

Use of Probiotics for the Management of Acute Gastroenteritis in Children: An Update

*Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek, ||Rok Orel, ¶Silvia Salvatore, #Raanan Shamir, **Johannes B. van Goudoever, ††Yvan Vandendriessche, ††Zvi Weizman, and *Bartłomiej M. Zalewski, on behalf of the Working Group on Probiotics and Prebiotics of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

See “Evidence-based Usage of Probiotics for Pediatric Acute Gastroenteritis” by Merenstein on page 146.

ABSTRACT

Since the publication of the 2014 European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Working Group (WG) on Probiotics and Prebiotics guidelines for the management of acute gastroenteritis (AGE), new evidence concerning the efficacy of probiotics has become available. This document provides updated recommendations on the use of probiotics for the treatment of AGE in previously presumed healthy infants and children. A systematic literature search was performed. All pooled analyses were explicitly performed for the current report. The WG graded the recommendations and assessed the certainty of the supporting evidence using the Grading of Recommendations, Assessment Development, and Evaluations tool. The recommendations were formulated if at least 2 randomized controlled trials that used a given probiotic were available. Despite the large number of identified trials, the WG could not identify 2 randomized controlled trial of high quality for any strain that provided benefit when used for treating AGE. The WG made *weak* recommendations *for* (in descending order in terms of the number of trials evaluating any given strain): *Saccharomyces boulardii* (low to very low certainty of evidence); *Lactobacillus rhamnosus* GG (very low certainty of evidence); *L reuteri* DSM 17938 (low to very low certainty of evidence); and *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 (very low certainty of evidence). The WG made a *strong* recommendation *against* *L helveticus* R0052 and *L rhamnosus* R0011 (moderate certainty of evidence) and a *weak* recommendation *against* *Bacillus clausii* strains O/C, SIN, N/R, and T (very low certainty of evidence).

Key Words: children, diarrhea, guideline, infants, microbiota, probiotics

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From the *Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland, the †Department of Translational Medical Science, Section of Paediatrics, University Federico II, Naples, Italy, ‡Children’s Hospital Zagreb, University of Zagreb School of Medicine, University J.J. Strossmayer School of Medicine, Osijek, Croatia, the §Department of Paediatric Gastroenterology, Ospedale Pediatrico Giovanni XXIII, University of Bari, Bari, Italy, the ||Department of Gastroenterology, Hepatology and Nutrition, University Medical Centre Ljubljana, University Children’s Hospital Ljubljana, Ljubljana, Slovenia, the ¶Department of Pediatrics, “F. Del Ponte” Hospital, University of Insubria, Varese, Italy,

What Is Known

- Acute gastroenteritis has a high prevalence in children.
- Oral rehydration is the key treatment and should be applied as soon as possible.
- Many guidelines recommend the use of probiotics with documented efficacy in the management of acute gastroenteritis.
- Recent evidence has questioned the efficacy and safety of probiotics.

What Is New

- These updated recommendations replace the 2014 European Society for Paediatric Gastroenterology, Hepatology, and Nutrition document.
- Despite the large number of identified trials, we could not identify 2 randomized controlled trials of high quality for any strain that provided benefit when used for treating acute gastroenteritis.
- Weak recommendations for some new specific strains are made, whereas the use of other (combinations of) strains is discouraged.

In 2014, the Working Group (WG) on Probiotics and Prebiotics of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published its guidelines for the management of acute gastroenteritis (AGE) in children. The guidelines concluded that the use of the following probiotics may be

and the #Institute for Gastroenterology, Nutrition and Liver Diseases, Schneider Children’s Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, **Amsterdam UMC, University of Amsterdam and Vrije Universiteit Amsterdam, Emma Children’s Hospital, Paediatrics, Amsterdam, The Netherlands, ††KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, and the †††Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel. Address correspondence and reprint requests to Hania Szajewska, MD, Department of Paediatrics, The Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland (e-mail: hania@ipgate.pl).

considered in the management of children with AGE, in addition to rehydration therapy: *Lactobacillus rhamnosus* GG (LGG) (low quality of evidence, strong recommendation) and *Saccharomyces boulardii* (low quality of evidence, strong recommendation). Less compelling evidence was available for *L reuteri* DSM 17938 (very low quality of evidence, weak recommendation). Other strains or combinations of strains were evaluated, but evidence on their efficacy was weak (1). Since 2014, new evidence concerning the efficacy of probiotics has become available, including a high impact publication showing that LGG, a probiotic with a positive recommendation, is not efficacious in the treatment of AGE (2). The efficacy of other probiotics also has been questioned (3,4).

The purpose of this document developed by the ESPGHAN WG on Probiotics and Prebiotics, working within the ESPGHAN Special Interest Group on Gut Microbiota and Modifications, is intended to provide updated recommendations for the use of probiotics for the treatment of AGE in previously healthy infants and children. Children with underlying diseases such as chronic disorders or immunodeficiency are not covered.

METHODOLOGY

The methods used for the development of this document are described in Table S1 (Supplemental Digital Content, <http://links.lww.com/MPG/B830>). In brief, all systematic reviews and/or meta-analyses, and subsequently published randomized controlled trials (RCTs) that compared the use of probiotics, as a single ingredient, in all delivery vehicles and formulations, at any dose, with no probiotic (ie, placebo or no treatment), were eligible for inclusion. Probiotics were defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (5).

Participants were children with clinically diagnosed AGE (regardless of the definition used by the investigators), including in- and outpatients. The focus of the WG was on young children, preferably living in geographic Europe. Studies were, however, not excluded if the above criteria were not met.

The outcome measures of interest were the duration of diarrhea (regardless of the definition used by the investigators); the need for hospitalization for outpatients (or the duration of hospitalization for inpatients); and the percentage of children recovered by 48 hours (also defined as the absence of diarrhea on day 2). The authors of the original trials often evaluated other outcomes. For pragmatic reasons,

the WG, however, decided to focus on outcomes for therapeutic studies suggested in the literature (6).

The WG decided to evaluate strain(s) only, rather than brand or trade names, because the same brands may change composition and/or manufacturing practices over time and may have a different composition in different locations. Even when avoiding brand names, the WG is aware that different manufacturers may supply taxonomically equivalent probiotic microorganisms. Depending on the country, the same probiotic microorganism(s) may be available as food supplements, as registered pharmaceutical products, or incorporated into foods, which is linked with different regulatory processes and quality control. The matrix, as well as the production processes and conditions, may potentially affect the characteristics and functionality of the probiotic microorganism. It is likely that effect of a specific strain may depend on the matrix. Consequently, the taxonomically equivalent probiotics are presented jointly, regardless of the manufacturer. In this document, the effectiveness of well-specified probiotics was analyzed regardless of the regulatory status. Nonviable microorganisms, that is, those not meeting the definition of a probiotic (5), were not considered.

