



# CMAM Forum

Collaborating to improve the management of acute malnutrition worldwide

## Environmental Enteric Dysfunction – an Overview

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## Abbreviations

|                |                                       |
|----------------|---------------------------------------|
| <b>EED</b>     | Environmental Enteric Dysfunction     |
| <b>ELISA</b>   | Enzyme Linked Immunosorbent Assay     |
| <b>GDP</b>     | Gross Domestic Product                |
| <b>L : M</b>   | Lactulose : Mannitol (test)           |
| <b>LC-PUFA</b> | Long Chain Polyunsaturated Fatty Acid |
| <b>LMIC</b>    | Low and Middle Income Countries       |
| <b>mRNA</b>    | Messenger Ribonucleic Acid            |
| <b>PCR</b>     | Polymerase Chain Reaction             |
| <b>SIBO</b>    | Small Intestinal Bacterial Overgrowth |
| <b>WASH</b>    | Water, Sanitation and Hygiene         |

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# 1 Scope

This Technical Brief aims to provide a general audience with an up-to-date and accessible overview on Environmental Enteric Dysfunction and its relevance to child health. It is aimed at practitioners, policymakers and other stakeholders involved and interested in the reduction of childhood undernutrition, and also those involved in general child health in low- and middle-income countries (LMICs).

## 2 Introduction

Environmental Enteric Dysfunction (EED) refers to an incompletely defined syndrome of mucosal and submucosal inflammation, reduced intestinal absorptive capacity and reduced barrier function, which is widespread in LMICs. EED occurs in adults and children. It is usually asymptomatic, but is important due to its association with undernutrition. It has been hypothesised that EED may also have a role in the reduced efficacy of orally administered vaccines such as polio and rotavirus in LMICs, and the increased risk of serious infection seen in children with varying types and degrees of undernutrition. However, despite its potentially crucial impact on child health and development it is currently unclear exactly what causes EED and how it can be treated or prevented.

## 3 Defining EED

### 3.1 Terminology

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 LMICs.<sup>1</sup> It was observed that villi (microscopic protrusions on the small intestinal wall that absorb nutrients) 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 quality of 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 as ‘Environmental Enteric Dysfunction’.

### 3.2 Case definition

There is no universally accepted case definition or specific diagnostic criteria for EED and it is thought not to have immediately apparent symptoms. Importantly, diarrhoea is not a necessary component. The key demonstrable abnormal features (on microscopic examination of the small intestinal lining: villous flattening, crypt hyperplasia and lymphocytic infiltration of lamina propria<sup>\*2-5</sup>) are not unique to EED.

### 3.3 Similar conditions

Tropical sprue (a syndrome of chronic diarrhoea, malabsorption and malnutrition seen in residents of tropical countries) and EED were initially thought to be the same process, with symptomatic tropical sprue the ‘tip of the iceberg’ of pathology largely represented by EED, but this distinction remains unclear.<sup>6</sup> There are also some similarities with other chronic gut inflammatory conditions like coeliac disease and inflammatory bowel disease (Crohn’s disease and ulcerative colitis).<sup>7</sup>

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\* = Histology (microscopic) findings in EED: flattening of villi, enlargement of indentations found between villi, and infiltration of layers of the small intestinal lining by white blood (immune) cells.

## 4 Impact of EED on health and nutrition

### 4.1 Impact on nutrition and development

Childhood EED has been associated with chronic undernutrition (manifesting as stunting) for as long as it has been a recognised entity, although it is not entirely clear which of these two is the primary instigator and which the consequence. There are many ways, other than malabsorption, in which chronic intestinal inflammation could impact on growth. One proposed mechanism is appetite suppression, since this is often a key factor restricting children's food intake.<sup>8</sup> Another is growth hormone signalling. For example, in paediatric Crohn's disease, growth failure is linked to an imbalance in growth hormone (GH) and insulin-like growth factor 1 (IGF-1) brought about by chronic intestinal inflammation.<sup>9</sup> A similar situation may occur in EED: indeed lower levels of IGF-1 are associated with higher blood inflammatory markers in Zimbabwean infants.<sup>10</sup>

