

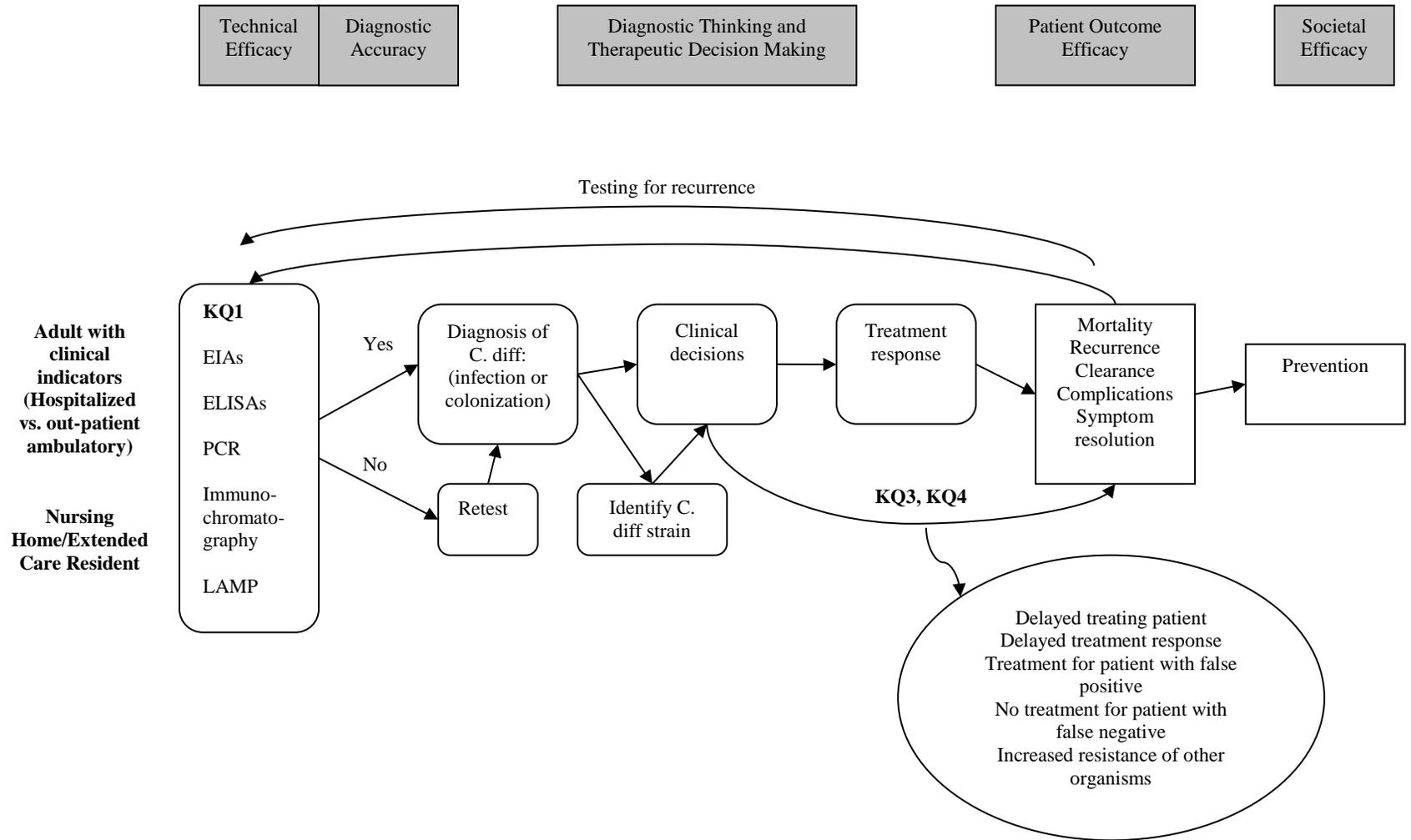
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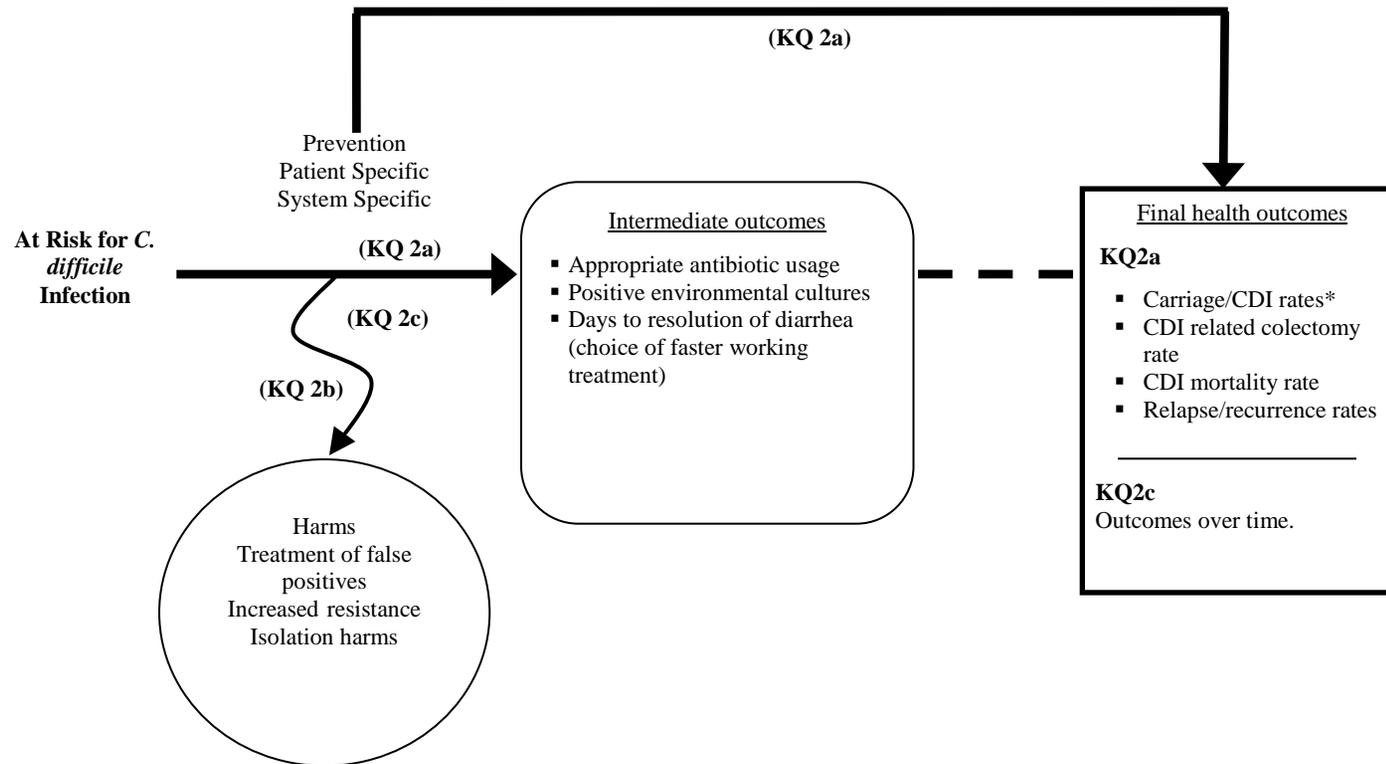
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# Appendix A: Analytic Frameworks

