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Systematic review with meta-analysis: *Saccharomyces boulardii* for treating acute gastroenteritis in children—a 2020 update

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Summary

Background: There is still controversy with regard to the efficacy of individual probiotic strains for the management of acute gastroenteritis.

Aim: To update evidence on use of *Saccharomyces boulardii* for treating acute gastroenteritis in children.

Methods: The Cochrane Library, MEDLINE and EMBASE databases were searched from inception to December 2019 for randomised controlled trials (RCTs) that compared use of *S boulardii* with no *S boulardii* (defined as placebo or no treatment). The grey literature was searched through Google search. Authors of the original papers and *S boulardii* manufacturers were contacted for additional data.

Results: Twenty-nine RCTs (among them, 20 newly identified trials) were included. Only 38% of trials adequately generated their randomisation sequence, only 17% adequately concealed allocation and only one trial adequately blinded participants, study personnel and outcome assessors. However, 83% provided complete outcome data. None of the trials evaluated the effect of *S boulardii* on stool volume. Compared with placebo or no treatment, *S boulardii* use reduced the duration of diarrhoea (23 RCTs, n = 3450, mean difference −1.06 day, 95% CI −1.32 to −0.79; high heterogeneity [I^2 = 90%]) (very low quality of evidence). *S boulardii* use was also associated with a reduced duration of hospitalisation (8 RCTs, n = 999, mean difference −0.85 day, 95% CI −1.35 to −0.34; I^2 = 91%) (very low quality of evidence). *S boulardii* reduced the risk of diarrhoea on day 2 to day 7 (low quality of evidence).

Conclusions: In children with acute gastroenteritis, low- to very low-quality evidence suggests that *S boulardii* confers a benefit for several diarrhoeal outcomes.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Alexander Ford, and it was accepted for publication after full peer-review.

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1 | INTRODUCTION

Worldwide, acute gastroenteritis, often referred to as 'acute infectious diarrhoea,' is a significant cause of morbidity and mortality in children. It also accounts for a substantial number of out-patient or emergency department visits and hospitalisations. Oral rehydration therapy is the mainstay of treatment for acute gastroenteritis and should be applied promptly.[1,2] However, despite proven efficacy, oral rehydration remains underused. Several guidelines recommend using probiotics with proven efficacy and safety for the management of children with acute gastroenteritis as an adjunct to rehydration therapy.[1-3] Two strains most commonly recommended are *Lactobacillus rhamnosus GG* (*L rhamnosus* GG)[4,5] and *Saccharomyces boulardii* (*S boulardii*).[5] However, there is still controversy with regard to the efficacy of individual strains, even those included in the recommendations. This is because data to support using individual strains are often limited or had methodological limitations. Moreover, at least with regard to some probiotics, high-quality null studies were recently published.[6-8]

Saccharomyces boulardii is a widely available probiotic yeast.[9] Our previous meta-analysis (originally published in 2007[10] and updated in 2009[11]) of data from nine randomised controlled trials (RCTs) involving 1117 participants showed that *S boulardii* is moderately effective in treating children with acute gastroenteritis, mainly by shortening the duration of diarrhoea. The exact mechanisms by which *S boulardii* might exert its actions are unclear. However, possible mechanisms include interference with pathogen attachment, interaction with normal microbiota, inactivation of toxins (eg *Clostridioides* (*Clostridium*) *difficile* toxins), antisecretory effects via normalisation of the transcellular transport of chloride and reduced loss of sodium and water, and immunomodulatory effects, both within the lumen and systemically.[9] In the last few years, a number of new relevant studies have been published not included in published systematic reviews. Here, our aim was to systematically update evidence on the effects of *S boulardii* compared with placebo or no intervention for treating acute gastroenteritis in children. The intention is that this updated meta-analysis will serve as a basis for revising the guidelines for the management of acute gastroenteritis in children.

2 | METHODS

The methodology was similar to one followed in our earlier systematic review on a similar topic.[12] The protocol was submitted for registration with the International Prospective Register of Systematic Reviews (PROSPERO) on 30 September 2019 (ID: 152 832); however, formal registration was still pending at the time of the writing of this manuscript. The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis[13] and the PRISMA statement[14] were followed for this systematic review and meta-analysis. Ethical approval was not needed.

2.1 | Criteria for considering studies for this review

All relevant RCTs that compared use of *S boulardii* (as a single ingredient, in all delivery vehicles and formulations, at any dose, regardless of the strain manufacturer and designation) with no *S boulardii* (defined as placebo or no treatment) were eligible for inclusion. The *primary* outcome measures of interest were the duration of diarrhoea and stool volume. The *secondary* outcome measures were the effects of *S boulardii* on the course of diarrhoea, including the percentages of children with diarrhoea at various times intervals (as specified by the investigators), the percentage of children with diarrhoea lasting longer than 7 days, the duration of hospitalisation and adverse events. Other outcomes evaluated by the authors of the original trials were also considered if clinically relevant to this review.

2.2 | Search methods for identification of studies

To identify relevant evidence, the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE and EMBASE databases were searched from their inception to December 2019. The principal search text word terms and MESH headings used were as follows: diarrhea/diarrhoea, diarrh*, gastroenteritis, probiotic*, *Saccharomyces boulardii* (for details, see Table S1**).** No language restrictions were imposed. Additionally, the grey literature was searched through Google. The reference lists from identified studies and key review articles, including previously published systematic reviews with or without a meta-analysis, were also searched to identify any other relevant studies. If needed, the authors of the original papers and the manufacturers of *S boulardii* were contacted for additional data. Letters to the editor, abstracts and proceedings from scientific meetings were excluded, unless data needed for this review were obtained from the authors. The ClinicalTrials.gov and ClinicalTrialsRegister.eu websites were also searched for RCTs that were registered but not yet published.

2.3 | Data collection and analysis

Using a standardised form, two reviewers (BMZ & MK) undertook the literature search, data extraction and quality assessment. The data (extracted by one reviewer and checked by the second reviewer) included baseline characteristics, inclusion criteria, experimental and control treatments, setting, dose and funding.

