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Probiotics/ Prebiotics/ Synbiotic Supplementation in Reducing the Severity of Gastroenteritis among Children of 0-12 Years Age

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Abstract

This systematic review evaluates all clinical studies that cumulatively analyse how the use of probiotics, prebiotics or symbiotic have reduced the severity of gastroenteritis (GE) among children aged 0-12 years. A PRISMA based approach was done to search English language, full text articles in PUBMED/Medline and Google Scholar databases which resulted in analysis of 26 full text clinical trials. Overall, the included studies were of moderate quality. The individual studies were all prospective in nature and varied in terms of age of participants, duration of follow up and combination of probiotic/ prebiotic/ symbiotic used. Accounting for the vast heterogeneity, risk of bias across the studies, only standardized means were taken for selected studies were taken in quantitative synthesis. When mean number of hours of diarrhoea was considered, 10 of the 26 studies were included, which resulted in effect estimate of -0.49 [-0.87, -0.12] [Chi2=116.22, I2= 92%, p=0.01] and when the number of days of diarrhoea was considered only 4 studies were included with an effect estimate of 0.19 [-0.52, 0.90] [Chi2=55.46, I2=95%, p=60]. These results should be interpreted with caution considering the individual variations among the included trials. Thus, probiotic/ prebiotic/ symbiotic supplementation can be used as an adjuvant to the existing treatment protocol of oral rehydration with fluids but not as a replacement. A uniform methodological protocol for assessing these components should be drawn in order to estimate their efficacy and their real time clinical benefits.

Introduction

Gastroenteritis (GE) clinically refers to the acute or chronic inflammation of the digestive tract including stomach and intestinal mucosa [1]. It is predominantly characterised by diarrhoea, vomiting, elevated body temperature and abdominal cramps. Comparing adults and children, GE contributes to mortality as high as 1.5 to 2.5 million per year, especially amongst the latter group because of severe diarrhoea and dehydration [1,2].

The peak age for infection is between 6 months and 2 years, and the mode of spread is by the faecal-oral or respiratory route. Acute viral (approx. 70% of all infections) and bacterial (10-20%) gastroenteritis cannot be definitively told apart on clinical grounds alone. Bloody, mucous diarrhoea and high fever tend to be associated with a bacterial cause, while acute viral gastroenteritis is more commonly accompanied by respiratory manifestations and longer-lasting vomiting [3]. In children with mild illness, symptoms can be managed at home. Oral rehydration therapy is the mainstay of treatment for mild dehydration and 3-5 days antibiotic regimens in moderate to severe cases prevent hospitalization and return to the emergency department [3-5].

To arrive at correct diagnosis, information should be sought about recent contact with people with gastroenteritis, nature and frequency of stool and vomitus, fluid intake and urine output, travel, and use of antibiotics and other drugs that may cause diarrhoea. Diarrhoea and vomit being non-specific symptoms, enquiry regarding high fever, prolonged symptoms, or signs of any other nature should also be carefully recorded.

The global standard of care for treating acute gastroenteritis in children is 5-10 days of oral rehydration therapy, which saves lives and may reduce the duration of the illness by 20% [6,7]. Drugs rarely "treat" GE as they deal with the symptoms rather than causes of disease and may distract from the use of appropriate fluid therapy. The WHO now recommends rehydration with a reduced osmolarity ORS. The official WHO ORS or a solution comprised of ½ teaspoon salt and 6 teaspoons sugar per 1 L water may be used [7]. Emergence of antimicrobial resistance and substitution by pro/prebiotics to alter the gut microflora, in the recent years have made a paradigm shift in management of gastroenteritis. Probiotic refers to the live microbes that can be formulated into many different types of products, including foods, drugs, and dietary supplements, while a

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prebiotic includes dietary substances (mostly consisting of non-starch polysaccharides and oligosaccharides poorly digested by human enzymes) that nurture a selected group of microorganisms living in the gut [7-9]. Synbiotic is nothing but a combination of both pre/ probiotic. Numerous evidences exist on the additional beneficial offered by the pre/probiotics in altering the gut microflora and subsequent improvements in infectious conditions [9-12]. Thus, the aim of this review is to evaluate clinical studies that cumulatively analyse how the use of probiotics, prebiotics or symbiotic have reduced the severity of gastroenteritis among children aged 0-12 years.

Methodology

Protocol registration

To locate, analyse, and summarize all relevant study findings, the systematic review was conducted utilizing objective and transparent procedures in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) Guidelines [13]. For this systematic review, the review protocol was priorly registered during initial searches in PROSPERO and is under review. The registration id is 365088 [14].

Screening for eligibility

The identification and screening of the articles were based on the following PICO statement.

Population:

- Children aged 0-12 years diagnosed with gastroenteritis or having symptoms of diarrhoea, bloody stools, nausea, vomiting.
- Healthy children who are prospectively assessed for the incidence of gastroenteritis or having symptoms of diarrhoea, bloody stools, nausea, vomiting.

Intervention: Oral supplementation of any form of probiotic/ prebiotic/ symbiotic alone or in combination with or without Oral rehydration solution (ORS).

Comparison: Placebo, no control, or other forms of probiotic/ prebiotic/ symbiotic.

Outcome: Reduction in symptoms and severity of gastroenteritis assessed either qualitatively or quantitatively.

Inclusion criteria

- English language articles, published between January 2000 to September 2022 assessing the incidence, severity, remission/ resolving of gastroenteritis among children were included.
- Articles which investigated severity of gastroenteritis either qualitatively (characteristics of stool sample) or quantitatively (in terms of duration of diarrhoea, vomiting, hospital stay or microbial colony count, frequency of symptoms, etc) were all included.
- Only randomised/ non- randomised control trials in which a prebiotic/ probiotic/ synbiotic intervention was given and compared were included.

Exclusion criteria

- Articles of the following type were excluded: grey literatures, Commentaries, Observational studies, cohort/ case-control studies, Review articles, expert opinion, conference papers, blog posts, discussion articles, systematic reviews, and meta-analysis.
- Publications without an abstract and those that were outside of the study's domain were excluded.

Search strategy

From January 2000 to September 2022, a broad literature search was conducted in PubMed, and the Google Scholar host database. The keywords used in the search were gastroenteritis, children, probiotic, prebiotic, antibiotic, and trial. The combination of the following terms was included in the search strategy using Boolean operators AND, OR. In PubMed, the articles were searched through the medical subject headings (MeSH) terminologies. The search terms are given in Annexure 1 for PubMED/Medline. For Google Scholar, the similar combination words were used. Additionally, bibliographic search of the eligible articles was also carried to include maximum number of studies.