Figure 1. Framework for diagnostic testing and treatment



**Figure 2. Analytic framework for CDI prevention**



## Appendix B. Search Strings

Search String for Diagnostics (not filtered for study design)

- 1 difficile.mp.
- 2 limit 1 to (english language and humans)
- 3 (animals not (humans and animals)).sh.
4. 2 not 3
- 5 limit 4 to (addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits)
6. 4 not 5

## Appendix C. Excluded Studies

(reason for exclusion appears in italics after each reference)

### Key Question 1

1. Agaronov M, Karak SG, Maldonado Y, et al. Comparison of GeneXpert PCR to BD GeneOhm for detecting *C. difficile* toxin gene in GDH positive toxin negative samples. *Ann Clin Lab Sci* 2012; 42(4):397-400. PMID: 23090736. *indeterminate standards only*
2. Baker I, Leeming JP, Reynolds R, et al. Clinical relevance of a positive molecular test in the diagnosis of *Clostridium difficile* infection. *Journal of Hospital Infection* 2013; Aug;84(4):311-5. PMID: 23831282. *reference standard not applied to all samples*
3. Behroozian AA, Chludzinski JP, Lo ES, et al. Detection of mixed populations of *Clostridium difficile* from symptomatic patients using capillary-based polymerase chain reaction ribotyping. *Infect Control Hosp Epidemiol* 2013; Sep;34(9):961-6. PMID: 23917911. *typing only*
4. Boyanton BL, Jr., Sural P, Loomis CR, et al. Loop-mediated isothermal amplification compared to real-time PCR and enzyme immunoassay for toxigenic *Clostridium difficile* detection. *J Clin Microbiol* 2012; Mar;50(3):640-5. PMID: 22189114. *reference standard not applied to all samples*
5. Catanzaro M, Cirone J. Real-time polymerase chain reaction testing for *Clostridium difficile* reduces isolation time and improves patient management in a small community hospital. *American journal of infection control* 2012; Sep;40(7):663-6. PMID: 22153847. *reference standard not applied to all samples*
6. Chapin KC, Dickenson RA, Wu F, et al. Comparison of five assays for detection of *Clostridium difficile* toxin. *J Mol Diagn* 2011; Jul;13(4):395-400. PMID: 21704273. *reference standard not applied to all samples*
7. Church DL, Chow BL, Lloyd T, et al. Evaluation of automated repetitive-sequence-based PCR (DiversiLab) compared to PCR ribotyping for rapid molecular typing of community- and nosocomial-acquired *Clostridium difficile*. *Diagn Microbiol Infect Dis* 2011; Jun;70(2):183-90. PMID: 21596222. *typing only*
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11. Dubberke ER, Han Z, Bobo L, et al. Impact of clinical symptoms on interpretation of diagnostic assays for *Clostridium difficile* infections. *J Clin Microbiol* 2011; Aug;49(8):2887-93. PMID: 21697328. *patients not randomly or consecutively selected*
12. Eckert C, Burghoffer B, Lalande V, et al. Evaluation of the chromogenic agar chromID *C. difficile*. *J Clin Microbiol* 2013; Mar;51(3):1002-4. PMID: 23269743. *culture study only*
13. Eckert C, Van Broeck J, Spigaglia P, et al. Comparison of a commercially available repetitive-element PCR system (DiversiLab) with PCR ribotyping for typing of *clostridium difficile* strains. *J Clin Microbiol* 2011; Sep;49(9):3352-4. PMID: 21775548. *typing only*
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18. Han Z, McMullen KM, Russo AJ, et al. A *Clostridium difficile* infection "intervention": change in toxin assay results in fewer *C difficile* infection cases without changes in patient outcomes. *American journal of infection control* 2012; May;40(4):349-53. PMID: 21794950. *reference standard not applied to all samples*
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## Key Question 2

