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Alimentary Pharmacology & Therapeutics

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Journal:	*Alimentary Pharmacology & Therapeutics*
Manuscript ID:	APT-0678-2010.R1
Wiley - Manuscript type:	Meta-analysis
Date Submitted by the Author:	24-Aug-2010
Complete List of Authors:	Szajewska, Hania; The Medical University of Warsaw, Department of Paediatrics Horvath, Andrea; The Medical University of Warsaw, Department of Paediatrics Piwowarczyk, Anna; The Medical University of Warsaw, Department of Paediatrics
Keywords:	H. pylori < Topics, Meta-analyses < Topics, Probiotics/prebiotics < Topics, Diarrhoea < Topics

Meta-analysis: the effects of *Saccharomyces boulardii* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment

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Short title: *S boulardii* and *H pylori* eradication rates

Key words
RCT, *H pylori*, probiotics, microbiota

Word count: 4119

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ABSTRACT

Background: Problems with currently recommended *Helicobacter pylori* eradication therapies include unsatisfactory eradication rates and/or therapy-associated side effects.

Aim: To investigate the effects of *Saccharomyces boulardii* as supplementation to standard triple therapy on *H pylori* eradication rates and therapy-associated side effects.

Methods: The Cochrane Library, MEDLINE, and EMBASE databases were searched in July 2010, with no language restrictions, for randomised controlled trials (RCTs); additional references were obtained from reviewed articles.

Results: Five RCTs involving a total of 1307 participants (among them only 90 children) met the inclusion criteria. Compared with placebo or no intervention, *S boulardii* given along with triple therapy significantly increased the eradication rate (four RCTs, n=915, relative risk [RR] 1.13, 95% confidence interval [CI] 1.05 to 1.21) and reduced the risk of overall *H pylori* therapy-related adverse effects (five RCTs, n=1305, RR 0.46, 95% CI 0.3 to 0.7), particularly of diarrhoea (four RCTs, n=1215, RR 0.47, 95% CI 0.32 to 0.69). There were no significant differences between groups in the risk of other adverse effects.

Conclusions: In patients with *H pylori* infection, there is evidence to recommend use of *S boulardii* along with standard triple therapy as an option for increasing the eradication rates and decreasing overall therapy-related side effects, particularly diarrhoea.

INTRODUCTION

The most commonly prescribed triple therapy, consisting of use of a proton pump inhibitor with clarithromycin and amoxicillin, remains the recommended first-choice treatment for *Helicobacter pylori* infection.[1 2 3] One major problem with this therapy, as well as with other *H pylori* eradication regimens, is unsatisfactory eradication rates largely due to the increased resistance to antibiotics, primarily to clarithromycin.[4 5 6] In addition, adverse effects are experienced by about 5% to 30% of patients receiving *H pylori* eradication therapy and further contribute to treatment failure.[7] Measures to overcome these problems include the use of probiotics, which are live microbial food ingredients that are beneficial to health.[8] The rationale for the use of probiotics as adjunctive treatment for *H pylori* infection is based on the results of studies that have shown that various lactobacilli (eg, *Lactobacillus johnsonii* La1, *L acidophilus* CRL 639, *L casei*), or their metabolic products, can inhibit or kill *H pylori* in vitro.[9 10]

A recent systematic review[7] evaluated the effects of supplementation with probiotics on *H pylori* eradication rates and side effects of anti-*H pylori* treatment. Fourteen randomised controlled trials (RCTs) of varying methodological quality involving 1671 patients were identified. In patients with *H pylori* infection, probiotic supplementation improved eradication rates. In two RCTs that evaluated patients with eradication failure, probiotic supplementation also improved eradication rates. Probiotics reduced therapy-related side effects overall and individual symptoms of diarrhoea, epigastric pain, nausea, and taste disturbance.

