A Case Study of Fecal Microbiota Product to Treat Malnutrition

PROBLEM:
Malnutrition is the leading cause of child mortality worldwide and the gut microbiota may play a significant role in the pathology of malnutrition. According to a study comparing the gut microbiota of healthy and severely malnourished children from the same slum area of Dhaka, Bangladesh, starvation disrupts the development of a healthy microbiome in the crucial two years after birth. This disruption persisted even after the malnutrition was treated with high-nutrient foods. Dr. Jeff Gordon and his team compared the diversity and proportions of different species in samples obtained from healthy children and found that the relative abundances of 24 species strongly correlated with the child's age when the sample was taken. They found that the proportions of the 24 species changed as the children grew older, and that particular microbial compositions correlated with age across all the children. When the researchers analyzed the gut microbiota of starving children from the same part of Dhaka, they found that the microbial composition did not correspond to the children's actual age but instead to a microbiome of a younger healthy child. The discrepancy was greatest in the most severely malnourished children. Although the microbiota temporarily “matured” after feeding treatment had improved the children's weight and nutritional status, it soon returned to a 'young for age' status. More extensive analysis of the microbiomes of the malnourished children showed that they were less diverse and that many species were less abundant than in healthy children of similar age. The results suggest that the composition of gut microbiota, which is known to contribute to immune function and nutrient extraction, could play a significant role in malnutrition.¹

In another study, Dr. Michelle Smith and her team transplanted stool samples from Malawian infants into sterile baby mice. Even though all mice ate the same food, those that received stool from an underweight infant with kwashiorkor (a severe form of protein malnutrition) put on less weight and developed weaker bones than those which received a healthy baby’s microbiome.² The study revealed that disturbances in microbiome assembly and function (e.g., those prompted by enteropathogen infection) affect the risk for kwashiorkor; and, in a self-reinforcing pathogenic cascade, malnutrition affects gut microbiome functions involved in determining nutritional status, thus further worsening health status.³

According to Smith and Gordon, the nutritional status of children might be modifiable through manipulation of the gut microbiota.⁴ Gordon has stated that he is interested in the next

generation of foods that are microbiota-directed, readily available, affordable, and culturally acceptable.5

Fictitious Scenario:
Imagine that researchers develop a new microbiota-based food intervention that enhances the representation and beneficial functions of growth-promoting gut microbes to produce durable repair of microbiota immaturity in malnourished children and produce better long-term clinical outcomes. The product is an odorless, tasteless powdered preparation, made from purified and freeze-dried intestinal bacterial cultures derived from the stool of a single healthy donor. The therapeutic goal of the product is long-term engraftment.

The product will be added to ready-to-use therapeutic food (RUTF). RUTF is a standardized, fortified peanut-based meals handed out by aid organizations to feed malnourished children. This pathway of administration was selected because the distribution channels for RUTF are already in place. Nitrogen flush packaging will allow for an unrefrigerated shelf life of up to 2 years.6 The RUTF will be processed in accordance with USDA standards for RUTFs which requires adherence to applicable World Health Organization’s Codex Alimentarius Standards and FDA’s Current Good Manufacturing practices. The effectiveness of the intervention will be studied using a cluster randomized trial of 12 villages in which six villages are randomized to intervention (bacteria supplemented RUTF) and six villages to control (traditional RUTF).

At present, USDA (not FDA) regulates RUTF and considers it a food, not a drug. Under current guidelines, addition of microbiota product to a RUTF would not be allowed by USDA or WHO, which clearly outlines what ingredients and micronutrients can be added to RUTF.7

Questions for Working Group:
● Is this product a microbiota transplant or a probiotic?
● With the added microbiota product, should the RUTF product still be considered a food or is it now a medical food, food additive, dietary supplement or drug?

Important Definitions
● Food - articles used for food or drink for man or animals; chewing gum; and articles used for components of food.8 Within this broad category are subcategories of food that the Center for Food Safety and Applied Nutrition (CFSAN) regulates and that are defined below:

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7 https://www.ams.usda.gov/sites/default/files/media/CID%20Therapeutic%20Food,%20Ready-To-Use.pdf
8 FDCA, Sec. 201(f) (codified at 21 U.S.C. § 321(f)).
o Food additives/GRAS additives – any substance that is a component of food or otherwise affects the characteristics of food. Most food additives are considered generally recognized as safe (GRAS) additives because they are generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of their intended use.\(^9\) Food additives or GRAS substances must be consistent and able to be characterized.

o Medical food – a food which is formulated to be consumed or administered enterally\(^10\) under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.\(^11\) Medical foods do not need pre-market notification or approval but must contain conventional food, approved food additives or GRAS substances.

- Dietary supplement – a product that is intended to supplement the diet and contains any of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; or a concentrate, metabolite, constituent, or extract; or combination of any of the above. The product must be a substance historically used by man to supplement the diet; intended for ingestion in pill, capsule, tablet, powder or liquid form; not represented for use as a conventional food or as the sole item of a meal or diet; and labeled as a “dietary supplement.”\(^12\) A new dietary supplement (NDI) must go through the NDI approval pathway which requires, among other things that the ingredient can be characterized and that FDA be notified.

- Drug – an article that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or in other animals.\(^13\)

- For products manufactured in the US but made SOLELY for distribution outside the US, manufacturers must follow US rules regarding production and export (i.e. follow good manufacturing standards and brand food “solely for export” see FDCA sec 801(e) (1)) but the product itself would be governed by the food and drug laws of receiving country.

\(^9\) FDCA, Secs. 201(s), 409; 21 C.F.R. § 170.30.
\(^10\) In other words, administered through the mouth.
\(^11\) Section 5(b) of the Orphan Drug Act, 21 U.S.C. § 360ee(b)(3).
\(^12\) Dietary Supplement Health and Education Act (DSHEA) of 1994, Pub. L. No. 103-417, 108 Stat. 4153; FDCA, Sec. 413(c); 21 U.S.C. § 350(b).
\(^13\) 21 U.S.C. § 321(g).