Imperial College London

MRC London Institute of Medical Sciences

Health outcomes in Undernutrition: the role of nutrients, gut dysfunction and the gut microbiome (HUNGer)

Health outcomes in **U**ndernutrition: the role of **N**utrients, **G**ut dysfunction and the gut microbiome (HUNGer)

The HUNGer consortium is comprised of a multi-disciplinary, multi-national consortium of world leading researchers, with expertise in physiology and nutrition, through to clinical research, public health and agriculture in LMIC settings. The HUNGer consortium was awarded the MRC Confidence in Global Nutrition and Health award in 2018.

The HUNGer consortium is developing a programme of work that will directly address United Nations Sustainable Development Goal 2 (SDG-2): ***End hunger, achieve food security and improve nutrition, and promote sustainable agriculture*.** We believe there are a number of critical unanswered questions regarding the role of the gut in undernutrition, which if answered could significantly improve the effective management and prevention of undernutrition.

The following document represents the consensus opinion of the HUNGer consortium concerning the key challenges that currently limit the effective management and prevention of undernutrition and the most promising potential solutions.

In Summary

- Despite the success of current nutritional therapies there remains significant morbidity and mortality associated with all types of undernutrition.
- Despite the negative impact of undernutrition on the gut, there has been little focus on restoring and maintaining gut functional capacity.
- We believe there is an urgent need for improved assessment methods of gut functional capacity, in particular for digestion and absorption.
- We believe that gut functional capacity can be improved with the supply of fermentable carbohydrates.
- We believe optimisation of amino acid availability is required for the restoration of normal gut functional capacity.
- Legumes offer the potential to restore gut functional capacity, in a food structure which delivers these nutrients to appropriate sites in the gut.
- Legumes provide a locally available, environmentally friendly, culturally acceptable, sustainable and affordable solution for restoring gut health, not an emergency fix.
- To accelerate the achievement of the UN Sustainable Development Goals for improved nutrition and health, there is an urgent need for population-based solutions to reverse the current trend of declining legume consumption in most low- and middle-income countries (LMICs).
- The HUNGer consortium will take a multi-national, multi-disciplinary food-based approach which will enhance gut function with the aim of improving acute and chronic health outcomes, in LMIC populations with undernutrition and populations at risk of undernutrition.

