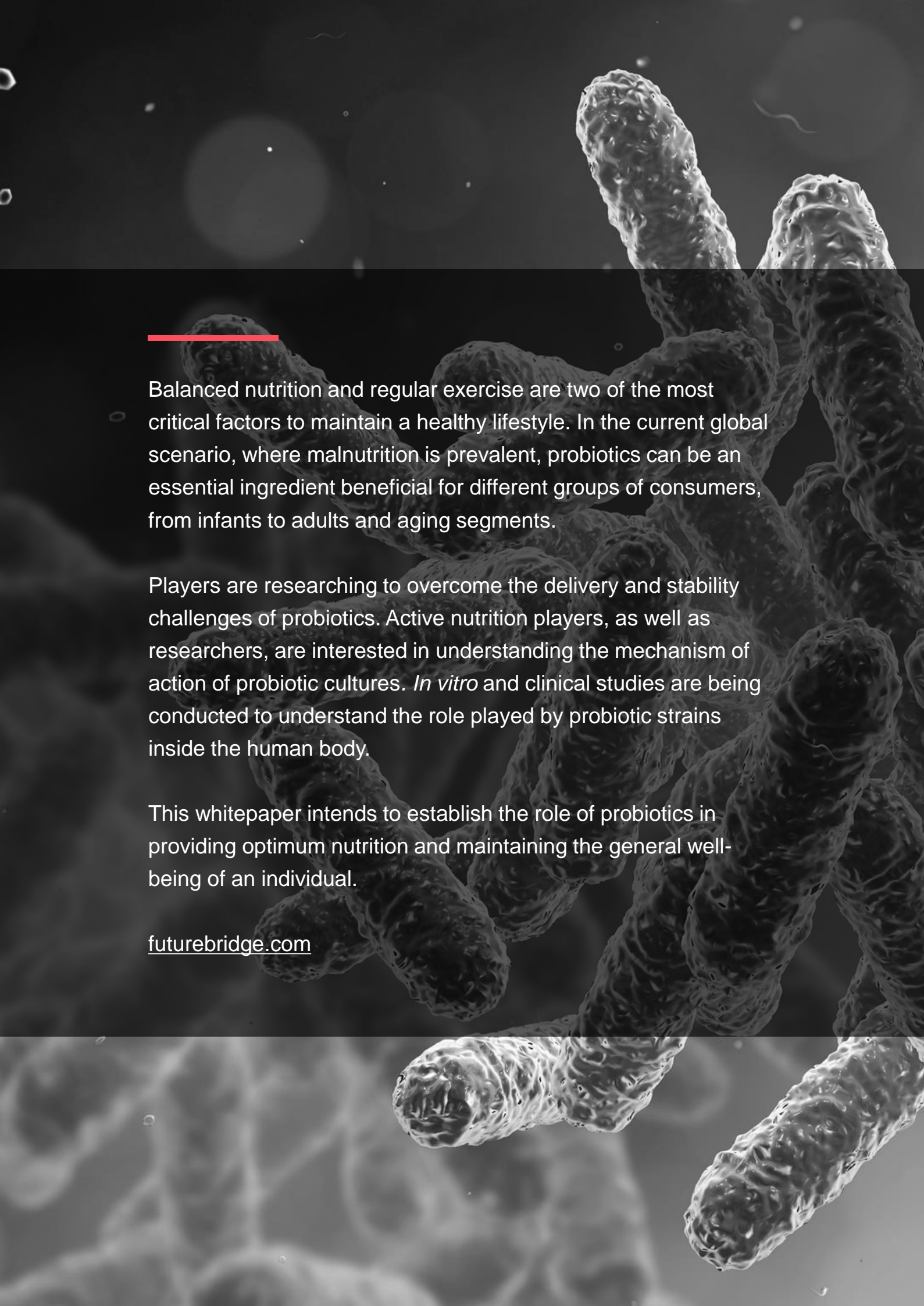




WHITE PAPER

# Probiotics – Can it Solve the Problem of Malnutrition?

FutureBridge

A grayscale, high-magnification microscopic image of numerous probiotic bacteria, likely Lactobacillus or Bifidobacterium species. The bacteria are rod-shaped with a textured, slightly irregular surface. They are scattered across the frame, with some appearing in sharp focus and others blurred in the background, creating a sense of depth. A thin red horizontal line is positioned above the first paragraph of text.

Balanced nutrition and regular exercise are two of the most critical factors to maintain a healthy lifestyle. In the current global scenario, where malnutrition is prevalent, probiotics can be an essential ingredient beneficial for different groups of consumers, from infants to adults and aging segments.

Players are researching to overcome the delivery and stability challenges of probiotics. Active nutrition players, as well as researchers, are interested in understanding the mechanism of action of probiotic cultures. *In vitro* and clinical studies are being conducted to understand the role played by probiotic strains inside the human body.

This whitepaper intends to establish the role of probiotics in providing optimum nutrition and maintaining the general well-being of an individual.

[futurebridge.com](http://futurebridge.com)

# What is the prevalence of malnutrition?

Globally, malnutrition is one of the most important causes of morbidity and mortality. It has been responsible for ill-health among children. Under-nutrition accounted for approximately 45% of deaths, whereas overweight and obesity accounted for nearly four million deaths among children under five years, worldwide.