EED has been observed alongside stunting in The Gambia, Guatemala, Nepal, Bangladesh and Malawi.<sup>11-15</sup> A 2008 systematic review of effectiveness of existing complementary feeding interventions for malnutrition amongst 6-24 month-olds suggested only moderate benefits, and that EED may be a key factor limiting effectiveness.<sup>16</sup> Nutritional intervention alone may not be fully addressing the problem of stunting amongst infants and children in LMIC settings – with EED possibly explaining this shortfall.<sup>17</sup>

Malnutrition has devastating consequences for child health. Undernutrition (foetal growth restriction, stunting, wasting, micronutrient deficiency and insufficient breastfeeding) is estimated to be responsible for 45% of deaths in under-fives worldwide.<sup>18</sup> Severe wasting is associated with an almost nine-fold increase in odds of death.<sup>19</sup> Stunting – difficult to reverse beyond two years of age – has long-lasting effects on health and development.<sup>20,21</sup> A meta-analysis in 2007 suggested that each year 200 million children do not reach their developmental potential due to stunting.<sup>22</sup> Certain non-communicable diseases in adulthood are associated with stunting in childhood, perhaps through epigenetic regulation (which refers to long-term alteration in gene expression) or chronic inflammation.<sup>23</sup>

### 4.2 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, preventing them from entering the body, while at the same time avoiding unhelpful immune responses against foods, the microbiota (see section 7.2.3.), 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 it is, for example, in Crohn's disease) and may impair anti-pathogen surveillance capacity. Despite the fact that this process may be very important in EED pathogenesis, it 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 to our understanding of mucosal immunity coming from work with mouse models of human disease, and it is possible that approaches utilising model animal systems will further our understanding of EED and even guide clinical and public health management in the future.<sup>24-26</sup>

### 4.3 Impact on oral vaccine response

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 LMICs.<sup>7,27-29</sup> Small intestinal bacterial overgrowth (SIBO), itself perhaps associated with EED (see section 7.2.5), has also been implicated in enteral vaccine failure. A study of 5-9 year-olds in Chile showed association between abnormally high breath hydrogen (a marker of abnormal bacterial presence in the small intestine that could be linked to EED – see section 7.2.5) and decreased antibody responses to oral cholera vaccine.<sup>30</sup>

## 5 Diagnosis: how do we identify the child with EED?

To confirm the diagnosis of EED beyond doubt requires demonstration of the features of EED described in section 3.2, which can only be done via endoscopy and small intestinal biopsy. The inherent risks of this procedure cannot be justified for screening for this common condition at a population level or in the context of epidemiological studies. Instead, less invasive tests that measure proxy biomarkers are used to quantify gut inflammation and reduced barrier function.

### 5.1 The dual sugar absorption test

To date, the most frequently used test for EED is the dual sugar absorption test. 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 absorbed by the small intestine in proportion to absorptive surface area. Both lactulose and mannitol are excreted intact in urine following minimal metabolism. Urinary mannitol therefore gives an index of absorptive function (the more mannitol present in urine, the more efficiently it has been absorbed in the intestine). Lactulose should not be absorbed, and if it is present in urine, this indicates impaired barrier function. In the L:M test, a standardised solution of lactulose and mannitol is administered orally and all urine produced over the next two or five hours collected. The amounts of lactulose and mannitol in urine are normally expressed as a ratio (lactulose divided by mannitol) with higher ratios meaning greater abnormality. An L:M ratio of above 0.07-0.12 is usually considered indicative of EED,<sup>11,31,32</sup> although the exact number is often more informative.

L:M tests in EED studies of children were first carried out in the late 1980s in The Gambia, where the variation in L:M ratio was associated with almost half of the stunting observed.<sup>33,34</sup> Since then, L:M testing has revealed high prevalence of EED amongst infants and children in many LMIC settings including Zambia, Malawi, Bangladesh, India, Nepal, Brazil and Guatemala and amongst Aboriginal communities in Australia.<sup>5,11-15,32,35-50</sup>

The L:M test requires cooperation and understanding from the participant which may present a challenge when performing the test in very young children. Ensuring complete collection of all urine voided over up to five hours is difficult in infants and requires parental patience. Urine bags often do not adhere sufficiently and can become contaminated with faeces, rendering the test void. Measurement of lactulose and mannitol in urine is measured by Enzyme Linked Immunosorbent Assay (ELISA), anion exchange chromatography or mass spectrometry. All of these methods require centralised laboratory equipment and expertise, and results are not always comparable between laboratories.

