

## ROLE OF PROBIOTICS IN PEDIATRICS

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### ABSTRACT

The development of antibiotic therapy has created a therapeutical place for relatively new category pharmaceutical products: probiotics. Probiotics have been the topic of many studies over the past 20 years. The main definition of probiotics is live and vital micro-organisms able to benefit human health when consumed, in adequate amount, as part of a food or a nutritional supplement. Probiotics are widely used in pediatrics. In this review we have described clinical indications for probiotic use, the most used probiotic stains in pediatrics and the most appropriate dosage forms, containing probiotics for children.

**KEYWORDS:** Probiotic, Children, Antibiotics

### INTRODUCTION

Although interest in the health, illnesses, and well-being of the young dates back to Antiquity, the term *pediatrics* is relatively modern, originating in the latter half of the 19th century with the emergence of a distinct and organized specialty within medicine. The literature covering that development, and the history of medical interest in children more generally, is vast, characterized by contributions from clinician-historians and, especially after the 1960s, historians, anthropologists, sociologists, and other social scientists [1].

Indisputable one of the most significant medicines in medicine are vaccines and antibiotics. These two categories medicines have created a therapeutic revolution in medicine because infectious diseases have accompanied human evolution from ancient times. Rare smallpox, polio, plague, cholera in the past were taken for normal human companions and have occurred mainly in the form of epidemics and pandemics [48]. Vaccines represent the most successful and sustainable tactic to prevent and counteract infection. Vaccine generally improves immunity to a particular disease upon administration by inducing specific protective and efficient immune responses in all of the receiving population. The main known factors influencing the observed heterogeneity for immune responses induced by vaccines are gender, age, co-morbidity, immune system, and genetic background [28].

The purpose of childhood vaccination is for active immunization against infectious diseases [2], as well as to ensure herd immunity [3] in the population [4]. In different countries all over the World children are vaccinated according to the National Immunization Guidelines.

The use of antibiotics in the past 80years has saved millions of human lives and facilitated technological progress [5]. Antibiotics are main cluster of drugs for treatment of child infections and illnesses. They are the most commonly prescribed medicines for children, relatively expensive and consume 60-70% of the budget for treatment of child illnesses, with exclusion only in malign sickness [6]. The development of antibiotic therapy has created a therapeutical place for

relatively new category pharmaceutical products: probiotics. Probiotics have been the topic of many studies over the past 20 years. Metchnikoff and Tissier were the first to make scientific suggestions concerning the probiotic use of bacteria. They suggested that these bacteria could be administered to patients with diarrhea to help restore a healthy gut flora [42].

The increasing knowledge about the composition and activities of the microflora has shown the close link between the bacteria and the health of the human organism. For this reason it has focused attention on the possibility of modulating the gut flora. The use of probiotics and prebiotics has increased enormously in recent years, more for real beneficial effects demonstrated in patients than for their safety profiles [49]. Food products fermented by lactic acid bacteria have long been used for their proposed health promoting properties. In recent years, selected probiotic strains have been thoroughly investigated for specific health effects. Properties like relief of lactose intolerance symptoms and shortening of rotavirus diarrhoea are now widely accepted for selected probiotics. Some areas, such as the treatment and prevention of atopy hold great promise. However, many proposed health effects still need additional investigation. In particular the potential benefits for the healthy consumer, the main market for Probiotic products, require more attention. Also, the potential use of probiotics outside the gastrointestinal tract deserves to be explored further. Results from well conducted clinical studies will expand and increase the acceptance of probiotics for the treatment and prevention of selected diseases [47].

## **PROBIOTIC DEFINITION**

The internationally endorsed definition of probiotics is live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Other definitions advanced through the years have been restrictive by specification of mechanisms, site of action, delivery format, method, or host. Probiotics have been shown to exert a wide range of effects. The mechanism of action of probiotics (e.g., having an impact on the intestinal micro biota or enhancing immune function) was dropped from the definition to encompass health effects due to novel mechanisms and to allow application of the term before the mechanism is confirmed [29].

