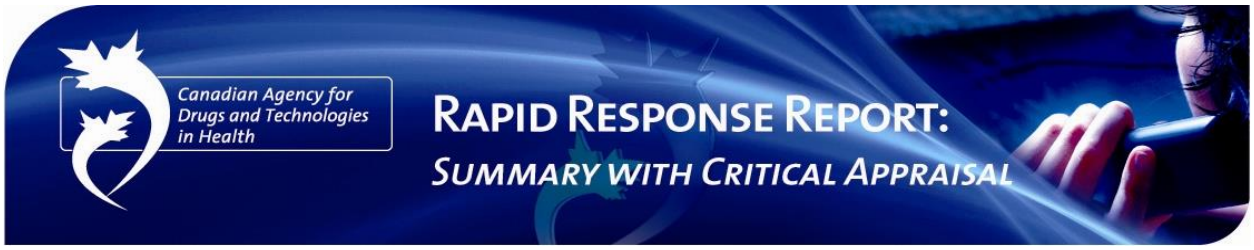

TITLE: Concurrent Probiotic and Antibiotic Use for In-Patients: A Review of the Clinical and Cost-Effectiveness

DATE: 09 November 2015

CONTEXT AND POLICY ISSUES

Antibiotics are some of the most frequently prescribed medications worldwide.[1] In addition to contributing to antibiotic resistance, antibiotic therapy may disturb the colonization resistance of gastrointestinal (GI) flora to pathogenic bacteria, resulting in a range of symptoms that include, most notably, diarrhea.[1] Antibiotic-associated diarrhea (AAD) occurs between 5% and 39% of patients who take antibiotics,[2,3] with higher percentages seen in hospitalized patients who may develop serious, or even fatal, cases of AAD from *Clostridium difficile* infection (CDI).[4-6] AAD is characterized by a change in the normal stool frequency, with at least three loose or watery stools daily for three days.[4] It develops within 12 weeks of exposure to antibiotics,[2] with early onset occurring within two to seven days.[4]

Probiotics are live organisms that are thought to improve the microbial balance of the host and counteract disturbances in the GI flora.[1] They, therefore, may protect the host from a microbial imbalance in the GI tract occurring after antibiotic therapy, reducing the risk of colonization and infection by pathogenic bacteria.[1,6]

Infection prevention groups such as the Society for Healthcare Epidemiology of America/ Infectious Diseases Society of America do not always recommend probiotic usage for adjunctive therapy with antibiotics.[6] However, Health Canada has made a claim that a specific probiotic formulation, namely, Bio-K+, composed of three *Lactobacillus* strains, helps to reduce the incidence of *Clostridium difficile*-associated diarrhea (CDAD) in hospitalized patients.[6]

The purpose of this report is to determine whether there is clinical and cost-effectiveness evidence to support the practice of using probiotics in conjunction with antibiotics as prophylactic treatment to maintain normal bacterial flora in the GI tract of hospitalized patients on antibiotics.

RESEARCH QUESTIONS

1. What is the clinical effectiveness, including safety, of concurrent probiotic and antibiotic use for in-patients?

2. What is the cost-effectiveness of concurrent probiotic and antibiotic use for in-patients?

KEY FINDINGS

Two systematic reviews (SRs)/meta-analyses (MAs) and one randomized controlled trial (RCT) on adult in-patients reported protective effects of probiotics on the incidences of antibiotic-associated diarrhea (AAD), *Clostridium difficile*-associated diarrhea (CDAD), *Clostridium difficile* infection (CDI), and *Clostridium difficile* disease (CDD) as well as the incidence of adverse events. One SR/MA on adult in-patients reported that, although there is suggestive evidence that probiotics may be effective in preventing CDAD, it was not strong enough to be the basis for a general policy change. One RCT on adult in-patients, aged 65 years or older, found no protective effects of probiotics on the incidences of AAD, CDAD, and adverse events as well as on hospital length of stay (LOS). Evidence from one economic evaluation that was conducted alongside the aforementioned RCT on adult in-patients, aged 65 years or older, suggested that the intervention was unlikely to be cost-effective.

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, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, published between January 1, 2010 and October 15, 2015.

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	Hospitalized patients requiring antibiotics
Intervention	Probiotics in combination with antibiotics
Comparator	Antibiotics alone
Outcomes	Q1: clinical effectiveness, including safety (e.g., reduced cases of AAD, benefits, harms) Q2: cost-effectiveness
Study Designs	Health technology assessments, SRs, MAs, RCTs, non-randomized studies, and economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2010. Primary studies that were reviewed in the included SRs or MAs were excluded.

