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SUMMARY WITH CRITICAL APPRAISAL

Probiotics for Antibiotic-Associated Diarrhea and *Clostridium difficile* Infection: A Review of Clinical Effectiveness

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Abbreviations

AAD	Antibiotic-associated diarrhea
CDAD	*C.difficile*-associated diarrhea
CDI	*C.difficile* infection
NRS	Numerical Rating Scale
OR	Odds ratio
RR	Relative risk
RCT	Randomized controlled trial

Context and Policy Issues

When patients are treated for antibiotics for any reason, they are susceptible to unexplained diarrhea.[1] Antibiotics-associated diarrhea (AAD) is thought to result from disruptions in microbiota and mucosal integrity of the gastrointestinal tract.[1] In addition to antibiotics use, AAD is also associated with *Clostridium difficile (C.difficile)*, old age, extended hospitalization, and comorbidities.[1] Antibiotics cause a reduction in the normal microflora, allowing *C.difficile* to more easily colonize and infect patients.[2] *C.difficile* is a gram-positive obligatory anerobic spore-filling bacillus and is a common cause of AAD.[3] When *C.difficile* is involved, AAD is referred to as *C.difficile*-associated diarrhea (CDAD).[3]

Mild cases of AAD may be addressed by reducing the use of antibiotics, supportive care, or changes in diet.[1] Serious cases of AAD and CDAD may cause relapse in almost 25% of patients and may require other antibiotics such as metronidazole and vancomycin; however there is serious morbidity and cost associated with extensive use of these antibiotics.[1,3]

Specific strains of probiotics may be administered to normalize microbiota and suppress pathogenic bacteria colonization.[1,3] Probiotics are living microorganisms which confer a health benefit when ingested.[4] They improve the nutritional and microbiological balance of the gastrointestinal tract.[5] The most commonly available probiotics for commercial use are *Lactobacillus* and *Bifidobacterium* genera (i.e., bacteria) and *Saccharomyces* genus (i.e., yeast).[4] Probiotics may be administered in liquid, powder or capsule form, as a single strain or as a mixture.[5] The clinical benefits of specific probiotics may not be generalized to others because their effectiveness depends on their capacity to resist gastric acid and bile after consumption, and their ability to adhere to the intestinal mucosa.[5] These characteristics in turn are influenced by their strain, dosage, length of treatment, and mode of delivery.[4]

The purpose of this report is to review the clinical effectiveness of probiotics for preventing, treating and otherwise, managing AAD, CDAD, and *C.difficile* infections (CDI).

Research Questions

1. What is the clinical effectiveness of concurrent probiotic and antibiotic use for preventing antibiotic-associated diarrhea and *C.difficile* infection?
2. What is the clinical effectiveness of probiotics for treating and managing antibiotic-associated diarrhea and *C.difficile* infection?

Key Findings

No clear patterns have emerged regarding the impact of probiotics on preventing AAD, CDAD, and CDI. Relative to placebo, active control, or treatment, probiotics reduced the risk of AAD but there were certain conditions under which the reduction was not statistically significant. The findings on the effectiveness of probiotics at preventing CDAD were mixed. Two systematic reviews reported that probiotics were better at preventing CDAD compared to placebo or no treatment, but three other reviews did not show significant differences in effect. Similarly, the effect of probiotics on preventing infection varied across three systematic reviews and two RCTs. The relative impact of probiotics on gastrointestinal adverse events varied with the set of comparators. Probiotics did not have a significant effect when compared with placebo only, no treatment only, placebo or usual care, and placebo or no treatment. Only when intestinal distention was added to pain did probiotics show significant effect relative to no treatment. When active control was included to placebo and no treatment in the comparator arm, probiotics significantly decreased the risk of adverse events.

None of the studies reported on the effectiveness of probiotics in treating AAD or CDAD, but one RCT reported that a mixture of four probiotics was only as effective as placebo at treating CDI.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines. The search was limited to English language documents published between January 1, 2013 and August 8, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults diagnosed with or at risk for antibiotic-associated diarrhea or *C. difficule* infection
Intervention	Q1: Probiotics (mixed strains, individual strains [e.g., *S. boulardii, L. acidophilus, L. rhamnosus*], and Kefir) in combination with antibiotics. Q2: Probiotics (mixed strains, individual strains [e.g., *S. boulardii, L. acidophilus, L. rhamnosus*], and Kefir)
Comparator	Other probiotics (mixed strains, single strains, or kefir); Antibiotics alone Placebo; No treatment
Outcomes	Clinical effectiveness (e.g., infection rates) and safety

Study Designs	Health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR 2,[6] and the included randomized controlled trials (RCTs) were critically appraised using the Downs and Black checklist.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 346 citations were identified in the literature search. Following screening of titles and abstracts, 303 citations were excluded and 43 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the potentially relevant articles, 31 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Table 2 and Table 3.

Study Design

Ten systematic reviews[2,8-16] and two RCTs[17,18] were included in this review. The systematic reviews included partially overlapping sets of 54 RCTs published between 1977 and 2017.

Country of Origin

The reviews were published by authors in Canada,[13,16] China,[15] Denmark,[9] Iran,[12] Poland,[14] and the United States.[8,10,11] One was published by authors in the United States, Australia and Canada.[2] The two RCTs were conducted in Italy[18] and the United States.[17]

Patient Population

All studies enrolled adults or children who were at risk for AAD, CDAD or CDI because they were being treated with antibiotics. Only data from adults were included in this review. One of the RCTs enrolled 33 adults[17] diagnosed with CDI.

Interventions and Comparators

The intervention in all of the studies was one or more probiotics for the prevention of AAD or CDAD. Additionally, patients in one RCT were being treated for CDI.[17] The probiotics included but were not limited to *Lactobacillus (L.)* genera,[8-10,12,13,15,17] *Bifidobacterium (B.)*

genera,[10,15,17,18] *Saccharomyces (S.)* genera,[9,10,12,14] *Leuconostoc cremoris*, *C. Streptococcus*,[10,12] and Enterococcus.[12]

The comparators included in the systematic reviews were placebo only,[8,11,13] placebo or no treatment[9,14,15], placebo or usual care,[10,16] or placebo, active control or no treatment.[2,12] Usual care was not defined in two systematic review.[10,16] The comparators in the RCTs were placebo[17] or no treatment.[18]

Outcomes

The outcomes of interest reported in the systematic reviews were incidence of AAD,[2,8,9,12,14-16]incidence of CDAD,[2,11,13-15] incidence of CDI or other infection,[2,10,14,16] and incidence of other adverse events.[2,10,14]

The RCTs reported on duration and rate of CDAD,[17] incidence of CDI recurrence,[17] incidence of adverse events (i.e., gastrointestinal disorders),[17] incidence of diarrhea,[18] incidence of adverse events (i.e., local signs of infection, intestinal distension or pain, incidence of gastric pain, and level of gastric pain.[18]

Summary of Critical Appraisal

Critical appraisal of the studies is summarized below and details are available in Appendix 3, Table 4 and Table 5.

