathogenic bacteria) crossing the gut wall itself and activating the immune system. Chronic inflammation is triggered, which may be a direct cause of growth failure (as described above) and may impair antipathogen surveillance capacity. The nature of this chronic inflammation remains poorly understood. This is partly because it is a difficult phenomenon to study, since biopsy samples from children with EED are scarce. However, in recent years there have been a number of fundamental advances in our understanding of mucosal immunity coming from work with mouse models of human disease, and it is possible that approaches utilizing animal model systems will further our understanding of EED and even guide clinical and public health management in the future [23–25]. Lastly, although the exact mechanism is unclear, EED has been implicated in the poor response to oral vaccines (polio and rotavirus) seen in children living in low- and middle-income countries [7, 26–28].

### Diagnosis: How do we identify the child with EED?

To confirm the diagnosis of EED beyond doubt requires demonstration of the histological features of EED. This can only be done by endoscopy and small intestinal biopsy. The logistical challenges of this have led investigators to seek simpler biomarkers for EED: less invasive tests that measure proxy biomarkers are used to quantify gut inflammation and reduced barrier function.

### The dual sugar absorption tests

To date, the most frequently used tests for EED are the dual sugar absorption tests. The most commonly implemented of these at present is the lactulose:mannitol (L:M) test, although other sugars, such as xylose and rhamnose, can be used. Lactulose is a large sugar that is not normally absorbed by the small intestine. Mannitol is a smaller sugar that is absorbed by the small intestine in proportion to absorptive surface area. In the L:M

test, after oral ingestion, both lactulose and mannitol are excreted intact in the urine following minimal metabolism. Urinary mannitol therefore gives an index of absorptive capacity, while the presence of lactulose in the urine indicates impaired barrier function. Higher urinary L:M ratios reflect greater abnormalities of one or both functions [8, 29, 30].

The L:M test requires cooperation and understanding from the participant and the carer, which may present a challenge when the test is performed in very young children. Ensuring complete collection of all urine voided over up to 5 hours and avoiding contamination with feces is difficult in infants and requires parental patience. Measurement of lactulose and mannitol in urine can be performed by enzyme-linked immunosorbent assay (ELISA), anion exchange chromatography, or mass spectrometry. All of these methods require centralized laboratory equipment and expertise, and the results are not always comparable between laboratories.

### Emerging biomarkers

New biomarkers of EED are being actively investigated. Current markers of gut inflammation are measured in feces: calprotectin [31–34]; myeloperoxidase, neopterin, and  $\alpha$ -1-antitrypsin [35]; mRNA [36]; REG1b [37]; lactoferrin [38]. Markers of gut permeability are measured in blood: zonulin; [39] EndoCAB; [11, 12, 18, 39] soluble CD14 [18]. Lastly, a marker of total enterocyte mass is also measured in blood: citrulline [40].

By investigating and testing markers for their hypothesized roles in the establishment and maintenance of EED, our understanding of the processes causing EED will hopefully improve. For example, small intestinal epithelial cells from a child with EED are assumed to differ in the kinds of proteins they produce from those from a child without EED. Certain mRNA transcripts with roles in inflammatory pathways have been shown to be present more often in the stool of Malawian children with abnormal L:M ratios [36].

Most new markers have been evaluated in association with stunting rather than according to histological changes or the L:M test. Future studies may compare new markers against indicators other than anthropometry, including assessing their abilities to closely reflect short-term changes in EED as defined by a gold standard diagnostic test. Such markers would be useful for evaluating the effects of interventions against EED in trials where follow-up is comparatively brief.

### Epidemiology: Who has EED? What are its risk factors?

EED was first recognized in adults. A 1971 study of US Peace Corps volunteers is frequently referred to as the first to demonstrate that EED can be acquired

and lost according to environment [41]. Participants were assessed during and after placement in India and Pakistan. Gut absorptive function tests and biopsies confirmed abnormalities during residence abroad and recovery within 1 or 2 years after return to the United States. At the time, an environmental cause was suggested. A later study of Zambian adults demonstrated the same histological abnormalities, which varied with season, further implying an environmental cause [4]. In the early 1990s, community-wide studies revealed that EED was a widespread and pervasive problem in infants and children. An abnormal L:M test was almost universally acquired by the end of infancy in The Gambia [12, 42, 43] and was associated with stunting among infants and children in many low- and middle-income country settings, including Zambia, Malawi, Bangladesh, India, Nepal, Brazil, and Guatemala and among Aboriginal communities in Australia [5, 8–12, 30, 31, 40, 42–57]. In 1999, a large study measured intestinal permeability and absorptive capacity among asymptomatic adults in 14 countries across the world [58]. Abnormalities of both intestinal absorption and permeability were, in general, found in tropical rather than temperate countries. However, average intestinal absorptive capacity by country also correlated very closely with national gross domestic product per capita, independently of climate, suggesting that poverty may play a more significant role.

Putting these studies together, a consistent picture has emerged: EED seems highly prevalent in low- and middle-income country settings, is acquired during infancy, and persists into adulthood, but can perhaps be cured or improved with change in environment. It is strongly associated with stunting in infants and children.

### Etiology: What causes EED?

#### Nutritional deficiency

Zinc is known to aid recovery of the intestinal mucosa following diarrhea [48] and is recommended as part of standard therapy for diarrhea by the World Health Organization. Zinc deficiency is associated with abnormal L:M ratio in Malawian children [53]. Vitamin A deficiency is associated with abnormal L:M ratio and stunting in Brazilian children [50]. In The Gambia, the least abnormal L:M ratios are observed during the mango season, when vitamin A intake is highest [49]. However, trials of both vitamin A and zinc have had mixed impacts on growth and/or EED markers among children in low- and middle-income countries [47, 49, 50, 52, 59, 60]. Multiple micronutrient supplementation in Zambian adults has yielded improvements in the histological features of EED [61].