By reviewing all the titles and abstracts according to the exclusion and inclusion criteria, two authors (TY and MQN) individually selected papers published. A comparison of papers was completed between the two authors and in case of any disagreement, discussion was carried to settle the differences. Using SPSS software (IBM corp. Statistical Package for Social Sciences software for windows; version 20.0 Armonk, New York), the inter-rater agreement between the authors was 0.85, which is a good result.

Data extraction

The data extraction from the final set articles was done using a data extraction form. It includes the first author's name, year of publication of the article, the aim of the study, objectives of the study, study design, study summary, results, and outcome [Table 1] [14-53] of interest.

Quality Assessment of Individual Studies

The methodological quality of the reviewed studies was assessed using Joanna Briggs Institute (JBI) critical appraisal checklist (2017) [54]. This checklist comprises of 13 questions which should be answered using yes/no/unclear/not applicable. For yes, the score is 1, and for no/unclear/not

Table 1: Summary of Study characteristics of all the included studies [check Xcel doc sheet 1] study characteristics.

Master Data Sheet- Summary Findings							
Author/Year	**Country**	**Participants**	**Sample Size**	**Intervention**	**Outcomes**	**Follow-Up Duration**	**ADDITIONAL ANALYSIS**
Rosenfeldt V, et al. (2002) [14]	Denmark	children with median age 22 months	n=43	5 day regimen L reuteri DSM12246 or placebo	duration of diarrhoea	approx 14 days	nil
Costa-Ribeiro H, (2003) [15]	Brazil	male children <2 years age	n-124	ORS with or without LGG	urine, stool output, diarrhoea and vomitting	Not clearly mentioned	nil
Salazar-Lindo E, et al. (2004) [32]	USA	male children of 3-36 months age	Randomized=179 At completion=125	milk formula with or without L casei	Primary outcome- rate of treatment failureand rate of unresolved diarrhoea, duration of diarrhoea, stool output, total ORS intake Secondary outcome-Total study formula intake, total energy intake, volume of vomittus, volume of urine	Not clearly mentioned	nil
Lin JS, et al. (2009) [45]	Taiwan	children under 12 years	Randomized = 1062 At completion =986	L casei rhamnosus [2x 3g sachets per day for 5days], L rhamnnosus T cell [3x1.14g per day for 5 days], multiple probiotics [12 strains-5x 5g per day for days] and control	Incidence, frequencyand episodes of AGE, URTI per person per month	7 months	nil
Fang SB, et al. (2009) [28]	Taiwan	children of 9-72 months age	n=23	Simethicone 80mg/day with daily Lcr35 0 CFU/day [control], 2x10[8] CFU/day [low dose], 6x 10[8]/day [high dose]	Fecal rota virus count	baseline, 24 hrs, 3 days	nil
Grandy G, et al. (2010) [29]	Bolivia	children hospitalized for acute rotavirus diarrhoea aged 1 - 23 months	Randomized=76 At completion=64	Oral rehydration therapy plus placebo; Oral rehydration solution plus *Saccharomyces boulardii* ; or Oral rehydrationsolution plus a compound containing *Lactobacillus acidophilus* , *Lactobacillus rhamnosus, Bifidobacterium longum andSaccharomyces boulardii* . 2 times daily for 5 days mixed in 20ml of water	duration of diarrhoea, of fever, of vomiting and of hospitalization	24hrs, 48 hrs, 72 hrs everyday for 5 days after discharge	nil
Vandenplas Y, et al. (2011) [53]	Belgium	3-186 months age with acute diarrhoea	n=111	Probiotical (Streptoccoccus thermophilus, Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium infantis, fructo-oligosaccharides	duration of diarrhoea, number of children with normal stools and treatment satisfaction by physicians	Not clearly mentioned	nil
Francavilla R, et al. (2012) [16]	Italy	Children (6–36 months old), hospitalised with acute diarrhoea	Randomized=74 At completion=69	suspension of freeze-dried L. reuteri DSM 17938 in a mixtureof sunflower oil and medium-chain triglyceride oil and placebo	Primary outcomes: the rate of unresolved diarrhoea after 3 days of treatment (proportion of patients in each study group with continuing diarrhoea) (duration of diarrhoea (time in hours from admission until cessation of diarrhoea). Secondary outcomes: (i) the duration of hospitalisation (time in hours from admission until discharge from hospital) (ii) total intake of oral rehydration solution (volume of ORS taken from admission until cessation of diarrhoea expressed in millilitres per kilogram of body weight).	7 days	ITT
Dinleyici EC, et al. (2014) [23]	Turkey	chldren 3-120 months age	Randomized = 256 At completion=209	Synbiotic [LGG+BB], placebo	duration of diarrhoea and stool output	Not clearly mentioned	nil