The WG followed the approach developed earlier (1) and did not provide a recommendation on the use of probiotics in general. Instead, the WG is reporting evidence and recommendations related to a specific probiotic strain or their combinations. As previously, the WG adopted the position that at least 2 adequate and well-controlled studies, each convincing on its own, are needed to establish the effectiveness of an intervention. Consequently, the recommendations were formulated if at least 2 RCTs that used a given probiotic were available. If there was only 1 RCT, regardless of whether or not it showed a benefit, no recommendation was formulated. Moreover, if any outcome of interest was reported in one RCT only, it was not considered for the recommendations.

Probiotics have to be described by genus, species, and strain designations. Consequently, if the strain designation (used by the depositor for the strain) was not given or the probiotic product was not otherwise identifiable, no recommendation was made.

The WG graded the recommendations and assessed the certainty of the supporting evidence using the GRADEpro software (<https://gdt.grade.org>), developed by the Grading of Recommendations, Assessment Development, and Evaluations Working Group (7).

The certainty of evidence (also called quality of the evidence) is categorized as high, moderate, low, or very low based on

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consideration of the risk of bias, the directness of evidence, consistency, and precision of the estimates. *Low* and *very low-certainty of evidence* indicates that the estimated effects of interventions are very uncertain, and further research is very likely to influence resulting recommendations. The strength of recommendations is expressed as either *strong* or *weak (conditional)*. For interpretation of strong and weak (conditional recommendation), see Table S2 (Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Final recommendations were based on combined evidence on outcomes of interest, together with the assessment of the certainty of the evidence (depicted in Grading of Recommendations, Assessment Development, and Evaluations tables, see Table S2, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). The wording of recommendations was specified prior to formulating the recommendations (Table S3, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

A draft of the guidelines was evaluated by all of the WG members. All critical feedback was discussed during a meeting held in Rome (September 8, 2019), and changes and a second draft were evaluated by all WG members until 30 January 2020. The prefinal draft of this document was submitted for public consultation on February 28, 2020 via the ESPGHAN Web site. ESPGHAN members and all interested parties were invited to submit written comments

within 10 days. The WG intends to revise the recommendations not later than in 5 years and produce an updated document.

SUMMARY OF EVIDENCE

Table S4 summarizes the characteristics of 16 systematic reviews and meta-analyses published since 2010, including 9 reviews focusing on all probiotics (8–16), and 7 strain-specific systematic reviews (*LGG* only (17); *S boulardii* only (18–21); *Bacillus clausii* O/C, SIN, N/R, and T only (22); *L reuteri* DSM 17938 (23)). Overall, more than 150 RCTs were identified (see Table S5 for the references). Only a few RCTs included in the systematic reviews overlap.

Three systematic reviews and meta-analyses were performed specifically for the purposes of this document (17,21,23). All pooled analyses reported in this document were taken from the above meta-analyses or were explicitly performed for the current report.

GENERAL STATEMENT

Despite the large number of identified trials, the WG could not identify 2 RCTs of high quality for any strain that provided benefit when used for treating AGE.

Table 1 summarizes the WG recommendations, and Table S6 summarizes Grading of Recommendations, Assessment

TABLE 1. Probiotics for the management of acute gastroenteritis

Weak recommendations for

(In descending order in terms of the number of trials evaluating any given strain)

S boulardii (250–750 mg/day, for 5–7 days) (low to very low certainty of evidence)

L rhamnosus GG ($\geq 10^{10}$ CFU/day, typically 5–7 day) (very low certainty of evidence)

L reuteri DSM 17938 (1×10^8 to 2×10^8 to 4×10^8 CFU/day, for 5 days) (low to very low certainty of evidence)

L rhamnosus 19070–2 and *L reuteri* DSM 12246 (2×10^{10} CFU of each strain/d, for 5 days) (very low certainty of evidence)

Strong recommendation against

L helveticus R0052 and *L rhamnosus* R0011 (moderate certainty of evidence)

Weak recommendation against

Bacillus clausii strains O/C, SIN, N/R, and T (very low certainty of evidence)

No recommendation

No strain specification	<i>L acidophilus</i> (24)
	<i>B longum</i> , <i>B lactis</i> , <i>L acidophilus</i> , <i>L rhamnosus</i> , <i>L plantarum</i> , <i>Pediococcus pentosaceus</i> (25)
Only 1 RCT available, strain identification available	<i>Bacillus clausii</i> UBBC-07 (26)
	<i>L acidophilus rhamnosus</i> 573L/1, 573L/2, 573L/3 (27)
	<i>L delbrueckii</i> var <i>bulgaricus</i> , <i>L acidophilus</i> , <i>S thermophilus</i> , <i>B bifidum</i> (strains LMG-P17550, LMG-P 17549, LMG-P 17503, and LMG-P 17500) (28)
	<i>L paracasei</i> strain ST11 (29)
Only 1 RCT available, no strain identification	<i>B lactis</i> , <i>Lactobacillus</i> , and <i>B bifidum</i> , and <i>L rhamnosus</i> (30)
	<i>B longum</i> , <i>B lactis</i> , <i>L acidophilus</i> , <i>L rhamnosus</i> , <i>L plantarum</i> , and <i>Pediococcus pentosaceus</i> (25)
	<i>L acidophilus</i> , <i>B bifidum</i> , <i>L bulgaricus</i> (31)
	<i>L acidophilus</i> , <i>L paracasei</i> , <i>L bulgaricus</i> , <i>L plantarum</i> , <i>B breve</i> , <i>B infantis</i> , <i>B longum</i> , <i>S thermophilus</i> (32)
	<i>L casei</i> (33)
	<i>L sporogenes</i> (<i>Bacillus coagulans</i>) (34)
	<i>L sporogenes</i> (35)
	<i>LGG</i> , <i>L acidophilus</i> , <i>L casei</i> , <i>L plantarum</i> , <i>B infantis</i> (36)
Two or more RCTs available, no strain identification	<i>Bacillus clausii</i> (37–39)
	<i>Bacillus mesentericus</i> and <i>Clostridium butyricum</i> and <i>E faecalis</i> (40,41)—(further specified by the manufacturer by email communication) as <i>Bacillus subtilis</i> TO-A (FERM BP-07462), <i>Enterococcus faecium</i> T-110 (FERM BP-10867), and <i>C butyricum</i> TO-A (FERM BP-10866), respectively. However, not deposited in any culture collection.
	<i>L acidophilus</i> and <i>L rhamnosus</i> and <i>B longum</i> and <i>S boulardii</i> (42,43).
	<i>L acidophilus</i> and <i>B bifidum</i> (44–46)
	<i>L acidophilus</i> and <i>B bifidum</i> at 4°C and <i>L acidophilus</i> and <i>B bifidum</i> at room temp (47)
	<i>L acidophilus</i> and <i>B infantis</i> (48,49)
Safety concerns (50,51)	<i>E faecium</i> SF68 (28,52)
Methodological issues (1)	<i>Escherichia coli</i> Nissle 1917 (53,54)

LGG = *Lactobacillus rhamnosus GG*; RCT = randomized controlled trial.

