Probiotic Use in the Prevention of Clostridium Difficile Infection

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Clostridium difficile infection (CDI) is produced by an anaerobic bacterium, and it is the leading cause of community and hospital antibiotic-associated diarrhea (AAD) in the U.S. and Europe (Carroll & Bartlett, 2011; Sun & Hirota, 2015). The Centers for Disease Control and Prevention (CDC) reports half a million CDI cases were diagnosed in the U.S. during 2011, with over 83,000 cases of recurrence and 29,000 deaths (CDC, 2015). Costs for treating CDI and its primary impact, CDI associated diarrhea (CDAD), in the U.S. are estimated to range between $8,911 to $30,049 per patient or a total of $5.4 billion annually (Desai et al., 2016; Nanwa et al., 2015). Additionally, patients can experience significant suffering and reduction in quality of life through diarrhea, fever, abdominal pain, nausea, and hypovolemia (Weaver et al., 2017).

Antibiotic (Abx) use is the primary risk factor for development of CDI, with up to 13% of patients developing CDI with Abx (Sumberac, 2014). Abx treatment can reduce normal gastrointestinal (GI) microflora and colonization resistance, increasing CDI risk (Evans & Safdar, 2015). Probiotics (PBs) are live microbial organisms which may theoretically counteract these impacts to GI microflora. PBs are also hypothesized to provide anti-pathogen effects through secretion of bacteriocins, competition for nutrients, and improvement of immunological functions of GI mucosa (Allen et al., 2013).

Although the potential link between PBs and reduction of CDI risk through enhancement of GI flora has been studied, current guidelines have not found significant evidence to definitively recommend or not recommend PBs for the prevention of CDI (McDonald et al., 2018). Guidelines do note that PBs may be considered. As such, clinical practice in this area is not consistent (Shen et al., 2017). Additionally, while other preventative techniques such as hand-washing have helped prevent CDIs, the incidence of CDIs in the U.S. more than doubled between 2000 and 2009 (Dubberke, et al., 2014). The most recent data available from 2011 does include a potential plateauing of the CDI rates, but it remains the most common healthcare associated infection in the

U.S. (Dubberke & Olsen, 2012; Pharmacy Times, 2018).

Given the size and importance of the CDI impact, this analysis will evaluate the efficacy of PBs for prevention of CDI among adults receiving Abx. To guide investigation of the literature related to these issues, the following PICO question was developed: "In adults receiving Abx treatment, does the use of PBs, compared to no PBs, reduce the rate of CDI?"

Literature Review

Utilizing the developed PICO, a literature search was conducted through the PubMed, Cochrane, TRIP, EMBASE, National Guideline Clearinghouse, and Google Scholar databases. Additional articles were reviewed utilizing applicable references from the initial search. Over 30 articles were critiqued for applicability and eight were chosen, including one Cochrane systematic review (SR) with meta-analysis (MA), one additional SR with MA, one SR with an Individual Patient Data (IPD) MA, three Random Controlled Trials (RCT), one quasi-experimental cohort study, and one clinical practice guideline.

The most comprehensive analysis was a Cochrane SR and MA from Goldenberg et al. (2017) assessing the efficacy and safety of PBs for preventing CDAD with Abx use in adults and children. Secondary outcomes included CDI without diarrhea, adverse events (A/E), and AAD. Subgroup analyses were conducted for adults vs. children, setting, strain of PBs, dose of PBs as well as baseline risk of CDAD. Databases searched through 3/21/2017 included PubMed, EMBASE, CENTRAL, the Cochrane IBD Group Specialized Register, and an extensive grey literature search. There were 31 RCTs including 8,672 patients. Inclusion criteria encompassed any RCT investigating PB use of various strains and doses for prevention of CDAD or CDI. Exclusion criteria included existing CDAD, existing PB use, or being immunocompromised. The results showed that PB use was safe, and there was a reduced risk of CDAD infection with concurrent use of PBs in adults and children if the baseline CDAD risk was over 5%. Specifically,

the use of PBs decreased CDAD incidence from 4.0% to 1.5%, RR 0.40 (0.30-0.52). The effect size showed a 60% reduction with a number needed to treat (NNT) of 42 patients. No differences were discovered in subgroup analyses among age, setting, or PB species.

