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AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders

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Probiotics are live microorganisms that, when consumed in adequate amounts, confer a health benefit on the host.[1] The probiotics industry is growing rapidly, with sales in the United States alone expected to exceed $6 billion in 2020.[2] However, probiotics are a source of significant cost with unclear benefit. Patients routinely ask clinicians whether they should be taking probiotics and, if so, which products. These questions present a dilemma, given that none of the probiotic preparations being studied are currently manufactured as drugs, that is, with the intent of treating, mitigating, or preventing disease. Rather, the typical classification of probiotics as dietary supplements has been associated with diminishment of the rigor of clinical studies, including capturing adverse events and efficacy end points. To date, general practitioners and gastroenterologists have minimal guidance regarding the use of probiotics for gastrointestinal disorders.

In this technical review, the American Gastroenterological Association (AGA) Institute reviews probiotic formulations that have been studied to prevent or treat common disorders of the gastrointestinal tract. This review provides evidence-based information to guide both clinicians and patients regarding whether probiotics might play a role in the management of these disorders. When sufficient evidence exists, this review also suggests which individual

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Conflicts of interest

These authors disclose the following: Adam V. Weizman has served on an advisory board for Abbvie and Ferring Pharmaceuticals and as a speaker for Janssen, Abbvie and Ferring. Purna C. Kashyap serves on the advisory board of Novome Biotechnologies and is an ad hoc consultant for Otsuka Pharmaceuticals and Pendulum Therapeutics. The remaining authors disclose no conflicts. All members were required to complete disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland. Panel members disclosed all potential conflicts of interest according to the AGA Institute policy. No Guideline Panel member was excused from participation in the process owing to disqualifying conflict.

Supplementary Material

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probiotic strains or combinations of strains might be superior to others, or which clinical contexts warrant further research with probiotics. Other microbiome-targeting therapies, including antibiotics and fecal microbiota transplantation, are beyond the scope of this project, which focuses exclusively on probiotics. Similarly, prebiotics and synbiotics have been omitted from this review in order to focus on single-strain and multispecies formulations of probiotics. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was employed to assess the quality of evidence and to inform the AGA's development of the accompanying clinical guidelines regarding the role of probiotics in the management of gastrointestinal conditions.

Objectives of the Review

This technical review addresses the following focused clinical questions with respect to probiotic use for gastrointestinal conditions:

1. In symptomatic adults with confirmed *Clostridioides difficile* infection, should probiotics be used as part of the treatment regimen?
2. In adults and children receiving antibiotic therapy for any indication except *C difficile* infection, should probiotics be used to prevent *C difficile*–associated diarrhea?
3. In adults and children with Crohn's disease, should probiotics be used for induction or maintenance of remission?
4. In adults and children with ulcerative colitis, should probiotics be used for induction or maintenance of remission?
5. In adults and children with ileal pouch–anal anastomosis for chronic ulcerative colitis, should probiotics be used for prevention or maintenance of remission of pouchitis?
6. In symptomatic children and adults with irritable bowel syndrome, should probiotics be used to improve global response or abdominal pain severity?
7. In children with acute infectious gastroenteritis, should probiotics be used to reduce the duration or severity of diarrhea?
8. In preterm, low-birth-weight newborns, should probiotics be used to prevent necrotizing enterocolitis, sepsis, and all-cause mortality?

Methods

Overview of the Systematic Review Process

This technical review was developed to support the development of AGA guidelines regarding the potential role of probiotic use in conditions frequently managed by gastroenterologists. The Technical Review Panel was composed of both clinical and methodological experts. The development of this systematic review included the following steps:

1. development of the research questions and identification of outcomes critical to decision-making;
2. search of the literature for high-quality previously published systematic reviews and primary studies;
3. risk-of-bias assessment;
4. quantitative meta-analysis or narrative synthesis; and
5. assessment and presentation of the certainty of evidence.

Methods for deriving focused clinical questions, systematically reviewing and rating the quality of evidence for each outcome, and rating the overall quality of evidence were based on the GRADE framework, which has been described in detail previously.

Formulation of Clinical Questions and Determining Outcomes of Interest

The Panel formulated and prioritized the questions to be addressed by this guideline using the PICO (population, intervention, comparison, outcomes) format.[3] The final set of questions and statements was approved by the AGA Governing Board. Members of the Technical Review and Guideline Committees selected patient-important outcomes for each question a priori. The Panels rated the relative importance of each outcome for decision-making on a scale of 1–10. Outcomes receiving a score of 7–10 were considered critical for decision-making, 4–6 were considered important for decision-making, and 1–3 were considered less important for decision-making. The final list of PICO questions and outcomes deemed critical for decision-making are presented above.

Literature Search Strategy and Study Selection

Initially, the literature search was conducted to identify potentially relevant systematic reviews published on the PICO questions of interest that fit predetermined eligibility criteria and were of high methodological rigor. A systematic review was eligible for inclusion if it evaluated 1 or more of the previously determined patient-important outcomes of interest, provided a quantitative estimate of effect, and was rated by the Technical Review Panel to have Moderate or High confidence based on AMSTAR (A Measurement Tool to Assess Systematic Reviews) 2 criteria.[4] During a face-to-face meeting, the Technical Review and Guideline Panels collectively re-evaluated the previously identified evidence base along with the new evidence and independently determined the certainty of evidence as outlined below. For 2 of the PICO questions, complementary and mutually exclusive systematic reviews were identified; thus, we included systematic reviews for both induction and maintenance of remission for Crohn's disease and for ulcerative colitis. If relevant systematic reviews were identified, then additional searches were conducted through December 2018 for studies published since the systematic reviews. For questions not guided by a previously published systematic review, the literature search was conducted de novo.

A search of the medical literature was conducted by an information specialist using the following databases: MEDLINE (1950 to June 2018), EMBASE and EMBASE Classic (1947 to June 2018), and the Cochrane Central Register of Controlled Trials. This search was updated to include additional studies that were published from June to December 2018.

The search strategy comprised controlled vocabulary, including the National Library of Medicine's Medical Subject Headings and keywords. Search concepts common to all searches were "probiotics," "probiotic agent," "synbiotics," "synbiotic agent," "beneficial microbes," and "beneficial bacteria." We excluded trials exclusively conducted within populations harboring major comorbidities, including cancer, human immunodeficiency virus/acquired immune deficiency syndrome, cystic fibrosis, spinal cord injury, organ failure or transplantation, and other severe conditions. Methodological filters were applied to limit retrieval of trials that included only animals and not humans. Corresponding authors of studies were contacted to provide additional information on trials when required. Two attempts were made to contact the author. If there was no response after 2 attempts, the study was excluded based on incomplete information.

We included studies of children (younger than 18 years) and/or adults (18 years and older), depending on relevance to the clinical question and the amount of published evidence. Specifically, we excluded trials focusing on treatment of *C difficile* infection (CDI) exclusively in children or treatment of acute gastroenteritis exclusively in adults, whereas prevention of necrotizing enterocolitis (NEC) is relevant to neonates only. The interventions were orally ingested or rectally administered (for ulcerative colitis only) live microbes, either single-strain or multispecies, with defined species or strain and dose. The comparators were placebo or standard of care. Trials of synbiotics were included only when the non-microbial portion of the synbiotic was tested separately in a control arm, so that the specific effect of the probiotic could be evaluated. Comparative effectiveness studies were included only when an appropriate control arm existed. Given significant overlap between 2 groups of 3 PICO questions, for these groups we combined searches before sorting references according to the relevant PICO question. One combined search included treatment of CDI, prevention of *C difficile*–associated diarrhea (CDAD), and treatment of acute gastroenteritis. The other combined search included induction and maintenance of remission in Crohn's disease, induction and maintenance of remission in ulcerative colitis, and treatment and prevention of pouchitis. Literature searches for the remaining PICO questions were performed individually.

Studies were restricted to those written in the English language. Letters, notes, case reports, and comments were excluded. Abstracts of the citations identified by the initial search were evaluated independently and in duplicate by 2 or 3 authors (G.P., A.W., and P.K.) for eligibility. Full-text versions of all potentially relevant studies were obtained and evaluated in detail. Authors searched reference lists of eligible studies for additional references. The results of the literature search selection process are presented in Figures 1–7.

Data Extraction and Risk-of-Bias Assessment

Data were extracted by 2 or 3 Panel members (G.P., A.W., and P.K.) to a Microsoft Excel spreadsheet (Microsoft, Redmond, WA). The following clinical data were extracted for each trial, if available: author last name, publication year, country of origin, funding source, protocol registration, study duration, strain and dose of probiotic, pediatric or adult subjects, and outcome measures, including adverse events. Authors assessed risk of bias of eligible studies independently and in duplicate using the Cochrane risk-of-bias tool for randomized

controlled trials.[5] Authors discussed risk-of-bias judgments to reach consensus; however, if consensus could not be reached, a third author provided consultation until a decision was made.

Analytic Approach

When possible, a pooled effect estimate was calculated for each comparison. If studies did not report means and SDs but reported medians and interquartile ranges, they were converted and added to the quantitative synthesis using methods from the Cochrane Handbook.[5,6] Quantitative analyses were expressed as a relative risk (RR) or odds ratio (OR) for categorical variables and mean difference (MD) for continuous variables. The DerSimonian and Laird method for random-effect or fixed-effects models (when pooling <3 clinical trials) was applied to determine the overall effect size with 95% confidence intervals (CIs). When quantitative pooling was not possible, a narrative summary of the results was developed. Heterogeneity between studies was assessed using a χ^2 test of homogeneity with a .10 significance level and I^2 statistic. Subgroup analyses were performed to examine the effect for individual probiotic species/strains. When more than 10 studies were available in an analysis, publication bias was evaluated using funnel plot asymmetry. Review Manager (RevMan), version 5.3 (Rev-Man for Windows 2008; Nordic Cochrane Center, Copenhagen, Denmark) was used to conduct all statistical analyses and generate forest plots, risk-of-bias tables, and funnel plots.

Certainty of Evidence

The GRADE approach was used to assess the certainty (ie, quality) of evidence (CoE).[7] Across each outcome, evidence from randomized controlled trials starts at high quality and can be downgraded due to concerns about risk of bias, inconsistency (or heterogeneity), indirectness, imprecision, and/or publication bias.[8] Due to inherent limitations in observational studies (lack of a prognostic balance), evidence from observational studies starts at low quality and is potentially downgraded based on the aforementioned factors, or can be upgraded on the basis of a large magnitude of effect, a dose–response gradient, or opposing residual confounding. The quality of the evidence was first evaluated across the body of evidence for each outcome and then across outcomes for each PICO question. The quality of the evidence can be rated as “High,” “Moderate,” “Low,” or “Very Low.” Additionally, for each PICO question, an evidence profile, using the GRADEpro Guideline Development Tool (www.gradepro.org) was prepared. Recently published GRADE guidance on specific wording for narrative statements to reflect the CoE[9] guided the description of the certainty in the Results section.

Question 1: In Symptomatic Adults With Confirmed *C difficile* Infection, Should Probiotics Be Used as Part of the Treatment Regimen?

Results

CDI is typically treated with oral antibiotics, such as vancomycin and fidaxomicin, but during the past decade there has been a significant rise in recurrent CDI,[10] highlighting the need for novel adjunct therapies. The use of fecal microbiota transplantation to successfully

treat multiple recurrent CDI provides proof-of-principle evidence that altering the gut microbiota can restore health in this context,[11] although the body of evidence regarding probiotics has been less convincing. A Cochrane review published in 2008[12] included 4 studies that examined the use of probiotics in conjunction with conventional antibiotics for the treatment of an initial episode or of recurrence of CDI in adults.[13–16] To update the evidence base, the Technical Review Panel reviewed 4501 titles and abstracts, assessed 4 new full-text articles for eligibility, and identified 1 additional study[17] for inclusion (Figure 1).