Pieścik-Lech M, (2013) [52]	Poland	Children aged 4 to 60 months with AGE	Randomized=88 At completion=81	LGG plus randomly either smectite (3 g) or placebo as an adjuvant to the standard rehydration therapy	Primary outcome - duration of diarrhea, defined as the time from randomization until the last diarrheal stool, or as at least 12 h with no stool. Secondary outcome - stool frequency, consistency of stools, [QI]:need for antibiotic therapy, (yes/no),vomiting (yes/no; how many times), diarrhea recurrence,tolerance of the study products, need for hospitalization (yes/no, how long), need for unscheduled intravenous rehydration therapy (yes/no, how long),adverse events.	Not clearly mentioned	ITT
Huang YF, et al. (2014) [26]	Japan	Pediatric patients aged 3 months to 14 years	n=159	Receive supportive treatment (intravenous fluid oral rehydration solutions, oral rice, and half- strength milk formula; control group) or add-on BIO-THREE treatment in addition to the supportive treatment [oral BIO-THREE 3 times daily	Fecal culture for microbe	7 days	nil
Sindhu KN, et al. (2014) [31]	India	Children between the ages of 6 months and 5 years with diarrhea, positive for either rotavirus or Cryptosporidium species	n=124	Probiotic LGG was a gelatin capsule with 1 × 10[10] organisms and 170 mg of microcrystalline cellulose; the placebo contained 170 mg cellulose	Intestinal function, immune response, and clinical outcomes in Indian children with cryptosporidial or rotavirus diarrhea	Not clearly mentioned	nil
Nocerino R, et al. (2015) [48]	Italy	Healthy children 12-48 months age	Randomized =432 At completion=391	Cow's milk or rice fermentation wit L casei CBAL74 and placebo	Episodes of AGE, URTI	Not clearly mentioned	ITT
Freedman SB, et al. (2015) [19]	Canada	3 to 48 months, attended day care, and were diagnosed as having gastroenteritis	Randomized = 886 At completion=827	combination product containing 2 Lactobacillus strains—L helveticus Rosell-52 (5%) and L rhamnosus Rosell-11 (95%).	Primary outcome- proportion of children missing at least one full day of day care related to vomiting, diarrhea, dehydration, fever, or fluid refusal, within 2 weeks of randomization. Secondary outcomes- 1. Unscheduled visits to a health care provider related to vomiting, diarrhea, dehydration, fever, or fluid refusal, within 2 weeks.2. A subsequent hospital visit at which time intravenous rehydration fluids were administered within 2 weeks of randomization.3. Duration of (a) vomiting and (b)diarrhea defined as the time from treatment initiation until the last diarrheal stool or episode of vomiting.4. Number of days of (a) day care and (b)work absenteeism.	14 days	ITT
Das S, et al. (2016) [17]	India	Children of 3 months to 5 years age	Randomized = 60 At completion=58	S boulardii 5oomg/day, placebo in sachets as lyophilised powder	Primary outcome- Duration of diarrhoea Secondary outcome- duration of vomitting, duration of fever, duration of hospital saty, need for parentral rehydration, events of diarrhoea ≥7 days and adverese events	Not clearly mentioned	ITT
Mennini M, et al. (2016) [49]	Italy	3–72 months of age with acute gastroenteritis	n=60	oral rehydration solution (ORS) and 31 an ORS plus gelatin tannate (ORS+G)	Primary oucome- number of bowel movements 48 and 72 h after initiating treatment. Secondary outcome-duration of diarrhea, stool characteristics and adverse events	24, 48, 72 hours	nil
Laursen RP, et al. (2017) [46]	Denmark	8-14 month old infants	Randomied=290 At completion==285	1g maltodextrin powder +BB-12+ LGG or placebo	Primary output-No of days absent, Days of diarrhoea	12 weeks	ITT

applicable, the score is 0. A total score of 9 and more indicates that the study is of good quality, between 4 and 8 indicates fair quality, and below 4 is considered poor quality. The first two authors performed the quality assessment, and the disagreements were resolved in consultation with the third author. The overall inter-rater agreement was ƙ= 0.82 indicating good agreement.

The Cochran Review Manager Software 5.4.1 (Cochrane Revman -UK) was used to identify the risk of bias across the reviewed studies. The risk of bias was categorized as low, unclear, or high.

Results

Search results

A total of 460 articles were generated in the database and bibliographic search. Finally, based on the inclusion and exclusion criteria, 26 out of 33 articles studying over 5,683 participants were selected for the review using the PRISMA flowchart [Figure 1]. The exclude 6 articles were secondary analysis of the already included trials and had assessed different outcomes. Hence, they were removed to avoid repetition.

Quality of included studies

The methodological quality assessment as per the JBI checklist is given in Table 2. Most of the included studies were of moderate quality with respect to study design, sampling, randomization, and allocation of intervention. All being clinical trials, the lack of sufficient clarity in the methodology and presence of attrition led to variation between the individual studies. The results of bias risk assessment are shown in Figure 2, and the summary of the individual studies is presented in Figure 3. A study found to have the least score of 2 while over 10 of the 26 studies were of high quality.

Risk of bias across the included studies was assessed using Cochrane tool revealed that most of the studies lacked in appropriate reporting of their findings leading to poor validity of their findings.

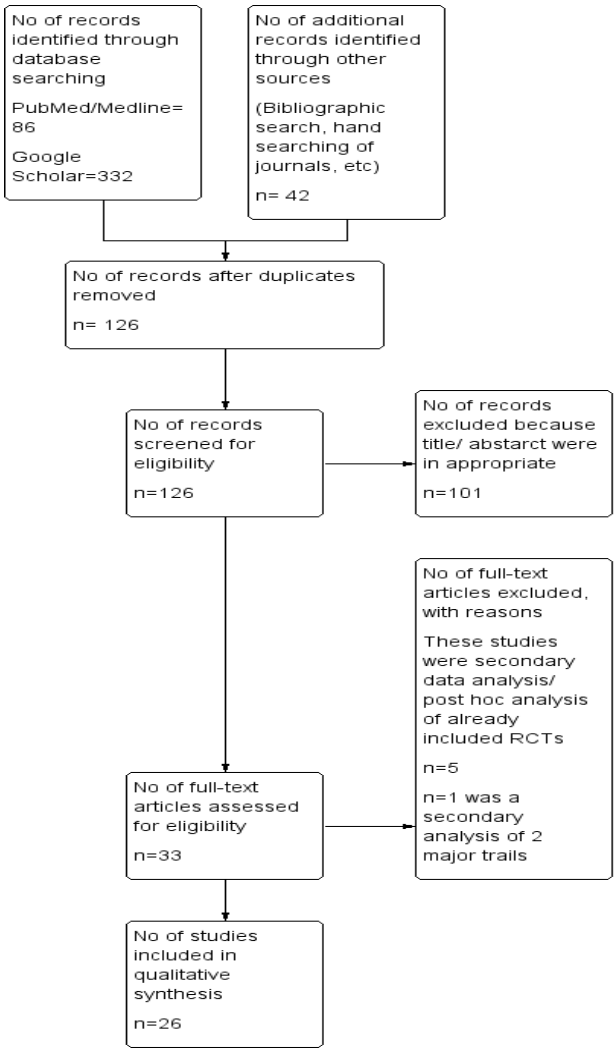

Figure 1: PRISMA Flow Chart.

Table 2: JBI Checklist for the Included Studies [check Xcel doc sheet 2] study characteristics.

