Nutritional and Health-Related Environmental Studies Section

Technical Meeting on Environmental Enteric Dysfunction, Microbiome and Undernutrition

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Despite progress made to date, a large proportion of the population in low- and middle-income countries (LMICs) still live in environments characterized by poor water, sanitation and hygiene (WASH) conditions. According to the WHO and UNICEF, an estimated 2.5 billion people remain without access to improved sanitation facilities (2015)[1]. In addition, many LMICs continue to struggle with a high burden of undernutrition, demonstrated by the nearly 805 million undernourished people worldwide, the vast majority of which live in LMICs (2012-2014)[2]. Environmental enteric dysfunction (EED), a subclinical inflammatory disorder of the gut, is also highly common among impoverished inhabitants of environments with poor sanitation and hygiene, such as those often found in LMICs, and has gained increasing interest as a key pathway linking unsanitary living conditions with different forms of undernutrition (stunting, wasting, underweight, etc.)[3-10]. It is hypothesized that the failure of health interventions, specifically targeting malnutrition in LMICs, can be directly attributed to EED[11]. Likewise, oral vaccines have been observed as being less immunogenic in children from LMICs suggesting that EED may cause altered mucosal immunity in these children[11].

EED is the result of recurring infection in the small intestine via the faecal-oral ingestion route. Constant exposure to commensal and/or pathogenic bacteria in the small intestine induce inflammatory processes, partial villous atrophy, and crypt hyperplasia through a T-cell mediated process, resulting in increased intestinal permeability, decreased nutrient absorption, bacterial translocation, and innate and acquired immune system activation[12]. However, individuals affected typically remain asymptomatic – rarely having overt gastrointestinal symptoms or diarrhoea[11]. These EED-related histological changes of the gut, though, result in harmful health effects including malabsorption and ineffective utilisation of nutrients, as well as a blunted innate immune response, potentially leading to oral vaccine failure and increased susceptibility to infection[11]. One of the most significant impacts of EED may be on undernutrition and potentially growth faltering in children[5]. Moreover, EED potentially contributes to poor response to nutrition therapy[11]. This may ultimately increase child morbidity and mortality, reduce cognitive development, and reduce adult economic productivity.

Multiple studies are underway to explore the complex relationship between WASH, EED, and child malnutrition, health and development[13-15].While this condition is still poorly understood, there is a growing body of evidence that suggests the intermediate biological mechanisms of undernutrition and EED are interrelated in a complex manner – acting both synergistically and as part of a feedback system. A chronically damaged and inflamed gut may increase the likelihood of developing a bodily predisposition to becoming undernourished through several pathways; while being undernourished further compromises healthy intestinal lining, thus increasing susceptibility to additional infection. Chronic inflammation, a symptom of EED, has been associated with altered absorption and ineffective utilisation of micronutrients and macronutrients. Likewise, repetitive infection causing chronic immune activation may result in absorbed nutrients (e.g. amino acids) being diverted towards inflammatory processes instead of being used as building blocks or for serving their metabolic functions[16].

Furthermore, malabsorption may lead to perturbed micronutrient homeostasis, as in the case of iron[17], which can result in anaemia and suboptimal organ development in children. Iron deficiency can also disturb intestinal permeability in children[18].Vitamin A and zinc are crucial for maintaining optimal gut health in early life[19], and may be influential to preventing and treating EED. Vitamin A preserves gut integrity and is associated with increased permeability of the mucosal lining and increased susceptibility to enteric infection under deficient conditions[20-23]. Fluctuations in zinc homeostasis may develop when reduced absorptive capacity, resulting from damaged intestinal mucosa, occurs due to EED[24, 25]. This zinc imbalance both further exacerbates intestinal abnormalities and perpetuates EED through several pathways, including higher susceptibility to enteric infections, disturbed barrier function, and the onset of chronic systemic inflammation[26].

The gut microbiome is subject to a growing trend in scientific interest – it plays vital physiological, immunological, and nutritional/metabolic roles in humans, and has been recognised as one of the primary mediators in several pathological conditions including EED[27]. Small intestine bacterial overgrowth (SIBO), a disorder marked by symptoms including diarrhoea, malnutrition, weight loss and malabsorption, is associated with nutritional deficiencies and should be considered as an additional component to EED linking unsanitary living conditions to child undernutrition and growth faltering[28,29]. Numerous studies have revealed that specific relationships exist between the gut microbiome and both human metabolism and body composition in healthy individuals, but their relevance to individuals with EED warrants further investigation[30]. Indeed, children diagnosed with inflammatory intestinal disorders – similar to EED - have altered body composition (the relative amounts of fat and lean tissue) and show a decrease in lean tissue, which can persist over time[31]. Also, in stunted children, often suffering from EED, a greater accumulation of body fat and a lower gain in lean mass was observed[32].