Another SR with a MA by Lau & Chamberlain (2016) assessed the impact of PBs on CDAD incidence in inpatient and outpatient settings. Subgroup analyses included the type of PB, age, and inpatient/outpatient status. A literature search of RCTs was conducted in the PubMed, Cochrane, and Google Scholar databases from 1966-2015. Twenty-six RCTs and 7,957 patients were included in the analysis. Inclusion criteria were RCTs comparing use of any strain of PB versus placebo or no intervention. PBs must have been initiated within 3 days of the start of Abx and continued for at least the entire duration of Abx use. Exclusion criteria included PB use for existing CDAD. The results showed PBs reduced CDAD risk to 1.5%, compared to 3.8% in the control group, RR 0.395 (0.294–0.531) with a NNT of 43. The benefit was greater for inpatients versus outpatients, but this might be explained by the small number of outpatient studies and thus lower overall power to detect effects. No differences were found related to age or PB species.

Johnston et al. (2018) conducted a different type of SR utilizing IPD for the MA. The objective was to determine whether PB prophylaxis reduced the odds of CDI. Secondary outcomes included A/E. Subgroup analyses included baseline CDI risk, single species PB, multi-species PB, multi-Abx use, and PB dose. Databases searched included PubMed, EMBASE, and Cochrane from inception to 4/11/16. Inclusion criteria were RCTs with any age participants comparing Abx with concomitant PB to Abx with either placebo, alternative prophylaxis, or no treatment. Authors of 32 eligible studies were contacted and 14 studies that did not provide IPD were excluded, leaving 18 RCTs, 6,851 patients. The results of the IPD analysis showed an incidence of CDAD in the PB group of 1.1% vs 2.5% in the control groups, OR 0.37 (0.25–0.55), with a NNT of 71. An adjusted model for subgroup analysis was similar with an OR 0.35 (0.23-0.55), and no differences in age, sex, A/E, inpatient/outpatient, PB dose, or high-risk Abx characteristics. However, the

subgroup analysis did show multi-species PB were more beneficial than single species PB (OR 0.33 for MPB vs 0.41 for SPB), and baseline CDI risk >= 5% and/or multiple Abx use resulted in higher CDI incidence and higher benefit from PBs.

Several individual RCTs were also reviewed. Ouwehand et al. (2014) looked at the effect of a specific combination of PB strains on the incidence of CDI, incidence of AAD, and associated A/E at two different doses compared to placebo. The sample was obtained over four months in 2010 from a large hospital in China and included a total of 503 participants, randomized and allocated 1:1:1 to a high dose PB group, a low dose PB group, and a placebo group. Inclusions were males and females ages 30-70, inpatient, Abx therapy for 3-14 days started <36 hours prior to study. Exclusions included current/existing diarrhea, existing PB use, active intestinal disease, prior c-diff infection within last 3 months, or immunosuppression. The study was triple-blind with a specific four strain PB dose administered daily up to 7 days after final Abx use (10-21 days total), with subjects being equally randomly stratified by gender, age, and duration of Abx treatment. The results of the RCT showed an incidence of CDAD in both the high and low dose PB groups of 1.8% vs 4.8% in the placebo group, with an OR 0.29 (0.07–1.25) and NNT of 33.6. There were no risk differences in the doses of the PB tested, and there were fewer A/E in both PB groups compared to the placebo group (4.2% compared to 7.2%).

Another RCT by Allen et al. (2013) investigated the clinical efficacy of using a high-dose, multi-strain PB in older hospitalized patients for the prevention of AAD and CDD. Secondary outcomes included analyses of multiple A/E, quality of life (QOL), and cost-effectiveness. Of those recruited, 1,493 (50.1%) were randomized and allocated to the PB arm and 1,488 (49.9%) to the placebo arm. The patients included a mix of medical and surgical elderly patients being treated in wards in five United Kingdom hospitals. Inclusion criteria were inpatient status, ≥ 65 years old, and exposure to one or more Abx in the preceding 7 days or about to initiate the start of Abx. Exclusion criteria included pre-existing diarrheal disorders, immunocompromised, or any other

relevant complicating or serious conditions. The study was double-blind, placebo-controlled, with participants given either a high-dose multi-strain PB or placebos for 21 days. The results of the trial showed the frequency of CDAD was low in both groups but a little lower in the PB arm at 0.8% vs 1.2% in the placebo group, RR 0.71(0.34 to 1.47), p=0.35. As shown, the 95% confidence interval (CI) included a 0 effect within the range, and the difference was not statistically significant. There were no statistically significant differences in A/E or QOL, and the use of PBs in this scenario was determined to not be cost-effective.