Development, and Evaluations analyses for probiotics with recommendations (selected outcomes).

PROBIOTIC WITH RECOMMENDATIONS

The following probiotics were evaluated in 2 or more RCTs, and the formulation of a recommendation was possible: LGG; *L reuteri* DSM 17938; *S boulardii*; *B clausii* O/C; SIN, N/R, and T, *L helveticus* R0052 and *L rhamnosus* R0011; and *L rhamnosus* 19070-2 and *L reuteri* DSM 12246.

• Weak recommendations for

Below, probiotics with *weak* recommendations for use in clinical practice are discussed in descending order in terms of the number of trials evaluating any given strain (or strains). If any one of these probiotics will be considered for the management of AGE, it should be used as an adjunct to oral rehydration therapy (55), and should not replace any fluid and dietary recommendations.

S boulardii

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	23 RCTs, n = 3450, MD -1.06 d (-1.32 to -0.79), $I^2 = 90\%$	250–750 mg/day (typically 5–7 days)	Very low
Duration of hospitalization	8 RCTs, n = 999, MD -0.85 d (-1.35 to -0.34), $I^2 = 91\%$		Very low
Need for hospitalization (for outpatients)	2 RCTs, n = 233, RR 1.08 (0.62 to 1.87), $I^2 = 0\%$		Very low
Diarrhea on day 2	2 RCTs, n = 463, RR 0.75 (0.67 to 0.84), $I^2 = 0\%$		Low

In addition to the previously identified meta-analysis (56), 2 new meta-analyses (19,20) were identified. The meta-analyses differed concerning the search dates and inclusion/exclusion criteria. For this document, the most recent meta-analysis was considered (21). In this meta-analysis, 29 RCTs that randomized 4217 participants (2152 in the experimental group and 2065 in the control group) were included. Only 38% of trials adequately generated their randomization sequence, only 17% of trials adequately concealed allocation, and only 1 trial adequately blinded participants, study personnel, and outcome assessors. However, 83% provided complete outcome data. The pooled results demonstrated that, compared with placebo or no intervention, the administration of *S boulardii* reduced the duration of diarrhea by 1 day (23 RCTs, n = 3450, mean difference [MD] -1.06 day, 95% confidence interval [CI] -1.32 to -0.79; high heterogeneity [$I^2 = 90\%$]) (very low certainty of evidence) (Fig. S1, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). *S boulardii* use was also associated with a reduced duration of hospitalization (8 RCTs, n = 999, MD -0.85 d, 95% CI -1.35 to -0.34; $I^2 = 91\%$) (very low certainty of evidence) (Fig. S1, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Two RCTs reported the need for hospitalization and found no difference between the *S boulardii* and control groups (2 RCTs, n = 233, relative risk [RR] 1.08, 95% CI 0.62 to 1.87, $I^2 = 0\%$) (very low certainty of evidence) (Fig. S2, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Compared with the

placebo or no intervention groups, the use of *S boulardii* significantly reduced the risk of diarrhea on day 2 (2 RCTs, n = 463, RR 0.75, 95% CI 0.67 to 0.84, $I^2 = 0\%$) (low certainty of evidence) (Fig. S3, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

In 13 trials (1599 participants), the *S boulardii* CNCM I-745 strain was used. In the remaining 10 trials (1851 participants), there was no information on the strain designation. Regardless of the strain designation, the duration of diarrhea was reduced (MD -0.99 d [-1.27 to -0.70], $I^2 = 85\%$ vs -1.12 d [-1.68 to -0.57], $I^2 = 91\%$, respectively). The test for subgroup differences suggested that there is no significant difference ($P = 0.66$).

Only 1 RCT (57) was considered to be at low risk of bias with regard to adequate randomization, allocation concealment, blinding, and follow-up. This study confirmed the efficacy of *S boulardii* (retrospectively identified as *S boulardii* CMCM I-745) in reducing the duration of diarrhea if administered within 72 hours after the onset of the disease.

Recommendation	Healthcare professionals (HCPs) may recommend <i>S boulardii</i> (at a dose of 250–750 mg/day, for 5–7 days) for the management of AGE in children
Certainty of evidence	Low to very low
Grade of recommendation	Weak

L rhamnosus GG (LGG)

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	16 RCTs, n = 3949 MD -0.83 d (-1.13 to -0.53), $I^2 = 98\%$	Daily doses $\geq 10^{10}$ CFU or $< 10^{10}$ CFU were effective; however, the latter produced results of borderline significance	Very low
	5 RCTs*, n = 2409, MD -0.68 (-1.82 to 0.45), $I^2 = 98\%$	Various Daily doses 1.2×10^8 to 1×10^{10} to 2×10^{10} to 2×10^{12} CFU	Very low
Duration of hospitalization (for inpatients)	5 RCTs, n = 1790 MD -1.22 d (-2.33 to -0.1); $I^2 = 99\%$	Daily doses 1.2×10^8 to 1×10^{10} to 2×10^{10} to 2×10^{12} CFU.	Very low
Need for hospitalization (for outpatients)	Not reported	Not reported	–
Diarrhea on day 2	1 RCT†, n = 36, RR 0.37 (0.17 to 0.84).	1×10^{10} CFU	Very low

*Studies considered to be at low risk of bias.

†As this outcome was reported in 1 trial only, it was not considered for the recommendations.

Since 2014, 1 systematic review focusing exclusively on LGG was identified (17) with later published comments (58,59). The Cochrane Library, MEDLINE, and EMBASE databases were searched from May 2013 (end of the last search) to January 2019. Eighteen RCTs (n = 4208) were included.

Concerning outcomes of interest for this document, compared with placebo or no treatment, LGG use was associated with a

reduced duration of diarrhea (16 RCTs, n = 3949, mean difference, MD -0.83 d, 95% CI -1.13 to -0.53, high heterogeneity, $I^2 = 98%$) (Fig. S4, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). LGG was effective when used at a daily dose of $\geq 10^{10}$ CFU or $< 10^{10}$ CFU; however, the latter produced results of borderline significance. LGG was more effective when used in European countries compared with non-European countries, mainly when considered by region.