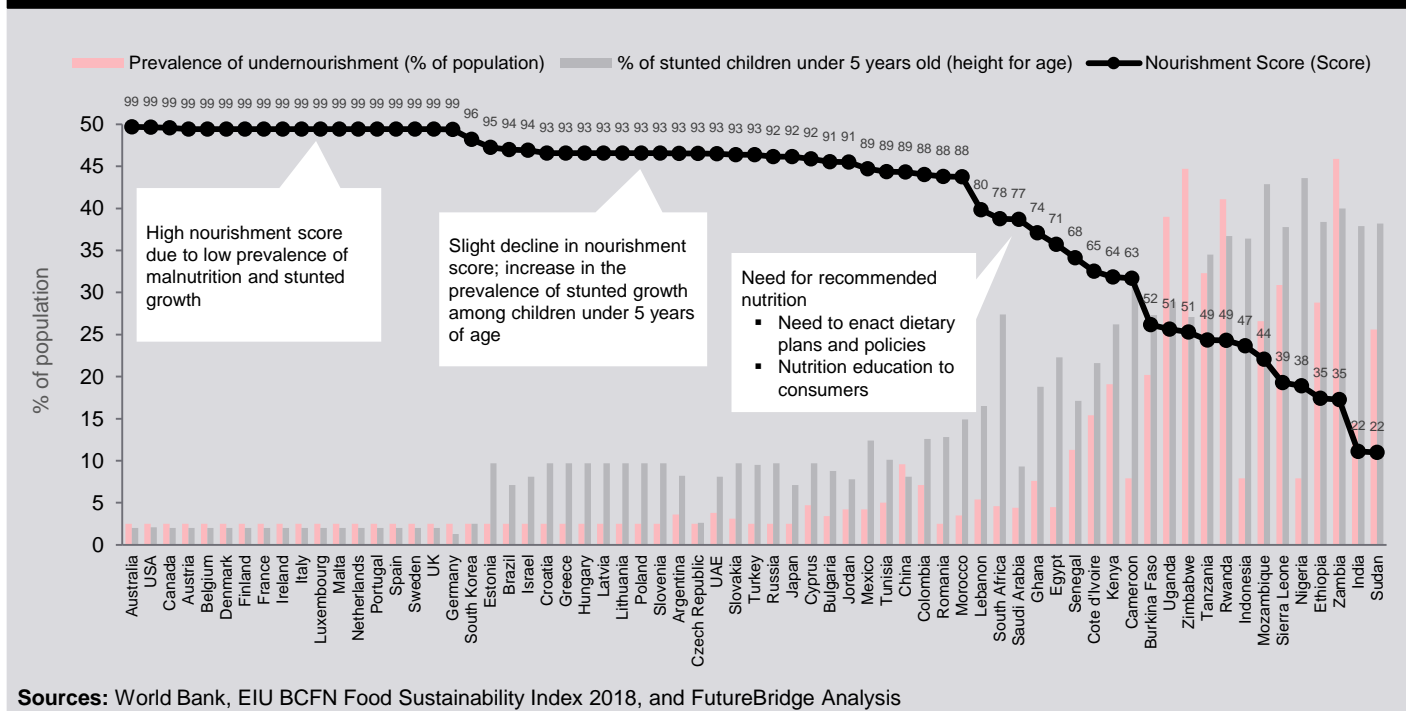
## Impact of malnutrition

According to the [Global Nutrition Report](#), 2018, children experience multiple forms of malnutrition globally. Nearly 4% of children under five years of age experience stunted growth despite the effort and investment of countries to control malnutrition. Approximately 3.62% of children were both stunted and wasted, while 1.87% were overweight and stunted. Additionally, the report showed that there are nearly 15% of infants with low birth weight.

*Exhibit 1* represents the prevalence of undernourishment and the proportion of stunted children under five years reported in the [Food Sustainability Index, 2018](#), by the Economist Intelligence Unit (EIU).

According to the study, approximately 32.8% of women in their reproductive years were suffering from anemia. Further, 32.5% of non-pregnant women and 40.1% of

**EXHIBIT 1: Malnutrition and Micronutrient Deficiency Reported in Different Countries, 2018**



Sources: World Bank, EIU BCFN Food Sustainability Index 2018, and FutureBridge Analysis

pregnant women were anemic. As per the data gathered between 2013 and 2018, approximately 41% of infants were exclusively breastfed, which is a slight improvement from 37% of infants solely breastfed between 2005 and 2012.

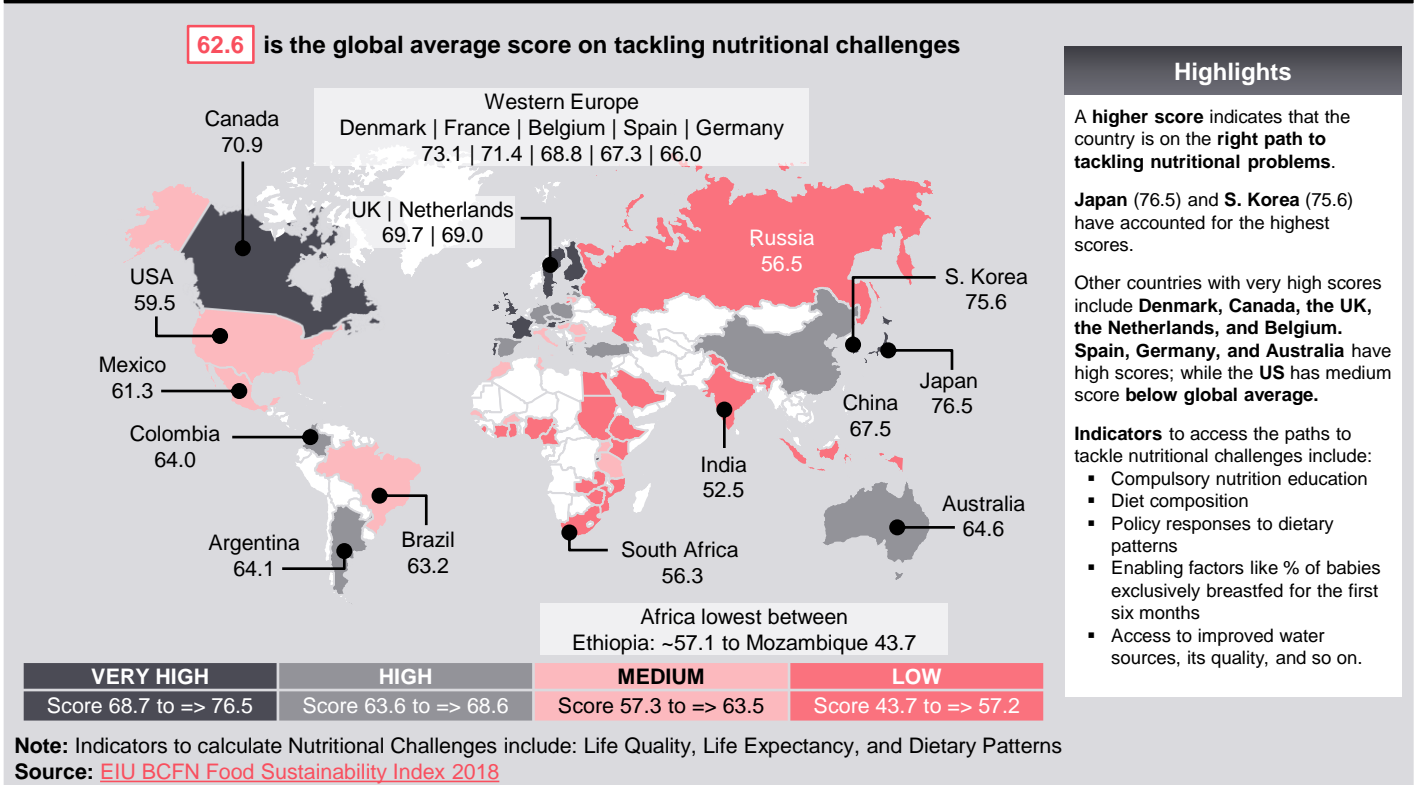
According to the African Child Policy Forum in 2018, approximately 60% of children could not meet the minimum meal frequency threshold. It reported that nearly 90% of children are malnourished, and the number of stunted children reached about 60 million in Africa.