2.4 | Assessment of risk of bias in included studies

The Cochrane Collaboration's tool for assessing risk of bias was used. The risk of bias parameters included the type of randomisation method (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias).

Additionally, selective reporting (reporting bias) and other types of bias were considered. If an item could not be evaluated due to missing information, it was rated as having an unclear risk of bias.[13]

The GRADE (Grading of Recommendations, Assessment Development and Evaluations) approach was used to assess the quality of the supporting evidence for selected outcomes (ie the primary outcome measures, duration of hospitalisation and the risk of diarrhoea on specific days) using the GRADEpro software (https://gdt.gradepro.org).[15] The quality of the evidence (also called certainty of evidence) is categorised as high, moderate, low or very low based on consideration of the risk of bias, the directness of evidence, consistency and precision of the estimates. *Low* and *very low-quality evidence* indicates that the estimated effects of interventions are very uncertain, and further research is very likely to influence resulting recommendations.

2.5 | Measures of treatment effect

The dichotomous outcomes, the results for individual studies and pooled statistics were reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The continuous outcomes were reported as the mean difference (MD) between the treatment and control groups with 95% CI.

2.6 | Dealing with missing data

We assessed pooled data using available case analysis, ie an analysis in which data are analysed for every participant for whom the outcome was obtained, rather than intention-to-treat analysis with imputation.

2.7 | Assessment of heterogeneity

Heterogeneity was quantified by χ^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. For χ^2 test, the level of significance was $P < 0.10$. All analyses were based on the random-effects model.

2.8 | Assessment of reporting biases

For the primary outcomes, when at least 10 RCTs were available, publication bias was assessed using the funnel plot proposed by Egger et al [16] A $P < .05$ implicates publication bias.

2.9 | Data synthesis (statistical methods)

The data were analysed using Review Manager (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In cases when the standard deviations were not presented, efforts were made to obtain missing data from the authors of the original studies. As only some of the authors responded, in case of failure, missing data were estimated from standard errors, confidence intervals or p-values using the calculator function in the RevMan software. The same RevMan calculator was used in the case of trials with more than one experimental arm which could have been combined into one arm.

2.10 | Subgroup analyses

For the primary outcomes, subgroup analyses based on factors that could potentially influence the magnitude of the treatment response were planned for the following: (a) Dose of *S boulardii*; (b) Countries by the Human Development Index status [Very High/High vs Medium/Low]); (c) Setting (out-patient *vs* in-patient); (d) Strain designation (*S boulardii* CNCM I-745 [also known as *S cerevisiae* Hansen CBS 5926][9] *vs* any other strains). The rationale for the latter was based on the position of the European Food Safety Authority (EFSA) which, at least on one occasion, concluded that there was no sufficient evidence that *S boulardii* CNCM I-745 (*S cerevisiae* Hansen CBS 5926) strain was identical with another *S boulardii* strain (ie *S cerevisiae* var. *boulardii* CNCM I-3799).[17] Additionally, at least one study[18] demonstrated that the differences in the in vitro properties of probiotics may depend on the product source (matrix) and production processes and conditions. Whether or not these manufacturing differences translate into the differences in vivo and into clinical outcomes is a matter of discussion; however, manufacturing standards may be relevant.

In case of significant statistically significant heterogeneity in the primary outcome across studies, additional analyses were performed to determine the impact of allocation concealment (adequate *vs* inadequate and/or unclear), blinding (open trial *vs* double-blind trials) and completeness of outcome data.

We also planned an analysis based on the duration of diarrhoea to assess whether the findings were affected by including only trials at low risk of bias (defined as those with adequate randomisation, allocation concealment, blinding and at least 80% follow-up). However, only one RCT fulfilled these criteria.

3 | RESULTS

For a flow diagram documenting the identification process for eligible trials, see Figure S1. Detailed characteristics of the included RCTs are presented in Table S2, and characteristics of the excluded trials are presented in Table S3.

Ultimately, 29 RCTs that randomised 4217 participants (2152 in the experimental group and 2065 in the control group) were included.[19-47] Among the included trials, there were 20 RCTs identified since our previous systematic review. In addition, one registered trial was identified as still recruiting at the time of the writing of this manuscript (ClinicalTrials.gov Identifier NCT03684538).

The age of the participants in the included trials ranged from 1 month to 15 years. However, the majority, ie 21 trials, enrolled children aged 60 months or less. The sample size in all included trials ranged from 27 to 420 participants. The power calculation was performed in 11 trials only. Included trials were carried out in countries such as Argentina (1 trial), Bolivia (1 trial), Brazil (1 trial), Burma (1 trial), India (8 trials), Indonesia/India (1 trial), Iran (1 trial), Italy (1 trial), Mexico (1 trial), Pakistan (6 trials) and Turkey (7 trials). The included studies were mostly single-centre trials. Twenty-eight trials reported study setting, of which 21 RCTs were carried out in in-patients only; 5, in out-patients only; and 2, in in- and out-patients. One RCT reported data on a small subset of patients treated in the emergency department. The latter group was not predefined by us, and it was reported separately due to the differences in health care organisations between the countries.

The most commonly administered daily dose of *S boulardii* was 500 mg (18 RCTs). However, the daily doses ranged from <300 mg (6 RCTs) to 400 mg (1 RCT) to 600 mg (1 RCT) to 4000 mg (1 RCT). In two trials, the doses were mixed or unknown. The duration of the intervention typically lasted 5 days (20 trials); however, occasionally, it lasted 3 days (1 trial), 6 days (3 trials), 7 days (2 trials), 10 days (1 trial) or was unspecified (2 trials).

The comparator treatment was placebo in 11 trials and no *S boulardii* (oral rehydration solution or no intervention) in the remaining trials. In all studies, *S boulardii* was used in addition to rehydration therapy consisting of an oral rehydration solution and/or intravenous rehydration.