The systematic reviews were appraised with the AMSTAR 2 checklist.[6] One review met all but one of the requirements as the review authors did not explain their selection of the study designs for inclusion.[2] All of the remaining reviews described their population, intervention, comparators, and outcomes of interest; however an explicit statement that the review methods were established *a priori* was reported in only one review.[11] The PRISMA methodology for conducting systematic reviews was cited in four reviews,[10,12,13,16] and all but one review[9] included multiple databases.

Regarding limitations, the list of excluded studies was not provided in seven of the reviews[8-10,12,13,15,16] however the exclusion criteria were indicated. Other missing criteria were details of the study selection and data extraction processes,[8] the characteristics of included studies,[8] the quality assessment process for primary studies,[8] a conflict of interest statement,[13] study selection details,[14] a quality assessment tool,[15] and likelihood of publication bias.[8,15] The findings from these reviews may not be reproducible, given gaps in descriptions of their methodologies. In addition, authors had potential conflicts of interest involving sponsorship by manufacturers of probiotics.[8,14] The results of these two studies may be biased in favour of probiotics.

The RCTs strengths included stating their objectives and clearly describing their inclusion and exclusion criteria, patient characteristics, interventions, comparators, and outcomes.[17,18] Details of blinding and sample size calculations were missing in both RCTs.[17,18] Furthermore it was unclear whether analyses were conducted per protocol and there were no declarations of conflict.[17,18] Lack of blinding may have affected the assessment of incidence of diarrhea and adverse events as the assessors may have had expectations of the impact of probiotics relative to placebo and no treatment. Both RCTs were small in size, enrolling 31[17] and 64[18] patients, respectively. It is unclear whether these sample sizes were sufficient to determine a significant effect of the intervention. Without reference to pre-determined protocols, it is not possible to determine whether there were modifications made to the methodology that may have biased the results in favor of the

intervention or its comparators. Finally, given that there may have been financial conflicts of interest, the results may be biased in favour of probiotics.

Summary of Findings

Findings are summarized below and details are available in Appendix 4, Table 6 and Table 7. The results reported in the systematic reviews are reported first followed by the RCTs.

1. *What is the clinical effectiveness of concurrent probiotics and antibiotic use for preventing antibiotic-associated diarrhea and C.difficile infection?*

The objectives of the studies were to evaluate the effectiveness of probiotics in preventing AAD,[2,8,9,12,14-16,18] CDAD,[2,11,13-15,17] CDI or other infections,[2,10,16-18] and other adverse events,[2,10,14,17,18] in patients who were on antibiotics. The mixed findings that were observed may have resulted from differences in the sets of studies that were included in the various meta-analyses, probiotic strains, and comparators.

Prevention of AAD: Probiotics significantly reduced the incidence of AAD relative to placebo or no treatment in eight systematic reviews[2,8,9,12,14-16] although the evidence suggests that some strains of probiotics may be more effective than others. While *Bacillus lecheniformis* significantly reduced the incidence of AAD in patients older than 65 relative to no treatment, *L. acidophilus, L. casei Shirota, S. cerevisiae* (boulardii) lyo, mixture of L. acidophilus and B. bifidum, and mixture of *L. acidophilus* CUL60, CUL21, *B. bifidum* CUL20 and *B. lactis* CUL34 were not effective in reducing AAD in this population.[15] Based on a meta-analysis of two RCTs, a mixture of *L. rhamnosus* R011 and *L. helveticus* R052 did not demonstrate efficacy in preventing AAD in adults of all ages.[8] Another meta-analysis of five studies also indicated that probiotics were no more effective than placebo in reducing the incidence of AAD in adults older than 65 years.[12] The single RCT that reported on prevention of AAD, found that none of 37 patients being treated with probiotics following tooth extraction had AAD while 5 out of 27 (18.5%) who received only antibiotics had AAD.[18] The statistical significance of the difference was not reported.[18]

Prevention of CDAD: Five systematic reviews involving meta-analyses[2,11,13-15] and one RCT[17] reported on the effectiveness of probiotics in preventing CDAD. A meta-analysis of 24 studies involving 7,800 patients who were receiving antibiotic treatment for a variety of unreported reasons demonstrated that probiotics were significantly more effective than placebo, active control, or no treatment in preventing CDAD.[2] Another meta-analysis of probiotics versus placebo involving 4,841 in-patient adults receiving antibiotics also demonstrated similar findings.[13] The remaining three meta-analyses reported that probiotics had no preventative effects relative to placebo,[11] placebo or no treatment,[14] or no treatment.[15] These studies enrolled 3,461 residents of acute and post-acute care facilities, 3,114 adults, and 3,562 patients aged 65 years and older, respectively. The patients were being treated with antibiotics for reasons that were reported in the individual studies but not in the systematic reviews. The included RCT found that CDAD lasted for fewer days (0 to 2 days versus 0 to 13 days; $P = 0.039$) in 16 patients with CDI treated with probiotics compared with 15 patients with CDI on placebo.[17] This study did not report on the incidence CDAD.

Prevention of infection: Three systematic reviews[2,10,16] and both RCTs[17,18] reported on incidental reduction of infection. The probiotic groups had fewer incidents of infection relative to the placebo or no treatment groups.[2,10,16] The difference was not statistically significant in one of the meta-analyses.[2] Across the two RCTs, the probiotic group and its

comparator (placebo or no treatment) had one incident of infection each.[17,18] The evaluation of the incidence of infection must take into account the impact of antibiotics that were used to treat patients in all of the included studies.