As per the report by the [World Health Organization \(WHO\)](#) in 2018, common childhood diseases accounted for deaths of nearly 6.2 million population that include children and adolescents below 15 years. WHO proposed that affordable and straightforward interventions, such as adequate nutrition and safe water, can help control malnutrition.

### Measures initiated by countries to address malnutrition

The prevalence of malnutrition remains high across all regions worldwide, commonly among children below five years, pregnant and lactating women, and diabetic males. Malnutrition has been impacting the social and economic development of different countries.

## EXHIBIT 2: Nutritional Challenges Scores for Different Countries, 2018



Based on the [Global Nutrition Report](#) 2018, 124 countries out of the analyzed 141 have recorded one or more forms of malnutrition. Challenges in providing standard nutrition and diet to the population are the leading cause of malnourishment.

As depicted in *Exhibit 2*, governments of different countries have undertaken measures to tackle nutritional challenges. Measures implemented by government bodies include compulsory nutrition education, diet and dietary policies, exclusive infant breastfeeding up to the first six months, and better water quality, among others.

Countries have initiated several approaches to address the issue of malnutrition. However, based on the Global Nutrition Report, only 94 out of 194 countries were on track for at least one of the nine assessed nutrition targets. Thus, it becomes imperative to identify challenges in providing standard nutrition and then address the issue of malnutrition.

### **Can probiotics help impact the growing concern of malnutrition?**

Bill Gates, through the Bill and Melinda Gates Foundation, has been conducting studies to resolve health issues and inequality. Participating as a recipient of the 2019 Professor Hawking Fellowship at Cambridge University, Bill Gates described the [criticality of malnutrition and global hunger](#).

Additionally, he mentioned that probiotics have the potential to emerge as an essential tool to limit malnutrition. However, it becomes critical to gain an in-depth understanding of the role of the microbiome in the human body and its impact on proper nutrition during the early stages of development.

Over the last two decades, probiotic bacteria have become prominent due to the escalating pieces of scientific evidence that indicate health benefits. Probiotic bacteria demonstrate a profound impact on the human body that includes:

- Maintaining healthy microbial balance and regulate homeostasis
- Producing post-biotics that show desirable effects on the microbiome and human health
- Boosting the host's immune response

## **What are the current applications of probiotics?**

### **Probiotics as a nutritional ingredient**

The microbiome is the term coined for the cumulative genome of all microbes

present in the human body, including symbiotic and pathogenic microorganisms. Probiotics are the microbes consumed to restore the balance of beneficial organisms in the human body.

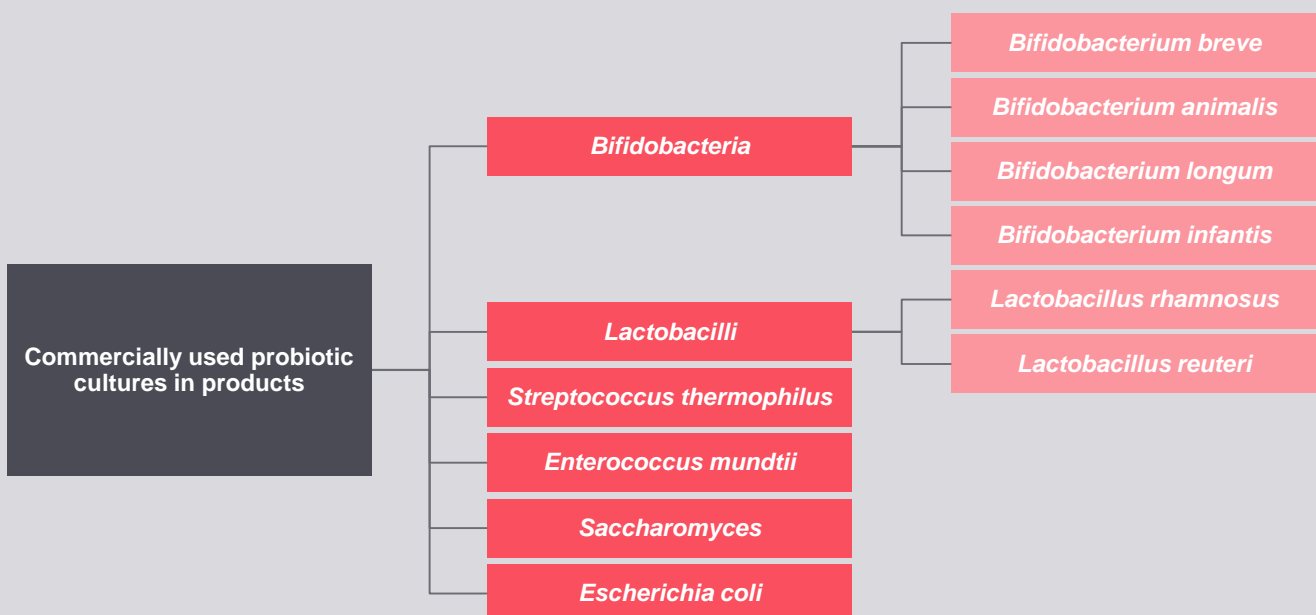
### Probiotic foods in the market

Traditionally, probiotic foods include dairy and dairy products. However, recently, probiotics in non-dairy products such as chocolate, cereals, and beverages have been introduced in the market. Drivers for the application of probiotics in food products include an increase in awareness regarding the health benefits of probiotics and growth in the number of probiotic culture suppliers. Further, health professionals recognize probiotics and their beneficial effects on human health and nutrition.