3.1 | Risk of bias in included studies

Most trials were at risk of bias for at least one of the domains (see Figure S2). Only 11 (38%) of trials adequately generated their randomisation sequence, only 5 (17%) adequately concealed allocation and only 1 trial blinded all involved parties (ie participants, study personnel and outcome assessors). However, most of the trials [24 (83%)] provided complete outcome data defined as at least 80% follow-up. Only one trial was considered to be at low risk of bias with regard to adequate randomisation, allocation concealment, blinding and follow-up.[26]

GRADE analysis for selected outcomes is presented in Table S4.

3.2 | Heterogeneity and publication bias

Significant heterogeneity (I^2 = 90%) was found for the duration of diarrhoea (the only primary outcome which was assessed). There was also evidence of publication bias for this outcome (P = .0008) (Figure S3).

3.3 | Effects

A summary of all of the results is presented in Table 1.

3.3.1 | Stool volume

None of the included trials assessed the effect of *S boulardii* on stool volume.

3.3.2 | Duration of diarrhoea

A meta-analysis of 23 RCTs (3450 participants) showed a reduction in the duration of diarrhoea for those treated with *S boulardii* compared with placebo or no treatment (MD −1.06 days [−1.32, −0.79]; high heterogeneity [I^2 = 90%]; very low quality of evidence) (Figure 1 and Table S4).

As intended, a number of pre-planned subgroup analyses related to the primary outcome were performed.

- *Dose. S boulardii* was effective when used at a daily dose <300 mg/d (5 RCTs, n = 873, MD −0.84 d [−1.50 to −0.18]; high heterogeneity [I^2 = 91%]); or 500 mg/d (15 RCTs, n = 2248, MD −0.86 d [−1.05 to −0.66]; I^2 = 58%); or >500 mg/d (1 RCT, n = 41, MD −2.76 d [−3.69 to −1.83]). In two remaining trials (n = 288), the dose was unclear (MD − 2.15 d [−3.26 to −1.05]; I^2 = 72%) (Figure S4**).** The test for subgroup differences suggests that there is a significant difference (P = .0002), meaning that dose does modify the treatment effect. However, when the only RCT evaluating a daily dose of 4000 mg with a small number of participants (n = 41) was excluded, subgroup differences were not detected (P = .96).
- *Countries by the Human Development Index status. S boulardii* was effective when used in very high/high Human Development Index countries (8 RCTs, n = 1347, MD −0.96 [−1.40, −0.52]; high heterogeneity [I^2 = 90%]) and in medium/low Human Development Index countries (15 RCTs, n = 2076, MD −1.12 [−1.49, −0.76]; high heterogeneity [I^2 = 87%]) (Figure S5). The test for subgroup differences suggests that there is no significant difference (P = .57).
- *In-patients/out-patients.* There was reduction in the duration of diarrhoea in studies carried out in in-patients (18 RCTs, n = 2697, MD −1.19 d [−1.52, −0.85]; high heterogeneity [I^2 = 87%]) and in out-patients (6 RCTs, n = 702, MD −0.79 d [−1.20, −0.37]; high heterogeneity [I^2 = 84%]), as well as in those treated in the emergency department (1 RCT, n = 51, MD −0.75 d [−1.26, −0.24]) (Figure S6). The test for subgroup differences suggests that there is no significant difference (P = .21). However, a smaller number of trials and participants contributed to the out-patient group than to the in-patient group, indicating that the analysis may not be able to detect subgroup differences.
- *Strain designation.* 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 diarrhoea was reduced (MD −0.99 d [−1.27, −0.70], I^2 = 85% *vs* −1.12 d [−1.68, −0.57], I^2 = 91%, respectively). The test for subgroup differences suggests that there is no significant difference (P = .66) (Figure S7).

TABLE 1 Overview of the results

Outcome or subgroup	RCT (n)	Participants (n)	Statistical method, random effect model	Effect estimate (95% CI)	Heterogeneity, I^2 (%)
Stool output	—	—	—	—	—
Duration of diarrhoea (days)	23	3450	MD	−1.06 [−1.32, −0.79]	90%
Dose of *S boulardii*					
<300 mg	5	873	MD	−0.84 [−1.50, −0.18]	91%
500 mg	15	2248	MD	−0.86 [−1.05, −0.66]	58%
>500 mg	1	41	MD	−2.76 [−3.69, −1.83]	N/A
Unknown	2	288	MD	−2.15 [−3.26, −1.05]	72%
Countries by the HDI status (Very High/High- vs Medium/Low HDI)					
Very High/High HDI	8	1374	MD	−0.96 [−1.40, −0.52	90%
Medium/Low HDI	15	2076	MD	−1.12 [−1.49, −0.76]	87%
Setting					
In-patients	18	2697	MD	−1.19 [−1.52, −0.85]	87%
Out-patients	6	702	MD	−0.79 [−1.20, −0.37]	84%
Emergency department	1	51	MD	−0.75 [−1.26, −0.24]	N/A
Strain designation					
S boulardii CNCM I-745	13	1599	MD	−0.99 [−1.27, −0.70]	85%
Not specified	10	1851	MD	−1.12 [−1.68, −0.57]	91%
Duration of rotavirus diarrhoea	4	389	MD	−1.07 [−1.79, −0.34]	85%
Duration of hospital stay (days)	8	999	MD	−0.85 [−1.35, −0.34]	91%
Presence of diarrhoea on specific days					
On day 1	3	513	RR	1.00 [0.97, 1.03]	0%
On day 2	2	463	RR	0.75 [0.67, 0.84]	0%
On day 3	6	849	RR	0.61 [0.51, 0.74]	30%
On day 4	3	551	RR	0.61 [0.40, 0.93]	47%
On day 5	5	693	RR	0.32 [0.17, 0.62]	34%
On day 6	1	100	RR	0.48 [0.24, 0.96]	N/A
On day 7	1	88	RR	0.39 [0.20, 0.75]	N/A
>7 days	3	346	RR	0.25 [0.10, 0.63]	0%
Number of days with vomiting	6	792	MD	−0.42 [−0.72, −0.12]	95%
Frequency of stools					
Day 1	8	919	MD	−0.09 [−0.47, 0.28]	82%
Day 2	7	797	MD	−0.71 [−1.46, 0.05]	95%
Day 3	9	950	MD	−1.30 [−2.16, −0.44]	97%
Day 4	7	798	MD	−1.35 [−2.33, −0.38]	99%
Day 5	4	553	MD	−0.85 [−2.51, 0.82]	99%
Day 6	3	384	MD	−0.05 [−0.30, 0.19]	85%
Day 7	2	271	MD	−0.42 [−1.30, 0.46]	93%

Abbreviations: HDI, Human Development Index; RCT, randomised controlled trial; 95% CI, 95% confidence interval; MD, mean difference; RR, relative risk; N/A, Not applicable.

