Probiotic Fermented Foods

A scalable approach to promote gut health and improve nutrition

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Key messages

> The emerging human microbiome paradigm is shedding new light on the centrality of beneficial microbial communities to both enteric and overall human health, with important implications for human nutrition.

> As a result of inadequate diets and high infectious disease burden, children in resource-poor communities can become entrapped in the malnutrition-infection cycle in which undernutrition increases susceptibility to infection and subsequent infections exacerbate undernutrition.

> Interventions to promote a healthy gut microbiome can decrease host susceptibility to enteropathies, including diarrheal disease, and promote nutritional well-being.

> A sustainable approach in resource-poor settings is to build upon the age-old practice of fermenting foods as the vehicle for consistent intake of beneficial microorganisms.

> Locally produced probiotic fermented foods can be suitable for a range of appropriate, cost-effective, scalable, and sustainable approaches implemented at the household, community, and market levels.

Introduction

Enteric and diarrheal diseases are a major cause of child mortality. Annually, over half a million children under five die in low- and middle-income countries (LMICs) because of complications related to diarrhea.[1] With or without overt diarrhea, enteric infections account for 25% of child stunting globally and are a major contributor to impaired cognitive development.[2] Undernutrition of children and mothers, both chronic and acute, is the leading underlying cause of child morbidity and mortality. Global estimates indicate that undernutrition directly contributes to 45% of all child deaths, some 3.1 million annually.[2] In addition, at least 151 million children are affected by stunting, 51 million children are affected by wasting,[3] and 2 billion people suffer from deficiencies of essential micronutrients such as vitamin A, iron and zinc.[2] Enteric dysfunctions and undernutrition exhibit synergy, which amplifies the aforementioned deficits in child growth and development, limits a child's future potential, and provokes enormous losses of human capital.[2,4]

> "DNA sequencing has revolutionized our understanding of the role of microbes in human health and disease prevention"

Over the last two decades, technological and scientific advances stemming from the rapid development of high-throughput DNA sequencing techniques and studies on the composition and activity of the human microbiota have revolutionized our understanding of the role of microbes in human health and disease prevention. These advances enable innovative interventions, such as the introduction of health-promoting bacteria,

Schoolchildren enjoying Yoba probiotic yogurt in Uganda

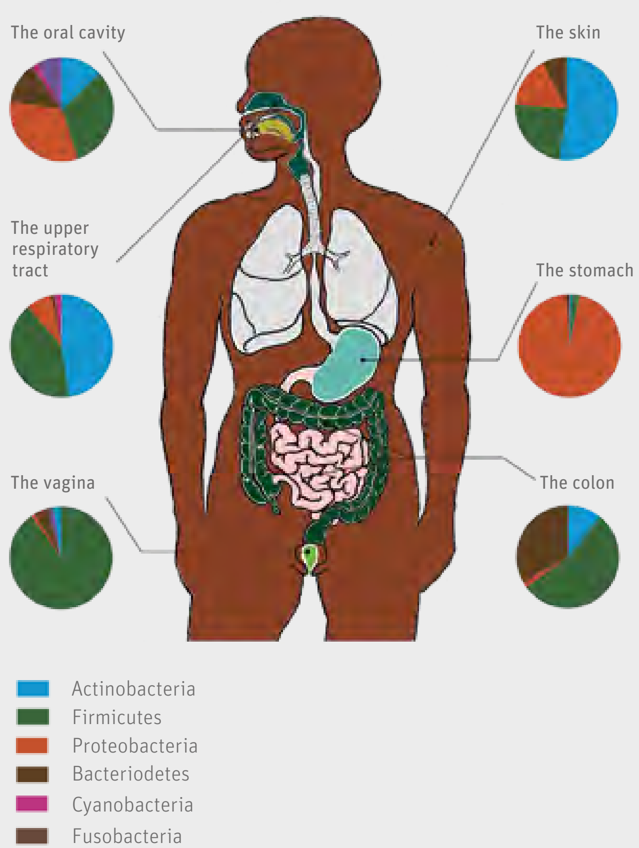
that can both lessen the burden of enteric and diarrheal disease and improve the nutritional status of young children around the world.[5,6,7] Such innovative technologies and approaches can build on the age-old traditional healthy practice of food fermentation to enhance gut health and prevent malnutrition in resource-poor communities. They additionally have the potential to sustainably scale up from the household to the global market level. More specifically, we propose that fermented foods containing probiotics can provide solutions to improve gut health with the potential for scaling up at low cost and affordably for resource-poor communities.