Prevention of other adverse events: Patients in the probiotic groups had fewer adverse events but the differences were not significant compared with placebo, active control and no treatment.[2] Probiotics did not have a significant effect on incidence of gastrointestinal disorders when compared with placebo only;[17] on the incidence of gastric pain when compared with no treatment only in a small RCT involving 64 patients;[18] on the incidence of cramping, nausea, fever, soft stools, flatulence, and taste disturbance when compared with placebo or usual care;[10] and on the incidence of undisclosed adverse events when compared with placebo or no treatment.[14] However, when intestinal distention was evaluated alongside pain probiotics demonstrated a significant effect relative to no treatment.[18] Furthermore, when active control was included in the comparator arm along with placebo and no treatment, probiotics significantly decreased the risk of adverse events.[2]

2. *What is the clinical effectiveness of probiotics for treating and managing antibiotic-associated diarrhea and C.difficile infection?*

None of the systematic reviews or RCTs reported on the treatment of patients with AAD or CDAD. A single RCT that enrolled patients with CDI undergoing treatment with antibiotics, reported that one patient out of 15 patients who were treated with a combination of L.*acidophilus* NCFM, L.*paracasei* Lpc-37, B.*lactis* Bi-07 and B.*lactis* Bl-04. Similarly one out of 13 treated with placebo had one recurrence of CDI.[17] The results suggested that the mixture of probiotics was only as effective as placebo at treating CDI, although the statistical significance of the difference was not reported.[14]

Limitations

Overall, there were few limitations regarding the quality of the included systematic reviews and RCTs. There was considerable overlap of the RCTs that were included in the meta-analyses (systematic reviews). See Appendix 6, Table 8. While it may appear that there were a good number of systematic reviews included in this report, none of them reported on an exclusive set of RCTs. The overlap in RCTs may explain the similarity in results among some systematic reviews. On the other hand, there was considerable heterogeneity in the RCTs included across the systematic reviews. The sources of heterogeneity included definitions of diarrhea, location of the studies, conditions for which patients were being treated, the antibiotics with which patients were being treated, the initial incidence and sources of infections at enrollment, strains, dosages, mode of delivery and duration of administration of probiotics, comparators, follow up periods, and study timeframes. Although conducting a meta-analysis is a proven method for quantitatively synthesizing data, combining data from studies with such diversity in characteristics may not be advisable.[4] All but two systematic reviews[8,15] combined results for multiple probiotics making it challenging to comment on the effectiveness of specific probiotics.

There was sparse or no information on some outcomes of interest. Only three systematic reviews[2,10,14] and the two RCTs reported on adverse events,[17,18] one RCT reported on the treatment of CDI[18] and none of the studies addressed the treatment of AAD, CDAD, or CDI.

There was variability in the available studies that reported on adverse events. While Shen et al. (2017)[10] reported on cramping, nausea, fever, soft stools, flatulence and taste disturbance), Barker et al. (2017)[17] labelled adverse events as gastrointestinal disorders, and Barone et al. (2017)[18] reported on gastric distention and pain. Furthermore, Goldenberg et al. (2017)[2] and Szajewska and Kołodziej (2015)[14] did not specify the types of adverse events reported.

Evaluating the relevance of the results to the Canadian context will require an assessment of the availability of the studied probiotics in Canada and an assessment of gastrointestinal differences between the Canadian population and the populations in which the RCTs were conducted that might impact the effect of probiotics.

Conclusions and Implications for Decision or Policy Making

Twelve relevant publications comprising 10 systematic reviews[2,8-16] and two RCTs[17,18] were identified. The findings from this review suggest that relative to placebo, active control, or treatment, probiotics reduced the risk of AAD[2,9,14,16] although there were certain conditions (such as the use of certain strains of probiotics and age of patients) under which the reduction was not statistically significant.[8,12,15] The findings on the effectiveness of probiotics at preventing CDAD were mixed. Two systematic reviews reported that probiotics were better at preventing CDAD compared to placebo, active control, or no treatment,[2,13] but three other reviews did not show significant effect when compared with placebo,[11] placebo or no treatment,[14] or no treatment.[15]. Probiotics significantly reduced the risk of infection in two reviews[10,16] but not in one review[2] and two RCTs.[17,18] The relative impact of probiotics on adverse events varied with the set of comparators.[10,14,17,18] Probiotics did not have a significant effect on incidence of gastrointestinal disorders when compared with placebo only;[17] on incidence of gastric pain when compared with no treatment only[[18] on incidence of cramping, nausea, fever, soft stools, flatulence, and taste disturbance when compared with placebo or usual care;[10] and on incidence of undisclosed adverse events when compared with placebo or no treatment.[14] When intestinal distention was evaluated alongside pain in a small RCT involving 64 patients, probiotics demonstrated a significant effect relative to no treatment.[18] Furthermore, when active control was included in the comparator arm with placebo and no treatment, probiotics significantly decreased the risk of adverse events.[2]

When interpreting the evidence, the heterogeneity of the RCTs that were included in the systematic reviews should be considered. More importantly, while the systematic reviews had some strengths, there were some limitations related to missing details about study selection and data extraction processes, the characteristics of included studies, the quality assessment process for primary studies, study selection details, and likelihood of publication bias. These limitations decrease the confidence in the results. [4]

Although RCTs were included spanning 1977 to 2017, no clear patterns have emerged regarding the impact of probiotics on preventing AAD, CDAD, and CDI. None of the studies reported on the effectiveness of probiotics in treating AAD or CDAD, but one RCT reported that a mixture of four probiotics was only as effective as placebo at treating CDI.