Commercially available probiotic cultures for food and pharmaceutical applications include *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Bacillus*, and yeast, among others. Entities that provide probiotics for such applications include Danone, DuPont, Ganeden, and Abbott, among others.

As depicted in *Exhibit 3*, different strains of *Bifidobacteria* and *Lactobacilli* are available for application in various products that include infant formulae, weight management solutions, digestive capsules, dietary supplements, and health supplements, among others.

#### EXHIBIT 3: Probiotic Cultures used in Food Products



Source: FutureBridge analysis

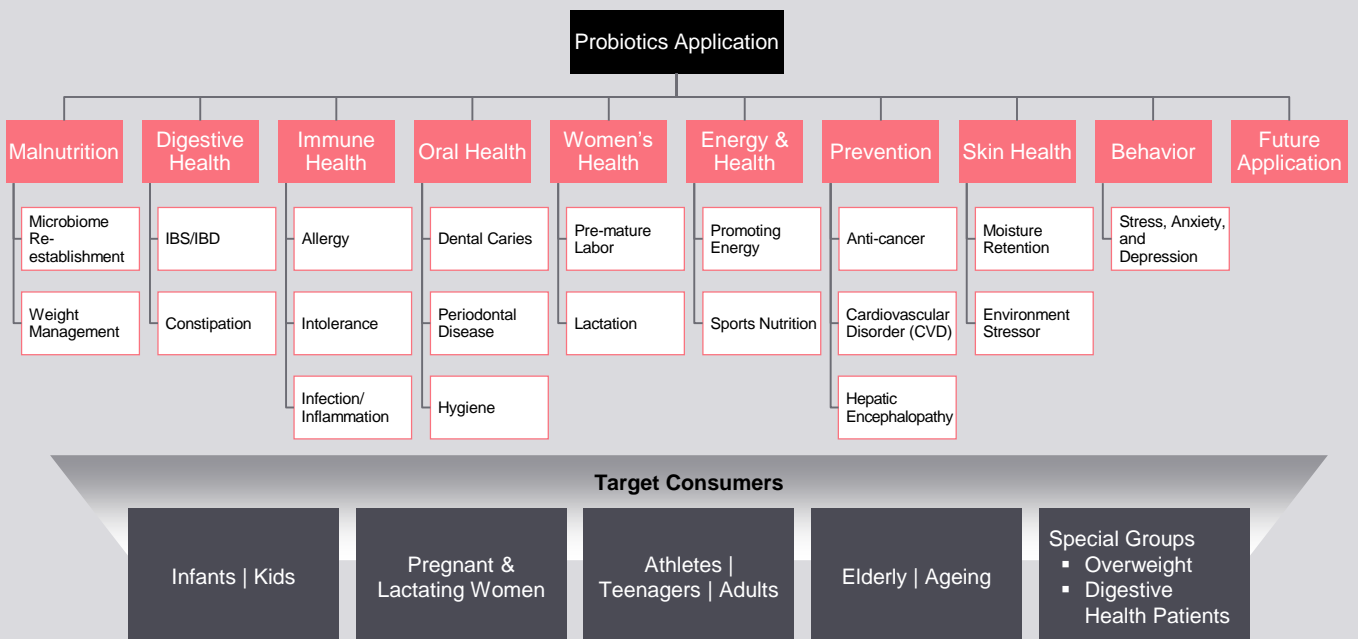
Exhibit 4 illustrates active players that have launched probiotic foods. These active players include Danone, GanedenBC30, Nestlé, DuPont, and Coca-Cola, along with start-ups such as BIOHM, GnuBiotics, Epigamia, and YoFix, among others.

**EXHIBIT 4: Entities Providing Probiotic Foods**



Source: FutureBridge analysis

**EXHIBIT 5: Application of Probiotics**



Source: FutureBridge analysis

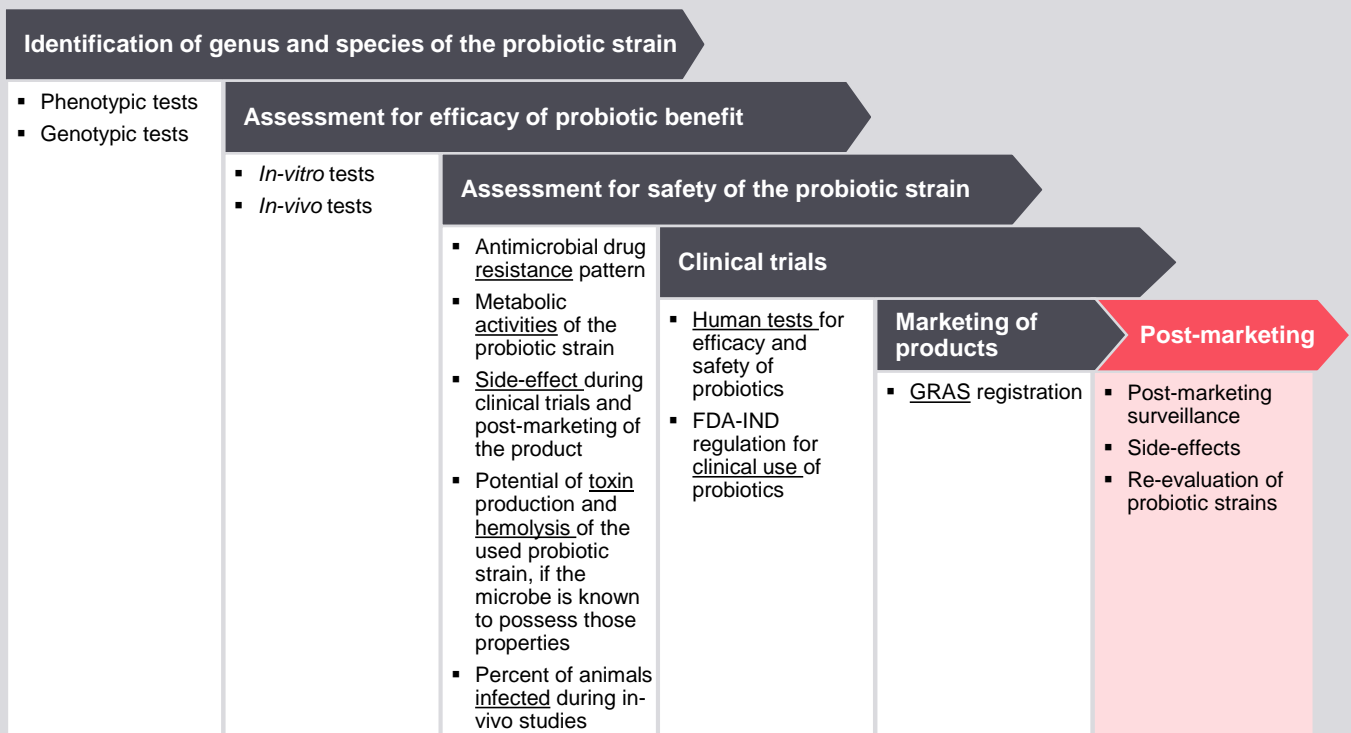
As depicted in *Exhibit 5*, probiotic bacteria show a wide range of applications and caters to various target consumers that include infants, lactating and pregnant women, adults, as well as the aging population.