Opponents of using a meta-analytical approach to assess the efficacy of probiotics argue that the beneficial effects of probiotics seem to be strain specific, thus, pooling data on different strains may result in misleading conclusions. A more favourable approach is to perform a meta-analysis that evaluates the effect of administering a clearly defined probiotic preparation (single or in combination). Given these considerations, the aim of the current review was to update and synthesise the available clinical trial evidence of the likely effects of *S boulardii* given in addition to standard eradication therapy on major clinical outcomes related to *H pylori*

eradication. The choice of the probiotic *S boulardii* was determined by the fact that it is widely available and commonly used in many countries.

METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis[11] and the PRISMA statement[12] were followed for this systematic review and meta-analysis.

Criteria for considering studies for this review

All relevant RCTs that compared use of *S boulardii* alone or during *H pylori* eradication therapy with use of placebo or no treatment were eligible for inclusion. Participants of any age had to be *H pylori*-infected subjects, as assessed by generally accepted methods (ie, the ^{13}C-urea breath test [UBT], histopathology, or the rapid urease test). The *primary* outcome measure was the rate of *H pylori* eradication, which had to be confirmed by a negative ^{13}C-UBT or other generally accepted method at least 4 weeks after treatment. The *secondary* outcome measures were the frequencies of adverse effects (overall and specific). The adverse effects of interest were any common gastrointestinal adverse effects that occurred during anti-*H pylori* therapy, including diarrhoea, taste disturbance, nausea, vomiting, bloating, loss of appetite, abdominal pain, constipation, and the need for discontinuation of the *H pylori* therapy.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and EMBASE databases were searched for relevant studies in July 2010. The principal search text word terms and MESH headings used were as follows: probiotic*, *Saccharomyces boulardii* and *S boulardii, Helicobacter pylori* and *H pylori.* Two (AH, AP) reviewers independently carried out the search, and they did not impose any language restrictions. The reference lists from identified studies and key review articles were also searched to identify any other relevant studies. The principal pharmaceutical company Biocodex (Gentilli, France) that manufactures *S*

boulardii was contacted to help identify published and unpublished data. The ClinicalTrials.gov website was also searched for RCTs that were registered but not yet published. Certain publication types (ie, letters to the editor, abstracts, proceedings from scientific meetings) were excluded, unless a full set of data was obtained from the authors.

Data collection and analysis

Three reviewers using a standardised approach independently undertook the literature search, data extraction, and quality assessment. The data sought included baseline characteristics of the patients, details of the *H pylori* eradication therapy, and details related to the use of experimental and control interventions (including dose and duration), type of outcome measure (primary vs secondary), methods of checking *H pylori* status, and/or assessment of side effects. Minor disagreements were resolved by discussion.

Assessment of risk of bias in included studies

The reviewers independently, but without being blinded to the authors or journal, assessed the risk of bias in the studies that met the inclusion criteria. The Cochrane Collaboration's tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation, allocation concealment, and blinding of participants, personnel and outcome assessors; and extent of loss to follow-up, ie, the proportion of patients in whom the investigators were not able to determine outcomes (incomplete outcome data). In all cases, an answer of '*yes*' indicates a low risk of bias, and an answer of '*no*' indicates a high risk of bias.[13]

Measures of treatment effect

The dichotomous outcomes, the results for individual studies, and pooled statistics are reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes (with 95% CI).

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.[14]

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. If heterogeneity was not revealed, we present results of only the fixed effects model. If there was substantial heterogeneity (over 50%), all analyses were based on the random effects model if it was still considered appropriate to pool the data.

Assessment of reporting biases

To test for publication bias, we planned to use a test for asymmetry of the funnel plot proposed by Egger et al.[15] 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 (on StatsDirect, version 2.3.8). However, the publication bias was not formally assessed using a funnel plot due to the small number of studies (<10) included in the analyses of the primary and secondary outcome measures.

Data synthesis (Statistical methods)

The data were analysed using Review Manager (RevMan) [Computer program. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008]. Absolute risk reduction (ARR) and number needed to treat (NNT), all with a 95% CI, were calculated using StatsDirect statistical software (version 2,7,8 [2010-03-15]).