The human microbiome as a new paradigm in health and nutrition

Children's nutritional status is directly associated with the integrity of their gut, also known as the enteric system. When the enteric environment is disturbed, a child is at increased risk of nutritional dysfunction due to nutrient malabsorption and enteric infections such as diarrheal disease.[3,8,9] The emerging human microbiome paradigm is shedding new light on the centrality of beneficial microbial communities to both enteric and overall human health. This complex enteric ecosystem hosts over 100 trillion microorganisms – the gastrointestinal microbiota – consisting of hundreds of different species of bacteria, archaea, fungi, protists, and viruses. The vast majority of these microorganisms live in a mutualistic or commensal relationship with their host. A healthy human gut provides a supportive habitat for microbiota, with a steady supply of nutrition for optimal growth and development. In turn, microbiota support digestive processes of the host, prevent colonization of the gut by pathogens, and promote proper development of intestinal epithelium and immune responses. Together, the gastrointestinal system and its microbiome serve as the first line of immune defense for the body, acting as a gatekeeper to allow the absorption of essential nutrients while preventing pathogenic infiltration.[11]

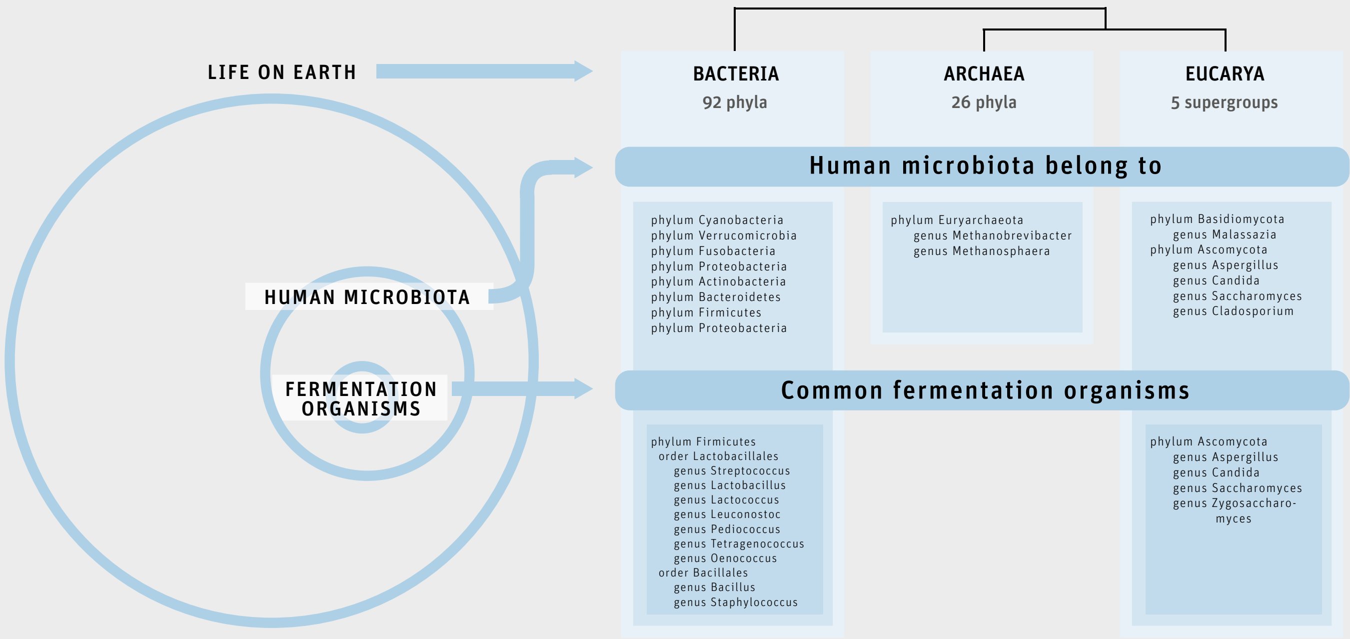
> "Growing evidence points to the critical role of the gut microbiome in determining nutritional outcomes"

A growing body of evidence points to the critical role of the gut microbiome in determining nutritional outcomes and supporting overall child health and development.[12,13] A healthy and homeostatic gastrointestinal system capable of maximizing the nutritional value of ingested foods fundamentally depends on



Credit: Image adapted with permission from the book *De microbemens* (The Microbe Man), authored by Remco Kort (2017, Atheneaeum – Polak & van Gennep).