Recent scientific studies indicate that the microbiome plays an intrinsic and essential role in balancing the immunological, digestive, as well as respiratory functions. Pieces of evidence have also been collected to support that probiotic bacteria can significantly alleviate the risk of infection among children as well as high-risk groups.

## How are probiotics regulated in this market?

[Guidelines for the evaluation of probiotics in food](#), which is a report published by Joint FAO/WHO Working Group, defines Probiotics as “*Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.*”

### EXHIBIT 6: Approach for Probiotic Efficacy and Safety Testing



**Source:** Joint Food and Agriculture Organization of the United Nations/World Health Organization Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food



As depicted in *Exhibit 6*, recommended guidelines and approach for evaluating a probiotic culture in food application are:

- Using phenotypic and genotypic tests to identify the genus and species of the probiotic strain; these tests will provide the clinical evidence to suggest strain-specific health benefits of the desired probiotics
- *In-vitro* tests to outline the probiotic effect and assess its mechanism
- Validating the beneficial health effects of probiotic agents with human clinical trials

Further, studies should also include assessment of the probiotic strain on specific parameters to determine its safety upon consumption.

- Antimicrobial drug resistance pattern
- Metabolic activities of the probiotic strain
- Side-effect during clinical trials and post-marketing of the product
- Potential of toxin production and hemolysis of the used probiotic strain, if the microbe is known to possess those properties
- Efficacy and extent of infection during in-vivo studies

### **Regulatory requirements for probiotics based on its type**

Probiotics can be sub-divided into:

- **Probiotic drugs:** Capsules, pills, etc.
- **Probiotic foods:** Foods such as yogurt, food ingredients, and dietary supplements
- **Direct-fed microbials:** Probiotics in feed/animal application
- **Probiotics 2.0:** Next-generation probiotics – genetically modified probiotics

Regulatory requirements for probiotics change based on its type – drug or food, as depicted in *Exhibit 7*. For probiotic medicines, the introduction of new strain/product is similar to the regulatory process for a new therapeutic agent, whereas probiotic food does not need any FDA approval for the introduction.

## EXHIBIT 7: Regulatory Process for Probiotics based on its Type



### Probiotic Drug: FDA-IND Regulation

- Investigational New Drug (**IND**) application to be submitted
- IND to be **authorized by FDA** before an investigational or biological product can be administered to humans
- **Proven safety and efficacy** for intended use of probiotics before marketing

### Probiotic Food: Dietary supplement

- Regulated by the **FDA Center for Food Safety and Applied Nutrition**
- Supplements must contain **≥1** of the following dietary ingredients
- Dietary supplements **do not need FDA approval** before being marketed
- Manufacturers need to **notify FDA** before marketing a product



Source: FutureBridge analysis

## A. Probiotic Drug

Regulatory processes for probiotic drugs are similar to a new therapeutical agent. The manufacturer needs to submit an Investigational New Drug (IND) application, and FDA authorizes for its further investigation or human consumption. FDA approval requires positive evidence on the safety and efficacy of the probiotic drug through preclinical and clinical studies, and then the drug is launched in the market.

## B. Probiotic Food: Dietary Supplement

[FDA](#)'s Center for Food Safety and Applied Nutrition (CFSAN) regulates dietary supplements and probiotic products under the "foods" category. According to the Dietary Supplement Health and Education Act ([DSHEA](#)), dietary supplements are consumed through the oral route and contains "dietary ingredients" to supplement the diet. DSHEA claims probiotics as "Live microbial dietary ingredient: A single-celled prokaryotic or eukaryotic microorganism that is intended to be viable at the point of ingestion."

Regulations state that supplements should include more than one of the following dietary ingredients, which are vitamins; minerals; herbs; other botanicals (excluding tobacco); amino acids; nutritional ingredients to supplement the diet and increase the total dietary intake; concentrates; metabolites; constituents; extracts; or a combination of any of the above. Additionally, for marketing a dietary supplement, FDA approvals are not required. However, manufacturers need to notify the FDA before selling a product.

## C. Probiotics 2.0

**Probiotic 2.0** are bioengineered probiotics developed using synthetic biology.

[ActoBio](#) (Belgium), a subsidiary of [Intrexon Corporation](#) (US), developed a probiotic delivery platform for the treatment of specific diseases. The entity has bioengineered safe, food-grade bacterium, *Lactococcus lactis*, to produce highly selective protein-based therapeutic agents for local delivery of the cure. These probiotics applications include cheese and other food products.

[Synlogic](#) (US) developed bioengineered probiotics that target phenylketonuria and prevent patients from breaking down Phenylalanine (PLA), an amino acid.

## What are the notable research activities in the probiotics segment?

Research studies on probiotics have increased over the past few years, with a rise in health concerns and awareness regarding probiotics, microbiomes, and digestive health.

