Prophylactic use of probiotics for gastrointestinal disorders in children

Celine Perceval, Hania Szajewska, Flavia Indrio, Zvi Weizman, Yvan Vandenplas

The gastrointestinal microbiome is a hot topic in clinical research. Beneficial effects of selected probiotics in the prevention of gastrointestinal disorders are mainly restricted to acute gastroenteritis, antibiotic-associated diarrhoea, infantile colic, and necrotising enterocolitis. However, no broad consensus exists to recommend the use of probiotics in the prevention of these conditions, mainly because of the different design of the studies done so far, resulting in little evidence for specific strains, dosages, and indications. More well designed studies are needed before recommendations can be proposed. At this stage, the evidence is insufficient to recommend the routine use of probiotics in infants and children for the prevention of gastrointestinal disorders.

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KidZ Health Castle, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium (C Perceval MD, Prof Y Vandenplas MD); **Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland** (Prof H Szajewska MD); **Department of Paediatrics, University of Bari, Bari, Italy** (F Indrio MD); **and Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel** (Prof Z Weizman MD)

Correspondence to:
Dr Yvan Vandenplas, KidZ Health Castle, UZ Brussel, 1090 Brussels, Belgium
yvan.vandenplas@uzbrussel.be

Introduction

A balanced microbiome is associated with eubiosis and health, whereas an unbalanced microbiome or dysbiosis is related to a lot of health problems, both within and outside the gastrointestinal tract. The question arises immediately: do we know the optimal balance of the gastrointestinal microbiota of the healthy infant and child? At this stage, the answer to this question is still unknown.

The differences between the gastrointestinal microbiota development in infants born through caesarean section versus natural delivery, or formula feeding versus breastfeeding, are well known.[1,2] The gastrointestinal microbiota of the mother is influenced during pregnancy by medications (eg, antibiotics and anti-acid medications), diet, stress, and many other factors.[3–5] The gastrointestinal microbiota of the breastfed baby born vaginally is generally considered as the healthy gut microbiota, but depends on the microbiota of the mother because the maternal perianal microbiota colonises the newborn baby. Moreover, the gastrointestinal microbiota of an exclusively breastfed infant depends on the secretor status of the mother, and on the amount of oligosaccharides secreted in the mother's milk.[6] Gastrointestinal microbiota composition depends also on gastrointestinal transit time,[7] and transit time is a factor of major effect on the composition of the gastrointestinal microbiome.

Prebiotic human milk oligosaccharides are the third most important component, after lactose and lipids, of mother's milk and enhance the development of a healthy bifidogenic microbiome. Protein is only the fourth most important component. These human milk oligosaccharides are virtually absent in cow milk and thus also in cow milk based infant formula. Therefore, supplementation of infant formula with prebiotic oligosaccharides to enhance the development of a bifidogenic microbiome seems a more physiological option than adding probiotics. Nevertheless, probiotics have also been added to infant feeding with the intention to prevent disease and thus result in a better health outcome. On the basis of the current literature, a case can be made for the use of specific sets of probiotic organisms during early life with the goal of a healthy pregnancy to term, and a healthy start to life with lowered risk of infections and inflammatory events.[8]

Probiotics and prevention

Probiotics are defined as live microorganisms that when administered in adequate amounts confer a health benefit on the host.[9] According to data from Denmark,[10] some parents define probiotics as a kind of medicine they only use if their child is ill. According to the same study,[10] parents worry that probiotics might cause an imbalance in the microbiome of a young child. Parental probiotic consumption practices are embedded in a cultural understanding of the child.[10] Parents accept the use of probiotics as treatment but are sceptical about their use in prevention.[10] The parents' perception of probiotics is determined by their level of information and knowledge. Because mother's milk is suggested to contain probiotic bacteria,[11] to administer probiotic strains is not unnatural. Many infant formulae are supplemented with probiotic bacteria. But when administered separated from food, as a supplement, probiotics are perceived as medication.[10] However, these findings should be validated worldwide because parental perception regarding preventive probiotic administration might differ in different parts of the world.

Pregnancy and breastfeeding

Probiotics administered during pregnancy and breastfeeding to the mother can be found in the gastrointestinal

Key messages

- Data indicate that selected probiotic strains are likely to prevent acute gastroenteritis, antibiotic-associated diarrhoea, infantile colic, and necrotising enterocolitis
- Studies differ in design and as a consequence, the evidence for a recommendation of probiotics is insufficient
- Because adverse effects are extremely rare, the strains studied in acute gastroenteritis, antibiotic-associated diarrhoea, infantile colic, and necrotising enterocolitis might also be used in acute gastroenteritis, antibiotic-associated diarrhoea, colic, and necrotising enterocolitis, considering that if the use of these strains do not harm, they might be of benefit

	Strains	Overall incidences of nosocomial diarrhoea		p value
		Probiotic	Placebo	
Saavedra et al (1994)[20]	*Bifidobacterium bifidum* and *Streptococcus thermophilus*	7%	31%	0·035
Hojsak et al (2015)[21]	*Bifidobacterium animalis* BB12	8%	6%	0·32
Szajewska et al (2001)[22]	LGG	7%	33%	0·002
Mastretta et al (2002)[23]	LGG	25%	30%	0·43
Bruzzese et al (2016)[24]	LGG	9%	33%	0·016
Urbańska et al (2016)[25]	10^9 CFU of *Lactobacillus reuteri* DSM17938	6%	8%	0·87
Wanke and Szajewska (2012)[26]	10^8 CFU of *L reuteri* DSM17938	33%	31%	0·78

CFU=colony-forming units. LGG=*Lactobacillus rhamnosus GG*.