Several other nutritional approaches have been proposed to tackle EED, for example, improving the

digestibility of food through fermentation, hydrolysis, or enzyme supplementation, or optimizing amino acid profiles to reduce gut inflammation and support repair [62]. Trials of n-3 (omega-3) long-chain polyunsaturated fatty acid (LC-PUFA), a dietary essential fatty acid thought to reduce intestinal inflammation, in The Gambia and of alanyl-glutamine, an essential precursor for rapidly replicating cells such as those lining the small intestine, in Brazil have yielded some positive results (**table 1**) [31, 51]. These interventional studies and others will improve our understanding of the possible nutritional causes of EED.

## Microorganisms

### *Nonspecific feco-oral contamination: Role of WASH*

Microorganisms in the gut may be important in the establishment and/or maintenance of EED. Their relative importance may differ according to geographic setting, season, age, and feeding practices. Bangladeshi children from cleaner households were observed to have lower risks of both abnormal L:M ratio and stunting than those from less clean households [11]. In

Malawian 3- to 5-year-olds, an abnormal L:M test was associated with lack of latrine access and low household water usage [63]. However, a recent systematic review of 14 trials of water, sanitation, and hygiene (WASH) interventions worldwide on anthropometric outcomes for children aged 0 to 18 years suggested a very modest impact of WASH on stunting (with no effect at all among children aged under 2 years) and no impact on underweight or wasting [65]. Observational study of infants and young children in Zimbabwe suggests that a significant proportion of the burden of feco-oral contamination is likely to come not only from well-characterized sources (food, water, and hands) but also from direct eating of soil and animal feces in the course of play and exploration [66]. Several multisite studies are currently ongoing to investigate the effectiveness of different WASH interventions against EED [67–69].

A recent systematic review concluded that good evidence exists for moderate beneficial effects of antibiotics on growth in prepubertal children in low- and middle-income countries [70]. Several antibiotic studies aimed at particular species of pathogen have included EED in their outcomes (**table 1**).

TABLE 1. Selected published trials conducted among children in low- and middle-income country settings where EED has been explicitly targeted<sup>a</sup>

Author and year	Setting	Age group	Intervention and duration	Results: L:M ratio	Results: anthropometry	Notes
Thurnham et al. 2000 [49]	India; rural	2–15 mo	Vitamin A single dose (inpatients) or for 8 wk (outpatients)	Improvement seen within 30 days	Not reported	
Galpin et al. 2005 [63]	Malawi; rural	3–5 yr	<i>Lactobacillus</i> 30 days	No difference	No difference	
Lima 2007 [51]	Brazil; rural	7 mo–7 yr	Alanyl-glutamine 10 days	Improvement	Improved WAZ and WHZ but no difference in HAZ	
Trehan et al. 2009 [64]	Malawi; rural	3–5 yr	Rifamixin 7 days	No difference	Not reported	SIBO itself not measured
Goto 2009 [55]	Bangladesh; urban	3–15 mo	Albendazole 3 monthly and secnidazole monthly for 9 mo	No difference	No difference	Possible reason for failure: high <i>Giardia</i> reinfection rate
van der Merwe et al. 2013 [31]	The Gambia; rural	3 mo	n-3 LC-PUFA for 6 mo	No difference	Improved MUAC at 9 and 12 mo	Cognition also examined: no difference
Ryan et al. 2014 [47]	Malawi; rural	1–3 yr	Zinc 14 days	Prevented deterioration	No difference	
			Albendazole single dose	Prevented deterioration	No difference	

EED, environmental enteric dysfunction; HAZ, height-for-age z-score; LC-PUFA, long-chain polyunsaturated fatty acid; MUAC, mid-upper-arm circumference; SIBO, small intestinal bacterial overgrowth; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score; WHO, World Health Organization

a. Searches for key papers and ongoing trials were conducted using PubMed 1966–June 2014, ClinicalTrials.gov, the WHO Clinical Trials Registry, the Cochrane Library, hand searches of the references of retrieved literature, discussions with experts, and personal experience from the field.

During the transition period from exclusive breastfeeding to complementary feeding, which frequently occurs much earlier than the recommended 6 months [71], infants are at risk for feco-oral contamination from complementary (weaning) foods. These may be prepared separately from family foods, stored for longer periods, and reheated inadequately [72]. It is during these vital months of high energy demand and immune system development that the benefits of exclusive breastfeeding are lost and a convergence of poor nutrition and feco-oral contamination takes place. The development of EED is also observed during this time. For example, moving from exclusive breastfeeding to mixed feeding and subsequent cessation of breastfeeding altogether are both seen alongside worsening of the L:M ratio in Nepali infants, and early breastfeeding cessation is associated with worse L:M ratio in Guatemalan infants [9, 45]. Although it is difficult to distinguish from the risk of nutritional deficiency that occurs with early cessation of breastfeeding, a possible cause of these observations may be the poor hygiene often associated with complementary feeding.

#### Specific pathogens

Linear growth-faltering has been linked to concurrent infection with multiple intestinal parasites (*Cryptosporidium* [73], amoeba [74], roundworm [75], and hookworm [76]). Elevated fecal lactoferrin was found among Ghanaian and Brazilian children with entero-aggregative *Escherichia coli* intestinal infection, and in Brazilian children, linear growth impairment was also found [38, 77]. The abnormal histological findings in EED have been linked to infection with hookworm and the bacterium *Citrobacter rodentium* [4]. The parasite *Giardia duodenalis* has been particularly implicated in abnormal L:M ratios in Nepal [9] and acute growth-faltering in Gambian infants [54]. Acute rotavirus infection has been associated with high L:M ratios in Bangladeshi and Peruvian children [48, 78].

More recent advances in molecular pathogen diagnostics, such as the polymerase chain reaction (PCR), have allowed greater range and sensitivity in detecting pathogens. In urban Bangladeshi infants, associations were found between stunting, diarrhea, and EED (measured by EndoCAB, an antibody formed in the bloodstream in response to movement of gut-resident gram-negative bacteria across a leaky gut wall) [39]. Amoeba, *Cryptosporidium*, and enterotoxigenic *E. coli* were important causes of diarrhea in these infants (associations with EED itself were not examined).