### A. Consumer survey on probiotic awareness

A [recent consumer survey](#) indicates that globally, 83% of consumers and 76% of the US consumers are aware of probiotics. The study also reports that:

- More than 50% of consumers perceive the positive health impact of probiotics,
- 41% of consumers knew its digestive health impact
- 21% of consumers mentioned immune health benefits and general health of probiotics

This survey was conducted to understand consumer awareness regarding probiotics and their impact on health. The study provides a better understanding of the reasons for the increase in consumer demand for probiotic products in the market.

### B. Research activities

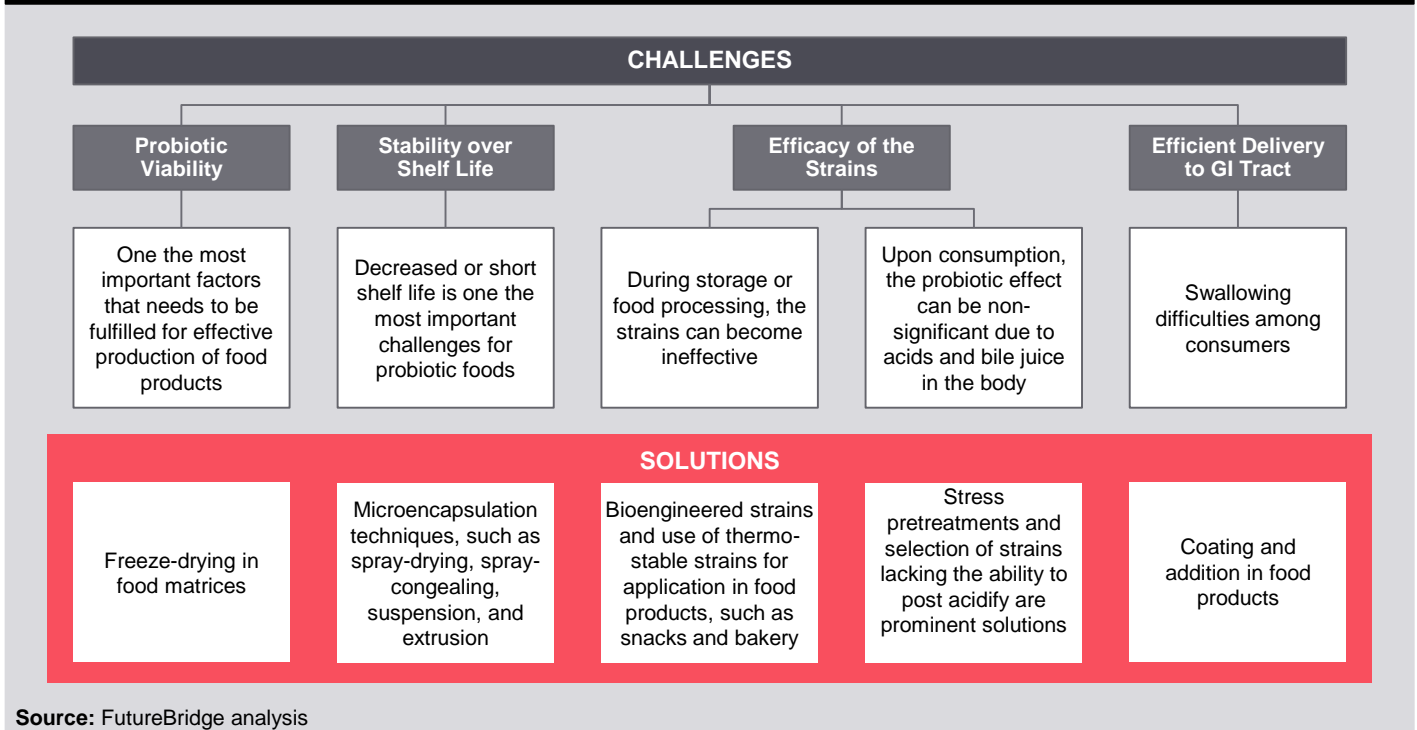
Active players in the probiotics market are focusing on research that can help overcome the challenges in the formulation and stability of probiotics.

#### Challenges in food application of probiotics

The increase in consumer demand for functional products and probiotics awareness is driving the use of probiotics in food applications. However, there exist a few challenges in the delivery of probiotics as well as their maintenance.

As illustrated in *Exhibit 8*, a few of such challenges include maintaining viability, prolonging the stability and shelf life, enhancing efficacy, and efficient delivery of the formulation.

### EXHIBIT 8: Challenges in Application of Probiotics



Active players such as GanedanBC30, have conducted research and use microencapsulation technology or stress pretreatment of strains to enhance the efficacy and stability of probiotics. A few players are investing in research to identify new probiotic strains with improved functionalities as well as properties, such as thermostability, which is useful for snacks and bakery applications. Players such as ActoBio and Synlogic have developed bioengineered probiotic cultures for targeted therapy, which also have application in targeted nutrition delivery.

A patented thermo-stable, spore-forming probiotic strain of *Bacillus coagulans*, launched by [GanedanBC30](#), a registered trademark of Kerry Group, is considered as one of the revolutionary probiotic cultures that overcome the enlisted formulation challenges.

#### Understanding and establishing the functions of probiotics

Entities including Danone, Abbott, and Nestlé are collaborating with academic institutes, such as the University of California, Wageningen University, and Utrecht University, to conduct preclinical and clinical studies on the effect of probiotic strains on the human body and assess the beneficial health impact.

## EXHIBIT 9: Significant Research on Probiotics

### A. Overcoming formulation challenges - GanadenBC30's *Bacillus coagulans*



Topical application to prevent infection and for skin health

Compositions comprising *Bacillus coagulans* for increasing the solubility and bioavailability of nutritional minerals - EP1719518A1

Methods for increasing the solubility of nutritional materials using probiotic lactic acid-producing bacteria - CA2339643A1

Probiotic grain-based compositions - DK2348888T3

### B. Assessing the functions of probiotics

**CHR HANSEN**

- *Bifidobacterium breve* Bif195 **protects** against **small-intestinal damage** caused by acetylsalicylic acid in healthy volunteers