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4. Deshpande A, Sitzlar B, Fertelli D, et al. Utility of an adenosine triphosphate bioluminescence assay to evaluate disinfection of *Clostridium difficile* isolation rooms. *Infect Control Hosp Epidemiol* 2013; Aug;34(8):865-7. PMID: 23838235. *not on topic*
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34. Wilson AP, Smyth D, Moore G, et al. The impact of enhanced cleaning within the intensive care unit on contamination of the near-patient environment with hospital pathogens: a randomized crossover study in critical care units in two hospitals. *Crit Care Med* 2011; Apr;39(4):651-8. PMID: 21242793. *not on topic*
35. Wong S, Jamous A, O'Driscoll J, et al. A *Lactobacillus casei* Shirota probiotic drink reduces antibiotic-associated diarrhoea in patients with spinal cord injuries: a randomised controlled trial. *Br J Nutr* 2014; Feb;111(4):672-8. PMID: 24044687. *not on topic*

### Key Question 3

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2. Clutter DS, Dubrovskaya Y, Merl MY, et al. Fidaxomicin versus conventional antimicrobial therapy in 59 recipients of solid organ and hematopoietic stem cell transplantation with *Clostridium difficile*-associated diarrhea. *Antimicrob Agents Chemother* 2013; Sep;57(9):4501-5. PMID: 23836168. *not design*
3. Cornely OA, Miller MA, Fantin B, et al. Resolution of *Clostridium difficile*-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. *J Clin Oncol* 2013; Jul 1;31(19):2493-9. PMID: 23715579. *subgroup analysis*
4. Cornely OA, Miller MA, Louie TJ, et al. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. *Clinical Infectious Diseases* 2012; Aug;55 Suppl 2:S154-61. PMID: 22752865. *subgroup analysis*
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6. Eyre DW, Babakhani F, Griffiths D, et al. Whole-genome sequencing demonstrates that fidaxomicin is superior to vancomycin for preventing reinfection and relapse of infection with *Clostridium difficile*. *J Infect Dis* 2014; May 1;209(9):1446-51. PMID: 24218500. *not on topic*
7. Huang JS, Jiang ZD, Garey KW, et al. Use of rifamycin drugs and development of infection by rifamycin-resistant strains of *Clostridium difficile*. *Antimicrob Agents Chemother* 2013; Jun;57(6):2690-3. PMID: 23545528. *not outcomes*
8. Jardin CG, Palmer HR, Shah DN, et al. Assessment of treatment patterns and patient outcomes before vs after implementation of a severity-based *Clostridium difficile* infection treatment policy. *Journal of Hospital Infection* 2013; Sep;85(1):28-32. PMID: 23834988. *not outcomes*

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12. Mullane KM, Cornely OA, Crook DW, et al. Renal impairment and clinical outcomes of Clostridium difficile infection in two randomized trials.[Erratum appears in Am J Nephrol. 2013;38(3):266]. Am J Nephrol 2013; 38(1):1-11. PMID: 23796582. *subgroup analysis*
13. Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections.[Erratum appears in Clin Infect Dis. 2011 Dec;53(12):1312 Note: Dosage error in article text]. Clinical Infectious Diseases 2011; Sep;53(5):440-7. PMID: 21844027. *subgroup analysis*
14. Petrella LA, Sambol SP, Cheknis A, et al. Decreased cure and increased recurrence rates for Clostridium difficile infection caused by the epidemic C. difficile BI strain. Clinical Infectious Diseases 2012; Aug;55(3):351-7. PMID: 22523271. *subgroup analysis*
15. Stewart DB, Berg A, Hegarty J. Predicting recurrence of C. difficile colitis using bacterial virulence factors: binary toxin is the key. J Gastrointest Surg 2013; Jan;17(1):118-24; discussion p.24-5. PMID: 23086451. *not outcomes*
16. Venugopal AA, Szpunar S, Sanchez K, et al. Assessment of 30-day all-cause mortality in metronidazole-treated patients with Clostridium difficile infection. Scand J Infect Dis 2013; Oct;45(10):786-90. PMID: 23746336. *not design*

## Key Question 4

1. Eyre DW, Walker AS, Wyllie D, et al. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. Clinical Infectious Diseases 2012; Aug;55 Suppl 2:S77-87. PMID: 22752869. *not design*
2. Im GY, Modayil RJ, Lin CT, et al. The appendix may protect against Clostridium difficile recurrence. Clin Gastroenterol Hepatol 2011; Dec;9(12):1072-7. PMID: 21699818. *not design*
3. Rampelli S, Candela M, Severgnini M, et al. A probiotics-containing biscuit modulates the intestinal microbiota in the elderly. J Nutr Health Aging 2013; Feb;17(2):166-72. PMID: 23364497. *not outcome*
4. Ting LS, Praestgaard J, Grunenbergs N, et al. A first-in-human, randomized, double-blind, placebo-controlled, single- and multiple-ascending oral dose study to assess the safety and tolerability of LFF571 in healthy volunteers. Antimicrob Agents Chemother 2012; Nov;56(11):5946-51. PMID: 22964250. *not outcome*

# Appendix D. Risk-of-Bias Assessment Form for Observational Studies

\_\_\_\_\_ *Author* \_\_\_\_\_ *Year* \_\_\_\_\_ [PMID] \_\_\_\_\_ *Reviewer* \_\_\_\_\_

