https://doi.org/10.22416/1382-4376-2026-36-3-74-89
UDC 616.33-008.314.4-085.24:615.33.031

Strain-Specific Efficacy of *Saccharomyces boulardii* CNCM I-745 in the Prevention of Antibiotic-Associated Diarrhea: A Systematic Review and Meta-Analysis

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Aim: to perform a systematic review and meta-analysis of the efficacy of *Saccharomyces boulardii* CNCM I-745 in the prevention of antibiotic-associated diarrhea (AAD) in adults and children.
Materials and methods. The protocol for this systematic review and meta-analysis was prospectively registered in the international PROSPERO database (CRD420261296647). In accordance with the PRISMA 2020 guidelines, a systematic literature search was conducted in MEDLINE/PubMed, Embase, the Cochrane Library, Scopus, and RSCI (Russian Science Citation Index) from the time first publications appeared to February 6, 2026. Studies evaluating the efficacy of *S. boulardii* CNCM I-745 (Enterol®) in the primary prevention of AAD and *Clostridioides difficile* infection (CDI) in adults and children were included.
Results. A total of 29 studies met the inclusion criteria and were included in the meta-analysis. The use of *S. boulardii* CNCM I-745 was associated with a statistically significant reduction in the incidence of AAD compared with control in the overall pooled analysis (OR 0.38; 95 % CI 0.32–0.45). Subgroup analysis confirmed the efficacy of the probiotic in both adults (20 studies, *n* = 3937; OR 0.45; 95 % CI 0.33–0.61) and children, in whom the effect was even more pronounced (7 studies, *n* = 1608; OR 0.31; 95 % CI 0.23–0.41). In the analysis of studies in which *S. boulardii* CNCM I-745 was used as part of *Helicobacter pylori* eradication regimens, a statistically significant reduction in AAD risk was also observed (13 studies, *n* = 2333; OR 0.36; 95 % CI 0.25–0.52). Additional analysis demonstrated a significant reduction in CDI risk with *S. boulardii* CNCM I-745 use (8 studies, *n* = 18,426; OR 0.67; 95 % CI 0.49–0.92).
Conclusions. The results of this meta-analysis demonstrate the high efficacy of *S. boulardii* CNCM I-745 in the prevention of AAD in adults and children, as well as in reducing the risk of CDI during antibiotic therapy from the very first day of treatment.
Keywords: antibiotic-associated diarrhea, *Clostridioides difficile*, *Saccharomyces boulardii* CNCM I-745
Conflict of interest: the authors declare no conflicts of interest.

For citation: Ivashkin V.T., Gorelov A.V., Khurmatullina A.R., Andreev D.N., Usenko D.V., Zaborovskiy A.V., Poluektova E.A., Trukhmanov A.S., Lapina T.L., Maslennikov R.V., Maev I.V. Strain-Specific Efficacy of *Saccharomyces boulardii* CNCM I-745 in the Prevention of Antibiotic-Associated Diarrhea: A Systematic Review and Meta-Analysis. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2026;36(3):74–89. https://doi.org/10.22416/1382-4376-2026-36-3-74-89

Штамм-специфичная эффективность *Saccharomyces boulardii* CNCM I-745 в профилактике антибиотик-ассоциированной диареи: систематический обзор и метаанализ

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Цель: проведение систематического обзора и метаанализа эффективности применения *Saccharomyces boulardii* CNCM I-745 в профилактике антибиотик-ассоциированной диареи (ААД) у взрослых и детей.
Материалы и методы. Протокол данного систематического обзора и метаанализа был предварительно зарегистрирован в международной базе PROSPERO (CRD420261296647). В соответствии с рекомендациями PRISMA 2020 проведен систематический поиск публикаций в базах данных MEDLINE/PubMed, Embase, Cochrane Library, Scopus и РИНЦ с момента появления первых публикаций по 6 февраля 2026 г. Включались исследования, оценивающие эффективность *S. boulardii* CNCM I-745 (лекарственный препарат «Энтерол®») в первичной профилактике ААД и инфекции *Clostridioides difficile* у взрослых и детей.
Результаты. В метаанализ было включено 29 исследований, соответствующих критериям включения. Применение *S. boulardii* CNCM I-745 было ассоциировано со статистически значимым снижением частоты ААД по сравнению с контролем в общем пуле исследований (отношение шансов [ОШ] 0,38; 95%-ный доверительный интервал [95% ДИ] 0,32–0,45). Анализ в подгруппах подтвердил эффективность пробиотика как у взрослых (20 исследований, *n* = 3937; ОШ 0,45; 95% ДИ 0,33–0,61), так и у детей, где эффект был еще более выраженным (7 исследований, *n* = 1608; ОШ 0,31; 95% ДИ 0,23–0,41). В анализе исследований, в которых *S. boulardii* CNCM I-745 применялся в составе схем эрадикации *Helicobacter pylori*, также было выявлено статистически значимое снижение риска ААД (13 исследований, *n* = 2333; ОШ 0,36; 95% ДИ 0,25–0,52). Дополнительный анализ продемонстрировал значимое снижение риска инфекции *Clostridioides difficile* на фоне приема *S. boulardii* CNCM I-745 (8 исследований, *n* = 18 426; ОШ 0,67; 95% ДИ 0,49–0,92).
Выводы. Результаты настоящего метаанализа демонстрируют высокую эффективность *S. boulardii* CNCM I-745 в профилактике ААД у взрослых и детей, а также снижении риска инфекции *Clostridioides difficile* на фоне антибиотикотерапии с первого дня ее проведения.
Ключевые слова: антибиотик-ассоциированная диарея, *Clostridioides difficile*, *Saccharomyces boulardii* CNCM I-745
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Ивашкин В.Т., Горелов А.В., Хурматуллина А.Р., Андреев Д.Н., Усенко Д.В., Заборовский А.В., Полуэктова Е.А., Трухманов А.С., Лапина Т.Л., Масленников Р.В., Маев И.В. Штамм-специфичная эффективность *Saccharomyces boulardii* CNCM I-745 в профилактике антибиотик-ассоциированной диареи: систематический обзор и метаанализ. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2026;36(3):74–89. https://doi.org/10.22416/1382-4376-2026-36-3-74-89

Introduction

Antibacterial drugs are among the most frequently prescribed classes of medications and have substantially contributed to reducing the burden of infectious diseases worldwide [1, 2]. However, in real-world clinical practice, the use of antibacterial drugs is often associated with adverse events, among which antibiotic-associated diarrhea (AAD) occupies a prominent place.