A final RCT by Selinger et al. (2013) examined the use of PBs to reduce the rate of both AAD and CDAD with Abx use. Secondary outcomes included A/E, length of hospital stay, and mortality. Subjects were inpatients in a hospital in the U.K. and were randomized with 117 allocated to PB arm and 112 to placebo. Inclusion criteria were being treated for an infection, 18+, and on Abx within the last 48 hrs. Exclusion criteria included diarrhea at screening, unable to take enteral medications, regular consumption of PB one week prior to admission, and certain severe or chronic conditions. The study was double-blind, placebo-controlled with participants given either the PB or placebo for the length of Abx treatment plus 7 days thereafter. The results showed a 0% rate of CDAD or AAD in the PB group with also a 0% CDAD rate in the placebo group but a 11.4% AAD rate. The rate for A/E, mortality, and length of stay were not statistically different in either group. The 0% rate of CDAD in all participants was an unexpected finding, but it was noted the study did not include any patients with high baseline CDAD risk.

An interesting quasi-experimental prospective cohort study designed by Maziade, Pereira, and Goldstein (2015) looked at CDI prevention efforts over a 10-year period in hospitals in Quebec. The primary outcome was incidence of CDI with PB prophylaxis efforts, with a secondary analysis for cost-effectiveness. During the study period, all 44,835 patients in one Quebec intervention hospital receiving Abx were given PB. The CDI rates for the intervention hospital were compared to an aggregate of 27 other Quebec hospitals of similar size and services

who did not provide routine PB prophylaxis over the same time frame. Other CDI prevention methods between the intervention hospital and the comparison group were approximately the same. The analysis showed the observed incidence of CDI in the intervention hospital was consistently significantly less over the study period. There were 2.3 CDI infections per 10,000 patient days at the intervention hospital compared to 8.3 at the comparison group. Additionally, the study estimated that use of the PB resulted in a mean per-patient savings up to $2,769. While recognizing the limitations of this type of study, the analysis showed continuously lower CDI rates from 2005 to 2014 which might be explained by the prophylactic use of PBs.

Utilizing a comprehensive SR, which included most of the discussed literature, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recently updated their overall guidelines for the diagnosis and management of CDI (McDonald et al., 2018). This guideline followed the standard IDSA process for guideline development that included a systematic weighting of the strength and quality of evidence using the GRADE system. After a literature search through December 2016, selected articles were provided to a 14-member panel of multidisciplinary experts. While the reviewed literature did include MAs, no new MA was conducted. Rather, the overall set of applicable research was reviewed for quality and strength and a consensus opinion was formed by the expert panel.

Recommendations for all facets of CDI diagnosis and management were produced, including the potential prophylactic use of PBs. The expert panel determined that based on the research there was insufficient data to provide recommendations for PB use in primary prevention of CDI. The panel noted that trials showing the most beneficial results involved patients with higher baseline CDI risks. The evaluation also noted significant heterogeneity in the existing literature making recommendations more difficult.

Synthesis

The combined data from the literature review encompassed a significant number of RCTs and participants. The largest SR review from Goldenberg et al. (2017) included 31 RCTs and 8,672 participants. While there was overlap, the other SRs and RCTs included an additional 1,017 participants, plus over 45,000 in the long-term cohort analysis. Each article also had different subgroups and other analyses, thus providing unique insights from each of the studies. With this comprehensive strength of the research base, synthesis of the literature provides a view of overall CDI/CDAD outcomes, as well as several outcome sub-themes related to differences in patient baseline risk, strains of PB, A/E, and costs. Other potential sub-themes including age and sex were, however, consistent across all analyses and revealed no differences in outcomes.

The primary outcome of interest, reduction of CDI or CDAD, was consistent across all included SRs, one of the RCTs, and the cohort analysis. In these analyses, the effect size benefit for use of PBs to reduce CDI risk from Abx was in the 60% or slightly higher range. One of the additional RCTs from Allen et al. (2013) also included a potential benefit, but it was significantly less, and the 95% confidence range from that study included a zero-effect level. Interestingly, the third RCT from Selinger et al. (2013) found no benefit, but there were no incidences of CDI/CDAD in any of the 229 participants in either PB or control groups. Finally, notwithstanding the limitations of a cohort study, Maziade et al. (2015) found a substantial reduction in CDI/CDAD incidence over a large number of participants over 10 years. Although the SRs included some overlaps of studies, there were enough differences in populations and analysis methods to provide reassurance of the outcome consistency from the different SRs.

