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# Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea

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## SUMMARY

### Background
Antibiotic-associated diarrhoea is a common complication of antibiotic use, but it can be prevented with administration of probiotics.

### Aim
To update our 2005 meta-analysis on the effectiveness of *Saccharomyces boulardii* in preventing antibiotic-associated diarrhoea in children and adults.

### Methods
The Cochrane Library, MEDLINE, and EMBASE databases were searched up until May 2015, with no language restrictions, for randomised controlled trials; additional references were obtained from reviewed articles. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.

### Results
Twenty-one randomised controlled trials (4780 participants), among which 16 were new trials, met the inclusion criteria for this updated systematic review. Administration of *S. boulardii* compared with placebo or no treatment reduced the risk of antibiotic-associated diarrhoea (as defined by the study investigators) in patients treated with antibiotics from 18.7% to 8.5% (risk ratio, RR: 0.47; 95% CI: 0.38–0.57, number needed to treat, NNT: 10; 95% CI: 9–13). In children, *S. boulardii* reduced the risk from 20.9% to 8.8% (6 randomised controlled trials, n=1653, RR: 0.43, 95% CI: 0.3–0.6); in adults, from 17.4% to 8.2% (15 randomised controlled trials, n=3114, RR: 0.49, 95% CI: 0.38–0.63). Moreover, *S. boulardii* reduced the risk of *Clostridium difficile*-associated diarrhoea; however, this reduction was significant only in children (2 randomised controlled trials, $n = 579$, RR: 0.25; 95% CI: 0.08–0.73) and not in adults (9 randomised controlled trials, $n = 1441$, RR: 0.8, 95% CI: 0.47–1.34).

### Conclusions
This meta-analysis confirms that *S. boulardii* is effective in reducing the risk of antibiotic-associated diarrhoea in children and adults.




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## INTRODUCTION

Antibiotic-associated diarrhoea (AAD) is defined as diarrhoea which occurs in conjunction with antibiotic administration and that cannot be explained by another process.[1] Essentially, any antibiotic can initiate AAD as early as just a few hours following antibiotic administration up to several months after its discontinuation.[2, 3] The prevalence of AAD depends on the definition of AAD, the antimicrobial agents, host factors such as extreme ages of life (<6 years and >65 years), or hospitalisation. In the paediatric population, it generally varies from 5% to 30%, but exceptionally, has been reported to be as high as 80% in very young hospitalised children.[4] In adults, the prevalence ranges from 5% to 70%.[5] The clinical presentation of AAD varies from mild diarrhoea to colitis or fulminant pseudomembranous colitis.[5] The two latter conditions manifest with abdominal pain, fever and bloody diarrhoea.

Probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.[6] In humans, *Saccharomyces boulardii*, a non-pathogenic yeast, is one of the most commonly used probiotics. Previously, we investigated the effects of *S. boulardii* in preventing AAD in children and adults.[7] A meta-analysis of data from five randomised controlled trials (RCTs) showed that *S. boulardii* is moderately effective in preventing AAD in children and adults treated with antibiotics for any reason (mainly respiratory tract infections). In the last few years, a number of new relevant studies have been published. Here, our aim was to update the 2005 assessment of the effects of *S. boulardii* compared with placebo or no intervention for preventing AAD in children and adults. This review was initiated as part of the development of guidelines on the use of probiotics for preventing AAD in children.

## METHODS

As previously, this systematic review and meta-analysis was conducted according to the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions,[8] with reporting following the PRISMA Statement.[9]

Electronic databases (see Search strategy) were systematically searched to identify studies appropriate for inclusion in this systematic review. Only RCTs were eligible for inclusion. Participants were adults and children who received antibiotics for any reason, including *Helicobacter pylori* eradication therapy. Patients in the experimental groups additionally received *S. boulardii* at any dose/duration. Subjects in the control group received placebo or no additional intervention. The *primary* outcome measure was the incidence of diarrhoea or AAD (as defined by the investigators). If both outcomes were reported, a more conservative outcome has been chosen for reporting in this meta-analysis. The *secondary* outcome measures were the incidence of *Clostridium difficile* diarrhoea; the need for discontinuation of the antibiotic treatment; the need for hospitalisation to manage the diarrhoea (in outpatients); the need for intravenous rehydration in any of the study groups; and adverse events.

### Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE and EMBASE databases were searched for relevant studies published up until May 2015. The principal search text word terms and MESH headings used were diarrhea/diarrhoea, antibiotic-associated/antibiotic associated, *Clostridium difficile, Helicobacter pylori,* probiotics and *Saccharomyces boulardii.* Furthermore, reference lists from the original studies and review articles identified were screened, and key experts in the field were approached for unpublished material. No limit was imposed regarding the language of publication. Two registers for clinical trials (www.clinicaltrials.gov, www.clinicaltrialsregister.eu) were screened. All potentially relevant articles were retained, and the full text of these studies examined to determine which studies met the inclusion criteria. One reviewer (MK) carried out data extraction, using standard data extraction forms, which was then assessed by the second reviewer (HS). Data were extracted as complete (available) case analyses. Studies reported in languages other than those familiar to the authors were translated. Disagreements were resolved by discussion. The Cochrane Collaboration's tool for assessing risk of bias in the included trials was used. Use of the following strategies associated with good quality studies was assessed: adequacy of sequence generation; allocation concealment; blinding of investigators, participants, outcome assessors, and data analysts; incomplete outcome data; and selective outcome reporting.[10] For assessing the quality of evidence for outcomes reported in the included studies, we chose to use the GRADE methodology and GRADEProfiler software (GRADEpro. [Computer program on www.gradepro.org]. Version [3.6, 2011]. McMaster University, 2011). The GRADE system offers four categories of the quality of the evidence (i.e. high, moderate, low and very low).[11]

Heterogeneity was quantified by $\chi^2$ 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. For the $\chi^2$ test, $P < 0.15$ indicates

significant heterogeneity, and for the $I^2$ statistic, a value >50% indicates substantial heterogeneity. All analyses were based on the random effects model if it was still considered appropriate to pool the data. To test for publication bias, a test for asymmetry of the funnel plot, as proposed by Egger *et al.*,[12] was used if sufficient (≥10) eligible trials were available.

*Statistical methods.* The data were analysed using the Review Manager (RevMan) [Computer program, Version 5.3.; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] and StatsDirect version 3.0.146 (StatsDirect Ltd, Sale, Cheshire, England) to generate forests plots and funnel plots. The binary measure (prevalence of diarrhoea or AAD) for individual studies and pooled statistics is reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% 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] Two subgroup analyses were planned based on the study population (children and adults), the indication for the antibiotic therapy (common infections and antibiotic therapy as part of *H. pylori* eradication therapy), and the type of antibiotics administered or the indication. However, only the first two analyses were feasible.

## RESULTS

Figure S1 documents the identification process for eligible trials. In addition to the previously identified five RCTs,[13–17] 16 new trials were included.[18–33] Except for three trials published in Chinese,[18] Portuguese[19] and Spanish[20] for which the translation was obtained, all of the remaining trials were published in English. Table S1 summarises characteristics of all the included RCTs, and Table S2 summarises characteristics of the excluded trials, including the reasons for exclusion. Moreover, three registered trials were identified. Among them, one RCT was completed but no publication was found (EU Clinical Trials Register, 2008-001426-14); one RCT was terminated but the results were not published (ClinicalTrials.gov, NCT01143272, Germany) and one RCT is not recruiting yet (ClinicalTrials.gov, NCT01463943, Brazil).

The 21 selected studies recruited a total of 4780 participants (2441 in the experimental group and 2339 in the control group) treated as in-patients and/or out-patients. Sample size calculations were only available in 11 trials. Twelve studies were placebo-controlled; in the remaining studies, there was no intervention in the control group. Fifteen trials were performed in adults, and six trials were performed in children.