Question	Response	Criteria	Justification
<b>Internal Validity</b>			
1. Is the study design prospective, retrospective, or mixed?	Prospective <input type="checkbox"/>	Outcome has not occurred at the time the study is initiated and information is collected over time to assess relationships with the outcome.	
	Mixed <input type="checkbox"/>	Studies in which one group is studied prospectively and the other retrospectively.	
	Retrospective <input type="checkbox"/>	Analyzes data from past records.	
2. Are inclusion/exclusion criteria clearly stated?	Yes <input type="checkbox"/>		
	Partially <input type="checkbox"/>	Some, but not all, criteria stated or some not clearly stated.	
	No <input type="checkbox"/>		
3. Are baseline characteristics measured using valid and reliable measures and equivalent in both groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
4. Is the level of detail describing the intervention adequate?	Yes <input type="checkbox"/>	Intervention described included adequate service details	
	Partially <input type="checkbox"/>	Some of the above features.	
	No <input type="checkbox"/>	None of the above features.	
5. Is the selection of the comparison group appropriate?	Yes <input type="checkbox"/>	Considering bipolar type, diagnostic assessment, other patient characteristics	
6. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results?	Yes <input type="checkbox"/>	Accounted for concurrent informal care.	
	Partially <input type="checkbox"/>		
	No <input type="checkbox"/>		
7. Any attempt to balance the allocation between the groups (e.g., stratification, matching, propensity scores)?	Yes <input type="checkbox"/>	(If yes, what was used?)	
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
8. Were outcomes assessors blinded?	<input type="checkbox"/>	Who were outcome assessors?	
9. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes <input type="checkbox"/>	Measure valid and reliable (i.e., objective measures, well validated scale, provider report); and equivalent across groups.	
	Partially <input type="checkbox"/>	Some of the above features (partially validated scale)	
	No <input type="checkbox"/>	None of the above features (self-report, scales with lower	

Question	Response	Criteria	Justification
		validity, reliability); not equivalent across groups	
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
10. Is the length of followup the same for all groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
11. Did attrition result in a difference in group characteristics between baseline and follow-p?	Yes <input type="checkbox"/>	(Measurement period of interest if repeated measures)	
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
12. If baseline characteristics are not similar, does the analysis control for baseline differences between groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
13. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e., retrospective designs where eligible at baseline could not be determined)	
	NA <input type="checkbox"/>	No confounders or effect modifiers included in the study.	
14. Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?	Yes <input type="checkbox"/>		
	Partially <input type="checkbox"/>	Some variables taken into account or adjustment achieved to some extent.	
	No <input type="checkbox"/>	Not accounted for or not identified.	
	Uncertain <input type="checkbox"/>	Could not be ascertained	
15. Are the statistical methods used to assess the primary outcomes appropriate to the data?	Yes <input type="checkbox"/>	Statistical techniques used must be appropriate to the data.	
	Partially <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained	
16. Are reports of the study free of suggestion of selective outcome reporting?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>	Not all prespecified outcomes reported, subscales not	

Question	Response	Criteria	Justification
		prespecified reported, outcomes reported incompletely.	
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
17. Funding source identified	No <input type="checkbox"/>		Industry, government, university, Foundation (funded by what money source?)
	Yes <input type="checkbox"/>	Who provided funding?	
	Uncertain <input type="checkbox"/>		
<b>Overall Assessment</b>			
18. Overall Risk of Bias assessment	Low <input type="checkbox"/>	Results are believable taking study limitations into consideration	
	Moderate <input type="checkbox"/>	Results are probably believable taking study limitations into consideration	
	High <input type="checkbox"/>	Results are uncertain taking study limitations into consideration	

## Appendix E. Description and Characteristics of Included Studies

### KQ1 Diagnostics

Appendix Table E1. Included diagnostics

Study Author	Country	Single or Multicenter	Sample	Patient Population	Number of Samples	N (patients)
Barkin, 2012 <sup>1</sup>	US	Single	Unformed	At least 18, able to enroll, had diarrhea defined as three or more bowel movements in 24hrs, had stool sample submitted for CDI testing per clinician discretion and fulfilled one or more criteria for increased risk of CDI. Prior history of CDI, nosocomial exposure in last 6 months, antibiotic PPI use within previous 3 months, age 65 or older or the presence of nasogastric or postpyloric feeding tube. Subjects excluded if currently being treated for documented CDI and then re-tested during study period. 80 men and 59 women.	272	139
Bruins, 2012 <sup>2</sup>	Netherlands	Single	Unformed	All unformed stool samples sent to our laboratory from hospitalized and unhospitalized patients with diarrhea, preferably those known to have CDI-associated symptoms or risk factors such as the recent use of antibiotics, were included in the study	986	NA
Buchan, 2012 <sup>3</sup>	US	Multicenter	Unformed	Patients suspected of having C. difficile-associated diarrhea patients suspected of having C. difficile-associated diarrhea were collected	540	540
Calderaro, 2012 <sup>4</sup>	Italy	Single	Not specified	Patients attending the University Hospital of Parma (Northern Italy) with a suspicion of CDI	306	306
Carroll, 2013 <sup>5</sup>	US	Multicenter	Unformed	Included in the study were leftover deidentified stool samples submitted to the clinical laboratory specifically for C. difficile testing according to the institution's routine practices.	1,875	1,875
Dalpke, 2013 <sup>6</sup>	Germany	Single	Unformed	Patients at the University Hospital Heidelberg between April and July 2012	448	333
de Boer, 2010 <sup>7</sup>	Netherlands	Single	Unformed	Three different panels of stool specimens were collected. One panel of 20 stool samples, which differed in consistency (unformed to watery, diarrhoeal), was collected at the Laboratory for Infectious Diseases. The second panel consisted of 161 clinical stool specimens from patients for whom a specific request for CDI was issued. The third panel a subset of 32 C. difficile toxigenic culture positive stool samples, that were part of a sample collection described previously	161	NA

