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Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children

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SUMMARY

Background
Saccharomyces boulardii is a non-pathogenic probiotic yeast considered useful against enteropathogens.

Aim
To assess the effectiveness of *S. boulardii* in treating acute infectious diarrhoea in children.

Methods
The following electronic databases were searched through August 2006 for studies relevant to acute infectious diarrhoea and *S. boulardii*: MEDLINE, EMBASE, CINAHL and The Cochrane Library; additional references were obtained from reviewed articles. Only randomized-controlled trials were included.

Results
Five randomized-controlled trials (619 participants) met the inclusion criteria. Combined data from four randomized-controlled trials showed that *S. boulardii* significantly reduced the duration of diarrhoea compared with control. The pooled weighted mean difference was −1.1 days (95% CI: −1.3 to −0.8) with a fixed model and remained significant in a random effect model. *Saccharomyces boulardii* significantly reduced the risk of diarrhoea on days 3, 6 and 7. Also the risk of diarrhoea lasting >7 days was significantly reduced in the *S. boulardii* group vs. control group (1 RCT, $n = 88$, RR 0.25, 95% CI: 0.08–0.83; NNT 5, 95% CI: 3–20).

Conclusions
There exists a moderate clinical benefit of *S. boulardii* therapy in otherwise healthy infants and children with acute gastroenteritis, mainly a shorter duration of diarrhoea. However, these results should be interpreted with caution due to methodological limitations of the included studies.

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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.[1, 2] In the vast majority of cases, acute diarrhoea is the result of a gut infection – mostly viral. The mainstay of therapy for dehydrating gastroenteritis is oral rehydration. However, it does not provide substantial shortening of the diarrhoeal episode nor a reduction in stool volume, prompting interest in adjunctive treatments.

Probiotics are living micro-organisms that, upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition.[3] The most commonly used probiotics are lactic acid bacteria, such as lactobacilli or bifidobacteria. The evidence from several meta-analyses[4–6] including one performed in our centre,[7] suggests that probiotics, mainly lactobacilli, have the potential to be useful in this situation but that further data are needed.

Saccharomyces boulardii is a non-pathogenic probiotic yeast considered to be useful against enteropathogens. Although the exact mechanism by which *S. boulardii* might exert its activity remains unclear, several possible mechanisms have been proposed, mostly based on results of *in vitro* and animal studies. These include inhibition of pathogen adhesion,[8] strengthening of enterocyte tight junctions,[9, 10] neutralization of bacterial virulence factors[11, 12] and enhancement of the mucosal immune response.[13–15]

Previously we have shown that *S. boulardii* effectively reduces the risk of antibiotic-associated diarrhoea.[16] The present review was undertaken to review and update data on the effectiveness and safety of *S. boulardii* in the treatment of acute diarrhoea. We decided to focus on only one probiotic strain. This is because critics of using a meta-analytical approach to assess the efficacy of probiotics argue that beneficial effects of probiotics seem to be strain-specific, thus, pooling data on different strains may result in misleading conclusions.

OBJECTIVE

To systematically review the effectiveness of *S. boulardii* in treating children with acute gastroenteritis.

METHODS

Criteria for considering studies for this review

In order to be included in the review, a study had to be a randomized-controlled trial (RCT) comparing *S. boulardii* with placebo or no additional intervention in treating acute diarrhoea (as defined by the investigators). The study also had to be performed in children. The **primary** outcome measures were duration of diarrhoea, stool output, the percentage of children with diarrhoea at various time intervals (as specified by the investigators), and the percentage of children with diarrhoea lasting longer than 7 days. The **secondary** outcome measures were stool frequency, vomiting, adherence (acceptance of the treatment) and adverse effects. In addition to these outcomes, *a priori* we decided to extract other data reported by the investigators if relevant to the current review.