- *Aetiology*. Only four RCTs included children with a priori diagnosed rotavirus acute gastroenteritis. Compared with the control group, *S boulardii* reduced the duration of diarrhoea (4 RCTs, n = 389, MD −1.07 d [−1.79, −0.34]; high heterogeneity [I^2 = 85%]) (Figure S8).

Additionally, pre-planned subgroup analyses based on trial methodological quality were performed. Statistically significant between-study heterogeneity persisted in subgroup analyses, suggesting that the differences in outcomes between studies were caused by factors other than differences in methodological quality (see Figures S9-S13).

3.3.3 | Duration of hospitalisation

A meta-analysis of eight RCTs (n = 999) showed a reduction in the duration of hospitalisation for those treated with *S boulardii* compared with the control group (MD −0.85 d [−1.35 to −0.34]; high heterogeneity [I^2 = 91%]; very low quality of evidence) (Figure 2 and Table S4).

3.3.4 | Presence of diarrhoea

Limited data showed that compared with placebo, *S boulardii* did not reduce the risk of diarrhoea on day 1 (3 RCTs, n = 513, RR 1.00 [0.97, 1.03]). However, *S boulardii* reduced the risk of diarrhoea on day 2 (2 RCTs, n = 463, RR 0.75 [0.67, 0.84]), on day 3 (6 RCTs, n = 849, RR 0.61 [0.51, 0.74]), on day 4 (3 RCTs, n = 551, RR 0.61 [0.40, 0.93]) and on day 5 (5 RCTs, n = 693, RR 0.32 [0.17, 0.62]). Three RCTs (n = 346) reported reduced risk of diarrhoea lasting >7 days (RR 0.25 [0.10, 0.63]). For all days, low quality of evidence (Figure 3 and Table S4).

3.3.5 | Stool frequency

Stool frequency was often reported in the included RCTs. A meta-analysis of the studies reporting stool frequency did show a reduction in the frequency of stools for those treated with *S boulardii* compared with controls at all time intervals; however, it was statistically significant at day 3 and day 4 (Figure S14).

3.3.6 | Vomiting

Six RCTs (n = 792) provided data on vomiting. A meta-analysis of these studies showed a reduction in the number of days with vomiting for those treated with *S boulardii* compared with controls (MD −0.42 d [−0.72, −0.12]; high heterogeneity [I^2 = 95%]) (Figure S15).

3.3.7 | Low risk of bias studies

Only one RCT (Correa et al[26]) was considered to be at low risk of bias with regard to adequate randomisation, allocation concealment, blinding and follow-up. This RCT conducted in Brazil assessed 186 children aged 6-48 months with acute gastroenteritis (mainly caused by rotavirus). The primary outcome was clinical cure of the diarrhoea. Compared with placebo, the addition of *S boulardii* (at a daily dose of 400 mg given within 72 hours after the onset of acute diarrhoea) reduced the frequency of diarrhoea at day 3 after the start of the intervention (29/95 *vs* 51/91; RR 0.54 [0.38; 0.66]), including in a subgroup of rotavirus-positive patients (14/48 *vs* 29/45; RR 0.45 [0.28; 0.74]).

3.3.8 | Adverse events

Data regarding therapy-related adverse events were collected in nine studies.[22,26-29,31,39-41] In eight of these trials, adverse events were not observed, and in one trial, a single patient in the *S boulardii*

