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Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection

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SUMMARY

Background
Unsatisfactory *Helicobacter pylori* eradication rates and therapy-associated side effects remain a problem.

Aim
To update our 2010 meta-analysis on the effects of *Saccharomyces boulardii* as supplementation to a standard eradication regimen on *H. pylori* eradication rates and therapy-associated side effects.

Methods
The Cochrane Library, MEDLINE and EMBASE databases were searched from July 2010 (end date of last search) to February 2015, with no language restrictions, for randomised controlled trials (RCTs); additional references were obtained from reviewed articles. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines.

Results
Eleven RCTs (2200 participants, among them 330 children) met the inclusion criteria. Of the 853 patients in the *S. boulardii* group, 679 (80%, 95% CI 77–82) experienced eradication compared with 608 of the 855 patients (71%, 95% CI 68–74) in the control group [relative risk (RR) 1.11, 95% confidence interval (CI) 1.06–1.17; moderate quality evidence]. *S. boulardii* compared with control reduced the risk of overall *H. pylori* therapy-related adverse effects (RR 0.44, 95% CI 0.31–0.64; moderate quality evidence), particularly of diarrhoea (RR 0.51, 95% CI 0.42–0.62; high quality evidence) and nausea [RR 0.6, 95% CI 0.44–0.83 (moderate quality of evidence)].

Conclusions
In the populations studied, the effectiveness of standard triple therapy was unsatisfactory. The addition of *S. boulardii* significantly increased the eradication rate, but it was still below the desired level of success. *Saccharomyces boulardii* significantly decreased some therapy-related side effects.

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INTRODUCTION

Helicobacter pylori infection eradication therapy should be personalised based on prior history and whether the patient is in a high-risk group for resistance.[1] According to the Maastricht IV/Florence Consensus Report,[2] in areas of low clarithromycin resistance, a proton pump inhibitor (PPI) with clarithromycin remains the recommended first-choice treatment. Bismuth-containing quadruple treatment is also an alternative. In areas of high clarithromycin resistance (over 15–20%), bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available, sequential treatment or a nonbismuth quadruple treatment is recommended. PPI–clarithromycin–metronidazole and PPI–clarithromycin–amoxicillin regimens are equivalent. More recently, for Western countries, 14-day concomitant therapy, 14-day bismuth quadruple therapy and 14-day hybrid sequential-concomitant therapy, have been suggested as the most effective treatment regimens.[1]

Major problems with current therapies are unsatisfactory eradication rates and therapy-related adverse effects, prompting interest in adjunctive treatments. According to the Maastricht IV/Florence Consensus Report, certain probiotics show promising results as an adjuvant treatment in reducing side effects.[2] Indeed, a number of systematic reviews and meta-analyses have shown that probiotic supplementation improved eradication rates and/or reduced side effects overall and individual symptoms of diarrhoea, epigastric pain, nausea and taste disturbance of anti-*H. pylori* treatment.[3–5] As the effects of probiotics seem to be strain specific, pooling data on different strains may result in misleading conclusions. A meta-analysis that evaluates the effect of administering a clearly defined, probiotic(s) provides more specific information.

Previously, we investigated the effects of *Saccharomyces boulardii*, a nonpathogenic yeast, as supplementation to standard triple therapy on *H. pylori* eradication rates and therapy-associated side effects.[6] Five randomised controlled trials (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 and reduced the risk of overall *H. pylori* therapy-related adverse effects, particularly of diarrhoea. There were no significant differences between groups in the risk of other adverse effects. 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.

In the last few years, a number of new relevant studies have been published. These studies have prompted interest in updating current evidence. Here, our aim was to update the 2010 assessment of the effects of *S. boulardii* as supplementation to a standard eradication regimen on *H. pylori* eradication rates and therapy-associated side effects.

