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INPLASY

Probiotics During Antibiotic Therapy: A Systematic Review of Timing, Strain Specificity, and Gut Microbiome Modulation

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2026 and was last updated on 28 May 2026.

INTRODUCTION

Review question / Objective This systematic review aimed to evaluate whether the timing of probiotic administration during systemic antibiotic therapy influences clinical and ecological outcomes, particularly antibiotic-associated diarrhea (AAD), Clostridioides difficile–related outcomes, microbiome recovery, and resistome modulation. The review specifically compared concurrent probiotic administration during antibiotics, concurrent administration with continuation after antibiotic completion, and post-antibiotic-only initiation strategies. The objective was not to determine whether probiotics are universally effective but rather to identify whether specific strain-specific probiotic regimens, timing strategies, and patient populations are associated with greater clinical benefit and improved microbiome-related outcomes.

Rationale Antibiotic therapy can significantly disrupt gut microbial ecology, impair colonization resistance, and contribute to antibiotic-associated diarrhea (AAD), Clostridioides difficile infection, and transient microbiome instability. Probiotics have therefore been increasingly investigated as nutritional and microbiome-modulating interventions during antibiotic exposure. However, current evidence remains inconsistent because probiotic effects appear highly strain-specific, population-dependent, and influenced by the timing of administration relative to antibiotic exposure. Existing literature often combines different probiotic formulations, ecological

methodologies, and timing strategies without clearly distinguishing concurrent, concurrent-plus-continuation, and post-antibiotic-only approaches. Furthermore, contemporary evidence integrating clinical outcomes with microbiome and resistome-related ecological findings remains limited. Therefore, this systematic review was conducted to synthesize recent comparative human evidence and clarify whether specific timing strategies and strain-specific probiotic regimens provide meaningful clinical or ecological benefits during and after antibiotic therapy.

Condition being studied The condition being studied is antibiotic-associated gastrointestinal and microbiome disruption occurring during or after systemic antibiotic therapy. This includes antibiotic-associated diarrhea (AAD), Clostridioides difficile–related outcomes (CDI/CDAD), transient gut microbiome instability, ecological dysbiosis, and antibiotic-related alterations in microbiome diversity and resistome profiles. The review specifically evaluates whether probiotic administration timing influences the prevention or modulation of these antibiotic-associated clinical and ecological complications in pediatric and adult populations receiving systemic antibiotics.

METHODS

Search strategy Electronic searches were conducted in MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, and CENTRAL (Cochrane Central Register of Controlled Trials). Additional searches included ClinicalTrials.gov, WHO ICTRP, backward and forward citation searching, and manual bibliography screening. Search strategies combined controlled vocabulary terms and keywords related to probiotics, antibiotics, antibiotic-associated diarrhea, Clostridioides difficile infection, microbiome disruption, dysbiosis, resistome, and antibiotic resistance genes. Terms included "probiotic*", "Lactobacillus", "Bifidobacterium", "Saccharomyces", "Bacillus clausii", "Limosilactobacillus reuteri", "antibiotic-associated diarrhea", "microbiome", "microbiota", "dysbiosis", "resistome", and "antibiotic resistance gene*". Searches were restricted to human studies published in English between January 1, 2020 and May 15, 2026. Two reviewers independently screened studies and extracted data according to predefined eligibility criteria. Full database-specific search strategies are provided in Supplementary Appendix 1.

Participant or population The review included pediatric and adult human populations receiving systemic antibiotic therapy in outpatient, inpatient, or hospital-based settings. Eligible participants included children treated for acute otitis media, acute rhinosinusitis, or upper respiratory infections, adults receiving Helicobacter pylori eradication therapy, hospitalized adults exposed to broad-spectrum antibiotics, spinal cord injury patients receiving proton pump inhibitors, and other individuals exposed to systemic antimicrobial regimens. Only comparative human studies evaluating probiotic administration during and/or after antibiotic exposure were included.

Intervention The interventions included defined probiotic strains or probiotic formulations administered during systemic antibiotic therapy, during antibiotic therapy with continuation after antibiotic completion, or initiated after antibiotic exposure. Evaluated probiotics included strain-specific and multispecies formulations such as Limosilactobacillus reuteri DSM 17938, Bacillus clausii, Lactobacillus casei Shirota, Saccharomyces boulardii, LAB4-based probiotic mixtures, BB-12 yogurt formulations, and multispecies probiotic combinations. Interventions were required to meet accepted probiotic definitions and provide extractable timing-specific administration data relative to antibiotic exposure.

Comparator Comparators included placebo, no probiotic intervention, standard care, or alternative probiotic timing strategies and formulations. Comparative groups varied according to individual study designs and included placebo-controlled randomized trials, no-treatment controls, and comparative analyses between different probiotic administration regimens during or after systemic antibiotic therapy.

Study designs to be included Eligible studies included randomized controlled trials (RCTs), quasi-randomized comparative trials, placebo-controlled studies, and comparative observational human studies evaluating probiotic administration during and/or after systemic antibiotic therapy. Non-comparative studies, mechanistic animal studies, in vitro investigations, narrative reviews, conference abstracts without extractable data, and studies lacking timing-specific probiotic interventions were excluded.

