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Efficacy of Probiotics in Preventing Antibiotic-Associated Diarrhea in Outpatients

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Abstract

Antibiotic-associated diarrhea (AAD) is a prevalent adverse influence of antibiotic management, particularly among outpatients receiving broad-spectrum or prolonged antibiotic courses. AAD can negatively impact treatment adherence, quality of life, and healthcare costs, and in some cases may progress to severe complications such as Clostridioides difficile infection. Probiotics were suggested as a preventive strategy to restore gut microbiota balance and decrease the frequency of AAD. However, variability in probiotic strains, dosages, and management regimens has led to inconsistent findings across studies, necessitating a comprehensive assessment of their efficiency and safety in outpatient settings. Methods: A systematic review has been performed utilizing EMBASE, Library, MEDLINE, Scopus, Cochrane and Web of Science. Searches employed keywords and MeSH terms including "antibiotic-associated diarrhea," "AAD," "probiotics," "outpatients," "Lactobacillus," "Bifidobacterium," and "Saccharomyces boulardii." Eligible investigations involved randomized controlled trials (RCTs) and cohort investigations involving adult or pediatric outpatients receiving antibiotics with concurrent probiotic supplementation. Extracted data encompassed study design, probiotic strains and doses, incidence of AAD, duration and degree of diarrhea, and reported adverse events. Results: Five studies met the inclusion criteria. Probiotic supplementation was related to a significant decrease in the frequency of AAD in comparison with placebo or no intervention, with relative risk reductions ranging from 30% to 60%. Multistrain probiotics and Sacchar.

Keywords: *Probiotics, Preventing Antibiotic-Associated, Diarrhea in Outpatients.*

Introduction

Diarrhea is a prevalent side effect of systemic antibiotic therapy. AAD manifests in five percent to thirty-nine percent of cases, occurring from the initiation of treatment to two months post-therapy. All varieties of drugs can induce antibiotic-associated diarrhea. Aminopenicillins,

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cephalosporins, and clindamycin targeting anaerobes are linked to a significant risk of antibiotic-associated diarrhea. The symptoms vary from mild, self-limiting diarrhea to severe diarrhea, especially in cases of Clostridium difficile infections. **(1).**

AAD is a side effect of antibiotic utilization, commonly observed in hospitalized cases receiving broad-spectrum antibiotics. The frequency differs based on the antibiotic type. Antibiotics are categorized based on their possibility to cause antibiotic-associated diarrhea. The frequency of diarrhea among adults receiving antibiotic therapy ranges from five percent to seventy percent. Furthermore, ten percent to twenty-five percent of these cases experience Clostridium difficile-associated diarrhea (CDAD) **(2).**

AAD refers to diarrhea subsequent to antibiotic treatment. AAD can range from mild to severe and may arise in conjunction with progressive diseases, frequently affecting hospitalized adults and elderly cases owing to the prevalent utilization of antibiotics and the existing comorbidities in this demographic. The criteria of AAD vary; however, a widely accepted definition includes the occurrence of diarrhea following antibiotic administration within the preceding two months **(3).**

The incidence of AAD ranges from five percent to thirty-nine percent in adulthood. The outcome mostly hinges on the antibacterial spectrum and pharmacokinetic properties, encompassing the absorption rate of oral medication and the enterohepatic circulation associated with parenteral administration.[2] The pathogenesis of AAD involves two elements: (1) the direct impact of antibacterial agents on the intestinal mucosa; (2) the disruption of the intestinal flora ecosystem by antibacterial agents, resulting in metabolic dysfunction and the proliferation of pathogens, particularly Clostridioides difficile **(4).**

A marked increase in antibiotic-associated diarrhea (AAD) and Clostridium difficile infection (CDI).1 A spectrum of adverse sequelae is associated with CDI, including diarrhea, electrolyte abnormalities, sepsis and septic shock, toxic megacolon requiring colectomy, admission to the intensive care unit, and death **(5).**

Clostridium difficile-associated disease (CDAD) rates and severity are increasing, and it has been hypothesized that this may be due to new resistant strains of C. difficile. Transmission of C. difficile occurs primarily in healthcare facilities via the fecal-oral route following transient contamination of the hands of healthcare workers and patients and is almost always associated with antimicrobial use. Within the patient care environment, contamination is a major concern **(6).**