Of note, the analysis of 5 RCTs (2409 participants) considered to be at low risk of bias with regard to adequate randomization, allocation concealment, blinding, and follow-up found that, compared with controls, LGG had no effect on the duration of diarrhea (MD -0.68 d, 95% CI -1.82 to 0.45; high heterogeneity, $I^2 = 98%$) (Fig. S4, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

A meta-analysis of 5 RCTs (n = 1790) showed a reduction in the duration of hospitalization for those treated with LGG compared with the control group (MD -1.22 d, 95% CI -2.33 to -0.10; high heterogeneity, $I^2 = 99%$) (Fig. S5, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). The analysis of 3 RCTs (1328 participants), however, considered to be at low risk of bias found no effect on the duration of hospitalization (MD -1.68 d, 95% CI -4.62 to 1.26; high heterogeneity, $I^2 = 99%$) (Fig. S5).

Limited data showed that, compared with placebo, LGG reduced the risk of diarrhea on day 2 (1 RCT, n = 36, RR 0.37, 95% CI 0.17 to 0.84). This outcome was, however, not considered for the recommendations.

Recommendation	HCPs may recommend <i>LGG</i> [at a dose of $\geq 10^{10}$ CFU/day, typically 5–7 days] for the management of AGE in children
Certainty of evidence	Very low
Grade of recommendation	Weak

***L reuteri* DSM 17938**

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	4 RCTs, n = 347, MD -0.87 d (-1.43 to -0.31); $I^2 = 72%$	Daily doses 1×10^8 to 2×10^8 to 4×10^8 CFU, for 5 days	Very low
Duration of hospitalization (for inpatients)	3 RCTs, n = 284, MD -0.54 d (-1.09 to 0.0); $I^2 = 83%$		Very low
Need for hospitalization (for outpatients)	Not reported		
Percentage of children recovered by 48 h (cure on day 2)	3 RCTs, n = 256, RR 4.54 (2.02 to 10.18); $I^2 = 53%$		Low

In addition to 2 RCTs identified previously (60,61), 2 new RCTs (62,63) that evaluated *L reuteri* DSM 17938 were published. All of these trials were included in a recent meta-analysis (23). The pooled results of 4 RCTs (347 participants) showed a reduction in the duration of diarrhea of -0.87 d (95% CI -1.43 to -0.31) for those treated with *L reuteri* DSM 17938 compared with placebo. High heterogeneity was found ($I^2 = 72%$) (Fig. S6, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Compared with the placebo or no intervention groups, the use of *L reuteri* DSM

17938 significantly reduced the duration of hospitalization; however, the difference was of a borderline statistical significance (3 RCTs, n = 284, MD -0.54 d, 95% CI -1.09 to 0.0; high heterogeneity, $I^2 = 83%$) (Fig. S6, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Compared with the placebo or no intervention groups, the use of *L reuteri* DSM 17938 significantly increased the cure rate on day 2 (3 RCTs, n = 256, RR 4.54, 95% CI 2.02–10.18, $I^2 = 53%$) (Fig. S7, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

Recommendation	HCPs may recommend <i>L reuteri</i> DSM 17938 (daily doses 1×10^8 to 2×10^8 to 4×10^8 CFU, for 5 d) for the management of AGE in children
Certainty of evidence	Low to very low
Grade of recommendation	Weak

***L rhamnosus* 19070-2 and *L reuteri* DSM 12246**

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	2 RCTs, n = 112, MD -0.97 d (-1.72, -0.22), $I^2 = 0%$	2×10^{10} CFU of each strain, for 5 days	Very low
Duration of hospitalization* (for inpatients)	1 RCT, n = 69, MD -1.10 d (-1.82, -0.38)		Very low
Need for hospitalization (for outpatients)	Not reported	–	–
Percentage of children recovered by 48 h	Not reported	–	–

*As this outcome was reported in one trial only, it was not considered for the recommendations

The WG formulated a weak recommendation on use of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246. It is, however, based on the findings from only 2 RCTs with a very limited number of subjects; thus, compared to other strains, this recommendation is more prone to changes when further studies are accomplished.

Two Danish double-blind RCTs assessed the efficacy of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 for the treatment of AGE, both in hospitalized children (n = 69, mean age 17.6 months) (64) and in nonhospitalized children attending day care (n = 43, mean age 22 months) (65). The pooled results from these 2 RCTs (n = 112) showed that, compared with the placebo, the administration of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 at a daily dose 2×10^{10} CFU of each strain, for 5 days, reduced the duration of diarrhea (MD -0.97 d, 95% CI -1.72 to -0.22, $I^2 = 0%$) (Fig. S8). In hospitalized children, the duration of hospitalization was 1 day shorter in the probiotic group (1 RCT, n = 69, MD -1.10 d, 95% CI -1.82 to -0.38) (Fig. S8). This outcome was, however, not considered for the recommendations.

Recommendation	HCPs may recommend <i>L rhamnosus</i> 19070-2 and <i>L reuteri</i> DSM 12246 (at a dose of 2×10^{10} CFU of each strain, for 5 days) for the management of AGE in children.
Certainty of evidence	Very low
Grade of recommendation	Weak

• **Strong recommendation against**

***L. helveticus* R0052 and *L. rhamnosus* R0011**

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	4 RCTs, n = 1133, MD -0.15 d, (-0.67 to 0.36), I ² = 67%	2 × 10 ⁹ to 8 × 10 ⁹ CFU/day for 5–10 days	Moderate
Duration of hospitalization (for inpatients)	Not reported		–
Need for hospitalization (for outpatients)	2 RCTs, n = 950, RR 1.52 (0.91 to 2.55) I ² = 0%	4–8 × 10 ⁹ CFU/d	Moderate
Percentage of children recovered by 48 h	Not reported		–