In total, 5 randomized placebo-controlled trials evaluating probiotics in conjunction with conventional antibiotics, examining a total of 223 adults (probiotics, n = 110; placebo, n = 113), were included in this review. Four different probiotic formulations were tested, with only *Saccharomyces boulardii* being tested in more than 1 study.[14,15] Enrollment criteria differed between the studies. One trial[17] enrolled only patients with an initial case of CDI, 3 trials[13,15,16] enrolled only patients with recurrent disease, and 1 trial[14] enrolled patients with either initial or recurrent CDI. The antibiotics administered were metronidazole (n = 1), vancomycin (n = 1), or either of these 2 antibiotics (n = 3). All 5 published studies contained uncertain or high risk of bias regarding blinding of outcome assessment and selective reporting. Similar to the Cochrane review,[12] data were not pooled for a combined analysis due to variations in recruitment criteria, outcome measures (eg, only 1 study[16] reported bacteriological cure), clinical heterogeneity related to initial disease state and antibiotic therapy, high dropout rates, and type of probiotic used. The evidence is summarized in Appendix 1.

The largest study,[14] which analyzed 124 subjects receiving metronidazole or vancomycin for initial or recurrent CDI, reported that *S boulardii* (1 g, 3×10^{10} cfu/d or placebo) may increase the cessation of diarrhea (RR, 1.33; 95% CI, 1.02–1.74, Low CoE), and may decrease the recurrence of diarrhea (RR, 0.59; 95% CI, 0.35–0.98, Low CoE). The second study[15] that examined *S boulardii* (1 g/d, cfu not reported or placebo) among 32 adults with recurrent CDI receiving either metronidazole or high-dose (2 g/d) or low-dose (500 mg/d) vancomycin also reported decreased recurrence of diarrhea in the probiotic arm compared to placebo, but only among those receiving high-dose vancomycin, which was non-randomly assigned to the sickest patients, and the CI of this effect did cross 1.0. One study[17] of 31 adults with initial CDI who were treated with either metronidazole or vancomycin and who received the 4-strain combination of *Lactobacillus acidophilus* ATCC 700396, *Lactobacillus paracasei* subsp *paracasei* ATCC 335, *Bifidobacterium animalis* subsp *lactis* ATCC SD5220, and *B animalis* subsp *lactis* ATCC SD5219 at a dose of 1.70×10^{10} cfu/d, reported that probiotics compared to placebo may reduce the duration of diarrhea, but the evidence is very uncertain (Very Low CoE). The other 2 studies each tested different strains of probiotic in even smaller trials. The first of these trials[16] reported that *Lactobacillus plantarum* 299v at a dose of 5×10^{10} cfu/d may not increase events of cessation of diarrhea vs placebo, but the evidence is very uncertain (RR, 0.93; 95% CI, 0.73–1.19, Very Low CoE). The other trial[13] reported that *Lactobacillus rhamnosus* ATCC 53103 may increase CDAD recurrence vs placebo, but the evidence is very uncertain (RR, 2.63; 95% CI, 0.35–19.85, Very Low CoE). The effect of specific probiotics was difficult to assess, given the small number of studies evaluated for each probiotic formulation. The most common adverse events reported were

mild gastrointestinal symptoms, with 1 study[14] reporting increased constipation among patients treated with *S boulardii* vs placebo. No serious adverse events were reported.

The overall CoE across all critical outcomes for probiotics as part of the treatment of *C difficile* infection was Low.

Discussion

The most recent Cochrane review[12] was published more than a decade ago, and an updated literature search identified just 1 additional trial[17] that evaluated an additional 31 participants. Therefore, the conclusions drawn by the previous meta-analysis were not markedly changed. The spectrum of enrolled subjects was not large enough to identify specific or potentially serious harms, and few total events were reported. Furthermore, the data contained substantial indirectness due to differences in enrollment criteria, with both initial and recurrent disease being studied, and due to differences in study design, with comparators ranging from placebo to low-dose or high-dose antibiotics. There also was a potential risk of publication bias due to multiple registered trials that were not linked to a published report. Finally, none of these studies enrolled children, so it is unclear whether these findings are generalizable to the pediatric population. A considerably larger body of evidence exists regarding a potential role for probiotics in the prevention of CDI among those taking antibiotics for other conditions; this evidence is reviewed in the next section.

Question 2: In Adults and Children Receiving Antibiotic Therapy for any Indication Except *C difficile* Infection, Should Probiotics Be Used to Prevent *C difficile*–Associated Diarrhea?

Results

Compared to the sparse body of data relevant to the treatment of CDI, the role of probiotics for the prevention of CDAD has been investigated more thoroughly. This review includes 39 studies[18–53] (M. Miller, unpublished data, 2008a, 2008b; S. Rafiq, unpublished data, 2007), all of which were identified in a Cochrane review published in 2017.[54] These studies evaluated a total of 9955 participants, although the baseline populations were remarkably heterogeneous: children, adults, and the elderly; inpatients and outpatients; high and low baseline risks of developing CDAD; and various antibiotic regimens prescribed for a wide range of clinical indications. Among the key findings from the published meta-analysis,[54] a complete case analysis of the 31 trials that reported incidence of CDAD (probiotics, n = 4525; placebo, n = 4147) revealed that reduce the risk of CDAD vs placebo (RR, 0.40; 95% CI, 0.30–0.52, Moderate CoE). Subgroup analysis revealed stratification of the effect size by baseline risk of CDAD. The Cochrane review defined baseline risk as the event rate in the control arm, and divided this risk post hoc into 3 groups (0%–2%, 3%–5%, and >5%), corresponding with low-, moderate-, and high-risk clinical scenarios.[54] Specifically, trials that enrolled patients with a >5% baseline risk of developing CDAD demonstrated a large risk reduction (RR, 0.30; 95% CI, 0.21–0.42, Moderate CoE), whereas a similar benefit was not identified among trials enrolling patients with a lower baseline risk of 3%–5% (RR, 0.53; 95% CI, 0.16–1.77, Moderate CoE) or a baseline risk of 0%–3% (RR, 0.77; 95% CI,

0.45–1.32, Moderate CoE). Among the 15 trials that reported on the detection of *C difficile* in the stool, probiotics did not reduce fecal detection rates (RR, 0.86; 95% CI, 0.67–1.10, Moderate CoE). Finally, among the 32 studies that reported adverse events, probiotics might reduce the risk of adverse events vs placebo (RR, 0.83; 95% CI, 0.71–0.97, Very Low CoE).[54]

The Technical Review Panel performed an updated search, reviewed 4501 titles and abstracts, assessed 24 new full-text articles for eligibility, and did not identify any more recent studies for inclusion (Figure 2). However, the team considered several factors in its decision to downgrade the overall CoE from Moderate to Low. Of the 39 studies included in the published meta-analysis,[54] 2[26,39] were published in abstract form only and 3 were unpublished data (M. Miller, unpublished data, 2008a, 2008b; S. Rafiq, unpublished data, 2007). Only 2 of the 39 studies were determined to have low risk of bias across all domains for all outcomes assessed. The Technical Review Panel also highlighted the potential risk of publication bias, given the large volume of registered trial protocols that were not associated with subsequent peer-reviewed publications. Furthermore, the overall effect estimate was heavily weighted by 5 trials enrolling patients with a >15% baseline risk of developing CDAD. Finally, the analysis of studies that reported incidence of CDI contained a wide CI that includes the potential for some benefit as well as some harm.

Subgroup analyses of individual probiotic formulations revealed that *S boulardii* (RR, 0.41; 95% CI, 0.22–0.79, Low CoE); the 2-strain combination of *L acidophilus* CL1285 and *Lactobacillus casei* LBC80R (RR, 0.22; 95% CI, 0.11–0.42, Low CoE); the 3-strain combination of *L acidophilus*, *Lactobacillus delbrueckii* subsp *bulgaricus*, and *Bifidobacterium bifidum* (RR, 0.35; 95% CI, 0.15–0.85, Low CoE); and the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *Streptococcus salivarius* subsp *thermophilus* (RR, 0.28; 95% CI, 0.11–0.67, Low CoE) might all reduce the risk of CDAD vs placebo. The complete body of evidence is presented in Appendix 2.

The overall CoE across all critical outcomes for probiotics, based on the best available evidence from *S boulardii*; or the 2-strain combination of *L acidophilus* CL1285 and *L casei* LBC80R; or the 3-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, and *B bifidum*; or the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *S salivarius* subsp *thermophilus*, for the prevention of CDAD in adults and children was Low.

Discussion

The overall evidence is promising for probiotics in general, and for certain strains and combinations of strains in particular, as a means of preventing CDAD after antibiotic use. Most of the included trials do not describe whether the probiotic formulations were rationally selected based on evidence of probiotic survival despite exposure to the prescribed antibiotics. The yeast *S boulardii* was the only single-strain probiotic to demonstrate a significant effect in reducing the incidence of CDAD. Antibiotics do not kill yeast typically, but they can increase the growth of some resident yeast by decreasing bacterial colonization; however, the exact mechanism by which *S boulardii* exerts a protective effect remains unclear. The rationale for using probiotics along with antibiotics is to accelerate recovery of

a disrupted gut microbiota and prevent opportunistic pathogens from being able to exploit the open niches resulting from antibiotic use. However, recent studies have shown that probiotics may alter the recovery path of gut microbiota after antibiotic use when compared to no intervention.[55] The clinical implications of such altered recovery remain to be determined. Furthermore, diet also may alter recovery after antibiotic use,[56] but clinical trials with probiotics typically do not account for dietary differences among participants.

A recently published network meta-analysis evaluated probiotics for the prevention of antibiotic-associated diarrhea.[57] The analysis included 51 trials enrolling 9565 participants receiving 10 different probiotic interventions and concluded that *L rhamnosus* ATCC 53103 had the highest probability of being the top-ranked intervention in terms of both effectiveness and tolerability. This result highlights how subtle differences in outcome measures—specifically, CDAD vs antibiotic-associated diarrhea—can affect how various treatments perform in meta-analyses.

Despite the relatively large number of published trials relevant to this PICO question, we did not identify any new trials published in the 20 months spanning from the conclusion of the search reported in the Cochrane review[54] to the conclusion of our updated literature search in December 2018. Our assessment of the previously identified trials raised significant concerns regarding risk of bias, significant population heterogeneity, and unknown potential for adverse events. Thus, the Technical Review Panel concluded that the overall CoE for this PICO question is Low.

Question 3: In Adults and Children With Crohn's Disease, Should Probiotics Be Used for Induction or Maintenance of Remission?

Results

Inflammatory bowel diseases (IBDs) encompass a heterogeneous group of immune-mediated diseases that are distinct in pathogenesis, manifestations, risk factors, and response to therapy. The etiology of IBDs is multifactorial, with contributions from genetic alterations, immune disturbances, environmental factors, and gut microbiota. Current treatment strategies rely primarily on targeting the immune system with pharmacologic agents, although there is increasing focus on microbiota-directed therapies. Disruptions of the gut microbiome have been well described at the compositional and functional levels in IBD, but whether they serve as the initial inciting event, function to perpetuate the underlying inflammation, or simply result from the altered gastrointestinal niche in IBD remains unclear. While there are multiple microbiome-targeting strategies, including diet, fecal microbiota transplantation, and prebiotics, this technical review focuses on the current evidence for use of probiotics in IBD.