Table 1: **Probiotics and prevention of nosocomial diarrhoea**

microbiota of the mother. However, there are scarce data on how the administration of probiotics to the mother might impact on the gastrointestinal tract of the infant. Prenatal administration of probiotics to pregnant women has mainly been studied focusing on the prevention of atopic dermatitis, with contradictory results.[12,13] A guideline by the World Allergy Organization did not recommend use of probiotics to reduce the risk of allergy in children.[14] However, the World Allergy Organization considered that a likely net benefit from using probiotics to prevent eczema exist. Specifically, the World Allergy Organization suggests: "using probiotics in pregnant women at high risk for having an allergic child"; "using probiotics in women who breastfeed infants at high risk of developing allergy"; and "using probiotics in infants at high risk of developing allergy".[14] All recommendations were conditional and supported by a very low quality of evidence.[14] Analysis of the role of probiotics in the prevention of atopic dermatitis shows that a positive effect might be related to the type of probiotic strain used, the method of administration, the onset time, the dose size, and the duration of treatment.[15] According to several reviews,[12,16,17] a combined prenatal and postnatal supplementation might be the most effective. Oral supplementation of probiotics to mothers after preterm birth might improve the time necessary to tolerate 50% of the enteral feeds by the preterm infants; however, this estimate is very imprecise.[18]

The evidence is insufficient to conclude whether an appreciable benefit or harm to neonates exists of either oral supplementation of probiotics administered to pregnant women at low risk for preterm birth or oral supplementation of probiotics to breastfeeding mothers of preterm infants after birth.

Diarrhoea

Diarrhoea of any cause (eg, nosocomial, infectious, and antibiotic associated) is a major health issue in infants and young children because of the high incidence of this condition during early childhood. Globally, every child younger than 3 years is reported to develop at least one episode of infectious gastroenteritis per year.[19]

In 1994, Saavedra and colleagues[20] were the first to report the benefit of supplementation of infant formula with *Bifidobacterium bifidum* and *Streptococcus thermophilus* in reducing the incidence of acute diarrhoea and rotavirus shedding in infants admitted to a chronic medical care hospital during the study period (table 1). By contrast, *Bifidobacterium animalis subsp lactis* BB12 was not effective in preventing nosocomial infections when given to children older than 1 year during hospital treatment for acute disease.[21]

Data regarding *Lactobacillus rhamnosus GG* (LGG) are somehow contradictory. Prophylactic use of LGG significantly reduced the risk of nosocomial diarrhoea in infants, particularly nosocomial rotavirus gastroenteritis, resulting in a number needed to treat of four.[22] However, formula supplementation with LGG was ineffective in preventing nosocomial rotavirus infections, whereas breastfeeding was effective.[23] A randomised controlled trial[24] showed that LGG (6×10^9 colony forming units [CFU] per day) together with vitamins B and C and zinc given for 15 days, starting on the first day of admission to hospital for treatment, to children aged 0·5–5·0 years resulted in a reduced incidence of nosocomial infections during the study.

According to a review,[27] administration of LGG and *B bifidum* and *S thermophilus* compared with placebo reduced the risk of health care-associated diarrhoea. Administration of two other probiotics (*Lactobacillus reuteri* DSM17938 and *Lactobacillus delbrueckii* H2B20) was ineffective.[27] Sufficient evidence exists for showing that LGG administrated in a dose of at least 10^9 CFU per day during a hospital stay can significantly reduce the risk for nosocomial diarrhoea on a regular paediatric ward.[28] Evidence of effectiveness of *L reuteri* DSM17938 in preventing nosocomial diarrhoea in children is absent.[25,26] On the basis of currently available evidence, LGG can be recommended when the use of probiotics for preventing nosocomial diarrhoea in children is considered, as recommended by the Working Group on Probiotics from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.[29,30]

Acute gastroenteritis is one of the most frequent infectious diseases during early childhood. Therefore, the effect of the administration of probiotics has been tested in the prevention of acute gastroenteritis. *B lactis* BB12, when added to an acidified infant formula, was shown to have some, albeit very modest, protective effect against acute diarrhoea in healthy children (table 2).[31] The difference in the incidence of diarrhoea during the study was not different in the probiotic supplemented and control group (13 [28%] of 46 patients in the supplemented group *vs* 17 [39%] of 44 patients in the control group). The number of days with diarrhoea did not differ between the groups but the daily probability to develop diarrhoea differed. Feeding infants with *B lactis* BB12 reduced the risk of getting

diarrhoea by a factor of 1·9.[31] *B animalis subsp lactis* BB12 given over a period of 3 months had no effect on the prevention of gastrointestinal and respiratory tract infections in healthy children who attended day care centres. Overall, the effect on the incidence of diarrhoea during the study period was not significant.[32] In a community-based, double-blind, randomised controlled trial[33] in India, children aged 1–3 years were randomly allocated to receive either control milk or the same milk fortified with 2·4 g per day of prebiotic oligosaccharide and $1·9\times10^7$ CFU per day of the probiotic *B lactis* HN019, resulting in significant reduction of dysentery, respiratory morbidity, and febrile illness. A daily administration of a combination of *B animalis subsp lactis* BB12 and LGG for 6 months in healthy infants did not reduce the number of episodes of diarrhoea, or the number of days the child was absent from child care.[34] Formulas containing *B lactis* BB12 and galacto-oligosaccharides and fructo-oligosaccharides did not show benefit in reducing infection rate compared with formulas with only *B lactis*.[35]

A placebo-controlled trial[36] with LGG showed a decreased incidence of diarrhoea in undernourished, formula-fed children in Peru, but not in breastfed children. The difference in gastrointestinal microbiota development in breastfed versus formula-fed infants might in part explain this observation, but breastmilk is also a source of protective IgA antibodies,[39] which might protect the infant from developing infectious diarrhoea. Outcomes in prevention might differ from outcomes in treatment, because two recent therapeutic trials[40,41] concluded that probiotics (a mixture of *L rhamnosus* R0011 and *Lactobacillus helveticus* R0052, and *LGG*) did not shorten the duration of acute gastroenteritis. In a multicentre study done in 928 children, the incidence of diarrhoea was significantly reduced with the consumption of fermented milk supplemented with *Lactobacillus casei* DN-114 001 (16%) compared with yogurt (22%).[37] Daycare infants fed a formula supplemented with *L reuteri* (American Type Culture Collection 55730) or *B lactis* BB12 had fewer and shorter episodes of diarrhoea, with no effect on respiratory illnesses.[38] Healthy children attending day care centres, with daily administration of *L reuteri* DSM17938 showed a significant effect in reducing episodes and duration of diarrhoea and respiratory tract infection, with consequent cost savings for the community.[42] The number of medical visits, antibiotic use, absenteeism from day school, and parental absenteeism from work were significantly reduced in the *L reuteri* group (p=0·01).[42] According to a review,[43] *L reuteri* is reported to be effective in reducing the incidence of diarrhoea in children attending day care centres.

