USAID
FROM THE AMERICAN PEOPLE

Beyond Z-scores: Measures to Advance Prevention and Treatment Outcomes in Child Malnutrition

Summary of Proceedings from a Symposium at the International Congress of Nutrition, Buenos Aires, Argentina on October 16, 2017

A Report from the Food Aid Quality Review

PREPARED BY:

DEVIKA SURI AND IRWIN ROSENBERG

AUGUST 2018

This report was produced for the United States Agency for International Development. It was prepared under the terms of contract AID-OAA-C-16-00020 awarded to the Friedman School of Nutrition Science and Policy at Tufts University.

FROM THE AMERICAN PEOPLE

This report is made possible by the generous support of the American people through the support of the Office of Food for Peace (FFP) of the Bureau for Democracy, Conflict and Humanitarian Assistance (DCHA), under terms of Contract No. AID-OAA-C-16-00020, managed by Tufts University. The contents are the responsibility of Tufts University and its partners in the Food Aid Quality Review Phase III (FAQR Phase III) and do not necessarily reflect the views of the United States Agency for International Development (USAID) or the United States Government.

Recommended citation: Suri DJ and Rosenberg IH. 2018. Beyond Z-scores: Measures to Advance Prevention and Treatment Outcomes in Child Malnutrition. Summary of Proceedings from a Symposium at the International Congress of Nutrition, Buenos Aires, Argentina on October 16, 2017. Report to USAID. Boston, MA: Tufts University.

For correspondence, contact:
Dr. Irwin Rosenberg
Tufts University
150 Harrison Ave, Boston MA 02111
Email: irwin.rosenberg@tufts.edu

ACRONYMS

BIA	Bio-electrical Impedance Analysis
DCHA	Bureau for Democracy, Conflict and Humanitarian Assistance
DIAAS	Digestible Ileal Amino Acid Score
DXA	Dual-energy X-ray Absorptiometry
EED	Environmental Enteric Dysfunction
FAQR	Food Aid Quality Review
FFP	The Office of Food for Peace
ICN	International Congress of Nutrition
MAM	Moderate Acute Malnutrition
MUAC	Mid-Upper Arm Circumference
PDCAAS	Protein Digestibility Corrected Amino Acid Score
SAM	Severe Acute Malnutrition
USAID	United States Agency for International Development
WHZ	Weight-for-Height Z-score

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

There is a growing imperative to measure the nutrition and health impact of food-based humanitarian assistance with more precision to better inform policy and practice. For many decades, researchers and programmers have relied mainly on anthropometric Z-scores and related cutoffs to determine the nutritional status of children to assess the impact of interventions. However, Z-scores may fail to distinguish important physiological or cognitive factors which can bias the interpretation of health, malnutrition or recovery. A symposium was organized at the 2017 International Congress of Nutrition (ICN) in Buenos Aires, Argentina, to consider three measures which add important contextual information and have implications for how we approach the treatment and prevention of child malnutrition. This paper provides a summary of the Symposium and key messages on research priorities, policy implications and programming guidance.

Several experts were asked to offer their perspectives on each of the three measures considered. The first measure was body composition, i.e. the proportion of lean and fat mass, which can be more useful than weight or height in predicting certain health outcomes. The second measure was environmental enteric dysfunction (EED), whose presence has been shown to be a predictor of child undernutrition. The third measure was dietary protein quality combined with biomarker serum amino acids, which have been shown to be associated with child malnutrition. Current research is being conducted on the use and interpretation of these three measures in the context of malnutrition. However, similar challenges remain among all three. The technology required to evaluate these three measures remains costly and highly-trained technicians are needed. In addition, there is ongoing debate as to which evaluation methods are the most accurate and meaningful. Furthermore, while these measures are being explored, they are still not the main drivers in making decisions about a program's effectiveness.

The Symposium discussed efforts to treat or prevent child malnutrition which need to move beyond measurement of Z-scores to determine treatment methods and understand the effects of food-based interventions. Further efforts are needed toward accessible technology, accepting the use of these new measures, and understanding how they should be interpreted. In the meantime, we should be taking what is already known about these three key areas into urgent consideration in research, policy and programming.

II. BACKGROUND

The United States Agency for International Development (USAID) spends upwards of $1.4 billion U.S. dollars per year on Title II emergency and non-emergency food aid, more than 1 million metric tons (1). As the need for food aid increases globally in the context of resurging famines and a rising number of hungry people, there is a growing imperative to measure the nutritional impact of this large dimension of humanitarian assistance with more precision and policy-implementing value. Tufts University's Food Aid Quality Review (FAQR) is a project supported by USAID which examines the effectiveness of food aid in addressing prevention and treatment of child malnutrition.