#### The gut microbiome

An imbalance of gut organisms, rather than the presence or absence of specific pathogens, may be important in EED and nutrition. The gut microbiota differs significantly between African and European infants [79] and between malnourished and well-nourished

children [80, 81]. Evidence that the microbiome affects nutritional status comes from an experiment where feces from malnourished children were transplanted into gnotobiotic (germ-free) mice that were fed a typical Malawian diet, resulting in the mice becoming malnourished [82]. There are no published studies to date of the gut microbiome in the specific context of EED.

#### *Helicobacter pylori* and small intestinal bacterial overgrowth

*Helicobacter pylori* is a bacterial infection best known as a cause of gastric ulcers. It has also been implicated in allowing the passage of live pathogens beyond the stomach through inhibition of stomach acid secretion [83]. In The Gambia, 15% of 0- to 20-month-olds and 46% of 40- to 60-month-olds had evidence of *H. pylori* infection, with higher prevalence among those acutely malnourished or with chronic diarrhea [84–86]. In urban Peru, a high frequency of *H. pylori* infection was noted among children and was associated with a subsequent higher risk of diarrhea [87].

The small intestine is where the majority of nutrient absorption occurs and where the histological abnormalities of EED are seen. In good health, the small intestine is relatively sterile compared with the large intestine. Small intestinal bacterial overgrowth (SIBO) is a condition that can arise secondary to bowel stasis seen, for example, in muscular disorders [88]. The gold standard for the diagnosis of SIBO is sampling and culture of fluid from the small intestinal lumen. In the 1970s and 1980s, small intestinal fluid samples from acutely malnourished Indian adults and Gambian and Nigerian children were found to be heavily contaminated with pathogenic bacteria and yeasts regardless of the presence of diarrhea [89–91]. In The Gambia, SIBO was observed in apparently healthy infants, peaking during the first few months of introduction of complementary foods, as exclusive breastfeeding ceases [92].

Testing the hydrogen content of exhaled air is a reasonable method of detecting the presence of bacteria in the small intestine, since the human body does not produce hydrogen except via metabolically active intestinal bacteria [93]. When measured at intervals following ingestion of a sugar substrate, a large, late peak in the hydrogen content of exhaled air indicates metabolism of the sugar by normally resident bacteria in the large intestine. An earlier, smaller peak indicates abnormal presence of bacteria in the small intestine. This early peak is associated with EED-like small intestinal histologic changes in slum-dwelling Brazilian infants [94], poverty in urban Brazilian children [95], malnutrition and malabsorption in Burmese infants [96], and enteral vaccine failure in Chile [97].

SIBO can be treated successfully with antibiotics [98]. Metronidazole targeted at SIBO (though likely impacting on specific bacterial or parasitic infections, such as *Giardia*, as well) aided recovery from

malnutrition in Jamaican children [99], but the nonabsorbable oral antibiotic rifamixin, also targeted at SIBO, was found not to improve L:M ratios in Malawian children [64]. Probiotics have also been investigated, although there is very limited evidence for their effectiveness in treating SIBO [88], and they have not been found to improve L:M ratios in Malawian children [63]. The role of SIBO—and its possible promotion via *H. pylori* infection—in the pathogenesis of EED is therefore still unclear.

#### **HIV enteropathy**

Enteropathy, with chronic diarrhea and weight loss, is common in severely immune-suppressed people with HIV infection and those who have progressed to AIDS [100]. The microscopic appearance of the gut in HIV infection is similar to that in EED, especially during late-stage illness. The HIV virus itself may cause direct damage to intestinal epithelium, while also permitting injury by other gut pathogens by weakening host defenses against them. This resultant enteropathy may itself drive HIV disease progression.

### **Which treatments have already been tried?**

**Table 1** summarizes selected published trials conducted among children in low- and middle-income country settings where EED has been explicitly targeted. The trials described therein have suggested beneficial effects of zinc, vitamin A, n-3 LC-PUFA, and alanyl-glutamine on L:M ratios. Ongoing studies are now building on these results.

### **How should our present knowledge of EED affect our practice today?**

Testing for EED in a therapeutic context, as part of routine management of moderate acute malnutrition (MAM), severe acute malnutrition (SAM), or stunting, is not presently indicated, since its etiology remains unclear and evidence for benefit from targeted treatments is lacking.

The significant impact of poor WASH on the general health of children is already well established, and there is already evidence that WASH interventions can reduce infectious morbidity and mortality in low- and middle-income country settings [101, 102]. A holistic approach to nutritional rehabilitation that includes attention to minimizing feco-oral contamination in the home or hospital environment should therefore already be prioritized. However, our emerging understanding of the possible benefits of these interventions, perhaps mediated via EED, on nutritional and immune status may further enhance the scale and types of WASH approaches undertaken. As new, noninvasive, cheap,

and quick biomarkers of EED and evidence for setting-specific etiology and effective treatments emerge, more specific recommendations will follow.

### **Current research, future priorities**

There are several ongoing randomized trials of interventions to prevent or treat EED (**table 2**). Research on EED is a rapidly expanding field. Questions requiring further work include:

- » What are the important causes of EED? Is it predominantly due to a specific pathogen, nutritional deficiency, or genetic predisposition?
- » How can we diagnose EED using a point-of-use test?
- » How prevalent is EED in different settings worldwide?
- » What is the impact of EED on child health? How are these effects mediated?
- » How can we best prevent EED?
- » Once EED is established, is there any role for providing direct (e.g., immunomodulatory) treatment for EED?

Further detailed longitudinal observational studies of EED are needed in varied demographic and geographic settings, focusing on the hypothesized period of establishment of EED (infancy). One ongoing example is the Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development (MAL-ED) network: coordinated birth cohorts in Peru, Brazil, Bangladesh, India, Pakistan, Nepal, Tanzania, and South Africa [103]. In addition to repeated measurement of L:M ratios, gut pathogens, and growth, enteral vaccine immunogenicity is being studied within this network.