Microbiota alterations are particularly well described for Crohn's disease,[58–60] a relapsing and remitting form of IBD characterized by segmental, asymmetrical, and transmural lesions throughout the gastrointestinal tract; by frequent surgical complications, including strictures, fistulas, and abscesses; and by extraintestinal manifestations.[61] A 2008 Cochrane Review[62] examining probiotics for the induction of remission in children and adults with Crohn's

disease identified just 1 study[63] that evaluated a total of 11 patients. This study did not show certain benefit with administration of *L rhamnosus* ATCC 53103 (OR, 0.80; 95% CI, 0.04–17.20, Very Low CoE). The review authors cited concerns regarding the study design, including lack of a power calculation and allowing concurrent use of corticosteroids. Furthermore, the study lacked detail regarding how and when induction was assessed, and the risk of bias with respect to allocation concealment was unclear. To bring the evidence base up to date, the Technical Review Panel assessed 2674 titles and abstracts and assessed 9 new full-text articles for eligibility, but did not find any more recent studies that met inclusion criteria (Figure 3A). Thus, this review contains a single small study (probiotics, n = 5; placebo, n = 6) relevant to induction of remission in Crohn's disease.[63]

In contrast, 11 trials are included in this technical review regarding the role of probiotics for maintenance of remission in children and adults with Crohn's disease. Of these, 7 studies evaluating 248 adults and children[63–69] were identified in a 2006 Cochrane review.[70] The Technical Review Panel's assessment of 2674 titles and abstracts and review of 12 new full-text articles identified an additional 4 studies[71–74] for inclusion, which analyzed an additional 430 adults, for a total of 678 subjects (probiotics, n = 343; placebo, n = 335; Figure 3B). Two studies[71,72] assessed the effectiveness of *Lactobacillus johnsonii* NCC 533 in preventing severe endoscopic relapse after surgical induction at either 12 weeks or 6 months in a total of 145 patients (probiotics, n = 71; placebo, n = 74). There was no difference between the probiotic and placebo (RR, 0.97; 95% CI, 0.52–1.83, Low CoE), and there was unclear risk of bias for random sequence generation and selective reporting in both studies. Another study[74] administered the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *Bifidobacterium longum* subsp *longum*, *Bifidobacterium breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* after surgical induction in a total of 94 patients (probiotic, n = 43; placebo, n = 51) and found no difference in relapse at 3 months. There was unclear risk of bias for outcome assessment. A previously identified study presented in abstract form[65] assessed 40 patients (probiotics, n = 20; mesalamine, n = 20) who received the same 8-strain combination or mesalamine after surgical induction. Similar to the larger published study, there was not a difference in endoscopic relapse at 12 months. However, the probiotic group received rifaximin for 3 months, followed by 9 months of probiotics, raising the possibility that results were confounded by the use of antibiotics. Furthermore, there was an unclear risk of bias for random sequence generation and allocation concealment and only the physicians participating in the study were blinded. A combined analysis of these 2 studies did not reveal a clear benefit for the 8-strain probiotic combination (RR, 0.54; 95% CI, 0.25–1.16, Very Low CoE). Finally, 2 studies[66,73] examined the effectiveness of *S boulardii* in a total of 191 patients (probiotic, n = 96; placebo/mesalamine, n = 95). There was no clear benefit with *S boulardii* in preventing relapse of CD (RR, 0.51; 95% CI, 0.10–2.54, Very Low CoE) compared to placebo or mesalamine. There was unclear risk of bias with respect to random sequence generation and incomplete reporting in both studies. One study[66] also had unclear risk of bias for allocation concealment and blinding, with the additional potential confounder that both groups received mesalamine but the probiotic group received a lower dose (2 g) compared to the control group (3 g). The evidence is summarized in Appendix 3.

The overall CoE across all critical outcomes for probiotics for the induction or maintenance of remission in children or adults with Crohn's disease was Low.

Discussion

There is currently no evidence to suggest that probiotics are beneficial for the induction or maintenance of remission in children or adults with Crohn's disease. None of the individual studies included in this technical review reported a significant benefit from probiotic therapy, and meta-analyses combining 2 studies each analyzing *L johnsonii* LA1, an 8-strain probiotic combination, or *S boulardii* revealed no clear benefit. However, the studies were heterogeneous with regard to patient population, probiotic tested, duration of treatment, concomitant therapy, and the control product. For maintenance of remission studies, the populations differed based on whether remission was induced by medical or surgical means. Most of the included studies enrolled small numbers of patients and might have lacked the statistical power to reveal clinically significant differences, should they exist. Only 1 study[64] enrolled children. For induction of remission in Crohn's disease, our finding of just 1 published study[63] examining 11 subjects highlights the lack of well-designed prospective trials in this area. These findings are consistent with a recently published systematic review and meta-analysis that examined the use of probiotics for adults with IBD.[75] Larger studies will be required to determine whether probiotics may be of benefit in Crohn's disease.

Question 4: In Adults and Children With Ulcerative Colitis, Should Probiotics Be Used for Induction or Maintenance of Remission?

Results

Ulcerative colitis is a chronic form of IBD characterized by mucosal inflammation that typically extends from the rectum proximally; as in Crohn's disease, extraintestinal manifestations are common.[76] Also similar to Crohn's disease, characteristic microbiome changes have been described for ulcerative colitis,[59,60,77] lending promise to the notion that microbiome-targeting therapies, including probiotics and, more recently, fecal microbiota transplantation,[78] might offer hope for patients.

This technical review includes 11 studies that examined the use of probiotics for induction of remission in children and adults with ulcerative colitis. A 2007 Cochrane review[79] identified 4 studies examining 236 adult subjects (probiotics, n = 106; placebo, n = 130),[80–83] although 1 of these studies[80] tested a synbiotic—the combination of probiotic *B longum* subsp *longum* with prebiotics fructo-oligosaccharide and inulin—vs placebo. The Technical Review Panel assessed 2674 titles and abstracts. Of 29 new potentially eligible studies that were reviewed in full text, 7 placebo-controlled trials[84–90] that examined probiotics in conjunction with conventional management for induction of remission of ulcerative colitis were identified and added to the evidence base (Figure 4A). These 7 more recently published trials enrolled a total of 532 patients, bringing the total evidence base to 768 subjects (probiotics, n = 399; placebo, n = 369). Two studies[84,88] enrolled children exclusively, among them 1[84] that only included children newly diagnosed with ulcerative colitis. In all, 5 different probiotics were tested: the 2-strain combination of *B breve* with *B bifidum*[81]; *B longum* Reuter ATCC BAA-999[90]; *Escherichia coli* Nissle 1917[82,86,89]; the 8-

strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*[83–85,87]; and *Lactobacillus reuteri* ATCC 55730.[88] The 8-strain combination was examined in 1 pediatric study[84] and 3 adult studies,[83,85,87] and *E coli* Nissle 1917 was tested in 3 studies—2 as an oral therapeutic[82,89] and 1 as an enema.[88] The other probiotics were tested in 1 study each: *L reuteri* ATCC 55730 as an enema[88] and both *B longum* Reuter ATCC BAA-999[90] and the 2-strain combination of *B breve* with *B bifidum*[81] administered orally. Two studies[86,88] administered probiotics as an enema. The duration of treatment was 7–12 weeks except in 1 study,[84] in which the 8-strain probiotic combination was administered for 1 year. The standard treatments varied among studies, with 1 study[89] utilizing antibiotics for treatment of ulcerative colitis.

Combined analyses of the individual probiotic formulations revealed the following. First, the effectiveness of the 8-strain probiotic combination was evaluated in 4 trials evaluating 367 patients (probiotics, n = 186; mesalamine or balsalazide, n = 181), including 1 study[84] that enrolled children. The duration of treatment varied among the studies and there was significant heterogeneity in study design. There was a potential for benefit, but it is very uncertain (RR, 1.72; 95% CI, 0.89–3.32, Very Low CoE), with significant heterogeneity in study design. For example, 1 trial[87] used the anti-inflammatory drug balsalazide as the control. There were multiple concerns regarding bias, including unclear risk with respect to blinding in multiple studies, 1 study with higher than expected attrition, and another study with unclear risk of bias with respect to allocation concealment. Second, the effectiveness of orally administered *E coli* Nissle 1917 compared to mesalamine to induce remission in ulcerative colitis was analyzed in 2 studies[82,89] evaluating 166 patients (probiotic, n = 82; mesalamine, n = 84). *E coli* Nissle 1917 suggested uncertain benefit (RR, 0.86; 95% CI, 0.49–1.49, Very Low CoE). One of the studies[82] had a high risk of bias for randomization, unclear risk of bias for allocation concealment and blinding, a withdrawal rate of 8.9%, and patients received both steroids and gentamicin 80 mg 3 times per day for 1 week in addition to probiotic or placebo. In the more recent study,[89] some of the patients received topical prednisolone as concomitant therapy at the time of enrollment. One other study[86] administered *E coli* Nissle 1917 as an enema to a total of 88 patients (probiotic 10 mL, n = 23; 20 mL, n = 23; 40 mL, n = 22; placebo, n = 20) with mild-to-moderate distal ulcerative colitis. There was no clear benefit for any probiotic dose compared to placebo in intention-to-treat analysis. Finally, *L reuteri* ATCC 55730, in enema form, was studied among 31 children (probiotic, n = 16; placebo, n = 15) with active distal ulcerative colitis. Probiotic enemas may increase clinical response vs placebo (RR, 1.83; 95% CI, 1.14–2.92, Low CoE). The results from the other newly identified studies did not show a benefit in induction of remission; each study tested a unique probiotic formulation. The evidence profiles are presented individually in Appendix 4.

The Technical Review Panel next compiled evidence regarding the use of probiotics for maintenance of remission in adults and children with ulcerative colitis. A 2011 Cochrane review[91] had identified 4 studies[92–95] enrolling a total of 664 adult patients (probiotics, n = 367; placebo or mesalamine, n = 297). We reviewed 2674 titles and abstracts, assessed 13 new full-text articles for eligibility, and included 2[96,97] additional placebo-controlled trials examining probiotics for maintenance of remission (Figure 4B). These 2 studies analyzed an

additional 241 adults, bringing the total to 905 subjects (probiotics, n = 488; placebo, n = 417). The new studies use different multispecies probiotic formulations administered for 48 weeks to 1 year, and there was unclear risk of bias with respect to outcome assessment. The 2-strain combination of *B breve* Yakult and *L acidophilus*[97] did not show appreciable benefit (RR, 1.15; 95% CI, 0.66–1.98, Low CoE). Similarly, the 3-strain combination of *Enterococcus faecalis* T-111, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A[96] did not show clear benefit (RR, 1.33; 95% CI, 0.83–2.15, Low CoE), with a large CI, few events, and unclear risk of bias with respect to allocation concealment and blinding. The previous meta-analysis[91] included 2 studies in which *E coli* Nissle 1917 was administered to a total of 430 patients (probiotics, n = 212; mesalamine, n = 218) and relapse was assessed at 12 weeks[92] (RR, 1.79; 95% CI, 0.82–3.92) or 12 months[93] (RR, 1.40; 95% CI, 0.90–2.18), showing no clear benefit compared to mesalamine. Both of these studies had unclear risk of bias with respect to allocation concealment and 1 of the studies[93] reported significant attrition, with a dropout rate of 46.5%. The data from remaining studies were not pooled, given that no prior studies utilized the same probiotic formulation; therefore, the results from the individual trials are presented in the evidence profiles summarized in Appendix 4.

The overall CoE across all critical outcomes for probiotics for induction or maintenance of remission in children or adults with ulcerative colitis was Low.

Discussion

The literature search updates conducted for this technical review more than doubled the number of published prospective trials that were included in the most recent Cochrane reviews that evaluated probiotics for the induction[78] and maintenance[91] of remission in adults and children with ulcerative colitis. Despite the addition of these more recent studies to the evidence base, a knowledge gap remains regarding the role of probiotics in these contexts. The quality of existing evidence is limited in many cases by study designs characterized by small sample sizes and concerns regarding risk of bias. Furthermore, the use of mesalamine as a comparator drug might blunt any beneficial effect of probiotics. As with the other focused questions, there also remains the possibility of publication bias, given that published articles are typically skewed toward positive study findings.

Conventional therapy combined with a probiotic does not appear to improve overall remission rates in patients with mild-to-moderate ulcerative colitis, although there is limited evidence that probiotics may provide modest benefits in terms of reduction of disease activity in mild-to-moderate ulcerative colitis. The efficacy of probiotics for patients with severe disease, as well as the efficacy of probiotics as alternatives to existing therapies, remains unknown. As reported in a recent meta-analysis,[75] among the promising individual formulations was the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*, which was reported in 2 prospective trials to be beneficial. However, this combination also was the most tested of all probiotic formulations for patients with ulcerative colitis, and combined case analyses of 4 studies did not reveal a clear benefit. Interestingly, the 2 trials that enrolled children exclusively reported a significant effect attributed to probiotics for induction of remission, suggesting that the

pediatric population might potentially benefit more than adults with ulcerative colitis. Additional studies are needed to expand upon this observation.