The lack of significant outcome observed in the Allen et al. (2013) and Selinger et al. (2013) studies have potential explanations and implications. In both studies, the incidence of CDI/CDAD was very low – 1.2% for the control group in Allen and 0% in Selinger. As such, the

power of the studies to detect any significant PB benefit was likely low given the small incidence and effect size. This observation corresponds to a potential plateauing / reduction in CDI/CDAD rates in the U.S and Europe (Dubberke & Olsen, 2012; Pharmacy Times, 2018). It has potential implications for the future cost/benefit of PB prophylaxis if CDI/CDAD rates continue to fall.

In terms of sub-theme commonalities and differences that emerged from the synthesis, the strongest common insight was related to baseline CDI/CDAD risk. Both Goldenberg et al. (2017) and Johnston et al. (2018) found a greater PB benefit for patients with higher baseline risk. However, baseline risk was not determined by any specific risk factors but rather by the surrogate of the CDI/CDAD event rate of the control groups. Neither of the two RCTs which showed low/no PB benefit included high baseline risk patients. Many factors could contribute to baseline risk, including the type and number of Abx used. However, only Johnston et al. (2018) included an analysis of multiple Abx, and while that study did find higher CDI/CDAD risk with multiple Abx, it was not used as a factor to determine baseline risk. Neither of the other two SRs compared type or number of Abx. Thus, while there was no common method for measuring baseline risk, the consistency of the surrogate results of the two SRs for this sub-theme should not be ignored.

Type and dose of PB was another sub-theme but with more variance. While the other two SRs did not reveal outcome differences based on PB species, Johnston et al. (2018) did show that multispecies PB were more effective. Since this was the SR that utilized IPD for analysis and a resulting smaller total size, the specific mixes of PB strains were potentially sufficiently different enough from the other SRs to cause the variance. Additionally, considering two of the RCTs had low/no PB effect, it is also possible these RCTs utilized PB strains that caused the lack of PB efficacy. Overall, the synthesis does not provide sufficient clarity about the type and dose of PB.

Considering A/E, PB use did not increase A/E in any of the analyses which included this measure. Additionally, both the Goldenberg et al. (2017) SR and the Ouwehand et al. (2014) RCT

demonstrated a reduction in A/E and overall symptoms. There was a wide variation in the categorization and measurement of A/E across the studies in the SRs, but no significant negative impacts from PBs in any of these measures.

Finally, different cost sub-themes emerged from some of the literature. In the large, long-term cohort analysis from Maziade et al. (2015), savings from PB use accruing from reduced CDI/CDAD treatment costs were estimated to be $2,769 per patient. Conversely, the RCT from Selinger et al. (2013) found use of PBs to not be cost-effective, due to the low/no instance of CDAD. Allen et al. (2013) found no differences in costs, while none of the SRs analyzed this component but did imply savings due to CDI/CDAD risk reduction and thus lower treatment cost. A recent study by Shin et al. (2017), utilizing MA data from the SRs in this review, did show that PBs could be cost-effective for older and higher-risk patients.

Based on the themes emerging from the synthesis of the literature, there is potential benefit from the use of PBs to reduce CDI/CDAD risk associated with Abx use. This benefit did not vary based on age or sex, but the PB benefit was greater for patients with a higher baseline CDI/CDAD risk. There were some inconsistencies in results related to the type and dose of PB, but most of the data did not show that to be a significant factor. The potential cost or cost savings of PB use was also not consistent but could be implied based on the SR results (Shin et al., 2017). Finally, there is consistent evidence that PBs do not increase A/E.

Although the current applicable guidelines do not include a recommendation for or against PB prophylaxis based on the lack of evidence, this literature synthesis suggests a recommendation for the consideration of PB use would be reasonable. Despite some of the inconsistencies, there is at least moderate quality evidence that PBs can help reduce CDI/CDAD risk with Abx use. The lack of A/E and the low cost of PBs make this recommendation more appealing and more feasible.