In summary, preventive administration of some specific probiotic strains most of the time results in a decreased incidence of acute gastroenteritis in regions with a very high incidence of the condition.

The prevention of antibiotic-associated diarrhoea has been the subject of many investigations, both in children and adults. The most commonly used probiotics are LGG, *Lactobacillus acidophilus*, *L casei*, *B ssp*, *Streptococcus ssp*, and the yeast *Saccharomyces boulardii*. Most of these trials show clear evidence of efficacy, with the two most effective strains being LGG and *S boulardii*. Evidence is also becoming available on the importance of the dose of probiotics in reducing the incidence of this type of diarrhoea, and the incidence of diarrhoea associated with *Clostridium difficile* after the use of antibiotics.[44] A yogurt combination of LGG, *L acidophilus*, and *B lactis* BB12 was reported to be an effective method to reduce the incidence of antibiotic-associated diarrhoea in children (table 3).[45] *Lactobacillus plantarum* DSM9843 was not better than placebo regarding the prevalence of loose or watery stools, mean number of loose or watery stools, or the incidence of abdominal symptoms during antibiotic administration.[46] *L reuteri* DSM17938 was not effective in the prevention of diarrhoea or antibiotic-associated diarrhoea in children.[47] *S boulardii* was shown to prevent antibiotic-associated

	Strain	Overall incidence of acute gastroenteritis		p value
		Probiotic	Placebo	
Chouraqui et al (2004)[31]	*Bifidobacterium lactis* BB12	28%	39%	0·30
Hojsak et al (2016)[32]	*B lactis* BB12	64%*	61%*	0·64
Sazawal et al (2010)[33]	*B lactis* HN019 and prebiotics	5·26 episodes	5·44 episodes	0·08
Laursen et al (2017)[34]	*B lactis* BB12 and LGG	64%	56%	0·14
Bocquet et al (2013)[35]	*B lactis* BB12	4·5 (3·0) episodes*	4·9† (3·2) episodes*	0·18
Oberhelman et al (1999)[36]	LGG	5·21	6·02	0·028
Pedone et al (2000)[37]	*Lactobacillus casei* DN-114 001	16%	22%‡	0·03
Weizman et al (2005)[38]	*Lactobacillus reuteri* ATC 55730 or *B lactis* BB12	0·02 episodes (*L reuteri*); 0·13 episodes (*B lactis*)	0·31 episodes	<0·001

Data are proportion (%) or mean (SD). LGG=*Lactobacillus rhamnosus GG*. *Common infections reported (not only acute gastroenteritis). †Prebiotics group. ‡Yoghurt.

Table 2: **Probiotics and prevention of acute gastroenteritis**

	Strains	Incidences of antibiotic-associated diarrhoea		p value
		Probiotic	Placebo	
Fox et al (2015)[45]	LGG *Bifidobacterium lactis* Bb-12 *Lactobacillus acidophilus* La-5*	0%	18%	0·025
Olek et al (2017)[46]	*Lactobacillus plantarum* DSM9843	39%	44%	0·26
Kołodziej and Szajewska (2018)[47]	*Lactobacillus reuteri* DSM17938	6%	11%	0·17
Shan et al (2013)[48]	*Saccharomyces boulardii*	4%	19%	<0·001

LGG=*Lactobacillus rhamnosus GG*. *Both probiotic and placebo groups received yoghurt.

Table 3: **Probiotics and prevention of antibiotic-associated diarrhoea**

diarrhoea in children admitted for hospital treatment because of a respiratory tract infection.The yeast was also effective as treatment of antibiotic-associated diarrhoea in children in the placebo group who ended up developing antibiotic-associated diarrhoea.[48]

According to a review,[49] moderate-quality evidence suggests that probiotics are associated with decreased incidence of antibiotic-associated diarrhoea in children (1 month–18 years) without an increase in adverse events. A Cochrane systematic review,[50] analysing data from 23 studies (3938 participants), estimates a pooled probiotic effect (relative risk [RR] 0·46, 95% CI 0·35–0·61) with a number needed to treat of ten. A post-hoc subgroup analysis to explore heterogeneity indicated that probiotics are effective among trials with a *C difficile* associated diarrhoea baseline risk over 5%. The weakness of this kind of meta-analysis is that all probiotic strains are grouped together, although some strains might be more effective than others. Among the various probiotics evaluated, LGG or *S boulardii* at 5–40×10^9 CFU per day might be appropriate given the modest number needed to treat and the likelihood that adverse events are very rare.[51] In a meta-analysis, LGG was reported to be effective in preventing antibiotic-associated diarrhoea in children and adults treated with antibiotics for any reason, although with a moderate to low quality of evidence.[52] Moderate-quality evidence suggests that probiotics are associated with a decreased risk of *C difficile* infection and very low-quality evidence suggests that probiotics are associated with fewer adverse events than placebo or no treatment.[53] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition recommends that, if the use of probiotics to prevent antibiotic-associated diarrhoea is considered because of the existence of risk factors such as class of antibiotics, duration of antibiotic treatment, age, need for admission for hospital treatment, comorbidities, or previous episodes of antibiotic-associated diarrhoea, LGG (moderate quality of evidence, strong recommendation), or *S boulardii* (moderate quality of evidence, strong recommendation) are recommended.[54] New information showed that LGG bacteria are sensitive to penicillin, which might make this probiotic ineffective in these circumstances.[55]