As a rule, AAD develops during antibiotic therapy or within several weeks after its completion, in the absence of other obvious causes [3]. The pathogenetic basis of AAD is intestinal dysbiosis associated with disruption of the taxonomic composition of the microbiota, reduced colonization resistance, impairment of the epithelial barrier, and inflammation of the intestinal mucosa [4]. The clinical consequences of AAD include reduced quality of life, decreased treatment adherence, prolonged hospitalization, and increased healthcare costs [5].

According to epidemiological studies, the incidence of AAD in the general population of patients receiving ABDs varies widely, from 5 to 30 % or more, depending on the antibiotic class, duration of treatment, patient age, and concomitant risk factors [6]. In hospitalized patients, the risk of AAD is substantially higher due to more severe baseline conditions, polypharmacy, and exposure to the hospital microbial environment [7]. In this group of patients, the risk of *Clostridioides difficile* infection (*C. difficile*, CDI) increases significantly, as CDI is associated with severe disease course, recurrences, higher mortality, and unfavorable long-term outcomes [8]. In addition to CDI, the risk of AAD in hospitalized patients may be determined by microorganisms such as *Clostridium perfringens, Klebsiella oxytoca, Staphylococcus aureus*, as well as certain strains of *Escherichia coli* and *Candida* spp. [9].

One of the most extensively studied and clinically used approaches to reducing the risk of AAD is the use of probiotics. According to the most recent systematic review and meta-analysis summarizing 15 comparative studies (*n* = 7427), the use of probiotics was associated with a statistically significant reduction in the risk of AAD in adults and children (RR 0.60; 95% CI: 0.43–0.82) [10]. A recent Cochrane meta-analysis also showed that probiotics are able to reduce the risk of CDI in patients receiving antibiotics (RR 0.50; 95% CI: 0.38–0.64), especially in high-risk groups [11].

Among all probiotics, one of the most extensively studied is *S. boulardii* CNCM I-745, a non-bacterial probiotic with unique biological properties, including resistance to antibiotics and gastric acidity, as well as antitoxic, anti-inflammatory,

and immunomodulatory effects [12]. Unlike bacterial probiotics, *S. boulardii* CNCM I-745 can be prescribed from the first day of antibiotic therapy without the need to maintain any time interval between probiotic and antibiotic intake, which improves treatment adherence and increases therapeutic effectiveness. Several meta-analyses summarizing the results of studies in adult and pediatric populations have demonstrated a significant reduction in AAD risk with *S. boulardii* CNCM I-745 compared with control [13, 14]. Most original studies included in the published meta-analyses investigated the best-studied and most clinically evaluated strain of *S. boulardii* — CNCM I-745 (previously designated as *Saccharomyces cerevisiae* CBS 5926), which in Russia is available as Enterol® [15]. Given that the strain *S. boulardii* CNCM I-745 is represented in the scientific literature by a broad evidence base, it was considered appropriate to perform a targeted strain-specific meta-analysis to systematically assess its efficacy in the prevention of AAD.

The aim of the present study was to perform a systematic review and meta-analysis to assess the efficacy of *S. boulardii* CNCM I-745 in the prevention of AAD in adults and children.

Materials and methods

Search strategy

The protocol for this systematic review and meta-analysis was prospectively registered in the international PROSPERO database (registration number: CRD420261296647). The literature search was conducted in the electronic databases MEDLINE/PubMed, Embase, the Cochrane Library, Scopus, and RSCI (Russian Science Citation Index) from database inception to February 6, 2026. Titles and abstracts in English and Russian were screened. For the MEDLINE/PubMed search, the following combinations of keywords were used: ("antibiotic-associated diarrhea"[Title/Abstract] OR "antibiotic associated diarrhoea"[Title/Abstract]) AND ("Saccharomyces boulardii"[Title/Abstract] OR probiotic*[Title/Abstract]). An additional search for studies on the prevention of clostridial infection was performed using the following query: ("Clostridioides difficile"[Mesh] OR "Clostridium difficile Infections"[Mesh] OR "Clostridioides difficile"[Title/Abstract] OR "Clostridium difficile"[Title/Abstract]) AND ("Saccharomyces boulardii"[Mesh] OR "Saccharomyces boulardii"[Title/Abstract]) AND (prevention[Title/Abstract] OR prophylaxis[Title/Abstract]). For the other databases, the search strategy was adapted accordingly.

Inclusion and exclusion criteria

Studies evaluating the efficacy of *S. boulardii* CNCM I-745 in the primary prevention of AAD and CDI in adults and children were included. During the selection process, all studies were examined for the strain used; studies in which strain identity could not be established or in which a strain other than CNCM I-745 was used were excluded. An important inclusion criterion was the availability of detailed statistics allowing incorporation of the results into the meta-analysis. For the AAD analysis, only randomized controlled trials (RCTs) were included. For the CDI analysis, due to the limited number of available publications, studies of various designs were allowed provided that they included a control group, including RCTs, non-randomized controlled clinical studies, and prospective and retrospective cohort studies. Animal studies, case reports and case series, studies without a control group, studies with insufficiently described interventions, studies not reporting relevant outcomes, studies not corresponding to the aim of meta-analysis, duplicate publications, and studies lacking original quantitative data were excluded.

In addition, studies devoted to other types of diarrhea, including associated with irritable bowel syndrome, infectious diarrhea, and inflammatory bowel disease, were excluded. Studies evaluating the efficacy of *S. boulardii* CNCM I-745 in the treatment of CDI or in secondary prevention of CDI, studies conducted in specific patient populations were also excluded.

Data extraction

Two independent investigators (A.R.K. and D.N.A.) extracted the data using standardized forms. The following variables were analyzed: year of publication, characteristics of the study population, diagnostic criteria for AAD and CDI, use of *S. boulardii* CNCM I-745, total sample size, and the number of patients who developed AAD and (or) CDI. Conflicts were resolved by third independent expert (Yu.A.K.).