Critical Appraisal of Individual Studies

The included SRs/MAs were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[7] The included RCTs were critically appraised using the Downs and Black instrument.[8] The included economic evaluation was critically appraised using the Drummond checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 226 citations were identified in the literature search. Following screening of titles and abstracts, 203 citations were excluded, and 23 potentially relevant reports from the electronic search were retrieved for full-text review. Eleven potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 28 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

The six publications comprised three SRs/MAs,[10-12] two RCTs,[2,3,5], and one economic evaluation.[2] One of the RCTs had been published twice, once as a health technology assessment report on both the clinical and cost-effectiveness[2] and once as a journal article on the clinical effectiveness.[5] The findings on the clinical effectiveness between the two reports[2,5] were identical.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

Study Design

All three SRs conducted MAs on all or subsets of the included studies, using random effects models,[10] random- and fixed-effects models,[11] and Bayesian hierarchical models[12] on pooled data. Two SRs/MAs conducted subgroup analyses on different study durations,[10] probiotic strains,[10] study qualities,[10,12] and sources of funding.[12] One SR/MA was published in 2013,[10] and two SRs/MAs were published in 2011.[11,12] All three SRs/MAs limited the study design to RCTs.[10-12]

One triple-blind RCT was conducted at a single site and published in 2014.[3] One double-blind RCT was conducted at five sites and published in 2013.[2,5]

One economic evaluation conducted a cost-utility analysis, using costs per quality-adjusted life-years (QALYs) from the health care perspective.[2]

Country of Origin

Two SRs/MAs were conducted in Canada.[10,12] One SR/MA was conducted in the United States (US).[11]

One RCT was conducted in China.[3] One RCT[2,5] and the economic evaluation on that RCT[2] were conducted in the United Kingdom (UK).

Patient Population

Three SRs/MAs included adult in-patients receiving antibiotics for various reasons.[10-12]

One RCT included adult in-patients, needing antibiotics for various reasons.[3] One RCT[2,5] and the economic evaluation on that RCT[2] included older adult in-patients, aged 65 years or older, either exposed to antibiotics in the preceding seven days or about to start antibiotic therapy.

Interventions and Comparators

The SRs/MAs compared probiotics against placebo or no treatment,[10] probiotics against placebo,[12] or probiotics against no treatment,[11] with concurrent antibiotic therapy. All three SRs/MAs included studies in which the timing of the administration of probiotics and antibiotics was not completely aligned.[10-12] For example, all three SRs/MAs[10-12] included an RCT[13] in which probiotics were administered within 36 hours of the administration of antibiotics to five days after the completion of antibiotic therapy. One SR/MA conducted subgroup analyses on different probiotic strains.[10]

The RCTs compared probiotics against placebo, with concurrent antibiotic therapy.[2,3,5] Probiotics included multiple *Lactobacillus* and *Bifidobacterium* strains.[2,3,5] The timing of the administration of probiotics and antibiotics was not completely aligned. Rather, the RCTs had overlapping administration, with longer antibiotic therapy[2,5] or longer probiotic therapy.[3] One RCT included multiple doses of probiotics.[3]

The economic evaluation compared probiotics against placebo in patients receiving antibiotics.[2]

Outcomes

The SRs/MAs reported on the incidences of AAD,[10] CDAD,[12] CDI,[10] and CDD[11] as outcomes. Follow-up durations of the included studies were not always reported and variable, from four weeks[12] to 84 days[10] following the treatment completion, where reported.

The RCTs reported on the incidences of AAD,[2,3,5] CDAD,[2,3,5] and adverse events[3] as well as the duration of diarrhea,[3] number of stools per day,[3] quality of life,[2,5] and hospital LOS[2,5] as outcomes. Follow-up durations of the RCTs ranged from one month[3] to 12 weeks,[2,5] following the treatment start[2,5] or completion.[3]

Appendix 2 provides the details of the characteristics of the included SRs/MAs, RCTs, and economic evaluation in Tables A1, A2, and A3, respectively.

