Pediatr Gastroenterol Hepatol Nutr. 2024 Jan;27(1):1-14
https://doi.org/10.5223/pghn.2024.27.1.1
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Review Article

Check for updates

Role of Probiotics in the Treatment and Prevention of Common Gastrointestinal Conditions in Children

Iva Hojsak [1,2,3] **and Sanja Kolaček** [1,2]

[1]Department of Pediatrics, Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital, Zagreb, Croatia
[2]Department of Pediatrics, University of Zagreb School of Medicine, Zagreb, Croatia
[3]Department of Pediatrics, University J.J. Strossmayer School of Medicine, Osijek, Croatia

OPEN ACCESS

Received: Apr 11, 2023
1st Revised: Jul 10, 2023
2nd Revised: Aug 28, 2023
Accepted: Aug 30, 2023
Published online: Jan 9, 2024

Correspondence to
Iva Hojsak
Department of Pediatrics, Referral Center for Pediatric Gastroenterology and Nutrition, Children's Hospital, Klaićeva 16, 10000 Zagreb, Croatia.
Email: ivahojsak@gmail.com
iva.hojsak@kdb.hr

ORCID iDs
Iva Hojsak
https://orcid.org/0000-0003-3262-5964
Sanja Kolaček
https://orcid.org/0000-0003-2673-4590

Funding
None.

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts. Although recommendations for probiotic use should be strain-specific, many systematic reviews, including recommendations from different societies, recommend probiotic use in general, providing no relevant information for healthcare professionals regarding which probiotic to recommend for which clinical indication, at what dose, and for how long. This narrative review aimed to present the available evidence on the use of probiotics in the prevention and treatment of common gastrointestinal diseases in children, considering the strain and dose used. Furthermore, this study summarizes the evidence on the possible side effects and quality of products containing probiotics.

Keywords: Gastroenteritis; Antibiotic-associated; Irritable bowel syndrome; *Helicobacter pylori*; *Lacticaseibacillus*; *Lactobacillus*; *Limosilactobacillus*; *Saccharomyces*

INTRODUCTION

Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts [1]. In 2014, the International Scientific Association for Probiotics and Prebiotics emphasized that the mode of action of probiotics varies between different genera and species, although some are strain-specific [2]. Unfortunately, many systematic reviews, including recommendations from different societies, recommend probiotic use in general, providing no relevant information for healthcare professionals regarding which probiotic for which clinical indication, at what dose, and for how long. Providing a concrete recommendation is often difficult, as many trials have used different strains at different doses and evaluated different outcomes, making comparisons between them very difficult and sometimes impossible.

Another question is whether the clinical effect is strain-dependent or whether the recommendation at the species level would suffice. A recently published review attempted to answer this question; however, evidence is limited and no head-to-head comparisons are available [3]. Therefore, considering the available evidence and drawing conclusions based on the strain and dose of probiotics used in clinical trials would be prudent.

Another novelty is the recent reclassification of the genus *Lactobacillus* which is now divided into 25 genera [4]. Therefore, some well-known probiotics have new names; *Lactobacillus rhamnosus* is *Lacticaseibacillus rhamnosus,* and *Lactobacillus reuteri* is *Limosilactobacillus reuteri.* However, the species and strain designations remain unchanged [4].

Hence, this narrative review aimed to present the available evidence on the use of probiotics in the prevention and treatment of common gastrointestinal diseases in children, considering the strain and dose used. Furthermore, this study summarizes the evidence on the possible side effects and quality of products containing probiotics.

INDICATIONS FOR PROBIOTIC USE

A summary of the probiotic strains and their combinations with the highest levels of evidence is presented in **Table 1**.

Acute gastroenteritis (AGE)

AGE is a common cause of morbidity and mortality among infants and children worldwide. Malnutrition and unsafe water and sanitation continue to be leading risk factors for diarrhea in developing areas [5]. AGE is an important health issue in developed countries. This leads to frequent visits to primary care physicians, increases the number of emergency department visits and hospital admissions, and consequently, imposes a high financial burden on healthcare and society [5]. Most AGE cases are caused by viral infections, and the mainstay of treatment is rehydration, mainly with oral rehydration solution. Furthermore, avoiding fasting and continuing feeding are important [5,6]. As a causal treatment is not available, studies have assessed the role of different supplement therapies, of which probiotics are one of the most well-studied.

Several randomized controlled trials (RCTs) have investigated the roles of different probiotic strains and their combinations in the treatment of AGE. Consequently, many systematic reviews and expert groups have advocated the use of probiotics in the management of AGE [7-10]. However, with new evidence from 2019, recommendations have begun to differ, with some societies questioning the efficacy of some strains that previously had positive recommendations [11,12]. This can be mainly observed in two recommendations, both made in 2020; the American Gastroenterology Association (AGA) made a conditional recommendation against the use of probiotics in children from North America with acute infectious gastroenteritis (based on the evaluation of 89 trials) [13]. By contrast, the

Table 1. Type of probiotic(s) that may be considered in the treatment or prevention of gastrointestinal disease/disorder