### 5.2 Emerging biomarkers

New biomarkers of EED are being actively investigated. These include markers of gut inflammation (calprotectin,<sup>45,51-53</sup> myeloperoxidase, neopterin,  $\alpha$ -1-antitrypsin,<sup>54</sup> mRNA,<sup>55</sup> REG1 $\beta$ <sup>56</sup> and lactoferrin<sup>57</sup> in faeces), gut permeability (zonulin,<sup>58</sup> EndoCAb<sup>10,14,15,58</sup> and soluble CD14<sup>10</sup> in blood) and gut absorptive capacity (citrulline<sup>46</sup> in blood).

By investigating and testing markers for their hypothesised roles in the establishment and maintenance of EED, our understanding of the processes causing EED will hopefully improve. For example, cells lining the small intestine of a child with EED are assumed to differ in the kinds of proteins they produce from those in a child without EED. The protein production activity of cells may be measured by examining the messenger ribonucleic acid (mRNA), which is an intermediary substance that is transcribed between DNA and the protein it encodes. 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.<sup>55</sup>

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 effects of interventions against EED in trials where follow-up is comparatively brief. However, a major challenge here is the lack of consensus over which test should form the gold standard.

## 6 Epidemiology: who has EED? What are its risk factors?

### 6.1 Adult studies

Although most research now focuses on children, EED was first recognised in adults. These early studies provided insight for all age groups. 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.<sup>59</sup> Participants were assessed during and after placements in India and Pakistan. Gut absorptive function tests and biopsies confirmed abnormalities during residence abroad and recovery within 1-2 years of return to the USA. 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.<sup>4</sup> In 1999, a large study measured intestinal permeability and absorptive capacity amongst asymptomatic adults in 14 countries across the world.<sup>60</sup> 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 (GDP) per capita, independent of climate, suggesting that at the individual level, poverty or environment may play a more significant role.

### 6.2 Paediatric studies

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<sup>15,34,48</sup> and associated with underweight in Guatemalan infants and with stunting in Gambian, Nepali and Bangladeshi and Malawian children.<sup>11-14</sup> Associations with various environmental risk factors were also demonstrated (see section 7).

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

## 7 Aetiology: what causes EED?

### 7.1 Nutritional deficiency

Moving from exclusive breastfeeding to mixed feeding and subsequent cessation of breastfeeding altogether are both seen alongside worsening of L:M ratio in Nepali infants.<sup>12</sup> Early breastfeeding cessation is associated with worse L:M ratio in Guatemalan infants.<sup>11</sup> A possible cause of these observations may be poor hygiene often associated with complementary feeding and/or nutritional deficiency.

Micronutrient deficiencies may play a role in EED, although if this is the case, it is difficult to know whether EED causes micronutrient deficiency through malabsorption, or if micronutrient deficiency causes EED through diminished ability to maintain a healthy intestinal lining. Zinc is known to aid recovery of the intestinal mucosa following diarrhoea,<sup>39</sup> and is recommended as part of standard therapy for diarrhoea by the World Health Organisation. Zinc deficiency is associated with abnormal L:M ratio in Malawian children.<sup>44</sup> However, trials of the effect of zinc supplementation on intestinal permeability and growth in infants have had mixed impacts<sup>38,61,62</sup> and in the authors' view there is insufficient evidence at present to support use of zinc supplementation to prevent stunting. Vitamin A deficiency is associated with abnormal L:M ratio and stunting in Brazilian children.<sup>41</sup> In The Gambia, the least abnormal L:M ratios are observed during the mango season, when vitamin A intake is highest.<sup>40</sup> However, trials of vitamin A have had mixed results on L:M ratios in children in LMICs.<sup>40,43</sup> It is again the authors' view that evidence is insufficient for routine use of vitamin A supplementation as a specific treatment for stunting. Combined supplementation of vitamin A and zinc has been shown to improve L:M ratios and stunting in Brazilian children.<sup>41</sup> Multiple micronutrient supplementation in Zambian adults has yielded improvements in the histological features of EED, although it is unclear which of the micronutrients were important in this context.<sup>63</sup>

Several other nutritional approaches have been proposed to tackle EED, for example, improving the digestibility of food through fermentation, hydrolysis or enzyme supplementation, or optimising amino acid profiles to reduce gut inflammation and support repair.<sup>64</sup> 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 positive results (see section 8).<sup>42,45</sup> These interventional studies, and others, will improve our understanding of the possible nutritional causes of EED.