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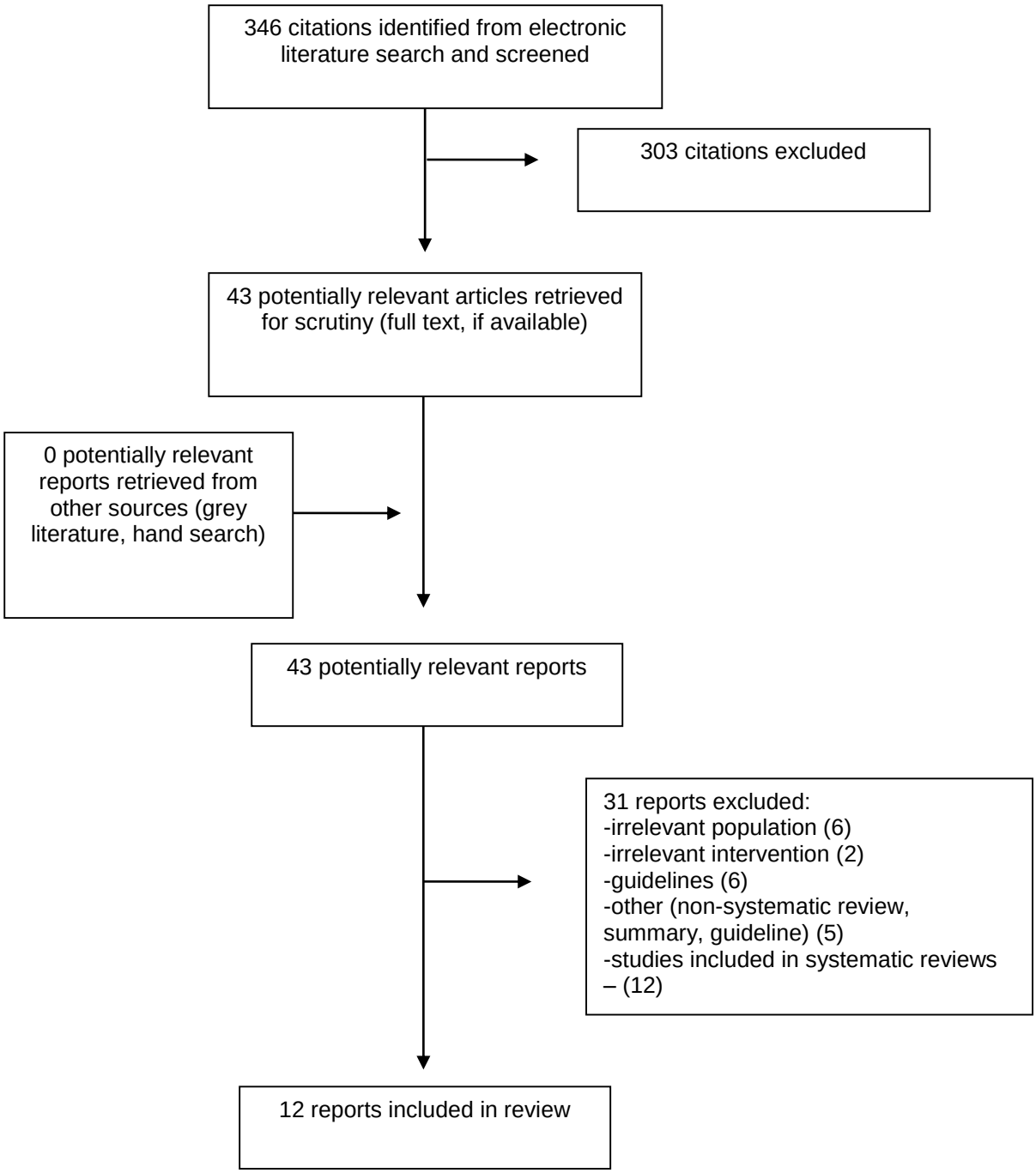
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
McFarland et al., 2018[8] United States	22 RCTs (The review included 228 RCTs)	Adults at risk for AAD (The review included children and adults with inflammatory bowel disease, irritable bowel syndrome, and *H.pylori* infection)	Intervention: Probiotics (*L. casei* DN-114001, *L. reuteri* ATCC 55730, *L. rhamnosus* GG, mixture of *L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2 or Bio-K+®, mixture of *L. acidophilus* La5 and *B. lactis* Bb12) for the prevention of AAD Duration of intervention: NR Comparator(s): Placebo (9 studies), NR (13 studies)	Incidence of AAD[a] F/u: NR Results from children and adults with inflammatory bowel disease, irritable bowel syndrome, and *H.pylori* infection were excluded
Blaabjerg et al., 2017[9] Denmark	9 RCTs (The review included 17 RCTs)	1,936 adult outpatients (aged > 15 years) at risk for AAD; treated with oral antibiotics (clarithromycin or levofloxacin with amoxicillin) for *H.pylori,* upper and lower respiratory tract infections, otitis media, and throat infections; in private practices, pharmacies, or hospitals (e.g., ambulatory settings, outpatient clinics)	Intervention: Probiotics (*L. rhamnosus GG* and *S. boulardii*) for the prevention of AAD Duration of intervention: NR Comparator(s): Placebo or no treatment	Incidence of AAD F/u: 1 to 5 weeks (NR in 2 studies)
Goldenberg et al., 2017[2] United States, Australia, and Canada	28 RCTs (Full review included 30 RCTs)	7,800 adults[b] (aged > 18 years) at risk for CDAD; receiving antibiotic therapy . (The review included children)	Intervention: Probiotics (any strain) for the prevention of CDAD Duration of intervention: NR Comparator(s): Placebo, active control, or no treatment	Primary: Incidence of CDAD Secondary: Incidence of AAD, incidence of infection (*C. difficile* or toxin in stool), adverse events F/u: 1 to 12 weeks Results from children were excluded

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Shen et al., 2017[10] United States	19 RCTs	6261 hospitalized adults (aged ≥18 years) at risk for CDI; receiving antibiotic therapy (intravenous, oral, or both)	Intervention: Probiotics (*L., Saccharomyces, B.,* and *Streptococcus genera*) alone or in combination (n = 3277) for the prevention of CDI Duration of intervention: 1 to 7 days after the first antibiotic dose, for 14 to 21 days or for 3 to 14 days after last antibiotic dose Comparator(s): Placebo or usual care (n = 2984)	Primary: Incidence of CDI Secondary: Adverse events F/u: 1 to 12 weeks
Vernaya et al., 2017[11] United States	5 RCTs	3,461 residents of acute and post-acute care facilities at risk for CDAD; aged ≥ 60 years; undergoing or planning to undergo antibiotic treatment	Intervention: Probiotics (*L.acidophilus, L.casei, L.casei imunitass, L.bulgaris, Streptococcus therophilus, Saccharomyces boulardii, B.bifidum, B.lactis,* and Actimel [Danone Boulevard]) for the prevention of CDAD Duration of intervention: during administration of antibiotics and for 1 week following Comparator(s): Placebo	Incidence of CDAD F/u: NR
Jafarnejad et al., 2016[12] Iran	30 double-blinded, placebo-controlled RCTs	7,260 patients at risk for AAD; on antibiotics; aged > 18 years	Intervention: oral probiotics (supplements or food; *L.[acidophilus, casei, reuteri, bulgaricus, paracasei, plantarum, rhamnosus, salivarius], B.[bifdum, lactis, longum, breve, clausii, infantis], Enterococci (faecium), Streptococci (thermophiles),* and the yeast *S boulardii*; alone or in combination Duration of intervention: 5 to 21 days for the prevention of AAD	Incidence of AAD F/u: NR

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Comparator(s): Placebo, active control, or no treatment	
Sinclair et al., 2016[13] Canada	10 double-blinded RCTs	4,841 adult inpatients at risk for AAD; receiving antibiotics for the prevention of CDI	Intervention: Lactobacillus spp. as single preparations or in combination (n=2554) for the prevention of CDAD and AAD Duration of intervention: NR Comparator: Placebo (n=2287)	Incidence of CDAD F/u: 5 days to 12 weeks
Szajewska and Kołodziej, 2015[14] Poland	15 RCTs (The review included 21 RCTs)	3,114 adult patients at risk for AAD and CDAD (The review included children)	Intervention: *Saccharomyces.boulardii* for the prevention of AAD Duration of intervention: NR Comparator(s): Placebo or no treatment	Incidence of AAD, CDAD, adverse events F/u: 2 weeks to 1 year Results on children and on the treatment of *H.pylori* were excluded
Xie et al., 2015[15]	6 RCTs	3,562 patients (aged ≥ 65 years) at risk for AAD and CDAD; treated with antibiotics	Intervention: *Bacillus.licheniformis, L. acidophilus, L. casei Shirota, Saccharomyces. cerevisiae (boulardii) lyo, mixture of L. acidophilus* and *B. bifidum,* a *mixture of L. acidophilus CUL60, CUL21, B. bifidum CUL20 and B lactis CUL34*; *for* the prevention of AAD Duration of intervention: NR Comparator(s): Placebo or no treatment	Incidence of AAD and CDAD F/u: NR
Pattani et al., 2013[16] Canada	16 RCTs	2,434 hospitalized patients on antibiotics[c] at risk for AAD and CDI	Intervention: Probiotics (*L.* genera, *Saccharomyces.boulardii,* and *Enterococcus* species) for the prevention of AAD and	Incidence of AAD and CDI F/u: 0 to 46 days