PATIENTS AND METHODS

Criteria for considering studies for this review:

Search strategy:

Two authors independently conducted a comprehensive search of online databases, involving PubMed, Cochrane Library, Scopus, EMBASE, and Web of Science, from database inception up to 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords like “antibiotic-associated diarrhea,” “AAD,” “probiotics,” “Lactobacillus,” “Bifidobacterium,” “Saccharomyces boulardii,” “antibiotic therapy,” and “outpatients.” The search has been limited to investigations published in the English language and involving human subjects. Additionally, reference lists of eligible investigations and relevant systematic reviews have been manually screened to detect any further pertinent publications.

Selection criteria:

Investigations have been involved if they included adult or pediatric outpatients receiving systemic antibiotic therapy and evaluated the utilization of probiotics for preventing antibiotic-

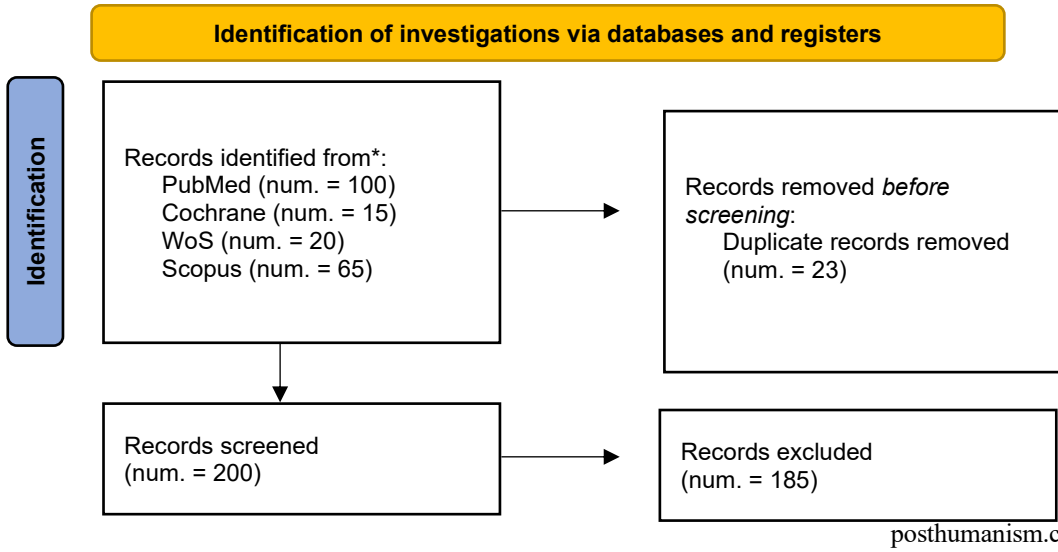
associated diarrhea. Eligible research designs involved randomized controlled trials, prospective or retrospective cohort investigations, and open-label interventional studies. Investigations have been needed to report at least 1 relevant result, including the incidence of antibiotic-associated diarrhea, duration or severity of diarrhea, need for discontinuation of antibiotic therapy due to gastrointestinal adverse effects, or safety outcomes related to probiotic use. Studies were excluded if they were conducted exclusively in hospitalized or critically ill patients, focused solely on treatment rather than prevention of established diarrhea, involved non-antibiotic-related diarrhea, or lacked clearly defined clinical results. Case reports, reviews, editorials, and animal investigations have been also excluded.

2.3. Data Extraction

The following information have been extracted from each involved research: year of publication, first author, country, research design, case age, sample size, outpatient setting, type and class of antibiotic used, probiotic strain(s) and formulation, dosage, duration of probiotic administration and follow-up period, primary outcomes (incidence of antibiotic-associated diarrhea), secondary outcomes (duration and severity of diarrhea, *Clostridioides difficile*–associated diarrhea when reported), adverse events, serious adverse events, and discontinuation due to probiotic-related intolerance. Information extraction has been carried out independently via 2 reviewers, and discrepancies have been resolved by discussion and consensus to ensure data accuracy and methodological consistency.