Composition of bacterial phyla present in the human microbiota



Credit: Remco Kort

Venn diagram indicating the estimated number of microbial phyla (= taxonomic group) on earth associated with the human body and involved in food fermentation. The diagram indicates that the bacterial phyla and their species involved in fermentation are a subset of those that are part of the human microbiota. Hence, microbes involved in food fermentation have their counterparts in the human body with similar physiological characteristics. Many isolates from the human body with probiotic properties can therefore be propagated during the process of fermentation in specific food matrices.

a healthy microbiome. In turn, dietary choices directly impact the composition and function of the gut microbiome.[14] Young children in resource-poor settings have inadequate diets that negatively affect their gut microbiome profile. They are also exposed to unsanitary conditions that increase the likelihood of persistent and repeated bouts of enteric infection. As a result of poor diet and high infectious disease burden, these children can become entrapped in a vicious cycle where undernutrition increases susceptibility to infection and then infection exacerbates nutrient deficiencies.[3,15,16,17] Interventions promoting a healthy gut microbiome can decrease host susceptibility to enteropathies, including diarrheal disease, and promote nutritional well-being.[18]

The benefits of a healthy gut microbiome far exceed the absence of intestinal disease and pathogenic domination. A healthy gut microbiome secretes compounds and produces metabolites that are beneficial to the intestinal environment and the host. By feasting on foods consumed by the host, the bacteria produce essential vitamins, such as vitamins B and K.[19] Overall immune function is also boosted by the microbiome, due to interaction of microbiota with immune cells present at the intestinal epithelium.[9] In addition, the microbiota play a key role in the production of immune-regulating short-chain fatty acids, which also act as a fuel for epithelial cells. Emerging evidence also suggests that gut dysbiosis likely impacts the long-term health of children into their adult years. Overweight, obesity, and certain associated chronic diseases have been linked to the compositional profile of the gut microbiome, with a marked difference in the overall microbiota makeup found in comparison to healthy-weight individuals.[12,20]

Toward a healthy gut microbiome

Although there is high variability between individuals and geographies in terms of gut microbiome composition, with similar functions often performed by different microbes, patterns of what could constitute a healthy microbiome are being recognized and hold promise in the design of gut health interventions.

Assembly of the gut microbiome starts at birth and matures into a stable configuration, primarily during the first three years of life.[21] Parturition is believed to supply the initial microbial load to neonates, with the vaginal and fecal microbiome of the mother and the skin of those handling the newborn acting as the primary sources.[22] Human milk helps colonize the infant's gut through microbes that are compositionally linked to the mother's microbiome, as well as oligosaccharides and other milk glycoconjugates that act as nutritious substrates for microbial symbionts, particularly of the *Bifidobacterium* genus.[23] Recent evidence shows that a healthy child's gut undergoes a maturation process that is most intense during the first two years of life and is characterized by specific microbial community configurations that distinguish an age-appropriate microbiome. Malnourished children, by contrast, exhibit gut microbiota configurations that remained behind in the development and resemble those of children many months younger.[12]

The mature homeostatic microbiome is characterized by high taxon diversity with a predominance of commensal microbiota. Taxon diversity enables the development of complex functional networks of both microbe-microbe and host-microbe natures. These functional networks operate as cooperative consortia that perform vital metabolic tasks for the host: the more numerous and interconnected such networks are, the greater the microbiome's stability and resilience.[21] Within the gut ecosystem, there is intense biochemical communication among microbes (both intra-species and inter-species) and host cells, an example of which is the quorum sensing mechanism.[24] The predominance of commensal and beneficial microbiota keeps pathogen populations in check through direct competition for nutrients and gut mucosal substrate, direct inhibition via production of bacteriocins, and immune system modulation. At the same time, the immune system shapes and shepherds the gut microbiome through a wide variety of molecular and cellular mechanisms.[13] External factors also play a key role in shaping the gut microbiome, with diet, medication, and age being the most prominent.[13] Recent research demonstrates that even short-term dietary changes can modify microbial community structure and overwhelm inter-individual differences in microbial gene expression.[25]

Box 1: Fermented foods

The origins of food fermentation as a food preservation method remain unclear, but it most likely began in the Neolithic Period over 10,000 years ago when populations shifted from food gatherers to food producers. Fermented foods provide a natural source of beneficial bacteria and yeasts and were traditionally produced by most human societies within the home as a means of preservation. Modern-day examples that are widely consumed include yogurt, kefir, cheese, sauerkraut, kimchi, fermented porridges, and injera. The ability to ferment foods enabled safe consumption of dairy and vegetable products regardless of season and improved shelf life without refrigeration. Fermented foods thus offer a foundation for promoting gut health that is safe, affordable, and accepted across societies in different forms. The use of affordable starter cultures can further enhance the quality and safe production of fermented foods and the resulting meals can be used as a platform for the delivery of beneficial microbes and strains optimized for specific age groups and nutritional needs.[28,29,30]