S boulardii is the only probiotic that can be recommended (low quality of evidence, conditional recommendation) to prevent diarrhoea associated with *C difficile*.[30,54] Other strains or combinations of strains have been tested in this indication, but sufficient evidence for efficacy is absent.[54] Despite the need for further research, hospital treatment for patients, particularly those at high risk of diarrhoea associated with *C difficile*, should be informed of the potential benefits and harms of probiotics.[30] *S boulardii*, and faecal microbiota transplantation have become valid forms of prevention or therapy of colitis caused by *C difficile*.[56] Analyses showed that the potential for using *S boulardii* as an antibiotic-associated prophylactic treatment for diarrhoea in inpatients in Belgium would result, on the basis of 831 655 hospital admissions with antibiotic administration in 2014, in €503 cost saving per patient.[57] For example, generalised use of *S boulardii* in adult inpatients treated with antibiotics could result in total annual savings up to €418 million for the Belgian health-care system.[57]

Infantile colic

The general incidence of infant colic is similar among formula-fed and breastfed infants.[58] The vast majority of published articles concerning infant colic have evaluated probiotics as a therapeutic tool and have shown that *L reuteri* DSM17938 was effective in reducing infant colic mainly in breastfed infants.[59] Six studies included for subgroup meta-analysis on probiotic treatment, notably *L reuteri*, showed that administration of probiotics is an effective treatment, with an overall mean difference in crying time at day 21 of –55·8 min per day (95% CI –64·4 to –47·3, p=0·001).[60]

Little data are available regarding the use of probiotics in the prevention of infant colic. To the best of our knowledge, only two clinical studies were published. The first trial included 468 infants, breastfed and formula-fed, showing that compared with placebo, the daily administration of *L reuteri* DSM17938, from day 3 for 90 days, resulted in a significant reduction in crying time by approximately 51 min per day at 1 month, and by 33 min per day at 3 months. The emergency room visits, lost parental working days, and use of additional medications in infants who received the probiotic agent were also significantly less. A cost–benefit analysis showed significant savings as well.[61] Preventive administration of *L reuteri* was shown to reduce the number of consultations because of colic, and to reduce health-care cost, both for the family (€88) and for the community (€104).[62,63] The second study was based on a secondary analysis of data from a trial of LGG supplementation, for the first 6 months of life in 184 infants. No differences were found between the infants exposed to early LGG supplementation, versus infants exposed to the control intervention.[64] In a third small study, with poorly defined methods, preventive administration of *Bifidobacterium breve* B632 and BR03 resulted in a mean duration of crying of 12·14 min on average in the probiotics group and of 46·65 min in the placebo group during the third month of supplementation. However, no differences were noticed during the first and the second months of supplementation.[65] In view of these conflicting results, further controlled large-scale strain-specific trials are warranted. *L reuteri* DSM17938 was recommended at a dose of 10^8 CFU once daily as preventive strategy of infantile colic (level-1 evidence, ie, at least one randomised controlled trial done).[30]

Although there is insufficient evidence for a recommendation, available data suggest that specific probiotic strains such as *L reuteri* DSM17938 might prevent infantile colic in some infants. Because *L reuteri* administration is reported to be safe, it is at the end a cost–benefit discussion.

Necrotising enterocolitis

The stepwise microbial gut colonisation might already be initiated prenatally by a distinct microbiota in the placenta and amniotic fluid.[66] The clinical meaning of these findings needs to be further evaluated. A gut microbiota associated with necrotising enterocolitis has been identified in meconium samples; *Clostridium perfringens* is associated with necrotising enterocolitis from the first meconium until just before necrotising enterocolitis onset.[65] By contrast, in postmeconium increased numbers of staphylococci were negatively associated with necrotising enterocolitis.[67]

L reuteri DSM17938 administered to preterm infants was shown to be safe and to significantly reduce feeding intolerance.[17] No differences were found for any other secondary outcomes such as necrotising enterocolitis, hospital stay, sepsis, and diarrhoea.[17]

A meta-analysis concluded that bifidobacterial administration reduced the relative risk of developing necrotising enterocolitis (RR 0·38, 95% CI 0·25–0·58; p<0·00001) or death (0·74, 0·60–0·92; p=0·006).[68] No difference in the overall incidence of sepsis was found (0·87, 0·73–1·03; p=0·11).[68] In a retrospective observational study,[69] the overall incidence of necrotising enterocolitis in 640 infants with very low birth weight with a median gestational age of 28·7 weeks that were given LGG was 33 (17%) of 197 infants compared with 45 (10%) of 443 before the implementation of the probiotic administration.[69] The conclusion of this trial was that LGG increased the risk of developing necrotising enterocolitis.[69] However, another group came to the opposite conclusion with a similar protocol of a retrospective observational study done in a low-income setting in that LGG significantly reduced necrotising enterocolitis stage 2 and the composite outcome of necrotising enterocolitis at stage 2 and mortality in preterm infants.[70] According to a strain specific network meta-analysis, only three of 25 studied probiotic treatment combinations showed significant reduction in mortality: the combination of *B bifidum* NCDO 1453 and *L acidophilus* NCDO 1748 (based on two studies with 494 infants); the combination of *B bifidum*, and *L acidophilus* (based on one study with 186 infants); and the combination of *B infantis*, *L acidophilus*, *L casei*, *L plantarum*, *L rhamnosus*, and *S thermophilus* altogether (based on one study with 150 infants).[71] Seven treatments reduced the overall incidence of necrotising enterocolitis: *B lactis* BB12 or B94 (based on five trials with 828 infants); *L reuteri* ATCC 55730 or DSM17938 (based on four studies with 1459 infants); LGG (based on six studies with 1507 infants); the combination of *B bifidum*, *B infantis*, *B longum*, and *L acidophilus* (based on two studies with 247 infants); the combination of *B infantis* ATCC 15697 and *L acidophilus* ATCC 4356 (based on one study with 367 infants); the combination of *B infantis* BB02, *B lactis* BB12, and *S thermophilus* TH-4 (based on two studies with 1244 infants); and the combination of *B longum* 35624 and LGG (based on two studies with 285 infants). Two treatments reduced late-onset sepsis: the combination of *B bifidum*, *B infantis*, *B longum*, and *L acidophilus* (based on two studies with 247 infants; and the combination of *B longum* R00175, *Lactobacillus helveticus* R0052, *L rhamnosus* R0011, and *S boulardii* CNCM I-1079 (based on three studies with 241 infants). Three treatments reduced time until full enteral feeding: *L reuteri* ATCC 55730 or DSM17938 (based on three studies with 626 infants); the combination of *B bifidum*, *B infantis*, *B longum*, and *L acidophilus* (based on two studies with 247 infants); and the combination of *B longum* BB536 and LGG (based on one study with 94 infants).[71] There was no clear overlap of strains, which were effective on multiple outcome domains.[71] The network meta-analysis showed efficacy in reducing mortality and morbidity only in a minority of the studied strains or combinations. This result might be because of an inadequate number, or size, of randomised controlled trials, or because of a true absence of effect for certain species. Further large and adequately powered randomised controlled trials with strains with the greatest apparent efficacy will be needed to precisely define optimal treatment strategies.

