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Systematic Review and Meta-Analysis: Safety and Efficacy of Saccharomyces *boulardii* for Prevention of Clostridioides *difficile* Infection

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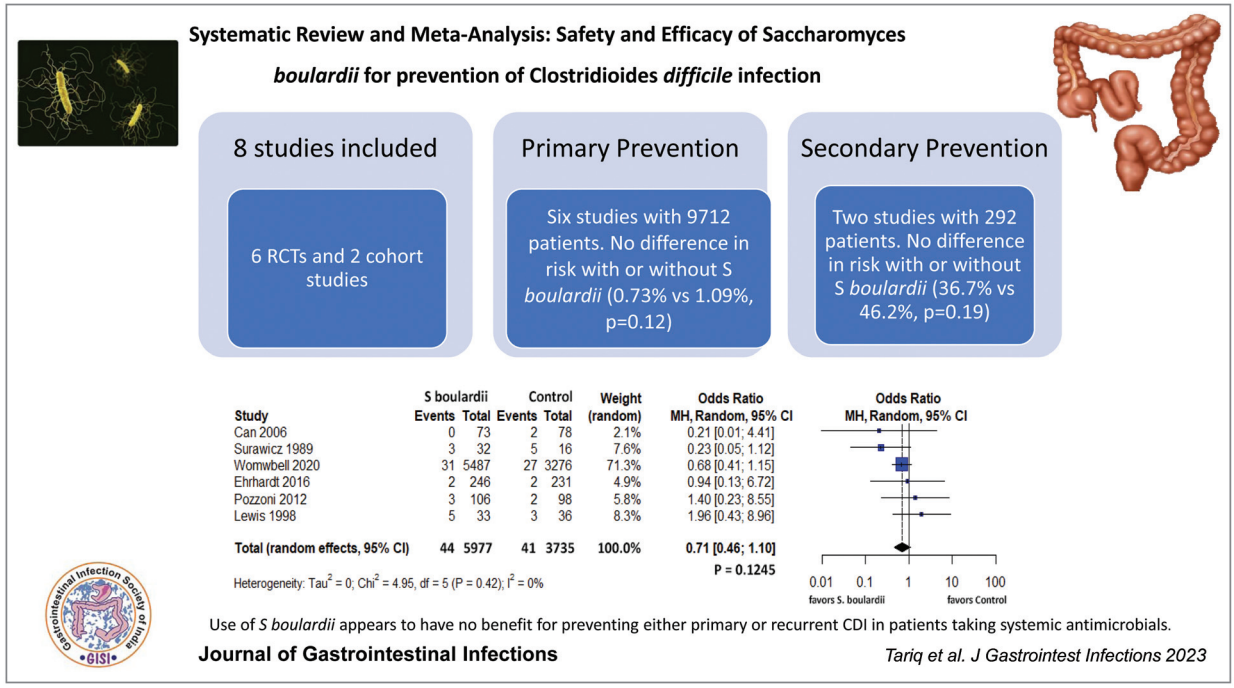

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Abstract

Background *Clostridioides difficile* infection (CDI) is associated with frequent recurrences. The role of probiotics in preventing CDI remains unclear despite patients frequently using them.

Methods We performed a systematic-review and meta-analysis to evaluate the role of *Saccharomyces boulardii,* a yeast probiotic, in preventing primary or recurrent CDI in patients on systemic antimicrobial therapy. We searched MEDLINE, Embase, and Web of Science up to December 2021 to identify studies (case-control, cohort, or clinical trial studies) reporting the use of systemic antimicrobials with or without *S. boulardii* and providing information on primary or recurrent CDI. Pooled odds ratios with 95% confidence intervals were calculated using a random effects model.

Results Eight studies (six randomized control trials and two cohort studies) were included. Six studies with 9,712 patients evaluated primary prevention. The rate of CDI in patients who received *S. boulardii* was 0.73% (44/5977) compared to 1.09% (41/3735) in the control group. Meta-analysis showed no difference in the risk of CDI among the two groups (odds ratio [OR], 0.71; 95%CI, 0.46–1.10; $p = 0.124$) with no significant heterogeneity ($I^2 = 0\%$). In two studies with 292 patients evaluating secondary prevention, the rate of recurrent CDI was 36.73% (54/147) on *S. boulardii* compared to 46.20% (67/145) in controls, with no significant difference ($p = 0.19$). Subgroup analysis of studies using *S. boulardii* (250 mg twice daily) showed no difference in the CDI risk with or without *S. boulardii.* No serious adverse events from *S. boulardii* were noted.