EED transcends traditional discipline boundaries, so its study requires collaboration among pediatricians, immunologists, gastroenterologists, epidemiologists, water and sanitation experts, nutritionists, and others. The fact that positive findings have been observed in studies investigating a wide range of causes for EED (both nutritional and infective) suggests that EED is likely to be multifactorial in nature and therefore probably not amenable to one single therapy. Understanding this complexity will be crucial to addressing the significant public health issues of childhood malnutrition and susceptibility to infection in low- and middle-income country settings.

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TABLE 2. Ongoing randomized trials of interventions to prevent or treat EED<sup>a</sup>

Trial name and design	Setting	Age group	Intervention and duration	Outcomes
Mesalazine in Environmental Enteropathy; double-blind, placebo-controlled, randomized trial	Kenya; urban	1–5 yr (SAM and stunting)	Mesalazine 28 days	Safety, growth, EED biomarkers
WASH Benefits Bangladesh; factorial cluster-randomized trial	Bangladesh; urban	Birth–2 yr	Nutrition and WASH interventions	L:M, growth, diarrhea, neurological development
WASH Benefits Kenya; factorial cluster-randomized trial	Kenya; rural	Birth–2 yr	Nutrition and WASH interventions	Above plus fecal neopterin, $\alpha$ -1-antitrypsin, myeloperoxidase
Sanitation, Hygiene, Infant Nutrition Efficacy Project; factorial cluster-randomized trial	Zimbabwe; rural	Birth–18 mo (plus mothers)	Infant nutrition and household WASH interventions	L:M, growth, fecal neopterin, EndoCAB, sCD14, immune activation markers, IGF-1, IGF-1:IGFBP3
Effectiveness of Micronutrient Supplementation and Fish Oil + Micronutrient Supplementation in the Treatment of Environmental Enteropathy; factorial double-blind, placebo-controlled, randomized trial	Malawi; rural	1–3 yr	Multiple micronutrients and highly purified fish oil 6 mo	L:M, growth, fecal human mRNA
n-3 LC-PUFAs for the Healthy Growth and Development of Infants and Young Children in South-west Ethiopia; factorial double-blind, placebo-controlled, randomized trial	Ethiopia; rural	6–12 mo (plus breastfeeding mothers)	n-3 LC-PUFA 12 mo	Growth, neurological development
Zinc Resistant Starch Project; single-arm, open label	Malawi; rural	3–5 yr	Resistant starch 28 days	L:M, growth, markers of zinc homeostasis
Intervention and Mechanisms of Alanyl-Glutamine for Inflammation, Nutrition and Enteropathy; factorial double-blind, placebo-controlled, randomized trial	Brazil; urban	2 mo–5 yr	Alanyl-glutamine 10 days	L:M, growth, fecal lactoferrin, fecal cytokines, diarrhea, markers of alanyl-glutamine metabolism

EED, environmental enteric dysfunction; LC-PUFA, long-chain polyunsaturated fatty acid; L:M, lactulose:mannitol; SAM, severe acute malnutrition; WASH, water, sanitation, and hygiene

a. Trials were ongoing as of June 2014.