### 7.2 Microorganisms

#### 7.2.1 Non-specific faeco-oral contamination; role of WASH

Microorganisms (bacterial, parasitic or viral) in the gut may be important in the establishment and/or maintenance of EED. Their relative importance may differ between geographical settings, season, age or feeding practices.

The key evidence for the possible importance of gut microorganisms in development of EED is from antibiotic studies. A recent systematic review concluded that good evidence exists in relation to moderate beneficial effects of antibiotics on growth in pre-pubertal children in LMICs.<sup>65</sup> Several antibiotic studies aimed at particular species of pathogen have included EED in their outcomes (see section 8).

Improving water, sanitation and hygiene (WASH) aims to reduce exposure to faeco-oral transmission of pathogens and other micro-organisms. There are a few published observational studies of WASH in association with EED. Bangladeshi children from cleaner households were observed to have lower risk of both abnormal L:M ratio and stunting compared to those from less clean households.<sup>14</sup> In Malawian



3-5 year-olds, an abnormal L:M test was associated with lack of latrine access and low household water usage.<sup>66</sup> However, a recent systematic review of 14 trials of WASH interventions worldwide on anthropometric outcomes for children aged 0-18 years suggested a very modest impact of WASH on stunting (with no effect at all amongst children aged under two years) and no impact on underweight or wasting.<sup>67</sup> Importantly, none of the selected trials were judged of high methodological quality (main problems were lack of reporting of participant adherence and, albeit unavoidably, no participant blinding) and intervention periods were short (9-12 months). WASH interventions are often difficult to do well, consistently and at scale. Observational study of infants and young children in Zimbabwe suggests that a significant proportion of the burden of faeco-oral contamination is likely to come not only from well-characterised sources (food, water and hands) but also from direct eating of soil and animal faeces in the course of play and exploration.<sup>68</sup> Several multi-site studies are currently ongoing to investigate effectiveness of different WASH interventions on EED.<sup>69-71</sup>

During the transition period from exclusive breastfeeding to complementary feeding, which frequently occurs much earlier than the recommended six months in LMICs<sup>72</sup>, infants are at risk of faeco-oral contamination from complementary (weaning) foods. These may be prepared separately from family foods, stored for longer, and reheated inadequately.<sup>73</sup> 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 faeco-oral contamination takes place. The development of EED is also observed during this time (from around two months of age onwards).

### 7.2.2 Specific intestinal pathogens

Undernutrition (but not explicitly EED itself) has been linked to concurrent infection with multiple intestinal pathogens including parasites (*Cryptosporidium*,<sup>74,75</sup> amoeba,<sup>76</sup> roundworm,<sup>77</sup> hookworm,<sup>78</sup> whipworm<sup>79</sup>) and bacteria (certain forms of *E. coli*,<sup>4,27,57</sup>). The abnormal microscopic findings in EED have been linked to infection with hookworm and the bacteria *Citrobacter rodentium*.<sup>4</sup> The parasite *Giardia duodenalis* has been particularly implicated in abnormal L:M ratios in Nepal,<sup>12</sup> lactose intolerance in Lesotho<sup>80</sup> and acute growth faltering in Gambian infants.<sup>47</sup> Rotavirus is the commonest cause of diarrhoea in developing country settings and could contribute to EED. It has been associated with high L:M ratios in Bangladeshi and Peruvian children.<sup>39,81</sup>

More recent advances in molecular pathogen diagnostics such as polymerase chain reaction (PCR) have allowed greater range and sensitivity in detecting pathogens. In urban Bangladeshi infants, associations were found between malnutrition, diarrhoea and EED (measured by EndoCAb, an antibody formed in the bloodstream in response to movement of gut-resident bacteria across a leaky gut wall).<sup>58</sup> Amoeba, *Cryptosporidium* and enterotoxigenic *E. coli* were important causes of diarrhoea in these infants and associated with acute malnutrition (associations with EED itself were not examined).

### 7.2.3 The gut microbiome

The gut contains trillions of microorganisms in a complex eco-system of their own. An imbalance, rather than the presence or absence of specific pathogens, may be important in EED and nutrition. Modern genome sequencing techniques allow us to identify and quantify all bacteria in the gut (microbiota), their genes (microbiome) and their metabolic products (metabolome). This field is rapidly expanding as new technological capacity allows quicker and cheaper sequencing. The gut microbiota differs significantly between African and European infants,<sup>82</sup> and between malnourished and well-nourished children.<sup>83,84</sup> Evidence that the microbiome affects nutritional status comes from one experiment where faeces from malnourished children were transplanted into mice reared in sterile conditions, resulting in the mice becoming malnourished.<sup>85</sup> There are no published studies to date of the gut microbiome in the specific context of EED, although this is one focus of the ongoing MAL-ED network (see section 10).