	Rosenfeldt V, et al. (2002) [14]	Costa-Ribeiro H, (2003) [15]	Salazar-Lindo E, et al. (2004) [32]	Lin JS, et al. (2009) [45]	Fang SB, et al. (2009) [28]	Grandy G, et al. (2010) [29]	Vandenplas Y, et al. (2011) [53]	R Francavilla R, et al. (2012) [16]	Dinleyici EC, et al. (2014) [23]	Pieścik-Lech M, (2013) [52]	Huang YF, et al. (2014) [26]	Sindhu KN, et al. (2014) [31]	Nocerino R, et al. (2015) [48]	Freedman SB, et al. (2015) [19]	Das S, et al. (2016) [17]	Xu L, et al. (2016)	Mennini M, et al. (2016) [49]	Laursen RP, et al. (2017) [46]	Corsello G, et al. (2017) [50]	Maragkoudaki M, et al. (2018) [30]	Kołodziej M, et al. (2018) [35]	Szymanski H, et al. (2019) [27]	Schnadower D, et al. (2021) [40]	Shin DY, et al. (2020)	Francesco D, et al. (2021)	Horne RG, et al. (2022) [43]	Altcheh J, et al. (2022) [42]
Was true randomization used for assignment of participants to treatment groups?	No	Unclear	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Was allocation to treatment groups concealed?	No	Yes	Yes	No	No	Unclear	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Were treatment groups similar at the baseline?	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No
Were participants blind to treatment assignment?	No	Unclear	Yes	No	No	Unclear	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Were those delivering treatment blind to treatment assignment?	No	Unclear	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Were outcomes assessors blind to treatment assignment?	No	Unclear	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No		Yes	Yes
Were treatment groups treated identically other than the intervention of interest?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No		Yes	Yes
Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	No	No	No	Unclear	No	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the trial design appropriate for the topic and any deviations from the standard randomized controlled trial design accounted for in the conduct and analysis of the trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
TOTAL SCORE	**8**	**6**	**12**	**7**	**6**	**6**	**13**	**13**	**9**	**13**	**8**	**12**	**13**	**13**	**12**	**11**	**13**	**13**	**13**	**13**	**13**	**12**	**13**	**2**	**10**	**12**	**12**

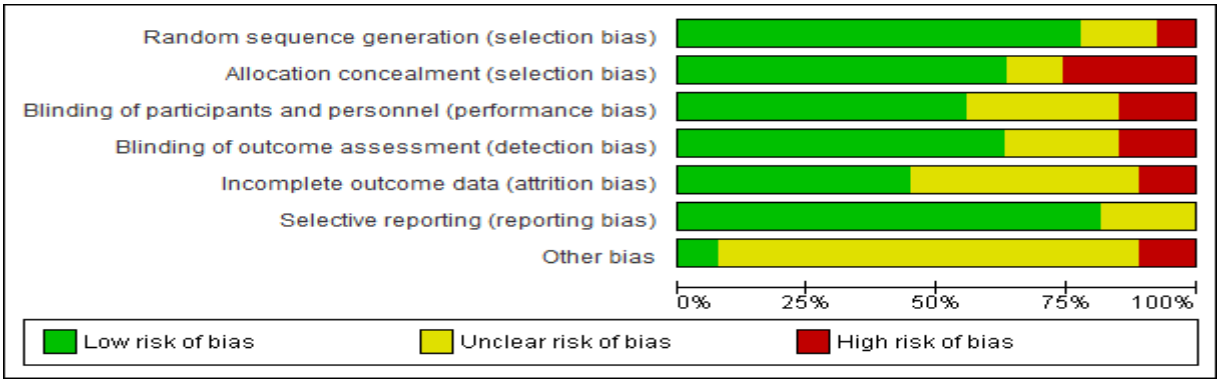

Figure 2: Risk of bias across the include studies.

Figure 3: Summary Findings.

Duration of Diarrhoea

Duration of diarrhoea after intervention was assessed as mean hours, days as well as using Modified Vesikari Scale. Heterogeneity across the studies was high in all the cases. When mean number of hours were considered, 10 of the 26 studies were included, which resulted in effect estimate of -0.49 [-0.87, -0.12] [Chi^2=116.22, I^2= 92%, p=0.01]. [Figure 4]. However, when the number of days were considered only 4 studies were included and the effect estimate was 0.19 [-0.52, 0.90] [Chi^2=55.46, I^2=95%, p=60] [Figure 5].

The MVS scores were estimated in 3 studies and were reported as number of participants with a score of ≥9 among those who suffered from diarrhoea. Since the estimates were calculated with respect to only those having that symptom, and not the whole intervention or control group, median values could not be computed for further analysis.

Other Outcomes

Reduction of gastroenteritis was quantitatively seen as mean duration of diarrhoea, vomiting, fever, number of days of hospitalizations, rate of relapse, days of absenteeism from day care/ school and faecal characteristics are some of the outcomes.

Amongst these only one study by Vandenplas Y, et al. (2011) [53] reported the physician satisfaction in terms of decreased number of additional prescriptions required for treating children with gastroenteritis.

Microbial count was estimated in regular faecal swabs or in dose dependent manner by Fang SB, et al. (2009) [28], Huang YF, et al. (2014) [26], and Horne RG, et al. (2022) [43]. These authors confirmed an alteration in the intestinal microflora and reduction of inflammation histopathologically.

Studies by Lin JS, et al. (2009) [45], Nocerino R, et al. (2015) [48], and Corsello G, et al. (2017) [50], primarily monitored the incidence, episodes of gastroenteritis in their participants along with other common infectious diseases like rhinitis, pharyngitis, etc.

Apart from these recent investigations on gastroenteritis in children is more focussed on identifying the immunomodulatory responses, assessing the genome of the causative agents, and determining its relationship with sIgA levels as done by Corsello G, et al. (2017) [50], and Horne RG, et al. (2022) [43].

Overall, none of the included reported any adverse events in administering probiotics to children.

Publication Bias

Funnel plots Figure 6 and Figure 7 showed no bias in terms of sample size, outcomes assessed.

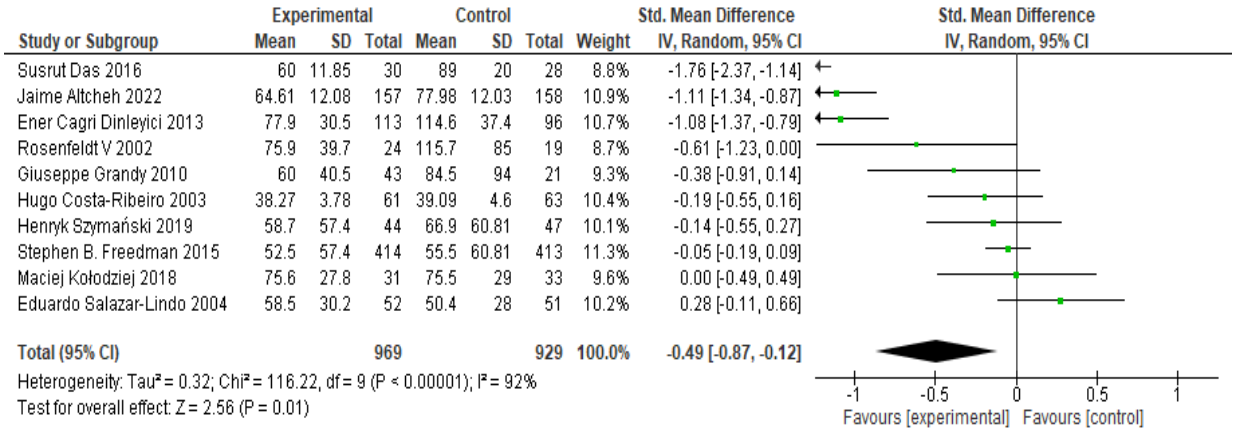

Figure 4: Forest plot for mean duration of diarrhoea (expressed as hours) post intervention.