For many decades, nutritionists have relied mainly on anthropometric measurements of height and weight—further transformed into height-for-age or weight-for-height percentiles or Z-scores—to determine nutritional status in children. However, anthropometric Z-scores fail to distinguish important dynamic and contextual factors which will greatly affect the success of interventions to treat or prevent malnutrition, as well as future implications of these interventions. In addition, there are contextual factors which can influence the potential effect of a supplementary food intervention on growth, such as the presence of EED, an as-yet undefined structural and functional change to the gut which impairs absorption of nutrients. Furthermore, the nutritional quality of the diet and related biomarker status is not reflected in Z-scores. In the case of protein, there is a complex combination of factors, including the food matrix, processing, and amino acid profile, which can impact its quality, absorption and utilization in the body for growth and other functions.

These three areas—body composition, EED and protein quality—represent some of the newer measures which give us more information about malnutrition, its context, potential target beneficiaries, outcomes and the impact of our food aid interventions. The purpose of this Symposium was to discuss the status of these newer indicators and move the agenda forward on research priorities, policy implications and program guidance.

III. SUMMARY OF PRESENTATIONS

BODY COMPOSITION

Presenters: Cornelia Loechl, International Atomic Energy Agency, Vienna, Austria and Susan Roberts, Tufts University, Boston, U.S.A. (presented by Dr. Irwin Rosenberg in her absence)

Key Points

- Lean mass and fat mass, rather than weight alone, are more useful for nutritional evaluation.
- Newer technologies are able to determine body composition in the field. They will make body composition measures more affordable and accessible. However, they need to be validated against reference methods.

Currently, interventions to treat moderate acute malnutrition (MAM) or severe acute malnutrition (SAM) rely on weight-for-height Z-score (WHZ) and/or mid-upper arm circumference (MUAC) both to screen individual children for treatment and to determine "recovery" from malnutrition. However, determination of body composition, i.e. the proportion of lean and fat mass, in the context of treatment of acute malnutrition may be more useful in the definition of healthy recovery and prediction of later relapse or health outcomes. The risk for obesity and chronic disease may be programmed by events early in life, and there is a positive association between greater rate of weight gain in early infancy and later fat mass and central fat distribution (2,3). While there is concern that supplementary foods for treatment of MAM may increase fat tissue (4), two recent studies using the newer technology of deuterium dilution have shown that supplementary foods are not associated with excess fat deposition during treatment of MAM (5,6).

There are a number of methods to assess body composition, each with varying strengths and weaknesses (**Table 1**). Despite its important implications in the treatment of malnutrition, evaluation of body composition is not often included in interventions, especially in a low-resource setting, where it can be challenging for several reasons, including:

- Costs associated with equipment, materials and/or adequate training for staff are high;
- Detection of very small differences in body composition to evaluate changes over short periods of time can be difficult with existing technology;
- Hydration factor varies with age and physiological states (e.g. pregnancy, severe acute malnutrition with edema and other clinical conditions); and
- Data on "normal" body composition is limited (e.g. for different ethnic groups).

Over time, costs of more technology-heavy body composition assessment methods such as deuterium dilution will decrease. In addition, more partnerships with groups which have funding and technological capacity will be needed both to refine methods and to build an evidence base around their use. At the same time, low-cost, lower-tech methods such as MUAC and skinfolds should still be used but they should be combined with functional tests such as muscle strength.

Table 1: Methods and Challenges in Assessing Body Composition

Method	**Challenges**
DXA	It is difficult for remote and pediatric populations because it requires a large scanner, the individual must lie completely still for several minutes and it involves a dose of radiation.
Deuterium dilution	This is expensive and time-consuming to conduct in large-scale population studies. Deuterated water is costly. Collection of urine or saliva is needed. Assumptions about hydration status may result in inaccurate estimates (especially in the context of edema).
Bio-electrical impedance **analysis** (BIA)	The BIA machine is simpler to use in the field but has a large margin of error (+/- 200 g lean tissue in malnourished infants). While this does not lend itself to detecting small changes over time, it could be used for cross-sectional evaluation.
Skinfold and MUAC measurements	Skinfold and MUAC measurements can be useful field methods if done correctly but they are sensitive to field errors and differences across assessors. There is potential to combine these methods to estimate muscle mass.
Body cell mass	This technique uses sodium iodide detectors and is independent of hydration changes but currently requires a large non-portable scanner so is not suitable for field studies.
Creatine dilution to determine muscle mass	This technique is promising but still under development for use in malnourished infants.
Future technologies	Newer technologies such as mobile phone and photo applications may combine low-cost portability and ease of use.