Study Author	Country	Single or Multicenter	Sample	Patient Population	Number of Samples	N (patients)
de Jong, 2012 <sup>8</sup>	Netherlands	Single	Unformed	A total of 150 patients were included during a 2-month period, of which 49.7% were male and the median age was 61 years (range 19–95). Most patients were admitted to the medical wards (56%), followed by the surgical (20.7%) and hematology/oncology wards (20.7%) and the intensive care units (2.6%)	150	150
Herrera, 2010 <sup>9</sup>	Mexico	Single	Not specified	All samples sent for detection of <i>C. difficile</i> toxins to the Laboratory of Clinical Microbiology	230	NA
Hirvonen, 2013 <sup>10</sup>	Finland	Single	Unformed	Inpatients with antibiotic associated diarrhea, ages 7-95	310	310
Hoegh, 2012 <sup>11</sup>	Denmark	Single	Not specified	Patients at Hvidovre Hospital having routine testing for <i>C. diff</i>	704	631
Humphries, 2013 <sup>12</sup>	US	Single	Unformed	adult inpatients were included in this study if they had a liquid stool specimen submitted to the clinical microbiology laboratory for <i>C. difficile</i> testing. All patients with a positive NAAT in the study were matched with an equal number of patients with negative NAAT results daily.	296	296
Kim, 2012 <sup>13</sup>	Korea	Single	Unformed	Severance hospital patients with diarrheal stool specimens submitted for testing.	127	127
Knetsch, 2011 <sup>14</sup>	UK	Single	Unformed	Diarrheal samples submitted to the Department of Microbiology at Leeds Teaching Hospitals	526	NA
Lalande, 2011 <sup>15</sup>	France	Single	Unformed	patients suspected of having CDIs	472	472
Le Guern, 2012 <sup>16</sup>	France	Single	Unformed	Inpatients. Criteria for rejection included formed stools or a duplicate specimen submitted during the last 7 days.	360	360
Leitner, 2013 <sup>17</sup>	Austria	Single	Unformed	Patients of both genders with specified request for clarification of CDI were tested, 65 males with an age range of 1-88 years and 115 females with age range 2-92 years.	180	180
Mattner, 2012 <sup>18</sup>	Germany	Single	Unformed	liquid stool samples sent to a university microbiology laboratory were investigated for toxigenic <i>C. difficile</i>	256	256
Noren, 2011 <sup>19</sup>	Sweden	Multicenter	Not specified	Consecutive stool specimens submitted for <i>C. difficile</i> diagnostics from hospitals and communities in Orebro County, Sweden, ages 3 months to 96 years	272	272
Noren, 2014 <sup>20</sup>	Sweden	Single	Not specified	Patients with clinical signs of CDI admitted to Hoglandet Hospital Eksjo and/or visited primary health care facilities	302	302
Planche, 2013 <sup>21</sup>	UK	Multicenter	Unformed	Faecal samples from both hospital and community patients submitted for routine testing for <i>C. difficile</i> . Had diarrhea not clearly attributable to an underlying disease or treatment from all hospital patients (aged $\geq 2$ years) and from individuals in the community (aged $\geq 65$ years), irrespective of <i>C. difficile</i> or other testing requests.	12402	10186
Qutub, 2011 <sup>22</sup>	Saudi Arabia	Single	Not specified	Patients admitted and suspected to have CDAD were evaluated, with majority of these patients having had received different types of antibiotics, including third generation of cephalosporins, quinolones, and macrolides.	150	150

Study Author	Country	Single or Multicenter	Sample	Patient Population	Number of Samples	N (patients)
Reller, 2010 <sup>23</sup>	US	Single	Unformed	Sequential weekday stool samples submitted for suspected <i>C. difficile</i>	600	600
Rene, 2011 <sup>24</sup>	Canada	Single	Unformed	Consecutive liquid fecal samples from unique patients submitted for routine CCNA	494	494
Shin, 2012 <sup>25</sup>	Korea	Multicenter	Not specified	patients with clinical signs compatible with CDI who were hospitalized in 3 teaching hospitals in Seoul City	243	243
Shin, 2012 <sup>26</sup>	Korea	Single	Unformed	Patients suspected of having CDI in a tertiary hospital.	253	NA
Strachan, 2013 <sup>27</sup>	UK	Single	Formed and Unformed	patient criteria: aged ≥65 years, taking or had recently taken antibiotics, a hospital inpatient, immunosuppressed, requested by the patient's clinician.	860	860
Viala, 2012 <sup>28</sup>	France	Single	Unformed	Patients at the Jean Verdier hospital in Paris suburb	94	89
Walkty, 2013 <sup>29</sup>	Canada	Multicenter	Unformed	Patients from Health Sciences Centre, St. Boniface Hospital, and Westman suspected of having CDI. Samples were excluded if stool submitted for a patient with a positive <i>C. difficile</i> test result in the preceding 7 days, and samples from patients less than 1 year of age.	428	428
Ylisiurua, 2013 <sup>29</sup>	Finland	Multicenter	Unformed	Hospitalized patients with diarrhea, more than half were over the age of 60 years.	884	NA
Zidaric, 2011 <sup>30</sup>	Slovenia	Multicenter	Formed and Unformed	Hospitalized and non-hospitalized patients suspected of having CDI	194	170