The daily dose of *S. boulardii* ranged from 50 mg to 1000 mg. There was high variability in the type of antibiotics administered, which were administered as single drugs or in combinations. In nine RCTs, antibiotics were administered as part of *H. pylori* eradication therapy consisting of proton pump inhibitors and two antibiotics. There was variability in the definition of outcome measures. The most commonly used definition of the diarrhoea was the presence of three or more loose (or watery) stools per 24 h, but criteria for its duration varied from 24 h to at least 48 h (Table S1). There were also wide differences in the duration of follow-up, which varied from 2 weeks to 1 year after the cessation of antibiotic treatment, or it was not specified.

The risk of bias assessment is presented in Figure S2. Only two trials were at low risk of bias.[13, 24] In the remaining trials, the limitations included unclear random sequence generation (14 trials), unclear or no allocation concealment (17 trials), unclear or no blinding of participants and personnel (14 trials), unclear or no blinding of outcome assessment (9 trials), and selective or unclear reporting (6 trials). Intention-to-treat analysis was performed in 14 trials. The GRADE assessment for outcomes related to *S. boulardii* administration and diarrhoea is presented in Tables S3 and S4. Using the GRADE, the overall quality of evidence for all assessed outcomes was rated as moderate to low.

### Effects of interventions

Treatment with *S. boulardii* compared with placebo or no treatment reduced the risk of AAD (as defined by the study investigators) in patients treated with antibiotics from 18.7% to 8.5% (RR: 0.47, 95% CI: 0.38–0.57, random effect model). No significant heterogeneity was found ($\chi^2$ = 28.44, $P$ = 0.10, $I^2$ = 30%; Figure 1). For every 10 patients receiving daily *S. boulardii* with antibiotics, one fewer would develop diarrhoea (NNT: 10, 95% CI: 9–13).

A reduction in the risk of AAD was found both in children and adults evaluated separately. In children, compared with placebo or no treatment, *S. boulardii* reduced the risk of diarrhoea from 20.9% to 8.8% (6 RCTs, $n$ = 1653, RR: 0.43, 95% CI: 0.30–0.60, NNT: 9, 95% CI: 7–12; Figure S3); in adults, compared with placebo or no treatment, *S. boulardii* reduced the risk of