Eligibility criteria Eligible studies were required to include human participants receiving systemic antibiotics, defined probiotic strains or formulations meeting accepted probiotic criteria, extractable timing-specific probiotic administration data, and clinically or ecologically relevant outcomes such as antibiotic-associated diarrhea

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(AAD), Clostridioides difficile–related outcomes, microbiome diversity, dysbiosis, or resistome-related endpoints. Included studies had to be published in English between January 1, 2020, and May 15, 2026. Exclusion criteria included non-comparative studies, animal or in vitro studies, studies without systemic antibiotic exposure, fermented-food interventions lacking defined probiotic strains, duplicate cohort publications without unique data, conference abstracts with insufficient methodological information, and studies lacking clinically or ecologically relevant outcomes.

Information sources Information sources included MEDLINE via PubMed, Embase, Scopus, Web of Science Core Collection, CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). Additional sources included backward and forward citation searching, manual bibliography screening, guideline screening, and supplementary source checking. All databases and supplementary sources were rechecked immediately before manuscript submission to identify newly indexed potentially eligible studies.

Main outcome(s) The primary outcomes included antibiotic-associated diarrhea (AAD) incidence, Clostridioides difficile infection or diarrhea (CDI/CDAD), and clinically relevant gastrointestinal adverse outcomes occurring during or after systemic antibiotic therapy. The review additionally evaluated whether probiotic timing strategies influenced the prevention or reduction of these outcomes. When available, effect estimates such as relative risks, comparative event rates, and timing-specific clinical outcomes were extracted from included studies.

Additional outcome(s) Additional outcomes included overall diarrhea incidence, adverse events, treatment adherence, microbiome diversity measures, ecological dysbiosis indicators, resistome-related findings, antibiotic-resistance gene abundance, microbial colonization changes, and exploratory microbiome recovery outcomes. Ecological endpoints such as alpha diversity, beta diversity, microbiota composition, and resistome modulation were interpreted as exploratory surrogate outcomes rather than validated patient-centered clinical endpoints.

Data management All retrieved citations were imported into a reference management system for duplicate removal and screening. Two reviewers independently screened titles, abstracts, and full-text articles according to predefined eligibility criteria. Data extraction was performed using a pre-tested standardized extraction form. Extracted variables included study design, participant characteristics, antibiotic exposure, probiotic strain or formulation, timing strategy, outcome measures, and adverse events. Disagreements between reviewers were resolved through discussion and consensus. Risk-of-bias assessments and evidence-certainty evaluations were conducted using RoB 2, ROBINS-I conceptual principles, and GRADE-informed approaches.

Quality assessment / Risk of bias analysis Risk of bias for randomized controlled trials was assessed using the revised Cochrane Risk of Bias tool (RoB 2). ROBINS-I conceptual principles were additionally considered when evaluating non-randomized comparative elements and subgroup-derived analyses. Assessments included evaluation of randomization processes, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Ecological microbiome and resistome analyses were further appraised for selective subsampling, incomplete longitudinal sampling, sequencing-platform heterogeneity, exploratory post hoc analyses, and indirectness relative to patient-important clinical outcomes. Overall evidence certainty was narratively evaluated using GRADE-informed principles.

Strategy of data synthesis Because of substantial clinical, methodological, and ecological heterogeneity across probiotic formulations, antibiotic exposures, timing strategies, populations, outcome definitions, and microbiome methodologies, formal quantitative meta-analysis was considered inappropriate. Therefore, findings were synthesized using a SWiM-aligned structured narrative synthesis approach. Studies were categorized according to probiotic formulation, timing strategy, patient population, antibiotic exposure, and outcome type. Greater emphasis was placed on clinically important outcomes such as antibiotic-associated diarrhea (AAD) and Clostridioides difficile–related outcomes, whereas microbiome and resistome findings were interpreted cautiously as exploratory ecological endpoints. When available, study-level numerical effect estimates and relative risks were descriptively summarized.

Subgroup analysis Subgroup interpretation was planned according to probiotic timing strategy, probiotic strain or formulation, antibiotic exposure type, patient population, and outcome category. Particular attention was given to pediatric versus

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adult populations, high-risk versus low-risk patient groups, microbiome-focused versus clinically focused studies, and concurrent versus post-antibiotic probiotic administration strategies. Vulnerable populations, including patients receiving proton pump inhibitors, spinal cord injury patients, and pediatric amoxicillin-clavulanate recipients, were additionally considered in narrative subgroup interpretation when sufficient comparative data were available.

Sensitivity analysis Formal quantitative sensitivity analyses were not performed because substantial methodological, clinical, and ecological heterogeneity precluded meta-analysis. However, narrative sensitivity considerations included interpretation according to study quality, risk-of-bias judgments, microbiome-focused secondary analyses, subgroup-derived findings, probiotic strain specificity, and timing-strategy differences. Greater interpretive weight was given to contemporary randomized controlled trials with lower overall risk of bias and clinically important outcomes.

Language restriction English language studies only.

Country(ies) involved Iraq.

Other relevant information This review followed the PRISMA 2020 recommendations and employed a SWiM-aligned narrative synthesis approach because methodological and ecological heterogeneity precluded formal meta-analysis. Contemporary studies published between 2020 and 2026 specifically focused on improving comparability across probiotic taxonomies, microbiome methodologies, and modern antibiotic-exposure practices. Researchers interpreted ecological microbiome and resistome findings cautiously as exploratory surrogate outcomes rather than validated patient-centered clinical endpoints.

Keywords probiotics; antibiotic-associated diarrhea; gut microbiome; nutritional support; antibiotic therapy; strain specificity.

Dissemination plans The findings of this systematic review will be disseminated through submission to a peer-reviewed international scientific journal and may additionally be presented at academic conferences, institutional scientific activities, and professional meetings related to microbiology, infectious diseases, probiotics, nutrition, and microbiome research.

Contributions of each author

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