METHODS

The same methodology that has been already presented in our previous review was followed.[6] PRISMA guidelines were followed.[7]

Criteria for considering studies for this review

In brief, all relevant RCTs that compared *S. boulardii* supplementation 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 [i.e. 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 from July 2010 (end date of last search) to February 2015. 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 reviewers (AH, MK) 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. Two registries for clinical trials (www.clinicaltrials.gov, www.clinicaltrialsregister.eu) were screened to identify published and ongoing studies. The references for identified studies were checked. Certain publication types (i.e. letters to the editor, abstracts and proceedings from scientific meetings) were excluded, unless a full set of data was obtained from the authors. In one case, we obtained by email additional information allowing us to assess the risk of bias and to clarify the results.

Data collection and analysis

Two reviewers, using a standardised approach, independently undertook the literature search, data extraction and quality assessment. The data sought included baseline characteristics of the study population, 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. Any disagreements were resolved by discussion. Two reviewers (AH, MK) independently assessed the risk of bias, with disagreements resolved by discussion with the third reviewer (HS).

The Cochrane Collaboration's tool for assessing risk of bias was used. For RCTs, risk of bias assessment includes the following criteria: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data and selective outcome reporting.[8]

For assessing the quality of evidence for outcomes reported in the included studies, we chose to use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and GRADEProfiler software (version 3.6, 2011). The GRADE system offers four categories of the quality of the evidence. High quality indicates high confidence that the true effect lies close to that of the estimate of the effect; moderate quality indicates moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality indicates that confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; and very low quality indicates very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.[9]

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. All analyses were based on the random effects model.[8]

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

Data synthesis

The data were analysed using the Review Manager (RevMan) (Computer program, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The dichotomous outcomes, the results for individual studies and pooled statistics are reported as the relative risk (RR) between the experimental and control groups with the 95% confidence interval (CI). The number needed to treat (NNT), with the 95% CI, was calculated, if there was a significant difference in the dichotomous outcome between the groups, using the formula recommended by the Cochrane Handbook [NNT = 1/ACR × (1−RR)], where ACR, assumed control risk, was an average control group risk.[8] Crude eradication rates were calculated with 95% CIs. The analyses were based on the intention-to-treat principle.

RESULTS

For a flow diagram documenting the identification process for eligible trials, see online Supporting Information (Figure S1). In addition to the previously identified five studies,[11–15] six new studies were identified.[16–21] Included studies are described with respect to their characteristics and risk of bias in Table S1 and Figure S2 respectively. For the characteristics of excluded trials, with reasons for exclusion, see Table S2. With the exception of one RCT by Cremonini *et al.*,[12] all included trials had a number of methodological limitations such as unclear sequence generation (7 RCTs),[13, 16–21] unclear allocation concealment (10 RCTs),[11, 13–21] and no or unclear blinding (9 RCTs).[13–21] One RCT published only in abstract form lacked adequate information to assess the overall risk of bias.[21] In only three RCTs,[11, 12, 18] the sample size calculations were available. Except for two trials published in Chinese,[19, 20] for which the translation was obtained, all remaining articles were published in English. The included trials randomised a total of 2200 patients. Nine trials enrolled only adults,[11–13, 15, 17–21] and two RCTs[14, 16] were undertaken exclusively in children (n =

330; age range: 3–18 years). One RCT included subjects aged 15 years or older; however, the mean age of the participants was 47.1 ± 11.4 years.[17] The sample size ranged from 42 to 661 participants. In all studies, *S. boulardii* was used in addition to standard triple therapy consisting of a PPI and two antibiotics. The duration of supplementation lasted from 1 week[20] to 2 weeks[11–13, 16–19, 21] to 4 weeks.[14, 15] In all included trials, clarithromycin was one of the antibiotics used; however, clarithromycin resistance was not assessed in any of the included trials. The daily dose of *S. boulardii* ranged from 100 mg[18] to 500 mg[12, 14, 16, 17, 19, 20] to 750 mg[15] to 1000 mg.[11, 13] In one RCT, the dose was not provided.[21] Two RCTs[11, 12] were placebo controlled; in the remaining nine trials,[13–21] there was no additional intervention in the control group. Except for one multi-centre trial,[13] the included studies were single-centre trials. The studies were undertaken in countries such as China (three RCTs[16, 19, 20]), Greece (one RCT[18]), Iran (one RCT[17]), Italy (one RCT[12]), Korea (two RCT[15, 21]), Romania (one RCT[14]) and Turkey (two RCTs[11, 13]).

