Full Length Research Paper

A meta analysis of the efficacy of *Saccharomyces boulardii* in children with acute diarrhea

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This study was performed to evaluate the efficacy of *Saccharomyces boulardii* in treating children with acute diarrhoea. Medicinal databases and review articles were screened with prespecified criteria for randomized controlled trials that reported the effects of *S. boulardii* and other antidiarrhoeal drugs in treating children with acute diarrhoea. The quality of the study was critically evaluated. A total of 678 articles were found and 8 articles were finally included. Heterogeneity test: Diarrhoea duration analysis (Qstatistic=33.58, $p<0.0001$, I^2=79%), stool frequency on day 3 analysis (Qstatistic=4.53, p=0.10, I^2 = 56%), stool frequency on day 4 analysis (Qstatistic=0, p=1.00, I^2=0%) and stool frequency on day 7 analysis (Q statistic=0.18, p=0.68, I^2=0%). The results of meta-analysis showed that when compared with the control group, *S. boulardii* was more effective in diarrhoea duration (MD=-0.92, 95% CI: -1.32 to -0.52), stool frequency on day 3 (MD=-1.92, 95% CI: -1.63 to -0.95), day 4 (MD=-0.51, 95% CI: -0.89 to -0.33) and day 7 (MD=-0.44, 95% CI: -0.72 to -0.16), respectively. The evidence currently available shows that *S. boulardii* treatment is used for children with acute diarrhoea.

Key words: *Saccharomyces boulardii*, acute diarrhoea, meta-analysis.

INTRODUCTION

Diarrhoea is defined as a change in bowel movements for an individual subject, characterized by an increase in the water content, volume and usually frequency of stools (WHO, 1995; Riedel and Ghishan, 1996). In the vast majority of cases, acute diarrhoea is the result of a gut infection mostly viral. The mainstay of therapy for acute diarrhoea is oral rehydration (Ilomuanya et al., 2011; Tijani et al., 2009). In recent years, education and the widespread usage of oral rehydration therapy have reduced the number of acute diarrhoea. However, the morbidity rate for diarrhoea still remains high, placing an enormous burden on the healthcare system. *Saccharomyces boulardii* is non-pathogenic probiotic yeast considered to be useful against enteropathogens. Although the exact mechanisms of *S. boulardii* remain unclear, several possible mechanisms have been proposed.

These including inhibition of pathogen adhesion,

strengthening of enterocyte tight junctions, neutralization of bacterial virulence factors and enhancement of the mucosal immune response (Brandao et al., 1998; Buts et al., 1990; Cetina-Sauri and Basto Sierra, 1994; Czerucka and Rampal, 1999; Pothoulakis et al., 1993; Qamar et al., 2001; Rodrigues et al., 1996; Tasteyre et al., 2002; Wilson and Perini, 1998). Though there are several studies (Canani et al., 2001; Sougioultzis et al., 2006; Chapoy, 1985; Saint-Marc et al., 1991) about *S. boulardii* in treating acute childhood diarrhoea, the conclusions of which are not credible because of small sample size and lacks of systemic evaluation of methodologic quality. In our present work, we makes a systemic review about clinical random control trials (RCTs) focused on *S. boulardii* in treating acute childhood diarrhoea in order to obtain the best evidence.

MATERIALS AND METHODS

Search sources and strategy

The search strategy was made according to working handbook

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systematically searched Medline (1991 to November 2011), EMbase (1991 to November 2011), CBMdisc (1991 to November 2011), and CNKI (1994 to November 2011) for randomized trials examining the efficacy of *S. boulardii* in treating acute childhood diarrhoea. In addition, we conducted a manual search of abstracts from selected conferences and we also searched by hand the bibliographies of all relevant trials. The text word terms and mesh headings used were: diarrhea/ diarrhoea, diarrh*, probiotic*, children, child*, *S. boulardii* and *S. boulardii*. Furthermore, the reference lists from the original studies and review articles were identified. The language was limited to English or Chinese.