Summary of Critical Appraisal

The SRs/MAs were of variable quality. It was not clear whether the SRs/MAs used an "a priori" design.[10-12] Some of the SRs/MAs did not describe their search strategy[11] or search results,[11,12] did not include grey literature in their search,[10] did not provide a list of excluded studies,[10,12] or did not assess the scientific quality of the included studies or the likelihood of publication bias.[11]

The RCTs were also of variable quality. Both RCTs described the aim of their studies, interventions, and main outcomes and findings.[2,3,5] One RCT provided detailed characteristics of the study subjects as well as those lost to follow-up, described the distribution of principal confounders, presented estimates of random variability and actual probability values, and conducted power calculations.[2,5] On the other hand, the other RCT provided limited descriptions of the study subjects lost to follow-up[3] and did not describe blinding.[3] Neither of the RCTs described whether the subjects asked to participate or included in the study were representative of the entire population of interest.[2,3,5]

The economic evaluation presented an explicit question and comprehensive description of the interventions, provided a cost-utility analysis using cost and benefit data from an RCT, and conducted univariate and probabilistic sensitivity analyses.[2] However, costs that were not collected from the RCT were sourced from outside the trial setting (e.g., based on discussions with laboratory staff or health care professionals or from the literature), with assumptions.[2]

Appendix 3 provides the details of the critical appraisal of the included SRs/MAs, RCTs, and economic evaluation in Tables A4, A5, and A6, respectively.

Summary of Findings

What is the clinical effectiveness, including safety, of concurrent probiotic and antibiotic use for in-patients?

The findings of the three SRs/MAs and two RCTs were mixed.

Incidence of AAD
For the incidence of AAD, two SRs/MAs[10,11] and one RCT[3] found protective effects of probiotics compared with placebo or no other treatment,[10] probiotics compared with no other treatment,[11] or probiotics compared with placebo.[3] One of the SRs/MAs[10] reported that the protective effects of probiotics were greater with higher-quality studies, shorter study durations, and certain probiotic strains, namely, *Lactobacillus* strains. The RCT[3] reported that the protective effects of probiotics were greater with higher doses of probiotics. However, one RCT on older patients[2,5] found no significant effects of probiotics compared with placebo.

Incidence of CDAD
For the incidence of CDAD, one RCT[3] found protective effects of probiotics compared with placebo. The RCT[3] reported that the protective effects of probiotics were greater with higher doses of probiotics. However, one RCT on older patients[2,5] found no significant effects of probiotics compared with placebo. One SR/MA[12] found protective effects of probiotics compared with placebo, which were greater with higher-quality studies and support from probiotic companies. The review, however, concluded that the evidence was not strong enough to be the basis for a general policy change.

Incidence of CDI
For the incidence of CDI, one SR/MA[10] found protective effects of probiotics compared with placebo or no other treatment.

Incidence of CDD
For the incidence of CDD, one SR/MA[11] found protective effects of probiotics compared with no other treatment.

Incidence of Adverse Events
For the incidence of adverse events, one RCT[3] found protective effects of probiotics compared with placebo. However, one RCT on older patients[2,5] found no significant effects of probiotics compared with placebo.

Number of Liquid Stools and Duration of Diarrhea
One RCT[3] reported that the number of liquid stools per day and the average duration of diarrhea decreased with higher doses of probiotics compared with placebo.

Quality of Life
One RCT on older patients[2,5] reported that the quality of life measures were similar between the probiotics and placebo arms of the trial.

Hospital LOS
For hospital LOS, one RCT on older patients[2,5] found no significant effects of probiotics compared with placebo.

What is the cost-effectiveness of concurrent probiotic and antibiotic use for in-patients?

The economic evaluation[2] was conducted alongside the aforementioned RCT on patients, aged 65 years or older.[2,5] The 2013 cost-utility analysis conducted in the UK from the perspective of the National Health Service (NHS) reported that the incremental cost-effectiveness ratio (ICER) associated with probiotic use compared with placebo at one year was estimated at £22,701 per QALY gained (i.e., $31,057 per QALY gained in 2013 Canadian dollars) when total health care costs were considered.[2] However, it was noted that the costs and benefits between the probiotic and placebo arms of the trial were similar.[2] Sensitivity analyses did not show any significant effect on difference in total health care costs between the two trial arms and the overall conclusion of the cost-effectiveness assessment.

Appendix 4 provides the details of the findings of the included SRs/MAs, RCTs, and economic evaluation in Tables A7, A8, and A9, respectively.

Limitations

The timing of the administration of probiotics and antibiotics was not completely aligned in the RCTs[2,3,5] and some of the studies reviewed by the SRs/MAs.[10-12] Therefore, the included studies were not completely aligned with the intervention and comparator of interest for this report.