Probiotics seem to be the most substantial advance in necrotising enterocolitis prevention at present because of the substantial range of beneficial effects at various levels of gut function and defence mechanisms.[30,72] Although some authors published strong evidence to support general effects of probiotics as a group, rather than focusing on strain-specific effects, others do question this approach and conclude that the evidence is insufficient to guide the selection of the most effective strains.[72–74] The authors of this Review strongly believe in strain and product specificity and think that extrapolation to unstudied strains and products could be harmful. The importance of strain specificity and demonstration of safety is highlighted because a specific product (Infloran) was reported to increase the overall incidence of necrotising enterocolitis.[75]

Regurgitation

Administration of *L reuteri* DSM17938 prevented regurgitation episodes during the first month of life in exclusively breastfed infants, compared with historical controls.[76] Prophylactic use of *L reuteri* DSM17938 from birth up to 3 months of age resulted in a decreased number of episodes of regurgitations per day (2·9 *vs* 4·6; p<0·01).[61] This finding is likely to be related to fast gastric emptying induced by the probiotic.[77] A synbiotic infant formula, supplemented with *B lactis* and fructo-oligosaccharides, with lactose and a protein ratio of 60% whey and 40% casein was tested in 280 infants for 3 months and resulted in a lower incidence of daily regurgitation (11% of all infants) than the median prevalence for a similar age according to historical data from literature (median value of 27% for regurgitation).[78] Some probiotic strains might enhance gastric emptying and therefore have a beneficial effect on functional gastrointestinal symptoms of the oesophagus and stomach.

L reuteri DSM17938 decreased dysbiosis in children treated with proton pump inhibitors.[79] After 12 weeks of treatment with a proton pump inhibitor, dysbiosis was diagnosed according to the results of a glucose hydrogen breath test in 36 (56%) of 64 children in the placebo group, compared with 4 (6%) of 64 children in the probiotic group (p<0·001).[79] Bacterial overgrowth was detected in 6 (5%) of 120 controls, which is similar to the group treated with *L reuteri* and proton pump inhibitors.[79]

The evidence from literature is insufficient to recommend routine administration of some specific probiotic strains for the prevention of regurgitation. However, no study suggested that probiotics might increase the risk for regurgitation. *L reuteri* DSM17938 might decrease the adverse effects of proton pump inhibitors on the gastrointestinal microbiota.

Constipation

A meta-analysis concluded that the evidence is insufficient to recommend prebiotics, probiotics, or synbiotics in the treatment of children with functional constipation.[80] Another meta-analysis showed that some probiotic strains increase stool frequency in Asian children.[81] A synbiotic infant formula, supplemented with *B lactis* and fructo-oligosaccharides, was tested in 280 infants for 3 months and showed a lower overall incidence of constipation (9 [3%] of 280 infants) than the median prevalence reported in literature (8%).[78] *L reuteri* DSM17938 administration to young infants resulted in a significant increase in mean number of defecations per day (4·2 *vs* 3·6; p<0.01).[61]

Helicobacter pylori

Lactobacilli, as an adjunct to triple therapy, increase *Helicobacter pylori* eradication rates and reduce the overall incidence of therapy-related diarrhoea in children.[82] According a meta-analysis of data obtained with *S boulardii* in 11 randomised controlled trials (2200 participants, among them 330 children), the yeast probiotic is likely to reduce the *H pylori* eradication rate with about 10% and to decrease the adverse effect of the eradication therapy.[83] A meta-analysis of five studies (434 participants), concluded that different *Lactobacillus* strains were detected in each study: *L acidophilus* and *L rhamnosus*, *L reuteri*, *L casei*, LGG, and compound *Lactobacillus* without detailed information of contained strains.[82] However, no data exist on the prevention of *Helicobacter pylori* infection by the administration of probiotics.

Small bowel bacterial overgrowth, irritable bowel syndrome, and inflammatory bowel disease

There are a few studies in adults showing that the clinical consequence of small intestinal bacterial overgrowth can be treated effectively by administration of probiotics. *L rhamnosus* R0011 ($1·9\times10^9$ CFU) and *L acidophilus* R0052 ($0·1\times10^9$ CFU) failed to decrease the overall incidence of small bowel bacterial overgrowth in children treated with omeprazole.[84] However, we could not find any information on the use of probiotics in the prevention of this condition.

Although there are some data reporting that some specific strains of probiotics alleviate pain in children with irritable bowel syndrome,[85–87] we could not find that on prevention. To the best of our knowledge, there are no randomised controlled trials evaluating whether preventive administration of probiotics might decrease the number of flares of inflammatory bowel disease in children.

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and EMBASE for randomised controlled trials between Jan 1, 2000, and Dec 31, 2018. Only randomised controlled trials were included. The search terms used were: "prevention" and/or "prophylaxis" and/or "prophylactic use" and "gastrointestinal disorder" and/or "gastrointestinal disease" and "infant" and/or "child" and/or "pediatric". Only articles in English were selected.