Search strategy for identification of studies

The following electronic databases were systematically searched for relevant studies: MEDLINE (1966 – August 2006), EMBASE (1980 to August 2006), Cumulative Index to Nursing and Allied Health (CINAHL; 1982 to August 2006), The Cochrane Database of Systematic Reviews (issue 3, 2006) and The Cochrane Controlled Trials Register (issue 3, 2006). The text word terms and MESH headings used were: diarrhea/diarrhoea, diarrh*, probiotic*, children, child*, *Saccharomyces boulardii* and *S. boulardii*. Furthermore, the reference lists from the original studies and review articles were identified. The pharmaceutical company Biocodex (Gentilli, France) that manufactures *S. boulardii* was contacted to help identify published and unpublished data. No limit was imposed regarding the language of publication, but certain publication types (i.e. letters to the editor, abstracts, proceedings from scientific meetings) were excluded.

Data extraction

Titles and abstracts identified according to the above-described search strategy were screened independently by all reviewers. All potentially relevant articles were retained and the full text of these studies examined to determine which studies satisfied the inclusion criteria. Data extraction were carried out independently by all

reviewers, using standard data extraction forms. We compared the extracted data to identify errors. One reviewer (HS) entered the data into The Cochrane Review Manager [REVMAN (Computer program), Version 4.2 for Windows, Oxford, England: The Cochrane Collaboration; 2003] for analysis. Discrepancies between the reviewers were resolved by discussion.

Study quality

The reviewers independently, but without blinding to the authorship or journal, assessed the quality of the studies that met the inclusion criteria. Use of the following strategies, associated with good quality studies, was assessed: (i) allocation concealment, (ii) blinding of investigators, participants, outcome assessors and data analysts (yes/no/not reported), (iii) intention-to-treat (ITT) analysis (yes/no) and (iv) comprehensive follow-up. Allocation concealment was considered adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before the entry of eligible participants into the study. However, the quality of the allocation concealment was considered unclear when randomization was used but no information about the method was available and inadequate, when inappropriate methods of randomization (e.g. alternate medical record numbers, unsealed envelopes, tossing the coin) were used. With regard to the ITT analysis, an answer of 'yes' meant that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, a 'no' meant that authors did not report use of ITT analysis and/or that we could not confirm its use on study assessment. To evaluate the completeness of patient follow-up, we determined the percentage of participants excluded or lost to follow-up.

Statistical methods

The data were analysed using The Cochrane Review Manager. The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. To perform a meta-analysis of continuous data using mean differences, one needs to extract the mean values of the outcomes, the standard deviations of the outcomes and the number of participants in whom the outcome was assessed in each of the two groups. All but one trial[17] reported these data. Missing information was sought from the authors but with no success. As a *P*-value was reported, we extracted standard deviation by first obtaining the corresponding *t*-value from a table of the *t*-distribution, and then transforming the *t*-value into a standard deviation as described in the Cochrane Reviewer's Handbook.[18] The binary measure for individual studies and pooled statistics was reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (CI). To perform a meta-analysis of binary outcomes, one needs to extract the number of subjects with an event and the total number of subjects in the group. Number needed to treat (NNT) was calculated as the inverse of the pooled absolute risk differences and 95% CI. The weight given to each study was based on the inverse of the variance. 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 the primary outcomes when there was statistically significant heterogeneity in outcomes across studies, sensitivity analyses according to each of the four parameters of trial methodological quality were conducted.

To test for publication bias, a test for asymmetry of the funnel plot proposed by Egger *et al.*[19] was used. This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalized effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate.

RESULTS

We initially identified eight articles. Table 1 summarizes the characteristics of the included trials. Five RCTs[17, 20–23] involving 619 participants (310 in the experimental group and 309 in the control group) met our predefined inclusion criteria. Except one made available by the manufacturer,[20] all were full peer-reviewed publications. The remaining three studies were excluded.[24–26] Table 2 summarizes characteristics of the excluded trials, including the reasons for exclusion.