The results of the RCTs conducted in China[3] may not be as generalizable to Canada. As well, the results of the RCTs[2,3,5] may not be generalizable to other, seriously debilitated and immunosuppressed individuals.[12]

One economic evaluation was identified, which was conducted on older patients in the UK.[2] Therefore, the evidence on cost-effectiveness was limited, and the results may not be generalizable to younger patients or patients in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Three SRs/MAs and two RCTs reported mixed findings on the clinical effectiveness of the administration of probiotics in conjunction with antibiotic therapy.

Two SRs/MAs[10,11] and one RCT[3] on adult in-patients reported protective effects of probiotics on the incidences of AAD, CDAD, CDI, and CDD as well as the incidence of adverse events. The protective effects of probiotics may be greater with shorter study durations,[10] with certain probiotic strains,[10] namely, Lactobacillus strains, and higher doses,[3] in higher-quality studies,[10,12] and with support from probiotic companies.[12] However, one SR/MA on adult in-patients reported that, although there is suggestive evidence that probiotics may be effective in preventing CDAD, that evidence was not strong enough to be the basis for a general policy change.[12] One RCT on adult in-patients, aged 65 years or older, found no protective effects of probiotics on the incidences of AAD, CDAD, and adverse events as well as on hospital LOS.[2,5]

Evidence from one economic evaluation, published in the UK and conducted alongside the aforementioned RCT on adult in-patients, aged 65 years or older, suggested that the intervention was unlikely to be cost-effective.[2]

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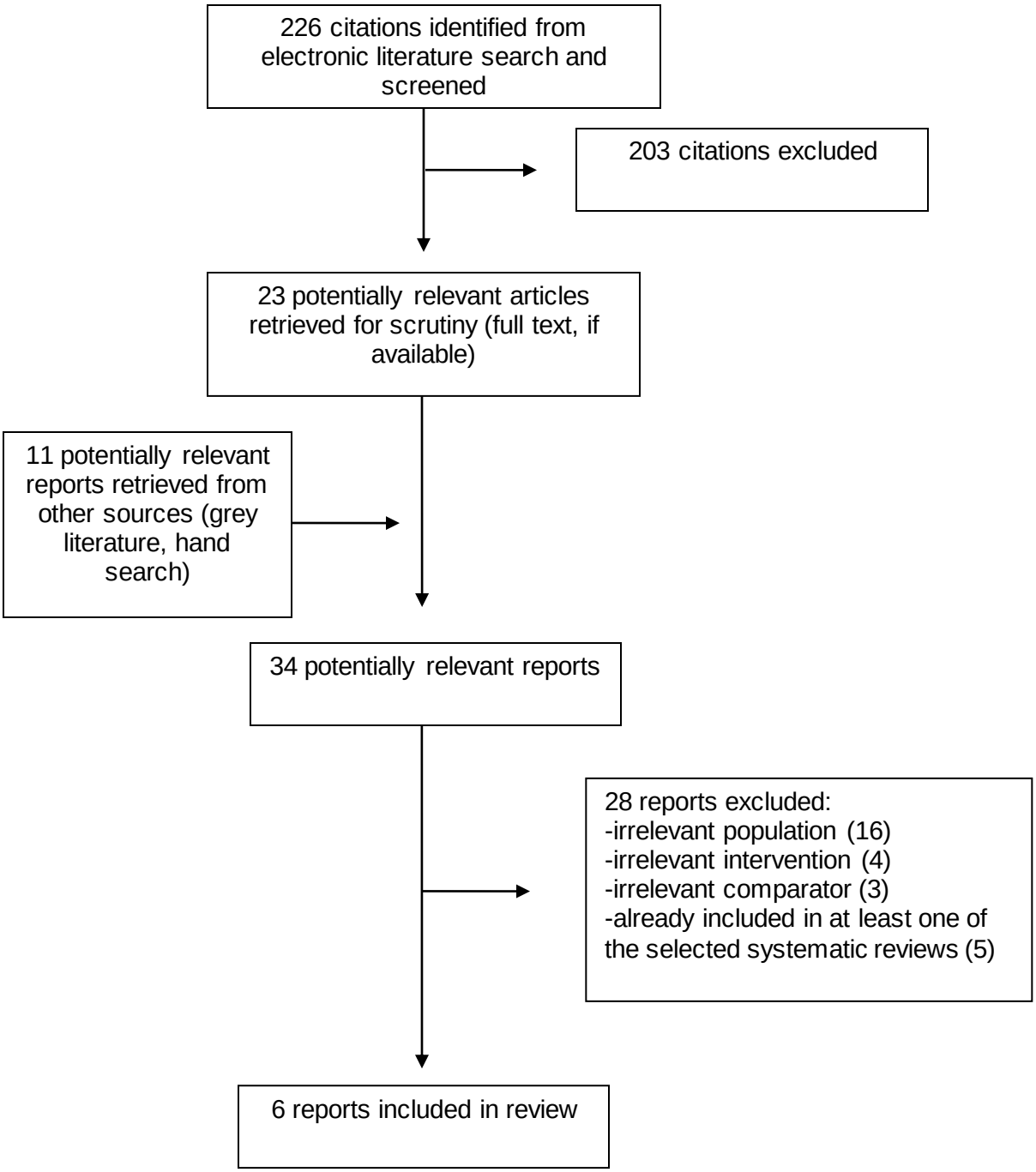
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Pattani[10] 2013 Canada	SR and MA of 16 RCTs in English, published between 1979 and 2012. Data were pooled and analyzed in random-effects models.	2,875 adult in-patients,* receiving antibiotics *Patients who had been admitted to medical or surgical wards or to wards devoted to acute care of elderly patients	Probiotics, with concurrent antibiotic therapy	Placebo or no other treatment, with concurrent antibiotic therapy	Outcomes: Incidence of AAD (15/16 studies), incidence of CDI (12/16 studies) Length of follow-up: Variable (duration of treatment plus up to 84 days, where reported)
Avadhani[11] 2011 US	SR and MA of 8 RCTs in English, published between 1995 and 2008. Data were pooled and analyzed in random-effects models (for AAD) or fixed-effects models (for CDD).	1,246 adult in-patients, aged 18-90 years and receiving antibiotics	Probiotics, with concurrent antibiotic therapy	Antibiotic therapy alone	Outcomes: Incidence of AAD (8/8 studies), incidence of CDD (4/8 studies) Length of follow-up: Not reported
Sinclair[12] 2011 Canada	SR and MA of 14 RCTs in English or French, published between 1994 and 2010. Data were pooled and analyzed in Bayesian hierarchical models.	2,122 adult in-patients, receiving antibiotics	*Lactobacillus*-based probiotics, with concurrent antibiotic therapy	Placebo, with concurrent antibiotic therapy	Outcomes: Incidence of CDAD (7/14 studies), incidence of adverse events (10/14 studies) Length of follow-up: Variable (duration of treatment plus up to 4 weeks, where reported)