Four RCTs were identified. A 2005 RCT conducted in Czech children ages 12 to 72 months with AGE treated as outpatients was found. Children receiving *L. helveticus* R0052 and *L. rhamnosus* R0011 (previously known as *L. acidophilus* Rosell-11 and *L. rhamnosus* Rosell-11 (n = 38), compared with placebo (n = 33), had a significantly shorter duration of diarrhea (4.0 ± 2.0 vs 5.45 ± 2.2 days, MD -1.45 days, 95% CI -2.5 to -0.4) (67). In contrast, 3 more recent RCTs produced negative results. A 2014 RCT assessed 112 Indonesian children aged 6 to 36 months with acute infectious diarrhea and moderate dehydration treated as outpatients. Compared with placebo, the addition to standard therapy (oral rehydration solution and zinc) of *L. rhamnosus* R0011 (1.9 × 10⁹ CFU) and *L. acidophilus* R0052 (0.1 × 10⁹ CFU/day) for 7 days had no effect on the duration of diarrhea (median [IQR] 61.5 hours [range 21–166] vs 68.5 h [range 13–165], respectively, P = 0.596) (68). A 2015 Canadian RCT performed in the Emergency Department, involving children aged 4 to 48 months receiving *L. helveticus*-52 (5%) and *L. rhamnosus* Rosell-11 (95%) at 2 doses (4 × 10⁹ CFU/day or 8 × 10⁹ CFU/day), or placebo, over 5 days, found no difference in the duration of diarrhea (59.1 ± 55.2 vs 84.0 ± 96.4 vs 63.5 ± 64.3 days, respectively). There was no difference in the need for hospitalization in the probiotic groups as well as in the placebo group (1 vs 0, respectively) (69). A 2018 RCT performed in Canada in which 886 children aged 3 to 48 months received a combination probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052, at a dose of 4.0 × 10⁹ CFU twice daily, or placebo, over 5 days, found no difference between groups in the duration of diarrhea (median duration of diarrhea: 52.5 hours [interquartile range, 18.3–95.8] and 55.5 hours [interquartile range, 20.2–102.3], respectively; P = 0.31) (4).

The pooled results of these 4 RCTs (n = 1133) performed for this review demonstrated that, compared with placebo or no intervention, the administration of *L. helveticus* R0052 and *L. rhamnosus* R0011 had no significant effect on the duration of diarrhea (MD -0.15 d, 95% CI -0.67 to 0.36), heterogeneity I² = 67% (Fig. S9).

The duration of hospitalization was not reported in any of the trials. The pooled results of 2 RCTs (n = 950) showed no significant difference in the need for hospitalization in outpatients (RR 1.52, 95% CI 0.91–2.55, no heterogeneity I² = 0%) (Fig. S10, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

Recommendation	HCPs should <i>not</i> recommend <i>L. helveticus</i> R0052 and <i>L. rhamnosus</i> R0011 for the management of AGE.
Certainty of evidence	Moderate
Grade of recommendation	Strong

• **Weak recommendation against**

***B. clausii* strains O/C, SIN, N/R, and T**

	Effect, MD or RR (95% CI)	Doses used in clinical trials	Certainty of evidence
Duration of diarrhea	7 RCTs, n = 1107, MD -0.40 d (-0.82 to 0.02); I ² = 92%	2–4 × 10 ⁹ CFU for 3–5 days	Very low
Duration of hospitalization (for inpatients)	3 RCTs, n = 291, MD -0.8 d (-1.45 to -0.15); I ² = 61%		Very low
Need for hospitalization (for outpatients)	Not reported		–
Diarrhea on day 2	Not reported		–

The probiotic currently available on the market contains different *B. clausii* strains, most including the strains intrinsically resistant to chloramphenicol (O/C), novobiocin, and rifampicin (N/R), tetracycline (T), or neomycin, and streptomycin (SIN). The molecular characterization of other *B. clausii* strains has been reviewed by Senesi et al (70).

A 2018 meta-analysis (22) identified 6 RCTs evaluating *B. clausii* strains O/C, SIN, N/R, and T (28,71–75). In addition, the WG identified 1 RCT evaluating *B. clausii* strains O/C, SIN, N/R, and T (76). The pooled analysis performed for this review found that, compared with the placebo or no intervention, the use of *B. clausii* strains O/C, SIN, N/R, and T reduced the duration of diarrhea; however, the difference was of borderline significance (7 RCTs, n = 1107, MD -0.40 d, 95% CI -0.82 to 0.02; I² = 92% (Fig. S11, Supplemental Digital Content, <http://links.lww.com/MPG/B830>). Moreover, the WG noted issues related to 2 of the included RCTs. One was a clinical study report available only via the company’s Web site (73). The other one was only available as an abstract (75). Both were published in 2008; however, to the best of our knowledge, neither was later published in a peer-reviewed journal. The exclusion of these 2 RCTs confirmed no significant difference between the study groups (5 RCTs, n = 773, MD -0.38 d, 95% CI -0.95 to 0.19, heterogeneity I² = 94%).

Of note, the analysis of 2 RCTs (28) (74) (ref. 74—published as thesis) considered to be at lower risk of bias with regard to adequate randomization, allocation concealment, blinding of outcome assessment, and follow-up found that, compared with controls, *B. clausii* strains O/C, SIN, N/R, and T had no effect on the duration of diarrhea (MD -0.06 d, 95% CI -0.45 to 0.32; heterogeneity, I² = 34%) (Fig. S11, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

In hospitalized children, the use of *B. clausii* O/C, SIN, N/R, and T reduced the duration of hospitalization (3 RCTs, n = 291, MD -0.8 d, 95% CI -1.45 to -0.15, heterogeneity I² = 61%) (Fig. S12, Supplemental Digital Content, <http://links.lww.com/MPG/B830>).

Recommendation	HCPs may <i>not</i> recommend <i>B. clausii</i> strains O/C, SIN, N/R, and T for the management of AGE in children.
Certainty of evidence	Very low
Grade of recommendation	Weak

PROBIOTICS WITH NO RECOMMENDATION

Several studies were identified with insufficient evidence to make a recommendation for or against use for reasons such as

methodological limitations, no strain specification, or the availability of only 1 RCT (Table 1). The WG has decided not to make any recommendation with regard to use of these probiotics. In countries in which probiotics with positive recommendations are not available, or because of their lower cost, healthcare professionals may consider selecting a probiotic based on the findings from 1 trial only, provided there is some evidence, even if limited, that documents its safety and efficacy for the management of acute diarrhea in children. It is essential to understand that such lack of evidence is not the same as evidence of no efficacy (“evidence of no efficacy” ≠ “no evidence of efficacy”).

FACTORS AFFECTING THE EFFICACY OF PROBIOTICS

The efficacy of probiotics depends on many variables. Registration as a “drug” or “medication” does not always guarantee the quality of the product. First, some products have a historical registration and would no longer qualify if a new application was done. Second, requirements for registration differ from country to country.