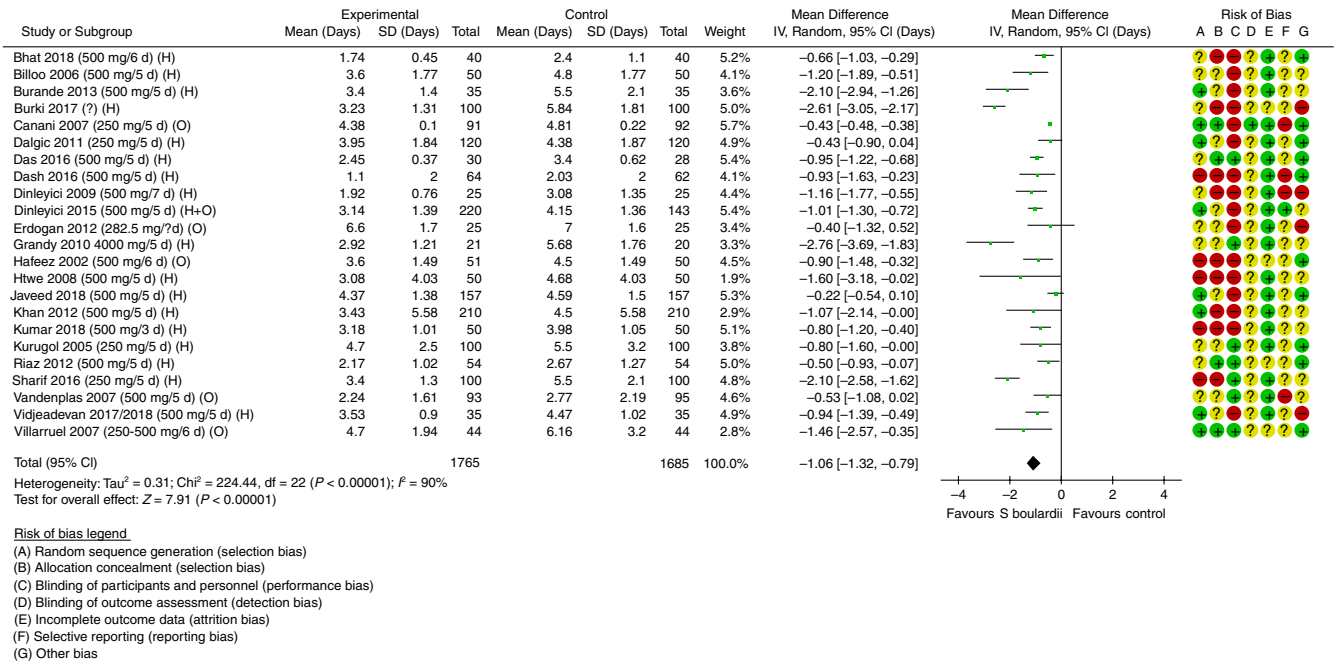

FIGURE 1 Forest plot of randomised controlled trials of *S boulardii* vs control in acute gastroenteritis. Effect on duration of diarrhoea (days)

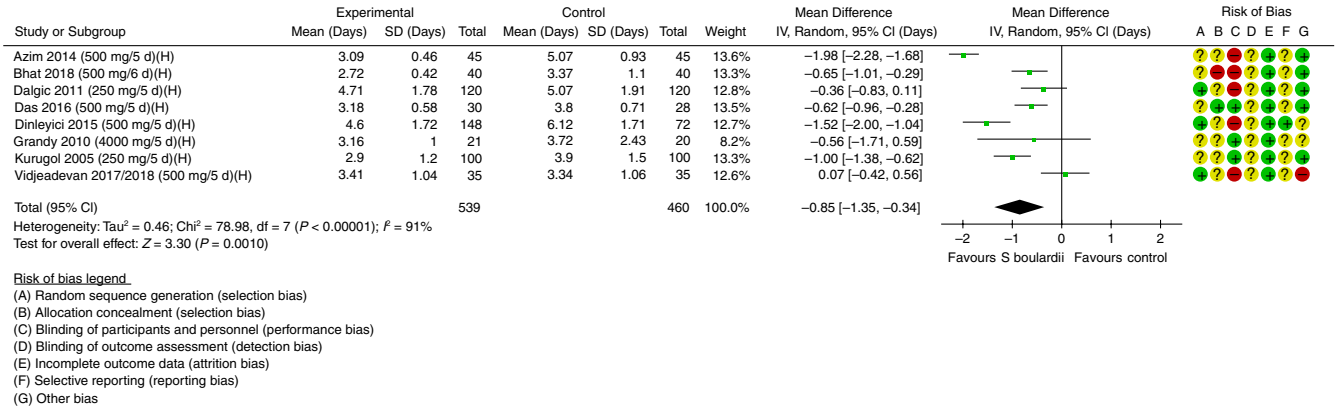

FIGURE 2 Forest plot of randomised controlled trials of *S boulardii* vs control in acute gastroenteritis. Effect on duration of hospitalisation (days)

group reported a meteorism.[39] In the remaining 20 trials, data on adverse events were not collected.

4 | DISCUSSION

4.1 | Principle findings

This systematic review identified 29 trials that randomised more than 4200 children with acute gastroenteritis. While the number of RCTs and participants is impressive, the quality of evidence supporting key findings was low to very low. Less than a half of the trials adequately generated their randomisation sequence, only a minority adequately concealed allocation, and only one of the trials blinded all the parties involved, ie, participants, study personnel and outcome assessors. Just one included trial was considered to be at low risk of bias. This study confirmed the efficacy of *S boulardii* (retrospectively identified as *S boulardii* CMCM I-745) in reducing the duration of diarrhoea if administered within 72 hours after the onset of the disease.

Overall, the addition of *S boulardii* to standard rehydration therapy compared with placebo or no treatment was associated with a reduced duration of diarrhoea by approximately 24 hours. While the effect was evident regardless of *S boulardii* dose, the most commonly used daily dose of at least 500 mg provided more benefit than a dose of <300 mg. *S boulardii* was effective when used in both very high/high and medium/low Human Development Index countries. However, there is more evidence from medium- to low-Human Development Index countries. Considering that strain specificity matters, and that a probiotic product used in clinical trials should specify the genus, species and strain designation, we assessed separately *S boulardii* CNCM I-745 (historically, this was the first *S boulardii* strain available) compared with other *S boulardii* strains. As data on the strain specification were not always available, attempts were made to identify the strain through contacting the author or the manufacturer. Regardless of the strain specification, the effect of *S boulardii* on the duration of diarrhoea was similar.

Stool volume was another primary outcome measure for this review. However, none of the trials evaluated the effect of *S boulardii* on stool volume. Such quantitative objective assessment of therapeutic agents in the management of acute gastroenteritis would be highly desirable, although it is challenging in clinical practice, hence, rarely assessed.

Only some of the studies evaluated the effect of *S boulardii* administration on the presence of diarrhoea. However, generally, *S boulardii* reduced the risk of diarrhoea with the highest effect on days 2, 3 and 4. For example, on day 3, the number needed to treat (NNT) was 4, which is clinically relevant. There was also reduced risk of diarrhoea lasting more than 7 days in the *S boulardii* group (NNT 12). Stool frequency was generally reduced; however, it was statistically and clinically important on day 3 and day 4 only. This is not surprising, as it corresponds with the usual time course of acute gastroenteritis.

Only 1/3 of the included trials collected data on adverse events. In these studies, adverse events were similar in both study groups.