Conclusion The use of *S. boulardii* appears to have no benefit for preventing either primary or recurrent CDI in patients taking systemic antimicrobials.

Keywords

- *Clostridioides difficile*
- *Saccharomyces boulardii*
- probiotics
- prevention
- antibiotic-associated diarrhea

Introduction

Clostridioides difficile infection (CDI) is the most common nosocomial infection in the United States, with almost half a million cases annually. Risk factors for CDI include those that predispose to microbial dysbiosis such as increasing age, inflammatory bowel disease, use of proton pump inhibitors and most importantly antibiotic exposure.[1,2] The optimal approach to reduce the risk of CDI in patients who require systemic antimicrobial therapy remains unclear. Adjunctive therapy with probiotics has been widely used by patients in hopes to decrease the risk of CDI with or without guidance of clinicians. The goal of probiotic therapy is to try to colonize the intestinal tract and hopefully mitigate the effects of microbiota disruption. In addition, probiotics may interact with the host immune system to decrease pathogen invasion and toxin production.[3] Although studies have shown most strains of probiotic to have good survival during passage through the gastrointestinal tract and remain metabolically active, most studies have shown very short persistence and transient engraftment if any.[4,5]

Saccharomyces boulardii is a specific yeast-derived probiotic with a direct inhibitory action against *C. difficile* toxins.[3] Two studies have shown that *S. boulardii* can upregulate specific anti-toxin A IgA expression in animal models of CDI.[6,7] Another study demonstrated that *S. boulardii* leads to hydrolyzation of toxins A and B by protease production, thereby decreasing the toxin receptor binding and reducing some of the enterotoxic effects of toxin A.[8] Due to the inhibiting toxin properties of *S. boulardii*, it is hypothesized to help decrease the risk of CDI recurrence, perhaps in a mechanism similar to the administration of monoclonal antibody bezlotoxumab that neutralizes toxin B.[9]

Current studies evaluating the outcomes of probiotics in preventing CDI are inconsistent. A meta-analysis evaluating the use of probiotics found that the administration of probiotics closer to the first dose of antibiotics reduced the risk of CDI by $> 50\%$ in hospitalized patients.[10] Another Cochrane review concluded that there was insufficient evidence to recommend probiotic therapy as an adjunct to CDI therapy for CDI.[11] However, given the effects of probiotics seem to be strain-specific and most of the prior meta-analyses have included different strains of probiotics together, we performed a comprehensive systematic-review and meta-analysis to evaluate the role of *S. boulardii* only for primary and secondary CDI prevention in patients receiving systemic antimicrobial therapy.

Methods

All procedures used in this meta-analysis were consistent with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[12] and MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria for observational studies.[13]

Selection Criteria

The studies considered in this meta-analysis were observational studies or clinical trials that evaluated patients on systemic antimicrobial therapy who did or did not receive *S. boulardii* and measured the incidence of primary or recurrent CDI. Primary prevention was defined as patients with no prior history of CDI receiving *S. boulardii* and secondary prevention was defined as patients with prior history of CDI receiving *S. boulardii* for prophylaxis of a future episode of CDI. We excluded studies that did not evaluate CDI as an outcome or if there were insufficient data to determine an estimated OR and 95% confidence interval (CI). Both studies with published full-text or studies available as abstracts were included.

Data Sources and Search Strategy

We conducted a comprehensive search of Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus from 2000 to December 2021. The search strategy was designed and conducted by study investigators (MWT and RT) and the Mayo Clinic library staff, independently. The search was limited to studies in the English language. Controlled vocabulary supplemented with keywords was used to search for studies of *S. boulardii* use and CDI. The main keywords used in the search were *Clostridioides difficile, Clostridium difficile*, *C. diff*, *C. difficile*, *Clostridium difficile* infection, *Clostridioides difficile,* CDI, *Clostridioides difficile*-associated diarrhea, *Clostridium difficile*-associated diarrhea or CDAD, or pseudomembranous colitis, or recurrence AND *S. boulardii* OR prophylaxis OR probiotics AND outcomes or infection. The search was limited to English-language publications. The actual strategy listing with all search terms and how they were combined is available in ►**Supplementary Appendix A** (available in the online version).