Study selection

Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full articles. The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (a) study design - RCTs; (b) population - children with acute diarrhoea; (c) intervention: *S. boulardii* versus placebo or no additional intervention; (d) outcome variable: duration of diarrhoea, stool frequency and adverse effects.

Data extraction

From each study, the following information was abstracted: author, year of publication, study design, characteristics of the population, simple size, treatment proposal, time of the therapy, duration of diarrhoea, stool frequency and adverse effects.

Assessment of study quality

Quality of the included studies was assessed based on a well-established, validated scale developed by Jadad et al. (1996). A Jadad score was calculated using the following 7 items: (i) Was the study described as a random trial? (ii) Was the randomization scheme described and appropriate? (iii) Was the study described as double-blind? (iv) Was the method of double blinding appropriate? (Where both the patient and the assessor appropriately blinded?) (v) Was there a description of dropouts and withdrawals? (vi) Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate. (vii) Deduct one point if the study was described as double blind but the method of blinding was inappropriate. The first five items were indications of good quality, and each counted as one point towards an overall quality score. The final two items indicated poor quality, and a point was subtracted for each if its criteria were met. The range of possible scores was 0 to 5 (0 being weakest and 5 being strongest). Any study with a Jadad score < 3/5 was considered to be of poor quality, and was excluded.

Statistical analysis

For dichotomous outcomes, we calculated mean difference (MD) and 95% confidence interval (CI). The MD was defined to represent the difference in continuous outcomes between the treatment and control groups. The MDs of different RCTs were combined by using the random effects model as previous described (Der and Laird, 1986), if true between-study heterogeneity exists or else using Mantel and Haenszel fixed-effects model instead (Mantel and Haenszel, 1959). Intertrial statistical heterogeneity was explored using the Cochran Q test with calculated I^2, indicating the

percentage of the total variability in effect estimates among trials that is, due to heterogeneity rather than to chance (Higgins et al., 2003). I^2 values of 50% or more indicate a substantial level of heterogeneity. All p values were two-sided with statistical significance set at α level of 0.05. We followed the "quality of reporting meta-analysis guidelines" for reporting and discussing these meta-analytical results (Moher et al., 1999). All the statistical analysis was carried out by the Cochrane collaboration's RevMan 5.0 software.

RESULTS

Study characteristics

There were 678 articles relevant to the search term and 8 articles (Billoo et al., 2006; Canani et al., 2007; Hafeez et al., 2001; Htwe et al., 2008; Ji et al., 2009; Kurugol and Koturoglu, 2005; Shen et al., 2008; Villarruel et al., 2007) involving 978 children with acute diarrhoea (group *S. boulardii*: 487 patients, group control: 491 patients) were included in this meta-analysis finally. Ages, weight, sex ratio, duration of diarrhoea and frequency of stools before admission were similar in each group, respectively. The flow chart for the selection of RCTs to be included in our analysis is shown in Figure 1. The characteristics of the included trials were shown in Table 1.

Methodologic quality assessment

All the trials included in this meta-analysis mentioned the term "random", but the detail method was illuminated in 1 article only. There were 7 trials mentioned the term 'double blind', but only 6 articles explained the detail method. All the 8 trials described the data of the patients who withdrew during the treatment. According to the Jadad score, 6 and 2 articles were regarded as high quality literature and low quality literature, respectively (Table 2).

Meta-analysis of diarrhoea duration

Eight papers contained data on the duration of the diarrhoea. A meta-analysis of eight RCTs (participants) showed a reduction in the duration of the diarrhoea (MD: -0.92 day, 95% CI: -1.32 to -0.52) for those treated with *S. boulardii* compared with placebo (Figure 2). The included studies were heterogeneous (Qstatistic=33.58, $P<0.0001$, $I^2=79\%$).