The GRADE assessment for outcomes related to *S. boulardii* administration and eradication and adverse effects is presented in Tables S3 and S4 respectively. Using the GRADE, the overall quality of evidence for all assessed outcomes was rated as moderate for eradication and overall adverse effects. For specific adverse effects, the GRADE was rated high only for diarrhoea.

Effects of interventions

Helicobacter pylori eradication rates. Data regarding the effects of *S. boulardii* supplementation on *H. pylori* eradication rates were available from nine trials,[11, 12, 14–18, 20, 21] which reported data from 1708 participants (1378 adults and 330 children) (Figure 1). In six RCTs,[14–17, 20, 21] the eradication rate was a primary outcome; in the remaining trials it was a secondary outcome.

Of the 853 patients in the *S. boulardii* group, 679 (80%, 95% CI 77–82) experienced eradication compared with 608 of the 855 patients (71%, 95% CI 68–74) in the control group. Thus, we found a significant difference between the *S. boulardii*-supplemented group and the control group with respect to *H. pylori* eradication rates (9 RCTs, $n = 1708$, RR 1.11, 95% CI 1.06–1.17; NNT 12, 95% CI 8–25). No significant heterogeneity was found ($\chi^2 = 4.75$, $P = 0.78$; $I^2 = 0\%$).

In the two RCTs[14, 16] that targeted children only, the eradication rate was improved in the *S. boulardii* group compared with the control group (2 RCTs, $n = 330$, RR 1.13, 95% CI 1.03–1.25). No significant heterogeneity was found ($\chi^2 = 0.1$, $P = 0.75$; $I^2 = 0\%$). Similarly, in the seven RCTs that included only adult participants, the eradication rate was improved in the *S. boulardii* group compared with the control group (RR 1.11, 95% CI 1.04–1.18). No significant heterogeneity was found ($\chi^2 = 4.51$, $P = 0.61$; $I^2 = 0\%$).

One RCT,[19] involving 100 patients, reported the eradication rate at 1 year only; thus, it was not included in the pooled results. However, this RCT also reported an increased eradication rate in the *S. boulardii* group compared with the control group (RR 1.31, 95% CI 1.03–1.67).

Adverse effects. Data regarding therapy-related adverse effects were available from all of the included trials (Figure 2). In one RCT,[17] which reported adverse effects each week for 4 weeks, we considered the highest number of adverse effects during the active treatment period.

Treatment with *S. boulardii* compared with placebo or no intervention reduced the risk of overall adverse effects (7 RCTs, $n = 1488$, RR 0.44, 95% CI 0.31–0.64; NNT 5, 95% CI 4–7). Significant heterogeneity was found ($\chi^2 = 16.36$, $P = 0.01$; $I^2 = 63\%$).

With regard to specific adverse effects, the risk of therapy-related diarrhoea was statistically lower in the *S. boulardii* group compared with the control group (9 RCTs, $n = 2018$, 12% vs. 24%, respectively, RR 0.51, 95% CI 0.42–0.62, NNT 7, 95% CI 6–9). No significant heterogeneity was found ($\chi^2 = 8.66$, $P = 0.37$; $I^2 = 8\%$). In addition, there was a significant difference between the groups in the frequency of nausea in the *S. boulardii* group compared with the control group (6 RCTs, $n = 1326$, 7.7% vs. 12.8%, RR 0.6, 95% CI 0.44–0.83, NNT 14, 95% CI 9–36). No significant heterogeneity was found ($\chi^2 = 2.45$, $P = 0.78$; $I^2 = 0\%$). However, we found no significant difference between the study groups with respect to epigastric pain, taste disturbance/dry mouth or abdominal gas/bloating (see Figure S3). In addition, 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 reported in two trials only.[18, 21] There was no significant difference between the study groups (2 RCTS, $n = 303$, RR 0.42,