AAD = antibiotic-associated diarrhea; CDAD = *Clostridium difficile*-associated diarrhea; CDD = *Clostridium difficile*-associated disease; CDI = *Clostridium difficile*-associated infection; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review; US = United States

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Ouwehand[3] 2014 China	Single-site triple-blind RCT, using computer-generated randomization lists	503 adult in-patients, aged 30-70 years and requiring antibiotic therapy for various diseases	High-dose and low-dose probiotics* for 10 to 21 days, with concurrent antibiotic therapy** for 3 to 14 days (n=168 for each dose) *HOWARU® Restore containing *Lactobacillus* and *Bifidobacterium* species (high-dose: 1.70 x 10^{10} CFU; low-dose: 4.17 x 10^{9} CFU) **penicillin, cephalosporin, and/or clindamycin	Placebo for 10 to 21 days, with concurrent antibiotic therapy*** for 3 to 14 days (n=167) ***penicillin, cephalosporin, and/or clindamycin	Primary outcomes: Incidence of AAD Secondary outcomes: Incidence of CDAD, duration of diarrhea, number of stools per day, incidence of adverse events Length of follow-up: 4 weeks since completion of antibiotic therapy
Allen[2,5] 2013 UK	Multi-site, double-blind RCT, using a computer-generated random allocation sequence	2,981 adult in-patients, aged ≥ 65 years and exposed to antibiotics in the preceding 7 days or about to start antibiotic therapy	Probiotics* for 21 days, with concurrent antibiotic therapy** for up to 9 weeks (n=1,493) *capsules containing two strains of lactobacilli and two strains of bifidobacteria (a total of 6 x 10^{10} organisms per day) **variable, including penicillins, cephalosporins, and other antibiotics	Placebo*** for 21 days, with concurrent antibiotic therapy** for up to 9 weeks (n=1,488) ***capsules containing inert maltodextrin powder ****variable, including penicillins, cephalosporins, and other antibiotics	Primary outcomes: Incidence of AAD, incidence of CDAD Secondary outcomes: severity and duration of AAD or CDAD, hospital LOS, quality of life, incidence of adverse events Length of follow-up: Up to 12 weeks since recruitment