ENVIRONMENTAL ENTERIC DYSFUNCTION (EED)

Presenters: Dr. Irwin Rosenberg, Tufts University, Boston, U.S.A. and Tahmeed Ahmed, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

Key Points

- Environmental enteric dysfunction (EED) is an often subclinical inflammatory, malabsorptive disorder of the gut, increasingly linked with child stunting.
- Non-invasive technologies to determine and quantify EED are still in development.
- The relationship between EED and supplemental foods is yet to be elucidated, but future food-based interventions will need to take factors related to EED into account in order to be more effective.

Globally, one-quarter of children are stunted (more than one-third in sub-Saharan Africa and South Asia) but we have yet to make a large impact in stunting rates through targeted nutritional interventions alone. EED may be a causative factor in stunting and a factor preventing nutritional interventions from being effective.

In the 1960s, new methods available to biopsy the small bowel revealed differences in mucosal structure between Western adults and adults in tropical, developing countries, including shortened villi, mucosal inflammation and reduced absorptive function. Similar changes occurred in expatriates living in tropical environment—minimal symptoms, some weight loss—which was named tropical sprue or enteropathy. These changes reversed without any intervention after the individuals returned home. The cause was unclear but environmental factors were implicated. However, due to uncertain relevance, interest in EED waned for several decades.

Today, EED is better defined but characterized as an acquired functional and structural change of the intestine (perhaps just the small bowel) in the absence of overt illness. It may be due to factors encountered in the environment of still-unknown type related to microbial contamination, diet, toxicity in water or food, or others factors yet to be identified. Poor sanitation and hygiene, as well as fecal contamination of the domestic environment have been shown to be associated with EED.

Recently, interest in EED has increased, as appears to be a reversible cause of malnutrition and stunting. EED which begins early in life can result in growth faltering due to malnutrition, predisposed susceptibility to infection with pathogens and increased severity of their consequences. The strongest evidence for EED was the association between enteropathogens and linear growth mediated through systemic inflammation (7). Several recent studies have shown varying indicators of EED associated with poor nutritional status and linear growth (8-10). It has also been found that the gut microbiome is different between healthy and malnourished children (11) and impaired gut microbiota development is causally related to undernutrition (12). EED is potentially reversible; it could be as important as reducing exposure to pathogens/contaminated environments (13) or improving response to oral vaccines in our efforts to reduce child malnutrition. However, this condition is difficult to diagnose, as children with EED may not show overt symptoms of gut infection, such as diarrhea (14).

All the current assessment methods (**Table 2**) involve obtaining subjects' serum, urine and/or feces. Serum is more invasive, but urine and feces can be challenging to collect, especially from very young children. Moving forward, a standard definition of EED is needed. New studies using this definition could provide clues to the relevance of EED as antecedent cause for malnutrition and increased infection. Clues to etiologic factors may be obtained so intervention studies can be planned; evidence is needed on how supplemental foods impact EED and, conversely, how EED impacts effectiveness of nutrition interventions. Remedies for EED could increase optimum utilization of food, perhaps by harnessing the gut microbiota. A new cost-effective strategy to combat EED and its consequences may result, particularly effective if applied right after birth (or before) to reduce impacts during rapid growth and development of infants and children. Finally, biomarkers for EED are now available but still need more work for optimization in terms of validation and field-friendly measures.

Table 2: Methods for Assessing Biomarkers of EED

Domain	**Biomarker**
Intestinal absorption	Mannitol recovery
Intestinal barrier function and permeability	Lactulose recovery
Intestinal inflammation	a-1 antitrypsin, neopterin, myeloperoxidase, CD53, HLA-DRA, MUC12, CDX1, S100A8, REG1A, TNF; Fecal host mRNA
Enterocyte damage	I-FABP
Intestinal regeneration	REG-1B
Microbial translocation	EndoCAb, LPS, sCD14, sCD163
Systemic inflammation	C-reactive protein, alpha-glycoprotein
Growth hormone activity	Insulin-like growth factor-1
Combined indicators	Lactulose:Mannitol ratio EE Score (2 x AAT category + 2 x MPO category + 1 x NEO category)

PROTEIN QUALITY

Presenters: Anura Kurpad, St. John's College, Bangalore, India and Ricardo Uauy, London School of Hygiene and Tropical Medicine, London, U.K.