Conclusion

The knowledge about the relation between the components of the gastrointestinal microbiome related to health outcomes is evolving quickly. Studies on the probiotic administration for the prevention of gastrointestinal disorders are scarce. Most studies focus on prevention of infectious, nosocomial, and antibiotic-associated diarrhoea or necrotising enterocolitis, with some studies on infantile colic. However, the studies on the prevention of necrotising enterocolitis differ in design and strains tested. As a consequence, there is no consensus to recommend the routine administration of probiotics to preterm infants to prevent necrotising enterocolitis. The possibility of serious adverse effects in preterm infants should be considered. No consensus exists on whether probiotics should be routinely administered to infants to prevent acute gastroenteritis, antibiotic-associated diarrhoea, or infantile colic. The strongest evidence for a benefit of preventive probiotic use in children is for the administration of *B lactis* for acute gastroenteritis, *S boulardii* and LGG for antibiotic-associated diarrhoea, and *L reuteri* DSM17938 for infantile colic, for regurgitation, and stool composition. Despite the scarcity of evidence, many infant formulae do contain probiotics and thus many infants are exposed to daily intake of probiotic strains. Evidence-based, the data are insufficient to recommend routine administration of probiotics for prevention of gastrointestinal disorders. However, preventive probiotic administration is also unlikely to be harmful or cause adverse effects.

Contributors

CP and YV co-wrote the first draft on the manuscript and did the literature search. HS, FI, and ZW reviewed and commented the different drafts of the manuscript. Every author approved the final draft.

Declaration of interests

HS reports personal fees from Nestle Nutrition Institute, personal fees and non-financial support from BioGaia, personal fees from Danone Nutricia, non-financial support from Dicopharm, non-financial support

from Winclove, and personal fees from Biocodex, outside the submitted work. FI reports personal fees from Nestle Nutrition Institute, personal fees and non-financial support from BioGaia, personal fees from Danone Nutricia, and personal fees from Sandoz, outside the submitted work. YV has participated as a clinical investigator, advisory board member, consultant, or speaker for Abbott Nutrition, Biogaia, Biocodex, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, United Pharmaceuticals, and Wyeth. CP, HS, FI, ZW, and YV declare no competing interests.

References

1 Dominguez-Bello MG. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* 2010; **107:** 11971–75.

2 Yasmin F. Cesarean section, formula feeding, and infant antibiotic exposure: separate and combined impacts on gut microbial changes in later infancy. *Front Pediatr* 2017; **5:** 200.

3 Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. *BMC Microbiol* 2016; **16:** 90.

4 Mitre E, Susi A, Kropp LE, Schwartz DJ, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr* 2018; **172:** e180315.

5 Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 2018; **555:** 623–28.

6 Lewis ZT, Totten SM, Smilowitz JT, et al. Maternal fucosyltransferase 2 status affects the gut bifidobacterial communities of breastfed infants. *Microbiome* 2015; **3:** 13.

7 Vandeputte D, Falony G, Vieira-Silva S, et al. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 2016; **65:** 57–62.

8 Reid G, Kumar H, Khan AI, et al. The case in favour of probiotics before, during and after pregnancy: insights from the first 1,500 days. *Benef Microbes* 2016; **7:** 353–62.

9 Hill C, Guarner F, Reid G, 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.

10 Andersen SS, Michaelsen KF, Laursen RP, et al. Why parents are skeptical about using probiotics preventively for small children: a Danish qualitative study. *BMC Complement Altern Med* 2018; **18:** 336.

11 Fernández L, Langa S, Martín V, et al. The human milk microbiota: origin and potential roles in health and disease. *Pharmacol Res* 2013; **69:** 1–10.

12 Panduru M, Panduru NM, Sălăvăstru CM, et al. Probiotics and primary prevention of atopic dermatitis: a meta-analysis of randomized controlled studies. *J Eur Acad Dermatol Venereol* 2015; **29:** 232–42.

13 Simpson MR, Dotterud CK, Storrø O, et al. Perinatal probiotic supplementation in the prevention of allergy related disease: 6 year follow up of a randomised controlled trial. *BMC Dermatol* 2015; **15:** 13.

14 Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. *World Allergy Organ J* 2015; **8:** 4.

15 Rather IA, Bajpai VK, Kumar S, et al. Probiotics and atopic dermatitis: an overview. *Front Microbiol* 2016; **7:** 507.

16 Li L, Han Z, Niu X, et al. Probiotic supplementation for prevention of atopic dermatitis in infants and children: a systematic review and meta-analysis. *Am J Clin Dermatol* 2018; **20:** 367–77.

17 Forsberg A, West CE, Prescott SL, et al. Pre-and probiotics for allergy prevention: time to revisit recommendations? *Clin Exp Allergy* 2016; **46:** 1506–21.

18 Grev J, Berg M, Soll R. Maternal probiotic supplementation for prevention of morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2018; **12:** CD012519.

19 Lo Vecchio A, Vandenplas Y, Benninga M, et al. An international consensus report on a new algorithm for the management of infant diarrhoea. *Acta Paediatr* 2016; **105:** e384–89.

20 Saavedra JM, Bauman NA, Oung I, et al. Feeding of *Bifidobacterium bifidum* and *Streptococcus thermophilus* to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet* 1994; **344:** 1046–49.

21 Hojsak I, Tokić Pivac V, Močić Pavić A, et al. *Bifidobacterium animalis subsp. lactis* fails to prevent common infections in hospitalized children: a randomized, double-blind, placebo-controlled study. *Am J Clin Nutr* 2015; **101:** 680–84.

22 Szajewska H, Kotowska M, Mrukowicz JZ, et al. Efficacy of *Lactobacillus GG* in prevention of nosocomial diarrhea in infants. *J Pediatr* 2001; **138:** 361–65.

23 Mastretta E, Longo P, Laccisaglia A, et al. Effect of *Lactobacillus GG* and breast-feeding in the prevention of rotavirus nosocomial infection. *J Pediatr Gastroenterol Nutr* 2002; **35:** 527–31.

24 Bruzzese E, Fedele MC, Bruzzese D, et al. Randomised clinical trial: a *Lactobacillus GG* and micronutrient-containing mixture is effective in reducing nosocomial infections in children, vs. placebo. *Aliment Pharmacol Ther* 2016; **44:** 568–75.

25 Urbańska M, Gieruszczak-Białek D, Szymański H, et al. Effectiveness of *Lactobacillus reuteri* DSM 17938 for the prevention of nosocomial diarrhea in children: a randomized, double-blind, placebo-controlled trial. *Pediatr Infect Dis J* 2016; **35:** 142–45.