Literature Screening

Two authors (R.T. and M.W.T) independently reviewed the titles and abstracts of the identified studies, and those that did not answer the research question of interest were excluded. The full texts of the remaining articles were reviewed to determine inclusion criteria fulfillment. The reference lists of articles with information on the topic were also reviewed for additional pertinent studies. We also searched the abstracts from major Gastroenterology and Infectious Diseases Society meetings and conferences from 2000 to 2021. A flow diagram of included studies is shown in ►**Fig. 1**.

Quality Assessment

The Cochrane Collaboration risk of bias tool was used to assess the methodologic quality of the included trials, including the methods used to generate the randomization schedule and conceal allocation, blinding, completeness of outcome data, and evidence of selective outcome reporting[14] (►**Supplementary Fig. S1**, available in the online version). The Newcastle–Ottawa scale was used to assess the methodologic quality of case–control and cohort studies.[15] In this scale, observational studies were scored across three categories using the following parameters: selection (four questions), comparability (two questions), and ascertainment of the outcome of interest (three questions). For each question, 1 point was given if the study met the criterion, except for comparability of study groups, in which 1 point was awarded if the study controlled for age, sex, or both, and 2 points if the study controlled other confounding factors (►**Table 1**). Studies with a cumulative score of 7 or more were considered high-quality studies, studies with score between 4 and 6 were considered moderate-quality and low-quality studies if score was less than 4. Any discrepancies were addressed by a joint re-evaluation of the original article.

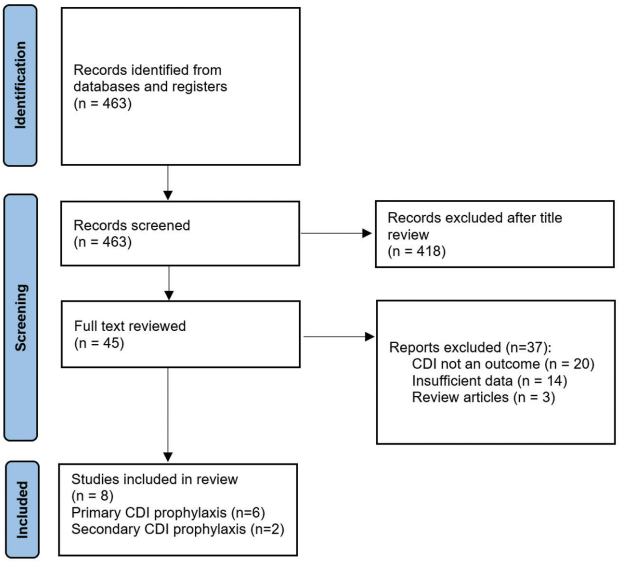

Fig. 1 Flowsheet of search strategy.

Data Abstraction

Data were independently abstracted to a predetermined collection form by two investigators (RT and MWT). Data were collected for each study, including study setting and design, year of publication, location, and primary outcome reported. Conflicts in data abstraction were resolved by consensus, referring to the original article. When data were missing, an attempt to contact primary authors was made for obtaining additional data.

Outcomes Assessed

Our primary analysis focused on assessing the risk of primary CDI and the risk of recurrent CDI in patients with history of CDI with or without *S. boulardii*.

Statistical Analyses

We used the random effects model described by DerSimonian and Laird[16] to calculate the pooled OR and 95% CI for each study. We assessed heterogeneity within groups with the I^2 statistic, which estimates the proportion of total variation across studies that is due to heterogeneity in study