Subgroup analysis and sensitivity analyses

For the primary outcome, pre-planned subgroup analysis based on age (adults vs children) was performed. Additionally, when there was statistically significant heterogeneity in the primary outcome across studies, sensitivity analyses were planned to determine the impacts of allocation concealment (adequate versus inadequate and/or unclear) and attrition (<20% versus ≥20%). The latter were not performed, as there was no heterogeneity in the primary outcome.

RESULTS

The literature search yielded 894 articles, of which six were reviewed in full text (**figure 1**).[16 17 18 19 20 21] Of these studies, five RCTs[17 18 19 20 21] met the inclusion criteria. All were published in English. These trials randomised a total of 1307 patients, of which 1227 were followed up. **Table 1** summarises the characteristics of the included studies. The characteristics of the excluded trials, with reasons for exclusion, are available upon request. Four studies enrolled only adults,[17 18 19 21] and one RCT[20] (n=90) was undertaken exclusively in children (age range: 3 to 18 years). The sample size ranged from 43 to 661 participants. In all studies, *S boulardii* was used in addition to standard triple therapy consisting of a proton pump inhibitor and two antibiotics. In all included trials, clarithromycin was one of the antibiotics used. The daily dose of *S boulardii* ranged from 500 mg[18 20] to 750 mg[21] to 1000 mg.[17 19] Two RCTs[17 18] were placebo controlled; in the remaining three trials,[19 20 21] there was no additional intervention in the control group. Except for one multi-centre trial,[19] the included studies were single-centre trials. The studies were undertaken in countries such as Italy (one RCT[18]), Korea (one RCT[21]), Romania (one RCT[20]), and Turkey (two RCTs[17 19]).

Risk of bias in included studies

With the exception of one RCT by Cremonini et al.,[18] all included trials had a number of methodological limitations (see **table 2).**

Heterogeneity

Significant heterogeneity (I^2 ≥50%) was found for the overall incidence of adverse effects (chi^2 =9.75, p=0.04, I^2=59%) and epigastric pain (chi^2 =4.75, p=0.09, I^2=58%). In all cases, the observed statistical heterogeneity was not judged to be clinically relevant (ie, studies consistently reported results in the same direction with clinically insignificant differences between the studies). However, there were too few studies to adequately determine heterogeneity.[22]

Effects of interventions

Primary outcome: *H pylori* eradication rates

Data regarding the effects of *S boulardii* supplementation on *H pylori* eradication rates were available from four trials,[17 18 20 21] which reported data from 915 participants (825 adults and 90 children) **(figure 2).** In two RCTs, the eradication rate was a primary outcome;[20 21] in the remaining two RCTs,[17 18] it was a secondary outcome.

We found a significant difference between the *S boulardii*-supplemented group and the control group with respect to *H pylori* eradication rates (four RCTs, n=915, RR 1.13, 95% CI 1.05 to 1.21). Of the 460 patients in the *S boulardii* group, 370 (80%, 95% CI 77% to 84%) experienced eradication compared with 324 of the 455 patients (71%, 95% CI 67% to 75%) in the control group. Thus, the administration of *S boulardii* along with the standard therapy resulted in a 9% higher absolute eradication rate (ARR 9%, 95% CI 3.6% to 14%). The number needed to treat (NNT) was 11 (95% CI 7 to 28). The pooled results of the three RCTs conducted in adults[17 18 21] showed a statistically significant increase in the eradication rate in favour of *S boulardii* compared with placebo or no treatment (3 RCTs, n=825, RR 1.12, 95% CI 1.04 to 1.22).