Meta-analysis of stool frequency on different days

Five studies provided a measure of variance at various time intervals. The meta-analyses of these studies showed a reduction in the frequency of stools for those treated with *S. boulardii* compared with the control on day 3 (MD 1.1 day, 95% CI: 1.3 to 0.83), day 4 (MD 1.1 day, 95% CI: 1.3 to 0.83) and day 7 (MD 1.1 day, 95% CI: 1.3
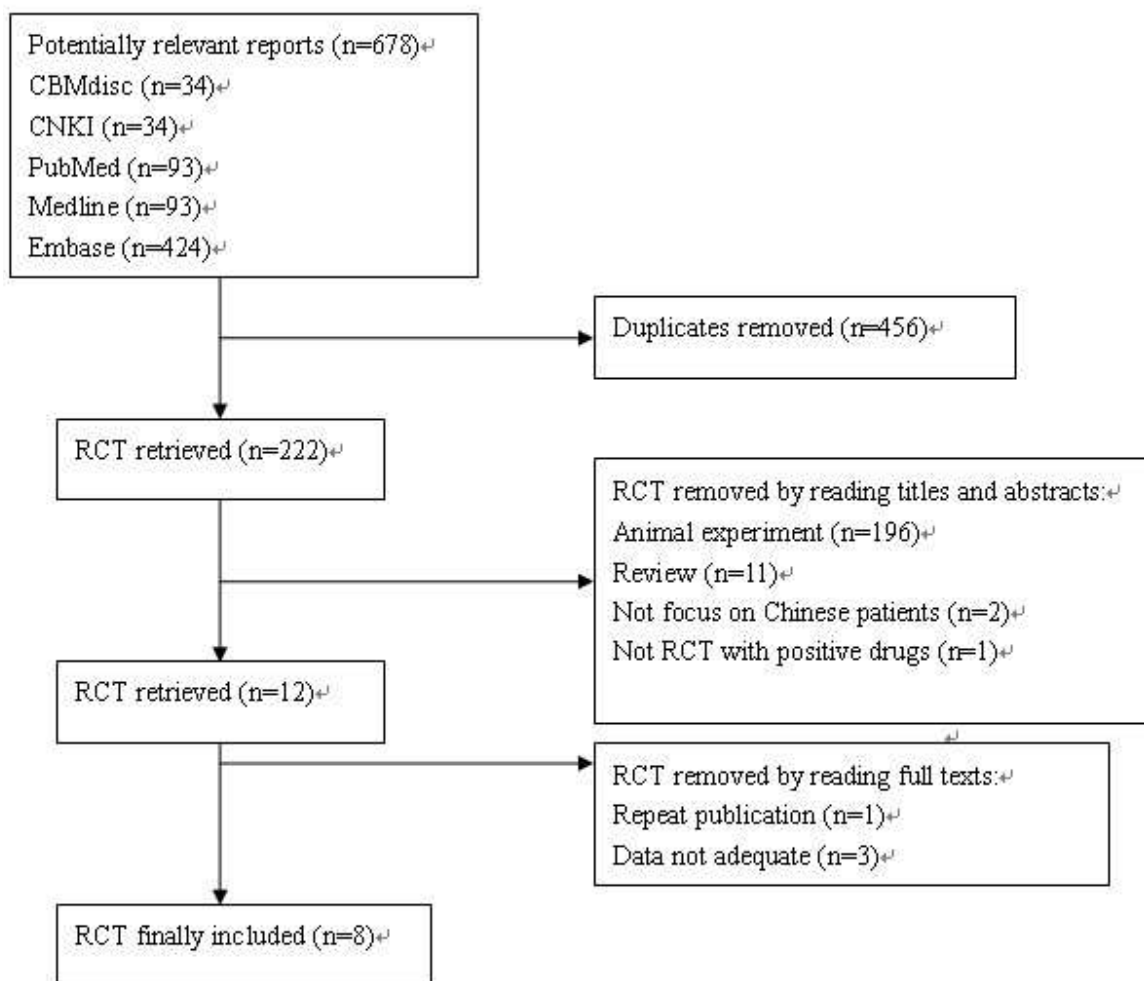
Figure 1. Chat for the search result and trials screen.

to 0.83), respectively (Figures 3, 4 and 5).