**Abbott**

- Prebiotic **GOS metabolism** by probiotic *Lactobacilli* and *Bifidobacteria*



- A **clinical study** to investigate the effect of a partially hydrolyzed infant formula with added **synbiotics** on the **development of allergic manifestations** in infants at high risk of developing allergy
- Infant formula containing **prebiotic mixture** scGOS/lcFOS (9:1) and *Bifidobacterium breve* M-16V to support adequate **growth and tolerance** in healthy infants
- Specific **synbiotics** in **early life protection** against diet-induced obesity in adult mice
- The combination of *Bifidobacterium breve* with non-digestible oligosaccharides suppresses airway inflammation in a murine model for **chronic asthma**

**Nestlé**  
Good Food, Good Life

- Early benefits of a starter formula enriched in **prebiotics and probiotics** on the **gut microbiota of healthy infants** born to HIV+ mothers
- **Feeding tolerance** of *Bifidobacterium animalis* ssp *lactis* strain Bb12 for partially hydrolyzed infant formula with 2'-FL (2'-fucosyllactose)
- Effect of a growing-up milk containing **synbiotics** on **immune function and growth in children**
- Comparing the effect of *Bifidobacterium animalis* subspecies *lactis* (*B lactis*) alone or with 90% GOS and 10% FOS **on infections** in infants
- Effect of infant formula containing a **low dose of probiotic** *Bifidobacterium lactis* CNCM I-3446 on immune and gut functions in C-section delivered babies

**Source:** Orbit Database, Clinical Trial Database, Web of Science, Science Direct, Pubmed, and FutureBridge Analysis

A few of the ongoing studies aim to understand the impact of probiotics consumption on the microbiome, infant health, or nutrient absorption. *Exhibit 9* depicts a few ongoing studies on probiotics to assess its impact and enhance its functionality. Clinical studies conducted by Danone and Nestlé validates the role of probiotics on maintaining gut microbiome.

### Research on the role of probiotics in preventing malnutrition

Entities, including academia, research institutes, and corporates, are investing in research on probiotics. The research findings can provide solutions for patients suffering from severe malnutrition, prevent pathogens from nutrient uptake, and facilitate targeted nutrition delivery.

Chr. Hansen in collaboration with the University of Copenhagen, Denmark, conducted a randomized, double-blind, placebo-controlled, parallel study to measure the effect of two probiotic strains on diarrhea in children with Severe Acute Malnutrition (SAM) when given together with the usually recommended treatment (ProbiSAM - [ISRCTN16454889](#), [PMID28079729](#), [PMID31169661](#)). A daily dose of a blend of *Bifidobacterium animalis subsp lactis* (*B. lactis*) and *Lactobacillus rhamnosus* (10 billion colony-forming units, 50:50) or placebo during hospitalization, followed by an 8- to 12-week outpatient treatment period was administered to patients. The results indicated that *B. lactis* and *L. rhamnosus* administration helped reduce diarrhea suffering days by 26% among outpatient children with SAM. However, further studies are required to confirm the role of probiotics in the follow-up of hospitalized children with SAM or community-based treatment of malnourished children.

Another study ([PMID28588566](#)) conducted on malnourished patients suffering from kwashiorkor and healthy children in Niger and Senegal concluded that 45 living, viable, and cultivable bacterial species were missing in the feces of children with kwashiorkor. Further, the kwashiorkor-associated gut microbiota showed an increase in potentially pathogenic bacteria - *Streptococcus gallolyticus*, *Fusobacteria*, and *Proteobacteria*. In addition, the study revealed that 12 of the missing bacterial species showed probiotic characteristics. The study concluded that microbiotherapy using identified probiotic strains could potentially improve the currently available treatment of severe acute malnutrition and prevent its relapse as well as death by re-establishing the healthy gut microbiota of patients. The research also aims at developing an experimental model with axenic mice, wherein the cocktail of desired probiotics would be tested to test the efficacy of the possible probiotics.

A similar study ([PMID12142965](#)) by Spanish institute, Instituto de Nutrición y Bromatología (CSIC), aimed to review the impact of fermented milk consumption among subjects suffering from malnutrition and diarrhea. The review showed that fermented milk that contains probiotics could help in the prevention of infection among children and accelerate the recovery rate from acute diarrhea caused by rotavirus. Fermented milk can also enhance the stimulation of the local immune defense by increasing the number of immunoglobulin-secreting cells re-infection.