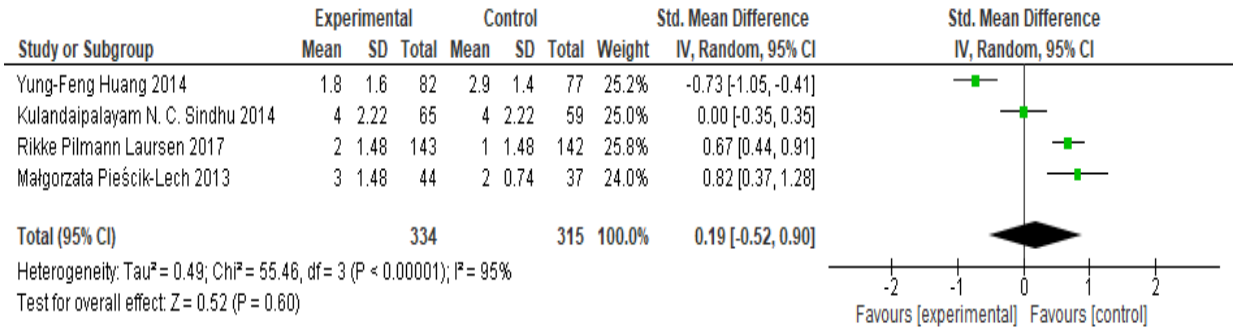

Figure 5: Forest plot for mean duration of diarrhoea (expressed as days) post intervention.

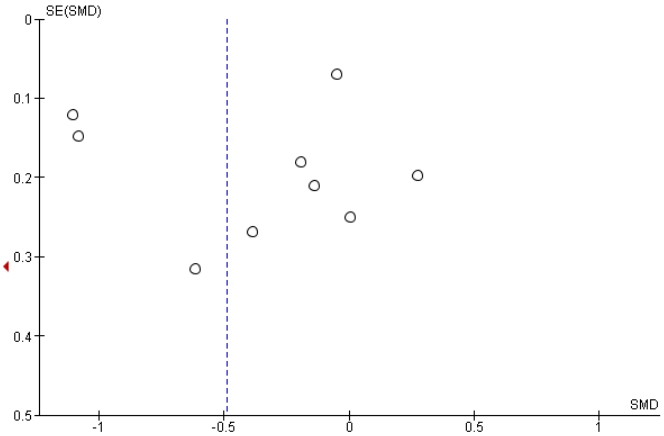

Figure 6: For studies assessing duration of diarrhoea post intervention assessed in hours.

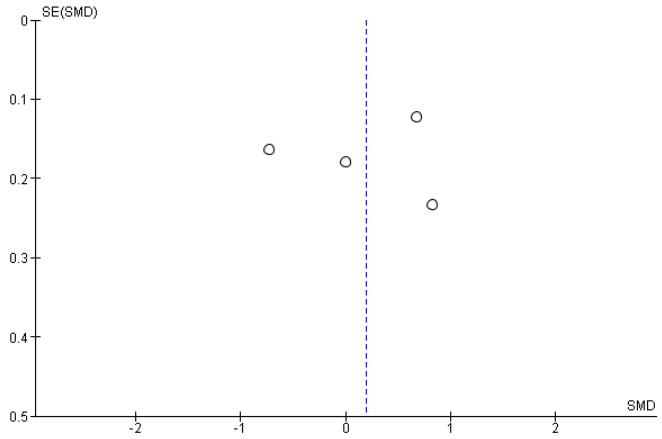

Figure 7: Funnel plot of comparison for studies assessing duration of diarrhoea post intervention in days.

Discussion

Summary findings

Our systematic review and meta-analysis showed that the administration of probiotics does not have significant effect in reducing diarrhoea, the principal symptom of gastroenteritis in children. Although, few individual studies showed significant reduction, the overall cumulative results are in supportive of those reported by Schnadower D, et al. (2021) [40]. Two of the largest trials the PERC- PROGUT and PECARN carried out in North America, Canada respectively, were analysed in this secondary analysis and concluded to reveal no specific clinical improvement conferred to probiotic supplementation.

Almost all the studies had their cases as those children having three or more episodes of watery stools in a 24-hour period as pe the WHO guidelines. Only those studies which monitored incidence were performed on healthy children wherein the probiotic supplementation was given in addition to their regular formula/ milk feed.

One of the important assessments which gave clinically relevant information amongst these studies was the use of Modified Vesikari Scale [MVS]. The MVS consists of scores range from 0 to 20, with higher scores indicating more severe disease. Its components include duration of diarrhoea (hr), maximum no. of watery stools per 24 hr, duration of vomiting (hr), maximum no. of vomiting episodes per 24 hr, maximum recorded rectal temperature (°C) and unscheduled health care visit, all of which are given a score of 0-3 depending on the severity. However only very few studies were reported using this.

Of the 26 studies, Rosenfeldt V, et al. (2002) [14], Costa-Ribeiro H, (2003) [15], Salazar-Lindo E, et al. (2004) [32], Vandenplas Y, et al. (2011) [53], Pieścik-Lech M, (2013) [52], Dinleyici EC, et al. (2014) [23], Mennini M, et al. (2016) [49], and Kołodziej M, et al. (2018) [35], reported the stool characteristics in terms of volume, colour, consistency. To evaluate the stool characteristics apart from stool volume, different scales were used: the Bristol Stool Form Scale [BSF], the Amsterdam Infant Stool Form Scale [AISF]. The BSF and AISF assess the severity of disease depending on the physical appearance, colour, and consistency of the stool. Only Kołodziej M, et al. (2018) [35], used ASIF scale while the remaining studies either used BSF or just reported quantitative measures.

