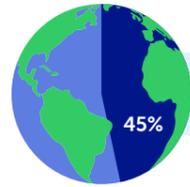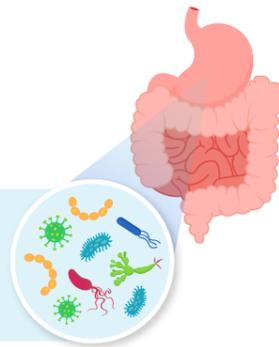## Childhood malnutrition is responsible for an estimated 45% of childhood mortality worldwide
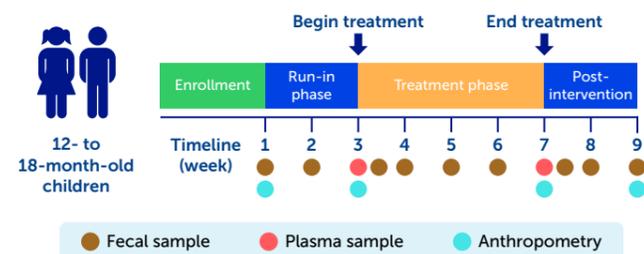

Undernutrition is associated with gut microbiota "immaturity"

One approach to address undernutrition is gut microbiota-directed complementary foods (MDCF) – specialized dietary formulations designed to promote gut health and microbial diversity in children, supporting weight gain, improved immune function and overall health

A randomized controlled feeding study conducted in undernourished Bangladeshi children
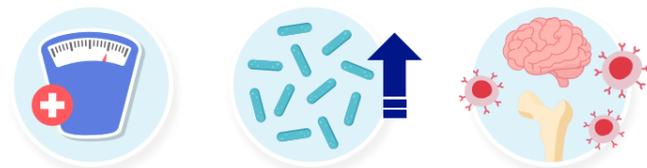
One MDCF was developed (MDCF-2) and tested aginst a control ready-to-use supplementary food (RUSF) in 12- to 18-month-old children

12- to 18-month-old children

Fecal sample   Plasma sample   Anthropometry

Ingredient (g/100g)	Control RUSF	Microbiota-directed MDCF-1	MDCF-2	MDCF-3
Chickpea flour	-	8	10	30
Peanut flour	-	7	10	-
Soy flour	-	5	8	14
Raw banana	-	19	19	-
Rice	18.9	-	-	-
Lentil	21.5	-	-	-
Powdered skimmed milk	10.5	11.5	-	-
Sugar	17	24.3	29.9	30.9
Soybean oil	29	22	20	22
Micronutrient premix	3.14	3.1	3.14	3.1
Protein	10.2	12.4	11.8	13.9
Fat	29.5	22.8	20.8	24.1
Carbohydrate	31.8	18.6	16.3	22
Fiber	4.7	3.3	4.5	5.6
Protein energy ratio (PER)	8.3	11.9	11.61	11.7
Fat energy ratio (FER)	53.6	49.3	46.2	45.7
Total calories per 100g	494.6	416.1	406.8	475.8

Compared to the RUSF, MDCF-2 significantly increased weight gain, abundances of growth-associated gut bacterial strains, and improved biomarkers of growth, bone formation, neurodevelopment and immune function in children with moderate acute malnutrition

These findings may be used to support the development of therapeutic foods for other health conditions associated with altered microbial patterns

Microbiome-targeted dietary regimens to combat pediatric malnutrition

Childhood undernutrition remains a serious global health problem, especially in low- and middle-income countries, and is responsible for an estimated 45% of childhood mortality worldwide[1]. In 2022, an estimated 148 million children under the age of five globally were stunted (i.e., short for their chronological age)[2], while 45 million children under 5 were wasted (i.e., underweight for their height). At the other end of the nutrition scale, the ready availability of nutrient-poor ultra-processed foods has contributed to 37 million children under 5 being designated as overweight. Survivors of malnutrition exhibit stunted growth, impaired cognitive development and vaccine responses, and metabolic abnormalities.