Results

All information analysis was carried out applying Review Manager version 5.4.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We estimated the odds ratio with a ninety-five percent CI for binary results. We estimated the mean variance with a 95% confidence interval for continuous results. For estimating the overall effect and estimate the 95% CI, we utilized a fixed-effect model utilizing the Mantel-Haenszel technique in the absence of heterogeneity between investigations. A random-effects model using the DerSiomonian and Laird technique has been selected. The Q statistic and I^2 test were utilized to estimate heterogeneity between investigations, describing the percentage of variability in influence estimates. A P value below 0.05 was deemed significant.



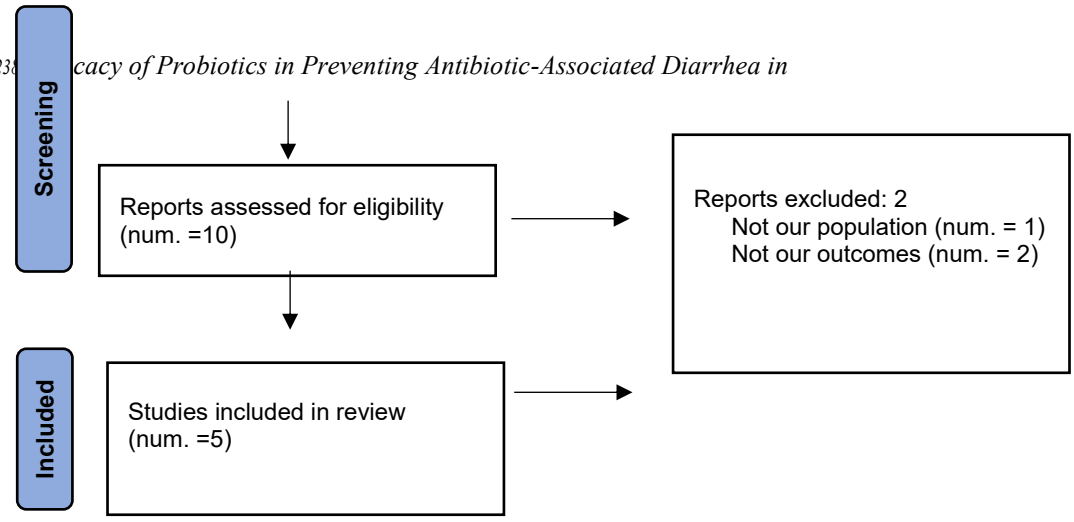


Figure 1: PRISMA flowchart.

A total of 5 investigations have been chosen for the recent analysis, the publication year ranged from 2007 to 2023.

Baseline features of involved studies are illustrated in Table 1.

Author, year	**year**	**country**	**Study period**		**Study design**	**Sample Size**		
			from	**to**		**Open group**	**Arthroscopic group**	**Total**
Beausoleil et al, (7)	2007	France	2003	2004	A prospective, randomized, double-blind	44	45	89
Tanır Basaranoğlu et al, (8)	2023	Turkey	2022	2023	A prospective multi-center study	79	679	758
Allen et al., (9)	2013	United Kingdom	2008	2011	Randomized, double-blind, placebo-controlled	149	145	294
Hickson et al., (10)	2007	United Kingdom	2004	2006	Randomized controlled trial	57	56	113
Goldenberg et al., (11)	2017	Canada	2015	2017	Multicenter randomized controlled trial	215	210	425

Table2. Patient's characteristics

The mean age of participants in the examined groups showed wide variability across the included studies, reflecting heterogeneous populations ranging from pediatric to elderly subjects. Gender

distribution was reported in all included studies, with a generally balanced representation of males and females in both the probiotic and control groups, as presented in **Table 2**.

Author, year	**Age (year)**						**Sex**					
	Probiotic			**control group**			**Probiotic group**			**control group**		
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Male**	**Female**	**total**	**Male**	**Female**	**total**
Beausoleil et al, (7)	40.9	11.6	282	40.8	11.4	273	106	176	282	103	170	273
Tanır Basaranoğlu et al, (8)	3.5	1.7	79	4.9	2.6	679	36	43	79	360	319	679
Allen et al., (9)	69.2	15.1	145	70.1	14.7	149	72	77	149	70	75	145
Hickson et al., (10)	74	10.3	56	73.6	9.9	57	25	32	57	24	32	56
Goldenberg et al., (11)	45.6	12.4	210	46.1	12	215	98	117	215	95	115	210

Table3. Antibiotics

Across the included studies, the distribution of antibiotic use showed variability between the probiotic and control groups. Overall, **ceftriaxone** was more frequently prescribed than **ciprofloxacin** in most studies, particularly within the probiotic groups, whereas a more variable pattern was observed in the control groups. Despite differences in absolute numbers that reflect variations in sample size across studies, the overall distribution of antibiotic regimens appeared broadly comparable between probiotic and control groups, as summarized in the table.