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			CDI Duration of intervention: NR Comparator(s): Usual care with or without placebo	

AAD = antibiotic-associated diarrhea; *B.* = *Bifidobacterium*; CDAD = *C. difficile*-associated diarrhea; CDI = C. difficile infection; F/u = follow up; *H.* = *helicobacter; L.* = *Lactobacillus*; NR = not reported; RCT = randomized-controlled trial

[a] Subsets of studies reported outcomes for specific probiotics

[b] This review excluded results from paediatric patients (0 to 18 years of age) and results on length of hospital stay for adults

[c] Each outcome involved subsets of the population

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Prevention of AAD				
Barone et al., 2017[18] Italy	Single-centre RCT	64 patients at risk for AAD; being treated with amoxicillin + clavulanic acid every 12 hours following tooth extraction between June 2016 and December 2016 Mean age (years): 57.2 ± 13.3 (intervention group), 53.7 ± 16.6 (comparator group)	Intervention: probiotic (B.*longum* + lactoferrin) every 12 hours (n = 37) Duration of intervention: NR Comparator: No adjunct treatment (n = 27) 600 mg Ibuprofen was administered to control pain	Incidence of diarrhea, incidence of adverse events (i.e., local signs of infection, intestinal distension or pain, incidence of gastric pain, level of gastric pain) F/u: 7, 14, and 21 days following extraction Excludes patients who were not on antibiotics (n = 42) and morbidity outcomes not related to infection
Treatment of CDI and prevention of CDAD				
Barker et al., 2017[17] United States	Single-centre RCT	33 patients with mild to moderate CDI and at risk for CDAD; being treated with vancomycin or metronidazole; enrolled between February 2013 and February 2015	Intervention: a four-strain oral probiotic capsule containing L.*acidophilus* NCFM, L.*paracasei* Lpc-37, B.*lactis* Bi-07 and B.*lactis* Bl-04 for treatment of CDI and prevention of CDAD Duration of intervention: NR Comparator: placebo capsule	Primary outcomes: duration and rate of CDAD, incidence of CDI recurrence Secondary outcomes: adverse events F/u: 0, 4, and 8 weeks

B. = Bifidobacterium; C. = Clostridium; CDAD = C.*difficile*-associated diarrhea; CDI = C.*difficile* infection; F/u = follow up; L. = Lactobacillus; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[6]

Strengths	Limitations
McFarland et al., 2018[8]	
• The population, intervention, comparators, and outcomes were described • The review authors provided adequate details of the included studies • The review authors accounted for risk of bias when discussing the results • Given that the relationship between the risk ratio and standard error in the funnel plot did not appear substantially skedded, the review authors suggested that a possible publication bias was not likely to markedly affect the results • Heterogeneity was assessed but not discussed	• An explicit statement that the review methods were established *a priori* was not found • The review authors did not explain their selection of the study designs for inclusion • Study selection and data extraction processes were not described • A list of excluded studies was not provided • The characteristics of included studies (including sources of founding) were not provided • High quality RCTs were included but the assessment process was not described (although a citation was provided) • The potential impact of risk of bias was not adequately assessed. • The likelihood of publication bias was not assessed • All three authors indicated potential conflicts of interest
Blaabjerg et al., 2017[9]	
• The population, intervention, comparators, and outcomes were described • The review authors explained their selection of the study designs for inclusion. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were prospective, randomized, controlled trials with placebo, active, or no treatment control arms. • Cochrane Collaboration's risk of bias tool was used for quality assessment of the individual studies and GRADE was used to evaluate the overall quality of the body of evidence • Sources of funding for the individual studies were included • The review authors justified combining the data from individual studies in a meta-analysis and investigated the causes of heterogeneity through sub-group analyses • The review authors accounted for risk of bias when discussing the results • Given that the relationship between the risk ratio and standard error in the funnel plot did not appear substantially skedded, the review authors suggested that a possible publication bias was not likely to markedly affect the results • The review authors declared that there were no conflicts of interest	• An explicit statement that the review methods were established *a priori* was not found • The review included only the Pubmed database • A list of excluded studies was not provided (although reasons for exclusion were provided) • The potential impact of risk of bias was not adequately assessed. Three out of nine included studies had low risk of bias. • Heterogeneity was considered moderate yet reasons for heterogeneity were not explored
Goldenberg et al., 2017[2]	
• The population, intervention, comparators, and outcomes	• An explicit statement that the review methods were

Strengths	Limitations
were described • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • Cochrane Collaboration's risk of bias tool was used for quality assessment of the individual studies and GRADE was used to evaluate the overall quality of the body of evidence • Sources of funding for the individual studies were included • The review authors investigated the causes of heterogeneity through sub-group analyses • The review authors accounted for risk of bias when discussing the results • Risk of bias was adequately assessed • Heterogeneity was satisfactorily discussed • The review authors adequately investigated publication bias • The review authors declared that there were no conflicts of interest	established *a priori* was not found • The review authors did not explain their selection of the study designs for inclusion
Shen et al., 2017[10]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • Cochrane Collaboration's risk of bias tool was used for quality assessment of the individual studies and GRADE was used to evaluate the overall quality of the body of evidence • Sources of funding for the individual studies were not disclosed but were used in the risk of bias assessment • The review authors investigated the causes of heterogeneity through sub-group analyses • The review authors accounted for risk of bias when discussing the results • Risk of bias was adequately assessed • Heterogeneity was satisfactorily discussed • The review authors adequately investigated and found no evidence of publication bias • The review authors declared that there were no conflicts of interest	• An explicit statement that the review methods were established *a priori* was not found although the PRISMA method was cited • Publication restrictions were not justified except for the timeframe which started the year the first case of CDAD was documented. • A list of excluded studies was not provided although the primary reason for exclusion was described • The review authors did not explain their selection of the study designs for inclusion.