Statistical analysis

Data analysis was performed using RevMan software (version 5.4.1, The Cochrane Collaboration) in the Microsoft Windows 11 environment. The results are presented as odds ratios (ORs) for AAD and CDI with 95 % confidence intervals (CI). Heterogeneity across studies was assessed using Cochrane's Q test and I^2 index; heterogeneity was considered significant at $p < 0.05$ and $I^2 > 50$ %. The choice of the statistical model for meta-analysis was based on the degree of heterogeneity between studies. In the absence of heterogeneity or in the presence of low heterogeneity ($I^2 \leq 50$ % and ≥ 0.05 according to Cochrane's Q test), a

fixed-effect model was applied. In the presence of moderate or high heterogeneity ($I^2 > 50$ % and/or $p < 0.05$), a random-effects model was used. Publication bias was assessed using a funnel plot, Begg and Mazumda's rank correlation test, and Egger's regression test.

Risk of bias assessment

The risk of bias in the included studies was assessed independently by two investigators. For randomized trials, the Cochrane RoB 2 (Risk of Bias 2) tool was used, which included assessment of the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For non-randomized studies, the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool was used, which assessed bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

Results

Study selection

The systematic search of PubMed, EMBASE, Scopus, the Cochrane Library, and RSCI identified 1053 publications. After removal of duplicates, 522 articles were screened. At the primary screening stage, most were excluded because of inappropriate intervention, non-relevant study population, lack of a control group, focus on treatment or secondary prevention of CDI, absence of clinical outcome data, or duplicate publication. Of the remaining 89 studies, a subsequent full-text eligibility assessment resulted in the exclusion of 60 studies, mainly due to inappropriate intervention, incomplete data for meta-analysis, and investigation of specific patient populations (Fig. 1). Ultimately, 29 studies were considered eligible and included in the present meta-analysis (Table 1).

Efficacy of S. boulardii CNCM I-745

When all studies on AAD prevention were pooled, the overall effect showed a statistically significant reduction in AAD incidence in the *S. boulardii* CNCM I-745 group compared with control: OR 0.38 (95% CI: 0.32–0.45), with moderate heterogeneity ($I^2 = 44$ %; $p < 0.00001$). Prophylactic use of *S. boulardii* CNCM I-745 during antibiotic therapy was associated with a statistically significant reduction in AAD incidence in both adults and children. In the adult meta-analysis (20 studies, $n = 3937$), the risk of

