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Efficacy of Probiotic Supplementation for Prevention of Antibiotic-Associated Diarrhoea in Adults: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 November 2025 and was last updated on 10 November 2025.

INTRODUCTION

Review question / Objective To systematically assess whether probiotic supplementation, as an adjunct to systemic antibiotic therapy, reduces the incidence of antibiotic-associated diarrhoea (AAD) in adults, and to quantify its effectiveness across different probiotic species and doses.

Rationale This study aims to provide robust, high-certainty evidence to guide clinicians by synthesizing newer trials published since 2015, performing subgroup analyses by species and dose, assessing risk of bias, and ensuring transparent, reproducible results. The results can inform the use of probiotics as a cost-effective strategy to reduce AAD incidence and improve patient outcomes in real-world settings.

Condition being studied Antibiotic-associated diarrhoea (AAD) is a common adverse effect of systemic antibiotic therapy, characterized by the passage of three or more loose or watery stools per 24 hours during or up to eight weeks after antibiotic use. AAD can affect between 5% and 35% of patients receiving antibiotics, depending on the antibiotic type, patient health status, and exposure to pathogens, and can lead to increased morbidity, prolonged hospital stays, greater healthcare costs, and significant reductions in quality of life.

The primary mechanism underlying AAD is the disruption of the normal gastrointestinal microbiota by antibiotics, which decreases the diversity of protective commensal bacteria and allows overgrowth of pathogenic organisms such as Clostridioides difficile. Most AAD cases, however, are not associated with specific pathogens, and the diarrhoea may be mild or severe, occasionally resulting in life-threatening complications, especially in vulnerable populations. Prevention of AAD is therefore a significant clinical goal, and the use of probiotics has emerged as a promising strategy to restore microbial balance and reduce risk.

METHODS

Search strategy The review included searches across the following electronic databases: PubMed, Scopus, Embase, and Cochrane CENTRAL. The search terms combined Medical Subject Headings (MeSH) and free-text keywords related to probiotics and antibiotic-associated diarrhoea. Examples include:

"probiotic" OR "Lactobacillus" OR "Bifidobacterium" OR "Saccharomyces" OR "Bacillus"

AND "antibiotic associated diarrhea" OR "AAD" OR "antibiotic-induced diarrhea"

AND "randomized controlled trial" OR "RCT" OR "clinical trial"

Reference lists of eligible studies and related reviews were also manually screened for additional trials. This comprehensive strategy was designed to identify all relevant randomized studies in English published between January 2015 and July 2025 concerning probiotic supplementation for the prevention of antibiotic-associated diarrhoea in adults.

Participant or population The review will address adult participants aged 18 years and older who are receiving one or more systemic antibiotics for any clinical indication, whether in inpatient, outpatient, or community care settings. These adults can be of any sex, background, or diagnosis requiring antibiotic treatment, irrespective of comorbidities or healthcare setting.
Studies of pediatric participants (under 18 years) are excluded, as are studies focused only on treatment (rather than prevention) of antibiotic-associated diarrhoea or those not reporting on the incidence of AAD as defined by three or more loose or watery stools per 24 hours during or within eight weeks after antibiotic therapy.

Intervention The intervention evaluated in this review is the administration of probiotic supplements given as an adjunct to systemic antibiotic therapy in adult patients. This includes any probiotic preparation, whether single-strain or multi-strain, regardless of species or genus (such as Saccharomyces boulardii, Lactobacillus spp., Bifidobacterium spp., Bacillus spp.), formulation (oral capsules, powders, liquids), dose, and duration.
Probiotic supplementation is administered concurrently with one or more antibiotics, with the aim of preventing the occurrence of antibiotic-associated diarrhoea (AAD). Variations in timing, dose, and strain composition are considered for subgroup analysis to assess differential efficacy.
The comparator groups include placebo, usual care, or no probiotic supplementation, allowing assessment of probiotic effectiveness against standard treatment or no intervention.