**Appendix Table E2. Included diagnostic studies tests**

Study Author	Number With CDI	Number Without CDI	Single vs Serial	Reference Standard	Tests
Barkin, 2012 <sup>1</sup>	36	236	Both	Toxigenic Culture	Meridian Premier Toxins A & B Microwell EIA Illumigene C. Difficile DNA Amplification Assay ImmunoCard C. difficile
Bruins, 2012 <sup>2</sup>	73	913	Single	Toxigenic Culture	ImmunoCard Toxins A & B TechLab QuickChek Complete Premier Toxin A&B Illumigene C. difficile TechLab C Diff Quik Chek GDH
Buchan, 2012 <sup>3</sup>	109	431	Single	CCNA and Toxigenic culture	Portrait Toxigenic C. difficile Assay Illumigene C. difficile Xpert C. difficile GeneOhm Cdiff
Calderaro, 2012 <sup>4</sup>	88	218	Single	Toxigenic Culture	C. DIFF QUIK CHEK COMPLETE Illumigene assay
Carroll, 2013 <sup>5</sup>	275	1600	Single	Toxigenic Culture	Verigene Clostridium difficile Nucleic Acid Assay
Dalpke, 2013 <sup>6</sup>	86	362	Single	Toxigenic Culture	BD MAX Cdiff Xpert C. difficile miniVIDAS
de Boer, 2010 <sup>7</sup>	16	145	Single	Toxigenic Culture	Xpect C.difficile A/B
de Jong, 2012 <sup>8</sup>	17	133	Single	Toxigenic Culture	ImmunoCard Toxin A and B
Herrera, 2010 <sup>9</sup>	13	217	Single	Toxigenic Culture	VIDAS CDA/B ImmunoCard A/B
Hirvonen, 2013 <sup>10</sup>	78	232	Single	Toxigenic Culture	GenomEra C. difficile assay
Hoegh, 2012 <sup>11</sup>	87		Single	Toxigenic Culture	ImmunoCard Toxins A+B
Humphries, 2013 <sup>12</sup>	124	172	Single	Toxigenic Culture	Illumigene C. difficile Premier Toxin A/B
Kim, 2012 <sup>13</sup>	11	116	Single	Toxigenic Culture	VIDAS C. difficile Toxin A&B AdvanSure RT-PCR
Knetsch, 2011 <sup>14</sup>	101	425	Single	Toxigenic Culture	BD GeneOhm Cdiff assay
Lalande, 2011 <sup>15</sup>	49	423	Single	Toxigenic Culture	Illumigene C. difficile assay
Le Guern, 2012 <sup>16</sup>	54	306	Single	Toxigenic Culture	BD Max Cdiff BD GeneOhm Cdiff

Study Author	Number With CDI	Number Without CDI	Single vs Serial	Reference Standard	Tests
Leitner, 2013 <sup>17</sup>	23	157	Single	Toxigenic Culture	Premier Toxins A&B BD MAX Cdiff assay
Mattner, 2012 <sup>18</sup>	43	213	Single	Toxigenic Culture	Ridascreen toxin A and B
Noren, 2011 <sup>19</sup>	50	222	Single	CCNA or Toxigenic culture	LAMP
Noren, 2014 <sup>20</sup>	88	214	Single	Toxigenic Culture	Illumigene LAMP Vidas CDAB assay
Planche, 2013 <sup>21</sup>	1034	11368	Single	CCNA or Toxigenic culture	Meridian Premier toxins A&B Techlab C diffi cile Tox A/B II Techlab C diff Chek-60 GDH+NAAT Techlab Tox A/B II + NAAT Techlab c-diff chek-60 + Techlab tox A/B II
Qutub, 2011 <sup>22</sup>	52	98	Single	CCNA	C. DIFF CHEK60
Reller, 2010 <sup>23</sup>	46	554	Single	CCNA	TechLab C. Diff Chek 60 TechLab C. diff Quick Chek TechLab Tox A/B Quik Chek
Rene, 2011 <sup>24</sup>	60	435	Single	CCNA or Toxigenic culture	Xpect C. difficile toxin A/B ImmunoCard Toxins A/B TechLab Toxin A/B Quik Chek Premier toxins A&B Prospect C. difficile toxin A/B TechLab QuikChek TechLab Toxin A/B II
Shin, 2012 <sup>25</sup>	70	173	Single	Toxigenic Culture	BD GeneOhm Cdiff assay Seeplex Diarrhea-B1 ACE detection assay
Shin, 2012 <sup>26</sup>	49	204	Single	Toxigenic Culture	GeneXpert C. diff Assay VIDAS C. difficile A & B assays
Strachan, 2013 <sup>27</sup>	98	762	Single	Toxigenic Culture	Premier C. difficile Toxin A & B
Viala, 2012 <sup>28</sup>	45	49	Single	Toxigenic Culture	BD GeneOhmCdiff Cepheid XPert C. difficile Illumigene C. difficile

Study Author	Number With CDI	Number Without CDI	Single vs Serial	Reference Standard	Tests
Walkty, 2013 <sup>29</sup>	63	365	Single	Toxigenic Culture	TechLab C. Diff Quik Chek TechLab Tox A/B Quik Chek Illumigene assay GDH+Tox A/B GDH+ CCTA GDH+tox A/B +CCTA GDH+illumigene GDH + tox A/B +illumigene
Ylisiurua, 2013 <sup>29</sup>	253	631	Single	Toxigenic Culture	RIDASCREEN EIA assay Illumigene LAMP assay RIDA GENE PCR assay
Zidaric, 2011 <sup>30</sup>	28	166	Single	Toxigenic Culture	BD GeneOhm Cdiff assay Cepheid Xpert C. difficile assay