Gastrointestinal disease/disorder	Type of probiotic(s) that may be considered
Acute gastroenteritis – treatment	*L. rhamnosus* GG
	S. boulardii
	L. reuteri DSM 17938
	Combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246
Antibiotic-associated diarrhea – prevention	*S. boulardii*
	L. rhamnosus GG
Infantile colics – reduction of crying time	*L. reuteri* DSM 17938
	B. lactis BB-12
Functional abdominal pain – pain intensity reduction	*L. reuteri* DSM 17938
Irritable bowel syndrome – reduction of pain frequency and intensity	*L. rhamnosus* GG
Helicobacter pylori – increase of the eradication rate and reduction of the treatment-related gastrointestinal side effects	*S. boulardii*

https://doi.org/10.5223/pghn.2024.27.1.1

European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group (WG) on Probiotics and Prebiotics position paper identified 16 systematic reviews and meta-analyses published from 2010 until September 2020 (more than 150 RCTs included) and made weak recommendations for the use of some probiotic strains and their recommendations (*Saccharomyces boulardii, Lacticaseibacillus rhamnosus GG, Limosilactobacillus reuteri* DSM 17938 and the combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246 [6]. These recommendations mainly differ because the evidence that recommendations were based on studies from North America, where the two most recent trials questioned the efficacy of probiotics [11,14], and the ESPGHAN considered RCTs published worldwide. A subgroup analysis based on the geographical setting of the RCTs demonstrated a higher efficacy of *L. rhamnosus* GG in Europe (5 RCTs, n=744, mean deviation [MD] −32 hours, [−49 to −15]) and Asia (6 RCTs, n=1,740, MD −24 hours, [−47 to −1.8]) than in other continents [6]. This could explain the differences between the ESPGHAN WG and AGA recommendations.

Since 2020, several new papers included in the most recent position paper from the ESPGHAN Special Interest Group on Gut Microbiota and Modifications from 2023 have been published [15]. This position paper provides a weak grade of recommendation with a low certainty of evidence for the use of *L. rhamnosus* GG ATCC 53103 (at a dose of ≥10^{10} CFU/day for 5–7 days) and *S. boulardii* (at a dose of 250–750 mg/day for 5–7 days). A weak grade of recommendation but very low certainty of evidence was provided for the use of *L. reuteri* DSM 17938 (at daily doses 1×10^8 to 4×10^8 CFU for 5 days) and a combination of *L. rhamnosus* 19070-2 and *L reuteri* DSM 12246 (at a dose of 2×10^{10} CFU for each strain for 5 days) [15]. It should be noted that the main effect was the shortening of diarrhea by approximately one day.

Two combinations had negative recommendations: a combination of *L. helveticus* R0052 and *L. rhamnosus* R0011 (certainty of evidence: moderate; grade of recommendation: strong) and *Bacillus clausii* strains O/C, SIN, N/R, and T (certainty of evidence: very low; grade of recommendation: weak) [15].

Prevention of antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) is a common complication that occurs in up to one-third of all patients treated with antibiotics [16]. Although almost all oral and intravenous antibiotics can cause AAD, the risk is higher with the use of aminopenicillins (with or without clavulanate), cephalosporins, and clindamycin [17]. Although the majority of patients present with mild diarrhea, some may also experience life-threatening fulminant pseudomembranous colitis. Therefore, efforts have been made to prevent AAD, and many RCTs aimed to identify efficacious probiotics.

In 2016, the ESPGHAN WG on Probiotics [18] addressed the prevention of AAD by using probiotics. This review identified two probiotic strains as efficacious: *L. rhamnosus* GG (recommendation: strong; quality of evidence: moderate) and *S. boulardii* (recommendation: strong; quality of evidence: moderate). Importantly, if the use of probiotics to prevent *C difficile*-associated diarrhea is considered, the use of *S. boulardii* (recommendation: conditional; quality of evidence: low) is recommended [18]. By contrast, the AGA in 2020 failed to formulate any recommendations on the use of probiotics for AAD prevention but conditionally recommended some probiotics for the prevention of *C. difficile* infection in children receiving antibiotic treatment [13]. A subsequent meta-analysis published in 2021 that included 33 RCTs confirmed the efficacy of *S. boulardii* CNCM I-745 and *L. rhamnosus* GG in AAD prevention in outpatients and hospitalized children [19].

https://doi.org/10.5223/pghn.2024.27.1.1

Although new data are now available, the recommendations in the new ESPGHAN position paper remain the same [15]. Therefore, if the use of probiotics for AAD prevention is considered owing to the presence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD diarrhea, high doses (≥5 billion CFU per day) of *S. boulardii* or *L. rhamnosus* GG may be recommended [15]. These strains should be initiated simultaneously with antibiotic treatment in outpatients and hospitalized children (certainty of evidence: moderate; grade of recommendation: moderate) [15].

Functional gastrointestinal disorders (FGID)

FGID, currently known as gut–brain interaction disorders, encompass various disorders in all age groups and are responsible for a large proportion of pediatric gastroenterologist consultations [20]. The definition of different FGIDs became more stringent after the introduction of the Rome criteria, which aimed to provide diagnostic guidance for every specific FGID [20,21]. The most common FGIDs are infantile colic, constipation, functional abdominal pain (FAP) not otherwise specified, and irritable bowel syndrome (IBS).

The etiology of FGID has not been completely elucidated; however, the prevailing focus for FAP disorders is visceral hypersensitivity, altered gastrointestinal motility, and alterations in the brain–gut axis interaction [22]. As the exact causal agent is unknown, different treatment strategies have been proposed, including probiotics [23].

Evidence that these two probiotic strains affect the treatment of infantile colic has been reported. The most-studied probiotic strain for this clinical indication is *L. reuteri* DSM 17938. Four RCTs (n= 345) were included in the 2018 individual participant data meta-analysis, and in breastfed infants, the use of *L reuteri* DSM 17938 (1×10^8 CFU/day) increased treatment success and reduced crying and/or fussing time [24]. However, the role of *L. reuteri* DSM 17938 in formula-fed infants is unclear [24].