Question 5: In Adults and Children With Ileal Pouch–Anal Anastomosis for Chronic Ulcerative Colitis, Should Probiotics Be Used for Prevention or Maintenance of Remission of Pouchitis?

Results

Refractory or complicated ulcerative colitis is often managed surgically by total abdominal proctocolectomy to remove the diseased bowel, with IPAA to facilitate passage of bowel movements without a stoma. Acute, relapsing, or chronic pouchitis is the most common post-surgical complication, occurring in more than one-half of patients.[98] Although the etiology of pouchitis is poorly understood, gut microbiota have been suggested to play a role, based on altered fecal microbial communities that associate with disease activity,[99] the use of antibiotics as the mainstay of pouchitis therapy,[100] and the possible therapeutic role of fecal microbiota transplantation.[101]

Of the 13 studies included in a comprehensive 2015 Cochrane review[102] of multiple different therapies for the treatment and prevention of pouchitis among adults with IPAA for ulcerative colitis, 6 studies[103–108] tested probiotics and were included in this technical review; these studies analyzed a total of 176 patients (probiotics, n = 93; placebo, n = 83). After screening 2674 titles and abstracts and assessing 2 new full-text articles, the Technical Review Panel added to the evidence base 1 trial[109] (Figure 5), which assessed 17 adults, bringing the total to 193 subjects (probiotics, n = 102; placebo, n = 91). The newly identified study found uncertain benefit with administering *C butyricum* compared to placebo in preventing relapse of pouchitis (RR, 0.22; 95% CI, 0.03–1.60, Very Low CoE). There was unclear risk of bias with respect to random sequence generation, allocation concealment, and blinding, and this study had small enrollment and a low event rate.

In the previously published meta-anlaysis,[102] the effectiveness of the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* was evaluated in 2 studies[104,107] reporting on a total of 76 patients (probiotic, n = 40; placebo, n = 36) for maintenance of remission of chronic pouchitis. There may be a benefit in the proportion of patients who maintained remission at 9–12 months when this probiotic formulation was compared to placebo (RR, 20.24; 95% CI, 4.28–95.81, Low CoE). Two different studies[105,108] tested the same 8-strain probiotic formulation against placebo or no treatment for the prevention of an initial episode of acute pouchitis among 68 patients (probiotic, n = 36; placebo/no treatment, n = 32). Patients receiving probiotics were more likely to have zero acute pouchitis episodes over 12 months compared to patients receiving placebo or no treatment (RR, 1.29; 95% CI, 1.03–1.61, Very Low CoE). Although 1 of these studies[105] had a placebo arm, the second trial[108] was an open-label study that contained a high risk of bias with respect to blinding; furthermore, the number of events was small. Smaller individual studies examining *L rhamnosus* ATCC 53103[106] or *B longum* subsp *longum*[103] found no clear benefit for either of these probiotics, although they were not likely

powered adequately to detect a clinical effect, if one exists. The evidence is summarized in Appendix 5.

The overall CoE across all critical outcomes for probiotics, based on the best available evidence from the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*, for the prevention or maintenance of remission of pouchitis is Very Low.

Discussion

Four published studies examine the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* for adults with IPAA in the setting of chronic ulcerative colitis. These studies revealed a potential benefit for adults with ulcerative colitis and IPAA, both in preventing a first episode of acute pouchitis and in maintaining remission after treatment for pouchitis. However, there has been concern regarding the commercial availability of this formulation, given that litigation between the manufacturer and patent holder has been ongoing. Whether other formulations of this 8-strain probiotic, or other strains or combinations of probiotics, might demonstrate similar beneficial effects in the setting of pouchitis is unclear, given that no other formulation has been tested as rigorously. It also remains unclear whether a potential benefit might exist for patients with IPAA resulting from familial adenomatous polyposis or other intestinal disorders, or for children with IPAA.

Question 6: In Symptomatic Children and Adults With Irritable Bowel Syndrome, Should Probiotics Be Used to Improve Global Response or Abdominal Pain Severity?

Results

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder with fluctuating symptoms that include abdominal pain or discomfort and alteration of stool form or frequency.[110] Diagnosis is based on symptoms outlined in the Rome criteria. The prevalence of IBS is approximately 20% in North America,[111] although the global prevalence is much lower,[112] especially if the most recent diagnostic criteria are applied.[113] The pathophysiology of IBS is incompletely understood, although multiple peripheral and central mechanisms have been implicated. These mechanisms include altered gastrointestinal motility, sensation, secretion, and barrier function, as well as abnormal brain–gut communication.[114]

The gut microbiota influence the majority of these physiological processes.[114] Transfer of gut bacteria from IBS patients to germ-free rodents can transfer pathologic phenotypes, including altered gastrointestinal transit time or decreased pain threshold.[115–117] Several studies have illustrated differences in gut microbiota composition between patients with IBS and healthy controls, with decreased α-diversity being the most consistent observation. However, a similar observation has been made in other chronic conditions, suggesting that

this finding is not specific to IBS.[113] The lack of known mechanisms by which probiotics may improve symptoms in IBS has not precluded their use, which is quite prevalent based on a survey of clinicians.[118] These findings highlight the need for further guidance to facilitate an evidence-based approach to the use of probiotics for IBS. In this technical review, we have compiled evidence from well-conducted randomized placebo-controlled clinical trials of probiotics in IBS to determine whether the use of probiotics is justified in IBS patients.

The Technical Review Panel did not identify a previously published systematic review that assessed the efficacy of probiotics for both children and adults with IBS; thus, we conducted a review of the literature from database inception through December 2018. The team screened 1617 titles and abstracts, assessed 216 full-text articles, and included 55 references[119–173] in this review (Figure 6). These studies analyzed a total of 5301 patients (probiotics, n = 2768; placebo, n = 2533). These 55 trials tested 44 different probiotic species/strains or combinations of species/strains; thus, for the majority of probiotics, the total body of evidence is derived from a single trial.

Three studies[135,138,150] tested *S boulardii* among a total of 232 adults with IBS (probiotic, n = 117; placebo, n = 115). The 3 studies used different outcome measures, but all reported an abdominal pain score. There was no difference between *S boulardii* and placebo (standardized MD, 0.26; 95% CI, −0.09 to 0.61, Very Low CoE), and there was unclear risk of reporting bias for all 3 studies. Two trials[121,124] assessed the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* for abdominal pain, assessed by visual analog scale, among a total of 73 adults with IBS (probiotic, n = 36; placebo, n = 37). This 8-strain combination may decrease abdominal pain (mean decrease, −3.78; 95% CI, −4.93 to −2.62, Very Low CoE). These studies contained a small overall sample size, wide CIs, and enrolled patients that varied with respect to IBS subtype. Furthermore, there was unclear risk of selection, reporting, and detection bias. *S boulardii* and the 8-strain combination were the only 2 probiotics or combinations of probiotics that had more than 1 trial measure the same outcome, thus facilitating combined case analyses.

For a number of other probiotics, a single trial found that probiotics may be beneficial in adults with IBS. For improvement of global IBS symptoms, these probiotics included *L plantarum* 299v[143]; *Saccharomyces cerevisiae* CNCM I-3856[160]; *E coli* DSM 17252[130]; the 4-strain combination *S salivarius* subsp *thermophilus, L delbrueckii* subsp *bulgaricus*, *L acidophilus*, and *B longum* subsp *longum*[129]; the 7-strain combination *L acidophilus* KCTC 11906BP, *L plantarum* KCTC 11876BP, *L rhamnosus* KCTC 11868BP, *B breve* KCTC 11858BP, *B animalis* subsp *lactis* KCTC 11903BP, *B longum* subsp *longum* KCTC 11860BP, and *S salivarius* subsp *thermophilus* KCTC 11870BP[144]; *B bifidum* MIMBb75[136]; the 3-strain combination of *L plantarum* CECT7484, *L plantarum* CECT7485, and *Pediococcus acidilactici* CECT7483[152]; the 14-strain combination of *Bacillus subtilis* PXN 21, *B bifidum* PXN 23, *B breve* PXN 25, *B longum* subsp *infantis* PXN 27, *B longum* subsp *longum* PXN 30, *L acidophilus* PXN 35, *L delbrueckii* subsp *bulgaricus* PXN 39, *L casei* PXN 37, *L plantarum* PXN 47, *L rhamnosus* PXN 54, *Lactobacillus helveticus* PXN 45,

Lactobacillus salivarius PXN 57, *Lactococcus lactis* PXN 63, and *S salivarius* subsp *thermophilus* PXN 66[166]; *C butyricum*[172]; and the 4-strain combination *B animalis* subsp *lactis* Bb12, *L acidophilus* LA-5, *L delbrueckii* subsp *bulgaricus* LBY-27, and *S salivarius* subsp *thermophilus*.[151] In contrast to the above studies that report a positive benefit, the 6-strain combination of *B longum* subsp *longum*, *B bifidum, B animalis* subsp *lactis, L acidophilus, L rhamnosus*, and *S salivarius* subsp *thermophilus*, was found to be inferior to placebo for global relief of symptoms in adults with IBS.[156]

Probiotics shown in a single trial to improve abdominal pain scores in adults with IBS included *L plantarum* 299v[143]; *L rhamnosus* ATCC 53103[119]; *Bacillus coagulans* MTCC 5856[168]; the 2-strain combination of *L acidophilus* SDC 2012 and SDC 2013[128]; *E coli* DSM 17252[130]; the 4-strain combination of *S salivarius* subsp *thermophilus, L delbrueckii* subsp *bulgaricus*, *L acidophilus*, and *B longum* subsp *longum*[129]; the 4-strain combination of *L rhamnosus* NCIMB 30174, *L plantarum* NCIMB 30173, *L acidophilus* NCIMB 30175, and *Enterococcus faecium* NCIMB 30176[153]; the 3-strain combination of *B longum* subsp *infantis* M-63, *B breve* M-16V, and *B longum* Reuter ATCC BAA-999[162]; and the 2-strain combination of *B longum* subsp *longum* and *L acidophilus*.[141]

For children with IBS, the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus*,[133] as well as *L rhamnosus* ATCC 53103,[132] may improve abdominal pain scores, and *B coagulans* Unique IS2 may reduce pain intensity and abdominal discomfort compared to no probiotics.[171]

Most importantly, the CoE in each of these individual trials was either Low or Very Low. The complete set of analyses is presented in Appendix 6.

The overall CoE across all critical outcomes for probiotics for the treatment of children and adults with IBS was Low.

Discussion

Mechanisms by which probiotics might improve symptoms in IBS remain largely unknown; hence, the choice of which probiotic to test in clinical studies has been largely empiric. This notion is reflected in our finding of 44 distinct probiotics or combinations of probiotics, which results in the majority of evidence for this PICO question derived from a single published trial with relatively small sample sizes and variable quality and risk of bias. Furthermore, the results from these clinical studies can be difficult to interpret due to lack of standardization, differences in study design, lack of subtype stratification, and differences in the dose or duration of therapy.

Our results are consistent overall with a recent meta-analysis of 53 trials that evaluated probiotics among a total of 5545 adults with IBS; the review authors did not find significant benefit in global symptom or abdominal pain scores when trials of single-strain probiotics were grouped and analyzed at the genus level, although the authors did report a potentially significant benefit from a combined case analysis of 19 trials that tested multistrain probiotics.[174] Another recent systematic review and meta-analysis focusing on the 8-strain

combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* also reported no significant benefit of the probiotics in terms of overall response.[175] Given the numerous individual probiotic strains that demonstrated benefit in the context of a single trial, one cannot exclude a potential benefit of probiotics for children and adults with IBS. However, the Technical Review Panel also identified numerous registered protocols that had neither peer-reviewed publications nor raw data available for review, highlighting the potential for publication bias. Although the breadth of data regarding probiotic use for IBS is substantial, no single strain or combination has been studied in a sufficiently rigorous manner.