Table 1 Characteristics of included studies

CDI prevention	Study	Design	Inpatient/ Outpatient	Location	Study period	*S boulardii* dose	Duration of *S. boulardii*	Follow-up
Primary	Can et al, 2006	Double-blind RCT	Inpatient	Turkey	Nov 2000 to Sep 2002	NA	NA	4 weeks after antibiotics
	Ehrhardt et al, 2016	Double-blind RCT	Inpatient	Germany	Jul 2010 to Oct 2012	250 mg BID	7 days after antibiotics	6 weeks after *S. boulardii*
	Lewis et al, 1998	Prospective cohort	Inpatient	UK	NA	113 mg BID	Duration of antibiotics	NA
	Pozzoni et al, 2012	Double-blind RCT	Inpatient	Italy	Apr 2009 to Jul 2010	5×10^9 CFU BID $= 250$ mg BID	7 days after antibiotics	12 weeks after antibiotics
	Surawicz et al, 1989	Double-blind RCT	Inpatient	US	NA	250 mg BID	2 weeks after antibiotics	17 days after antibiotics
	Wombwell et al, 2020	Retrospective cohort	Inpatient	US	Jan 2016 to Mar 2017	500 mg BID	Duration of antibiotics	NA
Recurrent	McFarland et al, 1994	Double-blind RCT	Both	US	Jun 1990 to Dec 1992	500 mg BID	4 weeks	8 weeks after *S. boulardii*
	Surawicz et al, 2000	Double-blind RCT	Both	US	Aug 1993 to Dec 1996	250 mg BID	4 weeks	4 weeks after *S. boulardii*

Abbreviation: RCT, randomized control trial.

patients, design, or interventions rather than chance. I^2 values greater than 50% were considered to suggest the presence of heterogeneity.[17] Due to the number of studies < 10, publication bias was not assessed. All p-values were two-tailed and for all tests (except heterogeneity), a probability level less than 0.05 was considered statistically significant. Calculations were performed and graphs were constructed using the R version 4.0.3 package 'meta' version 5.2-0.

Results

Search Results

The described search strategy revealed 463 potentially relevant studies; titles and abstracts were screened, and full papers were obtained for relevant articles (►**Fig. 1**). In all, 45 full-text articles were reviewed, of which 37 were excluded for various reasons most commonly due to lack of CDI data as an outcome (►**Fig. 1**). A total of eight studies were included in this meta-analysis of and all were full-text.

Characteristics of Included Studies

Of the eight studies included, six assessed primary prophylaxis and two assessed secondary prophylaxis. Six studies included hospitalized patients only and two included outpatients and hospitalized patients. Two studies were cohort, and the rest were randomized controlled trials. Study recruitment periods ranged from 1988 to 2017. All patients received systemic antibiotics. The dose of *S. boulardii* ranged from 226 mg to 1 g total daily dose. The follow-up time to assess for CDI occurrence was variable and ranged from the duration of antibiotics to 12 weeks (►**Table 1**).

Quality of Included Studies

The risk of bias of included studies is shown in ►**Supplementary Fig. S1**(available in the online version only). Most studies were considered low-risk bias based on the Cochrane risk of bias tool. For two cohort studies, the median score was 7 (range 7–8), rating as high-quality studies.

S. boulardii for Primary Prevention

Of the 9,712 patients (in six studies) evaluated for primary prevention of CDI, 61.5% (5,977) received *S. boulardii*. Among these, the rate of CDI was 0.73% (44/5,977) compared to 1.09% (41/3,735) of the group that did not receive *S. boulardii*. A meta-analysis using random effects model showed no difference in the risk of CDI among the two groups (odds ratio [OR], 0.71; 95%CI, 0.46–1.10; $p = 0.124$). There was no significant heterogeneity among the studies, with an I^2 value of 0.0% (►**Fig. 2**).

Sensitivity Analysis

This analysis was performed with one study removed from the six studies, which accounted for 90% of the total sample size to assess whether the study had a dominant effect on the summary.[18] Of the 949 participants in the remaining five studies, 51.6% (490/949) received *S.*

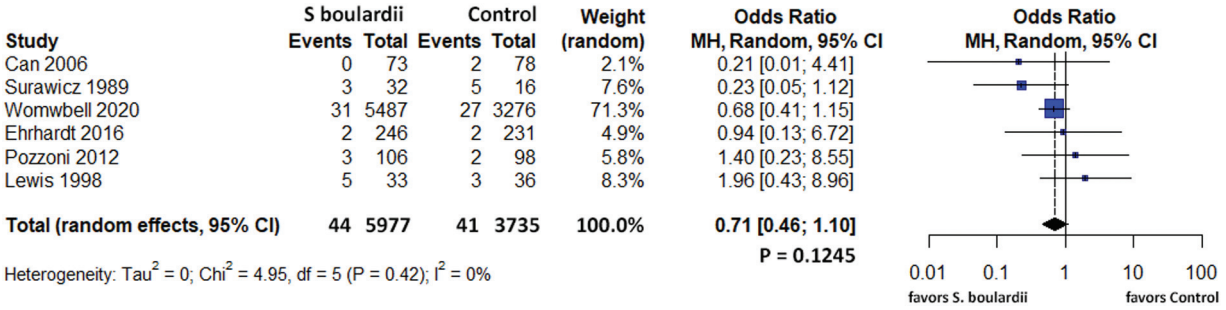

Fig. 2 Forest plot showing the efficacy of *S. boulardii* for the primary prevention of CDI.