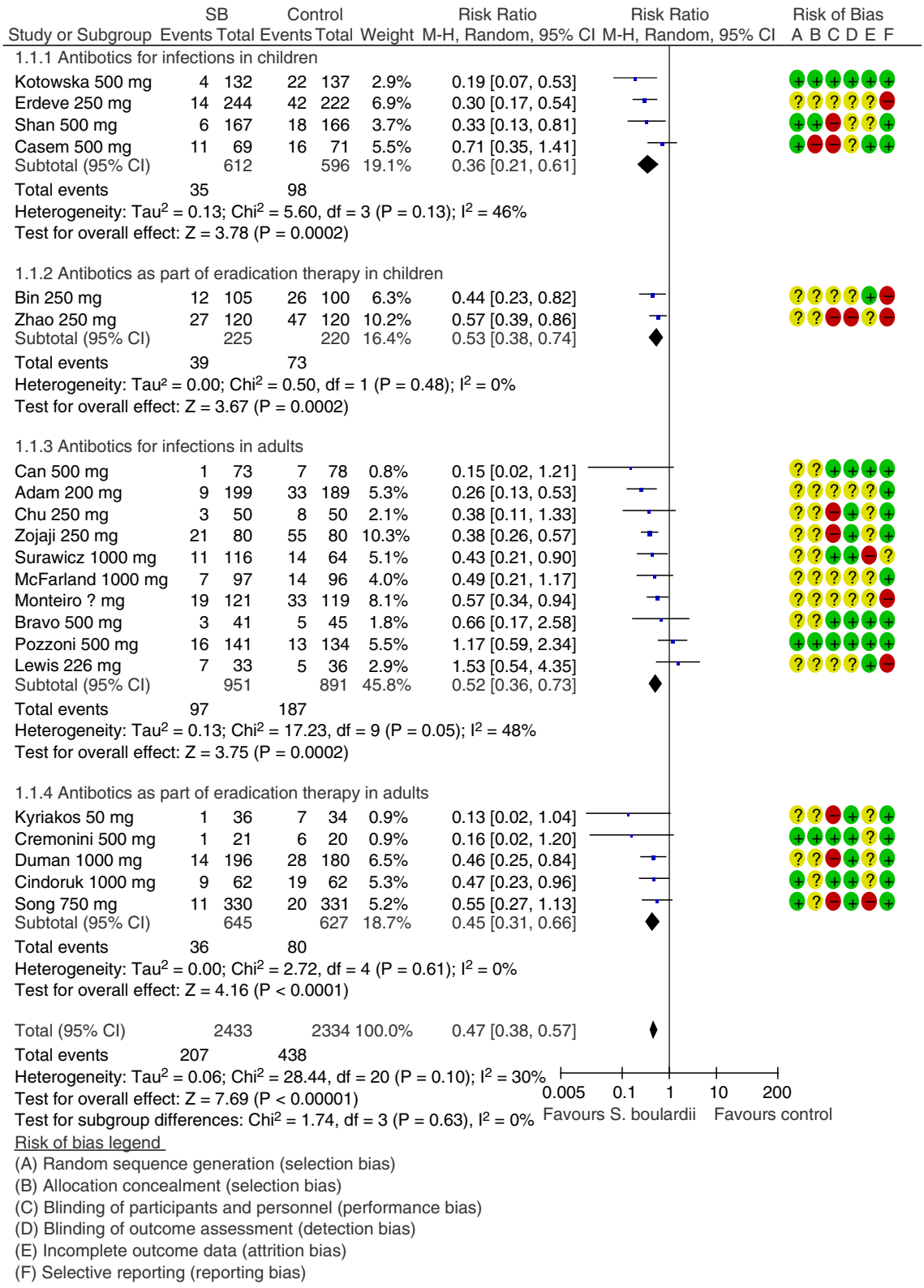


**Figure 1 |** Effect of *Saccharomyces boulardii* for preventing antibiotic-associated diarrhoea.

diarrhoea from 17.4% to 8.2% (15 RCTs, $n = 3114$, RR: 0.49, 95% CI: 0.38–0.63, NNT: 11, 95% CI: 9–15; Figure S4). Moreover, both in children and adults, preplanned subgroup analyses showed a reduction in the risk of diarrhoea associated with antibiotic treatment, regardless of the reason for which the antibiotics were used (i.e. as part of *H. pylori* eradication or for other reasons; Figure 1).

Eleven trials[13, 15–17, 20, 21, 24, 25, 27, 29, 30] evaluated the effect of *S. boulardii* in the prevention of *C. difficile*-associated diarrhoea. Among them, two RCTs were performed in children.[13, 25] Overall, the risk of documented *C. difficile*-associated diarrhoea was lower in the *S. boulardii* group compared with the placebo group, but the difference was not significant ($n = 2020$, RR: 0.64, 95% CI: 0.39–1.04, random effect model). No significant heterogeneity was found ($\chi^2 = 9.56$, $P = 0.39$, $I^2 = 6\%$). However, subgroup analysis based on age, showed that the administration of *S. boulardii* reduced the risk of *C. difficile*-associated diarrhoea in children (two RCTs, $n = 579$, RR: 0.25, 95% CI: 0.08–0.73), but not in adults (nine RCTs, $n = 1441$, RR: 0.80, 95% CI: 0.47–1.34; Figure 2).