Recently, another strain of *Bifidobacterium lactis* BB-12 (10^9 CFU/day), was tested in two RCTs [25,26]. These studies have reported increased treatment success and reduced crying times in the probiotic group.

Therefore, a recent ESPGHAN position paper [15] provided positive recommendations for *L. reuteri* DSM 17938 (at least 10^8 CFU/day for at least 21 days) and *B. lactis* BB-12 (at least 10^8 CFU/day, for 21–28 days) for the management of colic in breastfed infants (certainty of evidence: moderate; grade of recommendation: weak).

For FAP disorders, recommendations from relevant societies were limited to the AGA 2020 guidelines, and no recommendations were provided for the use of probiotics in symptomatic children and adults with IBS owing to the significant heterogeneity in study design, outcomes, and tested probiotics [13]. A recent ESPGHAN position paper included more recent data and indicated that the only probiotic strains evaluated in more than two RCTs were *L. reuteri* DSM 17938 (6 RCTs) and *L. rhamnosus* GG (5 RCTs) [15]. *L. reuteri* DSM 17938 has resulted in improved abdominal pain in three RCTs [27-29], reduced functional disability but not abdominal pain in one RCT [30], and was not better than a placebo in one trial [31]. A 2021 meta-analysis [32] identified six RCTs that evaluated *L. reuteri* DSM 17938 and three RCTs used *L. rhamnosus* GG compared to a placebo. *L. reuteri* DSM 17938 reduced the pain intensity and increased the

https://doi.org/10.5223/pghn.2024.27.1.1

number of days without pain in patients with FAP. For all the other outcomes, no significant differences were observed between the probiotic and placebo groups.

Another meta-analysis from 2021 evaluated the efficacy of probiotic therapy in children with IBS [33]. Nine RCTs involving 651 participants were included; however, three RCTs included not only patients with IBS, but also those with FAP. This review concluded that probiotics are effective in treating abdominal pain caused by IBS in children. However, the heterogeneity between the studies was high owing to the study design, duration of treatment, and evaluation of outcomes.

Considering available evidence ESPGHAN SIG considers *L. reuteri* DSM 17938 (at a dose of 10^8 CFU to 2×10^8 CFU/day) to reduce pain intensity in children with FAP and *L. rhamnosus* GG (daily dose from 10^9 CFU to 3×10^9 CFU twice daily) to reduce pain frequency and intensity in children with IBS (certainty of evidence: moderate; grade of recommendation: weak) [15].

Functional constipation is considered a widespread FGID in children, with a prevalence of approximately 10% [34]. The etiology of functional constipation is considered multifactorial and includes withholding behavior often observed in children with functional constipation, psychological factors, social conditions, and alterations in the intestinal microbiota [35,36]. The first-line treatment option in children is polyethylene glycol [37]. Unfortunately, for many patients, current treatment options do not provide sustained relief; symptoms often reoccur, and in some patients, last until adulthood; therefore, new treatment strategies have been proposed, including probiotics.

A recent 2021 systematic review and meta-analysis summarized the evidence for probiotic use in chronic constipation [38]. This systematic review identified 13 studies (n=965 children) and two follow-up studies (n=166 children) that compared different probiotic strains to either placebo or laxative treatment. The included RCTs were heterogeneous in study design, duration of treatment, diagnostic criteria, age of the included children, type of strain(s), and clinical outcomes; therefore, no clear conclusions could be drawn. The ESPGHAN 2023 position paper does not recommend the use of probiotics evaluated so far as a single therapy or co-adjuvant with laxatives for the treatment of functional constipation in children (certainty of evidence: moderate; grade of recommendation: weak) [15].

Helicobacter pylori (*HP*)

HP, a gram-negative microaerophilic bacterium isolated from the gastric mucosa in 1983 [39], commonly causes chronic infections, affecting almost every second person worldwide. A recently published meta-analysis of 73 countries across six continents revealed an overall prevalence of 44.3%, increasing to >80% in underdeveloped countries [40]. Although HP is acquired during childhood, the infection rate is significantly lower in children (32.6% vs. 48.6%), which is ascribed to the birth cohort effect and age-accumulated risk of infection [40].

HP can cause progressive gastric inflammation, contributing significantly to the etiopathogenesis of peptic ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma. However, in children, the infection seldom follows the same route, and most infected children are symptom free. Therefore, the latest pediatric guidelines [41,42] do not support a “test and treat” approach recommended for adults but propose an individualized decision adjusted to each infected child.

https://doi.org/10.5223/pghn.2024.27.1.1

The treatment consists of at least two antibiotics to which bismuth can be added, in conjunction with a proton pump inhibitor (PPI), provided as a triple, quadruple, sequential, or concomitant treatment, for 7–14 days [41,42]. However, the proclaimed treatment goal of HP eradication in at least 90% of patients [43], is rarely reached because of antibiotic resistance and therapy-associated side effects. A systematic review and meta-analysis performed in the World Health Organization (WHO) regions yielded an unacceptable frequency of primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin, which was >15% in all WHO regions and significantly increased over time in the majority of the regions. Treatment-associated side effects occur in 12–20% of pediatric patients and consist mainly of gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and abdominal pain, precluding treatment compliance in affected children [44].

In the search for a more efficacious treatment that will increase the eradication rate and decrease the frequency of side effects, the addition of probiotics has been addressed because of their potentially beneficial widespread effects, such as competitive exclusion of pathogens, colonization resistance, increased local IgA production, antibacterial substances, and short-chain fatty acid production [2].