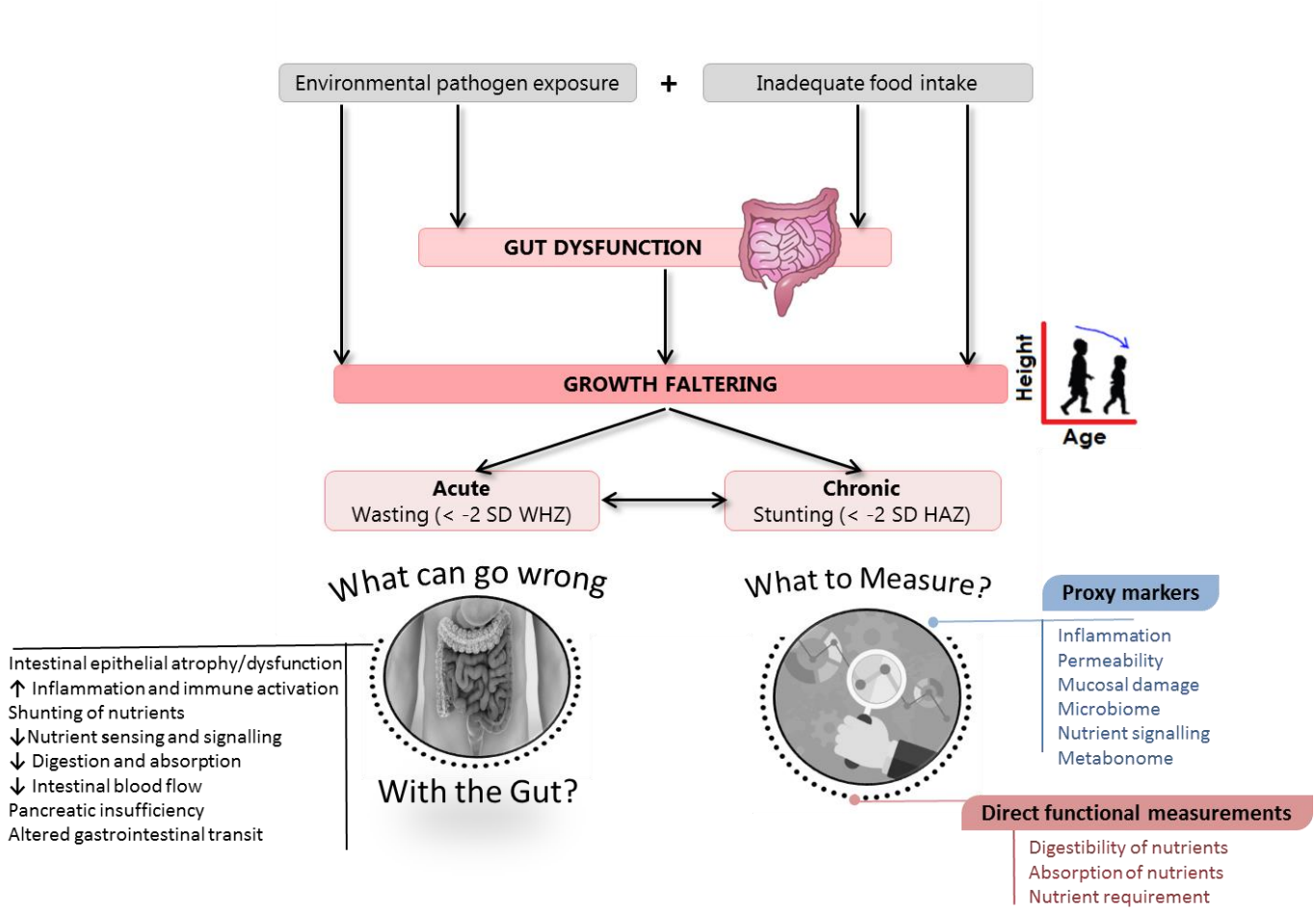

Fig 1. HUNGer consensus of target issue

HAZ = height-for-age Z-scores; WAZ= weight-for-age Z-scores

Despite the success of current nutritional therapies there remains significant morbidity and mortality associated with all types of undernutrition.

Globally, it is estimated that 45% of the 5.6 million child deaths can be attributed to undernutrition. Undernutrition manifests as wasting, stunting and underweight; In 2018, and estimated 151 million children under the age of 5 years are stunted, and 51 million children are wasted. In addition to health, undernutrition has implications for economic growth. The majority of undernutrition occurs in low- and middle-income countries (LMICs). Severe acute malnutrition (SAM) and severe stunting (severe chronic malnutrition) are both life-threatening conditions. Despite, current treatments that aim to reverse the nutritional status of individuals with undernutrition, there is still significant morbidity and mortality.

Despite the negative impact of undernutrition on the gut, there has been little focus on restoring and maintaining gut functional capacity.

Intestinal structure and function are impaired in undernutrition contexts. The greater the degree of structural impairment the worse the clinical outcomes, such as poor linear growth, sepsis and death. However, despite this our understanding of the complex interactions between undernutrition, environmental exposures and functional changes in the gut is limited. Current expert recommendations

are aimed at restoring the nutritional deficit but do not target gut functional capacity. Persistent gut dysfunction is likely to compromise nutritional rehabilitation, long-term growth and development. To accelerate the reduction in the global burden of undernutrition, we believe there is an urgent need for evidence-based nutritional interventions, aimed specifically, at restoring gut functional capacity.

We believe there is an urgent need for improved assessment methods of gut functional capacity, in particular for digestion and absorption.

Gut function encompasses the domains of digestion and absorption, barrier function, immune function, architecture, microbiome and motility. There is a lack of consensus in which are the best methods for assessing gut function in population studies. To date, studies have largely focused on barrier function and inflammation. Digestive and absorptive capacity remain largely neglected. Although changes in the gut microbiome are evident in undernutrition, the extent to which these contribute to gut functional capacity is unclear. Given the fundamental importance of digestion and absorption, *in vivo* methods to assess these domains are needed to direct evidence-based nutritional interventions in populations at risk of undernutrition.

We believe that gut functional capacity can be improved with the supply of fermentable carbohydrates.

Colonic microbial fermentation of carbohydrates leads to the generation of short-chain fatty acids (SCFAs). These have a positive influence on gut integrity and nutritional health by improving energy yield, production of vitamins and the stimulation of gut homeostasis, including anti-pathogen activities. Evidence suggests that the microbiota of children with undernutrition is immature and lacks the diversity needed to ferment a wide range of carbohydrates. Current ready-to-use therapeutic food (RUTF) does not address the fermentable carbohydrate needs of the gut microbiota. Our preliminary observations collected from children with SAM receiving legume supplementation, have showed that there are positive changes in the inter-relationships of normal gut microbes, intestinal permeability, and markers of gut barrier dysfunction and immune dysregulation. Therefore, we believe that there is an urgent need to define the fermentative capacity of the microbiome in undernutrition; this data would underpin the rational design of RUTF enriched with fermentable carbohydrate, which would improve gastrointestinal function. It is crucial to determine the effectiveness of these interventions in long term studies of gut functional capacity and health of the child.