Based on the findings from six RCTs, there was no need for discontinuation of antibiotic treatment.[13, 22, 25, 27, 28, 32] Based on data from two RCTs, there was no need for hospital treatment because of diarrhoea in the out-patients or intravenous rehydration in any of the study groups.[13, 22]

*Adverse events.* Data regarding therapy-related adverse effects were available from 16 of the included

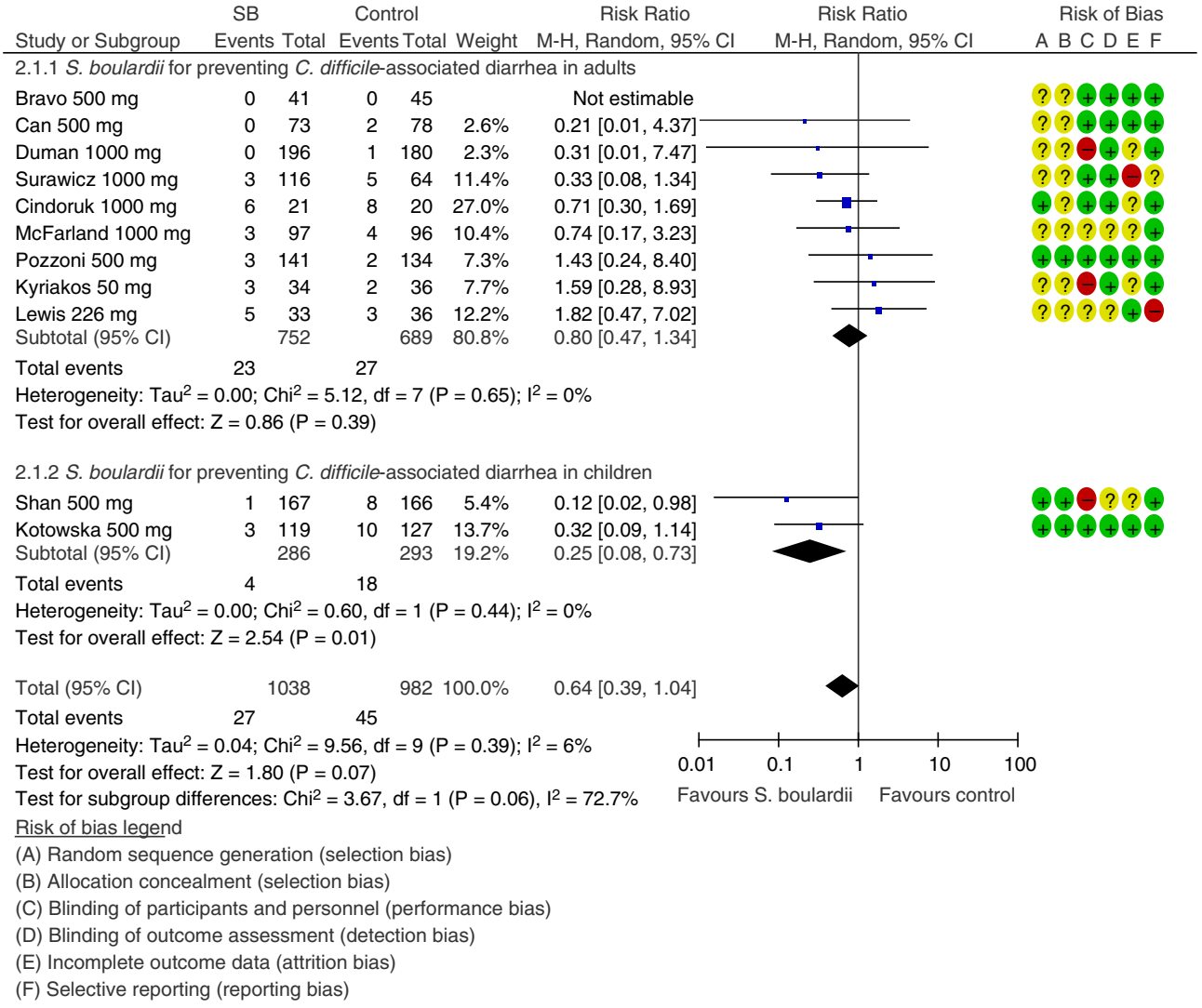


**Figure 2 |** Effect of *Saccharomyces boulardii* for preventing *Clostridium difficile*-associated diarrhoea.

trials.[13–17, 20, 22, 24–31, 33] In these trials, *S. boulardii* was well tolerated. Adverse events rate was similar in experimental and control groups.