"Even short-term dietary changes can modify microbial community structure"

The enormous potential of dietary interventions to promote a healthy gut microbiome has led to the development of a large market for so-called "probiotic" products in Europe, North America, and Asia. These products usually fall into two categories: supplements and foods. Supplements are typically commercialized in tablet or powder form; examples of foods with probiotic claims include a variety of premium beverages and yogurts. Both probiotic supplements and foods may offer an appropriate approach to promote gut health in resource-rich areas, but present serious drawbacks for sustainable utilization in resource-poor settings. Their premium positioning and pricing, as well as intellectual property restrictions, put them out of reach for the populations that stand to benefit the most from improved gut health.[26] Generic probiotics may increase affordability, but barriers to access remain. Consistent intake of supplements would require costly supply chain setups to meet a yet-to-materialize demand through local markets or health systems. In the case of com-

Micrograph of the "yogurt consortium" containing *Lactobacillus delbrueckii* subsp. *bulgaricus* (pink) and *Streptococcus thermophilus* (yellow)

TABLE 1: Potential benefits of regular consumption of locally produced fermented foods for nutrition and health as well as social and economic factors

Nutrition and health	
Immune response	Fermented food products can significantly improve both specific (e.g., targeted response against specific pathogens) and nonspecific immune responses (e.g., protection against foreign material perceived to be harmful).[31,32,33,34,35]
Diarrheal prevention and treatment	Beneficial microbiota used in clinical settings have been shown to reduce diarrheal duration by 14% and stool frequency on the second day of treatment by 13%.[36] Several strains have been shown to significantly prevent and/or treat diarrheal episodes, including *Lactobacillus rhamnosus GG,*[37] *Saccharomyces boulardii,*[38] *Lactobacillus reuteri,*[39] and *Bifidobacterium lactis.*
Carbohydrate digestibility	Microorganisms present in fermented foods thrive on that food's carbohydrates prior to ingestion by the host. This partial breakdown of carbohydrates by the microorganisms benefits the human body by enhancing digestibility.[40] Furthermore, fermenting lactose-containing foods – such as milk in yogurt production – has been noted to significantly reduce lactose content and improve digestion in lactose-intolerant individuals.[41]
Nutrient density	A fermentation process involving amylase-rich flour (ARF) and a small amount of lactic acid bacteria starter culture increases the flour's fluidity, enabling addition of more ARF for increased nutrient density.[44]
Production of essential nutrients	Beneficial bacteria at the gut level produce essential vitamin B_{12} and vitamin K, which can be absorbed at the colon rather than the small intestine, as occurs with orally consumed vitamins.[18]
Counteracting antinutritional factors	The ideal fermentation process provides optimum pH conditions for the degradation of phytate by phytase, thereby increasing the amount of bioavailable iron, zinc, and calcium, magnesium, and proteins.[42]
Aflatoxin degradation	Lactic acid bacteria fermentation can be used as an approach to significantly reduce aflatoxin levels within food.[43,44]
Heavy metal detoxification	The application of lactic acid bacteria and yeast as probiotics can be used to eliminate, inactivate, or reduce the bioavailability of toxic metals and toxins in food and feed.[45]
Social and economic	
Income generation and women's empowerment	Household and community production of fermented foods offer revenue-generating opportunities, particularly for women.[26]
Preservation	Fermentation promotes natural conservation of perishable foods, reducing food waste and creating preserved foods for later consumption and sale.[30]