## References

1. Cook GC, Kajubi SK, Lee FD. Jejunal morphology of the African in Uganda. *J Pathol* 1969;98:157–69.
2. Sullivan PB, Lunn PG, Northrop-Clewes C, Crowe PT, Marsh MN, Neale G. Persistent diarrhea and malnutrition—the impact of treatment on small bowel structure and permeability. *J Pediatr Gastroenterol Nutr* 1992;14:208–15.
3. Sullivan PB, Marsh MN, Mirakian R, Hill SM, Milla PJ, Neale G. Chronic diarrhea and malnutrition—histology of the small intestinal lesion. *J Pediatr Gastroenterol Nutr* 1991;12:195–203.
4. Kelly P, Menzies I, Crane R, Zulu I, Nickols C, Feakins R, Mwansa J, Mudenda V, Katubulushi M, Greenwald S, Farthing M. Responses of small intestinal architecture and function over time to environmental factors in a tropical population. *Am J Trop Med Hyg* 2004;70:412–9.
5. Campbell DI, Murch SH, Elia M, Sullivan PB, Sanyang MS, Jobarteh B, Lunn PG. Chronic T cell-mediated enteropathy in rural west African children: relationship with nutritional status and small bowel function. *Am J Trop Med Hyg* 2003;54:306–11.
6. Baker SJ, Mathan VI. Tropical enteropathy and tropical sprue. *Am J Clin Nutr* 1972;25:1047–55.
7. Korpe PS, Petri WA Jr. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med* 2012;18:328–36.
8. Goto K, Chew F, Torun B, Peerson JM, Brown KH. Epidemiology of altered intestinal permeability to lactulose and mannitol in Guatemalan infants. *J Pediatr Gastroenterol Nutr* 1999;28:282–90.
9. Goto R, Panter-Brick C, Northrop-Clewes CA, Manahdhar R, Tuladhar NR. Poor intestinal permeability in mildly stunted Nepali children: associations with weaning practices and Giardia lamblia infection. *Br J Nutr* 2002;88:141–9.
10. Weisz AJ, Manary MJ, Stephenson K, Agapova S, Manary FG, Thakwalakwa C, Shulman RJ, Manary MJ. Abnormal gut integrity is associated with reduced linear growth in rural Malawian children. *J Pediatr Gastroenterol Nutr* 2012;55:747–50.
11. Lin A, Arnold BF, Afreen S, Goto R, Huda TM, Haque R, Raqib R, Unicomb L, Ahmed T, Colford JM Jr, Luby SP. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. *Am J Trop Med Hyg* 2013;89:130–7.
12. Campbell DI, Elia M, Lunn PG. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. *J Nutr* 2003;133:1332–8.
13. Dewey KG, Adu-Afaruwah S. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Matern Child Nutr* 2008;4 Suppl 1:24–85.
14. Humphrey JH. Child undernutrition, tropical enteropathy, toilets, and handwashing. *Lancet* 2009;374:1032–5.
15. Garcia SE, Kaiser LL, Dewey KG. Self-regulation of food intake among rural Mexican preschool children. *Eur J Clin Nutr* 1990;44:371–80.
16. Sanderson IR. Growth problems in children with IBD. *Nat Rev Gastroenterol Hepatol* 2014.
17. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009;6:513–23.
18. Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntozini R, Mbuya MN, Jones A, Moulton LH, Stoltzfus RJ, Humphrey JH. Stunting is characterized by chronic inflammation in Zimbabwean infants. *PLoS One* 2014;9:e86928.
19. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J; Maternal Child Undernutrition Study Group. G. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;371:243–60.
20. Victora CG, de Onis M, Hallal PC, Blossner M, Shrimpton R. Worldwide timing of growth faltering: revisiting implications for interventions. *Pediatrics* 2010;125:e473–80.
21. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. *Lancet* 2007;369:60–70.
22. DeBoer MD, Lima AA, Oria RB, Scharf RJ, Moore SR, Luna MA, Guerrant RL. Early childhood growth failure and the developmental origins of adult disease: do enteric infections and malnutrition increase risk for the metabolic syndrome? *Nutr Rev* 2012;70:642–53.
23. Spencer SP, Wilhelm C, Yang Q, Hall JA, Bouladoux N, Boyd A, Nutman TB, Urban JF Jr., Wang J, Ramalingam TR, Bhandoola A, Wynn TA, Belkaid Y. Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. *Science* 2014; 343:432–7.
24. Bartelt LA, Roche J, Kolling G, Bolick D, Noronha F, Naylor C, Hoffman P, Warren C, Singer S, Guerrant R. Persistent G. lamblia impairs growth in a murine malnutrition model. *J Clin Invest* 2013;123:2672–84.
25. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* 2011;474:298–306.
26. Guerrant RL, Oria RB, Moore SR, Oria MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutr Rev* 2008; 66:487–505.
27. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. *Rev Infect Dis* 1991;13:926–39.
28. Soares-Weiser K, Maclellan H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev (Online)* 2012;11:CD008521.
29. Lunn PG. The impact of infection and nutrition on gut function and growth in childhood. *Proc Nutr Soc* 2000;59:147–54.
30. Hossain MI, Nahar B, Hamadani JD, Ahmed T, Roy AK, Brown KH. Intestinal mucosal permeability of severely underweight and nonmalnourished Bangladeshi children and effects of nutritional rehabilitation. *J Pediatr Gastroenterol Nutr* 2010;51:638–44.
31. van der Merwe LF, Moore SE, Fulford AJ, Halliday KE, Drammeh S, Young S, Prentice AM. Long-chain PUFA supplementation in rural African infants: a randomized controlled trial of effects on gut integrity, growth, and