4.1.1 | Limitations

While the methodology of this systematic review was robust, the findings are primarily limited by the available studies. The overall quality of studies was low to very low, largely due to missing information regarding randomisation procedures, allocation concealment and blinding, all of which affect internal validity. Unexplainable heterogeneity between individual trials is another important limitation. A number of subgroup analyses were conducted to investigate whether factors such as dose, country's Human Development Index, setting or aetiology modify the treatment effect. Overall, while some of the analyses revealed a significant subgroup effect,[48] high heterogeneity between findings within each group and/or the small number of trials and participants contributing to each subgroup resulted in uncertainty as to whether these subgroup differences matter.

Finally, the definition of acute gastroenteritis/diarrhoea and the inclusion criteria varied among included trials. Similarly, the outcomes (and their definitions) varied among included trials. Most of included

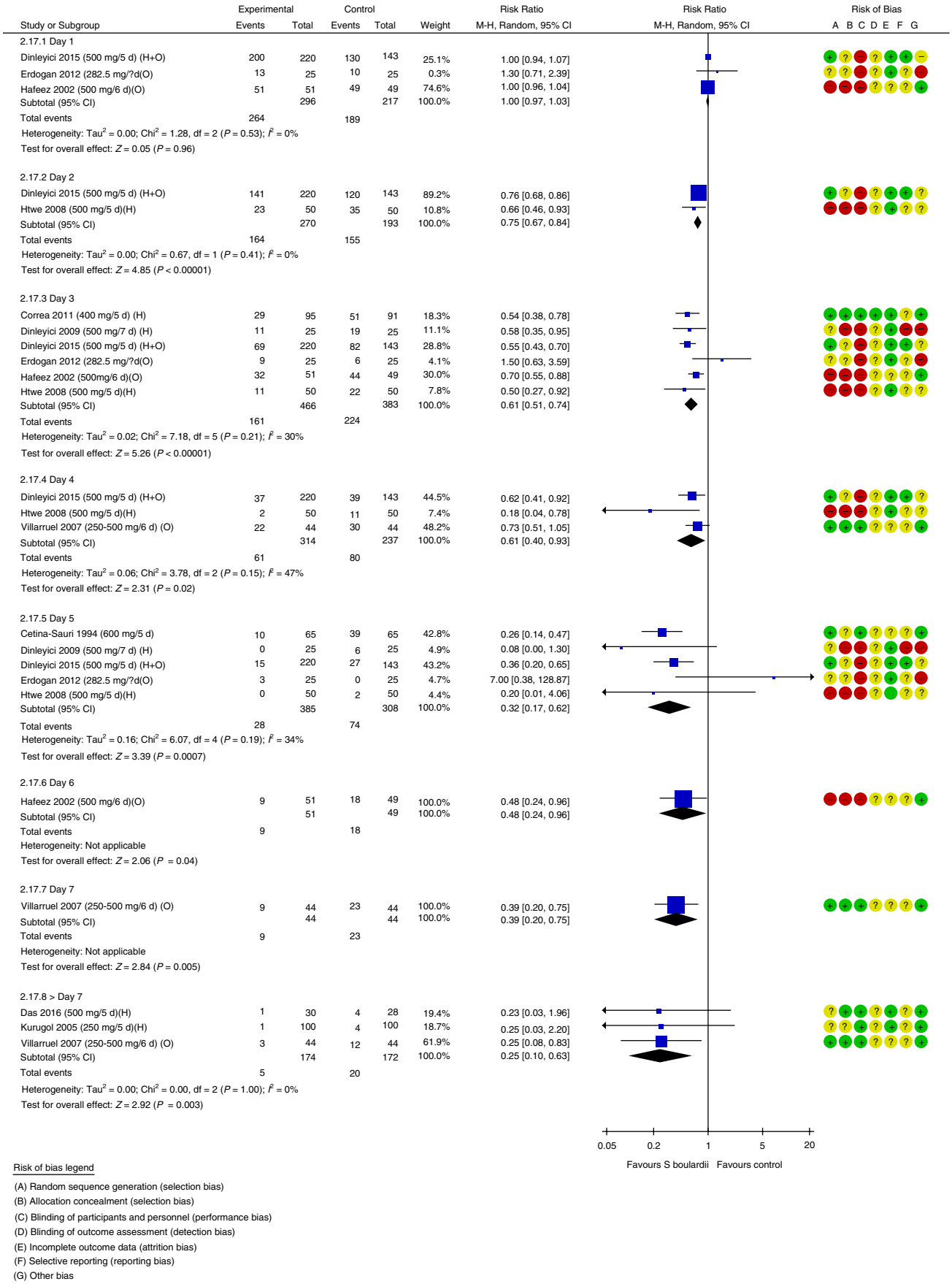

FIGURE 3 Forest plot of randomised controlled trials of *S boulardii* vs control in acute gastroenteritis. Presence of diarrhoea on any specific day of the intervention

trials involved children treated as in-patients. When interpreting the results, one should consider that the characteristics of the included patients and the severity of disease may differ between countries and settings. The criteria for hospital discharge, which are important when the duration of hospitalisation is assessed, were not reported in the included studies, and they are likely to differ between centres. Some outcomes were evaluated in only a subset of trials with a limited number of participants; thus, the findings, whether positive or negative, might be (non)significant by chance only.

4.1.2 | Agreements and disagreements with other studies or reviews

The findings are in line with the results of previously published meta-analyses evaluating the effects of *S boulardii* for the management of acute gastroenteritis.[49-51] These meta-analyses differed concerning the search dates and inclusion/exclusion criteria. However, similar to our original meta-analyses,[10,11] they consistently reported that compared with the placebo or no intervention groups, the use of *S boulardii* significantly reduced the duration of diarrhoea (11 RCTs, n = 1306, MD −0.99 d [−1.40 to −0.58]; high heterogeneity, I^2 = 83%; 17 RCTs, n = 2102, MD −0.82 d [−1.1 to −0.56], high heterogeneity, I^2 = 64.5%; and 5 RCTs, n = 548, MD −0.57 d [−0.83 to −0.3], no heterogeneity, I^2 = 0%, respectively). Compared with any previously published reviews, the current review included more trials involving more patients. Thus, the current meta-analysis more precisely defines the role of *S boulardii* in the management of acute gastroenteritis.