Three studies[20, 22, 23] were placebo-controlled. In the remaining two trials,[17, 21] there was no additional

Table 1. Characteristics of included trials

Number	Author (country)	Generation of allocation sequence	Allocation concealment*	Blinding	ITT*	FU† (%)	*N* (experimental/ control)	Inclusion criteria	Age	Dose (per day, mg)	Duration of intervention (days)	Definition of termination of diarrhoea	Aetiology of diarrhoea
1	Billoo *et al.*[21] (Pakistan)	No information about method	Unclear	No	Yes	100	50/50	Acute diarrhoea mild to moderate severity	2 months to 12 years	500	5	Not reported	HRV 18%, bacteria 19%
2	Cetina-Sauri and Busto[23] (Mexico)	Adequate (random table)	Unclear	Yes	Yes	100§	65/65	Acute non-bloody diarrhoea	3–36 months	600	4	Efficacy: <4 stools in 24 h and absence of liquid stools	No data
3	Hafeez *et al.*[17] (Pakistan)	Inadequate (even/odd numbers)	Inadequate	No	No‡	93	51/50	Acute watery diarrhoea mild to moderate severity	6 months to 5 years	500	6	Not reported	No data
4	Kurugol and Koturoglu[22] (Turkey)	No information about method	Not reported	Yes	No‡	86	100/100	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)	3 months to 7 years	250	5 (follow-up 14)	Time from the start of the treatment until the appearance of the first normal stools	HRV 42%, bacteria/parasites 10%, unspecified 49%
5	Villarruel *et al.*[20] (Argentina)	Adequate (computer-generated numbers)	Adequate	Yes	No‡	88	44/44	Acute mild to moderate diarrhoea ≥3 liquid or loose stools in the last 24, but <7 days duration, out-patients	3–24 months	<1 year 250; >1 year 500	6	Not reported	No data

* ITT, intention-to-treat analysis.
† FU, completeness of follow-up.
‡ Available case analysis (assessed by the reviewers).
§ Unclear how many participants were randomized at the start of the study.
HRV, human rotavirus.

Table 2. Characteristics of excluded trials

Trial ID	Study design, reason(s) for exclusion
Urganci *et al.*[25]	Non-randomized, prospective study
Chapoy[24]	Non-randomized, prospective study
Hochter *et al.*[26]	Randomized-controlled trial performed in adults

intervention in the control group. Two studies were based in countries with a high Human Development Index (HDI;[27] i.e. Argentina,[20] Mexico[23]), and three were based in countries with a medium HDI (i.e. Pakistan,[17, 21] Turkey[22]). The age of the participants varied from 2 months to 12 years. The daily dose of the study product was 250–750 mg. The duration of the intervention was 5–6 days. One trial did not report the duration of the intervention.[23] There was clinical heterogeneity among the trials in settings (in-patients[17, 21, 22] or out-patients[20]). One trial did not report the setting.[23] The aetiology of the diarrhoea was provided only in two RCTs.[21, 22] Only one RCT[22] reported the definition of the termination of diarrhoea. The methodological quality of the trials varied (Table 1). Only one trial used an adequate method to conceal allocation.[20] The method used in the remaining four trials was unclear or not reported. Three trials were described as 'double blinded'[20, 22, 23] and two trials were open.[17, 21] An adequate description of the ITT analysis was provided in only two RCTs.[21, 23] Withdrawals and dropouts were described adequately in all studies. All trials included an adequate number (i.e. ≥80%) of participants in the final analysis. We assessed the risk of bias as low (up to one inadequate criterion) in only two trials.[20, 23] The summary of the results is presented in Table 3.

Duration of diarrhoea

Four papers contained data on the duration of the diarrhoea.[17, 20–22] A meta-analysis of four RCTs (473 participants) showed a reduction in the duration of the diarrhoea (WMD −1.1 day, 95% CI: −1.3 to −0.83) for those treated with *S. boulardii* compared with placebo (Figure 1). Changing our meta-analysis model from fixed to random effects did not change the results. The included studies were homogeneous ($\chi^2 = 0.69$, $I^2 = 0$).