Efficacy of probiotic supplementation for HP eradication

The answer to the first question – whether probiotics alone are sufficient to achieve HP eradication in children – was negative. Based on the literature summary, Pacifico et al. [45] concluded that probiotics had a strain-dependent suppressive effect on HP colonization in asymptomatic children, although the most efficacious modalities did not surpass a 22.9% eradication rate; furthermore, the clearance could be a transitory effect as the HP reappeared after a 1-month wash-out period in 80% of children.

The second important question is whether the addition of probiotics to triple therapy increases eradication rates. Based on a literature search until September 2014 and November 2016, both the ESPGHAN and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition [41] and the Japanese Society guidelines [42] stated that the evidence is insufficient to provide an answer on the additional eradication value of adding probiotics as a supplement. However, since then, further randomized controlled trials comparing triple eradication therapy (two antibiotics+PPI) with and without the addition of probiotics have been published and summarized in four consecutive systematic reviews with meta-analyses and a recent position paper of ESPGHAN [15,46-49]. All the abovementioned systematic reviews concluded that the eradication rate was significantly higher in probiotic-supplemented therapy than in unsupplemented controls, particularly if provided in a high dose and long term (>4 weeks). However, the following restrictions were also apparent. First, the eradication rate, although increased by 8–15%, did not reach the recommended 90%. Second, the most published data are based on evidence obtained from adults. Significant heterogeneity was observed in the three treatment modalities and probiotics used. Except for *S. boulardii,* none of the probiotics were evaluated in more than one study. The evidence for *S. boulardii* indicated that in all the participants (18 RCTs, N=3,592; relative risk [RR], 1.09; 95% confidence interval [CI], 1.05–1.13), and also in a subgroup of children (3 RCTs, N=535; RR, 1.14; 95% CI, 1.03–1.25) supplementation to triple therapy significantly improved the eradication of HP [48]. Acknowledging all the abovementioned constraints, the ESPGHAN SIG [15] recommends that *S. boulardii* may be used along with the HP therapy to increase the eradication rate (certainty of evidence: very low; grade of recommendation: weak).

Role of probiotics in reducing the risk of eradication therapy-related adverse effects

Eradication therapy-related side effects are common, affecting compliance and consequently increasing the risk of eradication failure and antibiotic resistance; therefore, the effect of probiotics on their attenuation was addressed in all systematic reviews cited above. The meta-analysis of Feng et al. [47] (18 RCTs, N=2154; RR, 0.49; 95% CI, 0.38–0.65), and the pediatric subgroup by Lü et al. [46] (2 RCTS; RR, 0.37; 95% CI, 0.21–0.65) has demonstrated that in children, probiotics in general significantly reduced the risk of total therapy-related adverse effects, although the effect differed in terms of type of side effect and probiotic strain used. However, except for *S. boulardii,* results for all other probiotic strains (single strain or in combination) were limited to a single study only, and therefore cannot be used as a basis for sound recommendations. The most successfully treated adverse effects were diarrhea and vomiting, whereas the least successfully treated ones were headache and abdominal pain. A meta-analysis on the efficacy of *Lactobacillus*-supplemented triple therapy in children failed to identify a diminished risk of side effects but confirmed a reduced risk of diarrhea [49]. As for *S. boulardii*, its addition to therapy significantly diminished the risk of side effects in both adults and children (11 RTCs, N=2,464; RR, 0.47; 95% CI, 0.36–0.61), and in particular the risk of diarrhea, nausea, constipation, and bloating. Furthermore, supplementation with *S. boulardii* significantly diminished the need for HP treatment discontinuation [48]. Based on the evidence presented above, it is plausible to support the recommendation of the ESPGHAN that healthcare professionals may recommend the addition of *S. boulardii* to standard HP therapy to diminish treatment-related gastrointestinal side effects [15]. Further studies are required on all other probiotic strains.

PROBIOTIC TREATMENT-RELATED SAFETY CONCERNS

In contrast to drugs, probiotics are live microorganisms that colonize the colon and remain viable while exerting beneficial effects on the host. Therefore, safety concerns differ from other medicinal products, foods, and nutraceuticals, and as recently summarized elsewhere, they could be grouped into: production of deleterious metabolites/toxins, transfer of genes to human cells and other members of the gut flora (e.g., those responsible for antibiotic resistance), short- and long-term immunomodulation, and lastly, causing infectious complications in the host [50]. To prevent such developments, legislative and procedural frameworks have been provided by the European Food Safety Authority (EFSA) on how to assess potentially beneficial microorganisms with respect to the abovementioned safety issues [51]. Moreover, inventories of microorganisms with a long track record of safe use in human foods, such as the Qualified Presumption of Safety by the ESFA [52] or Generally Recognized as Safe by the Food and Drug Administration (FDA) in the USA are performed [53].

Once probiotic microorganisms have selected, safety concerns need to be evaluated in scientific studies through post-marketing surveillance, and if possible, through registries created to detect side effects associated with probiotic use. However, the only study aiming to catalog evidence on the safety aspects of six different probiotic strains/genera *(Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus,* and *Bacillus)* was published 10 years ago, including 622 studies, of which only 387 reported adverse events. In conclusion, the risk of adverse events was not increased in patients receiving probiotics in general (RR, 1.00; 95% CI, 0.93–1.07; p=0.999), or concerning gastrointestinal side effects, infections, other adverse events (RR, 1.06; 95% CI, 0.97–1.16; p=0.201), even in non-critically ill patients (RR, 0.79; 95% CI, 0.51–1.22; p=0.286). However, the authors concluded that systematic reporting was lacking,