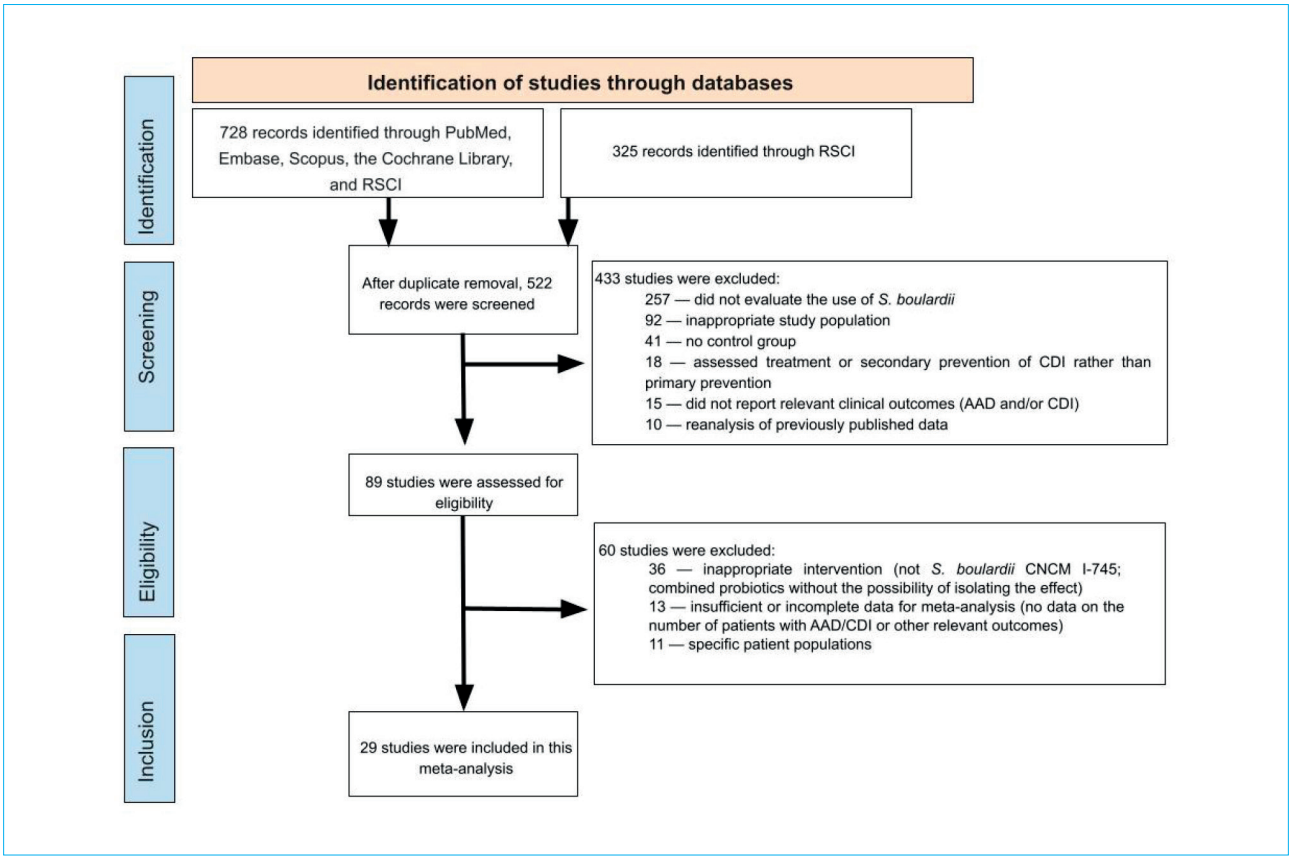

Figure 1. PRISMA flow diagram

Table 1. Characteristics of the included studies

Author, year	Country	Intervention, mg/day	Condition / indication for therapy	Duration of administration, days	Intervention group, *n*	Events in intervention group, *n*	Control group, *n*	Events in control group, *n*
Studies conducted in the adult population assessing AAD incidence								
Adam et al., 1977 [16]	France	200	No data	7	199	9	189	33
Monteiro et al., 1981 [17]	Portugal	1000	Any systemic antibiotic therapy	6	121	19	119	33
Surawicz et al., 1989 [18]	USA	1000	Any systemic antibiotic therapy	14	116	11	64	14
McFarland et al., 1995 [19]	USA	1000	Beta-lactam antibiotic therapy	6	97	7	96	14
Lewis et al., 1998 [20]	United Kingdom	226	Any systemic antibiotic therapy	14	33	7	36	5
Duman et al., 2005 [21]	Turkey	500	*H. pylori* eradication	14	204	12	186	21
Can et al., 2006 [22]	Turkey	500	Any systemic antibiotic therapy	14	73	1	78	7
Cindoruk, 2007 [23]	Turkey	1000	*H. pylori* eradication	14	62	9	62	19
Bravo et al., 2008 [24]	Chile	500	Beta-lactam antibiotic therapy	12	41	4	45	5
Chu et al., 2012 [25]	China	500	*H. pylori* eradication	14	50	3	50	8
Pozzoni et al., 2012 [26]	Italy	500	Any systemic antibiotic therapy	8	106	16	98	13
Ehrhardt, 2016 [27]	Germany	250	Any systemic antibiotic therapy	7	246	19	231	21
Chotivitayatarakorn et al., 2017 [28]	Thailand	565	*H. pylori* eradication	14	27	0	27	3
Seddik et al., 2019 [29]	Morocco	500	*H. pylori* eradication	10	100	2	99	46
Zhao et al., 2021 [30]	China	1000	*H. pylori* eradication	14	178	20	182	39
Maev et al., 2022 [31]	Russia	500	COVID-19 pneumonia	10	60	8	60	18
He et al., 2023 [32]	China	1000	*H. pylori* eradication	14	86	6	86	12
Sjomina et al., 2023 [33]	Latvia	500	*H. pylori* eradication	14	114	12	94	20
Yu et al., 2024 [34]	China	500	*H. pylori* eradication	10	63	0	63	3
Zhang et al., 2024 [35]	China	500	*H. pylori* eradication	14	48	5	48	5
Studies conducted in the pediatric population assessing AAD incidence Kotowska et al., 2004 [36]								
Kotowska et al., 2004 [36]	Poland	500	Otitis media and/or respiratory tract infections	7–9	119	4	127	22
Kyriakos et al., 2013 [37]	Greece	150	*H. pylori* eradication	14	36	1	34	7
Shan et al., 2013 [38]	China	500	Acute lower respiratory tract infection	5	167	6	166	18
Zhao et al., 2014 [39]	China	500	*H. pylori* eradication	14	120	27	120	47
Bin et al., 2015 [40]	China	500	*H. pylori* eradication	14	102	12	92	26
Wan et al., 2017 [41]	China	500	Extra-gastrointestinal infections requiring antibiotic therapy	14	213	22	195	57
Zhang et al., 2024 [42]	China	250	Extra-gastrointestinal infections requiring antibiotic therapy	7/14/21	70	7	47	13

End of Table 1. Characteristics of the included studies

Author, year	Country	Intervention, mg/day	Condition / indication for therapy	Duration of administration, days	Intervention group, *n*	Events in intervention group, *n*	Control group, *n*	Events in control group, *n*
Studies conducted in the adult population assessing CDI incidence								
Surawicz et al., 1989 [18]	USA	1000	Any systemic antibiotic therapy	14	32	3	16	5
Lewis et al., 1998 [20]	United Kingdom	226	Any systemic antibiotic therapy	14	33	5	36	3
Can et al., 2006 [22]	Turkey	500	Any systemic antibiotic therapy	14	73	0	78	2
Pozzoni et al., 2012 [26]	Italy	500	Any systemic antibiotic therapy	9	106	3	98	2
Ehrhardt, 2016 [27]	Germany	250	Any systemic antibiotic therapy	7	246	2	231	2
Wombwell et al., 2021 [43]	USA	1000	Any systemic antibiotic therapy	*	5487	31	3276	27
Maev et al., 2022 [31]	Russia	500	COVID-19 pneumonia	10	60	2	60	4
Wombwell et al., 2023 [44]	USA	500	Any systemic antibiotic therapy	*	4297	26	4297	40

Note: ** during treatment with antibacterial drugs.*
In AAD studies, the event was defined as AAD; in CDI studies, the event was defined as CDI.

AAD was lower in the *S. boulardii* CNCM I-745 group than in the control group: OR 0.45 (95% CI: 0.33–0.61), with moderate heterogeneity (I^2 = 51 %; p = 0.005), corresponding to an approximately 55 % reduction in the odds of developing AAD (Fig. 2). In children (7 studies, n = 1608), the effect was even more pronounced: OR 0.31 (95% CI: 0.23–0.41), with no heterogeneity (I^2 = 0 %; p < 0.00001), corresponding to an approximately 69 % reduction in the odds of AAD (Fig. 3). In a separate analysis of studies in which *S. boulardii* was used as part of *Helicobacter pylori* (*H. pylori*) eradication regimens (13 studies, n = 2333), a statistically significant reduction in AAD risk compared with control was also observed: OR 0.36 (95% CI: 0.25–0.52), with low heterogeneity (I^2 = 43 %). In addition, *S. boulardii* CNCM I-745 demonstrated efficacy in CDI prevention as well (8 studies, n = 18,426): OR 0.67 (95 % CI: 0.49–0.92); I2 = 0 %, p = 0.01 (Fig. 4).

Risk of bias assessment

According to the RoB 2.0 assessment, the highest risk of bias was identified in the domains of deviations from intended interventions and outcome measurement, whereas the lowest risk was observed in the domain of bias arising from the randomization process (Fig. 5). In non-randomized studies assessed using ROBINS-I, the highest risk of bias was also noted in the outcome measurement domain, while the most favorable ratings were observed in the domain of bias due to confounding (Fig. 6).

Egger's regression test did not reveal statistically significant asymmetry of the funnel plots (i.e., no evidence of publication bias) in any of the analyses: for AAD in adults, the intercept was –1.2 (95% CI: –2.93–0.66; p = 0.10); for AAD in children, the intercept was –0.75 (95% CI: –5.26–3.76; p = 0.69); and for CDI, –0.03 (95% CI: –1.43–1.38; p = 0.97). In all cases, the confidence intervals included zero and the p-values exceeded 0.05, indicating the absence of statistically significant asymmetry.

Subgroup analyses

A sensitivity analysis was performed including studies characterized by a low risk of systematic error according to the RoB 2 scale. In these studies, the pooled overall effect also indicated a statistically significant reduction in the incidence of AAD with prophylactic use of *S. boulardii* CNCM I-745 compared with control: OR 0.35 (95% CI: 0.21–0.58). Thus, both the direction and magnitude of the effect were maintained and were comparable to those of the primary analysis, with moderate heterogeneity (I^2 = 44 %; p < 0.00001).