Strengths	Limitations
Vernaya et al., 2017[11]	
• The population, intervention, comparators, and outcomes were described • The review methods were established *a priori* in a published protocol. Deviations were not mentioned. • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • A quality assessment of the individual studies was conducted using the Joanna Briggs Institute's Critical Appraisal Checklist for Randomized Control/Pseudo-Randomized Trials • The review authors adequately assessed heterogeneity • The review authors declared that there were no conflicts of interest	• The review authors did not explain their selection of the study designs for inclusion. • Sources of funding for the individual studies was not provided • The review authors did not discuss publication bias • Other than attrition risk, risk of bias was not discussed and was not accounted for in the discussion of results
Jafarnejad et al., 2016[12]	
• The population, intervention, comparators, and outcomes were described • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • A custom-designed tool was used for quality assessment of the individual studies • The review authors investigated the causes of heterogeneity through sub-group analyses • The review authors accounted for risk of bias when discussing the results • Heterogeneity was satisfactorily discussed • The review authors adequately investigated publication bias • The review authors declared that there were no conflicts of interest	• The review methods were established based on the PRSIMA guideline however reference was not made to a protocol • Publication restrictions were not justified. • A list of excluded studies was not provided although the reasons for exclusion were described • The review authors did not explain their selection of the study designs for inclusion. • Sources of funding for the individual studies were not included • Details of the tool that was used to assess risk of bias were not provided
Sinclair et al., 2016[13]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in triplicate	• The review methods were established based on the PRSIMA guideline however reference was not made to a protocol • The review authors did not explain their selection of the study designs for inclusion • A list of excluded studies was not provided although the reasons for exclusion were described

Strengths	Limitations
• The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • Cochrane Collaboration's risk of bias tool was used for quality assessment of the individual studies and GRADE was used to evaluate the overall quality of the body of evidence • The review authors investigated the causes of heterogeneity through sub-group analyses • Risk of bias was adequately assessed and accounted for when discussing the results • Heterogeneity was satisfactorily discussed • The review authors adequately investigated publication bias • The review authors declared that there were no conflicts of interest	• Sources of funding for the individual studies were extracted but not reported
Szajewska and Kołodziej, 2015[14]	
• The population, intervention, comparators, and outcomes were described • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • A list of excluded studies along with reasons for exclusion was provided • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in duplicate • Cochrane Collaboration's risk of bias tool was used for quality assessment of the individual studies and GRADE was used to evaluate the overall quality of the body of evidence • Sources of funding for a selection of the individual studies were included • Risk of bias was adequately assessed and accounted for when discussing the results • Heterogeneity was satisfactorily discussed • The review authors adequately investigated and found no publication bias	• An explicit statement that the review methods were established *a priori* was not found • The review authors did not explain their selection of the study designs for inclusion • One of two authors previously served as a speaker for the manufacturer of the probiotic being studied
Xie et al., 2015[15]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • Cochrane Collaboration's risk of bias tool was used for	• An explicit statement that the review methods were established *a priori* was not found • The review authors did not explain their selection of the study designs for inclusion • A list of excluded studies was not provided • The overall quality of evidence was assessed without reference to a specific tool or process • Risk of bias and heterogeneity were not adequately discussed. • The likelihood of publication bias was not assessed • Sources of funding for the individual studies were not

Strengths	Limitations
quality assessment of the individual studies • The review authors accounted for risk of bias when discussing the results • The review authors declared that there were no conflicts of interest	included
Pattani et al., 2013[16]	
• The population, intervention, comparators, and outcomes were described • The review used a comprehensive literature search strategy and keywords were provided. Publication restrictions were not justified. • Study selection and data extraction were performed in duplicate • The review authors provided adequate details of the included studies. All included studies were randomized controlled trials. • Quality assessment of the individual studies was conducted based on the Unites States Preventive Services Task Force recommendations • The review authors investigated the causes of heterogeneity through sub-group analyses • Risk of bias was adequately assessed and discussed • Heterogeneity was satisfactorily discussed • The review authors adequately investigated publication bias • The review authors declared that there were no conflicts of interest	• An explicit statement that the review methods were established *a priori* was not found although the PRISMA method was cited • The review authors did not explain their selection of the study designs for inclusion • A list of excluded studies was not provided • Sources of funding for the individual studies were not included

RCT = randomized-controlled trial

Table 5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black checklist[7]

Strengths	Limitations
Barone et al., 2017[18]	
• The objectives were clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention, comparator, and outcomes were described • Randomization was performed • Withdrawals were reported • *P*-values were reported for primary outcomes • The authors mentioned that there was no conflict of interest with any financial organization	• Blinding was not discussed • The sample size was not calculated • It is unclear whether analysis were conducted per protocol
Barker et al., 2017[17]	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention, comparator, and outcomes were described. • Randomization was performed in permuted blocks of four using a random-number generator • Withdrawals were reported • *P*-values were reported for primary outcomes • The authors mentioned that there were no transparency declarations	• Details of blinding were missing • The sample size was not calculated but the authors highlighted the small enrollment size as a limitation of the study • It is unclear whether analysis were conducted per protocol

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
McFarland et al., 2018[8]	
Probiotics (n = NR) vs. placebo or no treatment (n = NR) Incidence of AAD L. casei DN-114001 (n = 2 studies) • RR = 0.32 (95% CI 0.16, 0.63); I^2 = 0%; indicating that probiotics significantly reduced the incidence of AAD L. reuteri ATCC 55730 (n = 3 studies) • RR = 0.35 (95% CI 0.20, 0.61); I^2 = 0%; indicating that probiotics significantly reduced the incidence of AAD A mixture of L. acidophilus CL1285, L. casei LBC80R, and L. rhamnosus CLR2 or Bio-K+® (n = 3 studies) • RR = 0.56 (95% CI 0.40, 0.79); I^2 = 51%; indicating that probiotics significantly reduced the incidence of AAD A mixture of L. acidophilus La5 and B. lactis Bb12 (n = 6 studies) • RR = 0.67 (95% CI 0.47, 0.94); I^2 = 19%;indicating that probiotics significantly reduced the incidence of AAD L. rhamnosus GG (n = 6 studies) • RR = 0.55 (95% CI 0.25, 1.18); I^2 = 73%; indicating that probiotics reduced the incidence of AAD but that the impact was not statistically significant A mixture of L. rhamnosus R011 and L. helveticus R052 (n = 2 studies) failed to find significant efficacy for the prevention of AAD	*"Evidence from this review shows that there is clear strain-specificity and disease-specificity for probiotic products and every effort should be made to report specific probiotic strains or mixture of strains when analyzing the efficacy and safety of probiotics."*[8] (p. 11)
Blaabjerg et al., 2017[9]	
L.*rhamnosus GG* and S.*boulardii* vs. placebo or no treatment Incidence of AAD (n = 9 studies, n = 1936 patients) • RR = 0.53 (95% CI 0.37 to 0.76; I^2 = 47%); indicating that probiotics significantly reduced the incidence of AAD •	*"Using probiotics for the prevention of antibiotic-associated diarrhea reduces the risk of AAD by [52% or 53%]."*[9] (p. 14)
Goldenberg et al., 2017[2]	
Probiotics (n = NR) vs. placebo, active control, or no treatment (n = NR) Incidence of CDAD (n = 24 studies, 7800 patients) • RR: 0.41 (95% CI 0.30 to 0.57); indicating a statistically significant decrease in the risk of CDAD Incidence of AAD (n = 23 studies, 7036 patients) • RR: 0.62 (95% CI 0.51 to 0.76) indicating a statistically significant decrease in the risk of AAD Incidence of infection (n = 13 studies, 961 patients)	*"Probiotics are superior to placebo or no treatment for preventing C.difficile-associated diarrhea."*[2] (p. 22)