Secondary end points: adverse effects and compliance

Data regarding therapy-related adverse effects were available from all five of the included trials (**figure 3)**. We found a significant difference between the *S boulardii*-supplemented group and the control group with respect to the risk of overall adverse effects (five RCTs, n=1305, RR 0.46, 95% CI 0.3 to 0.7). Of the 665 patients in the *S*

boulardii group, 86 (12.9%, 95% CI 10.4% to 15.7%) experienced any adverse effect compared with 156 of the 640 patients (24.3%, 95% CI 21% to 27.8%) in the control group. Thus, the coadministration of *S boulardii* with the standard eradication therapy resulted in an 11.4% lower absolute adverse effects rate (ARR 11.4%, 95% CI 7.3% to 15.6%). The number needed to treat was 9 (95% CI 7 to 14).

In regard to specific adverse effects, the risk of therapy-related diarrhoea was statistically lower in the *S boulardii* group compared with the control group (four RCTs, n=1215, 5.6% vs 12.2%, respectively, RR 0.47, 95% CI 0.32 to 0.69, NNT 16, 95% CI 11 to 30). However, we found no significant difference between the study groups with respect to epigastric pain, taste disturbance/dry mouth, nausea, or abdominal gas/bloating (see **figure 2)**. Additionally, there was no significant difference between the groups in the frequency of vomiting, constipation, or other nonspecific reactions such as urticaria/skin reactions, palpitations, aphthous lesions in the mouth, belching, loss of appetite, blurred vision, or the presence of *Clostridium difficile* toxin. The forest plots for these outcomes are not presented, as these outcomes have been reported in only one or two trials. The need for discontinuation of the eradication treatment was not reported in any trial.

DISCUSSION

Summary of evidence

This meta-analysis of RCTs showed that in patients with *H pylori* infection, addition of *S boulardii* to triple therapy compared with placebo or no intervention improved eradication rates, reduced overall therapy-related adverse effects, and decreased some individual symptoms such as diarrhoea. As the majority of included patients were adults, our results may be applicable primarily to such a population.

Quality of the evidence

In our analysis, the studies seemed methodologically sound with regard to sequence generation, >80% follow-up, and intention-to-treat analysis. Potential limitations included unclear or inadequate allocation concealment and no blinding in some

trials. This can overestimate the effect and skew the results in favour of either treatment, depending on the biases of the investigators. Reassuringly, the direction of the effect for the primary outcome (eradication rate), as well as that for adverse effects, was similar and the benefit was reproducible, regardless of the methodological concerns. Study limitations also included a small sample size in some trials. In only two RCTs,[17 18] sample size calculations were available. However, to increase power is one of the reasons why a meta-analysis is performed within a systematic review.[23]

How the intervention might work

The exact mechanisms by which *S boulardii* might exert its actions in increasing the eradication rates are unclear. One possible explanation is that this beneficial effect is due to a reduction in therapy-related side effects and, consequently, better compliance with treatment. Additional mechanisms, discussed in detail elsewhere,[24] include interference with pathogenic toxins, preservation of cellular physiology, interference with pathogen attachment, interaction with normal microbiota, or contribution to the reestablishment of short chain fatty acid levels. In addition, stimulation or modulation of immune responses, both within the lumen and systemically, although not clearly linked to *H pylori* infection, may also contribute.

Agreement and disagreement with other studies or reviews

With regard to the eradication rate, overall gastrointestinal side effects, and risk of diarrhoea, the results of our review are in line with conclusions of the previous review by Tong et al.[7] discussed in the Introduction. The major question with regard to the meta-analysis by Tong et al. is whether it was appropriate to pool data on different probiotic microorganisms. The risk is that pooling data from different genera, species, strains, and doses of probiotics obtained in different settings and/or populations, presumably with variations in their native intestinal microbiota, may result in misleading conclusions. The results could be erroneously extrapolated to other probiotics, including those that have not been adequately studied. Given these considerations, our work focused on one type of a clearly defined, single-organism,

probiotic microorganism, specifically *S boulardii.* Thus, our results precisely define the effects of *S boulardii* supplementation on the rates of *H pylori* eradication, adverse effects, and patient compliance.