Adverse events

Adverse effects associated with *S. boulardii* were not reported in any of the RCTs.

DISCUSSION

A meta-analysis of data from RCTs showed that in otherwise healthy infants and children with acute diarrhoea, the usage of *S. boulardii* compared with control is associated with moderate therapeutic benefit that is reproducible regardless of the outcome measure studied (that is, duration of diarrhoea and number of stools). However, these results should be interpreted with caution as some of them are based on the limited data available. Whereas no adverse effects was observed in

any of the included trials, the administration of *S. boulardii* is not without risk. However, *S. boulardii* should be terminated when in immunocompromised subjects or in patients with other life-threatening illnesses managed in intensive care units. In which case, *S. boulardii* can cause fungaemia (Bassetti et al., 1998; Rijnders et al., 2000; Zunic et al., 1991). A total of eight literatures were finally included in this meta analysis. All these articles, including a sample size of 978 totally were RCTs. Jadad score in 6 out of the eight articles were more than three points.

All the trials included in this meta-analysis mentioned the term "random", but the detail method was illuminated in 1 article only. Obviously, the included trials were lack of well-designed randomizations. A well-designed rando-mized controlled trial requires a thorough understanding of randomization so that better results could be achieved. Randomization includes three important steps, namely sequence generation, allocation concealment and randomization implementation. Sequence generation is

Table 1. Characteristics of the 8 randomized clinical studies included in this meta-analysis.

Author (Country)	Year	Age	Treatment protocol (T/C)	Sample size (T/C)	Dose (per day, mg)	Duration of intervention (days)	Aetiology of diarrhoea
Billoo et al. (Pakistan)	2006	2 months to 12 years	T: *S. boulardii* C: Smecta	T: 50 C: 50	500	5	HRV 18%, bacteria 19%
Canani et al. (Italy)	2007	11 to 28 months	T: *S. boulardii* C: Smecta	T:91 C:92	500	6	No data
Hafeez et al. (Pakistan)	2001	6 months to 6 years	T: *S. boulardii* C: Smecta	T: 51 C: 50	500	6	No data
Htwe et al. (Belgium)	2008	3 months to 10 years	T: *S. boulardii* C: Smecta	T:50 C: 50	500	6	No data
Ji et al. (China)	2009	2 months to 7 years	T: *S. boulardii* C: Smecta	T: 46 C: 46	500	7	No data
Kurugol and Koturoglu (Turkey)	2005	3 months to 7 years	T: *S. boulardii* C: Smecta	T: 100 C: 100	500	5 (follow-up 14)	HRV 42%, bacteria/parasites 10%, unspecified 49%
Shen et al. (China)	2008	1 months to 8 years	T: *S. boulardii* C: Smecta	T: 64 C: 66	<1 year 250; >1 year 500	5	No data
Villarruel et al. (Argentina)	2007	3 to 24 months	T: *S. boulardii* C: Smecta	T: 35 C: 37	<1 year 250; >1 year 500	6	No data

Table 2. Characteristics of the 8 randomized clinical studies included in this meta-analysis.