The strains with which a study has been performed need to be appropriately identified at the genus, species, and strain level. There is an ongoing debate as to what level of evidence is deemed sufficient to support health claims. In the opinion of the WG, such studies should, however, be performed with the commercialized product, and obviously, the claim that is aimed at should be the primary endpoint of the clinical trials. At least 2 similar trials with the same primary endpoint should be independently performed by 2 different centers or 2 multicenter trials should be carried out before a claim can be considered. The dosage and matrix used in the clinical trials should be identical to those of the commercialized product. Except for antibiotic-associated diarrhea, a clear dose-response effect of probiotics has not been documented (77). The matrix in which the probiotic is administered may also affect the efficacy. Carrier matrices have a significant impact on the quality of probiotic products. Matrix components, such as proteins, carbohydrates, and flavoring agents, are shown to alter probiotic efficacy and viability (78,79). Furthermore, *in vivo* studies have revealed strain-dependent matrix effects on the gastrointestinal tract survival of probiotic bacteria (78,79). Therefore, although unnecessary in clinical settings, data on the pathogens causing AGE are important in study design and study report. By preference, the quality of each batch used for the clinical trials should be checked by an independent institution.

SAFETY OF PROBIOTICS

Generally, probiotics are considered safe for use in otherwise healthy populations (80). Several reports concluded that harms-related outcomes in trials evaluating probiotics are often lacking or inadequate (80,81). Risk factors for adverse events such as bacteremia or fungemia include critical illness; immunosuppression; prematurity; presence of structural heart disease; hospitalization; presence of a central venous catheter; and the potential for translocation of probiotics across the bowel wall (82,83). With regard to *S. boulardii*, the European Medicines Agency (84) recently warned about a potential risk of fungemia caused by *S. boulardii* in seriously ill or immunocompromised patients. Even if LGG is generally considered safe (85), a similar warning is likely with regard to LGG following a recent report of bacteremia in 6 children (aged 1–19 years) of 522 subjects receiving LGG in an intensive care unit. By applying whole-genome sequencing, considered to be the best approach to identify the source of blood culture isolates, investigators provided evidence that the bacteria recovered from the blood

were genetically identical (with the exception of a few point mutations) to the LGG present in the administered probiotic (86).

The effects of long-term administration of probiotics remain largely unknown. With regard to the management of AGE, probiotics are, however, used for a short time. Overall, more research is needed before absolute statements on the safety of probiotics, in general, or for individual probiotic strains, can be made.

SUMMARY OF THE RECOMMENDATIONS

For the use of probiotics in the management of children with AGE, the WG made the following *weak* recommendations *for* (in descending order in terms of the number of trials evaluating any given strain):

- *S. boulardii* (at a dose of 250–750 mg/day, for 5–7 days) (low to very low certainty of evidence).
- *L. rhamnosus GG* (at a dose $\geq 10^{10}$ CFU/day, typically 5–7 days) (very low certainty of evidence).
- *L. reuteri* DSM 17938 (daily doses 1×10^8 to 2×10^8 to 4×10^8 CFU, for 5 days) (low to very low certainty of evidence).
- *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246 (at a dose of 2×10^{10} CFU of each strain, for 5 days) (low to very low certainty of evidence).

The WG made the following *strong* recommendation *against*:

- *L. helveticus* R0052 and *L. rhamnosus* R0011 (moderate certainty of evidence).

The WG made the following *weak* recommendation *against*:

- *B. clausii* strains O/C, SIN, N/R, and T (very low certainty of evidence).

For other probiotics, the WG made no recommendation for or against use. In countries in which probiotics with positive recommendations are not available, or because of their lower cost, HCPs may consider selecting a probiotic based on the findings from 1 trial only, provided there is some evidence, even if limited, that documents its safety and efficacy for the management of AGE in children.

REFERENCES

1. Szajewska H, Guarino A, Hojsak I, 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. Karas J, Ashkenazi S, Guarino A, et al. A core outcome set for clinical trials in acute diarrhoea. *Arch Dis Child* 2015;100:359–63.
7. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.