Table 3. Summary of the results on the effectiveness of *Saccharomyces boulardii* vs. control

Comparison or outcome	RCT(s)	*N*	Statistical method	Effect size	NNT (if applicable)
Duration of diarrhoea (days)	4	473	WMD	−1.1 (−1.3 to −0.83)	
Cure					
On day 2	1	130	RR	4 (1.8–9.1)	4 (3–8)
On day 8	1	130	RR	1.9 (1.4–2.8)	3 (2–5)
Diarrhoea					
On day 3	1	101	RR	0.71 (0.56–0.90)	4 (3–12)
On day 4	1	88	RR	0.73 (0.5–1.1)	N.S.
On day 6	1	101	RR	0.49 (0.24–0.99)	6 (3–98)
On day 7	1	88	RR	0.39 (0.20–0.75)	4 (3–11)
>7 days	1	88	RR	0.25 (0.08–0.83)	5 (3–20)
Number of stools					
On day 1	1	130	WMD	−0.32 (−1.1 to 0.43)	
On day 3	3	331	WMD	−1.3 (−1.9 to −0.63)	
On day 4	2	218	WMD	−1.1 (−1.6 to −0.64)	
On day 6	2	201	WMD	−1.7 (−2.4 to −1.0)	
On day 7	1	88	WMD	−0.90 (−1.4 to −0.43)	
Hospitalization (days)	1	200	WMD	−1 (−1.4 to −0.62)	
Duration of vomiting (days)	1	200	WMD	−0.1 (−0.34 to 0.14)	

RCT, randomized-controlled trial; RR, relative risk; WMD, weighted mean difference; negative values indicate that the outcome was shorter (or reduced) in the *S. boulardii* group than in the control group; NNT, number needed to treat; CI, confidence interval.

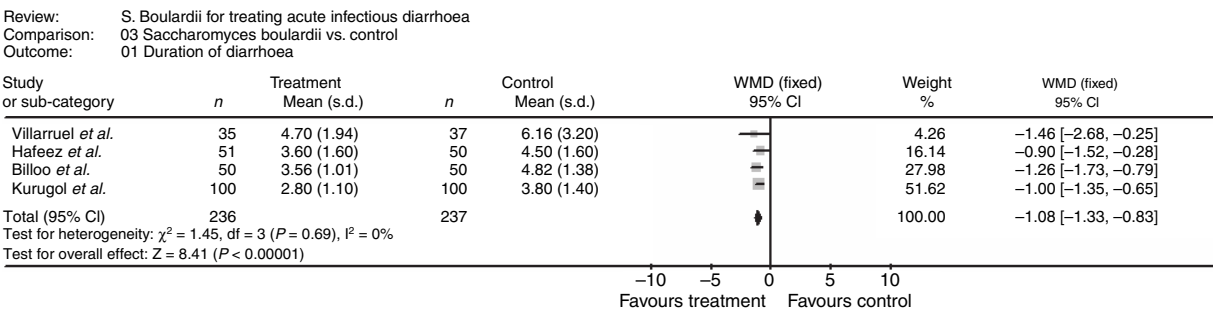

Figure 1. *Saccharomyces boulardii* vs. control. Mean duration of diarrhoea (hours).

Stool output

None of the included trials reported this outcome measure.

Cure

Based on the results of one RCT,[23] the relative chance of cure on days 2 and 4 of the intervention in the *S. boulardii* group compared with the control group was 4 (95% CI: 1.8–9) and 1.9 (95% CI: 1.4–2.8), respectively. The NNT was 4 (95% CI: 3–8) and 3 (95% CI: 2–5), respectively.

Presence of diarrhoea

Two papers contained information on diarrhoea at various time intervals.[17, 20] With one exception, there was a significantly reduced risk of diarrhoea on days 3, 6 and 7 in the *S. boulardii* group compared with the control group (Table 3).

Diarrhoea >7 days

One trial[20] showed a reduction in the risk of diarrhoea lasting >7 days for those treated with *S. boulardii* compared with control (RR 0.25, 95% CI: 0.08–0.83; NNT 5, 95% CI: 3–20).