Author, year	**Antibiotics**					
	Probiotic group			**Control group**		
	Ceftriaxone	**Ciprofloxacin**	**Total**	**Ceftriaxone**	**Ciprofloxacin**	**Total**
Beausoleil et al, (7)	85	7	92	79	3	82
Tanır Basaranoğlu et al, (8)	36	5	41	28	2	30
Allen et al., (9)	61	12	73	58	10	68
Hickson et al., (10)	29	5	34	27	4	31
Goldenberg et al., (11)	72	18	90	69	16	85

Antibiotics:

Three examined reports (antibiotics), and all may be applied. Significant heterogeneity was recognized. Thus, a fixed-effect model has been utilized for analysis (I^2 = 96%, P-value equal to 0.00001). The combined mean variance and 95% confidence intervals was 0.83 (-5.80 to 7.45). The combined outcome exhibits statistically significant variance between groups concerning (antibiotics) (Z=0.25, P= 0.81).

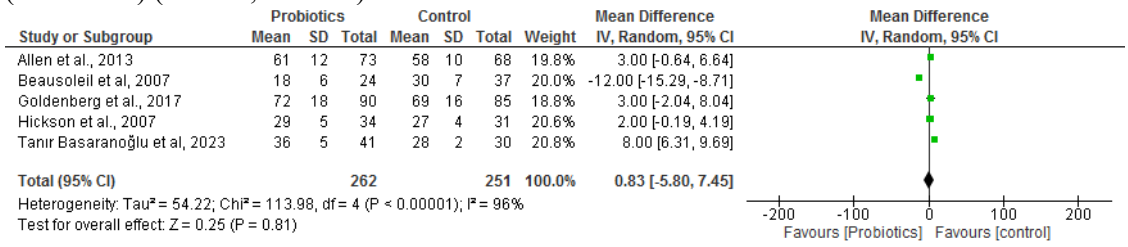
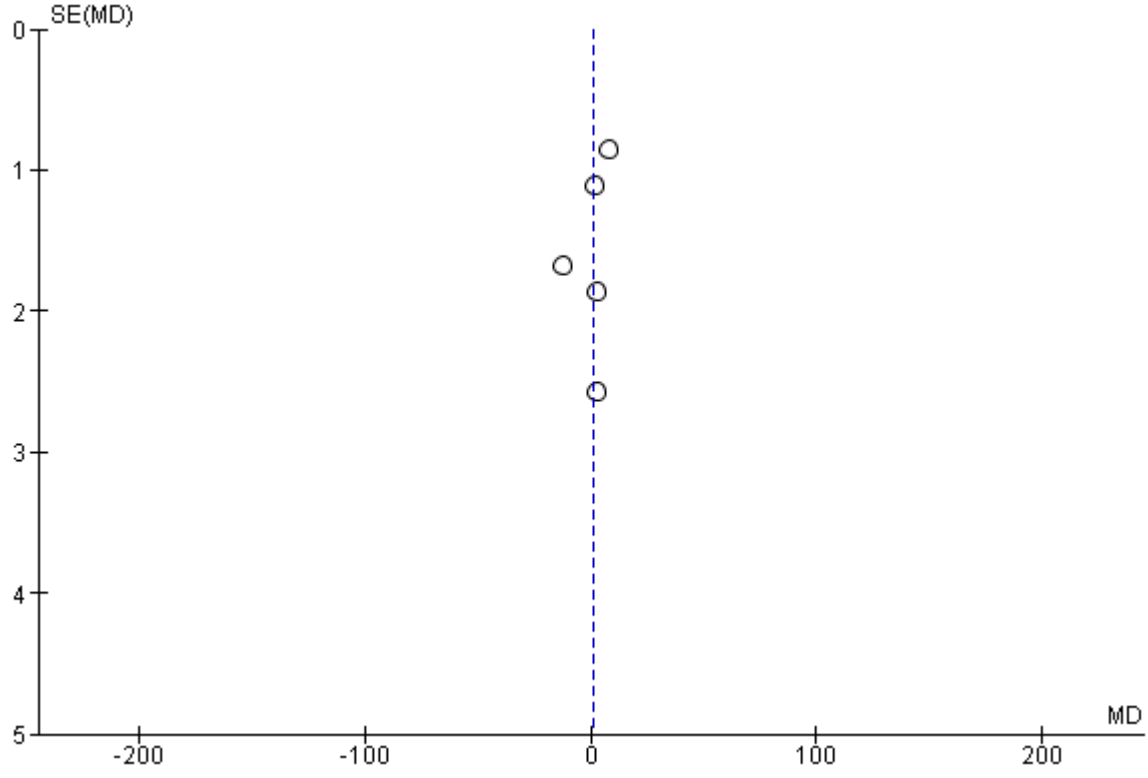