Our findings with regard to therapy-related diarrhoea are in line with and add to a previously published meta-analysis on the effects of *S boulardii* in preventing antibiotic-associated diarrhoea in children and adults.[25] This meta-analysis documented that treatment with *S boulardii* compared with placebo reduced the risk of antibiotic-associated diarrhoea from 17.2% to 6.7% (RR 0.43, 95% CI 0.23 to 0.78). Of note, the effect size with respect to diarrhoea was similar in the current and previous meta-analyses (reduction of 53% vs 57%, respectively). Collectively, these data support the use of *S boulardii* for the prevention of diarrhoea associated with antibiotic treatment, regardless of the reason for which the antibiotics were used.

A number of studies suggest that the dose of probiotic is important.[26 27 28 29] The daily doses of *S boulardii* ranged from 500 mg to 1000 mg. The largest effect on the eradication rate was observed in the largest, but open-label, RCT by Song et al.,[21] which used the daily dose of *S boulardii* 750 mg (corresponding to ≈22.5 x 10^9 CFU). Whether or not this dose contributed to the beneficial effect of *S boulardii* on the eradication rate is not clear, but it could not be excluded.

Can we be satisfied with the eradication rate?

In 2007, Graham et al.[30] proposed that one judge the effectiveness of *H pylori* eradication therapy against an established target, such as a "report card." According to the proposed classification system, only therapies that score excellent, ie, those that achieve ≥95% eradication success in the local populations, should be prescribed. In our review, the *H pylori* eradication rate in the triple therapy group was 71% and increased to 80% with *S boulardii* supplementation. Thus, even when supplemented with *S boulardii,* this treatment did not achieve the desired level of success. Nevertheless, when making clinical decisions, it seems reasonable to consider the mode of therapy with higher efficacy. Recently, it has been documented that

sequential therapy compared with standard triple therapy may be more effective for *H pylori* eradication.[31] Considering the beneficial effect of *S boulardii* documented in our analysis, one could speculate that the addition of *S boulardii* to the sequential therapy may result in even higher eradication rates. Further trials are needed to confirm this assumption.

Safety

Whereas no adverse effects other than those attributed to *H pylori* eradication therapy were observed in any of the included trials, the administration of *S boulardii* is not without risk. A recent systematic review[32] documented that some probiotic products, particularly *S boulardii* and *Lactobacillus* GG, have been shown to increase the risk of complications in specific patient groups. Of note, most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses managed in intensive care units. It was also stated that all case reports that detailed infections caused by certain probiotics (ie, *S boulardii* or *Lactobacillus* GG) are likely to reflect their wider use in the clinical setting rather than their increased virulence. Overall, probiotics are safe for use in otherwise healthy populations, but caution should be taken in patients with risk factors for adverse events (eg, patients with central venous catheters or increased bacterial translocation).

CONCLUSIONS

There is evidence to recommend the use of *S boulardii* as a safe option for increasing *H pylori* eradication rates, although only moderately, and decreasing overall therapy-related side effects, particularly diarrhoea, in settings where standard triple therapy is recommended and in non-risk populations. While caution is advised in view of the methodological concerns regarding some of the included studies, it is reassuring that there was consistency of the effect across studies with regard to these outcomes. As the majority of included patients were adults, studies in children are needed.

CONTRIBUTORS

HS initially conceptualised this study. AH and HS contributed to the initial protocol of the study. All authors were responsible for data collection, data analysis, data interpretation, and preparation of the report. HS assumed the main responsibility for the writing of this manuscript. All authors contributed to (and agreed upon) the final version.

ACKNOWLEDGMENTS, COMPETING INTERESTS, FUNDING

Authors' declaration of personal interest: H. Szajewska served as a speaker for Biocodex, the manufacturer of *S boulardii.* Two remaining authors declare no conflict of interest.

Declaration of funding interests: This study was funded in full by The Medical University of Warsaw.