8. Ahmadi E, Alizadeh-Navaei R, Rezai MS. Efficacy of probiotic use in acute rotavirus diarrhea in children: a systematic review and meta-analysis. *Caspian J Intern Med* 2015;6:187–95.
9. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev* 2010;11:Cd003048.
10. Applegate JA, Fischer Walker CL, Ambikapathi R, et al. Systematic review of probiotics for the treatment of community-acquired acute diarrhea in children. *BMC Public Health* 2013;13 suppl 3:S16.
11. Florez ID, Veroniki AA, Al Khalifah R, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. *PLoS One* 2018;13:e0207701.
12. Freedman SB, Pasichnyk D, Black KJ, et al. Gastroenteritis therapies in developed countries: systematic review and meta-analysis. *PLoS One* 2015;10:e0128754.
13. Gutierrez-Castrellon P, Ortiz-Hernandez AA, Llamosas-Gallardo B, et al. Efficacy of racecadotril vs. smectite, probiotics or zinc as an integral part of treatment of acute diarrhea in children under five years: a meta-analysis of multiple treatments [in Spanish]. *Gac Med Mex* 2015;151:329–37.
14. Salari P, Nikfar S, Abdollahi M. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. *Inflamm Allergy Drug Targets* 2012;11:3–14.
15. Sniffen JC, McFarland LV, Evans CT, et al. Choosing an appropriate probiotic product for your patient: an evidence-based practical guide. *PLoS One* 2018;13:e0209205.
16. Zorzela L, Ardestani SK, McFarland LV, et al. Is there a role for modified probiotics as beneficial microbes: a systematic review of the literature. *Benef Microbes* 2017;8:739–54.
17. Szajewska H, Kolodziej M, Gieruszczak-Bialek D, et al. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG for treating acute gastroenteritis in children—a 2019 update. *Aliment Pharmacol Ther* 2019;49:1376–84.
18. Dinleyici EC, Eren M, Ozen M, et al. Effectiveness and safety of *Saccharomyces boulardii* for acute infectious diarrhea. *Expert Opin Biol Ther* 2012;12:395–410.
19. Feizizadeh S, Salehi-Abargouei A, Akbari V. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics* 2014;134:e176–91.
20. Padayachee M, Visser J, Viljoen E, et al. Efficacy and safety of *Saccharomyces boulardii* in the treatment of acute gastroenteritis in the paediatric population: a systematic review. *South Afr J Clin Nutr* 2019;32:58–69.
21. Szajewska H, Kolodziej M, Zalewski BM. Systematic review with meta-analysis: *Saccharomyces boulardii* for treating acute gastroenteritis in children—a 2020 update. *Aliment Pharmacol Ther* 2020;51:678–88.
22. Ianiro G, Rizzatti G, Plomer M, et al. *Bacillus clausii* for the treatment of acute diarrhea in children: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2018;10:pii: E1074.
23. Patro-Golab B, Szajewska H. Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for treating acute gastroenteritis in children. An update. *Nutrients* 2019;11:2762.
24. Rafeey M, Ostadrahimi A, Boniadi M, et al. *Lactobacillus acidophilus* yogurt and supplement in children with acute diarrhea: a clinical trial. *Res J Med Sci* 2008;2:13–8.
25. Lee DK, Park JE, Kim MJ, et al. Probiotic bacteria, *B. longum* and *L. acidophilus* inhibit infection by rotavirus in vitro and decrease the duration of diarrhea in pediatric patients. *Clin Res Hepatol Gastroenterol* 2015;39:237–44.
26. Sudha MR, Jayanthi N, Pandey DC, et al. *Bacillus clausii* UBBC-07 reduces severity of diarrhoea in children under 5 years of age: a double blind placebo controlled study. *Benef Microbes* 2019;10:149–54.
27. Szymanski H, Pejcz J, Jawien M, et al. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains—a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006;23:247–53.
28. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomized clinical trial of five different preparations. *BMJ* 2007;335:340.
29. Sarker SA, Sultana S, Fuchs GJ, et al. *Lactobacillus paracasei* strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. *Pediatrics* 2005;116:e221–8.
30. Ahmadipour S, Mohsenzadeh A, Alimadadi H, et al. Treating viral diarrhea in children by probiotic and zinc supplements. *Pediatr Gastroenterol Hepatol Nutr* 2019;22:162–70.
31. Kowalska-Duplaga K, Fyderek K, Szajewska H, et al. Efficacy of Trilac® in the treatment of acute diarrhoea in infants and young children—a multicentre, randomized, double-blind placebo-controlled study. *Pediatrics Wspolczesna* 2004;6:295–9.
32. Dubey AP, Rajeshwari K, Chakravarty A, et al. Use of VSL[sharp]3 in the treatment of rotavirus diarrhea in children: preliminary results. *J Clin Gastroenterol* 2008;42 Suppl 3 Pt 1:S126–9.
33. Sugita T, Togawa M. Efficacy of *Lactobacillus* preparation bioactis powder in children with rotavirus enteritis. *Japan J Pediatr* 1994;47:2755–62.
34. Dutta P, Mitra U, Dutta S, et al. Randomised controlled clinical trial of *Lactobacillus sporogenes* (*Bacillus coagulans*), used as probiotic in clinical practice, on acute watery diarrhoea in children. *Trop Med Int Health* 2011;16:555–61.
35. Manyal AK, Phadke VD. Role of probiotic *Lactobacillus sporogenes* in the treatment of acute diarrhoea in children. *Int J Pharm Sci Res* 2015;6:767–71.
36. Veereman-Wauters G, Staelens S, Wijffels J. Pediatric intervention study with a probiotic mixture (Bacilac Forte) in acute gastroenteritis. *J Pediatr Gastroenterol Nutr* 2009;48:S114.
37. Bhat SGNS, Savio CD. Efficacy of probiotics in acute diarrhoea in children. *Dig Dis Sci* 2018;5:2625–34.
38. Vidjeadevan D, Ramesh S, Vinoth S. Role of *Saccharomyces boulardii* and *Bacillus Clausii* in children with acute diarrhea—a randomized control trial. *J Med Sci Clin Res* 2017;5:30910–4.
39. Vidjeadevan D, Vinoth S, Ramesh S. Role of *Saccharomyces boulardii* and *Bacillus clausii* in reducing the duration of diarrhea: a three-armed randomised controlled trial 2018;5:4.
40. Huang YF, Liu PY, Chen YY, et al. Three-combination probiotics therapy in children with salmonella and rotavirus gastroenteritis. *J Clin Gastroenterol* 2014;48:37–42.
41. Chen CC, Kong MS, Lai MW, et al. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhea. *Pediatr Infect Dis J* 2010;29:135–8.
42. Grandy G, Medina M, Soria R, et al. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. *BMC Infect Dis* 2010;10:253.
43. Teran CG, Teran-Escalera CN, Villarreal P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *Int J Inf Dis* 2009;13:518–23.
44. Kianifar HR, Farid R, Ahanchian H, et al. Probiotics in the treatment of acute diarrhea in young children. *Iran J Medical Sciences* 2009;34:204–7.
45. Oandasan M, Gatcheco F, Kapahmngan S, et al. Double blind placebo-controlled clinical trial on the efficacy and safety of Inforan berna capsules in the treatment of acute non-bloody diarrhea in infants. *Niepublikowane (Cytowane za 4)* 1999.
46. Phavichitr N, Puwdee P, Tantibhaedhyangkul R. Cost-benefit analysis of the probiotic treatment of children hospitalized for acute diarrhea in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health* 2013;44:1065–71.
47. Rerksuppaphol S, Rerksuppaphol L. *Lactobacillus acidophilus* and *Bifidobacterium bifidum* stored at ambient temperature are effective in the treatment of acute diarrhoea. *Ann Trop Paediatr* 2010;30:299–304.
48. Lee MC, Lin LH, Hung KL, et al. Oral bacterial therapy promotes recovery from acute diarrhea in children. *Acta Paediatr Taiwan* 2001;42:301–5.
49. Vivatvakin B, Kowitdamrong E. Randomized control trial of live *Lactobacillus acidophilus* plus *Bifidobacterium infantis* in treatment of infantile acute watery diarrhea. *J Med Assoc Thai* 2006;89 suppl 3:S126–33.
50. Szajewska H, Guarino A, Hojsak I, et al. Authors' response. *J Pediatr Gastroenterol Nutr* 2016;62:e12–3.
51. Holzapfel W, Arini A, Aeschbacher M, et al. *Enterococcus faecium* SF68 as a model for efficacy and safety evaluation of pharmaceutical probiotics. *Benef Microbes* 2018;9:375–88.