We believe optimisation of amino acid availability is required for the restoration of normal gut functional capacity.

Normal gut function requires an adequate daily supply of amino acids, but this requirement is increased during a period of restoration of normal gut functional capacity. Despite this, accurate combined measurements of protein digestibility and amino acid absorption are largely missing from all available studies on gut function. Intestinal barrier functions are achieved primarily by regulating mucin synthesis and tight junction proteins, which are critical in maintaining optimal gut health. As well as being essential for digestive enzyme secretions, Amino acids have trophic and cytoprotective effects on gut integrity, which supports linear growth and health. Human data has also highlighted that dietary intake of essential amino acids is insufficient in children with undernutrition. Therefore, securing a correct amino acid balance may be effective in improving

linear growth as well as supporting optimal gut function.

Legumes offer the potential to restore gut functional capacity, in a food structure which delivers these nutrients to appropriate sites in the gut.

Legumes are rich in the protein, fermentable carbohydrates, minerals and phytochemicals necessary to improve and sustain gut functional capacity and support a healthy gut microbiota. Their amino acid composition is complementary to commonly consumed staple cereals in LMIC. The matrix structure of legumes, is such that processing and formulation can be used to target the delivery of nutrients to the appropriate sites in the gastro-intestinal tract. However, antinutrients such as phytates, polyphenols, trypsin-inhibitors and saponins, which are also present, can modulate the availability of key nutrients. Further research is required to ameliorate their effect using genetics, breeding and post-harvest processing approaches. Legumes should be a key component of a healthy and sustainable diet in populations at risk of undernutrition.

Legumes provide a locally available, environmentally friendly, culturally acceptable, sustainable and affordable solution for restoring gut health, not an emergency fix.

Legumes are grown worldwide. Varieties adapted to local climates and agronomic conditions can be utilised to address nutritional requirements of local populations. They can grow in harsh environmental conditions, most are rain fed, with minimal transport requirements and agronomic inputs, meaning their environmental impact is less than most cereals. Their resilience, including pest resistance, ensures security of the local food supply chain. Legumes fix nitrogen and so allow farmers to improve soil quality and aid in nutrient cycling of soils. Although, legumes are more expensive than most cereals, they are a much cheaper protein source compared with animal protein. Once nutritionally improved legume crops are introduced into the food chain, increased demand will provide additional and sustainable markets for farmers. We believe adoption of these legume crops into the diet will maintain healthy gut function in a sustainable, long term manner, reducing the dependence on rescue therapies to treat undernutrition.

To accelerate the achievement of the UN Sustainable Development Goals for improved nutrition and health, there is an urgent need for population-based solutions to reverse the current trend of declining legume consumption in most low- and middle-income countries (LMICs).

In recent decades, legume consumption has steadily declined in LMIC, which is attributable to shifting dietary patterns and consumer preferences. To ensure the benefits of consuming legumes is realised, it is necessary to empower consumers to create demand and influence governmental policy on agricultural production and consumption, procurement and distribution in school and community based-feeding programmes which will include a nutrition education component to further raise awareness of the value of legumes for a balanced diet. The creation of appealing, convenient and affordable legume-based recipes and products is an essential step in maintaining levels of legume consumption and their associated health benefits. Farmers need incentives and improved legume value chains. We believe legume varieties should be optimised for better nutrition and climate resilience to accelerate progress towards global nutrition and health targets and as an investment in the human capital development of countries.