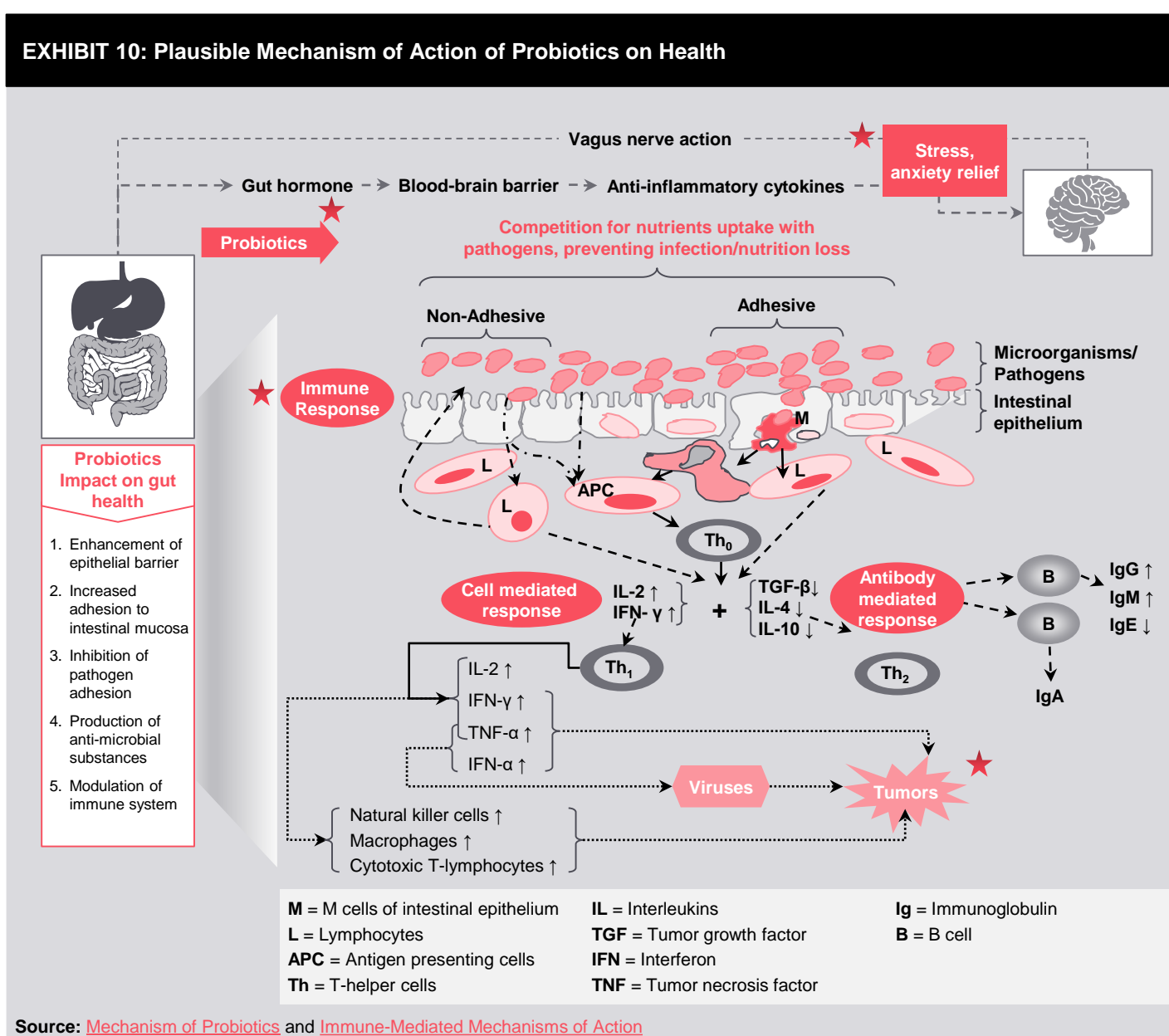
### C. Future research trends

Researchers, along with active players, are exploring probiotics to expand its application in different products that include sports nutrition, brain health products, psychotic drugs, and so on. Hence, it becomes imperative to understand the mechanism action of probiotics on health.

Research studies are being conducted to understand the impact of probiotics on the human body and how it can help in the enhancement of brain/behavior/energy.

Exhibit 10 depicts the plausible mechanism of action of probiotics on the gut-brain axis that is beneficial for gut, immune, and brain health.

**EXHIBIT 10: Plausible Mechanism of Action of Probiotics on Health**



Source: [Mechanism of Probiotics](#) and [Immune-Mediated Mechanisms of Action](#)

# What are the future implications of probiotics?

---

## Harmonization of regulation

[IPA Europe](#) called for a harmonized EU approach on probiotics for correct information on probiotic products. The probiotics industry in the EU has been urging for a viable solution to cater to the EU single market and allow generic as well as a meaningful indication of the product composition. Different geographies can use this solution and address the current confusion on product information and labeling.

Bill Gates, during his lecture at the 2019 Professor Hawking Fellowship at Cambridge University, mentioned that probiotics are key ingredients to solve malnutrition.

## Research focus

Clinical studies are focused not only to assess the effect of probiotics but also to gain in-depth awareness of the role of probiotics and their impact on the microbiome. Researchers are exploring the beneficial effects of probiotics on health conditions, such as obesity, autoimmune disorders and allergies, as well as respiratory disorders, such as asthma.

As reviewed in the article, "[Probiotics: Mechanisms of Action and Clinical Applications](#)," probiotics in the form of capsules or pills can help resolve the issue of malnutrition as well as other health conditions.

# Can probiotics help the overall well-being of individuals?

---

The applications of probiotics range from food, pharma to cosmetic products. Clearly, in recent years, probiotics emerged as one of the critical ingredients beneficial for different groups of consumers, from infants to adult and aging segments.

Clinical and pre-clinical studies indicate that there is a link between gut and brain mechanisms, thereby stressing the importance of maintaining gut health for brain health and behavior. Probiotics are essential to restore the gut microbiome balance and promote other health benefits, such as immunity, digestion, and stress relief.



Researchers are focused on establishing a link between early life nutrition and adult health, which indicates that optimum nutrition at the early stages of life plays an essential role in maintaining the health throughout the life-cycle of an individual. Established players such as Nestlé, Danone, and Abbott have introduced infant formulae and kids nutritional products supplemented with probiotics, such as *Lactobacillus* and *Bifidobacterium*, which claim health benefits, such as digestive health, growth, immunity, etc.

Further, players are also investing in understanding the mechanisms of action of probiotics on health. Pieces of evidence on the specific mechanism of action of probiotics and its health impact are essential. Thus, further clinical studies are required to validate the current hypothesis on the beneficial role of probiotics. Additionally, robust processes need to be developed to maintain safety as well as the stability of probiotics in products.

## References

---

1. [Global Nutrition Report, 2018](#)
2. [Food Sustainability Index, 2018](#)
3. [WHO – Child Malnutrition](#)
4. [UNICEF - Malnutrition Prevalence](#)
5. <https://www.gatesnotes.com/Health/Professor-Hawking-Fellowship-lecture>
6. [Probiotics in food – Health and nutritional properties and guidelines for evaluation](#)
7. [NIH-Probiotics](#)
8. [RAPS](#)
9. [FDA – Dietary Supplements](#)
10. [Public Meeting: Responsible Innovation In Dietary Supplements Combined Comments From IPA and IFAC](#)
11. [Demand for Probiotics at Every Meal](#)
12. [CAPS Probiotics](#)
13. [DSHEA](#)
14. [IPA Europe](#)
15. Company Websites
16. [Clinical Trial Database](#)
17. Orbit Database for Patents
18. [Scientific Database - PubMed, Science Direct, Wiley](#)
19. WebofScience by Thomson Reuters
20. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294522/>

**North America**

55 Madison Ave, Suite 400  
Morristown, NJ 07960  
USA  
T: +1 212 835 1590

**Europe**

328-334 Graadt van Roggenweg  
4th Floor, Utrecht, 3531 AH  
Netherlands  
T: +31 30 298 2108

**United Kingdom**

5 Chancery Lane  
London EC4A 1BL  
United Kingdom  
T: +44 207 406 7548

**Asia Pacific**

Millennium Business Park  
Sector 3, Building # 4, Mahape  
Navi Mumbai 400 710  
India  
T: +91 22 6772 5700

[futurebridge.com](http://futurebridge.com)