In our review, we focused on the administration of *S boulardii* alone. However, a 2018 network meta-analysis by Florez et al[52] concluded that the administration of *S boulardii* with zinc was one of the best-ranked interventions. Oral zinc administration is recommended in countries where zinc deficiency is common and/or in populations who have signs of malnutrition.[1-3]

The timing of the initiation of probiotic administration is likely to contribute to the overall effect. At least this has been documented with regard to *L rhamnosus* GG, which was more effective when used in children enrolled with diarrhoea lasting ≤5 days than when used in children with diarrhoea lasting >7 days.[12] For the purposes of this review, we performed a *post hoc* analysis based on the duration of diarrhoea prior to randomisation (≤72 h vs >72 h (or not specified). This *post hoc* analysis found that *S boulardii* was effective when used in children enrolled with diarrhoea lasting ≤72 h (6 RCTs, n = 854, MD −0.77 d [−1.12, −0.42]) and when used in children with diarrhoea lasting >72 h (or not specified) (17 RCTs, n = 2596, MD −1.17 d [−1.52, −0.81]. Further studies are needed to assess the effect of the timing of the initiation of *S boulardii* administration.

Our review did not indicate any safety issues with the use of *S boulardii*. While rare adverse events are unlikely to be observed in RCTs, in the literature, they have been reported as case reports. With regard to *S boulardii*, the European Medicines Agency (EMA)[53] recently warned about potential risk of fungaemia caused by *S boulardii* in seriously ill or immunocompromised patients [‘*There have been very rare cases of fungaemia (and blood cultures positive for Saccharomyces strains) reported mostly in patients with central venous catheter, critically ill or immunocompromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by Saccharomyces boulardii, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients.*’]. The summary of product characteristics and the package leaflet for medicinal products containing *S boulardii* have been updated by the EMA to include a new warning and contraindication [‘*Due to a risk of airborne contamination, sachets or capsules should not be opened in patient rooms. Healthcare providers should wear gloves during handling of probiotics for administration, then promptly discard the gloves and properly wash their hands*’].

5 | CONCLUSIONS AND FUTURE RESEARCH

This review builds on our previous systematic review and meta-analysis through the inclusion of new RCTs. It focuses on a single probiotic only; thus, it provides an answer to the question as to whether current evidence on *S boulardii* should change clinical practice. Based on very low quality evidence, *S boulardii* reduced the durations of diarrhoea and hospitalisation of in-patients. The small effect sizes of limited clinical relevance and methodological limitations of the included trials should be noted when interpreting these findings. Cost-effectiveness analyses are needed. The findings are most applicable to the populations studied. Considering safety issues, the decision whether or not to use *S boulardii* should take into account individual patient characteristics (eg presence of the critical illness, immunocompetence) and individual values and preferences (eg effect size with regard to shortening duration of diarrhoea or hospitalisation). High-quality RCTs are still needed, particularly in geographical locations where data are limited (eg European countries) with known rotavirus vaccination status. The findings of this review may inform guideline development groups about the efficacy of *S boulardii* for treating children with acute gastroenteritis.

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AUTHORSHIP

Guarantor of the article: Hania Szajewska.