Comparator The comparative interventions applied to the target population in the included studies are placebo, usual care, or no probiotic supplementation.
Placebo: Participants receive a placebo that matches the probiotic supplement in appearance, formulation, and administration schedule but contains no active probiotic strains.
Usual care: Participants receive the standard antibiotic therapy without any additional probiotic or placebo supplement.
No probiotic supplementation: Participants receive antibiotic therapy alone, without probiotic supplementation or placebo, serving as a control group to assess the effect of probiotic use.
These comparators allow for assessment of the efficacy of probiotics over no intervention or placebo in preventing antibiotic-associated diarrhoea.

Study designs to be included The review will include randomized controlled trials (RCTs) and quasi-randomized controlled trials to address the objective. These study designs provide the highest level of evidence for evaluating the efficacy of probiotic supplementation in preventing antibiotic-associated diarrhoea, reducing bias through random allocation of interventions. Non-randomized designs, observational studies, case reports, reviews, and animal studies will be excluded to maintain methodological rigor and ensure reliable synthesis of treatment effects.

Eligibility criteria Inclusion of full-text articles published in English between January 2015 and August 2024 to focus on recent and relevant evidence.
Exclusion of studies lacking extractable data on the incidence of antibiotic-associated diarrhoea (AAD) or those with ambiguous outcome definitions.
Exclusion of studies primarily focused on treatment rather than prevention of AAD.
Exclusion of reviews, editorials, conference abstracts, case reports, observational studies, and animal or in vitro studies to maintain a high level of evidence and methodological consistency.
Participants receiving only topical antibiotics or non-systemic antibiotic regimens were excluded.

Studies not peer-reviewed or published in gray literature without adequate quality control were excluded.

Information sources Major electronic bibliographic databases: PubMed, Scopus, Embase, and Cochrane CENTRAL databases were systematically searched to retrieve relevant randomized controlled trials related to probiotic supplementation and antibiotic-associated diarrhoea.
Reference lists of eligible studies and relevant systematic reviews were manually screened to identify any additional trials not captured in database searches.
Trial registries may be consulted (e.g., ClinicalTrials.gov, WHO ICTRP) to retrieve ongoing or unpublished studies, although this depends on availability and access.
Contact with corresponding authors of primary studies to request missing or additional data may be pursued if necessary for data completeness.
Grey literature sources such as conference proceedings, theses, dissertations, and unpublished data were generally excluded unless peer-reviewed or retrievable through databases.

Main outcome(s) The primary outcome of this review is the incidence of antibiotic-associated diarrhoea (AAD) in adult patients receiving probiotic supplementation versus control groups.
Relevant details include:
Definition of AAD: Passage of three or more loose or watery stools within a 24-hour period occurring during antibiotic treatment or up to eight weeks after antibiotic cessation.
Timing: Outcomes were measured during antibiotic treatment and followed for up to eight weeks post-therapy to capture both immediate and delayed diarrhoea onset.
Effect measures: The review reports relative treatment effects using risk ratios (RR) and 95% confidence intervals (CI).
Secondary outcomes (if reported) may include severity of AAD episodes, recurrence rates, adverse events related to probiotic supplementation, treatment adherence, and time to recovery.
Data were extracted on event counts or incidence rates within intervention and comparator arms for pooled meta-analytic synthesis.

Additional outcome(s) Nil.

Data management Record keeping: All literature search results were imported into reference management software for de-duplication and systematic screening.
Screening: Titles and abstracts were independently screened by two reviewers for eligibility, with full texts reviewed when necessary. Discrepancies were resolved by discussion or a third reviewer.
Data extraction: Standardized data extraction forms were used to collect relevant data on study characteristics, participants, interventions, comparators, outcomes, and risk of bias independently by two researchers.
Data storage: Extracted data and study characteristics were stored securely in spreadsheet and database files with regular backups.
Quality control: Cross-checking was performed to ensure accuracy and completeness before data synthesis.
Handling missing data: Contacting study authors for missing or unclear information was planned. Where necessary, statistical methods like continuity corrections were applied to zero-event data for effect size calculations.