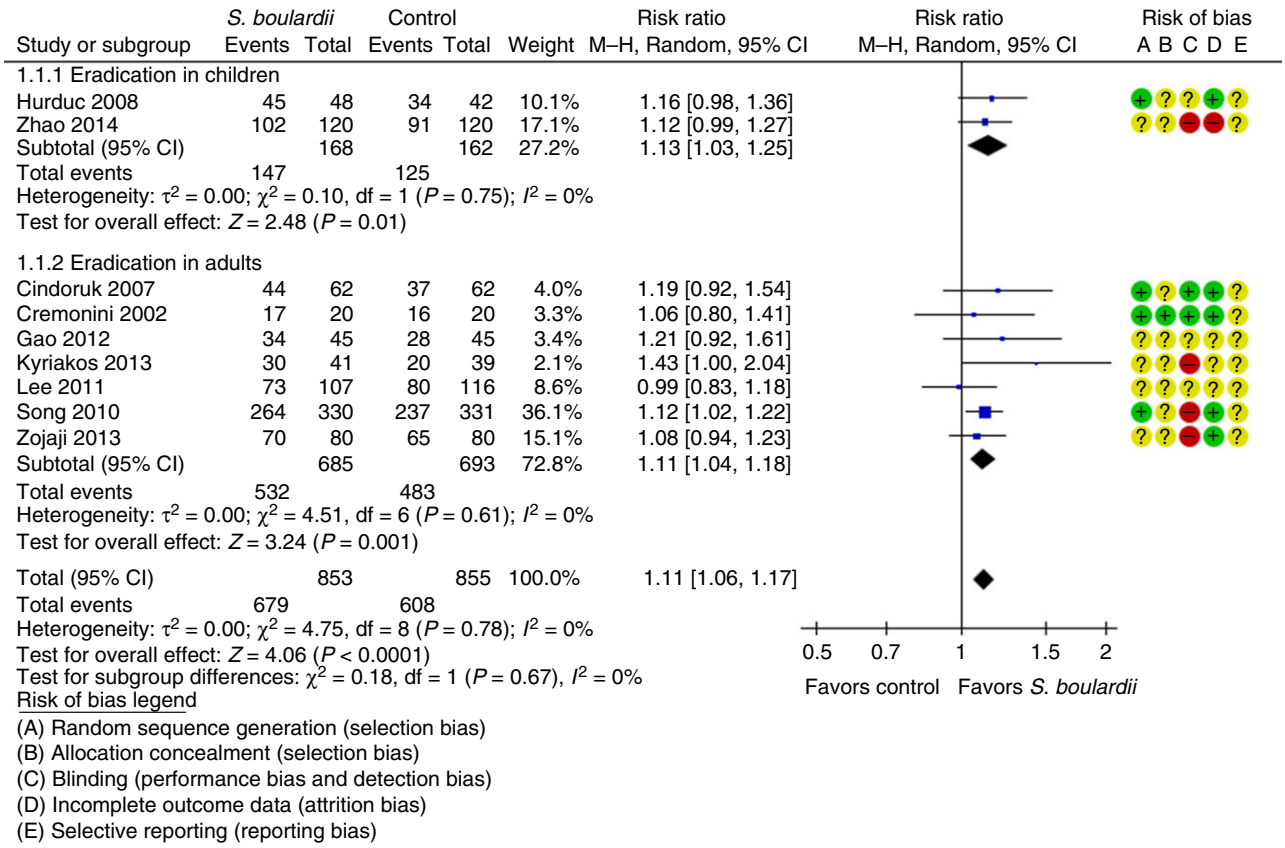

Figure 1 | Primary outcome: Effect of *Saccharomyces boulardii* (SB) on *Helicobacter pylori* eradication rates.