- cognitive development. *Am J Clin Nutr* 2013;97:45–57.
32. Savino F, Castagno E, Calabrese R, Viola S, Oggero R, Miniero R. High faecal calprotectin levels in healthy, exclusively breast-fed infants. *Neonatology* 2010; 97:299–304.
33. Hestvik E, Tumwine JK, Tylleskar T, Grahnquist L, Ndeezi G, Kaddu-Mulindwa DH, Aksnes L, Olafsdottir E. Faecal calprotectin concentrations in apparently healthy children aged 0–12 years in urban Kampala, Uganda: a community-based survey. *BMC Pediatr* 2011;11:9.
34. Fundaro C, Fantacci C, Ansuini V, Giorgio V, Filoni S, Barbaro F, Gasbarrini A, Rossi C. Fecal calprotectin concentration in children affected by SIBO. *Eur Rev Med Pharmacol Sci* 2011;15:1328–35.
35. Kosek M, Haque R, Lima A, Babji S, Shrestha S, Qureshi S, Amidou S, Mdou E, Lee G, Yori PP, Guerrant RL, Bhutta Z, Mason C, Kang G, Kabir M, Amour C, Bessong P, Turab A, Seidman J, Olortegui MP, Quetz J, Lang D, Gratz J, Miller M, Gottlieb M. Fecal markers of intestinal inflammation and permeability associated with the subsequent acquisition of linear growth deficits in infants. *Am J Trop Med Hyg* 2013;88:390–6.
36. Agapova S, Stephenson K, Manary M, Weisz A, Tarr PI, Mkakosya R, Maleta K, Shulman RJ, Manary M, Shaikh N. Detection of low-concentration host mRNA transcripts in Malawian children at risk for environmental enteropathy. *J Pediatr Gastroenterol Nutr* 2013;56:66–71.
37. Peterson KM, Buss J, Easley R, Yang Z, Korpe PS, Niu F, Ma JZ, Olortegui MP, Haque R, Kosek MN, Petri WA Jr. REG1B as a predictor of childhood stunting in Bangladesh and Peru. *Am J Clin Nutr* 2013;97:1129–33.
38. Steiner TS, Lima AA, Nataro JP, Guerrant RL. Enteroregative *Escherichia coli* produce intestinal inflammation and growth impairment and cause interleukin-8 release from intestinal epithelial cells. *J Infect Dis* 1998; 177:88–96.
39. Mondal D, Minak J, Alam M, Liu Y, Dai J, Korpe P, Liu L, Haque R, Petri WA Jr. Contribution of enteric infection, altered intestinal barrier function, and maternal malnutrition to infant malnutrition in Bangladesh. *Clin Infect Dis* 2012;54:185–92.
40. Wessells KR, Hess SY, Rouamba N, Ouedraogo ZP, Kellogg M, Goto R, Duggan C, Ouedraogo JB, Brown KH. Associations between intestinal mucosal function and changes in plasma zinc concentration following zinc supplementation. *J Pediatr Gastroenterol Nutr* 2013;57:348–55.
41. Lindenbaum J, Gerson CD, Kent TH. Recovery of small-intestinal structure and function after residence in the tropics. I. Studies in Peace Corps volunteers. *Ann Intern Med* 1971;74:218–22.
42. Lunn PG, Northrop-Clewes CA, Downes RM. Intestinal permeability, mucosal injury, and growth faltering in Gambian infants. *Lancet* 1991;338:907–10.
43. Campbell DI, McPhail G, Lunn PG, Elia M, Jeffries DJ. Intestinal inflammation measured by fecal neopterin in Gambian children with enteropathy: association with growth failure, *Giardia lamblia*, and intestinal permeability. *J Pediatr Gastroenterol Nutr* 2004;39:153–7.
44. Campbell DI, Lunn PG, Elia M. Age-related association of small intestinal mucosal enteropathy with nutritional status in rural Gambian children. *Br J Nutr* 2002;88:499–505.
45. Goto R, Mascie-Taylor CG, Lunn PG. Impact of intestinal permeability, inflammation status and parasitic infections on infant growth faltering in rural Bangladesh. *Br J Nutr* 2009;101:1509–16.
46. Mullen A, Gosset L, Larke N, Manno D, Chisenga M, Kasonka L, Filteau S. The effects of micronutrient-fortified complementary/replacement food on intestinal permeability and systemic markers of inflammation among maternally HIV-exposed and unexposed Zambian infants. *Br J Nutr* 2012;107:893–902.
47. Ryan KN, Stephenson KB, Trehan I, Shulman RJ, Thakwalakwa C, Murray E, Maleta K, Manary MJ. Zinc or albendazole attenuates the progression of environmental enteropathy: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2014.
48. Roy SK, Behrens RH, Haider R, Akramuzzaman SM, Mahalanabis D, Wahed MA, Tomkins AM. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *J Pediatr Gastroenterol Nutr* 1992;15:289–96.
49. Thurnham DI, Northrop-Clewes CA, McCullough FS, Das BS, Lunn PG. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. *J Infect Dis* 2000;182 Suppl 1:S23–8.
50. Chen P, Soares AM, Lima AA, Gamble MV, Schorling JB, Conway M, Barrett LJ, Blarer WS, Guerrant RL. Association of vitamin A and zinc status with altered intestinal permeability: analyses of cohort data from northeastern Brazil. *J Health Popul Nutr* 2003;21:309–15.
51. Lima NL, Soares AM, Mota RM, Monteiro HS, Guerrant RL, Lima AA. Wasting and intestinal barrier function in children taking alanyl-glutamine-supplemented enteral formula. *J Pediatr Gastroenterol Nutr* 2007;44:365–74.
52. Lima AA, Soares AM, Lima NL, Mota RM, Maciel BL, Kvalsund MP, Barrett LJ, Fitzgerald RP, Blarer WS, Guerrant RL. Effects of vitamin A supplementation on intestinal barrier function, growth, total parasitic, and specific *Giardia* spp infections in Brazilian children: a prospective randomized, double-blind, placebo-controlled trial. *J Pediatr Gastroenterol Nutr* 2010;50:309–15.
53. Manary MJ, Abrams S, Griffin IJ, Quimper MM, Shulman RJ, Hamzo MG, Chen Z, Maleta K, Manary MJ. Perturbed zinc homeostasis in rural 3–5-y-old Malawian children is associated with abnormalities in intestinal permeability attributed to tropical enteropathy. *Pediatr Res* 2010;67:671–5.
54. Lunn PG, Erinoso HO, Northrop-Clewes CA, Boyce SA. *Giardia intestinalis* is unlikely to be a major cause of the poor growth of rural Gambian infants. *J Nutr* 1999;129:872–7.
55. Goto R, Mascie-Taylor CG, Lunn PG. Impact of anti-*Giardia* and anthelmintic treatment on infant growth and intestinal permeability in rural Bangladesh: a randomised double-blind controlled study. *Trans R Soc Trop Med Hyg* 2009;103:520–9.
56. Kukuruzovic RH, Brewster DR. Small bowel intestinal permeability in Australian Aboriginal children. *J Pediatr Gastroenterol Nutr* 2002;35:206–12.
57. Behrens RH, Lunn PG, Northrop CA, Hanlon PW, Neale G. Factors affecting the integrity of the intestinal mucosa of Gambian children. *Am J Clin Nutr* 1987;45:1433–41.