FIGURE LEGEND

Figure 1. Identification process for eligible trials

Figure 2. Primary outcome: Effect of *S boulardii* (SB) on *H pylori* eradication rates

Figure 3. Secondary outcomes: Effect of *S boulardii* (SB) on *H pylori* eradication therapy-related adverse effects

Table 1. Characteristics of included studies

Study ID (Country)	Patients	Cont/Exp (Follow-up)	Eradication regimen (daily dose)	S boulardii group (daily dose)		Control group	Primary/secondary outcomes	H. pylori infection. Initial diagnosis/re-checking	Follow-up	Score system for assessing side effects
				mg	CFU					
Cindoruk et al. (Turkey) (17)	*H pylori*-positive symptomatic adults	62/62 (FU 62/62)	Lansoprazole (30 mg twice daily) Amoxicillin (1 g twice daily) Clarithromycin (500 mg twice daily) 14 days	1000 mg (in 2 doses, for 2 wk)	≈20 x 10^9 CFU *	Placebo	Side-effects/eradication success	Histology/UBT	6 wk	Questionnaire by De Boer
Cremonini et al. (Italy) (18)	*H pylori*-positive asymptomatic adults	21/22 (FU 20/21)	Rabeprazole (20 mg twice daily) Clarithromycin (500 mg twice daily) Tinidazole (500 mg twice daily) 1 wk	≈500 mg (in 2 doses, for 2 wk)*	10 x 10^9 CFU	Placebo	Side-effects/eradication rate	UBT/UBT	5 to 7 wk	Questionnaire by De Boer
Duman et al. (Turkey) (19)	*H pylori*-positive symptomatic adults	185/204 (FU 172/196)	Omeprazole (20 mg twice daily) Clarithromycin (500 mg twice daily) Amoxicillin (1 g twice daily) 2 wk	1000 mg (in 2 doses, for 2 wk)	≈20 x 10^9 CFU*	No treatment	Incidence of diarrhoea during and following the antibiotic treatment/duration of diarrhoea and frequency of bowel movements during a diarrhoeal episode	UBT, histology/not applicable	2 to 4 wk (14 – 45 days)	Interview
Hurduc et al. (Romania) (20)	*H pylori*-positive symptomatic children	42/48 (FU 42/48)	Omeprazole or Esomeprazole (1 mg/kg/day twice daily) for 3 weeks Amoxicillin (50 mg/kg/day twice daily) for 7-10 days Clarithromycin (15 mg/kg/day twice daily) for 7-10 days	500 mg (in 2 doses, for 4 wk)	≈10 x 10^9 CFU	No treatment	Eradication rate/Adverse events	Rapid urease test, histology/rapid urease test, histology	4 to 6 wk	Recorded in the questionnaire

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Song et al. (Korea) (21)	*H pylori*-positive symptomatic adults	331/330 (FU 296/309	Omeprazole (20 mg twice daily) Amoxicillin (1g twice daily) Clarithromycin (500 mg twice daily) 1 wk	750 mg (in 3 doses, for 4 wk)	22.5 x 10^9 CFU	No treatment	Eradication rate and side effects	UBT, histology/UBT	5 to 8 wk	Diary to record the therapy and side effects

CFU, colony forming units; FU, follow up; UBT, urea breath test

* Calculated by the reviewers based on the assumption *S boulardii* 50 mg = 10^9 CFU (by the end of the manufacturing process)

Table 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Study ID	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete data addressed?
Cindoruk et al. 2007 (17)	Yes	Unclear	Yes	Yes
Cremonini et al. 2002 (18)	Yes	Yes	Yes	Yes
Duman et al. 2005 (19)	Unclear	Unclear	No	Yes
Hurduc et al. 2008 (20)	Yes	Unclear	No	Yes
Song et al. 2010 (21)	Yes	Unclear	No	Yes

In all cases, an answer of '*yes*' indicates a low risk of bias, and an answer of '*no*' indicates a high risk of bias