95% CI 0.15–1.14). No significant heterogeneity was found ($\chi^2 = 0.0$, $P = 0.91$; $I^2 = 0\%$). No side effects related specifically to *S. boulardii* administration were reported.

DISCUSSION

Summary of evidence

In the populations studied, the effectiveness of standard triple therapy was unsatisfactory. The addition of *S. boulardii* significantly increased the eradication rate; however, it was still below the desired level of success. *Saccharomyces boulardii* reduced overall therapy-related adverse effects and decreased some individual symptoms such as diarrhoea and nausea. The GRADE quality of evidence assessment revealed moderate quality of evidence for eradication and overall adverse effects. For specific adverse effects, high quality evidence was revealed for diarrhoea only.

None of the trials reported on adverse effects other than those related to eradication therapy. However, *S. boulardii* consumption is not without risk in specific patient groups such as immunocompromised subjects or in patients with other life-threatening illnesses managed in intensive care units.[22] As previously, also in this updated analysis, the majority of included patients were adults; thus, the results may be applicable primarily to such a population.

Strengths and limitations

The major strength of our analysis is that it collates the largest number of studies available on one, well-defined probiotic, i.e. *S. boulardii*. We used a rigorous systematic review methodology. We employed several methods to reduce bias (i.e. comprehensive literature search, duplicate data abstraction, pre-specified criteria for methodological assessment and analysis). We did not impose restrictions by language or year of publication. Attempts were made to identify unpublished trials. However, this review has some limitations. The methodological quality of the included trials varied. Potential limitations included unclear allocation