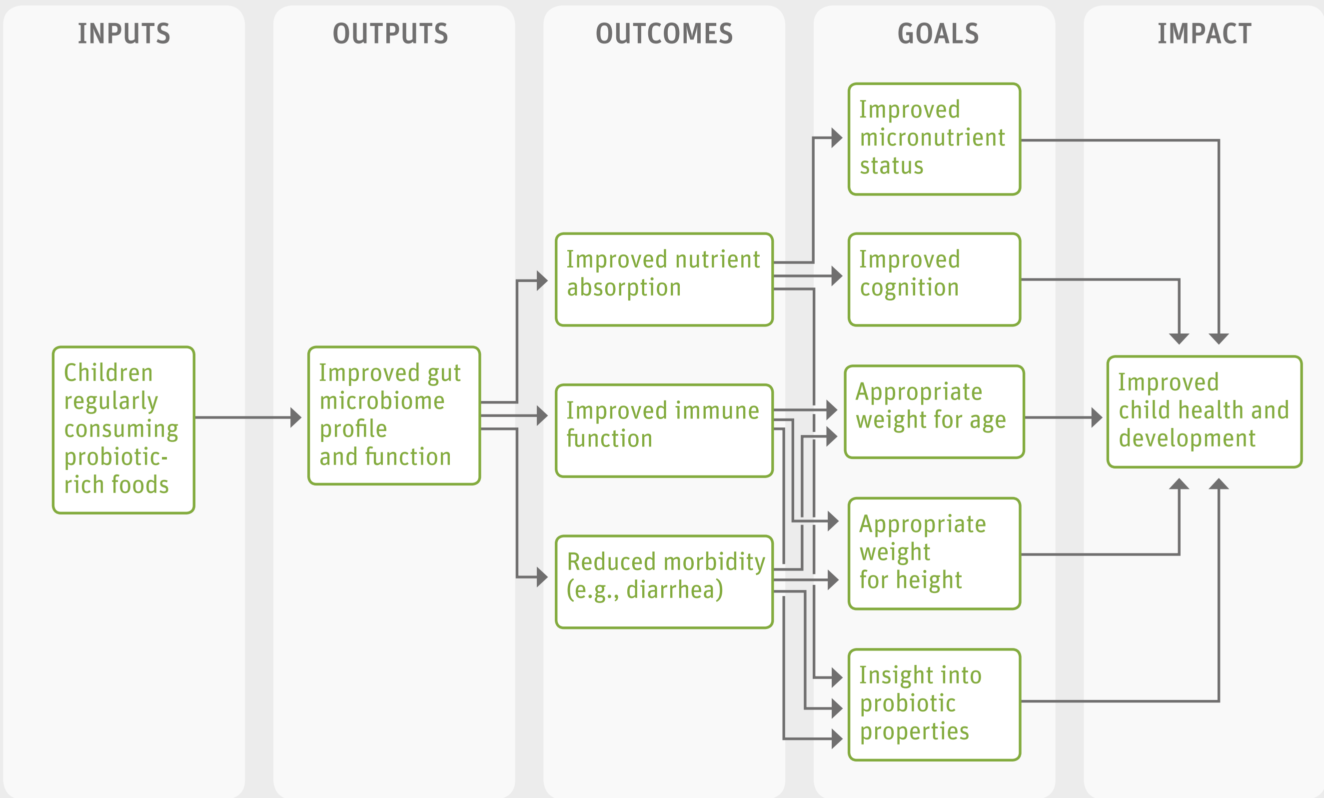
mercial foods, cold-chain transport and storage requirements often limit availability to urban and peri-urban areas. Last-mile challenges all but preclude rural and remote populations being served by either product category.

Probiotic fermented foods

In contrast, a much more sustainable approach in resource-poor settings is to build upon the age-old practice of fermenting foods (**Box 1**) as the vehicle for consistent intake of beneficial microorganisms. It is worth noting that naturally fermented foods intrinsically contain microorganisms with health benefits. However, these benefits have not been extensively studied or proven in scientific research due to the complexity, variability, and undefined nature of these foods. In addition, functional fermented foods or probiotic fermented foods are defined as foods with specific health benefits resulting from probiotic strains – often from human origin – present in the fermentation process. Both types of food are suitable for a range of appropriate, cost-effective, scalable, and sustainable approaches that can be implemented at the household, community, and market levels. **Table 1** lists the benefits that locally produced fermented foods could generate for nutrition, health, and socioeconomic purposes.

A particularly vulnerable age group that is likely to benefit from this intentional use of probiotic fermented foods is young children in resource-poor settings. Even in areas where such foods are already part of children's diets, for example in the form of yogurt or fermented porridges, targeted starter cultures may be used to enhance the probiotic profile of the fermented food and increase its beneficial impact on the child's

FIGURE 1: Logical framework representing the impact pathways of probiotic fermented foods for children



health. **Figure 1** depicts the pathways by which probiotic-rich fermented foods and a healthy gut microbiome can influence health outcomes and positively influence child health and development. It is presumed that regular access to and consumption of fermented food products, when combined with other interventions, lead to improved health and development through increased nutrient absorption, improved immune function, and decreased morbidity due to enteric infections.