#### 7.2.4 *Helicobacter pylori*

*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.<sup>86</sup> In The Gambia, 15% of 0-20 month-olds and 46% of 40-60 month-olds had evidence of *H. pylori* infection, with higher prevalence amongst those malnourished or with chronic diarrhoea.<sup>87-89</sup> In urban Peru, high frequency of *H. pylori* infection was noted amongst children and associated with subsequent higher risk of all-cause diarrhoea.<sup>90</sup> The role of *H. pylori* infection in EED is plausible but has not yet been directly examined.

#### 7.2.5 Small Intestinal Bacterial Overgrowth (SIBO)

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 to the large intestine. SIBO is a well-recognised condition arising from the bowel stasis seen in immobility and muscular disorders.<sup>91</sup> SIBO's clinical manifestations include those thought to occur in EED: nutrient malabsorption leading to malnutrition.

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 malnourished Indian adults and Gambian and Nigerian children were found to be heavily contaminated with pathogenic bacteria and yeasts regardless of the presence of diarrhoea.<sup>92-94</sup> 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.<sup>95</sup>

More recently, non-invasive diagnostic tests for SIBO have been employed. Testing the hydrogen content of exhaled air is a reasonable approximation of small intestinal bacterial presence, since the human body does not produce hydrogen except via metabolically active intestinal bacteria.<sup>96</sup> When measured at intervals following ingestion of a sugar substrate, a large, late peak in the hydrogen content of exhaled air depicts 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 histology changes in slum-dwelling Brazilian infants,<sup>97</sup> poverty in urban Brazilian children,<sup>98</sup> malnutrition and malabsorption in Burmese infants<sup>99</sup> and enteral vaccine failure in Chile.<sup>30</sup>

SIBO can be treated successfully with antibiotics.<sup>100</sup> Metronidazole targeted at SIBO (though likely impacting on specific bacterial or parasitic infections as well such as *Giardia*) aids recovery from malnutrition in Jamaican children<sup>101</sup> but the non-absorbable oral antibiotic rifamixin, also targeted at SIBO, was found not to improve L:M ratios in Malawian children.<sup>102</sup> Probiotics (beneficial bacteria species that are normally resident in healthy gut) have also been investigated, although there is very limited evidence for their effectiveness in treating SIBO<sup>91</sup> and they have not been found to improve L:M ratios in Malawian children.<sup>66</sup> The role of SIBO in the pathogenesis of EED is therefore still unclear.

#### 7.2.6 HIV enteropathy

Enteropathy, with chronic diarrhoea and weight loss, is common in severely immune-suppressed people with HIV infection and those who have progressed to AIDS.<sup>103</sup> 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, whilst also permitting injury by other gut pathogens by weakening host defences against them. This resultant enteropathy may itself drive HIV disease progression.

### 7.2.7 Toxins

The toxins aflatoxin, fumonisin and deoxynivaenol, which arise from moulds contaminating foods such as maize and peanuts, have been linked to impaired growth and gut inflammation in children but have not yet been studied in the specific context of EED.<sup>104</sup>

## 8 Which treatments have already been tried?

The following is a summary of selected published trials\* conducted amongst children in LMIC settings where EED has been explicitly targeted:

| Author & year                                    | Setting           | Age group          | Intervention & duration   | Results: L:M ratio                                     | Results: anthropometry                      | Notes  |
|--|-------------------|--------------------|---|--|---|--|
| <a href="#">Thurnham 2000</a> <sup>40</sup>      | India; rural      | 2-15 months        | Vitamin A single dose (inpatients) or for 8 weeks (outpatients) | Improvement seen within 30 days                        | <i>Not reported</i>                         |  |
| <a href="#">Galpin 2005</a> <sup>66</sup>        | Malawi; rural     | 3-5 years          | <i>Lactobacillus</i> 30 days                                    | No difference  | No difference                               |  |
| <a href="#">Lima 2007</a> <sup>42</sup>          | Brazil; rural     | 7 months – 7 years | Alanyl-glutamine 10 days  | Improvement  | Improved WAZ & WHZ but no difference to HAZ |  |
| <a href="#">Trehan 2009</a> <sup>102</sup>       | Malawi; rural     | 3-5 years          | Rifamixin 7 days  | No difference  | <i>Not reported</i>                         | SIBO itself not measured   |
| <a href="#">Goto 2009</a> <sup>49</sup>          | Bangladesh; urban | 3-15 months        | Albendazole 3 monthly & secnidazole monthly for 9 months        | No difference  | No difference                               | Possible reason for failure: high <i>Giardia</i> re-infection rate |
| <a href="#">van der Merwe 2013</a> <sup>45</sup> | The Gambia; rural | 3 months           | n-3 LC-PUFA for 6 months  | No difference  | Improved MUAC at 9 & 12 months              | Cognition also examined: no difference                             |
| <a href="#">Ryan 2014</a> <sup>38</sup>          | Malawi; rural     | 1-3 years          | Zinc 14 days<br><br>Albendazole single dose                     | Prevented deterioration<br><br>Prevented deterioration | No difference<br><br>No difference          |  |

**Table 1: Selected published trials**

The trials described above have suggested beneficial effects for zinc, vitamin A, n-3 LC-PUFA and alanyl-glutamine on L:M ratios, although none have seen large improvements. Ongoing studies are now building on these results.

\* = Searches (non-systematic) for key papers were conducted using PUBMED 1966 to June 2014; hand searches of the references and related citations of retrieved literature; discussions with experts; and personal experience from the field.

## 9 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 or severe acute malnutrition or stunting, is not presently indicated since its aetiology remains unclear and evidence for benefit from targeted treatments such as probiotics or antibiotics is lacking. Additional barriers to this scenario are imperfect existing tests and a lack of consensus over the diagnostic criteria of which these tests may be a part.

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 LMIC settings.<sup>105,106</sup> A holistic approach to nutritional rehabilitation that includes attention to minimising faeco-oral contamination in the home or hospital environment should therefore already be prioritised. 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, non-invasive, cheap and quick biomarkers for EED and evidence for setting-specific aetiology and effective treatments emerge, more specific recommendations will follow.

## 10 Current research, future priorities

There are several ongoing randomised trials of interventions to prevent or treat EED as of June 2014:

**Table 2: Ongoing research trials**

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

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 EED be diagnosed 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 EED best be prevented?
- Once 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 hypothesised 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: co-ordinated birth cohorts in Peru, Brazil, Bangladesh, India, Pakistan, Nepal, Tanzania and South Africa.<sup>107</sup> 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 between paediatricians, 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 multi-factorial 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 LMIC settings.

## 11 Further reading

### General reviews

Korpe PS, Petri WA. [Environmental enteropathy: critical implications of a poorly understood condition.](#) *Trends in Molecular Medicine*. 2012; **18(6)**: 328-36.

Prendergast A, Kelly P. [Enteropathies in the developing world: neglected effects on global health.](#) *The American Journal of Tropical Medicine and Hygiene*. 2012; **86(5)**: 756-63.

### Malnutrition and enteric infections

Lunn PG. [The impact of infection and nutrition on gut function and growth in childhood.](#) *The Proceedings of the Nutrition Society*. 2000; **59(1)**: 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.](#) *Nutrition Reviews*. 2008; **66(9)**: 487-505.

### EED and nutrition

McKay S, Gaudier E, Campbell DI, Prentice AM, Albers R. [Environmental enteropathy: new targets for nutritional interventions.](#) *International Health*. 2010; **2(3)**: 172-80.

Lindenmayer GW, Stoltzfus RJ, Prendergast AJ. [Interactions between zinc deficiency and environmental enteropathy in developing countries.](#) *Advances in Nutrition*. 2014; **5(1)**: 1-6.

### EED and WASH

Humphrey JH. [Child undernutrition, tropical enteropathy, toilets, and handwashing.](#) *The Lancet*. Sep 19 2009; **374(9694)**: 1032-1035.

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.](#) *Annals of the New York Academy of Sciences*. 2014; **1308(1)**: 118-28.

### EED and fungal toxins

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### H. pylori

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### Gut microbiome

Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. [Human nutrition, the gut microbiome and the immune system.](#) *Nature*. 2011; **474(7351)**: 327-36.

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