However, some form of baseline risk assessment should be utilized, with stronger consideration given to PB use with high baseline risk patients.

To further knowledge in this important area and influence future guidelines, additional studies would be helpful. These should include (a) a definition of baseline risk and studies with different baseline risk patients, (b) additional PB type/dose analyses, (c) age stratification studies, and (d) comprehensive cost-benefit analyses. Finally, if improvements in other CDI/CDAD reduction approaches continue to reduce the overall CDI/CDAD incidence, there may be a future time where potential current PB prophylaxis cost/benefit might no longer continue to be valid.

Conclusion

CDI related to Abx use is a continuing problem with significant financial and personal costs. PBs are theorized to potentially reduce this CDI risk. A PICO question was developed to investigate this issue and formulated as: "In adults receiving Abx treatment, does the use of PBs, compared to no PBs, reduce the rate of CDI?" Through a comprehensive search, review, and synthesis of the literature, a partial answer to this question emerged. In adults receiving Abx treatment, most of the reviewed literature showed the use of PBs can reduce the rate of CDI, but it was also clear the benefit from PBs was significantly greater for patients with a high CDI baseline risk. Additional sub-themes showed the PB benefit did not vary based on age or sex, and PB use did not increase A/E. Most of the data also showed that type and dose of PB was not a significant factor, but there were some inconsistencies. The cost-effectiveness of PBs was also not clear.

The clinical impact of this analysis suggests that PBs should be considered for CDI risk reduction, especially in patients with high baseline CDI risk. Since current guidelines do not currently find sufficient evidence to make that recommendation, additional research is needed related to definitions and stratifications of baseline risk, different PB types/dose, and cost-benefits compared to overall CDI incidence trends.

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Appendix A. Evidence Table

Author, Year, Title, Journal	LOE	Aim/Purpose	Theoretical framework /conceptual model	Design/Methods/ Instruments	Sample and Setting Information	Major Variables/ Interventions/ Definitions	Data Analysis	Outcome measures	Effect size/ Odd Ratio/ Risk Ratio	Strengths/ Limitations/Bias	Relevant findings	Qual
McDonald et, al. (2018). Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by IDSA and SHEA Clostridium difficile. Clin Infect Dis,66(7)	I	- Provide evidence-based recommendations intended to improve the diagnosis and management of CDI	- Based on Infectious Diseases Society of America (IDSA) Handbook on Clinical Practice Guideline Dev	- Expert panel utilizing systematic evidence-based literature search and review approach for applicable PICOs - Evidence graded and reviewed by panel who developed the guidelines by consensus	- N/A, Total sample across research included in the expert panel review not provided	- Multiple but for the purpose of PB assessment, IV was PB use or not; DV was CDI infection	- GRADE criteria for evidence - 14-member expert panel review and consensus development of guidelines based on strength and quality of evidence - MAs were included in review but no new MA was performed	- Reduction in CDI infection	- Combined MA not performed	S: Rigor of research approach; evidence grading; expert panel consensus review L: English only search	- No guideline regarding PB, based on insufficient data at this time - PB potentially effective for populations with higher CDI baseline risk - Significant heterogeneity in studies	High
Goldenberg et al. (2017). "Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children." Cochrane Database of Systematic Reviews, 12	I	- Assess the efficacy and safety of PBs for preventing CDAD or CDI associated with Abx use	- Cochrane model for systematic reviews	- SRMA: Literature search for RCTs investigating PB with Abx for prevention of CDAD, or CDI. from inception of major databases to 3/21/17, with extensive grey literature search	-31 RCTs, 8672 Pts - Adults and children (7,036 adults) - INCL: Any PB, any Abx, INPT, OUTPT - EXCL: Active diarrhea or CDAD, current PB use	- IVs: PB Use -DVs: INCD of CDAD (primary) or CDI, A/E or AAD (all secondary) - Intervention: PB use with Abx	- Outcomes pooled using a random-effects model to calculate RR and 95% CI. - Sensitivity analyses - Priori subgroup analyses for PB species, dose, adult/pediatric population - Post hoc subgroup analysis on baseline risk - Quality of evidence using GRADE criteria	- INCD of CDAD (primary) -Or CDI, adverse events or AAD (all secondary	- CDAD % in PB vs control: 1.5% vs 4.0%; RR 0.40 (0.30-0.52); ARR 2.5%; NNTB = 42 - A/E % PB vs control 14% vs 17%; RR 0.83 (0.71 to 0.97)	S: Large SRMA with diverse population; utilized Cochrane model. L: Heterogeneity of trials	-Moderate evidence PB ↓ CDAD risk -Benefit ↑ if HBR - PB ↓ A/E - No SS difference age, INPT/ OUTPT, PB species	High
Lau & Chamberlain (2016). Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Intl Jnl Gnl Med, 9	I	- Assess the impact of PBs on the INCD of CDAD in both INPT and OUTPT	- No specific framework or model	-SRMA: Literature search of published RCTs assessing the use of PB for prevention of CDAD in patients receiving Abx, across major DBs and Google Scholar from inception of DB to 10/2015	- 26 RCTs, 7,957 Pts -Children and adults (7,069 adults) - INCL: Any PB, any Abx, INPT or OUTPT - EXCL: PB for existing CDAD treatment	- IV: PB use - DV: INCD of CDAD - Intervention: PB use with Abx	-Fixed effects model with meta-analysis to calculate RR and 95% CI -Publication bias via funnel plot and Egger's and Begg's - Subgroup analyses for type of PB, age, INPT/OUTPT	- INCD of CDAD	-CDAD % in PB vs control: 1.5% vs. 3.8%; RR 0.395 (0.294–0.531); ARR: 2.3%.; NNTB = 43	S: Large, well designed SRMA; Diverse populations L: Did not include A/E analysis	- PBs ↓ CDAD risk - Benefit ↑ for INPT vs OUPT -No SS differences age, type/dose of PB	High