no studies investigated side effects as the primary outcome, interventions were mostly poorly documented, and long-term outcomes were unknown [54]. In the last 5 years, almost 100 systematic reviews on the efficacy of probiotics for the treatment of various clinical conditions have been published in PubMed, and adverse reactions, if reported, have not significantly increased. The same applies to children in the most recently published meta-analyses [55]. Following that, the safety of probiotics might not be an issue. However, Bafeta et al. [56] assessed the reported harm in 384 randomized controlled trials of probiotics (N=265, 69%), prebiotics, and symbiotics published between January 2015 and March 2018. Overall, 28% of the trials did not provide data on eventual harm, and methods for collecting harmful effects were not described in 97% of studies; when reported, the terms used were inadequate and generic, and only nine trials (2%) defined adverse and serious adverse effects and appropriately presented the number and nature of harms. The authors concluded that the evidence at this time was insufficient to answer questions regarding the safety of antibiotics [56].

In contrast to the negligible adverse side effects reported in randomized controlled trials, two recently published systematic reviews summarized cases and case reports of invasive infections associated with treatment with probiotic microorganisms. In the first published article, which included both adults and children, the total number of affected patients was 93, and the most commonly observed harm was fungemia in 35 patients (37.6%), sepsis in 29 (31.2%), bacteremia in 19 (20.4%), and endocarditis, abscess, pneumonia, empyema, and septic arthritis in the rest of the patients. The most frequent cause was *Saccharomyces* (50.5%), followed by *Lactobacillus* spp. (27.9%), and *Bifidobacterium* spp. (12.1%) [57]. An increased risk of infection is significantly associated with young and old age, antibiotic use, and *Clostridium difficile* infection [57]. Another recent systematic report summarized 49 cases in children: 35% were associated with *Lactobacillus*, 31% with *Bifidobacterium*, 29% with *Saccharomyces* spp., 4% with *B. clausii,* and 2% with *Escherichia coli* [58]. Among the 49 pediatric patients only one did not have associated comorbidities, and the most common conditions were prematurity (55%) and use of intravenous catheters (51%) [58]. Nearly 100 patients with diagnosed invasive infections caused by a consumed probiotic might be worrisome. However, this has to be viewed from the perspective of millions of consumers, creating the denominator, and the most common causal genera/species correlate with the most frequently used probiotic microorganisms in particular age groups.

Lastly, three reports were published on cases of infants who developed invasive infections caused by a microorganism that was present as a contaminant in the commercial probiotic product; two infants had sepsis [59,60] and one infant developed fatal gastrointestinal mucormycosis [61]. Problems related to the contamination of commercial probiotic products, post-manufacturing surveillance, and probiotic product quality control are discussed in the next section.

In conclusion, probiotics, as live microorganisms, have the potential for different adverse side effects, and invasive infections are particularly worrisome in patients of very young age (preterm infants), old age, immunocompromised status, and other serious comorbidities. Although side effects are very infrequently reported, which makes them appear safe, the current evidence is of poor quality and cannot answer questions on their safety.

QUALITY OF COMMERCIAL PROBIOTIC PRODUCTS

To confer a beneficial effect on the host, as defined by the International Society of Antimicrobial Chemotherapy [2], probiotic microorganisms must survive the hostile acidity of the stomach, bile in the duodenum, and enzymes in the small intestine and colonize the large bowel in sufficient numbers. Furthermore, concerning the number, viability, and functional capacity, which all have to be retained during the entire product shelf-life, beneficial bacteria must survive manufacturing procedures such as repetitive fermentation, cell harvesting, spray, freeze-drying, mixing with an appropriate matrix, storage conditions such as temperature, pH, oxygen exposure and humidity, and type of packaging, to mention just a few examples of the manufacturing determinants that can affect the biological activity of the final product [50,62,63]. Finally, the commercial product must contain only the strain or a combination that has a scientifically proven benefit for the host while avoiding contamination with other microorganisms. This is particularly important when probiotic products are intended for the treatment of defined gastrointestinal conditions in vulnerable populations, such as those described in this article, and not just to improve the GIT milieu in an otherwise healthy host [2]. Recently published reviews [64,65] have summarized the requirements that need to be considered during the manufacturing process to achieve a final probiotic product that will comply with the standards of relevant organizations, such as the EFSA [66,67] and FDA in the USA [68]. However, in Europe and the USA, probiotic products are mostly categorized as food and dietary supplements, for which the regulatory requirements for continuous monitoring and post-marketing quality control are much less stringent than those for licensed drugs. Therefore, the ESPGHAN raised questions regarding the safety, validity, and quality of commercial probiotic products and performed a literature search to assess these important issues [69]. In conclusion, the results revealed that probiotic products commonly contain species/strains not claimed on the label, sometimes composed of potentially pathogenic genera. Furthermore, the number of viable bacteria is often significantly lower and has decreased functional properties. Contamination is a common and particularly worrisome finding [69]. Following the ESPGHAN position paper, several more recently published reports [70,71], two of which were limited to neonates and children [72,73], also reported missing strains, decreased viability, inadequate resistance to acid and bile, and contamination with potentially pathogenic microorganisms. Therefore, several probiotic products on the market did not match their label claims.

In conclusion, the quality of commercial probiotic products is often unsatisfactory, and more stringent regulatory controls are required, particularly for vulnerable groups such as neonates and children, and when prescribed for defined clinical conditions [69].

CONCLUSION

Currently, available evidence supports the use of probiotics for the following clinical indications (**Table 1**).