Main Study Findings	Authors' Conclusion
• RR: 0.89 (95% CI 0.64 to 1.24); indicating a nonsignificant decrease in the risk of infection Incidence of adverse events (n = 28 studies, 7417 patients) • RR: 0.83 (95% CI 0.71 to 0.97); indicating a statistically significant decrease in the risk of adverse events	
Shen et al., 2017[10]	
Probiotics (n = NR) vs. placebo or usual care (n = NR) Incidence of CDI (n = 19 studies) • RR = 0.42 (95% CI, 0.30-0.57; P < 0.001); I^2 = 0.0%; *P* = 0.56; indicating a statistically significant reduction in CDI Adverse events (cramping, nausea, fever, soft stools, flatulence, and taste disturbance) (n = 15 studies) • Incidence: 14.2% (433 of 3056) vs.15.9% (439 of 2753) • RR = 0.89 (95% CI, 0.69-1.14; P = 0.35; I^2 = 48%); indicating that probiotics did not significantly reduce the incidence of adverse events	*"The cumulative evidence from 19 randomized trials demonstrates the efficacy of probiotics in preventing CDI among hospitalized adults taking antibiotics… Probiotics given within 2 days of the first antibiotic dose are more effective than if started later. However, there was no convincing evidence of superior efficacy for any of the tested probiotic formulations, delivery methods (drink or capsule), or probiotic doses."*[10] (p. 1895)
Vernaya et al., 2017[11]	
Probiotics (n = 1734) vs. placebo (n = 1727) Incidence of CDAD (n = 5 studies) • OR = 0.66 (95% CI, 0.26-1.66; *P* = 0.38) suggesting that probiotics were no more effective than placebo in reducing CDAD incidence in elderly hospitalized patients	*"…probiotics were not found to be more effective for the reduction of CDAD incidence in elderly hospitalized patients compared to placebo. However, reviewing the characteristics of the included studies revealed inconsistencies with regard to the type of bacteria, number of strains, form of administration (capsule versus probiotic drink), antibiotic administration and dosage."*[11] (p. 149)
Jafarnejad et al., 2016[12]	
Probiotics (n = 3805) vs. placebo (n = 3455) in all patients (30 studies) Incidence of AAD • RR: 0.69 (95% CI, 0.62-0.76); indicating that probiotics significantly lower the risk of AAD Probiotics (n = 2087) vs. placebo (n = 1739) Incidence of AAD in patients between 18 and 64 years (25 studies) • RR: 0.47 (95% CI, 0.40-0.56); indicating that probiotics significantly lower the risk of AAD Probiotics (n = 1718) vs. placebo (n = 1716) Incidence of AAD in patients > 65 years (5 studies) • RR: 0.94; 95% CI: 0.76-1.15; indicating that probiotics were no more effective than placebo in reducing the incidence of AAD in older adults	*"…the results emerging from our meta-analysis suggested that adjunct probiotic administration is associated with a reduced risk of AAD in adults but not in elderly people."*[12] (p. 511)
Sinclair et al., 2016[13]	
Probiotics (n = 2554) vs. placebo (n = 2287)	*"Our meta-analysis suggests that, on average, probiotics containing Lactobacillus spp. have a*

Main Study Findings	Authors' Conclusion
Incidence of CDAD • Proportion of patients: 1.8% (45/2554; range, 0% to 8%) vs. 3.9% (90/2287; range, 0% to 24%) • RR: 0.25 (95% CI, 0.08-0.47); indicating that probiotics significantly reduced the incidence of CDAD	*preventive effect on CDAD, with a pooled relative risk reduction of 75%. However, the wide CI around the predicted benefit in a future study includes an RR of 1 and reflects the presence of heterogeneity in the RRs across individual studies."*[13] (p. E715)
Szajewska and Kołodziej, 2015[14]	
Probiotics (n = 951) vs. placebo or no treatment (n = 891) Incidence of AAD • RR: 0.52 (95% CI: 0.36-0.73); indicating that probiotics significantly reduced the incidence of AAD Probiotics (n = 752) vs. placebo or no treatment (n = 689) Incidence of CDAD • RR: 0.80 (95% CI: 0.47-1.34); indicating that probiotics reduced CDAD but the impact was not statistically significant Probiotics (n = 645) vs. placebo or no treatment (n = 627) Incidence of *H.pylori* • RR: 0.45 (95% CI: 0.31-0.66); indicating that probiotics effectively eradicated *H.pylori* Adverse events Adverse events rate was similar in the probiotic and control groups.	*"…moderate quality evidence showed that the use of S. boulardii reduced the risk of AAD.. Even if included trials reported no adverse effects related to S. boulardii, its consumption is not without risk in specific patient groups such as immunocompromised subjects or in patients with other life-threatening illnesses managed in the intensive care unit"*[14] (p. 799)
Xie et al., 2015[15]	
Incidence of AAD (n = 1 study) Bacillus licheniformis (n = 110) vs. no treatment (n = 124) • RR: 0.50 (95% CI, 0.29-0.86); indicating that Bacillus licheniformis probiotic significantly reduced the incidence of AAD in patients 65 years and older There was no preventative effect for AAD and CDAD with the remaining probiotics (*L. acidophilus, L. casei Shirota, S. cerevisiae lyo*)	*"Our findings indicate that probiotics may not reduce the risk of AAD and CDAD in older patients. However, with current published data, it is difficult to draw concrete conclusions."*[15] (p. 133)
Pattani et al., 2013[16]	
Incidence of AAD Probiotics (n = 1169) vs. placebo (n = 1127) • RR: 0.61 (95% CI 0.47 to 0.79); indicating that probiotics significantly reduced the incidence of AAD relative to placebo Incidence of CDI Probiotics (n = 572) vs. placebo (n = 527) • RR: 0.37 (95% CI 0.22 to 0.61); indicating the probiotics significantly reduced the incidence of CDI relative to placebo	*"Our findings illuminate the benefits of probiotics in preventing both AAD and CDI in the specific patient population of adult inpatients requiring antibiotics. On the basis of the current review, probiotics can be recommended for such patients in the absence of contraindications; however, the prevalence of AAD and CDI should be taken into consideration before guidelines are developed."*[16] (p. e65)