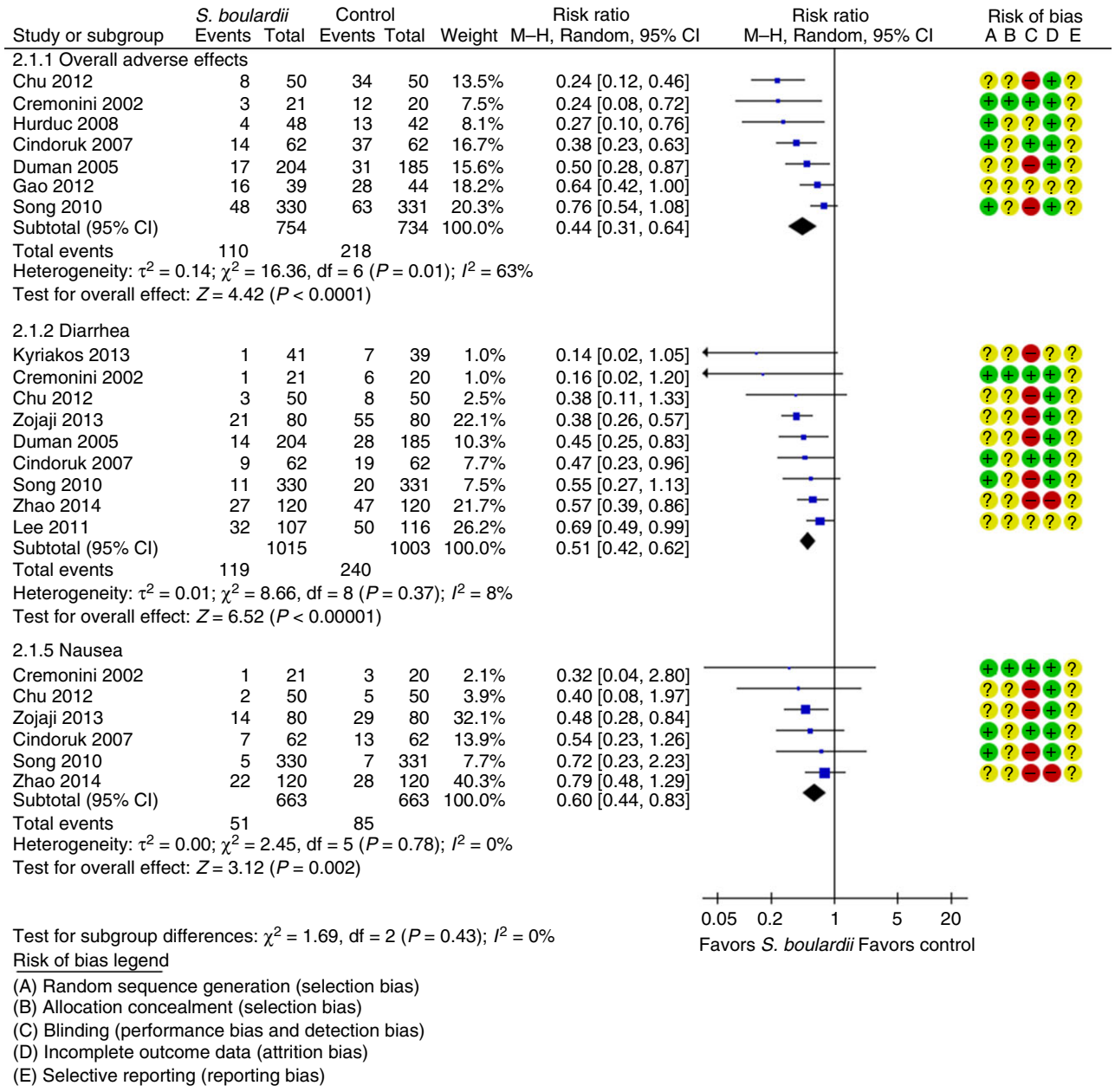

Figure 2 | Secondary outcomes: Effect of *Saccharomyces boulardii* (SB) on *Helicobacter pylori* eradication therapy-related adverse effects (overall adverse effects, diarrhoea, nausea).

concealment and no blinding in almost all trials. Study limitations also included a small sample size and lack of sample size calculations in some trials. Factors influencing the effectiveness of *H. pylori* therapy, such as the CYP2C19 genotype and antibiotic resistance, particularly clarithromycin resistance, were not evaluated in the included trials. Considering these limitations, it is reassuring that there was consistency of the effect across studies, particularly with regard to the outcomes such as *H. pylori* eradication rates and therapy-related diarrhoea.

Agreement and disagreement with other studies or reviews

A number of meta-analyses have been carried out and yielded very similar results; that is, probiotic supplementation improves the eradication rate and/or reduces the rate of side effects.[4–6] However, these meta-analyses pooled data

on various probiotics. Thus, it was not clear which probiotic strain(s) is/are effective. Perhaps, the most specific was the meta-analysis of nine RCTs involving 1163 subjects on the effects of *Lactobacillus*-containing probiotics.[23] Overall, compared with the control group, *Lactobacillus*-containing probiotics significantly increased the eradication rate [414/604 (68.5%) vs. 437/559 (78.2%), respectively, RR 1.14; 95% CI 1.06–1.22; NNT 10]. Thus, the small effect size was comparable with the one shown in our meta-analysis. In contrast to our findings with *S. boulardii* supplementation, no significant reduction in overall side effects was observed (RR 0.88; 95% CI 0.73–1.06). In the subgroup analysis, eradication rates raised significantly by 17% in the lactobacillus-administrated alone group, but there was no significant difference if multi-strain probiotics were administered. *Lactobacillus*-containing probiotics improved the eradication rates, both in adults and in children.

Our findings with regard to therapy-related diarrhoea add to a number of previously published meta-analyses, which documented that treatment with *S. boulardii* compared with placebo or no treatment reduced the risk of antibiotic-associated diarrhoea in children and adults.[24–26] 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.