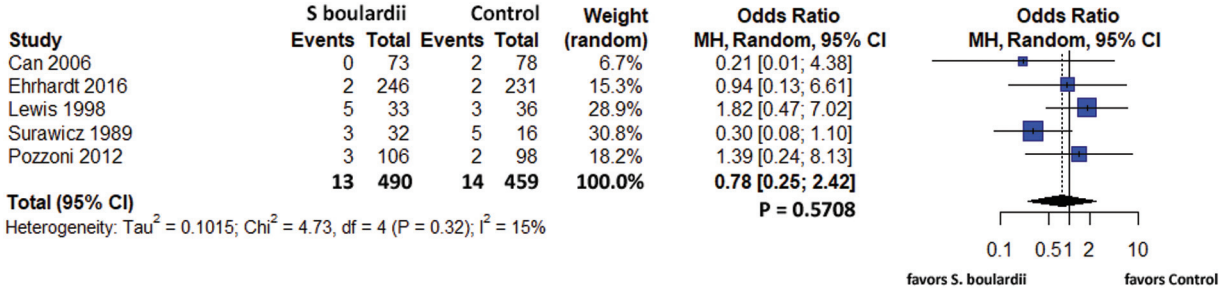

Fig. 3 Sensitivity analysis with one study removed.

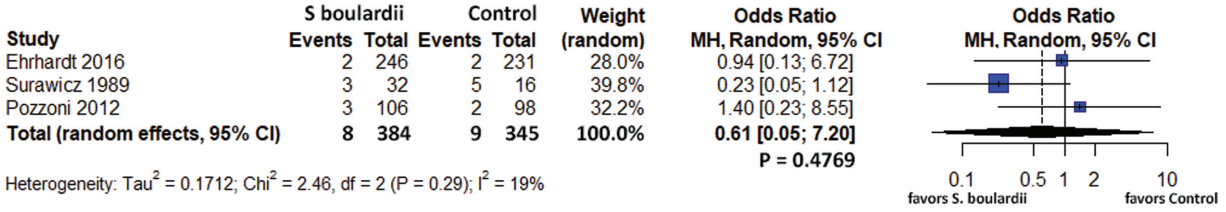

Fig. 4 Subgroup analysis based on the dose of *S. boulardii*.

boulardii where the rate of CDI was 2.65% (13/490) compared to 3.05% (14/459) in the group that did not receive *S. boulardii*. Meta-analysis using the random effects model showed no difference in the risk of CDI among the two groups (odds ratio [OR], 0.78; 95% CI, 0.25–2.42; $p = 0.571$). There was no significant heterogeneity among the studies, with an I^2 value of 15% (►**Fig. 3**).

Sub-Group Analysis of Studies using a Commonly used Dose 250 mg (Twice Daily)

Three studies used the same dosing of *S. boulardii* (250 mg twice daily), which was analyzed as a subgroup. Of the 729 participants in this subgroup, 52.7% (384/729) received *S. boulardii*. The rate of CDI was 2.08% (8/384) compared to 2.61% (9/345) in the group that did not receive *S. boulardii*. A meta-analysis using random effects model showed no difference in the risk of CDI among the two groups (odds ratio [OR], 0.61; 95%CI, 0.05–7.20; $p = 0.477$). There was no significant heterogeneity among the studies, with an I^2 value of 19% (►**Fig. 4**). Due to the small number of studies in this analysis ($n = 3$), publication bias was not assessed.

S. boulardii for Secondary Prevention

Among the 292 patients (in two studies) who were evaluated for the prevention of recurrent CDI, 50.3% (147/292) received *S. boulardii*. Among these, the rate of recurrent CDI was 36.73% (54/147) compared to 46.20% (67/145) in those who did not receive *S. boulardii*. Due to the small number of studies in this analysis ($n = 2$), meta-analysis and publication bias were not calculated.