A wide range of probiotics have been used as intervention in our included studies. Most used ones belong to *Lactobacillus spp*. family. Various other species like *Saccharomyces boulardii, Smectite, Bifidibacterium spp, Streptococcus spp.* The probiotic bacteria were used as a single strain or a combination of multiple strains. Fixed dose or age dependent doses were administered to the study participants in different modes in different studies. The various route of administration included capsules, in oil suspensions, powder in sachets, or in combination with the standard Oral Rehydration Solution (ORS). Seven of the 26 studies used more than a single strain of probiotic Lin JS, et al. (2009) [45], Grandy G, et al. (2010) [29], Vandenplas Y, et al. (2011) [53], Dinleyici EC, et al. (2014) [23], Huang YF, et al. (2014) [26], and Laursen RP, et al. (2017) [46]. Though individually these studies claimed an improvement in treatment outcomes on using multiple strains, the effect of these on improving the innate immunity thereby leading to better health outcome have not been studied extensively.

Only Mennini M, et al. (2016) [49], used gelatin tannate as the intervention instead of a probiotic and reported significant increase in stool consistence and shorter disease duration.

Even though a series of meta-analysis [55-58] have been published with similar research question, this review exclusively examines all those studies that have reported gastroenteritis and the specific reduction in symptoms or improvement in treatment outcomes reported on single/ multiple probiotic or prebiotic supplementation irrespective of the organism used. Our review findings are consistent with the existing literature in reporting that probiotic supplementation may not offer any additional benefit to the existing rehydration therapy. Molecular level analysis of the bacterial interaction with the intestinal mucosa may offer better insight to the host modulation response if any such exists [59-61]. Our major limitation is that only English language studies were considered eligible, thereby reducing the validity of our findings. Another hindrance will be the pooling of heterogenous studies with different probiotic interventions for different periods. This was done with the evidence that none of the included studies introduced live bacterial species as their intervention thus nullifying their individual pathogenic effect on the system. Also, only the standard mean difference was used for computing the meta- analysis thereby reducing the variations of mean.

Thus, on implication at clinical level, based on the individual methodological difference it can be concluded that probiotic supplementation can be used as an adjuvant to the existing treatment protocol of oral rehydration with fluids but not as a replacement. Uniform assessments with standardised scales in future offer better comparisons amongst individual studies.

References

1. Elliott EJ 2007. Acute gastroenteritis in children. *BMJ* 334: 35-40. https://doi.org/10.1136/bmj.39036.406169.80

2. King CK, Glass R, Bresee JS, Duggan C, Centers for Disease Control and Prevention 2003. Managing acute gastroenteritis among children. *MMWR Recomm Rep* 52: 1-16.

3. Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC 2019. Probiotics for the prevention of pediatric antibiotic-associated diarrhoea. *Cochr Datab Syst Rev* 2011: CD004827. https://doi.org/10.1002/14651858.CD004827.pub5

4. Freedman SB, Pasichnyk D, Black KJ, Fitzpatrick E, Gouin S, et al. 2015. Gastroenteritis therapies in developed countries: systematic review and meta-analysis. *PLoS ONE* 10: e0128754. https://doi.org/10.1371/journal.pone.0128754

5. Hartman S, Brown E, Loomis E, Russell HA 2019. Gastroenteritis in children. *Am Fam Physician* 99: 159-165.

6. Acute Gastroenteritis Guideline Team 2005. Cincinnati Children's Hospital Medical Center. Evidence-based care guidelines. Gastroenteritis.

7. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, et al. 2012. World Gastroenterology Organisation global guidelines: probiotics and prebiotics. *J Clin Gastroenterol* 46: 468-481. https://doi.org/10.1097/MCG.0b013e3182549092

8. Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JN, et al. 2011. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess* 1: 1-5.

9. Vassilopoulou L, Spyromitrou-Xioufi P, Ladomenou F 2021. Effectiveness of probiotics and synbiotics in reducing duration of acute infectious diarrhea in pediatric patients in developed countries: a systematic review and meta-analysis. *Eur J Pediatr* 180: 2907-2920. https://doi.org/10.1007/s00431-021-04046-7

10. Ahmadi E, Alizadeh-Navaei R, Rezai MS 2015. Efficacy of probiotic use in acute rotavirus diarrhea in children: A systematic review and meta-analysis. *Caspian J Intern Med* 6: 187-195.

11. Morgan RL, Preidis GA, Kashyap PC, Weizman AV, Sadeghirad B, et al. 2020. probiotics reduce mortality and morbidity in preterm, low-birth-weight infants: a systematic review and network meta-analysis of randomized trials. *Gastroenterology* 159: 467-480. https://doi.org/10.1053/j.gastro.2020.05.096

12. Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, et al. 2020. Probiotics for treating acute infectious diarrhoea. *Cochr Datab Syst Rev* 2020: CD003048. https://doi.org/10.1002/14651858.CD003048.pub4

13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group* 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 6: e1000097. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

14. Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Møller PL, et al. 2002. Effect of probiotic Lactobacillus strains on acute diarrhoea in a cohort of non-hospitalized children attending day-care centers. *Pediatr Infect Dis J* 21: 417-419.

15. Costa-Ribeiro H, Ribeiro TC, Mattos AP, Valois SS, Neri DA, et al. 2003. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. *J Pediatr Gastroentol Nutr* 36: 112-115.

16. Francavilla R, Lionetti E, Castellaneta S, Ciruzzi F, Indrio F, et al. 2012. Randomised clinical trial: *Lactobacillus reuter*i DSM 17938 vs. placebo in children with acute diarrhoea – a double-blind study. *Aliment Pharmacol Therapeut* 36: 363-369. https://doi.org/10.1111/j.1365-2036.2012.05180.x

17. Das S, Gupta PK, Das RR 2016. Efficacy and safety of *Saccharomyces boulardii* in acute rotavirus diarrhoea: double blind randomized controlled trial from a developing country. *J Trop Pediatr* 62: 464-470.