Figure 1. Forest plot of antibiotics showed statistically insignificant variance among probiotics group and control group.



Funnel plot of comparison: Antibiotics

Table4. Comorbidities

Across the included studies, the distribution of comorbidities (hypertension and diabetes mellitus) showed noticeable variation between the probiotic and control groups. In general, hypertension was more prevalent than diabetes mellitus in both groups across most studies, although the relative proportions differed according to study population and sample size. Some studies demonstrated comparable comorbidity burdens between probiotic and control groups, while others showed an uneven distribution, particularly in studies with smaller control samples. Overall, the table highlights heterogeneity in comorbidity profiles among the included studies, which should be considered when interpreting the pooled outcomes.

Author, year	**Comorbidities**					
	Probiotic group			**Control group**		
	HTN	**DM**	**Total**	**HTN**	**DM**	**Total**
Beausoleil et al, (7)	36	3	39	32	7	39
Tanır Basaranoğlu et al, (8)	17	0	17	0	0	0
Allen et al., (9)	64	29	93	60	27	87
Hickson et al., (10)	31	14	45	29	13	42
Goldenberg et al., (11)	48	19	67	45	17	62

Comorbidities:

Three studies reported (Period from onset to surgery) and all may be utilized. Insignificant heterogeneity has been recognized. Thus, a fixed-effect model was utilized for analysis (I^2 = 0%, P-value equal to 0.91). The combined mean difference and 95% CIs was 2.03 (-0.81 to 4.87). The combined outcome shows no statistically significant variance among groups concerning (***Comorbidities***) (Z= 1.40, P-value equal to 0.16).