Question 7: In Children With Acute Infectious Gastroenteritis, Should Probiotics Be Used to Reduce the Duration or Severity of Diarrhea?

Results

Acute infectious gastroenteritis is responsible for more than 1.5 million outpatient visits and 200,000 hospitalizations in the United States each year, and remains an important cause of global child mortality.[176] Although typically a self-limited condition, acute gastroenteritis extends its economic toll through daycare or school absences and caretakers' missed days of work. Currently, probiotics are administered in many outpatient, emergency center, and inpatient settings for the treatment of acute gastroenteritis in otherwise healthy infants and children.[177–179] A Cochrane review published in 2010[180] included 63 randomized and quasi-randomized trials enrolling a total of 8014 adults and children with acute diarrhea of presumed infectious origin that compared probiotics against placebo or no probiotic. From these 63 trials, the 58 studies[181–235] (K. Kowalska-Duplaga, unpublished data, 1999; M. Oandasan, unpublished data, 1999; A. Caragüe-Orendain, unpublished data, 2010) that enrolled infants and children younger than 18 years were included in this technical review. More than one-half of all children studied were enrolled in trials originating in just 3 countries—India, Italy, and Poland—while none of these 58 trials were conducted in the United States or Canada. Forty-one of these studies tested a single probiotic strain, while 17 studies tested combinations of between 2 and 8 organisms. The Cochrane review authors' meta-analyses revealed that probiotic use was associated with reductions in the mean duration of diarrhea, the mean stool frequency on day 2, and the risk of diarrhea lasting 4 or more days. The individual strains *L rhamnosus* ATCC 53103, *E faecium* SF68, and *S boulardii* each showed benefit in 1 or more of these primary outcomes. Importantly, the authors cited significant concerns regarding potential for bias in multiple domains in the majority of these studies.[180]

To bring this evidence up to date, the Technical Review Panel screened 4501 titles and abstracts, reviewed 54 new full-text articles, and identified an additional 31 trials[236–266] for inclusion (Figure 7). These more recent studies enrolled an additional 5873 participants and were conducted in 15 different countries, with 14 of the 31 trials originating in India, Turkey, and Pakistan. Of these 31 studies, the majority reported beneficial effects associated with probiotics, although 27 of these contained 1 or more concerns regarding risk of bias. Two of the studies with low risk of bias were large, multicenter, randomized, double-blind,

placebo-controlled trials conducted in North America. The first, conducted by the Pediatric Emergency Care Applied Research Network,[265] enrolled 943 children from 10 emergency departments in the United States; *L rhamnosus* ATCC 53103 was given at a dose of 1×10^{10} cfu twice daily for 5 days. The second, conducted by Pediatric Emergency Research Canada, [266] enrolled 827 children from 6 emergency departments in Canada; the 2-strain combination of *L rhamnosus* R0011 and *L helveticus* R0052 was given in a 95:5 ratio at a total dose of 4×10^9 cfu twice daily for 5 days. The primary outcome in both studies was the occurrence of moderate-to-severe gastroenteritis, defined as a total modified Vesikari scale symptom score (which ranges from 0 to 20, with higher scores indicating more severe disease) of 9 or higher. Neither study found a significant difference between the placebo and probiotic groups in the primary outcome. The 2-strain combination had been tested previously in a smaller multicenter study in Canada, and was found to not significantly alter the primary outcome of daycare absenteeism.[255] A fourth trial from this region, a single-center study conducted in the United States,[245] reported that *L rhamnosus* ATCC 53103 was no more effective than placebo in reducing the median time to normal stool consistency, or the number of diarrheal stools among 129 patients enrolled at a pediatric emergency department.

Of the 89 total studies included in this review, 58 reported on the duration of diarrhea as an outcome. Taken together, probiotics may decrease the mean duration of diarrhea by 21.91 hours (95% CI, 16.17–27.64, Low CoE). Among the 30 studies reporting on diarrhea lasting more than 3 days, probiotics may decrease the risk of prolonged diarrhea (RR, 0.62; 95% CI, 0.56–0.70, Low CoE), and among the 29 studies reporting on diarrhea lasting more than 4 days, probiotics may decrease the risk of prolonged diarrhea (RR, 0.50; 95% CI, 0.40–0.62, Low CoE). However, no significant differences between probiotic and placebo were found in a combined analysis of 20 studies that reported mean stool frequency on day 2, or in a combined analysis of 14 studies that reported mean stool frequency on day 3. In each of these combined case analyses, the evidence was uncertain.

The most frequently studied probiotic was *S boulardii*, which has been evaluated in 22 trials enrolling children with acute gastroenteritis. Ten of these 22 studies reported on mean duration of diarrhea, and analysis of this subset revealed that probiotics may reduce the number of hours with diarrhea (mean 28.77 fewer hours; 95% CI, 40.35 fewer hours to 17.18 fewer hours), but the CoE was Very Low. Eight of these 22 studies reported on the number of children with diarrhea lasting >4 days; similarly, *S boulardii* may reduce the frequency of prolonged diarrhea (RR, 0.45; 95% CI, 0.32–0.64, Very Low CoE). Another single-strain probiotic with a large body of evidence in the context of acute gastroenteritis was *L rhamnosus* ATCC 53103, which was evaluated in 19 trials, including the large multicenter trial conducted in the United States that was described above.[265] Combined case analysis of the 14 studies that reported on mean duration of diarrhea revealed that *L rhamnosus* ATCC 53103 may reduce the number of hours with diarrhea (mean 23.13 fewer hours; 95% CI, 33.94 fewer hours to 12.33 fewer hours), but the CoE was Low. Although *L rhamnosus* ATCC 53103 may reduce the proportion of children with diarrhea lasting more than 4 days (RR, 0.38; 95% CI, 0.27 to 0.54, Low CoE), these analyses did not reveal a difference between probiotic and placebo in terms of mean stool frequency on day 2 of illness, rates of severe infection defined by the Vesikari scale, or rates of hospitalization.

L acidophilus was studied in 7 trials. However, 4 of these studies, all identified in the 2010 Cochrane review, tested heat-killed preparations that do not meet the strict definition of probiotics. *L acidophilus* may reduce the number of hours with diarrhea (mean 7.79 fewer hours; 95% CI, 23.85 fewer hours to 8.28 more hours, Very Low CoE) and may reduce the rate of diarrhea lasting more than 3 days (RR, 0.59; 95% CI, 0.33 to 1.05, Low CoE), but the evidence is very uncertain. Similarly, *L reuteri* was studied as a single probiotic agent in 5 trials. *L reuteri* may reduce the number of hours with diarrhea (mean 24.36 fewer hours; 95% CI, 33.55 fewer hours to 13.17 fewer hours, Low CoE) and may reduce the proportion of children with prolonged diarrhea of more than 3 days (RR, 0.67; 95% CI, 0.47 to 0.95, Low CoE), based on the 4 trials that reported these 2 outcomes.

Of the combination probiotic therapies, the most frequently tested was the 2-species combination of *L acidophilus* and *B bifidum*, which has been studied in 7 trials enrolling children with acute gastroenteritis. Of the 6 trials that reported on duration of diarrhea, this combination may reduce the number of hours with diarrhea (mean 28.44 fewer hours; 95% CI, 45.72 fewer hours to 11.15 fewer hours), but the CoE was Low. On the other hand, the 2-strain combination of *L helveticus* R0052 with *L rhamnosus* R0011 was examined in 3 trials, including the large Canadian multicenter study described above. Combined analyses of these data reveal that probiotics may not affect the duration of diarrhea in hours (mean 1.72 fewer hours; 95% CI, 9.27 fewer hours to 5.83 more hours, Low CoE), and although they may increase hospitalization rates (RR, 1.52; 95% CI, 0.91 to 2.55, Moderate CoE), probiotics do not increase the risk of adverse events (RR, 0.85; 95% CI, 0.71 to 1.02, Moderate CoE). Other probiotic combinations were tested in fewer numbers of trials with smaller numbers of patients; the complete set of analyses is presented in Appendix 7.

The overall CoE across all critical outcomes suggesting that probiotics are not beneficial for the treatment of children with acute gastroenteritis is Moderate on the evidence from studies conducted in the United States and Canada.

Discussion

Guidelines published by multiple professional societies currently support the use of probiotics for otherwise healthy children who present with symptoms consistent with acute gastroenteritis.[177–179] These previous guidelines were supported by evidence primarily derived from studies conducted outside of North America; the majority of these studies report a beneficial effect due to probiotics in 1 or more outcomes. Many of these trials have risk of bias in 1 or more critical domains. Perhaps even more importantly, our team highlighted uncertainty with respect to indirectness of results, given that the majority of trials were conducted in eastern Europe and Asia. Thus, the generalizability of these results to the North American population is unclear. In addition to differences in host genetics and dietary practices, North America differs from these other global regions with respect to the endemic pathogens that most frequently cause acute infectious gastroenteritis in children. Our team did not identify a single trial conducted in the United States or Canada that reported a beneficial effect for a probiotic in the context of acute gastroenteritis in children. Thus, the applicability of findings from the trials that did report a beneficial effect is very uncertain.

The results of our combined case analyses are consistent with other systematic reviews and meta-analyses. A recent network meta-analysis reported that the majority of studies showing a beneficial effect for probiotics in the context of acute gastroenteritis had low to very low evidence quality.[267] In addition, a small number of species- or strain-specific systematic reviews and meta-analyses have been published. Consistent with our findings, previous analyses have reported limited evidence for the efficacy of *L acidophilus* LB,[268] along with the potential for benefit with probiotics *L reuteri*[269] and *S boulardii*.[270] None of the trials included in these 3 strain-specific systematic reviews were conducted in North America.

The Technical Review Panel identified multiple other concerns among the 89 trials included in this portion of the review. These concerns included many studies with very small sample size and the potential for reporting bias due to the lack of a pre-published registered protocol. We also identified among these studies a higher frequency compared to the studies included in the other 7 PICO questions, of high risk and unclear risk of bias within the 6 domains assessed. Taken together, our team found very little evidence in the published literature to support the continued routine use of probiotics for children with acute gastroenteritis in North America.

Question 8: In Preterm, Low-Birth-Weight Newborns, Should Probiotics Be Used to Prevent Necrotizing Enterocolitis, Sepsis, and All-Cause Mortality?

Preterm birth, defined as delivery before 37 weeks gestational age, affects 1 in 10 newborns in the United States and 15 million pregnancies worldwide each year. Prematurity places infants at increased risk of mortality and multiple morbidities, including sepsis and NEC.[271] NEC is an inflammatory necrosis of a portion of the bowel, most typically the terminal ileum and proximal ascending colon, that predisposes survivors to long-term sequelae, such as short bowel syndrome, parenteral nutrition–associated liver injury, and impaired neurodevelopment. Although the etiology of NEC remains unclear, distinct fecal microbiota signatures in infants with NEC compared to otherwise healthy preterm, low-birth-weight infants provide rationale that targeting the gut microbiota with probiotics might prevent morbidity and mortality in this population.[272] We identified a recent systematic review and network meta-analysis comparing various probiotics for the prevention of mortality and morbidity in preterm infants.[273] This study identified 63 trials[274–336] examining 15,712 infants that compared single- and multiple-strain probiotics to placebo for the patient-important outcomes of severe NEC (stage II or higher based on Bell's criteria), all-cause mortality, culture-proven sepsis, NEC-related mortality, duration of hospitalization, weight at 37 weeks gestational age or at discharge, time to establish full enteral feeds (days), and feeding intolerance.

Combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or the 4-strain combination of *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*) proved to be the only interventions with moderate- or high-quality evidence of reduced all-cause mortality relative to placebo (OR,

0.56; 95% CI, 0.39–0.80, High CoE). Compared to placebo, combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*; OR, 0.35; 95% CI, 0.20–0.59; High CoE), *B animalis* subsp *lactis* (including DSM 15954; OR, 0.31; 95% CI, 0.13–0.74; High CoE), *L reuteri* (DSM 17938 or ATCC 55730; OR, 0.55; 95% CI, 0.34–0.91; High CoE), and *L rhamnosus* (ATCC 53103 or ATC A07FA or Lcr35; OR, 0.44; 95% CI, 0.21–0.90; Moderate CoE) were the interventions with moderate- or high-quality evidence that significantly reduced rates of severe NEC (stage II or higher). Whereas combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *Enterococcus* spp (*L acidophilus*, *B longum* subsp *longum*, and *E faecalis*; or *Lactobacillus gasseri* PTA-5845, *B longum* subsp *infantis* PTA-5843, and *E faecium* PTA-5844; or *L acidophilus*, *B longum* subsp *longum*, and *E faecium*; or *L acidophilus*, *B longum* subsp *infantis*, and *E faecalis*; OR, 0.28; 95% CI, 0.16–0.49; Low CoE), combinations of *Bifidobacterium* spp and *S salivarius* subsp *thermophilus* (*B longum* subsp *infantis*, *B bifidum*, and *S salivarius* subsp *thermophilus*; or *B longum* subsp *infantis* DSM 33361, *B animalis* subsp *lactis* DSM 15954, and *S salivarius* subsp *thermophilus* TH-4; OR, 0.38; 95% CI, 0.19–0.75; Low CoE), and the 2-strain combination of a *B subtilis* and *E faecium* (OR, 0.23; 95% CI, 0.08–0.63; Low CoE) were the interventions with low- or very low-quality evidence of reduction in NEC when compared to placebo.

Among the interventions with moderate- or high-quality evidence relative to placebo, combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *S boulardii* (*L rhamnosus*, *L acidophilus*, *B longum* subsp *longum*, and *S boulardii*; or *L acidophilus*, *B bifidum*, and *S boulardii*; MD, −3.30; 95% CI, −5.91 to −0.69; High CoE) significantly reduced days to reach full enteral feeds. Combinations of *Lactobacillus* spp and *Bifidobacterium* spp (*L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B bifidum*; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*; MD, −2.15; 95% CI, −3.78 to −0.51; Low CoE) and *L reuteri* (DSM 17938 or ATCC 55730; MD, −2.62; 95% CI, −4.53 to −0.71; Low CoE) demonstrated low- or very-low-quality evidence for significant reduction in days to reach full enteral feeds. *B animalis* subsp *lactis* (MD, −13.00; 95% CI, −22.71 to −3.29; High CoE) and *L reuteri* (DSM 17938 or ATCC 55730; MD, −7.89; 95% CI, −11.60 to −4.17; High CoE) were the only interventions with moderate- or high-quality evidence of a significant reduction in days of hospitalization compared to placebo. The evidence is summarized in Appendix 8.

The overall CoE across all critical outcomes for probiotics for the prevention of NEC, sepsis, and all-cause mortality among preterm, low-birth-weight newborns, based on the best available evidence from the 2-genus combination of 1 or more *Lactobacillus* spp plus 1 or more *Bifidobacterium* spp, *B animalis* subsp *lactis*, *L reuteri* (DSM 17938 or ATCC 55730), and *L rhamnosus* (ATCC 53103 or ATC A07FA or Lcr35) is Moderate/High.

Discussion

The depth and breadth of quality data supporting the use of probiotics for preterm infants is noteworthy. Probiotics typically are used with caution among immunocompromised, critically ill, or otherwise fragile populations, primarily due to concerns regarding potential translocation of the ingested live microbes from the intestine into the bloodstream. In this vulnerable population of premature infants, however, these data strongly suggest that probiotics may protect from mortality and do not increase rates of sepsis. Nonetheless, risks and benefits should be considered carefully, given the possibility of manufacturing contaminants, such as the fungal contaminant that led to a fatal case of gastrointestinal mucormycosis in a preterm infant,[337] and given that some centers already have very low rates of NEC due to other standard practices, such as robust donor breast milk feeding programs.[338]

Moderate- to high-certainty evidence demonstrates the superiority of combinations of *Lactobacillus* spp and *Bifidobacterium* spp, *B animalis* subsp *lactis*, *L reuteri*, and *L rhamnosus* over alternative preventive probiotic treatments. Combinations of *Lactobacillus* spp, *Bifidobacterium* spp, and *Enterococcus* spp, as well as the combination of *B subtilis* and *E faecium*, provide the largest reduction in NEC; however, this is supported by low- to very low-certainty evidence. Prioritization of these strains in future trials may be informative, as would be studies that define optimal doses, timing, and frequency of administration. Overall, these data suggest that microbiome-targeting therapies have the potential to reduce mortality, morbidity, length of hospital stay, and other significant costs associated with preterm birth.

Summary and Conclusions

While probiotics have become an integral part of clinical care, we found that, in the majority of the 8 contexts that were examined, there was either insufficient evidence to recommend the use of probiotics as a part of clinical practice or there was a significant knowledge gap that precluded us from making any conclusions. We did, however, find potential utility for the use of individual or combinations of specific probiotic strains in the prevention of NEC and all-cause mortality among preterm, low-birth-weight infants with Moderate/High CoE, prevention of CDAD with Low CoE, and prevention of pouchitis with Very Low CoE. On the other hand, we found that probiotics are not beneficial for treatment of acute gastroenteritis in children in North America with Moderate CoE. It is important to note that although the technical review findings are based on the highest quality of clinical evidence currently available, the potential benefit of probiotic strains or lack thereof is not based on a mechanistic understanding of how probiotics exert such effects. Hence, with additional studies in the future, these conclusions may change. In this technical review, we focused on specific gastrointestinal conditions in which probiotics were being used routinely for adults and children, and in which sufficient clinical studies were available to evaluate their utility. However, this does not imply that such evidence does not exist for other gastrointestinal and non-gastrointestinal disorders. In fact, there is accumulating evidence in support of probiotic use in liver and metabolic diseases, as well as *Helicobacter pylori* infection, among other conditions, and these could be explored in subsequent technical reviews.

There are several systematic reviews and meta-analyses that have examined the utility of probiotics in disease states, but the results vary based on the approach of the reviews and the quality of the clinical studies included in the analyses. Therefore, it is not surprising that some of our conclusions differ from those of previous reviews on the topic. It is becoming increasingly clear that the effect of a probiotic strain cannot be extrapolated to all probiotics and, in fact, the biological effect of probiotics is species- and strain-specific. Thus, we felt it would not be appropriate to combine the clinical effects of diverse strains under a single umbrella termed *probiotics* when assessing their utility. Our decision to assess the utility of individual or specific combinations of probiotic strains, rather than the effect of probiotics as a group, was one of the key considerations in our review and represents a key point of difference compared to other recent reviews. Of note, some published trials, most notably many of the earlier studies, did not describe the tested probiotic species at the strain level. Thus, our analyses might not have captured all studies that evaluated a particular organism.

Other unique aspects of our approach may explain differences in our conclusions compared to other reviews. We only included randomized, placebo-controlled trials in our updating of existing evidence from high-quality systematic reviews, and we performed a de novo analysis to include both adults and children in the context of IBS. Additionally, we used the GRADE approach, which considers the risk of bias, inconsistency (or heterogeneity), indirectness, imprecision, and/or publication bias when assessing the certainty of evidence. Among the challenges we faced was lack of appropriate reporting by some authors, due in part to the fact that requirements for reporting clinical trials have evolved over the past few decades, as well as the difficulty with assessing publication bias, given that findings from a large number of registered protocols were never published, potentially skewing the body of evidence toward positive results.

Despite the specificity and stringency of our methods, there are nonetheless limitations in our technical review. We considered the strain specificity when evaluating the outcomes but there are inherent differences in the study design of probiotic trials that could not be completely accounted for in our review. These include differences in dosing and duration of treatment, study population, inclusion and exclusion criteria, use of adjunctive therapies, and outcome measurements. In addition, the lack of large multicenter studies in the majority of instances makes it difficult to assess reproducibility across populations.

The lack of regulatory requirements for over-the-counter probiotics, which are largely considered dietary supplements, affects the quality of results from clinical studies. There are attributes that are unique to probiotic studies and require consideration as they are inadequately and inconsistently addressed in clinical studies. Currently, there are no guidelines for reporting data on product testing in clinical trials, which would include but would not be limited to manufacturing conditions, such as specific media type and culture conditions, strain viability, and shelf life of the product. As a result, it is difficult to compare results of the same strain if it is marketed by different manufacturers. In addition, for the majority of the available probiotics, there is a lack of understanding of the mechanism by which it exerts a biological effect. Finally, there is inadequate harms reporting in the majority of published studies of probiotics.

Knowledge Gaps and Future Directions

Our review not only highlights the challenges in making clinically actionable conclusions from probiotic studies, but also offers an opportunity to implement changes to future studies to improve the utility of such results.

1. In addition to the existing guidance on reporting findings from a clinical trial, there is a pressing need for guidelines that are specific for probiotic studies to improve transparency, reliability, and clinical applicability. In addition to better characterization and reporting of the probiotic strains, these would include ways to address heterogeneity among studies and uniform harms reporting.
2. The scientific rationale for use of specific probiotic strains in disease states needs to be better defined and this would require understanding the mechanism and the site of action of probiotic strains or their products, the need for engraftment of probiotic strains and, if required, the conditions needed to facilitate engraftment, and potential off-target effects.
3. Multicenter studies must be appropriately designed to assess the clinical efficacy of specific probiotic strains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

AGA	American Gastroenterological Association
CDAD	*Clostridioides difficile*–associated diarrhea
CDI	Clostridioides difficile infection
CI	confidence interval
CoE	certainty of evidence
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome

IPAA	ileal pouch–anal anastomosis
MD	mean difference
NEC	necrotizing enterocolitis
OR	odds ratio
PICO	population, intervention, comparison, outcomes
RR	relative risk

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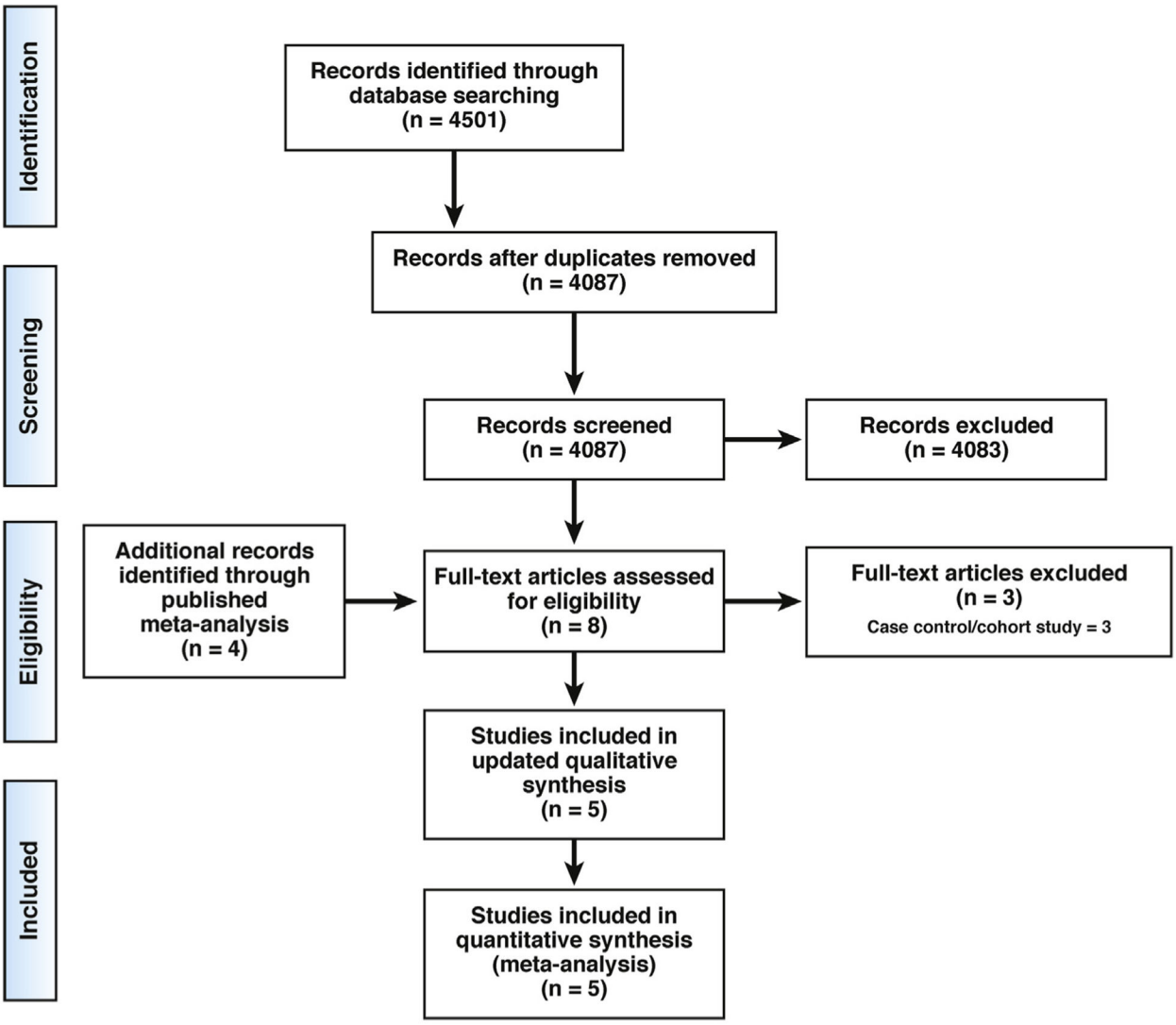