## KQ2 Prevention

See Appendix G

## KQ3 Standard Treatment

**Appendix Table E3. New included studies standard antibiotic treatments**

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control(s) / Study Duration	Outcomes Evaluated
<b>Newly identified trials</b>			
<p>Johnson, 2014<sup>31</sup></p> <p>Region: Australia, Canada, Europe, United States</p> <p>Funding source: Industry</p>	<p>Population: Hospitalized or ambulatory patients aged <math>\geq 18</math> years with CDI and non-life-threatening medical conditions</p> <p>Mean age: 64 % women: 52 Ethnicity: not reported</p> <p>Inclusion criteria: CDI symptoms (<math>\geq 3</math> loose stools in 24 h) and confirmed toxin</p> <p>Severity: mild (3–5 bowel movements BM/day; WBC <math>\leq 15\,000/\text{mm}^3</math>; mild or absent abdominal pain due to CDI), moderate (6–9 BM/day; WBC, 15 001–20 000/<math>\text{mm}^3</math>; mild, moderate, or absent abdominal pain due to CDI); or severe (10 or more BM/day; WBC <math>\geq 20\,001/\text{mm}^3</math>; severe abdominal pain due to CDI). Any one of the defining characteristics could have been used to assign a severity category, and the more severe category was used when characteristics overlapped.</p>	<p>N=555 randomized (289 in Study 301, 266 in Study 302)</p> <p>Intervention 1: Vancomycin 125 mg 4 times/day (n=266)</p> <p>Intervention 2: Metronidazole 375 mg 4 times/day (n=289)</p> <p>Treatment duration: 10 days Followup period: 28 days after treatment period</p>	<p>a. Clinical cure, defined as resolution of diarrhea (attainment of bowel movements with a hard or formed consistency on average or 2 or fewer BM/day with a loose or watery consistency on average) and absence of severe abdominal discomfort due to CDI for more than 2 consecutive days including day 10.</p> <p>b. Time to resolution of diarrhea</p> <p>c. Recurrence of CDI, defined as a confirmed CDI diagnosis</p> <p>d. Nonresponse or change in therapy (scored as failure)</p> <p>e. Adverse events</p>
<p>Cornely, 2012<sup>32</sup></p> <p>Region: Canada, Europe, United States</p> <p>Funding source: Industry</p>	<p>Population: Symptomatic inpatient (68.2%) or outpatient patients age 16 or older</p> <p>Mean age: 63 % women: 61 Ethnicity: not reported</p> <p>Inclusion criteria: Toxins A or B in stool and <math>\geq 3</math> loose stools in 24 h preceding randomization</p>	<p>N=535 randomized (509 in modified ITT population); 124 with severe infection (24.4%)</p> <p>Intervention 1: Vancomycin 125 mg 4 times/day (n=257)</p> <p>Intervention 2: Fidaxomicin 200 mg 2 times/day with intervening placebo</p>	<p>a. Clinical cure, defined as resolution of diarrhea (3 or fewer unformed bowel movements for 2 consecutive days) for the duration of treatment and no further need for treatment as of the 2<sup>nd</sup> day after the last dose of study drug. A “substantial reduction” in unformed bowel movements but residual mild</p>

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control(s) / Study Duration	Outcomes Evaluated
	Severity: severe disease was defined by meeting any of the following: WBC count >15,000 cells/mm <sup>3</sup> , serum creatinine > 1.5 mg/dL, or temperature >38.5 C	(n=252)  Treatment duration: 10 days Followup period: 28 days	abdominal discomfort was also considered a clinical cure if no additional therapy was needed within 2 days of treatment completion b. Recurrence, # of patients (defined as return of 3 or more unformed bowel movements in 24 h, a positive stool toxin test, and need for retreatment within 30 days of treatment completion) c. Sustained cure (clinical cure without recurrence) d. Adverse events
<b>Newly identified observational study</b>			
Wenisch, 2012 <sup>33</sup>  Region: Austria  Funding source: none received	Population: Hospitalized adults with mild CDI  Mean age: 77 % women: 63% Ethnicity:  Inclusion criteria: Clinical symptoms of mild CDI (stool frequency <4 times daily and no signs of severe colitis) and microbiological evidence of toxin	N=265 (60 received no treatment and were excluded from analysis)  Intervention 1: Metronidazole 500 mg 3 times/day (oral) (n=121)  Intervention 2: Metronidazole 500 mg 3 times/day intravenous (n=42)  Intervention 3: Vancomycin 250 mg 4 times/day (oral) (n=42)	a. All-cause 30-day mortality b. Relative risk of 30-day mortality after adjustment for sex, age (>65 years), and severity of comorbidity c. Clinical cure d. Clinical recurrence e. Adverse events
<b>Previously identified studies</b>			
Louie 2011 <sup>34</sup>  Region: Canada, United States  Funding source: Industry	Population: Adults with acute symptoms of CDI and a positive result on a stool toxin test  Mean age: 62 % women: 56  Inclusion criteria: 16 years of age or older with a	N=629  Intervention 1: Fidaxomicin 200 mg 2 times/day (n=302)  Intervention 2: Vancomycin 125 mg 4 times/day (n=327)	a. Clinical cure, defined by the resolution of diarrhea (i.e., three or fewer unformed stools for 2 consecutive days), with maintenance of resolution for the duration of therapy and no further requirement (in the investigator's