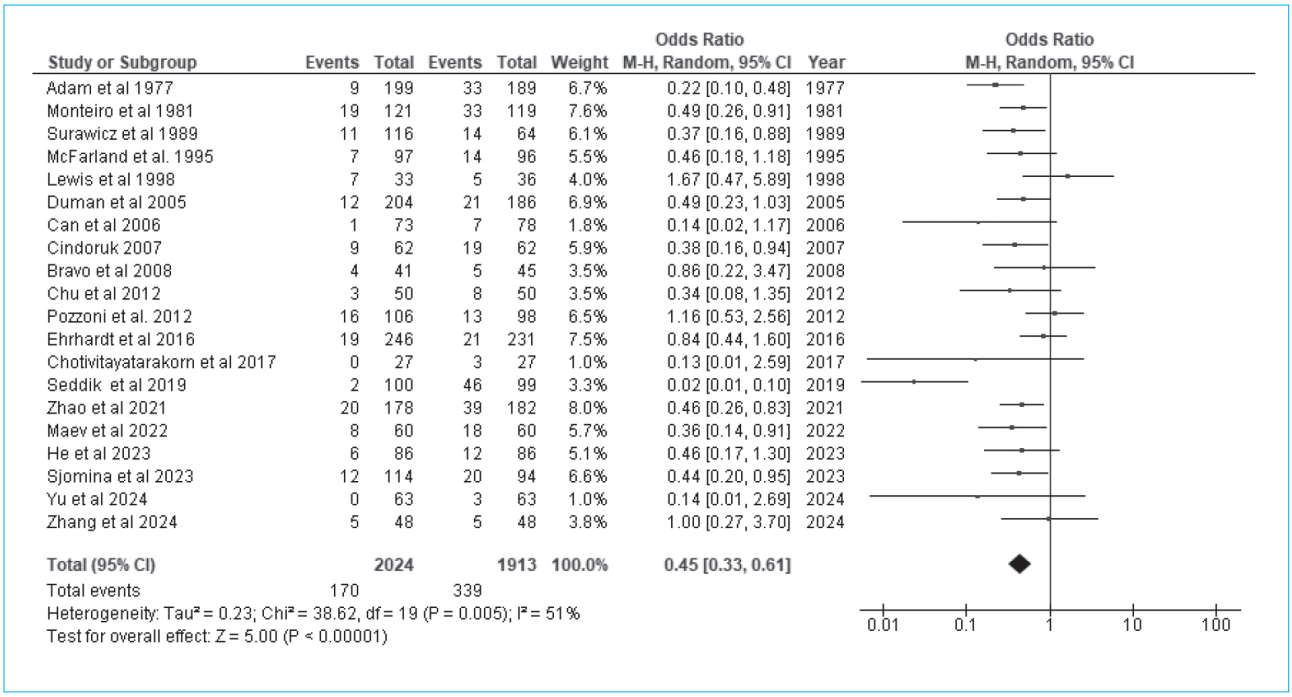

Figure 2. Forest plot of the efficacy of *S. boulardii* CNCM I-745 in the prevention of AAD in adults

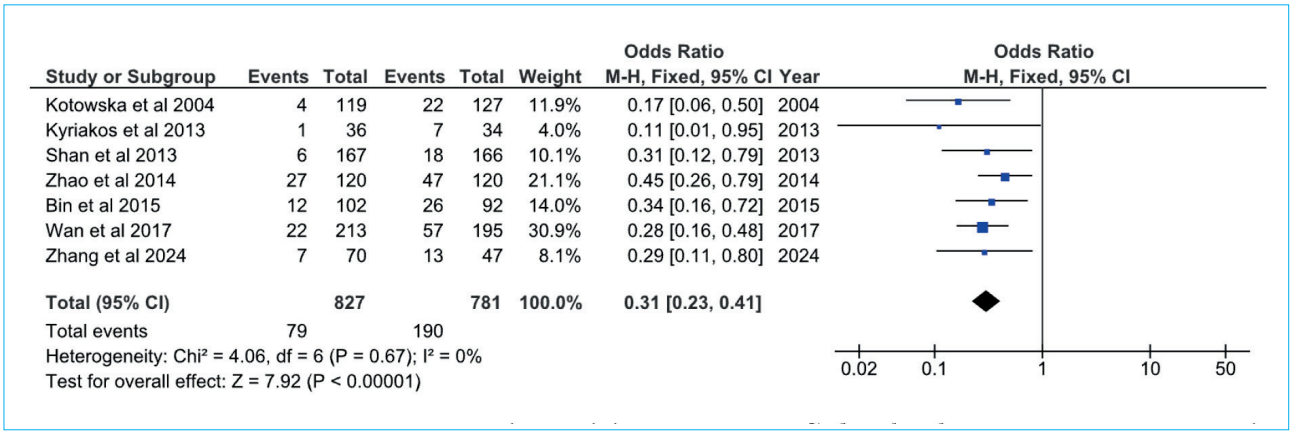

Figure 3. Forest plot of the efficacy of *S. boulardii* CNCM I-745 in the prevention of AAD in children

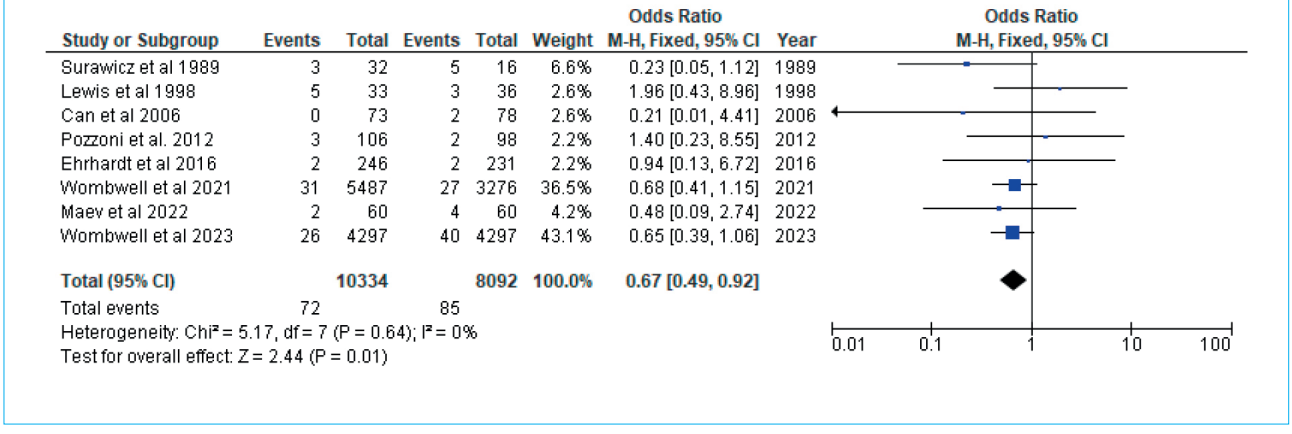

Figure 4. Forest plot of the efficacy of *S. boulardii* CNCM I-745 in the prevention of CDI