AAD = antibiotic-associated diarrhea; CDAD = *Clostridium difficile*-associated diarrhea; CFU = colony-forming unit; LOS = length of stay; RCT = randomized controlled trial; UK = United Kingdom

Table A3: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Allen[2] 2013 UK	Cost-utility analysis (i.e., cost per QALY), from UK NHS (i.e., health care) perspective	Probiotics* versus placebo** for 21 days, with concurrent antibiotic therapy*** for up to 9 weeks *capsules containing 2 strains of lactobacilli and 2 strains of bifidobacteria (a total of 6×10^{10} organisms per day) **capsules containing inert maltodextrin powder ***variable, including penicillins, cephalosporins, and other antibiotics	2,981 adult in-patients, aged $\geq$ 65 years and exposed to antibiotics in the preceding 7 days or about to start antibiotic therapy	1 year	If the hospital discharge date was not known, the end of follow-up was assumed to be the discharge date. Missing data on antibiotic dose were replaced by the most common value. For missing data on antibiotic daily intake or duration of intake, a full course was assumed.

NHS = National Health Service; QALY = quality-adjusted life-year; UK = United Kingdom

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Included Systematic Reviews and Meta-Analyses Assessed Using AMSTAR[7] link to AMSTAR checklist

Strengths	Limitations
Pattani, 2013[10]	
• There was duplicate study selection and data extraction. • A comprehensive literature search was performed for published studies. A detailed search strategy and a flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, and the included studies were rated on their quality (i.e., good, fair, or poor). • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the findings of studies were appropriate. • The likelihood of publication bias was assessed to be moderate. • No conflict of interest was declared.	• It is unclear whether an "a priori" design was used. • Grey literature was not included. • A list of the excluded studies was not provided.
Avadhani, 2011[11]	
• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The status of publication (i.e., grey literature) was used as an inclusion criterion. It was noted that no unpublished studies were located. • A list of the included and excluded studies was provided. • The characteristics of the included studies were provided. • The methods used to combine the findings of studies were appropriate. • No conflict of interest was declared.	• It is unclear whether an "a priori" design was used. • No detailed search strategy was provided. • The scientific quality of the included studies was assessed and documented, and the included studies were not rated on their quality. • The scientific quality of the included studies was not used in formulating conclusions. • The likelihood of publication bias was not assessed.
Sinclair, 2011[12]	
• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. A detailed search strategy and was provided. • The status of publication (i.e., grey literature) was used as an inclusion criterion.	• It is unclear whether an "a priori" design was used. • No flow diagram for the search results was provided. • A list of the excluded studies was not provided.

Table A4: Strengths and Limitations of Included Systematic Reviews and Meta-Analyses Assessed Using AMSTAR[7] link to AMSTAR checklist	
Strengths	**Limitations**
• A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, and the included studies were rated on their quality, based on their risk of bias identified by the Cochrane Collaboration. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the findings of studies were appropriate. • The likelihood of publication bias was assessed to be low.	• No statement was made on any conflict of interest.

GRADE = Grading of Recommendations Assessment, Development and Evaluation

Table A5: Strengths and Limitations of Included Clinical Studies Assessed Using Downs and Black[8] link to Downs and Black	
Strengths	**Limitations**
Ouwehand, 2014[3]	
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The interventions were described. • The distributions of principal confounders in each intervention group of study subjects were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • Actual probability values were reported. *External validity* • There was no explicit reason to doubt that the trial design was representative of the care setting. *Bias* • The study was triple-blind. • The statistical tests used to assess the main outcomes were appropriate. • Compliance was reported to be excellent (i.e., >99% in all intervention groups). • The main outcome measures appeared accurate (i.e., valid and reliable).	*Reporting* • The characteristics of study subjects lost to follow-up were not described. *External validity* • It was unclear whether the subjects asked to participate or included in the study were representative of the entire population of interest.