Figure 1. Identification process for eligible trials

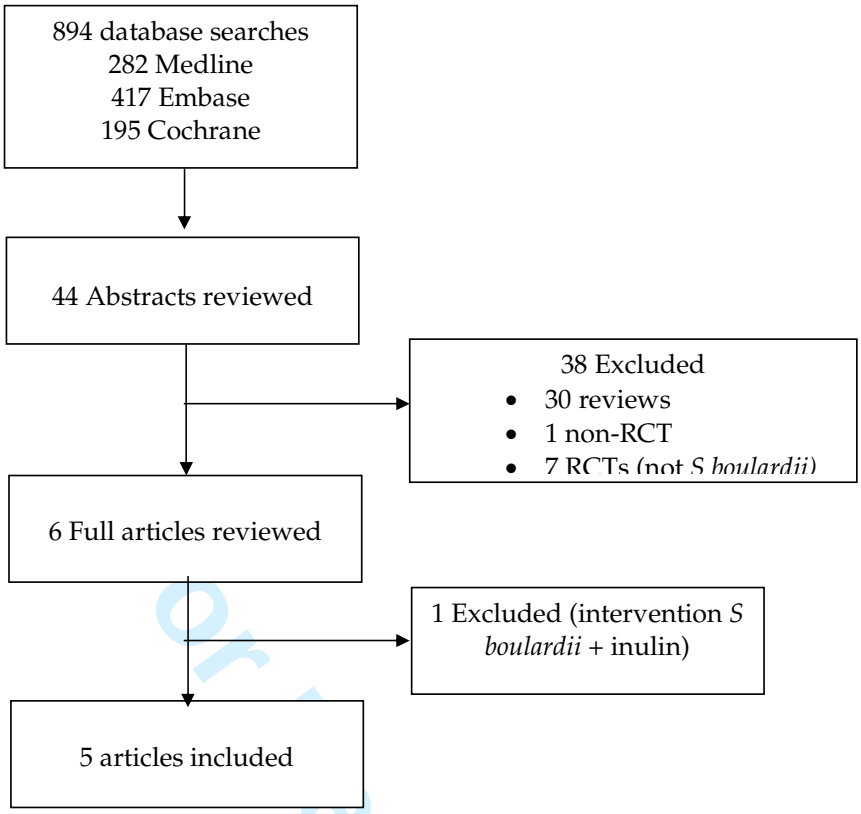


Figure 2. Primary outcome: Effect of *S boulardii* (SB) on *H pylori* eradication rates