Local entrepreneur producing probiotic yogurt in Tanzania

Examples of locally produced probiotic fermented foods include a state-supported program in Argentina, Yogurito, and a grassroots initiative for the local production and distribution of an affordable probiotic yogurt in East Africa, Yoba for Life.[46] In Argentina, a fermented milk containing probiotic *Lactobacillus rhamnosus* CRL1505 has been incorporated into the official nutritional programs of northern Argentinian provinces and provided to more than 300,000 children on school days. In East Africa, the Yoba for Life Foundation developed an innovative starter culture containing the probiotic bacterium *Lactobacillus rhamnosus* yoba 2012, the generic variant of the world's best-documented probiotic strain *L. rhamnosus* GG.[47] One gram of the Yoba starter culture enables the production of 100 liters of probiotic yogurt. This concept has been adopted by local entrepreneurs and currently more than 200 production units in Uganda, Tanzania, and Kenya are transforming nutritious milk into Yoba's even healthier probiotic fermented yogurt reaching over 250,000 consumers.[26]

These examples illustrate the potential of probiotic fermented foods to cost-effectively and sustainably promote gut and overall health in resource-poor settings.[47,48] However, in order to fully realize this potential, several issues need to be addressed through research, piloting of interventions, policy development, and legislation (**Table 2**).

"The growing knowledge of the host-microbiome relationship has the potential to create substantial positive impact on the health and lives of millions"

Looking ahead

As the human microbiome scientific revolution continues to unfold, it brings forth an exciting opportunity to put the cutting edge of science at the service of the most vulnerable populations. The growing knowledge of the host-microbiome relationship has the potential to create substantial positive impact on the health and lives of millions of underprivileged children and families throughout the world.

Most of the research in this field has thus far focused on isolating specific bacterial and yeast strains and subspecies, testing them for clinical benefits, and developing probiotic products based on them. A more promising, translational approach for low-resource settings is to identify commonly consumed fermented foods, characterize their microbiological profile, and assess the impact of the intrinsic strains on gut health, as well as the potential of boosting them with microbial communities or strains with known efficacy and health benefits. The probiotic fermented foods will in this way serve as a vehicle for beneficial microbes, as well as a source of naturally enriched and sustainably produced healthy and appealing food.[49] This concept enables a wide range of opportunities for production and marketing at the household, community, and market levels.[50]

Looking further into the future, we can envision what the next generations of probiotic fermented food will look like. We expect to see the emergence of fermented foods made by using starter cultures containing locally sourced probiotics, obtained from donors who showed a specific health characteristic when exposed to challenging environments and poor diets.[33] In parallel, we envisage the development of fermented foods containing genetically engineered strains enhancing the nutritional properties of the food, e.g., by specific conversion of certain proteins or carbohydrates in the food ingredients, or by delivering vitamins, bioactives or functional (digestive) enzymes to the gastrointestinal tract of the consumer.

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TABLE 2: Issues to be addressed for the sustainable introduction and acceptance of local and regional probiotic fermented food concepts

Consumer and market insight	> Understanding of local preferences for fermented foods and relevant market dynamics in a variety of geographic regions and among different segments of the population.
Technical	> Greater documentation of the microbial composition and nutritional value of various fermented foods, particularly those produced at the household level and served to children.
	> Development of starter cultures, processing equipment, and technologies for household, community, or industrial production of fermented foods, with an emphasis on affordability and productivity at the household level and enablement of small and mid-sized fermented food cooperatives and businesses in low-income countries.
	> Investigation of the shelf life, storage requirements, and nutritional integrity of dried and processed starter cultures.
	> Development of quality management methods for fermentation processes and fermented food storage and consumption to ensure food and consumer safety.
Health impact	> Investigation of the efficacy and effectiveness of probiotically enhanced fermented foods in addressing challenges such as diarrheal disease and enteric infections, intestinal inflammation from environmental enteric dysfunction (EED), immune function and response, weight gain, linear growth, and micronutrient deficiencies – particularly during the introduction of complementary foods and the first few years of a child's life.
	> Investigation of the benefits of probiotics to boost ready-to-use therapeutic foods (RUTFs) and ready-to-use supplementary foods (RUSFs) to accelerate patient recovery and gut microbiome restoration.
	> Research on healthy microbiome profiles that takes into account ethnic, dietary, geographic, and lifestyle differences.
Regulatory and political	New legal, regulatory, and institutional frameworks at the national and international levels, enabling the full incorporation of fermented foods into complementary and school feeding policies.

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