18. Freedman SB, Williamson-Urquhart S, Schuh S, Sherman PM, Farion KJ, et al. 2014. Impact of emergency department probiotic treatment of pediatric gastroenteritis: study protocol for the PROGUT (Probiotic Regimen for Outpatient Gastroenteritis Utility of Treatment) randomized controlled trial. *Trials* 15: 170. https://doi.org/10.1186/1745-6215-15-170

19. Freedman SB, Sherman PM, Willan A, Johnson D, Gouin S, et al. 2015. Emergency department treatment of children with diarrhoea who attend day care: a randomized multi dose trial of a *Lactobacillus helveticus* and *Lactobacillus rhamnosus* combination probiotic. *Clin Pediatr* 54: 1158-1166. https://doi.org/10.1177/0009922815569200

20. Freedman SB, Williamson-Urquhart S, Farion KJ, Gouin S, Willan AR, et al. 2018. Multicenter trial of a combination probiotic for children with gastroenteritis. *New Engl J Med* 379: 2015-2026. https://doi.org/10.1056/NEJMoa1802597

21. Freedman SB, Xie J, Nettel-Aguirre A, Pang XL, Chui L, et al. 2020. A randomized trial evaluating virus-specific effects of a combination probiotic in children with acute gastroenteritis. *Nat Commun* 11: 25-33. https://doi.org/10.1038/s41467-020-16308-3

22. Freedman SB, Horne R, Johnson-Henry K, Xie J, Williamson-Urquhart S, et al. 2021. Probiotic stool secretory immunoglobulin A modulation in children with gastroenteritis: a randomized clinical trial. *Am J Clin Nutr* 113: 905-914. https://doi.org/10.1093/ajcn/nqaa369

23. Dinleyici EC, PROBAGE Study Group, Vandenplas Y, Dalgic N, Guven S, et al. 2014. *Lactobacillus reuteri* DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. *Acta Pædiatr* 103: e300-e305. https://doi.org/10.1111/apa.12617

24. Dinleyici EC, Dalgic N, Guven S, Metin O, Yasa O, et al. 2015. *Lactobacillus reuteri* DSM 17938 shortens acute infectious diarrhoea in a pediatric outpatient setting. *J Pediatr* 91: 392-396. https://doi.org/10.1016/j.jped.2014.10.009

25. Dinleyici EC, Kara A, Dalgic N, Kurugol Z, Arica V, et al. 2015. *Saccharomyces boulardii* CNCM I-745 reduces the duration of diarrhoea, length of emergency care and hospital stay in children with acute diarrhoea. *Benef Microb* 6: 415-421. https://doi.org/10.3920/BM2014.0086

26. Huang YF, Liu PY, Chen YY, Nong BR, Huang IF, et al. 2014. Three-combination probiotic therapy in children with Salmonella and rotavirus gastroenteritis. *J Clin Gastroenterol* 48: 37-42. https://doi.org/10.1097/MCG.0b013e31828f1c6e

27. Szymanski H, Szajewska H 2019. Lack of efficacy of *Lactobacillus reuteri* DSM 17938 for the treatment of acute gastroenteritis: a randomized controlled trial. *Pediatr Infect Dis J* 38: e237-e242. https://doi.org/10.1097/INF.0000000000002355

28. Fang SB, Lee HC, Hu JJ, Hou SY, Liu HL, et al. 2009. Dose-dependent effect of *Lactobacillus rhamnosus* on quantitative reduction of faecal rotavirus shedding in children. *J Trop Pediatr* 55: 297-301. https://doi.org/10.1093/tropej/fmp001

29. Grandy G, Medina M, Soria R, Terán CG, Araya M 2010. 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* 10: 253. https://doi.org/10.1186/1471-2334-10-253

30. Maragkoudaki M, Chouliaras G, Moutafi A, Thomas A, Orfanakou A, et al. 2018. Efficacy of an oral rehydration solution enriched with *Lactobacillus reuteri* DSM 17938 and zinc in the management of acute diarrhoea in infants: a randomized, double-blind, placebo-controlled trial. *Nutrients* 10: E1189. https://doi.org/10.3390/nu10091189

31. Sindhu KN, Sowmyanarayanan TV, Paul A, Babji S, Ajjampur SS, et al. 2014. Immune response and intestinal permeability in children with acute gastroenteritis treated with *Lactobacillus rhamnosus GG*: a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 58: 1107-1115. https://doi.org/10.1093/cid/ciu065

32. Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M, Chea-Woo E, Sack RB 2004. *Lactobacillus casei* strain GG in the treatment of infants with acute watery diarrhoea: a randomised, double-blind, placebo controlled clinical trial. *BMC Pediatr* 4: 1-9. https://doi.org/10.1186/1471-2431-4-18

33. Salazar-Lindo E, Figueroa-Quintanilla D, Caciano MI, Reto-Valiente V, Chauviere G, et al. 2006. Effectiveness and safety of *Lactobacillus LB* in the treatment of mild acute diarrhoea in children. *J Paediatr Gastroenterol Nutr* 44: 571-576. https://doi.org/10.1097/MPG.0b013e3180375594

34. Kołodziej M, Szajewska H 2017. Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: protocol of a randomised controlled trial. *BMJ Open* 7: e013928. http://dx.doi.org/10.1136/bmjopen-2016-013928

35. Kołodziej M, Bebenek D, Konarska Z, Szajewska H 2018. Gelatine tannate in the management of acute gastroenteritis in children: a randomised controlled trial. *BMJ Open* 8: e020205. http://dx.doi.org/10.1136/bmjopen-2017-020205

36. Noguera T, Wotring R, Melville CR, Hargraves K, Kumm J, et al. 2014. Resolution of acute gastroenteritis symptoms in children and adults treated with a novel polyphenol-based prebiotic. *World J Gastroenterol* 20: 12301-12307. https://doi.org/10.3748/wjg.v20.i34.12301

37. Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean MJ, et al. 2017. Randomised controlled trial of *Lactobacillus rhamnosus* (LGG) versus placebo in children presenting to the emergency department with acute gastroenteritis: the PECARN probiotic study protocol. *BMJ Open* 7: e018115. http://dx.doi.org/10.1136/bmjopen-2017-018115

38. Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, et al. 2018. *Lactobacillus rhamnosus GG* versus placebo for acute gastroenteritis in children. *N Engl J Med* 379: 2002-2014. https://doi.org/10.1056/NEJMoa1802598

39. Schnadower D, Tarr PI, Freedman SB 2019. *Lactobacillus rhamnosus GG* oJers no benefit over placebo in children with acute gastroenteritis. *Aliment Pharmacol Therapeut* 50: 620-622. https://doi.org/10.1111/apt.15418

40. Schnadower D, Sapien RE, Casper TC, Vance C, Tarr PI, et al. 2021. Association between age, weight, and dose and clinical response to probiotics in children with acute gastroenteritis. *J Nutr* 151: 65-72. https://doi.org/10.1093/jn/nxaa313