## **REGULATION OF PROBIOTICS**

There is no statutory or regulatory definition of probiotics in the United States. The most widely used definition of probiotics is the definition proposed in the 2001 report of a Joint FAO/WHO Expert Consultation on "Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live [30] Lactic Acid Bacteria [31]." In that document, probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host [32]."

Clearly, the FDA has regulatory authority over probiotic products and regulates manufacturers' responsibilities, including the labeling and safety of these products, whether in food, supplement, or drug form. Of note, on 24 August 2007, the FDA issued regulations that require current good manufacturing practices for dietary supplements to be phased in over the next few years. Although these regulations do not address verification of efficacy claims, hopefully they will improve the compositional quality (identity, purity, and strength) of probiotic supplements in the US market. However, manufacturers of foods and supplements are not required to obtain premarket approval of claims of efficacy or safety [29].

In European Union probiotics are sold as food supplements. Food supplements are regulated Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002.

## CLINICAL INDICATIONS FOR PROBIOTICS

Probiotics are used to treat or prevent a broad range of human diseases, conditions, and syndromes. Many studies have provided evidences of probiotic effectiveness for the treatment and prevention of acute diarrhea, antibiotic-induced diarrhea, prevention of cow milk–induced food allergy in infants and young children, prevention of traveler's diarrhea, relapsing *Clostridium difficile*–induced colitis.

Despite much progress in the understanding of pathogenesis and of management, diarrhoea illnesses remain one of the most important causes of global childhood mortality and morbidity. Infections account for most illnesses, with pathogens employing ingenious mechanisms to establish disease. In the developed world, an upsurge in immune-mediated gut disorders might have resulted from a disruption of normal bacterial-epithelial cross-talk and impaired maturation of the gut's immune system. Oral rehydration therapies are the mainstay of management of gastroenteritis, and their composition continues to improve. Drugs are of little use, except for specific indications although new agents that target mechanisms of secretory diarrhoea show promise, as do probiotics [51].

A number of studies have demonstrated the ability of probiotics to reduce the frequently observed intestinal adverse effects associated with the clinical use of antibiotics [7, 21-27]. Researchers have announced for significant results: children who received antibiotics for respiratory infections and *Lactobacillus rhamnosus* strain GG had a ~70% reduction in diarrheal symptoms, compared with the group receiving placebo [21]. In another study, in which 202 children receiving oral antibiotics were followed, 8% of the children who received *Lactobacillus* GG concurrently with antibiotics experienced diarrheal symptoms, compared with 26% of the placebo group [7, 22].

There are also studies indicating that probiotics may be useful for prevention of respiratory infections in children, dental caries, irritable bowel syndrome, and inflammatory bowel disease [7]. There are areas of medical use that have been proposed for future probiotic applications. Areas of future interest for the application of probiotics include colon and bladder cancers, diabetes, and rheumatoid arthritis. The probiotics with the greatest number of proven benefits are *Lactobacillus rhamnosus* strain GG and *Saccharomyces boulardii* [7]. Most of indications of probiotics are demonstrated on table 1.

**Table 1: Clinical Indications for Probiotics**

Indication for Probiotic Use	Probiotic Strain	Reference
Acute diarrhea.	<i>Lactobacillus rhamnosus</i> , <i>Lactobacillus</i> GG, e <i>Lactobacillus reuteri</i> , <i>Saccharomyces boulardii</i>	[7-18]
Antibiotic-associated diarrhea.	<i>Lactobacillus rhamnosus</i> strain GG, <i>Saccharomyces boulardii</i>	[7, 21-27]
Lactose malabsorption.	<i>Lactobacillus bulgaricus</i> and <i>Streptococcus</i> <i>salivarius</i> subsp. <i>thermophilus</i>	[7,19,20]
Constipation	<i>Lactobacillus casei</i> PXN 37, <i>Lactobacillus</i> <i>rhamnosus</i> PXN 54, <i>Streptococcus</i> <i>thermophiles</i> PXN 66, <i>Bifidobacterium breve</i> PXN 25, <i>Lactobacillus acidophilus</i> PXN 35, <i>Bifidobacterium infantis</i> (child specific) PXN 27, and <i>Lactobacillus bulgaricus</i>	[50]