A burgeoning body of evidence indicates that undernutrition is not caused solely by food insecurity and is influenced by a range of environmental factors such as maternal nutritional status, poor sanitation, and

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infection by pathogens[3]. Because the gut microbiota impacts host physiology via the harvesting of key nutrients from diet, priming innate and adaptive immune responses, shoring up epithelial barrier integrity, and providing colonization resistance to enteropathogens, it has emerged as a compelling target for treating undernutrition[4]. Studies that characterize the developmental biology of the gut microbiota in infants and young children have revealed that healthy growth is associated with linear growth, and that disruption of this developmental program is causally linked to the pathogenesis of undernutrition (termed "microbiota immaturity"). These studies have also shown that treatment of current therapeutic foods to undernourished Bangladeshi children only transiently rescues this dysbiosis, likely because they were not designed with a consideration of the developmental biology of the gut microbial community[5,6]. Thus, we hypothesized that treatment of undernourished children with microbiota-directed complementary foods (MDCFs) to repair their gut microbiota immaturity would improve health-related outcomes such as improved gut barrier function, immune function, metabolism, and linear growth.

Locally available, culturally accepted food ingredients were tested in gnotobiotic mice for their ability to promote the absolute abundances of growth-associated gut bacterial strains that are underrepresented in the microbiota of children with moderate and severe acute malnutrition (MAM and SAM, respectively)[6]. Lead food ingredients from these screens (peanut, chickpea flour, soybean flour and banana) were assembled into MDCF prototypes that selectively increased the abundances of targeted taxa and improved biomarkers of growth in gnotobiotic mice and gnotobiotic piglets[6]. These prototypes were then advanced to a randomized, double-blind study to test their effects in Bangladeshi children with MAM[6]. MDCF-2, which contained all four lead ingredients and lacked milk powder significantly increased weight gain, abundances of growth-associated gut bacterial strains, and improved biomarkers of growth, bone formation, neurodevelopment and immune function in children with MAM, compared to a ready-to-use supplementary food (RUSF)[6,7]. Following this work, a trial with greater statistical power and longer treatment was performed on 120 Bangladeshi children with MAM that were fed either MDCF-2 or RUSF over three months. MDCF-2 produced a rate of weight gain that was significantly greater than that observed with RUSF, even though the caloric density of MDCF-2 is 15% lower than that of RUSF[8]. Two growth-associated *Prevotella copri* metagenomic-associated genomes are key utilizers of MDCF-2 glycans[9,10].

Our work has also examined how MDCFs, via microbial metabolism of constituent nutrients, might induce changes in host signaling that lead to improved growth. These efforts led to the identification of a gut microbial fatty acid amide hydrolase (FAAH) enzyme encoded by a growth-associated *Faecalibacterium prausnitzii* strain that catalyzes the hydrolysis and synthesis of a diverse pool of bioactive compounds such as *N*-acylated conjugates of amino acids, dopamine, and GABA that could potentially be manipulated for more precise and effective therapies[11]. We observed that administration of MDCF-2 reduced gut luminal levels of oleoylethanolamide, a lipid mediator that is known to mediate satiety and stimulate fat utilization[11]. Thus, combating the profound loss of appetite exhibited by undernourished children represents a beneficial effect of MDCF-2 treatment[11].

Next-generation formulations of therapeutic foods must also account for the unique nutritional demands of the human brain. The Guatemala study showed that children from villages that received a high-calorie, low-protein nutritional supplement compared to those that received a protein-rich supplement had lower cognitive test results and earnings as adults[12]. Much attention and resources have been directed toward improving nutrition during the critical first 1,000 days of life, and consequently, the development of specific organs and organ systems in late childhood and adolescence have been neglected[13]. Although the human brain reaches approximately 85% of its adult mass by 3 years of age, evidence indicates that brain development extends well beyond the first 1,000 days[14]. Notably, the brain undergoes anatomic remodeling at multiple time scales and levels of organization throughout life[15], with synaptic plasticity, myelination, and pruning having high energetic demands. Meeting these metabolic and nutritional requirements for promoting optimal brain development is of paramount societal importance.

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