Adverse Events

Three studies reported no adverse events related to *S. boulardii*.[19–21] One study reported constipation, abdominal pain, pruritus, headache, cutaneous rash, and fever. All adverse events were mild in severity. No cases of fungemia were recorded.[22] One study reported nine adverse events in the *S. boulardii* group including three with a new gastrointestinal disorder, one cardiac death, one cholecystitis, two cases of bacterial sepsis, one pulmonary empyema, and one renal failure. None of the side effects were related to *S. boulardii*.[23] Three studies included no data on adverse events.[18,24,25]

Discussion

We found that use of *S boulardii* was not associated with a decreased risk of primary or recurrent CDI in patients taking systemic antibiotics. A Cochrane review including 8,672 patients looked at probiotics for primary prevention of CDI in adults and children and suggested that probiotics are effective for preventing CDI with the number needed to treat being 42. However, of the 31 included studies, more than half had missing data and 21 had unclear or high risk of bias. A post-hoc subgroup analysis showed that probiotics were only effective among trials with a baseline CDI risk > 5%, which was higher than the average CDI risk in patients taking antibiotics. The results of the study were heavily influenced by five studies with CDI baseline risk > 15%, which was greater than the primary risk in any hospital setting.[26] Another significant limitation of the meta-analysis was pooling studies with different species or strains and dosages of probiotics.[27]

The PLACID trial published in 2013 is the largest double-blind RCT to date for the primary prevention of CDI with probiotics. The trial did not find lower frequency of CDI in elderly inpatients after the administration of *Lactobacilli* and *Bifidobacteria*. The main limitation of the trial was low rate of CDI that limited the power of the study.[28] Nevertheless, another meta-analysis that included the PLACID trial found no significant benefit of probiotics for the prevention of CDI.[29] In light of low-quality evidence, probiotics for prophylaxis of primary or recurrent CDI is not recommended by the American College of Gastroenterology[30] as well as the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America.[31]

The pooled results of our meta-analysis are generally in line with prior studies and suggest no benefits of *S. boulardii* for CDI prevention. Some studies included in our meta-analysis were published in the 1990s and showed promise regarding the benefits of *S. boulardii* for preventing primary or secondary CDI; however, among those studies, the CDI risk was a secondary outcome with the prevention of antibiotic-associated diarrhea as the primary outcome. Since then, most published trials have shown no benefits of *S. boulardii*. A recent single-center retrospective cohort study included in our meta-analysis merged hospital prescribing data with CDI case data included 8,763 CDI patients and showed a protective effect on CDI incidence with a rate of CDI with *S. boulardii* of 0.56% versus no *S. boulardii* of 0.82%, OR 0.57 (0.33–0.96).[18] This was the largest study in our meta-analysis driving most of the sample size for our results, hence a subgroup analysis excluding this study was performed which also showed no benefit of *S. boulardii*.

For primary CDI prevention, most studies used a dose of 250 mg of *S. boulardii* two times a day and one study used a lower dose of 113 mg two times a day. The subgroup analysis of only studies using 250 mg two times a day also did not find any benefit for preventing primary CDI with S. boulardi. For recurrent CDI prevention, both the trials used a higher dose of 1 g daily. The duration of *S. boulardii* was variable and ranged from the duration of antibiotics to 4 weeks, hence no analysis could be performed based on duration. No serious adverse events related to *S. boulardii* were reported and there were no cases of fungemia reported in any of the studies.

Strengths of our study included the comprehensive literature search, strict inclusion criteria, and subgroup analysis. Most studies were high quality with low risk of bias. Our study has limitations. These include small sample sizes, heterogeneous patient populations, inconsistent follow-up periods, and lack of microbiome data among the included studies. Data regarding individual antibiotics were not available; hence we could not access the impact of use of *S. boulardii* with different classes of antibiotics. Additionally, most studies were underpowered, with CDI as a secondary outcome in studies done to assess the prevention of antibiotic-associated diarrhea.

In conclusion, our study shows that *S. boulardii* did not have any benefit on the development of primary or recurrent CDI. We believe that further studies should focus on understanding the mechanism of probiotics in the prevention of CDI before conducting further expensive RCTs.

Ethical Statement

This was a systematic review and meta-analysis with data available publicly, no patients were enrolled and hence ethical approval was not obtained.