A clear gold standard for diagnosis of EED is not yet defined. The most widely used surrogate marker for epithelial integrity is the lactulose: mannitol test, in which the subject is given an oral solution containing lactulose and mannitol. Several serum and faecal biomarkers have been studied as indicators of intestinal inflammation with a few having only been studied in populations at risk for EED[11]. In this regard, more research is needed to assess potential biomarkers for the diagnosis of EED.

Considering the bidirectional relationship between EED and undernutrition, holistic and targeted nutrition interventions (prevention and treatment) are needed to concurrently mitigate the histological and functional changes associated with EED while correcting for nutritional deficiencies[33]. Improving WASH conditions and knowledge, attitudes, and practices (KAPs) is undoubtedly of great importance when trying to restore intestinal functionality. However, solely improving WASH conditions and KAPs is not sufficient to combat EED or mitigate subsequent child growth faltering, as demonstrated in Nepal[34]. Vitamin and mineral supplementation should be considered as a viable intervention as multiple studies have shown that iron, vitamin A, and zinc supplementation – given individually (vitamin A, zinc) or in combination (iron, vitamin and zinc) – ameliorate intestinal morphology, decrease intestinal permeability, improve gut functionality, and promote linear growth [20,21, 27, 35, 36]. However, nutritional status and intakes of specific micronutrients may also influence the gut microbiome. It appears that an increase in unabsorbed dietary iron through fortification or supplementation could modify the colonic microbiota equilibrium and favour growth of pathogenic strains over beneficial 'barrier' strains. Additionally, studies have revealed that providing micronutrient powders with iron to weaning infants adversely affects the gut microbiome, increasing pathogen abundance and causing intestinal inflammation[42-48].

The goal of the International Atomic Energy Agency (IAEA) is to enhance the capabilities of Member States to address needs related to the management of all forms of malnutrition. The IAEA contributes towards the global health nutrition agenda by promoting the use of stable isotope techniques in developing and evaluating nutrition interventions, which are more accurate and sensitive than conventional techniques, safe to use across all ages, and can be used in a community setting. Supporting the use of stable isotope techniques to assess the bioavailability of micronutrients – including iron and zinc – from foods and assessing an individuals' vitamin A status could provide Member States with the necessary evidence to design or improve the management of EED and undernutrition, especially as micronutrients have been demonstrated as having a function in both exacerbating (deficiency) and treating (adequate intake) EED. Stable isotope techniques have, in fact, already been identified by an expert group as the method of choice for evaluating the role of zinc nutrition in EED vulnerable children[37]. Furthermore, these techniques were recognized as a potent tool in investigating micronutrient absorption in children with EED, and as such, they were included in the report of the Second World Congress of Pediatric Gastroenterology, Hepatology and Nutrition[41]. Stable isotopes can also be used to assess body composition (deuterium dilution technique), which could be crucial in investigating the impact EED has on the quality of growth in early life. There is also emerging evidence that demonstrates the potential use of breath tests with ^{13}C-labelled sugars (sucrose and glucose) as a novel, non-invasive biomarker of gut integrity and absorptive capacity to diagnose children with EED and detect SIBO[38,39]. Stable isotopes can also be effectively used to measure the metabolic activity of the gut microbiome, which could contribute towards revealing the microbiome's influence on EED and undernutrition[40].

Keeping in mind the promising role of stable isotope techniques to contribute to a better understanding of the relationships between EED, the microbiome and undernutrition, the IAEA plans to organize a Technical Meeting to discuss the multifaceted and interrelated challenges and research gaps in the area of EED.

Meeting Objectives

This technical meeting will take place over the course of three days, 28-30 October 2015, and bring together experts working in the field of EED and experts knowledgeable in the application of stable isotope techniques in nutrition. The meeting will have the following objectives:

- Discuss current knowledge and gaps on the causes and consequences of EED
- Share experiences related to the implementation and evaluation of programmes to prevent and treat EED in infants, children, and adults
- Discuss technical issues and strategies related to the management of EED and undernutrition, including tests for diagnosis
- Identify knowledge gaps in the field of EED where the IAEA can add value by supporting the use of stable isotope techniques

List of Topics

- Interactions between EED and undernutrition
- Nutrition interventions in children and adults suffering from EED and undernutrition
- Effects of EED on growth, body composition and functional outcomes
- Application of novel, low-cost, non-invasive methods of diagnosis of inflammation, permeability and SIBO with a focus on stable isotope techniques
- Contribution of stable isotope techniques to assess absorption of micronutrients (zinc, iron, and vitamin A) in the context of EED

Expected outcome

The outcome of the Technical Meeting will be recommendations that identify the role of the IAEA in the global effort to address EED and undernutrition through the application of stable isotope techniques.

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