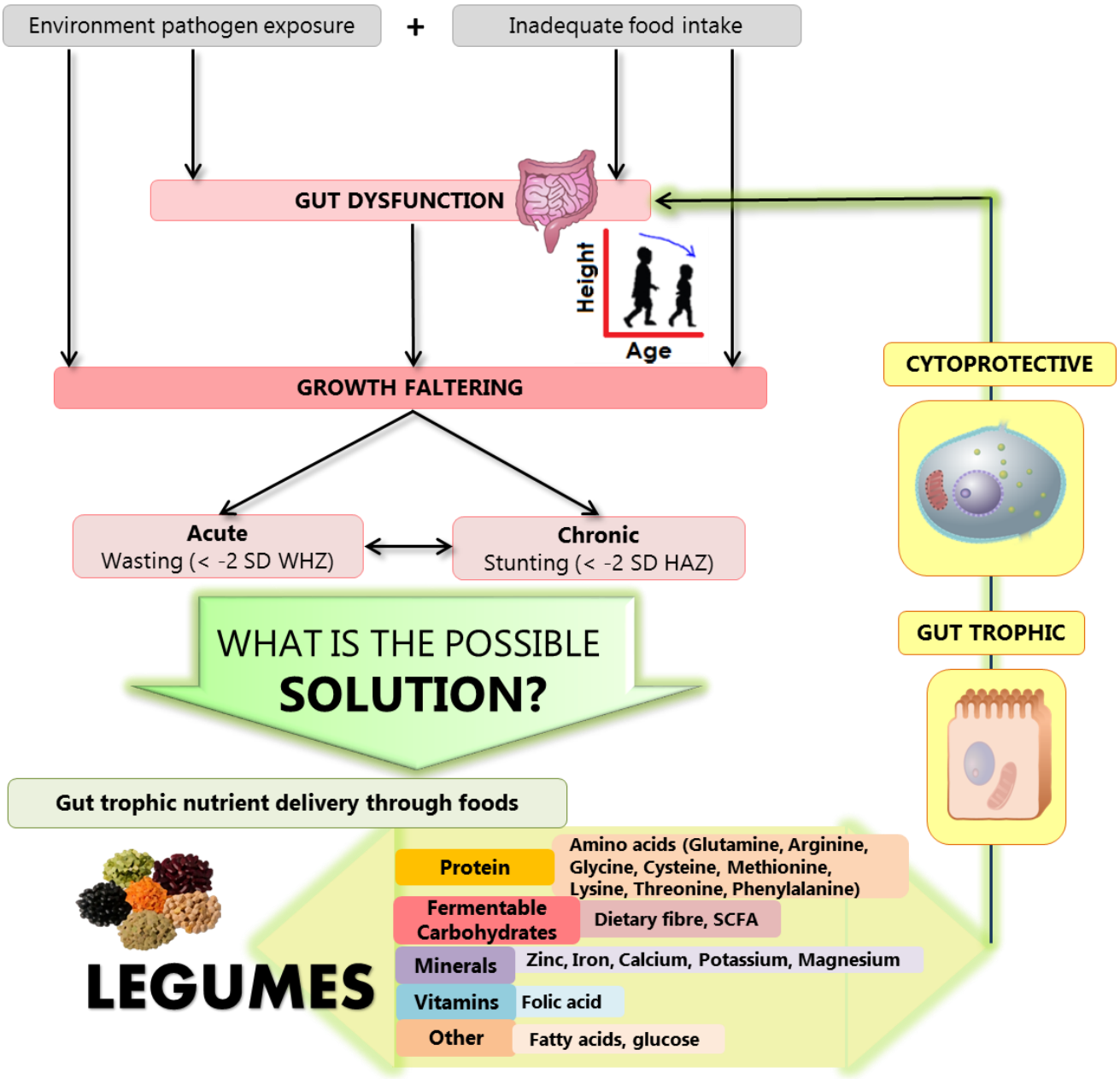

Fig 2. HUNGer consensus of possible solution

The HUNGer consortium will take a multi-national, multi-disciplinary food-based approach which will enhance gut function with the aim of improving acute and chronic health outcomes, in LMIC populations with undernutrition and populations at risk of undernutrition.

Consortium members

Gael Delamare	Campden BRI Group
Dr Kanta Chandwe	Children's Hospital-UTH
Dr Warren Lee	Food and Agriculture Organization of the United Nations
Dr Lesley Drake	Imperial College London
Prof Gary Frost	Imperial College London
Prof Elaine Holmes	Imperial College London
Dr Aaron Lett	Imperial College London
Prof Kath Maitland	Imperial College London
Prof Julian Marchesi	Imperial College London
Dr Jonathan Swann	Imperial College London
Dr Alex Thompson	Imperial College London
Kevin Walsh	Imperial College London
Dr Victor Owino	International Atomic Energy Agency
Prof Claire Domoney	John Innes Centre
Abimbola Adesanmi	National Home grown School Feeding Programme, University of Ibadan
Dr Jennifer Ahn-Jarvis	Quadram Institute Bioscience
Dr Kendall Corbin	Quadram Institute Bioscience
Dr Cathrina Edwards	Quadram Institute Bioscience
Dr Suzanne Harris	Quadram Institute Bioscience
Dr Fred Warren	Quadram Institute Bioscience
Prof Peter Wilde	Quadram Institute Bioscience
Dr Claire Bourke	Queen Mary University of London
Prof Andrew Prendergast	Queen Mary University of London
Dr Ruairi Robertson	Queen Mary University of London
Prof Paul Kelly	Queen Mary University of London and University of Zambia School of Medicine
Dr Sarita Devi	St. John's Research Institute
Dr Anura Kurpad	St. John's Research Institute
Dr Nirupama Shivakumar	St. John's Research Institute
Prof Jens Rehfeld	University of Copenhagen
Prof Christine Edwards	University of Glasgow
Dr Douglas Morrison	University of Glasgow
Prof Tom Preston	University of Glasgow

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