41. Schnadower D, O'Connell KJ, VanBuren JM, Vance C, Tarr PI, et al. 2021. Association between diarrhea duration and severity and probiotic efficacy in children with acute gastroenteritis. *Am J Gastroenterol* 116: 1523-1532. https://doi.org/10.14309/ajg.0000000000001295

42. Altcheh J, Carosella MV, Ceballos A, D'Andrea U, Jofre SM, et al. 2022. Randomized, direct comparison study of Saccharomyces boulardii CNCM I-745 versus multi-strained Bacillus clausii probiotics for the treatment of pediatric acute gastroenteritis. *Medicine (Baltimore)* 101: e30500. https://doi.org/10.1097/MD.0000000000030500

43. Horne RG, Freedman SB, Johnson-Henry KC, Pang XL, Lee BE, et al. 2022. Intestinal microbial composition of children in a randomized controlled trial of probiotics to treat acute gastroenteritis. *Front Cell Infect Microbiol* 12: 883163. https://doi.org/10.3389/fcimb.2022.883163

44. Cheng H, Ma Y, Liu X, Tian C, Zhong X, et al. 2022. A systematic review and meta-analysis: lactobacillus acidophilus for treating acute gastroenteritis in children. *Nutrients* 14: 682. https://doi.org/10.3390/nu14030682

45. Lin JS, Chiu YH, Lin NT, Chu CH, Huang KC, et al. 2009. Different effects of probiotic species/strains on infections in preschool children: A double-blind, randomized, controlled study. *Vaccine* 27: 1073-1079. https://doi.org/10.1016/j.vaccine.2008.11.114

46. Laursen RP, Larnkjær A, Ritz C, Hauger H, Michaelsen KF, et al. 2017. Probiotics and child care absence due to infections: a randomized controlled trial. *Pediatrics* 140: e20170735. https://doi.org/10.1542/peds.2017-0735

47. Yi DY, Jo S, Lee YM, Kim JH, Kim W, et al. 2020. Effect of a new *Lactobacillus plantarum* product, LRCC5310, on clinical symptoms and virus reduction in children with rotaviral enteritis. *Medicine* 99: 38. https://doi.org/10.1097/MD.0000000000022192

48. Nocerino R, Paparo L, Terrin G, Pezzella V, Amoroso A, et al. 2015. Cow's milk and rice fermented with *Lactobacillus paracasei* CBA L74 prevent infectious diseases in children: A randomized controlled trial. *Clin Nutr* 36: 118-125. http://dx.doi.org/10.1016/j.clnu.2015.12.004.

49. Mennini M, Tolone C, Frassanito A, Midulla F, Cucchiara S, et al. 2017. Gelatin tannate for acute childhood gastroenteritis: a randomized, single-blind controlled trial. *Paediatr Drugs* 19: 131-137. https://doi.org/10.1007/s40272-016-0207-z

50. Corsello G, Carta M, Marinello R, Picca M, De Marco G, et al. 2017. Preventive effect of cow's milk fermented with lactobacillus paracasei CBA L74 on common infectious diseases in children: a multicenter randomized controlled trial. *Nutrients* 9: 669. https://doi.org/10.3390/nu9070669

51. Russo L, Danza ML, Basile I, Soardo S, Capocasale G, et al. 2020. Use of a probiotic mixture containing Bifidobacterium animalis subsp. lactis BB-12 and Enterococcus faecium L3 as prophylaxis to reduce the incidence of acute gastroenteritis and upper respiratory tract infections in children. *Minerva Pediatr (Torino)* 3: 222-229. https://doi.org/10.23736/s2724-5276.20.05925-3

52. Pieścik-Lech M, Urbańska M, Szajewska H 2013. *Lactobacillus GG (LGG)* and smectite versus LGG alone for acute gastroenteritis: a double-blind, randomized controlled trial. *Eur J Pediatr* 172: 247-253. https://doi.org/10.1007/s00431-012-1878-2

53. Vandenplas Y, De Hert SG, PROBIOTICAL-study group 2011. Randomised clinical trial: the synbiotic food supplement Probiotical vs. placebo for acute gastroenteritis in children. *Aliment Pharmacol Ther* 34: 862-867. https://doi.org/10.1111/j.1365-2036.2011.04835.x

54. Joanna Briggs Institute. Checklist for Systematic Review and Syntheses.

55. Huang R, Xing HY, Liu HJ, Chen ZF, Tang BB 2021. Efficacy of probiotics in the treatment of acute diarrhea in children: a systematic review and meta-analysis of clinical trials. *Transl Pediatr* 10: 3248-3260. https://doi.org/10.21037/tp-21-511

56. Szajewska H, Kołodziej M, Gieruszczak-Białek D, Skorka A, Ruszczyński M, et al. 2019. Systematic review with meta-analysis: Lactobacillus rhamnosus GG for treating acute gastroenteritis in children – a 2019 update. *Alim Pharmacol Therapeut* 49: 1376-1384. https://doi.org/10.1111/apt.15267

57. Szajewska H, Kołodziej M, Shamir R 2019. Lactobacillus rhamnosus GG offers no benefit over placebo in children with acute gastroenteritis. Authors' reply. *Alim Pharmacol Therapeut* 50: 622-623. https://doi.org/10.1111/apt.15431

58. Patro-Gołąb B, Szajewska H 2019. systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for treating acute gastroenteritis in children. An update. *Nutrients* 11: 2762. https://doi.org/10.3390/nu11112762

59. Florez ID, Veroniki AA, Al Khalifah R, Yepes-Nunez JJ, Sierra JM, et al. 2018. Comparative effectiveness and safety of interventions for acute diarrhoea and gastroenteritis in children: A systematic review and network meta-analysis. *PLoS One* 13: e0207701. https://doi.org/10.1371/journal.pone.0207701

60. Carter B, Fedorowicz Z 2012. Antiemetic treatment for acute gastroenteritis in children: an updated Cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. *BMJ Open* 2: e000622. http://dx.doi.org/10.1136/bmjopen-2011-000622

61. Gruber JF, Becker-Dreps S, Hudgens MG, Brookhart MA, Thomas JC, et al. 2018. Timing and predictors of severe rotavirus gastroenteritis among unvaccinated infants in low- and middle-income countries. *Epidemiol Infect* 146: 698-704. https://doi.org/10.1017/S0950268818000626