Author, Year, Title, Journal	LOE	Aim/Purpose	Theoretical framework /conceptual model	Design/Methods/ Instruments	Sample and Setting Information	Major Variables/ Interventions/ Definitions	Data Analysis	Outcome measures	Effect size/ Odd Ratio/ Risk Ratio	Strengths/ Limitations/Bias	Relevant findings	Qual
Johnston et al. (2018) Microbial Preparations (Probiotics) for the Prevention of Clostridium difficile Infection in Adults and Children: An Individual Patient Data Meta-analysis of 6,851 Participants. Infection Cntl & hosp epi, 39(7)	I	- Determine whether probiotic prophylaxis reduce the odds of CDI in adults and children taking Abx	- No specific framework or model	- SRMA: Literature search for RCTs investigating PB with Abx for prevention of CDI - IPD meta-analysis of RCTs, adjusting for risk factors	-18 RCTs, 6,851 Pts (6,801 adults) - INCL: Any PB, any Abx, INPT or OUTPT - EXCL: PB for CDAD treatment, Studies that did not provide IPD	- IV: PB use - DVs: INCD of CDI (primary), INCD A/E (secondary) - Intervention: PB use with Abx	- Publication bias via funnel plot - Pooled IPD across trials analyzed using linear mixed model - Adjusted model analysis including age, INPT / OUTPT, high risk Abx for studies providing data - Priori subgroup analyses: baseline CDI risk, SPB/MPB, multi Abx use, and PB dose - Quality of evidence using GRADE criteria	-INCD of CDI (primary) - Or INCD A/E (secondary)	- CDAD % in PB vs control: 1.1% vs 2.5%; OR 0.37 (0.25–0.55); ARR: 1.4%. NNTB = 71 -Adj model: OR 0.35 (0.23-0.55) - MPB more beneficial than SPB (OR 0.33 for MPB vs 0.41 for SPB)	S: IPD analysis L: Some missing outcome data, but all analyses robust to sensitivity analysis for missingness	- PB ↓ CDI risk - Benefit ↑ if HBR (≥5%) and/or multi Abx use -MPB ↑ benefit vs SPB - No SS difference in adult/pediatric, INPT/ OUTPT, PB dose, high-risk Abx, or A/E	High
Ouwehand et al. (2014). Probiotics reduce symptoms of antibiotic use in a hospital setting: A randomized dose response study. Vaccine, 32(4)	II	- Study effect of a specific combination of PB strains on the INCD of CDI, AAD and associated A/E at two strengths compared to placebo	- Based on prior research showing reduction in CDI from use of PBs	- Triple-blind, RCT, dose-ranging study with a 1:1:1 allocation ratio among three parallel study groups - Subjects equally stratified by gender, age and duration of Abx treatment	- Adults 30-70 yr, Hosp in China - High dose PB (168), low-dose (168), placebo (167) - INCL: Abx use - EXCL: current diarrhea, existing PB use, immunosuppressed	- IV: dose of PB high, low, none - DVs: INCD of AAD, INCD of CDAD, A/E Intervention: PB or placebo for 10–21 days, based on length of Abx use	- ANOVA for compliance - INCD of AAD and CDI by group, number of days on Abx, age, and gender - Chi-square test or Fisher's exact test - Multivariate analysis of AAD and CDAD INCD - Likelihood ratio, Cochran's test of linear trend for dose-response	- INCD of AAD. -INCD of CDAD -INCD of A/E	- CDAD % same in both PB groups vs control: 1.8% vs 4.8%; OR 0.29 (0.07–1.25); NNT with high dose product was 33.6. -A/E 4.2% PB groups vs 7.2%	- S: Strong design, methods, statistical analysis L: INPT only, specific PBs	- Specific PB strain ↓ CDAD -Dose level of tested PBs did not affect CDAD risk - A/E were ↓ in both PB doses than placebo	High
Allen et al. (2013). A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and Clostridium difficile diarrhea in older people admitted to hospital. Health Tech Assm,17(57)	II	- Determine if the utilization of a high-dose, multi-strain PB in older INPTs is clinically and cost-effective in the prevention of AAD and CDAD	- Based on prior research showing reduction in CDAD from use of PBs	-RCT: Multicenter, randomized, double-blind, placebo-controlled, parallel-arm trial with 1:1 allocation among 2 groups	- Adults ≥ 65, from multiple INPT wards in five Hosps in UK. - PB (1493), Placebo (1488) -INCL: Exposed to one or more oral or parenteral Abx(s); EXCL: Pre-existing diarrheal disorders, immunocompromised	-IVs: PB vs. placebo -DVs: INCD of AAD (within 8 weeks) and CDD (within 12 weeks) -Intervention: 21 days of two strains of lactobacilli and two strains of bifidobacteria	- Chi-squared test or Fisher's exact test for outcome proportion - t-test or Mann–Whitney method for continuous - QOL by change in survey from baseline to 8 weeks - Cost Effectiveness Analysis by participant	- INCD of CDD within 12 weeks, INCD AAD within 8 weeks -Secondary: multiple A/E, QOL, cost-effective	- CDAD % in PB vs placebo: 0.8% vs 1.2% -RR 0.71(0.34 to 1.47)	S: Size, rigor, detailed reporting L: Many potential confounding variables; Possibly underpowered due to low % INCD	-PBs possibly effective in preventing CDAD, but 95% CI includes no effect - Determined to not be cost effective - No differences in A/E, QOL	Med