An effective *H. pylori* therapy should reliably provide high (i.e. 90% or more) eradication rates in patients with infections with susceptible strains.[27, 28] Our analysis documented that the *H. pylori* eradication rate in the triple therapy group increased with *S. boulardii* supplementation from 71% to 80%. Thus, even when supplemented with *S. boulardii,* this treatment did not achieve the desired level of success. A number of factors may have played a role. First, it is unclear whether the choice of *H. pylori* eradication therapy in the included trials was ideal for the local population, particularly considering the increasing rates of clarithromycin resistance in many parts of the world.[2] The duration of *H. pylori* therapy might not have been adequate. In principle, a 14-day treatment regimen is considered superior to a 7- or 10-day treatment regimen. However, in some studies, the latter treatment regimens were used. Second, factors related to *S. boulardii,* such as doses and duration of therapy, must be considered. The largest effect on the eradication rate was observed in the largest, but open-label, RCT by Song *et al.*[15] Interestingly, in this trial, the daily dose of *S. boulardii* was 750 mg (corresponding to $\approx 22.5 \times 10^9$ CFU); however, it was administered for 4 weeks; however, the duration of *H. pylori* eradication therapy was only 7 days (considered inferior to 14-day treatment). Whether or not this dose/duration of treatment contributed to the beneficial effect of *S. boulardii* on the eradication rate is not clear, but it could not be excluded.

Considering that the addition of *S. boulardii* to standard triple therapy did not provide a clinically relevant increase in *H. pylori* eradication rates, an open question remains regarding whether future studies are needed. If so, the choice of *H. pylori* eradication regimen is crucial, as the ethics of using inferior regimens in *H. pylori* randomised trials has been questioned.[29–31] Trials should be restricted to comparison between therapies that achieve at least 90%, and preferably 95% or greater, success rates.[32] Currently, concomitant therapy, bismuth quadruple therapy and hybrid sequential-concomitant therapy (all of 14-day duration) have been suggested as the most effective treatment regimens.[1] As variations in the efficacy of these therapies have been reported, future trials assessing the addition of *S. boulardii* may be substantiated in settings with less optimal eradication rates. *Saccharomyces boulardii* supplementation potentially may increase *H. pylori* eradication rates by approximately 9%. Moreover, considering that current *H. pylori* regimens were associated with increased rates of side effects,[33] studies to evaluate the effect of *S. boulardii* on therapy-associated side effects may be warranted to further optimise the most effective treatments.

CONCLUSIONS

Moderate quality evidence showed that the use of *S. boulardii* reduced the risk of therapy-related side effects, particularly diarrhoea (high quality evidence). It also increased the *H. pylori* eradication rate (moderate quality evidence); however, the eradiation rate was still below the desired level of success. New, improved *H. pylori* eradication therapy regimens taking into account clarithromycin and metronidazole resistance are available. Considering the beneficial effect of *S. boulardii* documented in our analysis, one could speculate that the addition of *S. boulardii* therapy may result in even higher eradication rates or reduced side effects that potentially may threaten compliance with the treatment. Further trials are needed to confirm this assumption. As the majority of included patients were adults, studies in children, using optimal therapies, are needed.

AUTHORSHIP

Guarantor of the article: H. Szajewska.

Author contributions: 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. HS is guarantor of the article.

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Declaration of personal interests: H. Szajewska has served as a speaker for Biocodex, the manufacturer of *Saccharomyces boulardii*. The two remaining authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Identification process for eligible trials.

Figure S2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

Figure S3. Secondary outcomes: Effect of *Saccharomyces boulardii* (SB) on *Helicobacter pylori* eradication therapy-related adverse effects (epigastric pain, taste disturbance/dry mouth, abdominal gas/pain and need for discontinuation).

Table S1. Characteristics of included studies.

Table S2. Characteristics of excluded studies.

Table S3. GRADE evidence profile summarising the effect of *Saccharomyces boulardii* supplementation vs. placebo or no intervention on *Helicobacter pylori* eradication.

Table S4. GRADE evidence profile summarising the effect of *Saccharomyces boulardii* supplementation vs. placebo or no intervention on *Helicobacter pylori* adverse effects.

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