Author (Country)	Year	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion criteria	Jaded score
Billoo et al. (Pakistan)	2006	No information about method	Unclear	No	Acute diarrhoea mild to moderate severity	4
Canani et al. (Italy)	2007	No information about method	Unclear	Yes	Acute diarrhoea mild to moderate severity	4
Hafeez et al. (Pakistan)	2001	Inadequate (even/odd numbers)	Inadequate	Yes	Acute watery diarrhoea mild to moderate severity	4
Htwe et al. (Belgium)	2008	No information about method	Unclear	Yes	Acute diarrhoea mild to moderate severity	4
Ji et al. (China)	2009	No information about method	Not reported	Yes	Acute diarrhoea mild to moderate severity	3
Kurugol and Koturoglu (Turkey)	2005	No information about method	Not reported	Yes	Acute diarrhoea (liquid or mucous or bloody stools passed at least twice as frequently than usual for a minimum of 24 h before admission but not longer than 7 days)	4

Table 2. Contd.

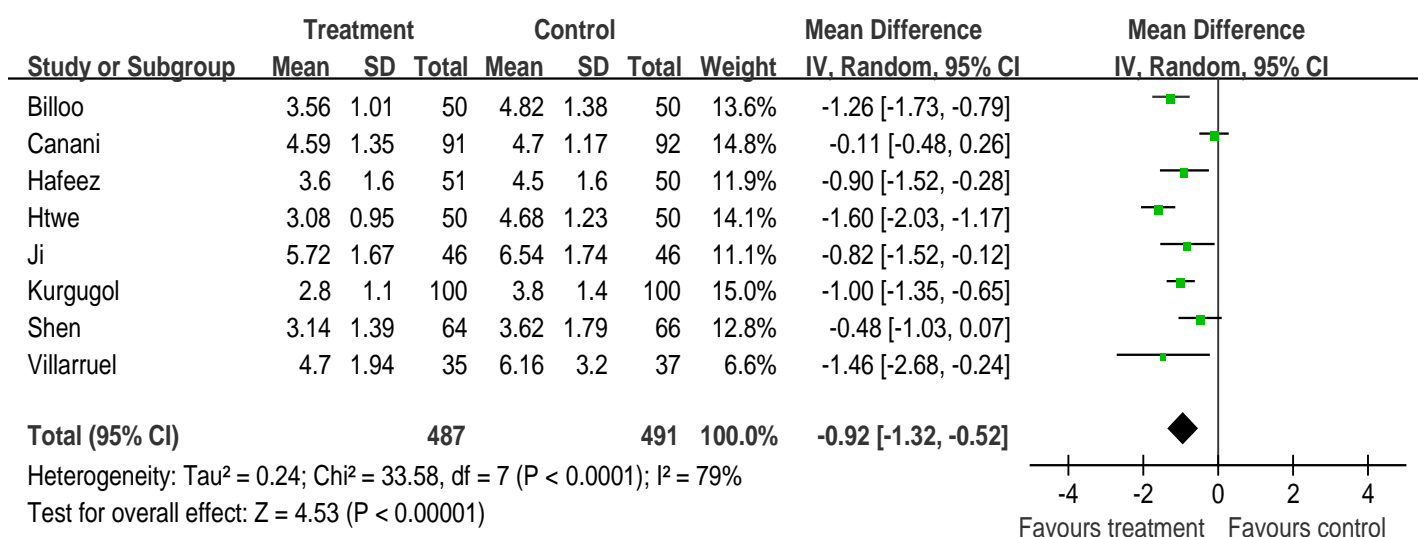|						
Shen et al. (China)	2008	No information about method	Not reported	No	Acute diarrhoea mild to moderate severity	2
Villarruel et al. (Argentina)	2007	Adequate (computer-generated numbers)	Adequate	Yes	Acute mild to moderate diarrhoea ‡3 liquid or loose stools in the last 24, but <7 days duration, out-patients	4