Key Points

- Inadequate dietary protein quality is associated with stunting.
- Current methods of assessing dietary protein quality are complex, have questionable accuracy and may vary across individuals and contexts.
- There is a need for simpler assessment of protein quality to target strategies to improve dietary protein quality to address malnutrition and stunting.

Young children in developing countries are often at risk of nutrient deficiencies due to a diet heavily reliant on staple crops. This includes high-quality protein—the ability of a food or diet to meet human protein and amino acid requirements—which is often overlooked and is implicated in growth. Amino acids are necessary for a myriad of metabolic processes,

including growth, tissue repair, immune functioning and cognition. Unmet protein needs can result in growth retardation and stunting. This can affect infants both before and after birth. Risk of country-level population protein inadequacy calculated from food balance sheet data using utilizable protein, but not total protein, is associated with stunting rates (15). At the individual level, low circulating amino acids are associated with stunting (16).

The main challenges for protein digestibility corrected amino acid score (PDCAAS) and newer digestible ileal amino acid score (DIAAS) are the availability of human fecal and ileal digestibility data (**Table 3**). Ileal digestibility represents the true digestibility of protein, since it is not confounded by colonic bacteria which could fix nitrogen. This is further complicated by the lack of data for children, who may have different digestion of protein compared with adults. It is also becoming clear that individual amino acids within a food protein have different digestibility. Methods to determine amino acid digestibility in humans include the indicator amino acid oxidation technique and the dual isotope method. Furthermore, there appear to be differences in digestibility among individuals and in different environments. Therefore, we need to consider whether digestibility is an "intrinsic" protein quality or whether diverse conditions also need to be considered. Finally, the indispensable amino acid requirement pattern for children is still speculative, as it is based on a factorial model derived from adult requirements. Amino acid patterns for catch-up growth and other contexts are needed.

Dietary protein quality is an important factor in growth and nutritional status. However, determination of the protein quality of foods and diets is still imprecise and complex. We need more data on two fronts: 1) We must ensure that the indispensable amino acid requirements for children are appropriate and accurate in "ideal" and "non-ideal" settings; and 2) We need more human ileal digestibility data in varying ages and contexts. Finally, we need further research into the role that protein quality plays in specialized nutritious foods and other interventions to prevent and treat child malnutrition.

Table 3: Methods and Challenges in Assessing Protein Quality

Method	**Challenges**
Protein digestibility corrected amino acid score (PDCAAS)	PDCAAS is a composite of a protein's (fecal) digestibility and the amino acid score (how well the amino acid profile meets the requirement). Human digestibility data is limited. Debate of truncation of the AA score persists.
Digestible ileal amino acid score (DIAAS)	DIAAS is a newer measure which uses ileal digestibility (instead of fecal) of each amino acid. Ileal digestibility data for humans is even more limited than PDCAAS. Methods for obtaining ileal digestibility data include: - Indicator amino acid oxidation method for digestibility; and - Dual isotope method. Digestibility values to be used, listed in order of accuracy: 1. Human true ileal digestibility values; 2. Growing pig - True ileal amino acid digestibility values; 3. Prediction equation: human values from growing pig values; 4. Growing lab rat - True ileal amino acid digestibility values; and 5. Fecal protein digestibility values.

IV. CONCLUSIONS AND RECOMMENDATIONS

The use of anthropometric Z-scores alone to measure child malnutrition may lead to an underestimation of the extent of problems to be addressed. Because of this, the range of actions required to provide effective treatment should be reexamined. This Symposium outlined three measures which potentially add important information to the context of malnutrition.

First, during growth and treatment of malnutrition, body composition gives important information about lean versus fat mass accretion, which has implications for future under- and overnutrition. Second, in the context of EED, food-based strategies alone may not be enough to overcome the effect of chronic, subclinical infections/inflammation associated with malnutrition. Third, protein quality, not just quantity, should be considered in dietary evaluations and food-based interventions due to its important role in growth and development. A summary of the research priorities, policy implications and programming guidance from this symposium can be found in **Table 4.**

While technology currently exists to assess these three measures, the methods are still expensive, sometimes difficult to use in the field and lack universally agreed upon "gold standards" of measurement. While further research is needed, we can and should use what we know about these three measures in current programming and evaluation of interventions. We also need to focus efforts on promoting the acceptance of these new measures and understanding how they should be interpreted. Finally, these new measures should not be used on their own but used in combination with several indicators and a broader contextual view in order to enhance our understanding of child malnutrition and health outcomes.