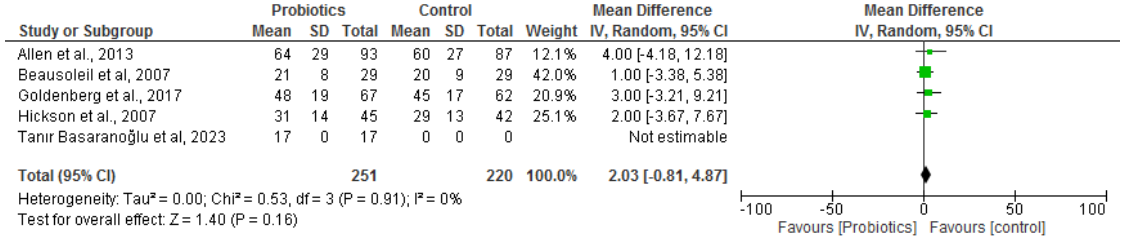
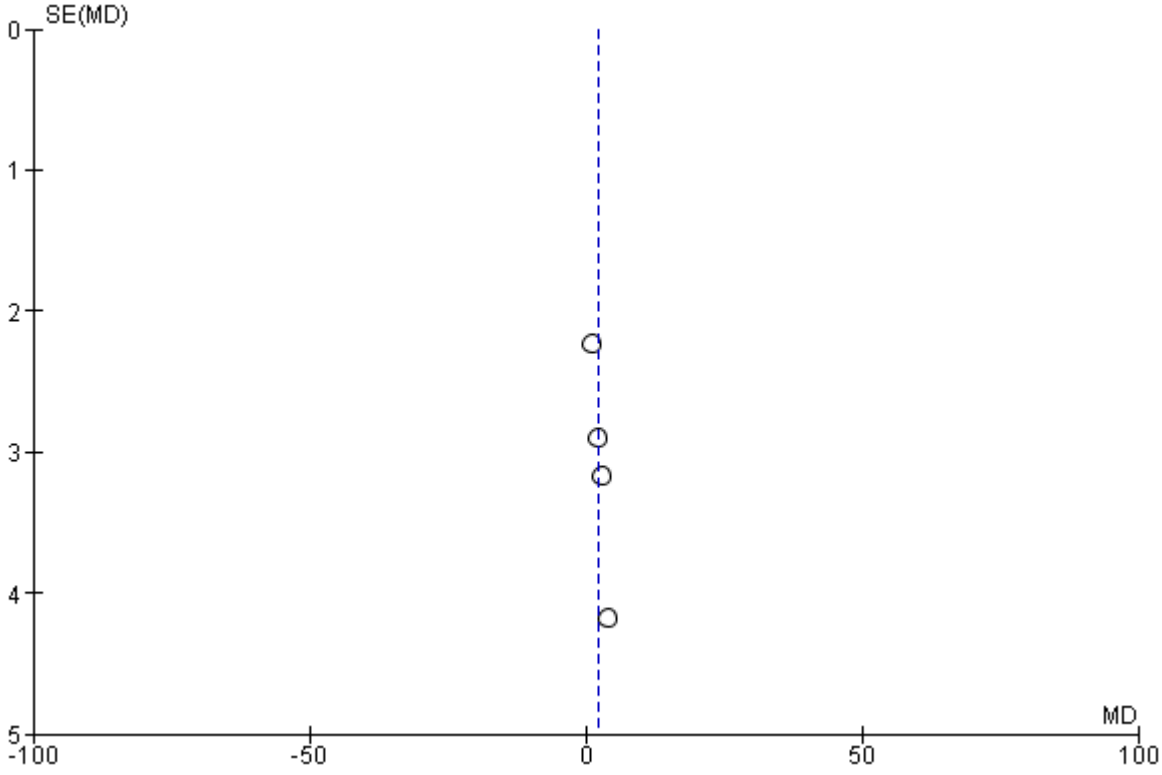
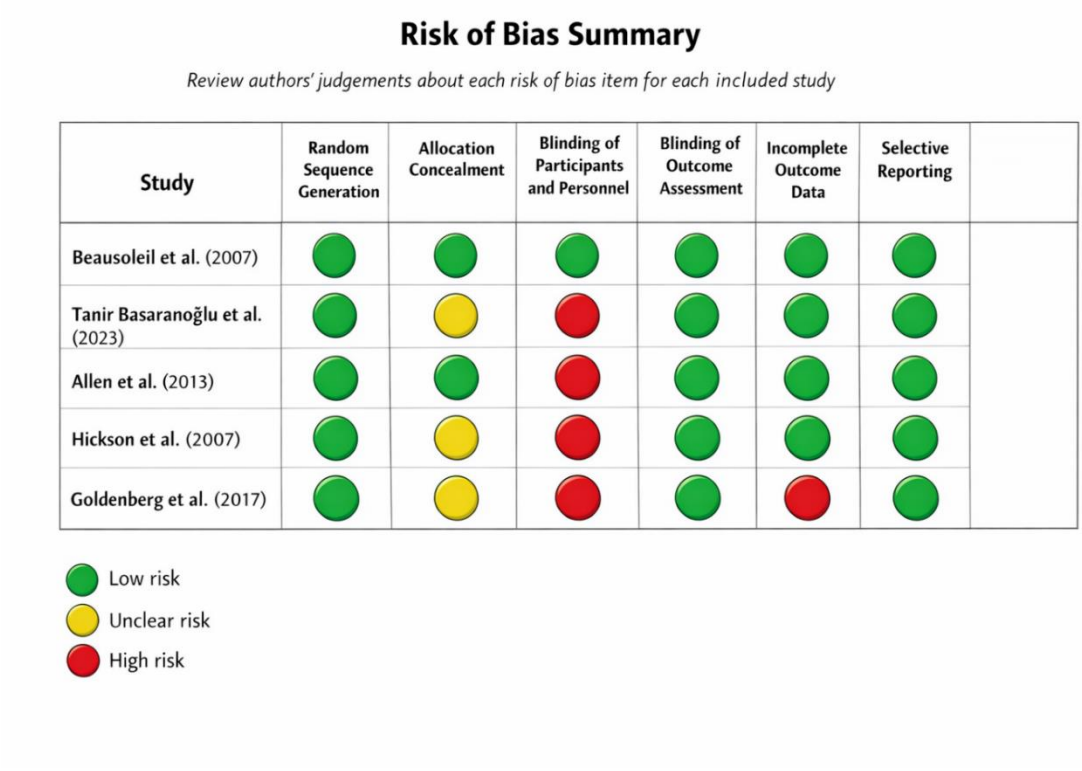