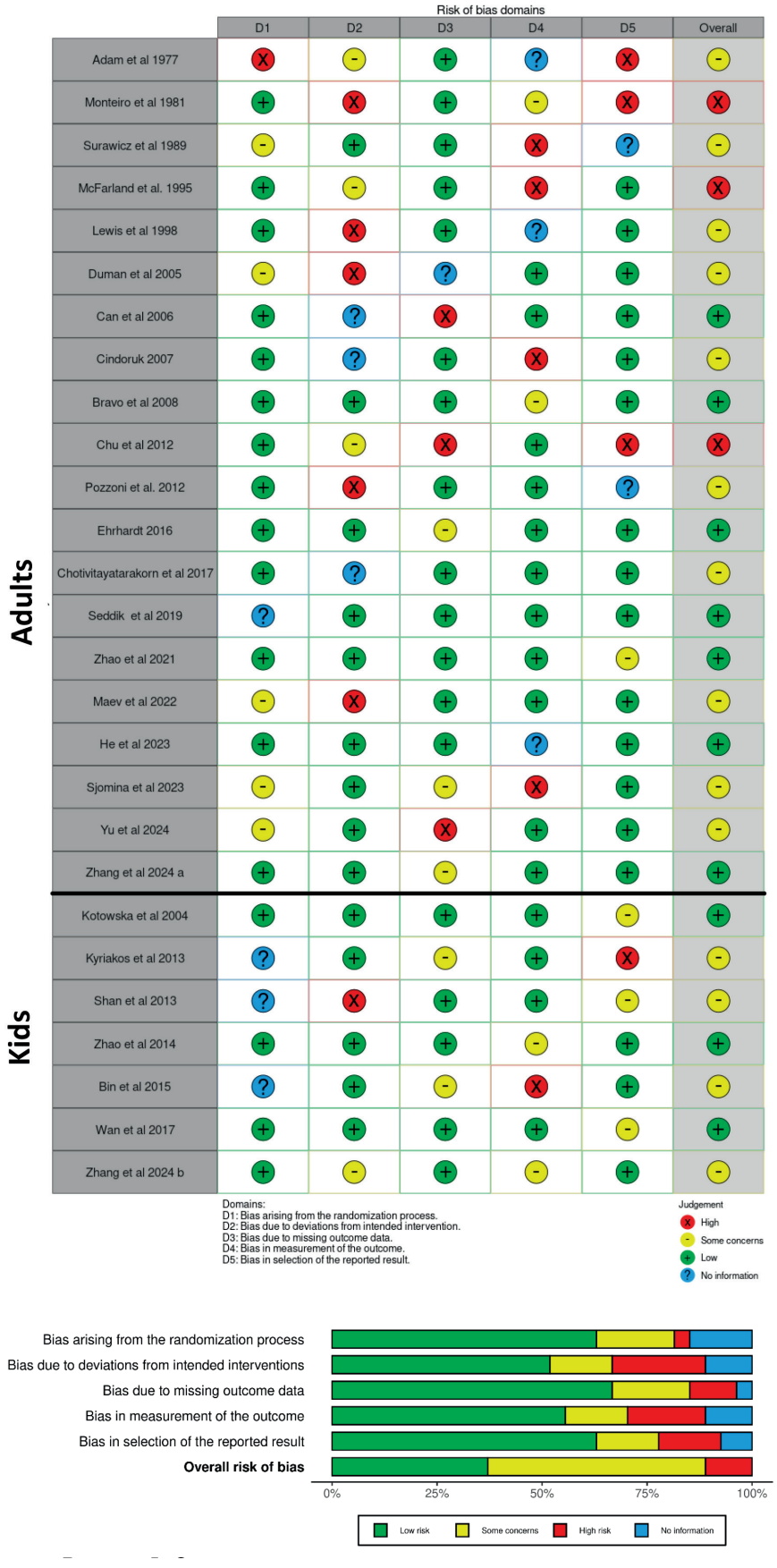

Figure 5. Assessment of included randomized controlled studies using the Cochrane RoB 2 tool