*Publication bias.* The funnel plot for publication bias is presented in Figure S5. There was no evidence of publication bias among trials on *S. boulardii* and AAD.

## DISCUSSION

### Summary of evidence

This systematic review and meta-analysis has confirmed our previous findings that *S. boulardii* administration, concomitantly with antibiotics, compared with placebo or no intervention, reduces the risk of AAD in adults and children treated with antibiotics for any reason. The NNT to avoid one case of AAD was 10. There is also evidence that *S. boulardii* may reduce the risk of *C. difficile*-associated diarrhoea; however, this finding was significant only in a subgroup of children and the wide confidence interval calls for caution. For all outcomes, the GRADE quality of evidence assessment revealed moderate to low quality of evidence. One characteristic that makes our meta-analysis distinct from other reviews is that it focuses exclusively on only one well-defined probiotic, *S. boulardii;* thus, the findings can be directly applied to clinical practice.

The mechanism by which *S. boulardii* exerts its action in preventing AAD and *C. difficile*-associated diarrhoea remains unclear. However, a number of mechanisms have been suggested, as discussed in detail elsewhere.[34, 35] One of the mechanisms, which has been demonstrated in animals, involves the production of a 54 kDa serine protease that inactivates a receptor for toxin A of *C. difficile* and directly degrades *C. difficile* toxins A and B.[36] Another mechanism involves secretion of increased levels of secretory immunoglobulin A (IgA) and IgA antitoxin A.[37] Moreover, both *in vitro* and *in vivo* studies have shown that *S. boulardii* exerts its anti-inflammatory activity, in part, by modulating host MAP kinase signalling pathways. In particular, *S. boulardii*-conditioned media inhibited IL-8 production induced by either IL-1β or toxin A in a dose-dependent fashion.[38] Additional mechanisms include competition for attachment sites and blocking *C. difficile* adherence to cells *in vitro*.[39, 40]

### Strengths and limitations

An important strength of this systematic review and meta-analysis is the use of rigorous methodology developed by the Cochrane Collaboration. We employed several methods to reduce bias (i.e. comprehensive literature search, pre-specified criteria for methodological assessment and analysis, no restrictions by language or year of publication, attempts to identify unpublished trials). However, one major limitation is that the methodological quality of the included trials varied. Only two trials were at low risk of bias. Finally, an important limitation is the difference in how AAD and/or diarrhoea were defined in the included trials. We noted a small sample size and lack of sample size calculations in many trials; however, the total sample size in the meta-analysis was sufficient to draw trustworthy conclusions.

### Agreement and disagreement with other studies or reviews

Our findings add to an accumulated body of evidence from previously published meta-analyses, which documented that treatment with probiotics compared with placebo or no treatment reduces the risk of AAD in children and adults.[41–44] The effect size was comparable with one shown by us in the current meta-analysis. In large part, these meta-analyses pooled data on various probiotics. However, in the meta-analysis by Hempel *et al.*, subgroup analysis based on the probiotic genus was performed. This subgroup analysis of 16 RCTs showed that a yeast-based intervention [*Saccharomyces boulardii* (*cerevisiae*) or Hansen CBS 5926] reduced the risk of AAD by 52% (RR: 0.48, 95% CI: 0.35–0.65). Similar to our meta-analysis, trials in which antibiotics were used as part of *H. pylori* eradication therapy, typically consisting of proton pump inhibitors and two antibiotics, were included. However, there is evidence that the use of proton pump inhibitors, which are part of *H. pylori* eradication regimens, increases the risk of gastrointestinal (and respiratory) tract infections.[45, 46] Thus, our approach was to report the evidence on the effect of *S. boulardii* as supplementation to *H. pylori* eradication therapy separately. 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.