Quality assessment / Risk of bias analysis The quality assessment and risk of bias analysis for the included studies were conducted as follows:
The Cochrane Risk of Bias 2 (RoB 2) tool was used to evaluate the risk of bias within each randomized controlled trial.
Domains assessed included bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.
Each domain was judged as "low risk," "some concerns," or "high risk" of bias, with an overall risk of bias assessment assigned to each study.
Two independent reviewers performed the assessment, and disagreements were resolved through discussion or by a third reviewer.
The risk of bias assessments were used to inform the interpretation of meta-analytic results and sensitivity analyses to assess the robustness of findings to study quality.
The results of the risk of bias assessment were summarized in tables and figures within the review for transparency.

Strategy of data synthesis Effect size measures for the primary outcome (incidence of antibiotic-associated diarrhoea) will be calculated using risk ratios (RR) with 95% confidence intervals (CI).
Pooled estimates will be computed using inverse variance-weighted meta-analysis with both random-effects models: Restricted Maximum Likelihood (REML) and DerSimonian–Laird methods, to accommodate between-study heterogeneity.

Statistical heterogeneity will bewas assessed using Cochran's Q test and quantified using the I^2 statistic. Thresholds were applied to interpret the level of heterogeneity.
Subgroup analyses will bewere performed based on probiotic species/genus, daily dose, and duration to explore potential sources of heterogeneity and differential effects.
Mixed-effects meta-regression analyses will bewere conducted to evaluate the influence of continuous and categorical moderators such as dose and species on effect sizes.
Sensitivity analyses involved the leave-one-out method, whereby each included study was sequentially removed to assess its impact on overall results.
Publication bias will be was assessed through visual inspection of funnel plots and formally tested using Egger's regression test.

Statistical analyses will bewere performed using appropriate meta-analysis software to ensure consistency and reproducibility.

This comprehensive analytic approach supports robust estimation of probiotic efficacy and exploration of factors influencing effect size variances.

Subgroup analysis Subgroup analyses in this review were performed to evaluate whether the effect of probiotics varied according to specific study or participant characteristics. The following subgroups were analyzed:
Probiotic species/genus: Effect sizes were stratified based on the specific probiotic strains used, such as Saccharomyces boulardii, Lactobacillus spp., Bifidobacterium spp., and Bacillus spp., to identify differential efficacy among strains or genera.
Dosage: Studies were grouped based on the daily dose of probiotics (e.g., ≥10^10 CFU/day vs. lower doses) to assess dose-response relationships and optimal dosing strategies.
Duration of intervention: Effects were compared between short-term versus longer-duration probiotic regimens to evaluate whether duration influences efficacy in preventing AAD.
Setting and population risk: Potential differences in effect were explored in subpopulations such as hospitalized patients versus outpatients or high-risk versus low-risk groups.
Study quality: Subgroup analyses based on risk of bias assessments (low vs. some concerns or high) were performed to test the robustness of findings.
Geographical regions: If data permitted, studies were stratified by geographic location to evaluate regional variations in probiotic efficacy.

Sensitivity analysis Sensitivity analyses in this review will be conducted to assess the robustness and reliability of the pooled results. These analyses involved:

Leave-one-out analysis: Sequentially removing one study at a time from the meta-analysis to observe the influence of each individual study on the pooled effect size, checking if any study had a disproportionate impact.

Excluding studies at high risk of bias: To evaluate whether including studies with some concerns or high risk affected the overall conclusions, pooled analyses were repeated restricted to low risk of bias studies.

Alternative statistical models: Using different meta-analytic models or effect size measures to test consistency of findings.

Handling of missing or zero-event data: Testing whether different approaches for continuity correction or missing data imputation affected the results.

Language restriction English.

Country(ies) involved India.

Keywords Probiotics, Antibiotic-associated diarrhoea, Systematic review, Meta-analysis.

Contributions of each author
Author 1 - Tejas M - Conceptualization and design of the study protocol. Conducting literature searches and screening records. Data extraction and synthesis. Drafting and revising the manuscript.
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Author 2 - Ramya S - Statistical analysis and meta-analysis execution. Performing subgroup and sensitivity analyses. Interpretation of statistical results. Contributing to manuscript data presentation and results sections.
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