V. ACKNOWLEDGEMENTS

This Symposium would not have been possible without the support of the USAID Office of Food for Peace and their ongoing commitment to improving Title II programming in order to address food insecurity in vulnerable populations. The time and support offered to the Food Aid Quality Review by Title III awardees, both headquarters and field staff, as well as Food for Peace Officers abroad and in Washington, D.C. and the Policy and Technical Division of FFP headquarters were also invaluable to informing this study. The authors thank Patrick Webb and Kristine Caiafa for their assistance in planning and executing this Symposium, and the presenters for their participation in the Symposium.

Table 4: Summary of Research, Policy and Programming Recommendations

	Research Priorities	Policy and Programming Implications
Overall	More research is needed in order to improve upon current methods of evaluation and understand the influence of these 3 measures in the context of food-based interventions.	Efforts to treat or prevent child malnutrition need to move beyond Z-scores and include measures which capture other dimensions of malnutrition.
Body Composition	Partnerships with groups which have funding and technological capacity to refine methods, reduce costs and build an evidence base around the use of technologies such as deuterium dilution.	Measures of body composition should be included as outcome measurements in food-based (or other) interventions looking at growth in treatment of child malnutrition. Include when testing products for recovery from malnutrition, weight/height gain. If technical capacity and budget allow, deuterium dilution is the gold standard. In addition, or if deuterium dilution is not available, use a combination of MUAC and skinfolds measurements.
Environmental Enteric Dysfunction (EED)	1) A standard definition of EED; 2) Scaling and application of biomarkers which are precise, accurate and field-friendly; and 3) Treatment for EED and how it affects outcomes in malnutrition interventions.	Enough evidence exists showing that enteric function matters and needs to be considered as a factor in etiology of malnutrition, and a potential modifier of response to foods and other interventions.
Protein Quality	1) Review of indispensable amino acid requirements for children to ensure that they are appropriate and accurate in "ideal" and "non-ideal" settings; 2) More human ileal digestibility data in varying age groups and contexts; and 3) Studies which take protein quality into consideration when evaluating effectiveness of products and interventions.	Newer measures of protein quality should be incorporated into demonstration and intervention evaluations. When considering protein quality in programs, determine if data is available as preferred measure of protein quality DIAAS of diet using ileal digestibility. If not possible, evaluate the contribution of animal source foods and complementary protein sources to total protein intake to estimate quality protein intake.

VI. RESOURCE AND GUIDANCE DOCUMENTS

Body Composition

- Assessment of Body Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques, International Atomic Energy Agency, Vienna, 2009. https://www-pub.iaea.org/books/iaeabooks/7982/Assessment-of-Body-Composition-and-Total-Energy-Expenditure-in-Humans-Using-Stable-Isotope-Techniques
- Wells JCK. Toward Body Composition Reference Data for Infants, Children, and Adolescents. Advances in Nutrition 2014; 5(3): 320S–329S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013189/

Environmental Enteric Dysfunction (EED)

- Kosek et al. Assessment of Environmental Enteropathy in the MAL-ED Cohort Study: Theoretical and Analytic Framework. Clinical Infectious Diseases 2014; 59(Suppl 4): S239–S247. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204611/
- Prendergast et al. Assessment of Environmental Enteric Dysfunction in the SHINE Trial: Methods and Challenges. Clinical Infectious Diseases 2015; 61(Suppl 7): S726–S732. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4657593/
- Syed S, Ali A and Duggan C. Environmental Enteric Dysfunction in Children: A Review. Journal of Pediatric Gastroenterology and Nutrition 2016; 63(1): 6–14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4920693/

Protein Quality

- Dietary protein quality evaluation in human nutrition. Report of an FAO Expert Consultation. Food and Agriculture Organization of the United Nations. Rome, 2013. http://www.fao.org/ag/humannutrition/35978-2317b979a686a57aa4593304ffc17f06.pdf