### Implications for practice

With regard to specific recommendations, one important question remains whether the use of *S. boulardii* should be considered in all subjects receiving antibiotics or only in select populations. The findings of our meta-analysis apply to patients similar to those enrolled in the trials. Both children and adults were well represented, except for those of extreme ages (<6 months and >65 years).

The decision of whether to treat or not to treat a very young or an older individual will require clinical judgement. In clinical trials, *S. boulardii* was safe and well tolerated, also in those of extreme ages. However, special concern is needed in specific populations such as immune-compromised subjects or in patients with other life-threatening illnesses managed in intensive care units. In those populations, *S. boulardii* can cause fungaemia.[47]

Risk factors for developing AAD include the type of antimicrobials used. The results of this meta-analysis show that *S. boulardii* significantly reduces the risk of diarrhoea in patients treated with antibiotics in general. However, they do not allow conclusions about the efficacy of *S. boulardii* in preventing diarrhoea attributable to any single antibiotic class. Again, the decision to treat or not to treat an individual treated with a specific antibiotic with *S. boulardii* will require clinical judgement.

The optimal dose of probiotics, including *S. boulardii,* has not been established. However, at least one recent study showed that probiotic efficacy improves in a dose-dependent manner.[48] In the current systematic review and meta-analysis, various doses of *S. boulardii* were used with no clear dose-dependent effect. Until more data on the optimal dose of *S. boulardii* become available, a daily dose of not less than 250 mg but not more than 500 mg in children and not more than 1000 mg in adults could be used to match the doses used in RCTs.

To match clinical trials showing a clear benefit, *S. boulardii* administration should be started early in the course of antibiotic treatment before alteration of the gut flora and overgrowth of pathogens occurs. Based on the published trials, it seems appropriate to continue the administration of *S. boulardii* for the duration of antibiotic treatment. Whether longer administration is necessary is not clear, as *S. boulardii* was administered after cessation of antibiotic therapy in only two RCTs with no clear benefit. On the other hand, as diarrhoea may occur up to several months following cessation of such treatment, some cases of AAD may have been missed.

## CONCLUSIONS

As numerous different probiotic products are available, it is important to know the efficacy of a specific product, not of probiotics in general. The current meta-analysis helps to resolve such uncertainty. In cases in which an antibiotic is recommended, moderate quality evidence showed that the use of *S. boulardii* reduced the risk of AAD. The findings apply to both children and adults. Even if included trials reported no adverse effects related to *S. boulardii,* its consumption is not without risk in specific patient groups such as immunocompromised subjects or in patients with other life-threatening illnesses managed in the intensive care unit.[47] Although available data are encouraging, it seems that the prudent use of antibiotics remains the best method of preventing AAD.

## AUTHORSHIP

*Guarantor of the article*: HS.

*Author contributions*: HS initially conceptualised this study. Both 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. Both authors contributed to (and agreed upon) the final version.

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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.

**Figure S3.** Effect of *S. boulardii* for preventing antibiotic-associated diarrhoea in children.

**Figure S4.** Effect of *S. boulardii* for preventing antibiotic-associated diarrhoea in adults.

**Figure S5.** Funnel plot for publication bias.

**Table S1.** Characteristics of the included studies.

**Table S2.** Characteristics of the excluded studies.

**Table S3.** GRADE evidence profile summarising the effect of *Saccharomyces boulardii* supplementation vs. placebo or no intervention on antibiotic-associated diarrhoea.

**Table S4.** GRADE evidence profile summarising the effect of *Saccharomyces boulardii* supplementation vs. placebo or no intervention on *Clostridium difficile*-associated diarrhoea.

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