26 Wanke M, Szajewska H. Lack of an effect of *Lactobacillus reuteri* DSM 17938 in preventing nosocomial diarrhea in children: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2012; **161:** 40–43.

27 Wanke M, Szajeweska H. Probiotics for preventing healthcare-associated diarrhea in children: a meta-analysis of randomized controlled trials. *Pediatr Pol* 2014; **89:** 8–16

28 Trivić I, Hojsak I. Use of probiotics in the prevention of nosocomial infections. *J Clin Gastroenterol* 2018; **52** (suppl 1)**:** S62–65.

29 Hojsak I, Szajewska H, Canani RB, et al. Probiotics for the Prevention of nosocomial diarrhea in children. *J Pediatr Gastroenterol Nutr* 2018; **66:** 3–9.

30 Cameron D, Hock QS, Kadim M, et al. Probiotics for gastrointestinal disorders: Proposed recommendations for children of the Asia-Pacific region. *World J Gastroenterol* 2017; **23:** 7952–64.

31 Chouraqui JP, Van Egroo LD, Fichot MC. Acidified milk formula supplemented with *bifidobacterium lactis:* impact on infant diarrhea in residential care settings. *J Pediatr Gastroenterol Nutr* 2004; **38:** 288–92.

32 Hojsak I, Močić Pavić A, Kos T, et al. *Bifidobacterium animalis subsp. lactis* in prevention of common infections in healthy children attending day care centers—randomized, double blind, placebo-controlled study. *Clin Nutr* 2016; **35:** 587–91.

33 Sazawal S, Dhingra U, Hiremath G, et al. Prebiotic and probiotic fortified milk in prevention of morbidities among children: community-based, randomized, double-blind, controlled trial. *PLoS One* 2010; **5:** e12164.

34 Laursen RP, Larnkjær A, Ritz C, et al. Probiotics and child care absence due to infections: a randomized controlled trial. *Pediatrics* 2017; **140:** pii:e20170735.

35 Bocquet A, Lachambre E, Kempf C, et al. Effect of infant and follow-on formulas containing *B lactis* and galacto- and fructo-oligosaccharides on infection in healthy term infants. *J Pediatr Gastroenterol Nutr* 2013; **57:** 180–87.

36 Oberhelman RA, Gilman RH, Sheen P, et al. A placebo-controlled trial of *Lactobacillus GG* to prevent diarrhea in undernourished Peruvian children. *J Pediatr* 1999; **134:** 15–20.

37 Pedone CA, Arnaud CC, Postaire ER, et al. Multicentric study of the effect of milk fermented by *Lactobacillus casei* on the incidence of diarrhoea. *Int J Clin Pract* 2000; **54:** 568–71.

38 Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics* 2005; **115:** 5–9.

39 Schneider C, Illi M, Lötscher M, et al. Isolation of antibodies from human plasma, saliva, breast milk, and gastrointestinal fluid. *Methods Mol Biol* 2017; **1643:** 23–31.

40 Freedman SB, Williamson-Urquhart S, Farion KJ, et al. Multicenter trial of a combination probiotic for children with gastroenteritis. *N Engl J Med* 2018; **379:** 2015–26.

41 Schnadower D, Tarr PI, Casper TC, et al. *Lactobacillus rhamnosus GG* versus placebo for acute gastroenteritis in children. *N Engl J Med* 2018; **379:** 2002–14.

42 Gutierrez-Castrellon P, Lopez-Velazquez G, Diaz-Garcia L, et al. Diarrhea in preschool children and Lactobacillus reuteri: a randomized controlled trial. *Pediatrics* 2014; **133:** e904–09.

43 Urbańska M, Szajewska H. The efficacy of *Lactobacillus reuteri* DSM 17938 in infants and children: a review of the current evidence. *Eur J Pediatr* 2014; **173:** 1327–37.

44 Guandalini S. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol* 2011; **45:** S149–53.

45 Fox MJ, Ahuja KD, Robertson IK, et al. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. *BMJ Open* 2015; **5:** e006474.

46 Olek A, Woynarowski M, Ahrén IL, et al. Efficacy and safety of *Lactobacillus plantarum* DSM 9843 (LP299V) in the prevention of antibiotic-associated gastrointestinal symptoms in children-randomized, double-blind, placebo-controlled study. *J Pediatr* 2017; **186:** 82–86.

47 Kołodziej M, Szajewska H. *Lactobacillus reuteri* DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: a randomized clinical trial. *Clin Microbiol Infect*. 2018; **25:** 699–704.

48 Shan LS, Hou P, Wang ZJ, et al. Prevention and treatment of diarrhoea with *Saccharomyces boulardii* in children with acute lower respiratory tract infections. *Benef Microbes* 2013; **4:** 329–34.

49 Johnston BC, Goldenberg JZ, Parkin PC. Probiotics and the prevention of antibiotic-associated diarrhea in infants and children. *JAMA* 2016; **316:** 1484–85.

50 Goldenberg JZ, Lytvyn L, Steurich J, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev* 2015; **12:** CD004827.

51 Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev* 2017; **12:** CD006095.

52 Szajewska H, Kołodziej M. Systematic review with meta-analysis: *Lactobacillus rhamnosus GG* in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther* 2015; **42:** 1149–57.

53 Goldenberg JZ, Mertz D, Johnston BC. Probiotics to prevent *Clostridium difficile* infection in patients receiving antibiotics. *JAMA* 2018; **320:** 499–500.

54 Szajewska H., Canani RB, Guarino A, et al. ESPGHAN Working Group for Probiotics and Prebiotics. Probiotics for the prevention of antibiotic-associated diarrhea in children. *J Pediatr Gastroenterol Nutr* 2016; **62:** 495–506.

55 Mantegazza C, Molinari P, D'Auria E, et al. Probiotics and antibiotic-associated diarrhea in children: a review and new evidence on *Lactobacillus rhamnosus GG* during and after antibiotic treatment. *Pharmacol Res* 2018; **128:** 63–72.

56 Dinleyici M, Vandenplas Y. *Clostridium difficile* colitis prevention and treatment In: Adv Exp Med Biol. New York: Springer, 2019.