VII. REFERENCES CITED

1. USDA, USAID. U.S. International Food Assistance Report [Internet]. 2015. Available from: https://pdf.usaid.gov/pdf_docs/PA00MHDH.pdf
2. Chomtho S, Wells JC, Williams JE, Davies PS, Lucas A, Fewtrell MS. Infant growth and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;87:1776–84. https://www.ncbi.nlm.nih.gov/pubmed/18541568
3. Wells JC, Fewtrell MS. Is body composition important for paediatricians? Arch Dis Child [Internet]. 2008;93:168 LP-172. Available from: http://adc.bmj.com/content/93/2/168.abstract
4. World Health Organization. Guidelines: Assessing and managing children at primary health-care facilities to prevent overweight and obesity in the context of the double burden of malnutrition. Updates for the Integrated Management of Childhood Illness (IMCI). Geneva; 2017.
5. Bahwere P, Balaluka B, Wells JC, Mbiribindi CN, Sadler K, Akomo P, Dramaix-Wilmet M, Collins S. Cereals and pulse-based ready-to-use therapeutic food as an alternative to the standard milk- and peanut paste-based formulation for treating severe acute malnutrition: A noninferiority, individually randomized controlled efficacy clinical trial. Am J Clin Nutr. 2016;103:1145–61. https://www.ncbi.nlm.nih.gov/pubmed/26984485
6. Fabiansen C, Yaméogo CW, Iuel-Brockdorf AS, Cichon B, Rytter MJH, Kurpad A, Wells JC, Ritz C, Ashorn P, et al. Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: A randomised 2 × 2 × 3 factorial trial in Burkina Faso. PLoS Med. 2017;14. http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002387
7. Kosek M, Haque R, Lima A, Babji S, Shrestha S, Qureshi S, Amidou S, Mduma E, Lee G, et al. 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. https://www.ajtmh.org/content/journals/10.4269/ajtmh.2012.12-0549
8. Arndt MB, Richardson BA, Ahmed T, Mahfuz M, Haque R, John-Stewart GC, Denno DM, Petri WA Jr., Kosek M, Walson JL. Fecal markers of environmental enteropathy and subsequent growth in Bangladeshi children. Am J Trop Med Hyg. 2016;95:694–701. https://www.ncbi.nlm.nih.gov/pubmed/27352872
9. McCormick BJJ, Lee GO, Seidman JC, Haque R, Mondal D, Quetz J, Lima AAM, Babji S, Kang G, et al. Dynamics and trends in fecal biomarkers of gut function in children from 1-24 months in the MAL-ED study. Am J Trop Med Hyg. 2017;96:465–72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5303054/
10. Hossain MI, Haque R, Mondal D, Mahfuz M, Ahmed AMS, Islam MM, Guerrant RL, Petri WA Jr., Ahmed T. Undernutrition, vitamin A and iron deficiency are associated with impaired intestinal mucosal permeability in young Bangladeshi children assessed by lactulose/mannitol test. PLoS One. 2016;11:1–10. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0164447
11. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, Benezra A, DeStefano J, Meier MF, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature [Internet]. 2014;510:417–21. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4189846&tool=pmcentrez&rendertype=abstract
12. Blanton L V, Barratt MJ, Charbonneau MR, Ahmed T, Gordon JI. Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics. https://www.ncbi.nlm.nih.gov/pubmed/27339978
13. Lin A, Arnold BF, Afreen S, Goto R, Huda TMN, Haque R, Raqib R, Unicomb L, Ahmed T, et al. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. Am J Trop Med Hyg. 2013;89:130–7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3748469/
14. Platts-Mills JA, Babji S, Bodhidatta L, Gratz J, Haque R, Havt A, McCormick BJJ, McGrath M, Olortegui MP, et al. Pathogen-specific burdens of community diarrhoea in developing countries:

A multisite birth cohort study (MAL-ED). Lancet Glob Heal. 2015;3. https://www.ncbi.nlm.nih.gov/pubmed/26202075
15. Ghosh S, Suri D, Uauy R. Assessment of protein adequacy in developing countries: quality matters. Br J Nutr. 2012;108:S77–87. https://www.ncbi.nlm.nih.gov/pubmed/23107551
16. Semba RD, Shardell M, Sakr FA, Moaddel R, Trehan I, Maleta KM, Ordiz MI, Kraemer K, Khadeer MA, et al. Child Stunting is Associated with Low Circulating Essential Amino Acids. EBioMedicine. Elsevier B.V.; 2016. https://www.ncbi.nlm.nih.gov/pubmed/27211567