AAD = antibiotic-associated diarrhoea; C. = Clostridium; CDAD = *C.difficile*-associated diarrhea; CDI = *C.difficile* infection; CI = confidence interval; L. = Lactobacillus; NR = not reported; OR = odds ratio; RR = relative risk

Table 7: Summary of Findings of Randomized Controlled Trials

Main Study Findings	Author's Conclusion
Randomized controlled trials	
Barone et al., 2017[18]	
Probiotic (n = 37) vs. no treatment (n = 27) Incidence of diarrhea: 0 vs. 5; *P* = NR Adverse events Local signs of infection @ day 7: None Incidence of intestinal distention or pain: 1 vs. 9; *P* = 0.001 Incidence of gastric pain: 4 vs. 9; *P* = 0.056 Mean NRS score (gastric pain) @ day 7: 1.08±1.93 vs. 1.56±1.91; *P* = NR Mean NRS score (gastric pain) @ day 14: 0.24±0.72 vs. 0.11±0.58; *P* = NR	"*From our preliminary data, due to the relatively low population, no absolute conclusions could be drawn…[More] patients are required to better clarify the role of antibiotics and probiotics for dental extractions.*"[18] (p. 155)
Barker et al., 2017[17]	
Probiotic (n = 16) vs. placebo (n = 15) Median duration of CDAD (cumulative days, IQR): 0.0 (0.0-2.0) vs. 1.0 (0.0-13.0); *P* = 0.039 Median number of days with CDAD (days) (IQR): 3.5 (1.0–8.0) vs. 12.0 (6.0–25.0); *P* = 0.005 Median CDAD rate (days of diarrhea/stool diary days submitted) (IQR): 0.1 (0.0–0.2) vs. 0.3 (0.1–0.5); *P* = 0.009 Incidence of 1 CDI recurrence: 7% (1/15) vs. 8% (1/13); *P* = NR Adverse events Incidence of GI disorders: 75% vs. 80%; *P* = NR	"*Combination probiotic treatment was associated with significant improvement in diarrhea outcomes for participants, compared with placebo.*"[17] (p. 3178)

CI = confidence interval, CDAD = *C.* difficile-associated diarrhea; CDI = C.difficile infection; GI = gastrointestinal; IQR = interquartile range; NRS = Numeric Rating Scale; SD = standard deviation

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Appendix 6: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	McFarland et al., 2018[8]	Blaabjerg et al., 2017[9]	Goldenberg et al., 2017[2] incidence of CDAD	Goldenberg et al., 2017[2] incidence of AAD	Goldenberg et al., 2017[2] incidence of infection	Goldenberg et al., 2017[2] incidence of adverse events	Shen et al., 2017[10]	Vernaya et al., 2017[11]	Jafarnejad et al., 2016[12]	Sinclair et al., 2016[13]	Szajewska and Kolodziej, 2015[14]	Xie et al., 2015[15]	Pattani et al., 2013[16]
Adam, 1977											X		
Allen, 2013			X	X		X	X	X	X			X	
Armuzzi, 2001a	X												
Armuzzi, 2001b	X								X				
Beausoleil, 2007			X	X		X	X		X				X
Bravo, 2008			X	X		X					X		
Can, 2006			X	X			X		X		X		X
Chatterjee, 2012		X							X				
Chu, 2012											X		
Cimperman, 2011	X								X				X
Cindoruk, 2007		X		X		X			X		X		
Cremonini, 2002									X		X		
De Vrese, 2011		X											
Dietrich, 2014	X												
Duman, 2005		X	X	X		X					X		
Ehrhardt, 2016			X			X	X		X				

Primary Study Citation	McFarland et al., 2018[8]	Blaabjerg et al., 2017[9]	Goldenberg et al., 2017[2] incidence of CDAD	Goldenberg et al., 2017[2] incidence of AAD	Goldenberg et al., 2017[2] incidence of infection	Goldenberg et al., 2017[2] incidence of adverse events	Shen et al., 2017[10]	Vernaya et al., 2017[11]	Jafarnejad et al., 2016[12]	Sinclair et al., 2016[13]	Szajewska and Kołodziej, 2015[14]	Xie et al., 2015[15]	Pattani et al., 2013[16]
Evans, 2016													
Fominykh, 2013			X	X		X							
Gao, 2010			X	X		X	X		X				X
Gotz, 1979									X				X
Hickson, 2007	X		X	X		X	X	X	X				X
Imase, 2008		X			X	X							
Kim, 2008		X											
Klarin, 2008					X	X							
Koning, 2008				X	X	X							
Lewis, 1998					X			X			X	X	X
Li, 2010												X	
Lonnermark, 2010			X	X	X	X							
McFarland, 1995			X	X	X	X	X				X		X
Miller, 2008a			X			X	X						
Miller, 2008b			X	X		X	X						
Monteiro, 1981											X		
Nord, 1997					X	X							
Ojetti, 2012	X	X											
Ouwehand, 2014			X	X		X	X						
Park, 2007		X											
Plummer, 2004			X	X	X		X	X				X	
Pozzoni, 2012			X	X		X	X	X	X		X		X
Psaradellis, 2010			X	X		X							

Primary Study Citation	McFarland et al., 2018[8]	Blaabjerg et al., 2017[9]	Goldenberg et al., 2017[2] incidence of CDAD	Goldenberg et al., 2017[2] incidence of AAD	Goldenberg et al., 2017[2] incidence of infection	Goldenberg et al., 2017[2] incidence of adverse events	Shen et al., 2017[10]	Vernaya et al., 2017[11]	Jafarnejad et al., 2016[12]	Sinclair et al., 2016[13]	Szajewska and Kołodziej, 2015[14]	Xie et al., 2015[15]	Pattani et al., 2013[16]
Rafiq, 2007			X				X						
Safdar, 2008			X	X		X	X					X	
Sampalis, 2010													X
Scaccianoce, 2008	X												
Selinger, 2013			X	X		X	X						
Shimbo, 2005					X	X							
Siitonen, 1990					X	X							
Song, 2010					X						X		X
Sullivan, 2004					X	X							
Surawicz, 1989			X	X	X	X	X				X		X
Thomas, 2001			X	X		X	X						X
Wenus, 2008			X	X	X		X						X
Wong, 2014			X	X		X	X						
Wright, 2014									X			X	
Zojaji, 2013		X									X		