Author Contributions

R.T.: concept, data interpretation, drafting and revision of manuscript; M.W.T.: data collection and interpretation, drafting and revision of the manuscript; M.H.: data collectionand interpretation; D.S.P.: concept, data interpretation, drafting and revision of manuscript; S.K.: concept, datainterpretation, drafting and revision of manuscript.

Data Availability Statement

This was a systematic review andmeta-analysis with data available publicly, and no new data were generated.

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None.

Conflict of Interest

None declared.

Acknowledgments

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References

1 Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. JAMA Intern Med 2017;177(06):784–791

2 Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. Antimicrob Agents Chemother 2013;57(05): 2326–2332

3 Parkes GC, Sanderson JD, Whelan K. The mechanisms and efficacy of probiotics in the prevention of *Clostridium difficile*-associated diarrhoea. Lancet Infect Dis 2009;9(04):237–244
4 Zmora N, Zilberman-Schapira G, Suez J, et al. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell 2018;174(06): 1388–1405.e21
5 Jacobsen CN, Rosenfeldt Nielsen V, Hayford AE, et al. Screening of probiotic activities of forty-seven strains of *Lactobacillus* spp. by in vitro techniques and evaluation of the colonization ability of five selected strains in humans. Appl Environ Microbiol 1999;65 (11):4949–4956
6 Buts JP, De Keyser N, De Raedemaeker L. *Saccharomyces boulardii* enhances rat intestinal enzyme expression by endoluminal release of polyamines. Pediatr Res 1994;36(04):522–527
7 Qamar A, Aboudola S, Warny M, et al. *Saccharomyces boulardii* stimulates intestinal immunoglobulin A immune response to *Clostridium difficile* toxin A in mice. Infect Immun 2001;69(04): 2762–2765
8 Pothoulakis C, Kelly CP, Joshi MA, et al. *Saccharomyces boulardii* inhibits Clostridium difficile toxin A binding and enterotoxicity in rat ileum. Gastroenterology 1993;104(04):1108–1115
9 Wilcox MH, Gerding DN, Poxton IR, et al; MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent clostridium difficile infection. N Engl J Med 2017;376(04):305–317
10 Shen NT, Maw A, Tmanova LL, et al. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. Gastroenterology 2017;152(08):1889–1900.e9
11 Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Cochrane Database Syst Rev 2008; (01):CD004611
12 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71):n71
13 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008–2012
14 Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928
15 Wells GASB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed October 7, 2022, at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
16 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(03):177–188
17 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337(8746):867–872
18 Wombwell E, Patterson ME, Bransteitter B, Gillen LR. The effect of *Saccharomyces boulardii* primary prevention on risk of hospital-onset *Clostridioides difficile* infection in hospitalized patients administered antibiotics frequently associated with *C. difficile* infection. Clin Infect Dis 2021;73(09):e2512–e2518
19 Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, van Belle G. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: a prospective study. Gastroenterology 1989;96 (04):981–988
20 Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. Clin Infect Dis 2000;31(04):1012–1017
21 McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. JAMA 1994;271(24):1913–1918
22 Pozzoni P, Riva A, Bellatorre AG, et al. *Saccharomyces boulardii* for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol 2012;107 (06):922–931
23 Ehrhardt S, Guo N, Hinz R, et al. *Saccharomyces boulardii* to prevent antibiotic-associated diarrhea: a randomized, double-masked, placebo-controlled trial. Open Forum Infect Dis 2016;3 (01):ofw011
24 Can M, Beşirbellioglu BA, Avci IY, Beker CM, Pahsa A. Prophylactic *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea: a prospective study. Med Sci Monit 2006;12(04): PI19–PI22
25 Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of *Saccharomyces boulardii* in the prevention of antibiotic-related diarrhoea in elderly patients. J Infect 1998;36(02): 171–174
26 Guh AY, Mu Y, Winston LG, et al; Emerging Infections Program Clostridioides difficile Infection Working Group. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. N Engl J Med 2020;382(14):1320–1330
27 Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 2017;12:CD006095
28 Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2013;382(9900):1249–1257
29 Vernaya M, McAdam J, Hampton MD. Effectiveness of probiotics in reducing the incidence of *Clostridium difficile*-associated diarrhea in elderly patients: a systematic review. JBI Database Syst Rev Implement Reports 2017;15(01):140–164
30 Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol 2021;116(06):1124–1147
31 McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66(07):987–994