Table A5: Strengths and Limitations of Included Clinical Studies Assessed Using Downs and Black[8] link to Downs and Black	
Strengths	**Limitations**
Confounding • The study subjects in different intervention groups were recruited from the same population over the same period of time. • The study subjects were randomized to intervention groups. • There was adequate adjustment for confounding in the analysis for the main findings. • Losses of study subjects to follow-up were taken into account. *Power* • Sample size calculations were provided, and the study appeared to have sufficient power to detect a clinically important effect.	
Allen, 2013[2,5]	
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The interventions were described. • The distributions of principal confounders in each intervention group of study subjects were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • The characteristics of study subjects lost to follow-up were described. • Actual probability values were reported. *External validity* • The subjects asked to participate in the study were representative of the entire population of interest. • The trial design was representative of the care setting. *Bias* • An attempt was made to blind the study subjects to the intervention they received. • An attempt was made to blind the staff measuring the main outcomes. • Results of any *post hoc* analyses were described. • The statistical tests used to assess the main outcomes were appropriate.	*External validity* • It is unclear whether the subjects included in the study were representative of the entire population of interest.

Table A5: Strengths and Limitations of Included Clinical Studies Assessed Using Downs and Black[8] link to Downs and Black	
Strengths	**Limitations**
• Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). *Confounding* • The study subjects in different intervention groups were recruited from the same population over the same period of time. • The study subjects were randomized to intervention groups. • Intervention assignment was concealed from both study subjects and staff until recruitment was complete and irrevocable. • There was adequate adjustment for confounding in the analysis for the main findings. • Losses of study subjects to follow-up were taken into account. *Power* • The study had sufficient power to detect a clinically important effect.	

Table A6: Strengths and Limitations of Economic Studies using Drummond[9] link to Drummond Checklist	
Strengths	**Limitations**
Allen, 2013[2]	
• An explicit question was posed in an answerable form, with both costs and effects, a comparison of alternatives, and a perspective. • A comprehensive description of the competing alternatives was given. • The costs and consequences were measured accurately in appropriate physical units and valued credibly. • Costs were collected from an RCT, where possible. • Given the time horizon of 1 year, no adjustment for differential timing was necessary. • An incremental analysis of costs and consequences of alternatives was performed. • Univariate and probabilistic sensitivity analyses were conducted.	• Costs that were not collected from an RCT were sourced from outside the trial setting (e.g., based on discussions with laboratory staff or health care professionals or from the literature), with assumptions. • The total cost, number of diarrhea cases, and patient quality of life between the two trial arms were similar, limiting the relevance of the ICERs.

ICER = incremental cost-effectiveness ratio; RCT = randomized controlled trial

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusions
Pattani, 2013[10]	
• "Pooled analyses revealed significant reductions in the risks of AAD (RR 0.61; 95% CI 0.47 to 0.79) and CDI (RR 0.37; 95% CI 0.22 to 0.61) among patients randomly assigned to co-administration of probiotics." (Page 1) • "For CDI, there was a substantially lower number of patients with available end points. The event rates were 18 (3.1%) of 572 patients in the intervention arm and 55 (10.4%) of 527 patients in the placebo arm (RR 0.37; 95% CI 0.22 to 0.61)." (Page 6)	• "Probiotics used concurrently with antibiotics reduce the risk of AAD and CDI." (Page 1)
Avadhani, 2011[11]	
• There was a protective effect of probiotics for AAD (RR 0.56; 95% CI 0.44 to 0.71) and for CDD (RR 0.29; 95% CI 0.18 to 0.46).	• "Probiotics are efficacious in preventing AAD and CDD among hospitalized adults." (Page 273)
Sinclair, 2011[12]	
• A Bayesian meta-analysis of *Lactobacillus*-based probiotics for the prevention of CDAD associated with the use of antibiotics showed a reduction in risk of CDAD (RR 0.17; 95% CI 0.04 to 0.42). • "The number of cases of CDAD across studies was relatively small, the studies varied greatly in background incidence of CDAD, and only two were considered at low risk of bias." (Page v) • "Probiotic therapy appears to be without risk of significant side-effects. However, there have been some case reports of serious side effects in seriously ill patients." (Page viii)	• "Although there is suggestive evidence that probiotics based on *Lactobacillus* may be effective in the prevention of CDAD, the evidence is not strong enough to be the basis for a general policy change." (Page v) • Accordingly, routine use of probiotic *Lactobacillus* cannot be presently recommended in the prevention of CDAD in hospitalized patients receiving antibiotics.