57 Vermeersch SJ, Vandenplas Y, Tanghe A, et al. Economic evaluation of *S. boulardii CNCM I-745* for prevention of antibiotic-associated diarrhoea in hospitalized patients. *Acta Gastroenterol Belg* 2018; **81:** 269–76.

58 Johnson JD, Cocker K, Chang E. Infantile colic: recognition and treatment. *Am Fam Physician* 2015; **92:** 577–82.

59 Sung V, D'Amico F, Cabana MD, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. *Pediatrics* 2018; **141:** e20171811.

60 Harb T, Matsuyama M, David M, et al. Infant colic-what works: a systematic review of interventions for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2016; **62:** 668–86.

61 Indrio F, Di Mauro A, Riezzo G, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation and functional constipation: a randomized clinical trial. *JAMA Pediatr* 2014; **168:** 228–33.

62 Savino F, Ceratto S, Poggi E, et al. Preventive effects of oral probiotic on infantile colic: a prospective, randomised, blinded, controlled trial using *Lactobacillus reuteri* DSM 17938. *Benef Microbes* 2015; **6:** 245–51.

63 Indrio F, Di Mauro A, Di Mauro A, et al. Prevention of functional gastrointestinal disorders in neonates: clinical and socioeconomic impact. *Benef Microbes* 2015; **6:** 195–98.

64 Cabana MD, McKean M, Beck AL, et al. Pilot analysis of early *LGG* for infant colic prevention. *JPGN* 2019; **68:** 17–19.

65 Giglione E, Prodam F, Bellone S, et al. The association *of bifidobacterium breve br03* and *b632* is effective to prevent colics in bottle-fed infants: a pilot, controlled, randomized, and double-blind study. *J Clin Gastroenterol* 2016; **50** (suppl 2)**:** S164–67.

66 Collado MC, Rautava S, Aakko J, et al. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci Rep* 2016; **6:** 23129.

67 Heida FH, van Zoonen AG, Hulscher JB, et al. A necrotizing enterocolitis-associated gut microbiota is present in the meconium: results of a prospective study. *Clin Infect Dis* 2016; **62:** 863–70.

68 Zhu XL, Tang XG, Qu F, et al. Bifidobacterium may benefit the prevention of necrotizing enterocolitis in preterm infants: A systematic review and meta-analysis. *Int J Surg* 2019; **61:** 17–25.

69 Kane AF, Bhatia AD, Denning PW, et al. Routine supplementation of *Lactobacillus rhamnosus GG* and risk of necrotizing enterocolitis in very low birth weight infants. *J Pediatr* 2018; **195:** 73–79.

70 Patel S, Chaudhari M, Kadam S, et al. Standardized feeding and probiotic supplementation for reducing necrotizing enterocolitis in preterm infants in a resource limited set up. *Eur J Clin Nutr* 2018; **72:** 281–87.

71 van den Akker CHP, van Goudoever JB, Szajewska H, et al. Probiotics for preterm infants: a strain-specific systematic review and network meta-analysis. *J Pediatr Gastroenterol Nutr* 2018; **67:** 103–22.

72 Pell LG, Loutet MG, Roth DE, et al. Arguments against routine administration of probiotics for NEC prevention. *Curr Opin Pediatr* 2019; **31:** 195–201.

73 Sanders ME, Benson A, Lebeer S, et al. Shared mechanisms among probiotic taxa: implications for general probiotic claims. *Curr Opin Biotechnol* 2018; **49:** 207–16.

74 Athalye-Jape G, Patole S. Probiotics for preterm infants - time to end all controversies. *Microb Biotechnol* 2019; **12:** 249–53.

75 Escribano E, Zozaya C, Madero R, et al. Increased incidence of necrotizing enterocolitis associated with routine administration of Infloran™ in extremely preterm infants. *Benef Microbes* 2018; **9:** 683–90.

76 Garofoli F, Civardi E, Indrio F, et al. The early administration of *Lactobacillus reuteri* DSM 17938 controls regurgitation episodes in full-term breastfed infants. *Int J Food Sci Nutr* 2014; **65:** 646–48.

77 Indrio F, Riezzo G, Raimondi F, et al. *Lactobacillus reuteri* accelerates gastric emptying and improves regurgitation in infants. *Eur J Clin Invest* 2011; **41:** 417–22.

78 Vandenplas Y, Analitis A, Tziouvara C, et al. Safety of a new synbiotic starter formula. *Pediatr Gastroenterol Hepatol Nutr* 2017; **20:** 167–77.

79 Belei O, Olariu L, Dobrescu A, et al. Is it useful to administer probiotics together with proton pump inhibitors in children with gastroesophageal reflux? *J Neurogastroenterol Motil* 2018; **24:** 51–57.

80 Koppen IJ, Benninga MA, Tabbers MM. Is there a role for pre-, pro- and synbiotics in the treatment of functional constipation in children? A systematic review. *J Pediatr Gastroenterol Nutr* 2016; **63** (suppl 1)**:** S27–35.

81 Huang R, Hu J. Positive effect of probiotics on constipation in children: a systematic review and meta-analysis of six randomized controlled trials. *Front Cell Infect Microbiol* 2017; **7:** 153.

82 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.

83 Szajewska H, Horvath A, Kołodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2015; **41:** 1237–45.

84 Hegar B, Hutapea EI, Advani N, et al. A double-blind placebo-controlled randomized trial on probiotics in small bowel bacterial overgrowth in children treated with omeprazole. *J Pediatr (Rio J)* 2013; **89:** 381–87.

85 Hojsak I. Probiotics in functional gastrointestinal disorders. *Adv Exp Med Biol* 2018; Published online Dec 22. DOI:10.1007/5584_2018_321.

86 Wegh CAM, Benninga MA, Tabbers MM. Effectiveness of probiotics in children with functional abdominal pain disorders and functional constipation: a systematic review. *J Clin Gastroenterol* 2018; **52** (suppl 1)**:** S10–26.

87 Guandalini S, Magazzù G, Chiaro A, et al. *VSL#3* improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. *J Pediatr Gastroenterol Nutr* 2010; **51:** 24–30.