Figure 1.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339]

Probiotics to treat CDI.

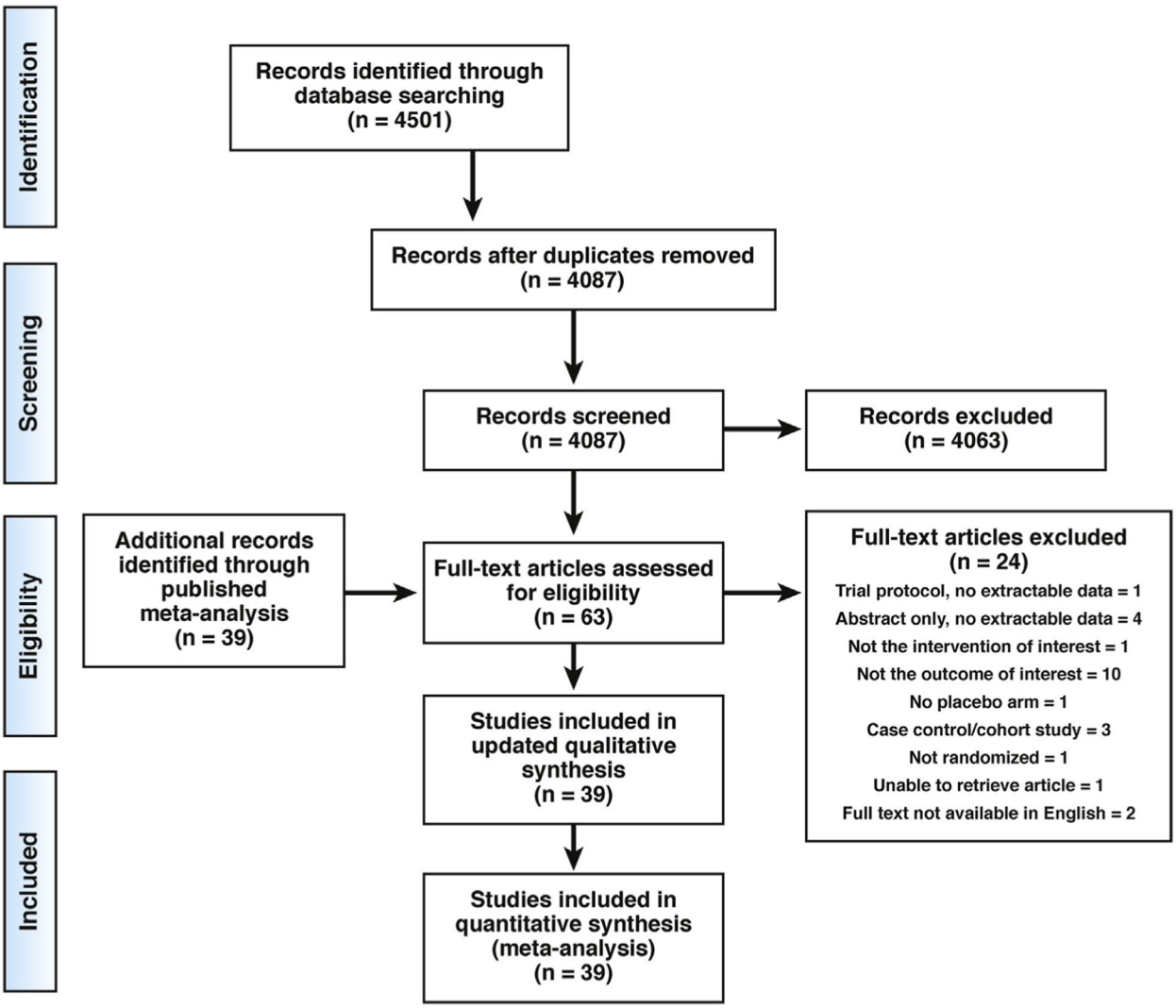

Figure 2.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339]

Probiotics to prevent CDAD.

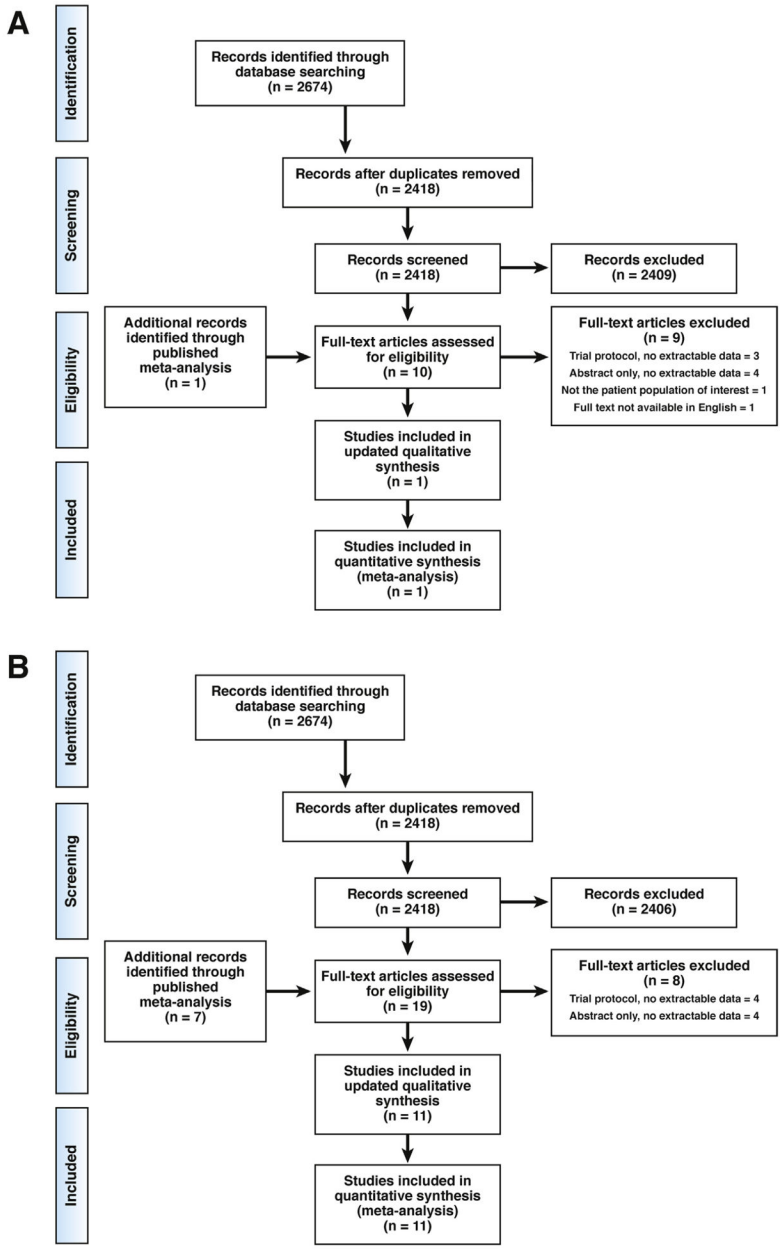

Figure 3.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339] (*A*) Probiotics to induce remission in CD. (*B*) Probiotics to maintain remission in CD.

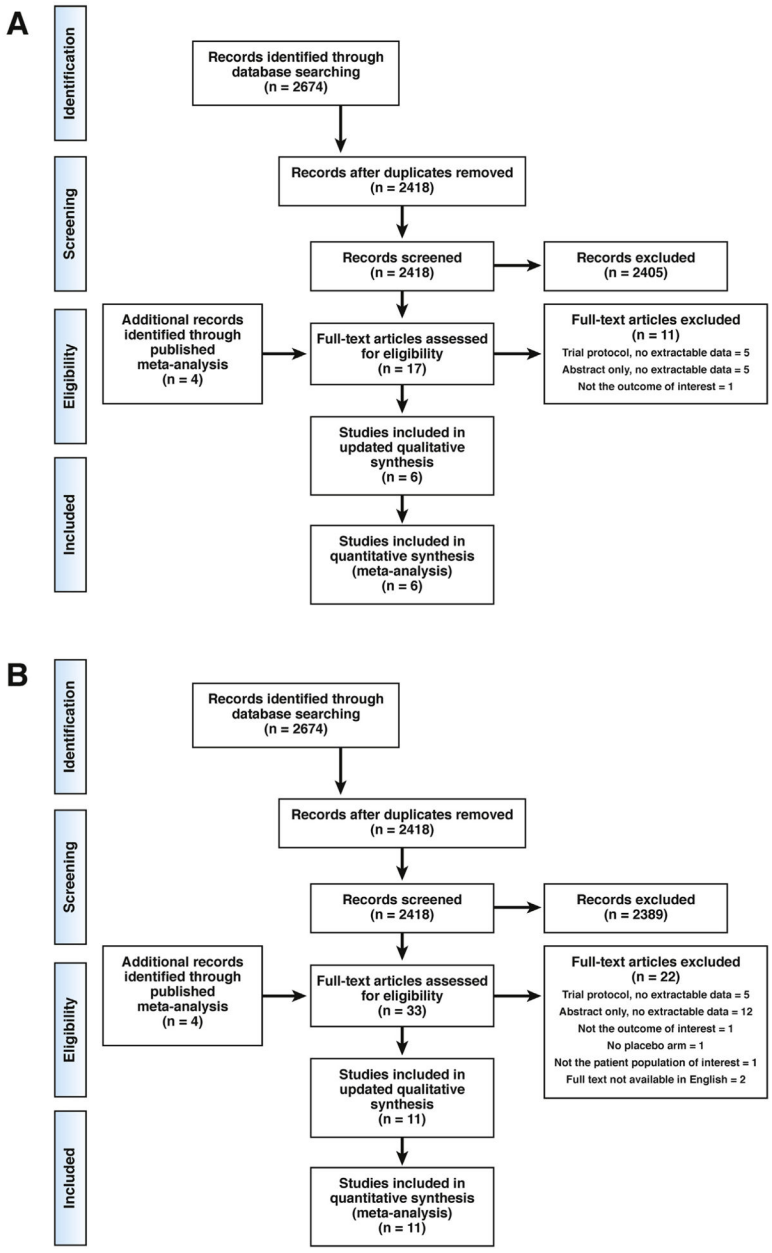

Figure 4.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339] (*A*) Probiotics for Induction of Remission in ulcerative colitis. (*B*) Probiotics to maintain remission in ulcerative colitis.