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REFERENCES

1. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious diseases society of america clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65:e45-e80.
2. 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;67:586-593.
3. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J Pediatr Gastroenterol Nutr*. 2014;59:132-152.
4. Szajewska H, Kolodziej M. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther*. 2015;42:1149-1157.
5. 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;58:531-539.
6. Schnadower D, Tarr PI, Casper TC, et al. *Lactobacillus rhamnosus* GG versus placebo for acute gastroenteritis in children. *N Engl J Med*. 2018;379:2002-2014.
7. Freedman SB, Williamson-Urquhart S, Farion KJ, et al. Multicenter trial of a combination probiotic for children with gastroenteritis. *N Engl J Med*. 2018;379:2015-2026.
8. 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-e242.
9. McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World J Gastroenterol*. 2010;16:2202-2222.
10. Szajewska H, Skorka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children. *Aliment Pharmacol Ther*. 2007;25:257-264.
11. Szajewska H, Skórka A *Saccharomyces boulardii* for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials. *Aliment Pharmacol Ther*. 2009;30:960-961.
12. Szajewska H, Kolodziej M, Gieruszczak-Bialek D, Skorka A, Ruszczynski M, Shamir R. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG for treating acute gastroenteritis in children – a 2019 update. *Aliment Pharmacol Ther*. 2019;49:1376-1384.
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available at: www.training.cochrane.org/handbook. Accessed on 10 December 2019.
14. Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. *Epidemiology*. 2011;22:128-128.
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)*. 1997;315:629-634.
17. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the substantiation of a health claim related to *Saccharomyces cerevisiae var. boulardii* CNCM I-3799 and reducing gastrointestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006. *EFSA Journal*. 2012;10:2801.
18. Grześkowiak Ł, Isolauri E, Salminen S, Gueimonde M. Manufacturing process influences properties of probiotic bacteria. *Brit J Nutr*. 2011;105:887-894.
19. Azim K, Sheikh TS, Khan SN. Efficacy of probiotics (*Sacchromyces bulardii*) in acute watery diarrhoea in children. *JRMC*; 2014;18:213-215.
20. Bhat S, Shreekrishna GN, Savio CD. Efficacy of probiotics in acute diarrhoea in children. *Int J Contemp Pediatr*. 2018;5:5.
21. Billoo AG, Memon MA, Khaskheli SA, et al. Role of a probiotic (*Saccharomyces boulardii*) in management and prevention of diarrhoea. *World J Gastroenterol*. 2006;12:4557-4560.
22. Burande MA. Comparison of efficacy of *Saccharomyces boulardii* strain in the treatment of acute diarrhea in children: a prospective, single-blind, randomized controlled clinical trial. *J Pharmacol Pharmacother*. 2013;4:205-208.
23. Burki MFK, Jabeen F. Efficacy of *Saccharomyces boullardii* in children with acute diarrhea. *Medical Forum Monthly*. 2017;28:112-116.
24. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ*. 2007;335:340.
25. Cetina-Sauri G, Sierra Basto G. Evaluation of *Saccharomyces boulardii* for the treatment of acute diarrhea in pediatric patients. [French]. *Ann Pediatr*. 1994;41:397-400.
26. Correa NB, Penna FJ, Lima FM, Nicoli JR, Filho LA. Treatment of acute diarrhea with *Saccharomyces boulardii* in infants. *J Pediatr Gastroenterol Nutr*. 2011;53:497-501.
27. Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose-free formula in children with rotavirus diarrhea: are they effective? *Pediatr Int*. 2011;53:677-682.
28. Das S, Gupta PK, Das RR. Efficacy and safety of *Saccharomyces boulardii* in acute rotavirus diarrhea: double blind randomized controlled trial from a developing country. *J Trop Pediatr*. 2016;62:464-470.
29. Dash DK, Dash M, Mohanty MD, Acharya N. Efficacy of probiotic *Saccharomyces boulardii* as an adjuvant therapy in acute childhood diarrhoea. *J Nepal Paediatr Soc*. 2016;36:250-255.
30. Dinleyici EC, Eren M, Yargic ZA, Dogan N, Vandenplas Y. Clinical efficacy of *Saccharomyces boulardii* and metronidazole compared to metronidazole alone in children with acute bloody diarrhea caused by amebiasis: a prospective, randomized, open label study. *Am J Trop Med Hyg*. 2009;80:953-955.
31. Dinleyici EC, Kara A, Dalgic N, et al. Saccharomyces boulardii CNCM I-745 reduces the duration of diarrhoea, length of emergency care and hospital stay in children with acute diarrhoea. *Benef Microbes*. 2015;6:415-421.
32. Erdoğan Ö, Tanyeri B, Torun E, et al. The comparition of the efficacy of two different probiotics in rotavirus gastroenteritis in children. *J Trop Med*. 2012;2012:1-5.
33. Grandy G, Medina M, Soria R, Teran CG, Araya M. 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
34. Hafeez A, Tariq P, Ali S, Kundi ZU, Khan A, Hassan M. The efficacy of Saccharomyces boulardii in the treatment of acute watery diarrhea in children: a multicentre randomized controlled trial. *J Coll Physicians Surg Pak*. 2002;12:432-434.
35. Htwe K, Khin SY, Tin M, Vandenplas Y. Effect of *Saccharomyces boulardii* in the treatment of acute watery diarrhea in Myanmar children: a randomized controlled study. *Am J Trop Med Hyg*. 2008;78:214-216.
36. Javeed A, Manzoor S, Wamiq S. Effect of oral *Saccharomyces boulardii* supplementation on the duration of acute watery diarrhea in children. *Pak J Med Health Sci*. 2018;12:212-214.
37. Khan A, Javed T, Chishti AL. Clinical efficacy of use of probiotic "*Saccharomyces boulardii*" In children with acute watery diarrhea. *Pak Paed J*. 2012;36:122-127.

38. Kumar A, Kumar D, Rajkumar D. To study the role of *Saccharomyces boulardii* in treatment of acute watery diarrhea in children aged 6 months to 5 years: prospective randomized control study. *J Dent Med Sci*. 2018;17:35-40.
39. Kurugol Z, Koturoglu G. Effects of *Saccharomyces boulardii* in children with acute diarrhoea. *Acta Paediatr*. 2005;94:44-47.
40. Ozkan TB, Sahin E, Erdemir G, Budak F. Effect of *Saccharomyces boulardii* in children with acute gastroenteritis and its relationship to the immune response. *J Int Med Res*. 2007;35:201-212.
41. Riaz M, Alam S, Malik A, Ali SM. Efficacy and safety of *Saccharomyces boulardii* in acute childhood diarrhea: a double blind randomised controlled trial. *Indian J Pediatr*. 2012;79:478-482.
42. Savas-Erdeve S, Gokay S, Dallar Y. Efficacy and safety of *Saccharomyces boulardii* in amebiasis-associated diarrhea in children. *Turk J Pediatr*. 2009;51:220-224.
43. Sharif MR, Kashani HH, Ardakani AT, Kheirkhah D, Tabatabaei F, Sharif A. The effect of a yeast probiotic on acute diarrhea in children. *Probiotics Antimicrob Proteins*. 2016;8:211-214.
44. Sirsat GM, Sankpal DM. Role of *Saccharomyces boulardii* in management of acute diarrhoea of children - a randomized controlled trial. *MedPulse Int J Pediatr*. 2017;4:68-72.
45. 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. *Int J Contemp Pediatr*. 2018;5:4.
46. Villarruel G, Rubio DM, Lopez F, et al. *Saccharomyces boulardii* in acute childhood diarrhoea: a randomized, placebo-controlled study. *Acta Paediatr*. 2007;96:538-541.
47. Vandenplas S, Badriul H, Thapa B, et al. Multi-centre DBRPC-trial in developing countries with *S boulardii* in acute gastroenteritis. *J Pediatr Gastroenterol Nutr*. 2007;44:e1-e360.
48. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: a tutorial. *Clin Epidemiol Glob Health*. 2019;7:192-198.
49. Dinleyici EC, Kara A, Ozen M, Vandenplas Y *Saccharomyces boulardii* CNCM I-745 in different clinical conditions. *Exp Opin Biol Ther*. 2014;14:1593-1609.
50. Feizizadeh S, Salehi-Abargouei A, Akbari V. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics*. 2014;134:e176-191.
51. Padayachee M, Visser J, Viljoen E, Musekiwa A, Blaauw R. 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.
52. Florez ID, Veroniki A-A, 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.
53. European Medicines Agency. https://www.ema.europa.eu/en/documents/psusa/saccharomyces-boulardii-cmdh-scientific-conclusions-grounds-variation-amendments-product-information/00009284/201702_en.pdf. Accessed 10 December 2019.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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