Frequency of stools

Four studies provided a measure of variance at various time intervals.[17, 20, 21, 23] A meta-analyses of these studies showed a reduction in the frequency of diarrhoea for those treated with *S. boulardii* compared with the control at all time intervals studied, except on day 1 (Table 3).

Vomiting

Based on the results of the only one RCT[22] to report this outcome, there was no difference in the duration of vomiting between the *S. boulardii* and the control group (mean difference −0.1 day, 95% CI: −0.34 to 0.14).

Duration of hospitalization

Based on the results of the only one RCT[22] to report this outcome, there was a reduction in the duration of hospitalization between the *S. boulardii* and the control group (mean difference 1 day, 95% CI: −1.4 to −0.62).

Adverse events

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

DISCUSSION

A meta-analysis of data from RCTs showed that in otherwise healthy infants and children with acute infectious gastroenteritis, the use of *S. boulardii* compared with control is associated with moderate therapeutic benefit that is reproducible regardless of the outcome measure studied (i.e. duration of diarrhoea, chance of cure or risk of diarrhoea at certain point intervals, number of stools and length of hospital stay). However, these results should be interpreted with caution as some of them are based on the limited data available.

The primary measure of outcome in most, albeit not all, trials was the duration of diarrhoea. However, this measure alone is not considered optimal. Instead,

criteria for quantitative diarrhoea are recommended by the World Health Organization for the evaluation of therapeutic agents in the management of acute diarrhoea.[28] The only study that reported such an outcome was not randomized, and thus, was not included in this review.[24] Nonetheless, it is worth mentioning that no significant reduction in the stool volume for those treated with *S. boulardii* compared with placebo was reported in this trial.

The included studies were carried out mainly in non-European countries. The findings are important and relevant primarily for countries where the studies were conducted. For doctors practicing in Europe, where the enteropathogens found in subjects with diarrhoea may not be representative of the pathogens causing diarrhoea in non-European countries, the generalizability of the efficacy findings may be of concern. Given the lack of data, unfortunately it is not possible to determine the impact of *S. boulardii* on diarrhoea caused by various aetiological agents.

Whereas no adverse effects were observed in any of the included trials, the administration of *S. boulardii* is not without risk. One caveat about *S. boulardii* is that it can cause fungaemia.[29–31] Most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses managed in intensive care units.

Previous studies

As mentioned in the Introduction section, the effect of various probiotics, mainly lactic acid bacteria, in the treatment of acute gastroenteritis has been studied in a number of RCTs. Despite the great variability between studies, nearly all trials demonstrated a beneficial effect of probiotics in reducing diarrhoea by approximately 1 day, and this effect was statistically significant in many studies. The results of this meta-analysis are therefore in line with the previous evidence suggesting that some probiotics, albeit not all, have the potential to be useful in the treatment of acute diarrhoea.

Limitations and strength of the analysis

Any meta-analysis is only as good as the constituent studies. All trials included in our analysis had methodological limitations, including unclear or inadequate allocation concealment, no ITT analysis and no blinding. Study limitations also included a small sample size in some trials and no widely agreed-on definition of the termination of diarrhoea.

Although the included studies were not significantly heterogeneous, given the small number of studies, statistical conclusions on determinants of heterogeneity might be flawed. Further, we cannot fully exclude publication bias. Although we did perform a statistical test for the detection of publication bias, we are aware that these tests have very low power in the meta-analysis of only a few trials. To limit the risk of publication bias, we did not impose restrictions by language or year of publication and made attempts to identify unpublished trials which strengthens our meta-analysis. Further strength comes from the fact that only one probiotic micro-organism was assessed.

Future research

The results emerging from our meta-analysis suggesting that *S. boulardii* may be effective for treating children with acute gastroenteritis are promising. However, further well-conducted clinical studies using validated outcomes are recommended to: (i) address the cost-effectiveness of using *S. boulardii* to treat children with acute diarrhoea, (ii) further delineate the groups (out-patient vs. in-patient, older vs. younger, viral vs. other aetiology of diarrhoea) deriving the greatest clinical benefit from *S. boulardii* therapy and (iii) determine the most effective dosing schedule.

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