Author, Year, Title, Journal	LOE	Aim/Purpose	Theoretical framework /conceptual model	Design/Methods/ Instruments	Sample and Setting Information	Major Variables/ Interventions/ Definitions	Data Analysis	Outcome measures	Effect size/ Odd Ratio/ Risk Ratio	Strengths/ Limitations/Bias	Relevant findings	Qual
Selinger et al. (2013). Probiotic VSL #3 Prevents Antibiotic-Associated Diarrhea in a Double-Blind Randomized, Placebo-Controlled Clinical Trial. The Journal of Hosp Infection, 84(2).	II	- Determine if the use of a specific PB along with Abx reduces the rate of CDAD and AAD in average risk INPT	- Based on prior research showing reduction in AAD from use of PBs	-RCT: multicenter, randomized, double-blind, placebo-controlled trial with a 1:1 allocation ratio among 2 groups - Subjects were equally stratified by gender, age, and duration of Abx treatment	- Adults age 18+, INPT in U.K. - PB (117), Placebo (112) - INCL: INPT on Abx within 48 hrs - EXCL: Current diarrhea, in ICU, immunosuppressed, certain high-risk conditions, use of PBs 1 week prior to admission	- IV: PB vs Placebo -DV: INCD of CDAD or AAD, A/E, LOS, mortality - Intervention: admin of PB or placebo, sachet BID for length of Abx course and 7 days thereafter	-Fisher's exact test and Student's t-test -Poor adherence (<80%) or major protocol breaches were excluded from analysis -ITT analysis on basis of last observation carried forward	- INCD of CDAD or AAD (Primaries) - LOS, A/E, Mortality (secondary)	- OR not possible - 0 cases CDAD in PB or control group -% AAD PB vs control, 0 vs 11	S: Rigor L: Only included average risk Pts; only one PB tested; possibly underpowered due to low % INCD	- No cases of CDAD in either PB or control group - No differences in A/E, LOS, mortality - Some improvement in AAD only - High risk Pts not included	Med/ Low
Maziade et al. (2015) A decade of experience in prevention of C diff Infection at a community hospital using the probiotics lactobacillus acidophilus CL1285, lactobacillus casei LBC80R, and lactobacillus rhamnosus CLR2, Clin Infect Diseases, 60(S2)	IV	- Determine if the addition of a specific MPB strain for all Pt on Abx reduced the incidence of CDI	- None specifically mentioned	- Q-E, prospective cohort study - PB initiative for all Abx Pt one Hosp vs comparison group of similar Hosp without PB initiative - All other CDI risk mgmt efforts (hand washing, etc) similar between intervention and comparison groups	- Intervention group: Pts in a 284 bed Hosp in Quebec, 44,835 inpatients over 10 years - Comparison group: Pts in an aggregate of 27 other Quebec Hosp of similar size and services over same time frame. Total number not provided	IV: MPB use -DV: INCD of CDI - episodes / 10K Pt days; Pt costs - Intervention: admin of PB for all Abx Pt in intervention Hosp	- Comparison of episodes of CDI per 10K Pt days between intervention Hosp and comparison Hosp group over 10 years - Analysis of financial impact on per Pt costs	-INCD of CDI per 10k Pt days - Costs per Pt	- N/A. Observed INCD of CDI with PB intervention 2.3/10K Pt days vs 8.3/10K Pt days in comparison group - $2,769 per Pt savings	S: Large population over 10 years L: Q-E cohort study; no comparison of likely potential confounding factors	- CDI rates at intervention Hosp were consistently and continuously lower compared with those at similar Hosps - PB use resulted in a mean per-Pt savings up to $2,769	Med