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Billoo	3.56	1.01	50	4.82	1.38	50	13.6%	-1.26 [-1.73, -0.79]	
Canani	4.59	1.35	91	4.7	1.17	92	14.8%	-0.11 [-0.48, 0.26]	
Hafeez	3.6	1.6	51	4.5	1.6	50	11.9%	-0.90 [-1.52, -0.28]	
Htwe	3.08	0.95	50	4.68	1.23	50	14.1%	-1.60 [-2.03, -1.17]	
Ji	5.72	1.67	46	6.54	1.74	46	11.1%	-0.82 [-1.52, -0.12]	
Kurgugol	2.8	1.1	100	3.8	1.4	100	15.0%	-1.00 [-1.35, -0.65]	
Shen	3.14	1.39	64	3.62	1.79	66	12.8%	-0.48 [-1.03, 0.07]	
Villarruel	4.7	1.94	35	6.16	3.2	37	6.6%	-1.46 [-2.68, -0.24]	
Total (95% CI)			**487**			**491**	**100.0%**	**-0.92 [-1.32, -0.52]**	

Heterogeneity: Tau² = 0.24; Chi² = 33.58, df = 7 (P < 0.0001); I² = 79%
Test for overall effect: Z = 4.53 (P < 0.00001)

Figure 2. Diarrhoea duration between the treatment group and the control group.

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Billoo	2.8	0.86	50	4.4	0.92	50	36.8%	-1.60 [-1.95, -1.25]	
Hafeez	2.76	0.85	51	3.96	0.93	50	36.9%	-1.20 [-1.55, -0.85]	
Shen	2.2	1.28	64	3.2	1.59	66	26.4%	-1.00 [-1.50, -0.50]	
Total (95% CI)			**165**			**166**	**100.0%**	**-1.29 [-1.63, -0.95]**	

Heterogeneity: Tau² = 0.05; Chi² = 4.53, df = 2 (P = 0.10); I² = 56%
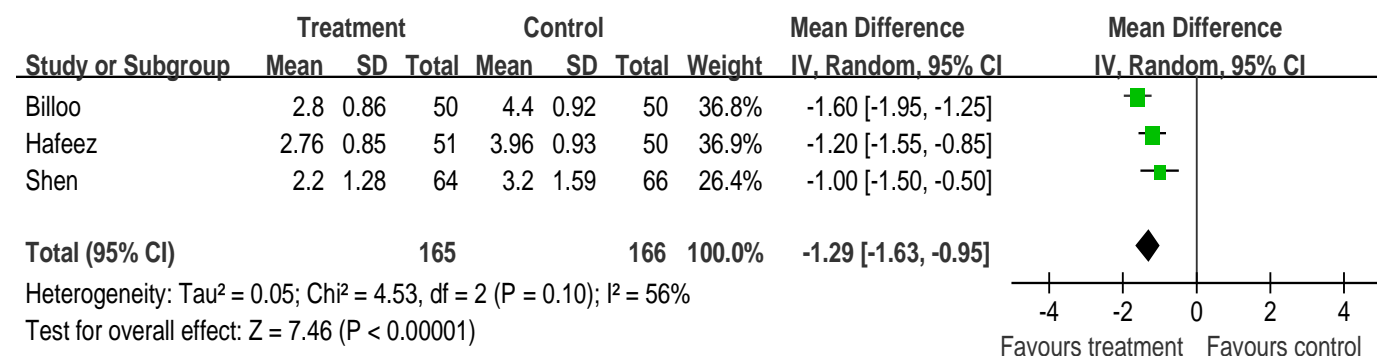Test for overall effect: Z = 7.46 (P < 0.00001)

Figure 3. Stool frequency on day 3 between the treatment group and the control group.

a method used to generate the random allocation sequence, including details of any restriction. Allocation concealment is to implement the random allocation sequence. Randomization implementation is to generate the allocation sequence. Well-men designed randomized controlled trials are required to evaluate *S. boulardii* treatment versus routine treatment in children. It was suggested that we should be careful for the randomization of every meta analysis.