- Prevention of AGE (*L. rhamnosus* GG ATCC 53103, *S. boulardii*, *L. reuteri* DSM 17938, and a combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246)
- Prevention of AAD (*L. rhamnosus* GG ATCC 53103 and *S. boulardii)*
- Treatment with infantile colic (*L. reuteri* DSM 17938 and *B. lactis* BB-12)
- Pain intensity reduction in children with FAP (*L. reuteri* DSM 17938), and pain frequency and intensity reduction in children with irritable bowel syndrome (*L. rhamnosus* GG)

https://doi.org/10.5223/pghn.2024.27.1.1

Increased *H. pylori* eradication rate and diminished treatment-related gastrointestinal side effects (*S. boulardii*)

REFERENCES

1. Food and Agricultural Organization of the United Nations and World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria [Internet]. World Health Organization; 2001 [cited 2023 Apr 11]. Available from: https://web.archive.org/web/20121022161702/http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf
2. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014;11:506-14.
PUBMED | CROSSREF
3. Jankiewicz M, Łukasik J, Kotowska M, Kołodziej M, Szajewska H. Strain-specificity of probiotics in pediatrics: a rapid review of the clinical evidence. J Pediatr Gastroenterol Nutr 2023;76:227-31.
PUBMED | CROSSREF
4. Zheng J, Wittouck S, Salvetti E, Franz C, Harris HMB, Mattarelli P, et al. A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. Int J Syst Evol Microbiol 2020;70:2782-858.
PUBMED | CROSSREF
5. Guarino A, Aguilar J, Berkley J, Broekaert I, Vazquez-Frias R, Holtz L, et al. Acute gastroenteritis in children of the world: what veeds to be done? J Pediatr Gastroenterol Nutr 2020;70:694-701.
PUBMED | CROSSREF
6. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, et al. Use of probiotics for the management of acute gastroenteritis in children: an update. J Pediatr Gastroenterol Nutr 2020;71:261-9.
PUBMED | CROSSREF
7. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H; European Society for Pediatric Gastroenterology, Hepatology, and NutritionEuropean Society for Pediatric Infectious Diseases. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr 2014;59:132-52.
PUBMED | CROSSREF
8. Gwee KA, Lee WW, Ling KL, Ooi CJ, Quak SH, Dan YY, et al. Consensus and contentious statements on the use of probiotics in clinical practice: a south east Asian gastro-neuro motility association working team report. J Gastroenterol Hepatol 2018;33:1707-16.
PUBMED | CROSSREF
9. Marchand V. [Using probiotics in the paediatric population]. Paediatr Child Health 2012;17:575-6. English, French.
PUBMED | CROSSREF
10. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, et al. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr 2014;58:531-9.
PUBMED | CROSSREF
11. Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, et al. *Lactobacillus rhamnosus* GG versus placebo for acute gastroenteritis in children. N Engl J Med 2018;379:2002-14.
PUBMED | CROSSREF
12. Szymański H, Szajewska H. Lack of efficacy of *Lactobacillus reuteri* DSM 17938 for the treatment of acute gastroenteritis: a randomized controlled trial. Pediatr Infect Dis J 2019;38:e237-42.
PUBMED | CROSSREF
13. Su GL, Ko CW, Bercik P, Falck-Ytter Y, Sultan S, Weizman AV, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. Gastroenterology 2020;159:697-705.
PUBMED | CROSSREF
14. Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, Poonai N, et al. Multicenter trial of a combination probiotic for children with gastroenteritis. N Engl J Med 2018;379:2015-26.
PUBMED | CROSSREF
15. Szajewska H, Berni Canani R, Domellöf M, Guarino A, Hojsak I, Indrio F, et al. Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN special interest group on gut microbiota and modifications. J Pediatr Gastroenterol Nutr 2023;76:232-47.
PUBMED | CROSSREF

16. Barbut F, Lalande V, Burghoffer B, Thien HV, Grimprel E, Petit JC. Prevalence and genetic characterization of toxin A variant strains of Clostridium difficile among adults and children with diarrhea in France. J Clin Microbiol 2002;40:2079-83.
PUBMED | CROSSREF

17. McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. J Infect Dis 1990;162:678-84.
PUBMED | CROSSREF

18. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. J Pediatr Gastroenterol Nutr 2016;62:495-506.
PUBMED | CROSSREF

19. Storr M, Stengel A. [Systematic review: clinical evidence of probiotics in the prevention of antibiotic-associated diarrhoea]. MMW Fortschr Med 2021;163 (Suppl 4):19-26. German.
PUBMED | CROSSREF

20. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology 2016.
PUBMED | CROSSREF

21. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016;150:1443-55.E2.
PUBMED | CROSSREF

22. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol 2015;12:159-71.
PUBMED | CROSSREF

23. Hojsak I. Probiotics in functional gastrointestinal disorders. Adv Exp Med Biol 2019;1125:121-37.
PUBMED | CROSSREF

24. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. Pediatrics 2018;141:e20171811.
PUBMED | CROSSREF

25. Nocerino R, De Filippis F, Cecere G, Marino A, Micillo M, Di Scala C, et al. The therapeutic efficacy of Bifidobacterium animalis subsp. lactis BB-12® in infant colic: A randomised, double blind, placebo-controlled trial. Aliment Pharmacol Ther 2020;51:110-20.
PUBMED | CROSSREF

26. Chen K, Zhang G, Xie H, You L, Li H, Zhang Y, et al. Efficacy of *Bifidobacterium animalis* subsp. *lactis*, BB-12® on infant colic - a randomised, double-blinded, placebo-controlled study. Benef Microbes 2021;12:531-40.
PUBMED | CROSSREF