58. Menzies IS, Zuckerman MJ, Nukajam WS, Somasundaram SG, Murphy B, Jenkins AP, Crane RS, Gregory GG. Geography of intestinal permeability and absorption. *Gut* 1999;44:483–9.
59. Imdad A, Bhutta ZA. Effect of preventive zinc supplementation on linear growth in children under 5 years of age in developing countries: a meta-analysis of studies for input to the lives saved tool. *BMC Public Health* 2011;11 Suppl 3:S22.
60. Radhakrishna KV, Hemalatha R, Geddam JJ, Kumar PA, Balakrishna N, Shatrugna V. Effectiveness of zinc supplementation to full term normal infants: a community based double blind, randomized, controlled, clinical trial. *PloS One* 2013;8:e61486.
61. Louis-Auguste J, Greenwald S, Simuyandi M, Soko R, Banda R, Kelly P. High dose multiple micronutrient supplementation improves villous morphology in environmental enteropathy without HIV enteropathy: results from a double-blind randomised placebo controlled trial in Zambian adults. *BMC Gastroenterol* 2014;14:15.
62. McKay S, Gaudier E, Campbell DI, Prentice AM, Albers R. Environmental enteropathy: new targets for nutritional interventions. *Int Health* 2010;2:172–80.
63. Galpin L, Manary MJ, Fleming K, Ou CN, Ashorn P, Shulman RJ. Effect of *Lactobacillus* GG on intestinal integrity in Malawian children at risk of tropical enteropathy. *Am J Clin Nutr* 2005;82:1040–5.
64. Trehan I, Shulman RJ, Ou CN, Maleta K, Manary MJ. A randomized, double-blind, placebo-controlled trial of rifaximin, a nonabsorbable antibiotic, in the treatment of tropical enteropathy. *Am J Gastroenterol* 2009;104:2326–33.
65. Dangour AD, Watson L, Cumming O, Boisson S, Che Y, Velleman Y, Cavill S, Allen E, Uauy R. Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children. *Cochrane Database Syst Rev* (Online) 2013;8:CD009382.
66. Ngure FM, Humphrey JH, Mbuya MN, Majo F, Mutasa K, Govha M, Mazarura E, Chaseskwa B, Prendergast AJ, Curtis V, Boor KJ, Stoltzfus RJ. Formative research on hygiene behaviors and geophagy among infants and young children and implications of exposure to fecal bacteria. *Am J Trop Med Hyg* 2013;89:709–16.
67. Arnold BF, Null C, Luby SP, Unicomb L, Stewart CP, Dewey KG, Ahmed T, Ashraf S, Christensen G, Clasen T, Dentz HN, Fernald LC, Haque R, Hubbard AE, Kariger P, Leontsini E, Lin A, Njenga SM, Pickering AJ, Ram PK, Tofail F, Winch PJ, Colford JM Jr. Cluster-randomised controlled trials of individual and combined water, sanitation, hygiene and nutritional interventions in rural Bangladesh and Kenya: the WASH Benefits study design and rationale. *BMJ Open* 2013;3:e003476.
68. ClinicalTrials.gov. SHINE Sanitation, Hygiene, Infant Nutrition Efficacy Project. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT01824940?term=shine&rank=3> Accessed July 2014.
69. ClinicalTrials.gov. Cluster randomised trial of improved sanitation in rural Orissa, India. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT01214785?term=orissa&rank=2> Accessed July 2014.
70. Gough EK, Moodie EE, Prendergast AJ, Johnson SM, Humphrey JH, Stoltzfus RJ, Walker AS, Trehan I, Gibb DM, Goto R, Tahan S, de Moraes MB, Manges AR. The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g2267.
71. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* (Online) 2012;8:CD003517.
72. Motarjemi Y, Kaferstein F, Moy G, Quevedo F. Contaminated weaning food: a major risk factor for diarrhoea and associated malnutrition. *Bull World Health Organ* 1993;71:79–92.
73. Checkley W, Epstein LD, Gilman RH, Black RE, Cabrera L, Sterling CR. Effects of *Cryptosporidium parvum* infection in Peruvian children: growth faltering and subsequent catch-up growth. *Am J Epidemiol* 1998;148:497–506.
74. Mondal D, Petri WA Jr., Sack RB, Kirkpatrick BD, Haque R. *Entamoeba histolytica*-associated diarrheal illness is negatively associated with the growth of preschool children: evidence from a prospective study. *Trans R Soc Trop Med Hyg* 2006;100:1032–8.
75. Hlaing T. Ascariasis and childhood malnutrition. *Parasitology* 1993;107 Suppl:S125–36.
76. Lunn PG, Northrop-Clewes CA. The impact of gastrointestinal parasites on protein-energy malnutrition in man. *Proc Nutr Soc* 1993;52:101–11.
77. Opintan JA, Newman MJ, Ayeh-Kumi PF, Affrim R, Gepi-Attee R, Sevilleja JE, Roche JK, Nataro JP, Warren CA, Guerrant RL. Pediatric diarrhea in southern Ghana: etiology and association with intestinal inflammation and malnutrition. *Am J Trop Med Hyg* 2010;83:936–43.
78. Zhang Y, Lee B, Thompson M, Glass R, Cama RI, Figueroa D, Gilman R, Taylor D, Stephenson C. Lactulose-mannitol intestinal permeability test in children with diarrhea caused by rotavirus and cryptosporidium. Diarrhea Working Group, Peru. *J Pediatr Gastroenterol Nutr* 2000;31:16–21.
79. Grzeskowiak L, Collado MC, Mangani C, Maleta K, Laitinen K, Ashorn P, Isolauri E, Salminen S. Distinct gut microbiota in southeastern African and northern European infants. *J Pediatr Gastroenterol Nutr* 2012;54:812–6.
80. Monira S, Nakamura S, Gotoh K, Izutsu K, Watanabe H, Alam NH, Endtz HP, Cravioto A, Ali SI, Nakaya T, Horii T, Iida T, Alam M. Gut microbiota of healthy and malnourished children in Bangladesh. *Front Microbiol* 2011;2:228.
81. Subramanian S, Huq S, Yatsunencko T, Haque R, Mahfuz M, Alam MA, Benezra A, DeStefano J, Meier MF, Muegge BD, Barratt MJ, VanArendonk LG, Zhang Q, Province MA, Petri Jr WA, Ahmed T, Gordon JI. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature* 2014;510:417–21.
82. Smith MI, Yatsunencko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, Kau AL, Rich SS, Concannon P, Mychaleckyj JC, Liu J, Houghton E, Li JV, Holmes E, Nicholson J, Knights D, Ursell LK, Knight R, Gordon JI. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science* 2013;339:548–54.
83. Windle HJ, Kelleher D, Crabtree JE. Childhood *Helicobacter pylori* infection and growth impairment in developing countries: a vicious cycle? *Pediatrics* 2007;119:e754–9.