Conclusion

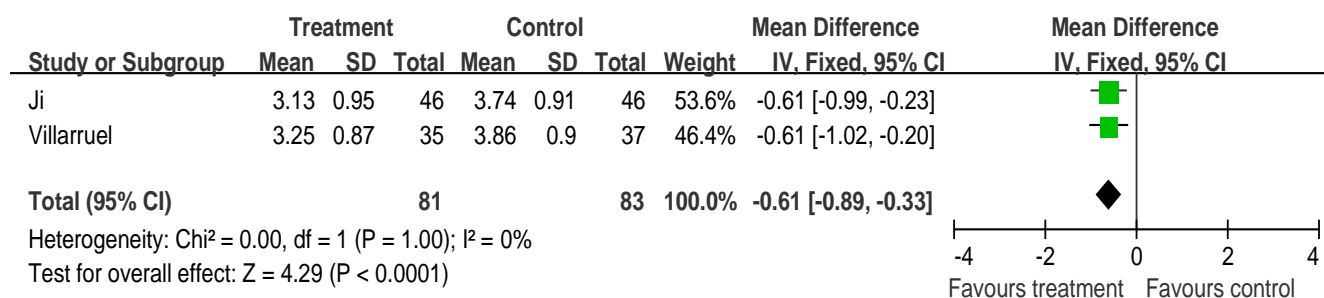In summary, our systemic review initially demonstrated

| Study or Subgroup | Treatment | | | Control | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ji	3.13	0.95	46	3.74	0.91	46	53.6%	-0.61 [-0.99, -0.23]	
Villarruel	3.25	0.87	35	3.86	0.9	37	46.4%	-0.61 [-1.02, -0.20]	
Total (95% CI)			81			83	100.0%	-0.61 [-0.89, -0.33]	

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.29 (P < 0.0001)

Figure 4. Stool frequency on day 4 between the treatment group and the control group.

| Study or Subgroup | Treatment | | | Control | | | | Mean Difference | Mean Difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ji	1.74	0.93	46	2.24	0.95	46	53.1%	-0.50 [-0.88, -0.12]	
Villarruel	1.58	0.85	35	1.96	0.92	37	46.9%	-0.38 [-0.79, 0.03]	
Total (95% CI)			81			83	100.0%	-0.44 [-0.72, -0.16]	

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.68); I² = 0%
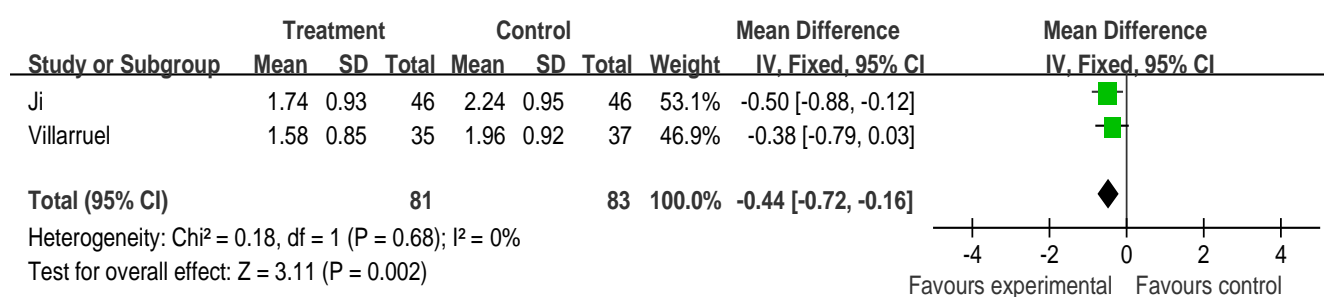Test for overall effect: Z = 3.11 (P = 0.002)

Figure 5. Stool frequency on day 7 between the treatment group and the control group.

the therapeutic effects of *S. boulardii* in children with acute diarrhoea. However, all the clinical trials involved were of small samples without blind methods, their results may remain some uncertainties. We urgently hope the high-quality, double-blinded, multi-centered RCTs will be carried out in the future to further confirm its efficacy and safety.

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