Prevention and treatment of allergic reactions.	Lactobacillus rhamnosus strain GG, Bifidobacterium animalis Bb12	[35-49]
Traveler's diarrhea.	Lactobacillus rhamnosus strain GG	[40-41]

## SAFETY CONCERNS OF PROBIOTICS

Newborn infants can develop infection from many species of resident micro flora. The mechanisms for these infections and route of contamination are unclear. Many strains of Lactobacilli and Bifidobacteria are generally recognized as safe for use in the food supply. Documented correlations between systemic infections and probiotic consumption are few, and they have all occurred in patients with underlying medical conditions. Sporadic lactobacillemia from environmental, dietary, or fecal lactobacilli has been very rarely reported. Case reports of *L. rhamnosus* (GG) infections possibly associated with probiotic consumption, in immunocompromised patients have been even less common [42-44]. From the safety point of view, according to current available information, Bifidobacteria, particularly *B. lactis*, has a uniquely strong safety profile, making it a good probiotic candidate for newborns and young infants. Lactobacilli, particularly *L. rhamnosus* (GG), also seems generally safe and be appropriate for older infants and children [42].

## PROBIOTICS APPROPRIATE FOR CHILDREN USE

Children differ from adults in a number of ways that are relevant to the development and use of medicines. These differences include the ways in which medicines are adsorbed, distributed, metabolised and excreted by the body (pharmacokinetics) and what medicines do to the body (pharmacodynamics) [33]. Children are often unable to take the dosage forms that are designed for adults [34]. Many researchers have announced that the compliance of the patients and the success of the treatment depend on the dosage form [46]. For example, tablets that allow for adult doses may need to be split before being given to younger children, based on an undemonstrated assumption that the distribution of the active substance within the tablet is uniform [34]. There is a huge number of probiotic products available on the commercial market. The probiotics suitable for children are produced in special dosage forms like: Chewable Tablets, powders, probiotic gummies, and drops. Most of them are made with natural colors and flavors. Access to a special dosage form of a medication is essential when administration to infants and children [45].

**Table 2: Food Supplements, Containing probiotics, Appropriate for Children Use**

Product	Manufacturer	Description
Nature's Plus AcidophiKidz	Nature's Plus	Gluten free Key ingredients: Rhododendron caucasicum, B. coagulans, fructooligosaccharides
Rainbow Light Probiolicious Gummies	Rainbow Light	Gluten free. Soy free. Key ingredients: ▪ 1 billion CFU Bio-Active Probiatic Defense per serving ▪ Lactobacillus Sporogenes ▪ Prebiotics from inulin and FOS
RAW Probiotics Kids	Garden of Life	Gluten free. The formula is specifically designed for kids' unique needs and includes raw,

		organic, and whole food probiotics. Key ingredients: <ul style="list-style-type: none"> <li>▪ 23 RAW and organic fruits and vegetables</li> <li>▪ RAW inulin</li> <li>▪ Over 5 billion live probiotic cells per daily serving</li> </ul>
Ultimate Flora Kids Probiotic Chewable Tablets	Renew Life	<ul style="list-style-type: none"> <li>• Natural berrylious tasting</li> <li>• No sugar or artificial sweetners</li> <li>• Naturally sweetened with tooth-friendly xylitol</li> <li>• No artificial flavors, colors, or preservatives</li> <li>• Dairy, soy, and gluten free</li> </ul> Key ingredients: <ul style="list-style-type: none"> <li>▪ 100% naturally sourced Lactobacillus GG</li> <li>▪ 5 billion cells per packet</li> <li>▪ Dairy-free formula</li> </ul>
Foods BerryDophilus Chewables	NOW	Key ingredients: <ul style="list-style-type: none"> <li>▪ Bifidobacterium lactis</li> <li>▪ Lactobacillus acidophilus</li> <li>▪ Lactobacillus salivarius</li> <li>▪ Lactobacillus plantarum</li> </ul>
Kids Daily Probiotic Gummies	Digestive Advantage	Key ingredients: <ul style="list-style-type: none"> <li>▪ Ganeden BC30 Probiotic</li> <li>▪ 500 million viable cells</li> <li>▪ Natural flavors with colors from fruits and vegetables</li> </ul>
Primadophilus Children	Nature’s Way	Key ingredients: <ul style="list-style-type: none"> <li>▪ Specially selected strains of freeze-dried bifidobacterium infantis</li> <li>▪ Bifidobacterium longum</li> <li>▪ Lactobacillus rhamnosus</li> <li>▪ Lactobacillus acidophilus microorganisms</li> </ul>
SeroLife	5 Dimensional Probiotic	Key ingredients: <ul style="list-style-type: none"> <li>▪ Lactobacillus acidophilus</li> <li>▪ Bifidobacteria longum</li> <li>▪ Bifidobacteria bifidum</li> <li>▪ Lactobacillus casei</li> <li>▪ Lactobacillus helveticus</li> </ul>
Florastor Kids	Biocodex	Key ingredients: <ul style="list-style-type: none"> <li>▪ Saccharomyces boulardii lyo</li> </ul>
Yum-Yum Dophilus	Jarrow Formulas	Key ingredients: <ul style="list-style-type: none"> <li>▪ 4 probiotic strains</li> <li>▪ MogroPure (Lo Han fruit extract, Momordica grosvenorii)</li> <li>▪ natural raspberry flavor</li> <li>▪ 1 billion cultures per serving</li> </ul>