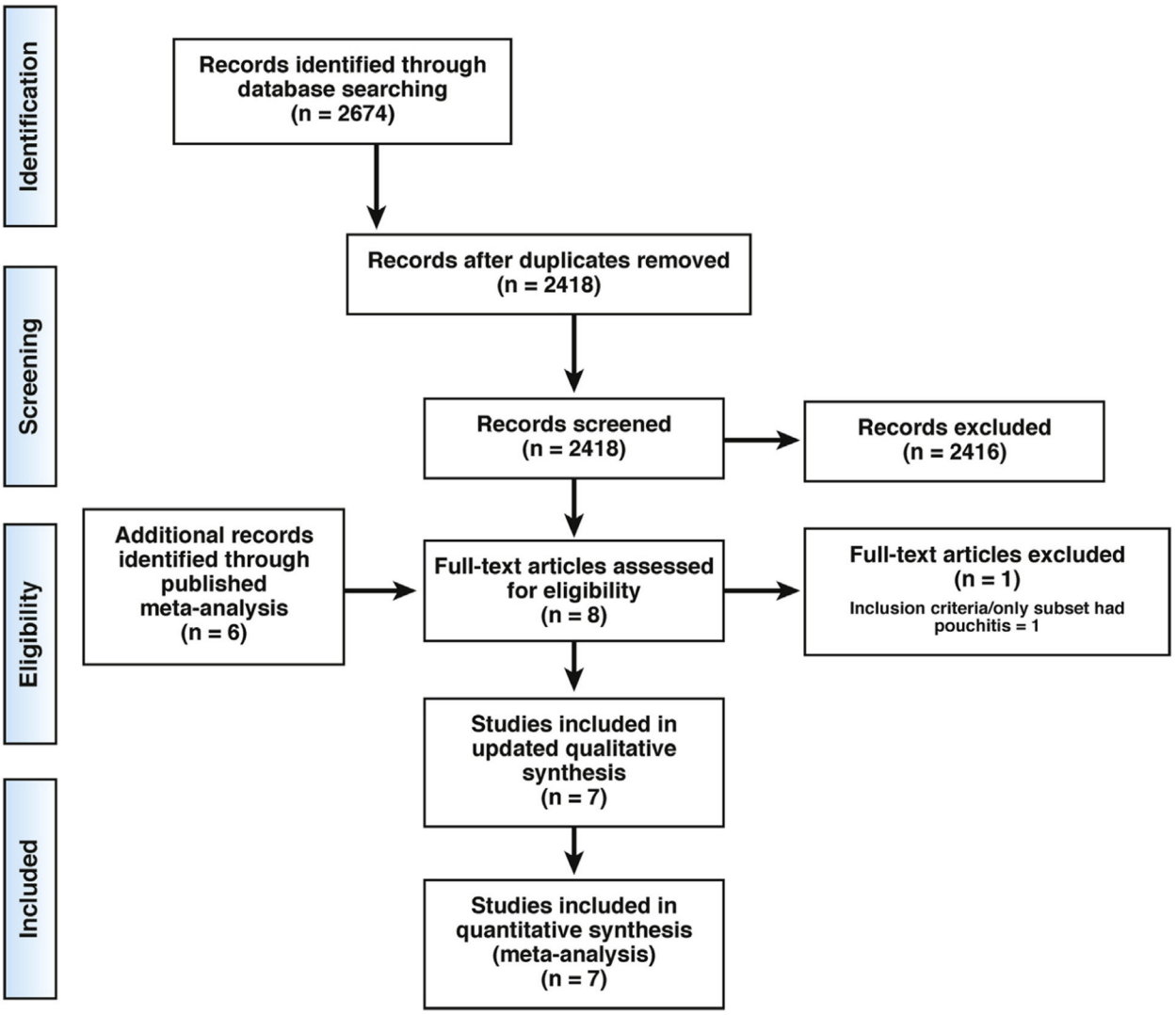

Figure 5.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339] Probiotics for pouchitis.

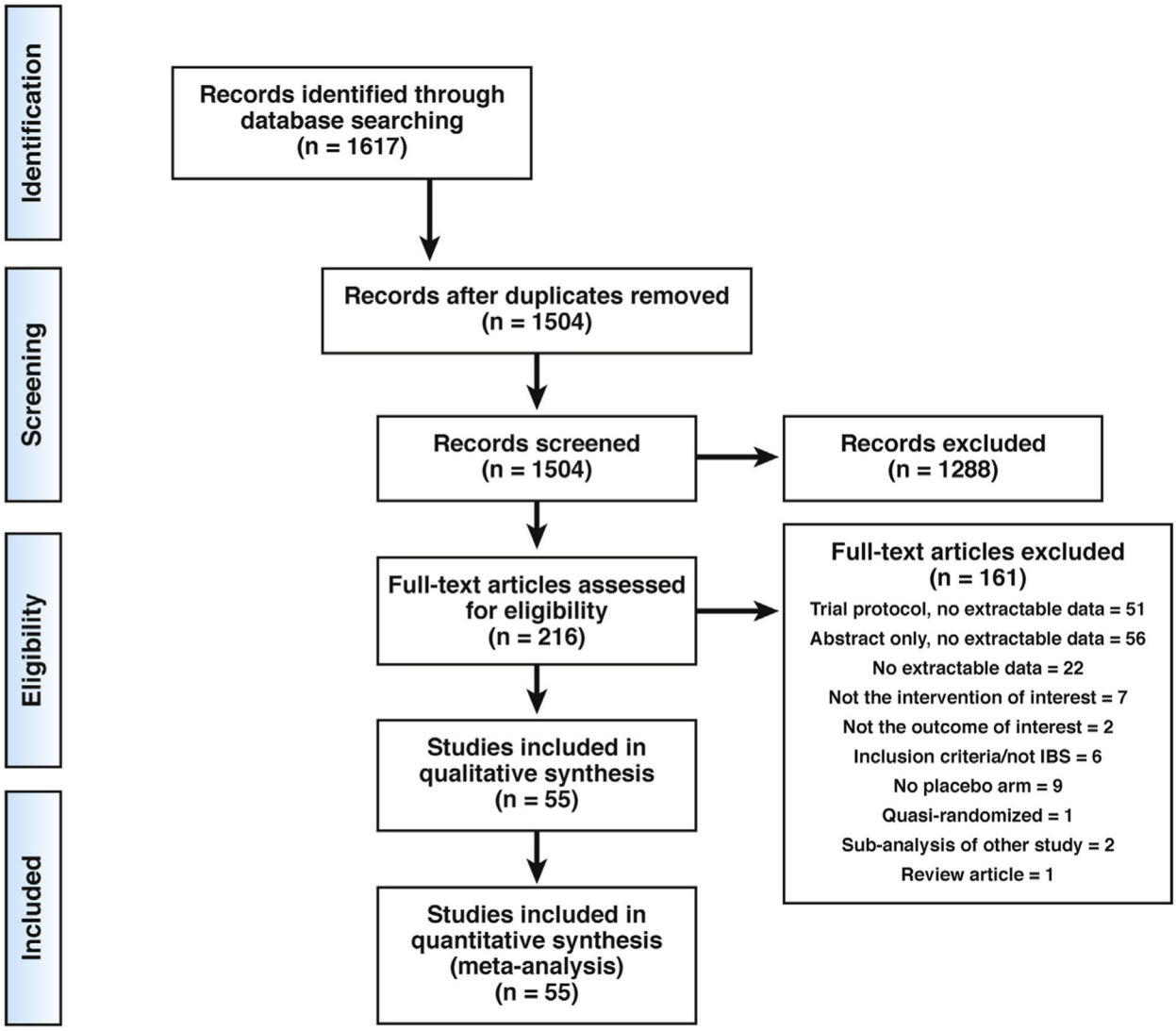

Figure 6.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339]

Probiotics to treat IBS.

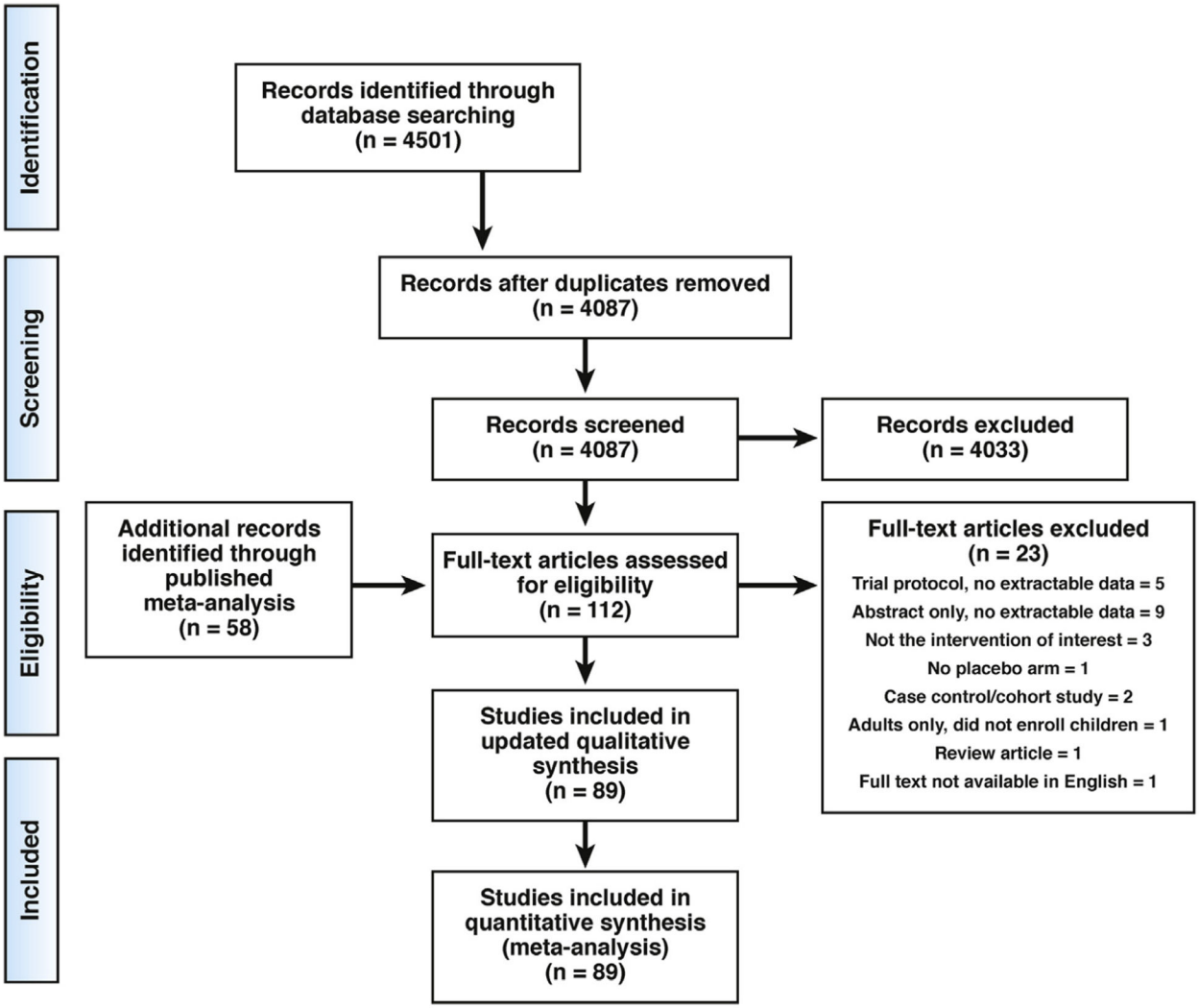

Figure 7.

Preferred Reporting Items for Systemic Reviews and Meta-Analysis flow diagram.[339] Probiotics to treat acute gastroenteritis.