84. Sullivan PB, Thomas JE, Wight DG, Neale G, Eastham EJ, Corrah T, Lloyd-Evans N, Greenwood BM. Helicobacter pylori in Gambian children with chronic diarrhoea and malnutrition. *Arch Dis Child* 1990;65:189–91.
85. Dale A, Thomas JE, Darboe MK, Coward WA, Harding M, Weaver LT. Helicobacter pylori infection, gastric acid secretion, and infant growth. *J Pediatr Gastroenterol Nutr* 1998;26:393–7.
86. Thomas JE, Dale A, Bunn JE, Harding M, Coward WA, Cole TJ, Weaver LT. Early Helicobacter pylori colonisation: the association with growth faltering in The Gambia. *Arch Dis Child* 2004;89:1149–54.
87. Passaro DJ, Taylor DN, Meza R, Cabrera L, Gilman RH, Parsonnet J. Acute Helicobacter pylori infection is followed by an increase in diarrheal disease among Peruvian children. *Pediatrics* 2001;108:E87.
88. Bures J, Cyrany J, Kohoutova D, Forstl M, Rejchrt S, Kvetina J, Vorisek V, Kopacova M. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010;16:2978–90.
89. Gorbach SL, Banwell JG, Jacobs B, Chatterjee BD, Mitra R, Mazumder DN, Sen NN. Tropical sprue and malnutrition in West Bengal. I. Intestinal microflora and absorption. *Am J Clin Nutr* 1970;23:1545–58.
90. Heyworth B, Brown J. Jejunal microflora in malnourished Gambian children. *Arch Dis Child* 1975;50:27–33.
91. Omoike IU, Abiodun PO. Upper small intestinal microflora in diarrhea and malnutrition in Nigerian children. *J Pediatr Gastroenterol Nutr* 1989;9:314–21.
92. Rowland MG, Cole TJ, McCollum JP. Weanling diarrhoea in The Gambia: implications of a jejunal intubation study. *Trans R Soc Trop Med Hyg* 1981;75:215–8.
93. Eisenmann A, Amann A, Said M, Datta B, Ledochowski M. Implementation and interpretation of hydrogen breath tests. *J Breath Res* 2008;2:046002.
94. Fagundes Neto U, Martins MC, Lima FL, Patricio FR, Toledo MR. Asymptomatic environmental enteropathy among slum-dwelling infants. *J Am Coll Nutr* 1994;13:51–6.
95. dos Reis JC, de Moraes MB, Oliva CA, Fagundes-Neto U. Breath hydrogen test in the diagnosis of environmental enteropathy in children living in an urban slum. *Dig Dis Sci* 2007;52:1253–8.
96. Khin Maung U, Bolin TD, Duncombe VM, Myo K, Nyunt Nyunt W, Pereira SP, Linklater JM. Epidemiology of small bowel bacterial overgrowth and rice carbohydrate malabsorption in Burmese (Myanmar) village children. *Am J Trop Med Hyg* 1992;47:298–304.
97. Lagos R, Fasano A, Wasserman SS, Prado V, San Martin O, Abrego P, Losonsky GA, Alegria S, Levine MM. Effect of small bowel bacterial overgrowth on the immunogenicity of single-dose live oral cholera vaccine CVD 103-HgR. *J Infect Dis* 1999;180:1709–12.
98. Tahan S, Melli LC, Mello CS, Rodrigues MS, Bezerra Filho H, de Moraes MB. Effectiveness of trimethoprim-sulfamethoxazole and metronidazole in the treatment of small intestinal bacterial overgrowth in children living in a slum. *J Pediatr Gastroenterol Nutr* 2013;57:316–8.
99. Heikens GT, Schofield WN, Dawson S. The Kingston Project. II. The effects of high energy supplement and metronidazole on malnourished children rehabilitated in the community: anthropometry. *Eur J Clin Nutr* 1993;47:160–73.
100. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg* 2012;86:756–63.
101. Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2005;5:42–52.
102. Cairncross S, Hunt C, Boisson S, Bostoen K, Curtis V, Fung IC, Schmidt WP. Water, sanitation and hygiene for the prevention of diarrhoea. *Int J Epidemiol* 2010;39 Suppl 1:i193–205.
103. Lang D. The MAL-ED Project: Deciphering the relationships among normal gut flora, enteric infection and malnutrition and their association with immune response to vaccines; 2010. Available at: [http://www.old-herborn-university.de/literature/books/OHUni\\_book\\_24\\_article\\_7.pdf](http://www.old-herborn-university.de/literature/books/OHUni_book_24_article_7.pdf).

## Further reading

### General reviews

- Korpe PS, Petri WA. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med* 2012;18:328–36.
- Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg* 2012;86:756–63.

### Malnutrition and enteric infections

- Lunn PG. The impact of infection and nutrition on gut function and growth in childhood. *Proc Nutr Soc* 2000; 59:147–54.
- Guerrant RL, Oria RB, Moore SR, Oria MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutr Rev* 2008;66:487–505.

### EED and nutrition

- McKay S, Gaudier E, Campbell DI, Prentice AM, Albers R. Environmental enteropathy: new targets for nutritional interventions. *Int Health* 2010;2:172–80.
- Lindenmayer GW, Stoltzfus RJ, Prendergast AJ. Interactions between zinc deficiency and environmental enteropathy in developing countries. *Adv Nutr* 2014;5:1–6.

### EED and WASH

- Humphrey JH. Child undernutrition, tropical enteropathy, toilets, and handwashing. *Lancet* 2009;374:1032–5.
- Ngure FM, Reid BM, Humphrey JH, Mbuya MN, Pelto G, Stoltzfus RJ. Water, sanitation, and hygiene (WASH), environmental enteropathy, nutrition, and early child development: making the links. *Ann NY Acad Sci* 2014;1308:118–28.

**EED and fungal toxins**

Smith LE, Stoltzfus RJ, Prendergast A. Food chain mycotoxin exposure, gut health, and impaired growth: a conceptual framework. *Adv Nutr* 2012;3:526–31.

***Helicobacter pylori***

Windle HJ, Kelleher D, Crabtree JE. Childhood *Helicobacter pylori* infection and growth impairment in developing countries: a vicious cycle? *Pediatrics* 2007;119:754–9.

**Small intestinal bacterial overgrowth (SIBO)**

Bures J, Cyrany J, Kohoutova D, Forstl M, Rejchrt S, Kvetina J, Vorisek V, Kopacova M. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010;16:2978–90.

**Gut microbiome**

Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. *Nature* 2011;474:327–36.