Children's Blend Probiotic	Udo's Choice	Lactobacillus Casei HA-108, Lactobacillus Rhamnosus HA-111, Lactobacillus Acidophilus HA-122, Lactobacillus Plantarum HA-119, Lactobacillus Fermentum HA-179, Bifidobacterium Bifidum HA-132, Bifidobacterium Breve HA-129.
Bio Balance baby, powder	Nobel	Main ingredients: Bifidobacterium lactis UABLA-12; Lactobacillus acidophilus DDS-1; Streptococcus thermophilus; Actilight (prebiotic); vitamin C, vitamin B1, vitamin B2, vitamin B6, vitamin B3, Zn.
Linex Baby	Sandos	Main ingredients: Bifidobacterium and maltodextrin
BioGaia ProTectis drops	BioGaia	BioGaia ProTectis drops is a dietary supplement containing <i>Lactobacillus reuteri</i> Protectis that has been tested in a number of clinical studies and proven both effective and safe for children.
Lactoflor Kids	Kendy Pharma	Lactobacillus helveticus, Bifidobacterium bifidum, B. longum, B. infantis, L. acidophilus, L. bulgaricus, Streptococcus thermophilus
Martians Lactobacillus,	Walmark	Lactobacillus helveticus, Bifidobacterium bifidum, B. longum, B. infantis, L. acidophilus, L. bulgaricus, Streptococcus thermophilus, vitamin D
Kids Chewables Daily Probiotic Formula	Culturelle	Lactobacillus GG - the ingredient in Culturelle Kids Chewables Daily Probiotic Formula - is clinically proven to help reduce occasional tummy troubles (like diarrhea and occasional digestive upset) by helping to restore the balance of good and not-so-good bacteria in children's digestive systems
Probiotics with Colostrum, Chewable Tablets	ChildLife	Key ingredients: <ul style="list-style-type: none"> <li>▪ Colostrum</li> <li>▪ Lactobacillus acidophilus</li> <li>▪ Bifidobacterium breve</li> <li>▪ Bifidobacterium longum</li> </ul>
Kids Probiotic Drops	MRM	Key ingredients: Bifidobacterium breve, Lactobacillus Rhamnosus GG

## CONCLUSIONS

In past two decades selected probiotic strains have been thoroughly investigated for specific health effects. The current uses of probiotics cover a wide range of diseases and ailments. Proven benefits of probiotics include the treatment of acute and post antibiotic-associated conditions. Properties like relief of lactose intolerance symptoms and shortening of rotavirus diarrhoea are now widely accepted for selected probiotics. Some areas, such as the treatment and prevention of

atopy hold great promise but more studies must be done for better evidences. Researchers propose many other health effects but still need additional investigations. The inclusion of probiotics in children's diet would give many benefits for children health and immune system. It is important to note that children are often unable to take the dosage forms that are designed for adults, so most appropriate dosage forms, containing probiotics are: oral drops, powders or chewable tablets.

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