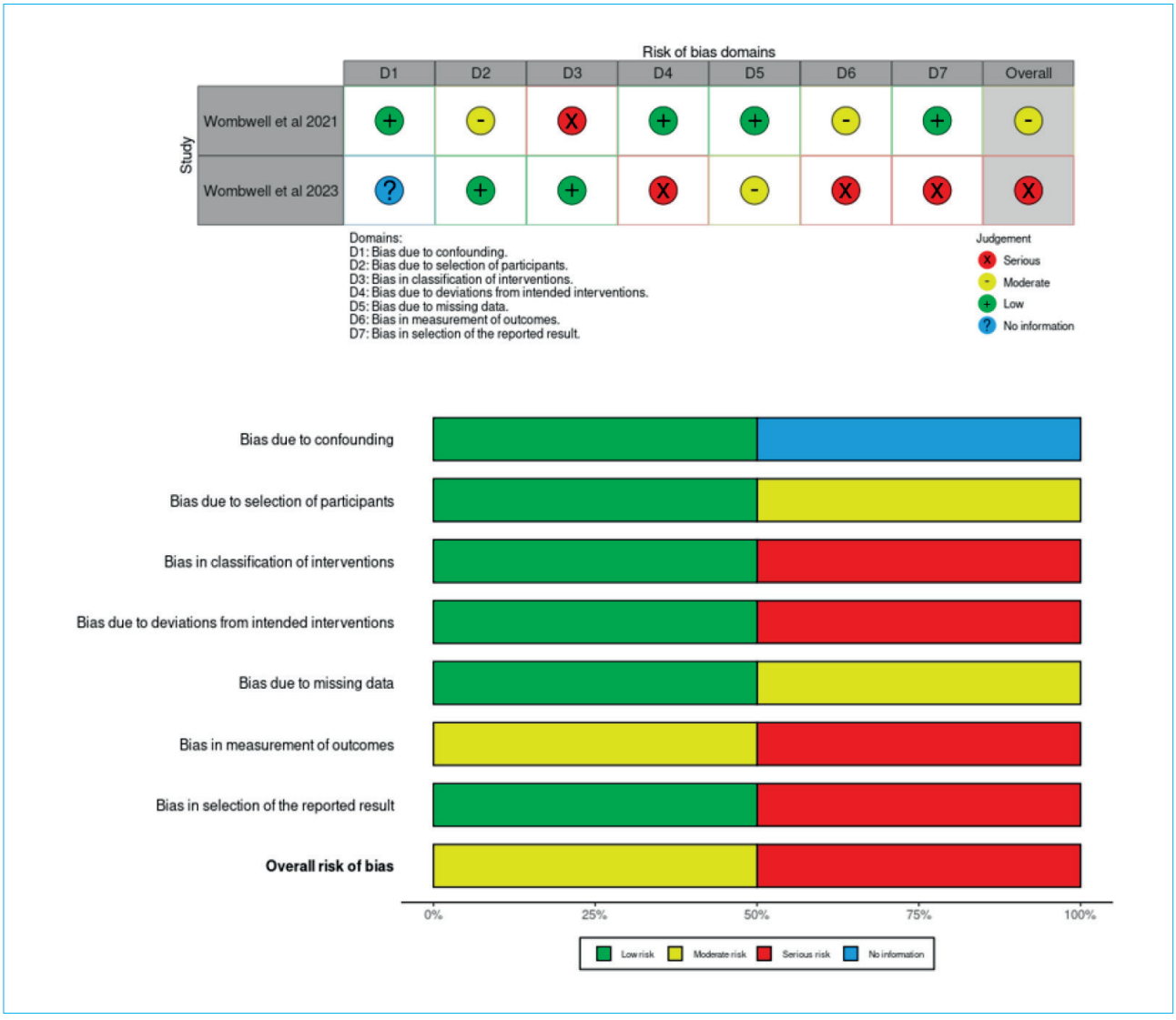

Figure 6. Assessment of included non-randomized controlled trials using the ROBINS-I tool

When analyzing the efficacy of *S. boulardii* CNCM I-745 in the prevention of AAD according to dose, the following results were obtained. For the dose of 250 mg/day, the pooled effect did not reach statistical significance: OR 0.53 (95% CI: 0.19–1.48), with substantial heterogeneity ($I^2 = 67$ %) and no statistically significant overall effect ($p = 0.23$). For the dose of 500 mg/day, a statistically significant reduction in the odds of developing AAD compared with control was observed: OR 0.36 (95% CI: 0.25–0.53), with less pronounced heterogeneity ($I^2 = 56$ %) and a marked overall effect ($p < 0.00001$). For the dose of 1000 mg/day, a statistically significant reduction in the odds of AAD was also demonstrated: OR 0.44 (95% CI: 0.32–0.61), with no heterogeneity ($I^2 = 0$ %) and a significant overall effect ($p < 0.00001$).

Discussion

AAD remains one of the most common complications of antibiotic therapy and, according to review data, may develop in a substantial proportion of patients (up to 30 %, depending on the population and the antibiotics used) [45]. Although most episodes of AAD are relatively mild, the clinical significance of the problem is determined by the risk of severe forms and, above all, by the possible toxigenic activity of CDI, which may lead to colitis, toxic megacolon, and death [46, 47].

In this context, the prevention of AAD and CDI is regarded as a clinically relevant strategy capable of reducing the frequency of complications associated with antibiotic therapy and potentially improving clinical outcomes.

Probiotics are among the most extensively studied preventive options for AAD, although their efficacy depends on the specific strain and the clinical scenario [48]. Among probiotics, *S. boulardii* CNCM I-745 is one of the most extensively studied microorganisms in the context of AAD prevention, as reflected in major systematic reviews and meta-analyses. An early systematic review and meta-analysis in adults showed a statistically significant reduction in the risk of AAD with *S. boulardii* (RR 0.47; 95% CI: 0.35–0.63) [14]. A subsequent meta-analysis demonstrated the efficacy of *S. boulardii* in preventing AAD in children (RR 0.43; 95% CI: 0.23–0.78) [13]. In recent years, considerable emphasis has also been placed on strain specificity in probiotic research [49]. The *S. boulardii* CNCM I-745 is among the most clinically studied and biologically characterized strains.

In 2024, the first meta-analysis focused specifically on *S. boulardii* CNCM I-745 in studies conducted in China was published [50], demonstrating a reduction in the incidence of AAD (RR 0.43; 9% CI: 0.40–0.48) and CDI (RR 0.30; 95% CI: 0.10–0.87). The results obtained in the present study were comparable with results of that meta-analysis (Table 2).

In the present study, the use of *S. boulardii* CNCM I-745 during antibiotic therapy was associated with a statistically significant reduction in the incidence of AAD compared with control (OR 0.38; 95% CI: 0.32–0.45). The effect was maintained when data from adult patients (OR 0.45; 95% CI: 0.33–0.61) and children (OR 0.31; 95% CI: 0.23–0.41) were analyzed separately. In addition, the use of *S. boulardii* CNCM I-745 was associated with a reduction in the incidence of CDI (OR 0.67; 95% CI: 0.49–0.92). The subgroup analysis showed that a statistically significant preventive effect was observed for doses of 500 mg/day (OR 0.36; 95% CI: 0.25–0.53) and 1000 mg/day (OR 0.44; 95% CI: 0.32–0.61). The observed gradient in dose-dependent efficacy is consistent with the general principle that the clinical effectiveness of probiotics is determined by achieving adequate exposure (including dose, strain viability and administration regimen), rather than merely prescribing the microorganism [51]. Recent clinical guidelines emphasize the advisability of using probiotics at the most effective doses [52, 53]. Thus, the effective doses identified in our meta-analysis are consistent with the recommendations of leading medical societies and with the prescribing information for Enterol®.