AAD = antibiotic-associated diarrhea; CDAD = *Clostridium difficile*-associated diarrhea; CDD = *Clostridium difficile*-associated disease; CDI = *Clostridium difficile* infection; CI = confidence interval; RR = risk ratio

Table A8: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Ouwehand, 2014[3]	
• "A significant dose-response effect on AAD was observed with incidences of 12.5, 19.6, and 24.6% with high-dose, low-dose, and placebo, respectively (p = 0.02)." (Page 458) • "CDAD was the same in both probiotic groups (1.8%) but different from the placebo group (4.8%; p = 0.04)." (Page 458)	• "The tested four strain probiotic combination appears to lower the risk of AAD, CDAD, and gastrointestinal symptoms in a dose-dependent manner in adult in-patients." (Page 458)

Table A8: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
• "Incidences of fever, abdominal pain, and bloating were lower with increasing probiotic dose." (Page 458) • "The number of daily liquid stools and average duration of diarrhea decreased with higher probiotic dosage." (Page 458) • "The adverse event rate in the placebo, high-dose, and low-dose group was 7.2%, 4.2%, and 4.2%, respectively." (Page 462) Adverse events reported included: allergy to seafood (2), arrhythmia (2), fever (10), headache (2), left upper arm fracture (1), runny nose (4), vomiting (4), and death (1), none of which were deemed related to the study product.	
Allen, 2013[2,5]	
• AAD, including CDAD, occurred with a similar frequency in the probiotic arm and placebo arm (RR 1.04; 95% CI 0.84 to 1.28). • CDAD occurred with a similar frequency in the probiotic arm and placebo arm (RR 0.71; 95% CI 0.34 to 1.47). • The frequency and duration of gastrointestinal symptoms during AAD were similar between the two study arms, except for the frequency of flatus which was higher in the probiotics arm (RR 1.26; 95% CI 1.00 to 1.59). • The quality of life measures were similar in the two arms. • The duration of hospital stay was similar between the two arms (median 4 days; range 1 to 11 days). • The frequency of serious adverse events and the proportion of the study participants experiencing at least one serious adverse events were similar between the two arms.	• The administration of probiotics seems unlikely to benefit older patients exposed to antibiotics.

AAD = antibiotic-associated diarrhea; CDAD = *Clostridium difficile*-associated diarrhea; CI = confidence interval; RR = risk ratio

Table A9: Summary of Findings of Included Cost Studies	
Main Study Findings	**Author's Conclusions**
Allen, 2013[2]	
• "The ICER associated with probiotic use at 1 year was estimated at £22,701 per QALY gained when total health-care costs were considered." (Page 44) • "One-way sensitivity analyses did not show any significant effect on difference in total health care costs between the trial arms and the overall conclusion of the cost-effectiveness assessment." (Page 44)	• "The high-dose, multi-strain preparation of lactobacilli and bifidobacteria evaluated in our study is unlikely to benefit unselected older in-patients exposed to antibiotics." (Page xvii)

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years

APPENDIX 5: Additional References of Potential Interest

Clinical Effectiveness of Concurrent Probiotic and Antibiotic Use in Both In-Patients and Out-Patients

Goldenberg J, Ma S, Saxton J, Martzen M, Vandvik P, Thorlund K, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. Cochrane Database Syst Rev [Internet]. 2013 [cited 2015 Oct 20];(5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006095.pub3/epdf

Johnson S, Maziade PJ, McFarland LV, Trick W, Donskey C, Currie B, et al. Is primary prevention of Clostridium difficile infection possible with specific probiotics? Int J Infect Dis. 2012 Nov;16(11):e786-e792.

Clinical Effectiveness of Concurrent Probiotic and Antibiotic Use in Patients Treated in Hospitals (i.e., not necessarily in-patients)

Bekar O, Yilmaz Y, Gulten M. Kefir improves the efficacy and tolerability of triple therapy in eradicating Helicobacter pylori. J Med Food. 2011 Apr;14(4):344-7.

Ma F, Zhou C, Wang J, Liu T, Liu J. Probiotics in the treatment of peptic ulcer infected by helicobacter pylory and its safety. Pak J Pharm Sci. 2015 May;28(3 Suppl):1087-90.

Zojaji H, Ghobakhlou M, Rajabalinia H, Ataei E, Jahani SS, Moghimi-Dehkordi B, et al. The efficacy and safety of adding the probiotic Saccharomyces boulardiito standard triple therapy for eradication of H.pylori: a randomized controlled trial. Gastroenterol Hepatol Bed Bench. 2013;6(Suppl 1):S99-S104.