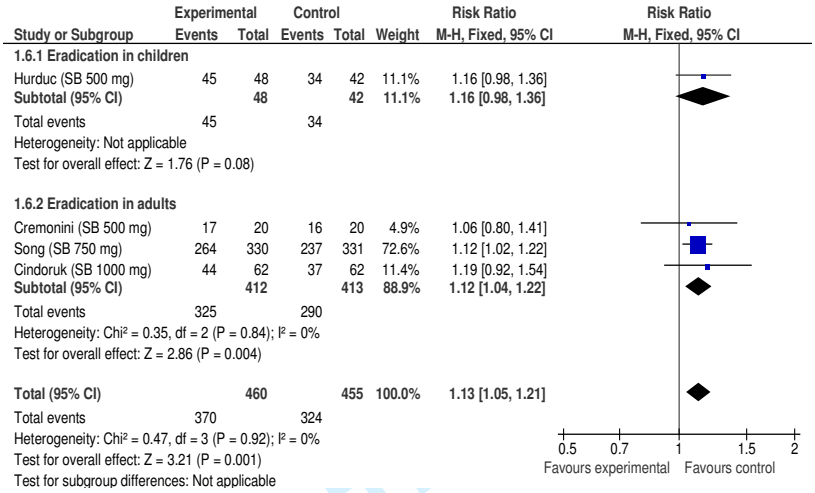
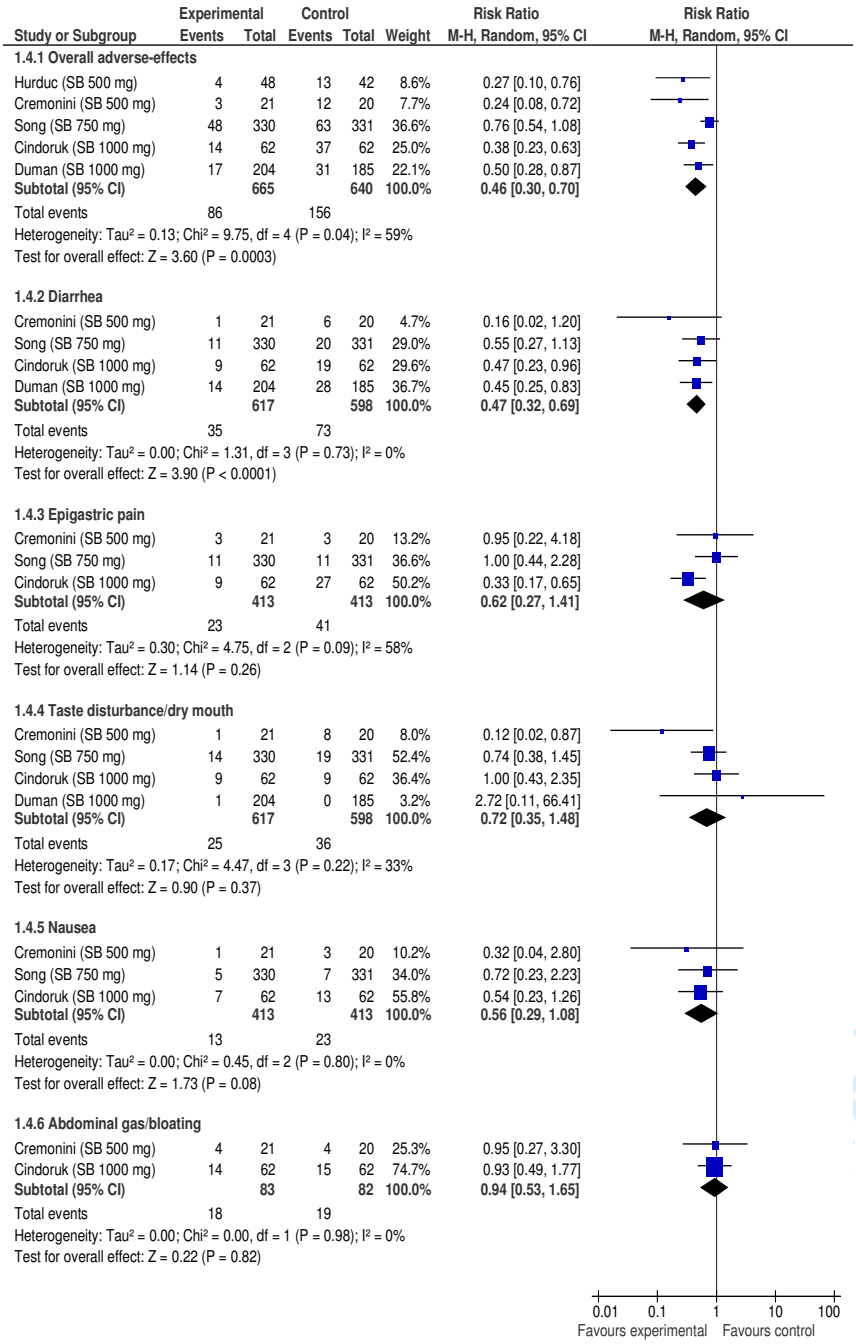


Figure 3. Secondary outcomes: Effect of *S boulardii* (SB) on *H pylori* eradication therapy-related adverse effects



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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14-15

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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