It is important to note that in the analyzed pool of comparative studies included in the present meta-analysis, *S. boulardii* CNCM I-745 was most frequently used in the setting of any systemic antibiotic therapy — in 13 of 29 included studies (44.8 %) — which enhances the external validity of the results for routine clinical practice. The high representation of this scenario is consistent with the fact that antibiotics remain widely prescribed in both outpatient and inpatient settings: according to Global-PPS data, antimicrobial agents were prescribed to 9.6 % of patients (487/5084) in outpatient departments of the Russian Federation in 2024, while the prescription rate reached 22.6 % in gastroenterology departments [54]. Comparable levels of antibiotic use have also been reported internationally: in the United States, more than 236 million outpatient antibiotic prescriptions were issued in 2022 (709 per 1000 population), and according to an EHR registry of 352 outpatient clinics, antibiotics were prescribed in approximately 121 cases per 1000 visits (about 12 %) in 2021–2023 [55, 56].

A similarly frequent clinical scenario in our study pool was eradication therapy for *H. pylori* infection (13 of 29 studies; 44.8 %), which is one of the most common settings for prescribing multicomponent antibacterial regimens. Despite a declining prevalence of *H. pylori* reported in some regions, systematic reviews indicate that infection rates remain high among adults in Russia, including in major metropolitan areas such as Moscow, supporting the continued relevance of diagnostic and timely eradication programs [57, 58].

Table 2. Comparison of the results of the meta-analysis by L.V. McFarland, T. Li [50] and the present study

Characteristic	McFarland L.V., Li T., 2024 [50]	Ivashkin V.T. et al., 2026
Databases	PubMed, Google Scholar, CNKI, CBM	PubMed, Embase, Cochrane, Scopus, RSCI
Population	China (adults and children)	Global population (adults and children)
Effect on AAD in adults	RR 0.36 (95 % CI: 0.33–0.45)	OR 0.45 (95% CI: 0.33–0.61)
Effect on AAD in children	RR 0.46 (95 % CI: 0.41–0.53)	OR 0.31 (95% CI: 0.23–0.41)
Effect on CDI	RR 0.30 (95 % CI: 0.10–0.87)	OR 0.67 (95% CI: 0.49–0.92)

Additional importance of AAD prevention in the context of eradication therapy is related to the growth of *H. pylori* antibiotic resistance: according to a recent meta-analysis [59], resistance to clarithromycin in Russia exceeds the 15 % threshold established by the Maastricht VI Consensus [60], which is also supported by a study investigating the characteristics of clarithromycin-resistant *H. pylori* strains in Russia [61]. As a result, more complex eradication regimens have increasingly been used in recent years [62]. However, increasing the number of regimen components is associated with a higher risk of adverse events, including AAD, reduced compliance, and, consequently, lower eradication efficacy regardless of the resistance level [63]. Therefore, adding a probiotic with proven efficacy, such as *S. boulardii* CNCM I-745, which reduces the frequency of AAD, may be considered one of the strategies for improving the tolerability and overall effectiveness of eradication therapy under current conditions [64]. The validity of this concept is supported by recently published data from the European Registry on the Management of *H. pylori* infection (2026), which showed that in a large cohort of patients receiving the probiotic *S. boulardii* (n = 4,404), eradication efficacy was increased (OR 2.32; 95% CI: 1.38–4.03), while the risk of adverse events was simultaneously reduced (OR 0.80; 95% CI: 0.66–0.97) [65].

The clinical efficacy of *S. boulardii* CNCM I-745 in AAD is supported by experimental studies and reviews describing the wide range of effects of this probiotic on pathogen-associated factors and inflammatory signaling pathways [66, 67]. One of the most likely mechanisms is believed to be the secretion of a protease capable of proteolytically modifying *C. difficile* toxin A and reducing its binding to brush border receptors, which in experimental models decreased the pathogenic effects of the toxin [68]. Anti-inflammatory effects have also been described, associated with the influence of *S. boulardii* CNCM I-745 on signaling pathways (including MAPK/ERK cascades) and a reduction in toxin-induced inflammation in experimental models [69]. Modulation of mucosal immunity, including increased production of secretory IgA in experimental studies, is regarded as an additional mechanism for enhancing anti-infective resistance at the level of the gut microbiota [70]. Contemporary data also indicate that *S. boulardii* CNCM I-745 exerts protective effects on the microbiota, promoting its recovery, reducing the severity of antibiotic-induced alterations, and supporting immune homeostasis, thereby contributing to the prevention of AAD [71]. Finally, studies using intestinal organoid models have shown that the secretome of *S. boulardii* CNCM I-745 can improve markers of epithelial barrier function and reduce the inflammatory response, which is conceptually consistent with its clinical preventive effect against AAD [72].

The strengths of this study include the strain-specific design of the meta-analysis of *S. boulardii* CNCM I-745, encompassing the entire available pool of comparative studies, which increases the applicability of the conclusions specifically to the strain investigated. In addition, an important feature of the present meta-analysis is the parallel evaluation of outcomes in adult and pediatric populations, since strain-specific systematic reviews are often limited to a single age group, which complicates the translation of results into clinical practice.

Among the limitations of our study is the inclusion of comparative studies with different designs for the CDI analysis; however, the consistency of our findings with those of the 2024 meta-analysis based exclusively on RCTs in a Chinese population supports the validity of the results obtained.

Conclusion

Thus, the results of the present meta-analysis demonstrate that the use of the probiotic *S. boulardii* CNCM I-745, marketed in Russia as Enterol®, is associated with a statistically significant 62 % reduction in the risk of AAD in the overall population, with the preventive effect ranging from 55 % in adults to 69 % in children. It was also shown that the use of *S. boulardii* CNCM I-745 is associated with a 33 % reduction in the likelihood of CDI during antibiotic therapy. The observed efficacy is based on the protective properties of the strain studied against antibiotic-induced changes in the intestinal microbiota. Unlike bacterial probiotics, *S. boulardii* CNCM I-745 can be administered from the first day of antibiotic therapy without the need to observe time intervals between antibiotic and probiotic intake. From a practical standpoint, dosing regimens for which a consistent effect was demonstrated in this meta-analysis (500–1000 mg/day) appear to be the most justified. Further studies should focus on investigating the potential use of this probiotic for the prevention of other complications of antibiotic therapy, as well as on the development of personalized preventive regimens taking into account the characteristics of the patient's microbiota and the spectrum of action of antimicrobial therapy.

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Submitted: 11.03.2026 Accepted: 13.04.2026 Published: 24.06.2026
Поступила: 11.03.2026 Принята: 13.04.2026 Опубликована: 24.06.2026