27. Romano C, Ferrau' V, Cavataio F, Iacono G, Spina M, Lionetti E, et al. *Lactobacillus reuteri* in children with functional abdominal pain (FAP). J Paediatr Child Health 2014;50:E68-71.
PUBMED | CROSSREF

28. Weizman Z, Abu-Abed J, Binsztok M. *Lactobacillus reuteri* DSM 17938 for the management of functional abdominal pain in childhood: a randomized, double-blind, placebo-controlled trial. J Pediatr 2016;174:160-164.e1.
PUBMED | CROSSREF

29. Jadrešin O, Hojsak I, Mišak Z, Kekez AJ, Trbojević T, Ivković L, et al. *Lactobacillus reuteri* DSM 17938 in the treatment of functional abdominal pain in children: RCT study. J Pediatr Gastroenterol Nutr 2017;64:925-9.
PUBMED | CROSSREF

30. Maragkoudaki M, Chouliaras G, Orel R, Horvath A, Szajewska H, Papadopoulou A. *Lactobacillus reuteri* DSM 17938 and a placebo both significantly reduced symptoms in children with functional abdominal pain. Acta Paediatr 2017;106:1857-62.
PUBMED | CROSSREF

31. Eftekhari K, Vahedi Z, Aghdam MK, Diaz DN. A randomized double-blind placebo-controlled trial of *Lactobacillus reuteri* for chronic functional abdominal pain in children. Iran J Pediatr 2015;25:e2616.
PUBMED | CROSSREF

32. Trivić I, Niseteo T, Jadrešin O, Hojsak I. Use of probiotics in the treatment of functional abdominal pain in children-systematic review and meta-analysis. Eur J Pediatr 2021;180:339-51.
PUBMED | CROSSREF

33. Xu HL, Zou LL, Chen MB, Wang H, Shen WM, Zheng QH, et al. Efficacy of probiotic adjuvant therapy for irritable bowel syndrome in children: a systematic review and meta-analysis. PLoS One 2021;16:e0255160.
PUBMED | CROSSREF

34. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr 2018;198:121-30.e6.
PUBMED | CROSSREF

35. Benninga MA, Voskuijl WP, Taminiau JAJM. Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr 2004;39:448-64.
PUBMED | CROSSREF

36. de Meij TG, de Groot EF, Eck A, Budding AE, Kneepkens CM, Benninga MA, et al. Characterization of microbiota in children with chronic functional constipation. PLoS One 2016;11:e0164731.
PUBMED | CROSSREF

37. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58:258-74.
PUBMED | CROSSREF

38. Wegh CAM, Baaleman DF, Tabbers MM, Smidt H, Benninga MA. Nonpharmacologic treatment for children with functional constipation: a systematic review and meta-analysis. J Pediatr 2022;240:136-49.e5.
PUBMED | CROSSREF

39. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273-5.
PUBMED

40. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2018;47:868-76.
PUBMED | CROSSREF

41. Jones NL, Koletzko S, Goodman K, Bontems P, Cadranel S, Casswall T, et al. joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in vhildren and adolescents (update 2016). J Pediatr Gastroenterol Nutr 2017;64:991-1003.
PUBMED | CROSSREF

42. Kato S, Shimizu T, Toyoda S, Gold BD, Ida S, Ishige T, et al. The updated JSPGHAN guidelines for the management of *Helicobacter pylori* infection in childhood. Pediatr Int 2020;62:1315-31.
PUBMED | CROSSREF

43. Graham DY, Javed SU, Keihanian S, Abudayyeh S, Opekun AR. Dual proton pump inhibitor plus amoxicillin as an empiric anti-*H. pylori* therapy: studies from the United States. J Gastroenterol 2010;45:816-20.
PUBMED | CROSSREF

44. Lai HH, Lai MW. Treatment of pediatric *Helicobacter pylori* infection. Antibiotics (Basel) 2022;11:757.
PUBMED | CROSSREF

45. Pacifico L, Osborn JF, Bonci E, Romaggioli S, Baldini R, Chiesa C. Probiotics for the treatment of *Helicobacter pylori* infection in children. World J Gastroenterol 2014;20:673-83.
PUBMED | CROSSREF

46. Lü M, Yu S, Deng J, Yan Q, Yang C, Xia G, et al. Efficacy of probiotic supplementation therapy for *Helicobacter pylori* eradication: a meta-analysis of randomized controlled trials. PLoS One 2016;11:e0163743.
PUBMED | CROSSREF

47. Feng JR, Wang F, Qiu X, McFarland LV, Chen PF, Zhou R, et al. Efficacy and safety of probiotic-supplemented triple therapy for eradication of *Helicobacter pylori* in children: a systematic review and network meta-analysis. Eur J Clin Pharmacol 2017;73:1199-208.
PUBMED | CROSSREF

48. Zhou BG, Chen LX, Li B, Wan LY, Ai YW. Saccharomyces boulardii as an adjuvant therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis with trial sequential analysis. Helicobacter 2019;24:e12651.
PUBMED | CROSSREF

49. Fang HR, Zhang GQ, Cheng JY, Li ZY. Efficacy of Lactobacillus-supplemented triple therapy for *Helicobacter pylori* infection in children: a meta-analysis of randomized controlled trials. Eur J Pediatr 2019;178:7-16.
PUBMED | CROSSREF

50. Grumet L, Tromp Y, Stiegelbauer V. The development of high-quality multispecies probiotic formulations: from bench to market. Nutrients 2020;12:2453.
PUBMED | CROSSREF

51. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Rychen G, Aquilina G, Azimonti G, Bampidis V, Bastos ML, Bories G, et al. Guidance on the characterisation of microorganisms used as feed additives or as production organisms. EFSA J 2018;16:e05206.
PUBMED | CROSSREF

52. European Food Safety Authority. Updated list of QPS-recommended microorganisms for safety risk assessments carried out by EFSA [Internet]. EFSA BIOHAZ Panel; 2023 Jan 25 [cited 2023 Apr 11]. Available from: https://zenodo.org/records/7554079

53. Food and Drug Administration. Generally Recognized as Safe (GRAS) [Internet]. Food and Drug Administration [cited 2023 Apr 11]. Available from: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
54. Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JN, Suttorp MJ, et al. Safety of probiotics used to reduce risk and prevent or treat disease. Evid Rep Technol Assess (Full Rep) 2011;(200):1-645.
PUBMED
55. Wallace C, Gordon M, Sinopoulou V, Akobeng AK. Probiotics for management of functional abdominal pain disorders in children. Cochrane Database Syst Rev 2023;2:CD012849.
PUBMED | CROSSREF
56. Bafeta A, Koh M, Riveros C, Ravaud P. Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota: a systematic review. Ann Intern Med 2018;169:240-7.
PUBMED | CROSSREF
57. Costa RL, Moreira J, Lorenzo A, Lamas CC. Infectious complications following probiotic ingestion: a potentially underestimated problem? a systematic review of reports and case series. BMC Complement Altern Med 2018;18:329.
PUBMED | CROSSREF
58. D'Agostin M, Squillaci D, Lazzerini M, Barbi E, Wijers L, Da Lozzo P. Invasive infections associated with the use of probiotics in children: a systematic review. Children (Basel) 2021;8:924.
PUBMED | CROSSREF
59. Barton LL, Rider ED, Coen RW. Bacteremic infection with Pediococcus: vancomycin-resistant opportunist. Pediatrics 2001;107:775-6.
PUBMED | CROSSREF
60. Brecht M, Garg A, Longstaff K, Cooper C, Andersen C. *Lactobacillus* sepsis following a laparotomy in a preterm infant: a note of caution. Neonatology 2016;109:186-9.
PUBMED | CROSSREF
61. Vallabhaneni S, Walker TA, Lockhart SR, Ng D, Chiller T, Melchreit R, et al. Notes from the field: Fatal gastrointestinal mucormycosis in a premature infant associated with a contaminated dietary supplement--Connecticut, 2014. MMWR Morb Mortal Wkly Rep 2015;64:155-6.
PUBMED
62. Grześkowiak Ł, Isolauri E, Salminen S, Gueimonde M. Manufacturing process influences properties of probiotic bacteria. Br J Nutr 2011;105:887-94.
PUBMED | CROSSREF
63. Duboux S, Van Wijchen M, Kleerebezem M. The possible link between manufacturing and probiotic efficacy; a molecular point of view on *Bifidobacterium*. Front Microbiol 2021;12:812536.
PUBMED | CROSSREF
64. Fenster K, Freeburg B, Hollard C, Wong C, Laursen RR, Ouwehand AC. The production and delivery of probiotics: a review of a practical approach. Microorganisms 2019;7:83.
PUBMED | CROSSREF
65. Jackson SA, Schoeni JL, Vegge C, Pane M, Stahl B, Bradley M, et al. Improving end-user trust in the quality of commercial probiotic products. Front Microbiol 2019;10:739.
PUBMED | CROSSREF
66. Sanders ME, Huis in't Veld J. Bringing a probiotic-containing functional food to the market: microbiological, product, regulatory and labeling issues. Antonie Van Leeuwenhoek 1999;76:293-315.
PUBMED | CROSSREF
67. European Food Safety Authority. Public consultation on the EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain [Internet]. European Food Safety Authority; 2020 Jan 16 [cited 2023 Apr 11]. Available from: https://www.efsa.europa.eu/en/consultations/call/public-consultation-efsa-statement-requirements-whole-genome
68. https://www.fda.gov/animal-veterinary/animal-food-feeds/generally-organized-safe-gras-notification-program, http://www.law.umaryland.edu/ProbioticsWhitePaper
69. Kolaček S, Hojsak I, Canani RB, Guarino A, Indrio F, Orel R, et al. Commercial probiotic products: a call for improved quality control. A position paper by the ESPGHAN working group for probiotics and prebiotics. J Pediatr Gastroenterol Nutr 2017;65:117-24.
PUBMED | CROSSREF
70. Wang Y, Liang Q, Lu B, Shen H, Liu S, Shi Y, et al. Whole-genome analysis of probiotic product isolates reveals the presence of genes related to antimicrobial resistance, virulence factors, and toxic metabolites, posing potential health risks. BMC Genomics 2021;22:210.
PUBMED | CROSSREF

71. Vecchione A, Celandroni F, Mazzantini D, Senesi S, Lupetti A, Ghelardi E. Compositional quality and potential gastrointestinal behavior of probiotic products commercialized in Italy. Front Med (Lausanne) 2018;5:59.
PUBMED | CROSSREF

72. Vermeulen MJ, Luijendijk A, van Toledo L, van Kaam AH, Reiss IKM. Quality of probiotic products for preterm infants: Contamination and missing strains. Acta Paediatr 2020;109:276-9.
PUBMED | CROSSREF

73. Dioso CM, Vital P, Arellano K, Park H, Todorov SD, Ji Y, et al. Do your kids get what you paid for? Evaluation of commercially available probiotic products intended for children in the republic of the philippines and the republic of Korea. Foods 2020;9:1229.
PUBMED | CROSSREF