52. D'Apuzzo V, Salzberg R. Treatment of acute diarrhea in pediatrics with *Streptococcus faecium*: results of a double blind study [in German]. *Ther Umsch* 1982;39:1033–5.
53. Henker J, Laass M, Blokhin BM, et al. The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. *Eur J Pediatr* 2007;166:311–8.
54. Henker J, Laass MW, Blokhin BM, et al. Probiotic *Escherichia coli* Nissle 1917 versus placebo for treating diarrhea of greater than 4 days duration in infants and toddlers. *Pediatr Infect Dis J* 2008;27:494–9.
55. Guarino A, Lo Vecchio A, Dias JA, et al. Universal recommendations for the management of acute diarrhea in nonmalnourished children. *J Pediatr Gastroenterol Nutr* 2018;67:586–93.
56. Dinleyici EC, Kara A, Ozen M, et al. *Saccharomyces boulardii* CNCM I-745 in different clinical conditions. *Expert Opin Biol Ther* 2014;14:1593–609.
57. Correa NB, Penna FJ, Lima FM, et al. Treatment of acute diarrhea with *Saccharomyces boulardii* in infants. *J Pediatr Gastroenterol Nutr* 2011;53:497–501.
58. Szajewska H, Kolodziej M, Shamir R Letter: *Lactobacillus rhamnosus* GG offers no benefit over placebo in children with acute gastroenteritis. Authors' reply. *Aliment Pharmacol Ther* 2019;50:622–3.
59. Schnadower D, Tarr PI, Freedman SB Letter: *Lactobacillus rhamnosus* GG offers no benefit over placebo in children with acute gastroenteritis. *Aliment Pharmacol Ther* 2019;50:620–2.
60. Francavilla R, Lionetti E, Castellana S, et al. Randomised clinical trial: *Lactobacillus reuteri* DSM 17938 vs. placebo in children with acute diarrhoea—a double-blind study. *Aliment Pharmacol Ther* 2012;36:363–9.
61. Dinleyici EC, Group PS, Vandenplas Y. *Lactobacillus reuteri* DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. *Acta Paediatr* 2014;103:e300–5.
62. Dinleyici EC, Dalgic N, Guven S, et al. *Lactobacillus reuteri* DSM 17938 shortens acute infectious diarrhea in a pediatric outpatient setting. *J Pediatr (Rio J)* 2015;91:392–6.
63. Szymanski 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.
64. Rosenfeldt V, Michaelsen KF, Jakobsen M, et al. Effect of probiotic *Lactobacillus* strains in young children hospitalized with acute diarrhea. *Pediatr Infect Dis J* 2002;21:411–6.
65. Rosenfeldt V, Michaelsen KF, Jakobsen M, et al. Effect of probiotic *Lactobacillus* strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *Pediatr Infect Dis J* 2002;21:417–9.
66. Foster LM, Tompkins TA, Dahl WJ. A comprehensive post-market review of studies on a probiotic product containing *Lactobacillus helveticus* R0052 and *Lactobacillus rhamnosus* R0011. *Benef Microbes* 2011;2:319–34.
67. Tlaskal P, Schramlova J, Kokesova A, et al. Probiotics in the treatment of diarrheal disease of viral etiology in children. *NAFAS* 2005;3:25–8.
68. Hegar B, Waspada IM, Gunardi H, et al. A double blind randomized trial showing probiotics to be ineffective in acute diarrhea in Indonesian children. *Indian J Pediatr* 2015;82:410–4.
69. Freedman SB, Sherman PM, Willan A, et al. Emergency department treatment of children with diarrhea who attend day care: a randomized multidose trial of a *Lactobacillus helveticus* and *Lactobacillus rhamnosus* combination probiotic. *Clin Pediatr (Phila)* 2015;54:1158–66.
70. Senesi S, Celandroni F, Tavanti A, et al. Molecular characterization and identification of *Bacillus clausii* strains marketed for use in oral bacteriotherapy. *Appl Environ Microbiol* 2001;67:834–9.
71. Lahiri K, Jadhav K, Gahlowt P, et al. *Bacillus Clausii* as an adjuvant therapy in acute childhood diarrhoea. *IOSR J Dent Med Sci* 2015;14:74–6.
72. Lahiri K, Dsouza J, Gahlowt P. Beneficial role of probiotic in acute childhood diarrhoea. *J Harmony Res Med And Hlth Sci* 2015;2:26–30.
73. Lahiri KR. GMA-CO Clinical Study Report: ENTER_L_01486. Sanofi-Aventis. https://www.sanofi.com/en/science-and-innovation/clinical-trials-and-results/our-disclosure-commitments/pharma/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/common/docs/clinical-study-results/ENTER_L_01486_summary.pdf. Accessed on May 2, 2020.
74. Maugo BM. Effectiveness of *Bacillus clausii* in Reducing Duration of Illness in Acute Diarrhoea in Children 6-59 Months of Age Admitted With Severe Dehydration. http://erepository.uonbi.ac.ke/bitstream/handle/11295/8325/DR._MAUGO_BRIAN_MAUGO_M.MED_-PAEDS_2012.pdf?sequence=1. Accessed July 30, 2019.
75. Urtula RP, Dacula CE. *Bacillus clausii* an adjunct treatment for pediatric patients with acute non-bloody diarrhea: a randomized, controlled clinical trial [Abstract]. http://ar14.library.sk/ar1-sllk/en/detail-sllk_un_cat-0013574-Bacillus-clausii-an-adjunct-treatmentfor-pediatric-patients-with-acute-nonbloody-diarrhea-a-randol. Accessed May 2, 2020.
76. Hamid F, Quaium SMMA, Rahman A. Comparative study of *Bacillus clausii* and multistrain probiotics in the management of acute diarrhoea in children. *Int J Res Med Sci* 2019;7:1156–60.
77. Ouweland AC. A review of dose-responses of probiotics in human studies. *Benef Microbes* 2017;8:143–51.
78. Flach J, Van der Waal MB, Van den Nieuwboer M, et al. The underexposed role of food matrices in probiotic products: reviewing the relationship between carrier matrices and product parameters. *Crit Rev Food Sci Nutr* 2018;58:2570–84.
79. Lee B, Yin X, Griffey SM, et al. Attenuation of colitis by *Lactobacillus casei* BL23 is dependent on the dairy delivery matrix. *Appl Environ Microbiol* 2015;81:6425–35.
80. Hempel S, Newberry S, Ruelaz A, et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep/Technol Assess (Full Rep)* 2011;200:1–645.
81. Bafeta A, Koh M, Riveros C, et al. Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota. *Ann Intern Med* 2019;170:143–4.
82. Boyle RJ, Robins-Browne RM. Tang ML Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006;83:1256–64.
83. Costa RL, Moreira J, Lorenzo A, et al. Infectious complications following probiotic ingestion: a potentially underestimated problem? A systematic review of reports and case series. *BMC Complement Altern Med* 2018;18:329.
84. European Medicine Agency. Annex II Amendments to the product information of the nationally authorised medicinal products. https://www.ema.europa.eu/en/documents/psusa/saccharomyces-boulardii-cmdh-scientific-conclusions-grounds-variation-amendments-product-information/00009284/201702_en.pdf. Accessed on May 2, 2020.
85. Sanders ME, Akkermans LM, Haller D, et al. Safety assessment of probiotics for human use. *Gut Microbes* 2010;1:164–85.
86. Yelin I, Flett KB, Merakou C, et al. Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. *Nat Med* 2019;25:1728–32.