Notes: AAD, Antibiotic Associated Diarrhea; Abx, Antibiotics; A/E, Adverse Effects; BID, Twice a Day; CDI, Clostridium Difficle Infection; CDAD, Clostridium Difficile-Associated Diarrhea; DV Dependent Variable; EXCL, Exclusions; HBR, High Baseline Risk; Hosp, Hospital; INCD, Incidence; INCL, Inclusions; IPD, Individual Participant Data; IV, Independent Variable; INPT, Inpatient; L, Limitations; LOS, Length of Stay; MA, Meta-Analysis; MPB, Multi-species Probiotic; OUTPT, Outpatient; PB, Probiotics; PICO, Problem Intervention Comparator Outcome; Pt, Patient; Q-E, Quasi-Experimental; QOL, Quality of Life; RCT, Random Controlled Trial; S, Strengths; SPB, Single Species Probiotic; SRMA, Systematic Review and Meta-Analysis; SS, Statistically Significant.

Appendix B. Synthesis Table

	Design	Sample	PB Impact on CDI/CDAD
Studies			
Goldenberg et al. (2017)	SR MA	- N = 8,672; 7,036 adults, MC - All ages, adult subgroup analysis	↓
Lau et al. (2016)	SR MA	- N = 7,957; 7,069 adults, MC - All ages, adult subgroup analysis	↓
Johnston et al. (2018)	SR, IPD MA	- N = 6,851; 6,801 adults, MC - All ages, adult subgroup analysis	↓
Ouwehand et al. (2014)	RCT	- N = 503 - Adults 30-70, hospital in China	↓
Maziade et al. (2015)	Q-E prospective cohort study	- N = 44,835, ages not specified - Large Quebec hospital, 10 years	↓
Allen et al. (2013)	RCT	- N = 2,981 - Adults ≥ 65, 5 hospitals in UK	← →, ↓
Clifford et al. (2018)	SR Expert panel-based guideline	- Total not provided	← →
Selinger et al. (2013)	RCT	- N = 229 - Adults ≥ 18, large hospital in UK	← →

Notes: CDI, Clostridium Diff Infection; CDAD, Clostridium Difficile-Associated Diarrhea; IPD, Individual Patient Data; MA, Meta-analysis; MC, Multi-center; PB, Probiotic; Q-E, Quasi-experimental; RCT, Random Controlled Trial; SR, Systematic review;