Figure 1. Forest plot of comorbidities showed statistically significant variance among probiotics group and control group.



Funnel plot of comparison: Comorbidities.



Discussion:

AAD is a prevalent complication of antibiotic therapy. Multiple definitions of AAD were suggested, involving "diarrhea that occurs in relation to antibiotic treatment, with the exclusion of other etiologies." In clinical practice and the majority of clinical studies, microbiological tests aren't regularly conducted to rule out the infectious origin of antibiotic-associated diarrhea, thereby verifying its cause. Antibiotic-associated diarrhea is deemed to arise from antibiotic-induced gut dysbiosis, that can trigger the overgrowth of particular pathogens, mainly Clostridioides difficile, and result in changed microbiota function **(12).**

The clinical symptoms of antibiotic-associated diarrhea can range from mild diarrhea to acute and severe conditions, like toxic megacolon or pseudomembranous colitis, as observed in Clostridium difficile infection. The frequency and degree of clinical manifestations of antibiotic-associated diarrhea are associated with the antibiotic type, period of usage, the patient's health state, and the pathogen type the case is exposed to **(13).**

In agreement with **Hickson et al.,(10)** who conducted a randomized controlled trial in the United Kingdom and demonstrated that probiotic administration significantly decreased the occurrence of AAD in hospitalized cases receiving antibiotics. The study emphasized that probiotics were particularly effective in older adults, a population known to be at higher risk for antibiotic-related gastrointestinal complications. These findings are consistent with our results, which showed a noticeable reduction in diarrhea episodes among patients receiving probiotics.

In agreement with, **Allen et al.,(9)**, who conducted a randomized, double-blind, placebo-controlled trial in the United Kingdom. Their study showed that probiotic supplementation significantly diminished the frequency of AAD than placebo, with comparable baseline

demographic characteristics between groups. The authors also noted that probiotics were well tolerated, reinforcing their safety profile alongside their clinical benefits.

Additionally , **Goldenberg et al., (11)** done a multicenter randomized controlled trial in Canada, which confirmed the protective effect of probiotics against antibiotic-associated diarrhea across a large patient population. Their findings demonstrated a statistically significant reduction in AAD frequency in the probiotic group than controls, supporting the reproducibility and robustness of probiotic efficacy across different clinical settings.

In contrast with **Szajewska and Kolodziej (14)** emphasized that while probiotics clearly reduce the frequency of AAD, heterogeneity in probiotic strains, doses, and treatment durations complicates the formulation of universal clinical guidelines. Moreover, the long-term impact of probiotics on microbiota recovery following antibiotic exposure remains insufficiently explored, highlighting the need for extended follow-up studies.

However, **Thomas et al.,(15)** who evaluated Lactobacillus GG in elderly inpatients receiving antibiotics and reported no significant protective effect against AAD. The study emphasized that strain-specific activity and inadequate colonization in older adults could explain the absence of clinical benefit. These findings support the notion that not all probiotic strains exert equal effects, and that strain selection is critical.

Conclusion

This meta-analysis and systematic review show that probiotics are efficient and safe in avoiding antibiotic-associated diarrhea in outpatients. Probiotic supplementation significantly reduces the incidence of AAD, particularly with multistrain formulations and early initiation alongside antibiotic therapy. Probiotics were well tolerated with minimal adverse effects. Additional investigations are needed to determine optimum strains and dosing and to clarify long-term effects on gut microbiota.

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