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control(s) / Study Duration	Outcomes Evaluated
	<p>diagnosis of CDI, defined by the presence of diarrhea (a change in bowel habits, with &gt;3 unformed bowel movements in the 24-hour period before randomization) and <i>C. difficile</i> toxin A, B, or both in a stool specimen obtained within 48 hours before randomization.</p>	<p>Treatment duration: 10 days Followup period: 30 days</p>	<p>opinion) for therapy for CDI as of the second day after the end of the course of therapy. b. Clinical recurrence, defined by the reappearance of more than three diarrheal stools per 24-hour period within 4 weeks after the cessation of therapy; <i>C. difficile</i> toxin A or B, or both, in stool; and a need for retreatment for CDI c. Median time to resolution of diarrhea d. All-cause mortality e. Adverse events</p>
<p>Zar, 2007<sup>35</sup>  Region: United States  Funding source: none stated</p>	<p>Population: Mild or severe symptomatic inpatient adults with comorbid conditions</p> <p>Mean age: 58 (47% &lt;60 years) % women: 45</p> <p>Inclusion criteria: <i>Clostridium difficile</i>-associated diarrhea (CDI), testing positive for <i>C. difficile</i> cytotoxin</p> <p>Severity: patients with <math>\geq 2</math> points were considered to have severe CDI based on an assessment score developed for this study. One point each was given for age &gt;60 years, temperature &gt;38.3 C, albumin level &lt;2.5 mg/dL, or peripheral WBC count &gt;15,000 cells/mm<sup>3</sup> within 48 h of enrollment. Two points were given for endoscopic evidence of pseudo-membranous colitis or treatment in the intensive care. All patients had received antimicrobial treatment prior to onset of CDI (&gt;90% within 14 days)</p>	<p>N=172 (mild 54%, severe 46% based on 150 patients completing trial)</p> <p>Intervention 1: Vancomycin (liquid) 125 mg 4 times/day + placebo pill (n=82)</p> <p>Intervention 2: Metronidazole (oral) 250 mg 4 times/day plus placebo liquid (n=90)</p> <p>Treatment duration: 10 days Followup period: 21 days</p>	<p>a. Cure, # of patients (defined as resolution of diarrhea by day 6 of treatment and a negative result of a <i>C. difficile</i> toxin A assay at days 6 and 10 of treatment) b. Relapse, # of patients (defined as recurrence of <i>C. difficile</i> toxin A-positive diarrhea by day 21 after initial cure) c. All-cause mortality</p>

Study / Region / Funding Source	Population / Age or Age Range / % Women / Ethnicity / Inclusion Criteria	Sample Size (N) / Intervention(s) / Control(s) / Study Duration	Outcomes Evaluated
<p>Wenisch, 1996<sup>36</sup></p> <p>Region: Austria</p> <p>Funding source: none stated</p>	<p>Population: Symptomatic adults hospitalized for a minimum of 5 days</p> <p>Mean age: 42 % women: 48</p> <p>Inclusion criteria: age of &gt;18 years and the presence of CDI. Diarrhea was defined as &gt;3 loose stools per day. CDI was diagnosed on the basis of the results of a <i>C. difficile</i> toxin assay and/or endoscopic evidence of typical colitis, with the finding of granulocytes in stools</p>	<p>N=126</p> <p>Intervention 1: Metronidazole 500 mg 3 times/day (n=31)</p> <p>Intervention 2: Fusidic acid 500 mg 3 times/day (n=29)</p> <p>Intervention 3: Vancomycin 500 mg 3 times/day (n=31)</p> <p>Intervention 4: Teicoplanin (injection) 400 mg 2 times/day (n=28)</p> <p>Treatment duration: 10 days Followup period: 30 days</p>	<p>a. Clinical cure, # of patients (defined as no loose stools, gastrointestinal symptoms, or fever and normalization of serum levels of C-reactive protein and leukocyte counts)</p> <p>b. Clinical failure (defined as persistence of diarrhea after 6 days of treatment)</p> <p>c. Clinical relapse (defined as the reappearance of CDI and other symptoms during the followup period)</p> <p>d. Adverse events</p>
<p>Teasley, 1983<sup>37</sup></p> <p>Region: United States</p> <p>Funding source: Veterans Affairs and industry</p>	<p>Population: Symptomatic inpatient adults</p> <p>Mean age: 65 % women: 1</p> <p>Inclusion criteria: <i>C difficile</i>-associated diarrhea and its cytotoxin. All patients had received antimicrobial treatment 14-55 days prior to diarrhea</p>	<p>N=101</p> <p>Intervention 1: Vancomycin 500 mg 4 times/day (n=56)</p> <p>Intervention 2: Metronidazole 250 mg 4 times/day (n=45)</p> <p>Study duration: 10 days Followup period: 21 days</p>	<p>a. Cure (defined as diarrhea resolved within 6 days of treatment, toleration of complete treatment course, and no relapse in the 21-day followup period)</p> <p>b. Treatment response based diarrhea resolution (defined as &lt;2 stools formed /day)</p> <p>c. Treatment failure (defined as <math>\leq 4</math> loose stools/day after 6 days of treatment.)</p> <p>d. Treatment relapse (defined as recurrence with 21 days of diarrhea with <math>\leq 4</math> loose stools/day for a minimum of 2 days)</p>

BM=bowel movements; CDI=*C. difficile* infection; h=hours; WBC= white blood cell counts

## KQ4 Nonstandard Treatment

Appendix Table E4. Included studies for FMT nonstandard treatments

Author, Year, Country,	Design, Funding Source	Population, Age, % Women, Race/ethnicity	Sample Size, Intervention(s), Control(s), Study Duration	Outcomes	Harms
<b>Newly identified studies</b>					
Dutta, 2014 <sup>38</sup> United States	Prospective Health organization, University	Adults aged 18-90 with CDI who experienced $\geq 3$ relapses, mean age 65 (range 18-89), 82% women, 74% white, 22% black, 4% Asian	27 FMT Followup: mean 21 months (range 10–34)	Resolution of diarrhea or symptoms, CDI, adverse events	Low-grade fever (n=5, 19%), bloating (n=3, 11%), both of which resolved spontaneously within 12–24 hours
Khan, 2014 <sup>39</sup> United States	Retrospective review Funding NR	Adults with recurrent CDI, mean age 65, 89% women, race/ethnicity NR	20 FMT Followup: 6 months	Resolution of diarrhea, recurrence, adverse events, patient satisfaction	None
Weingarden, 2014 <sup>40</sup> United States	Case series Government, University	Adults with recurrent CDI, median age 62 (range 29-87), 83% women, race/ethnicity NR	12 FMT Followup: 1 year+	Resolution of diarrhea or symptoms, CDI, recurrence	NR
Youngster 2014 <sup>41</sup> United States	Open-label feasibility study Health organization	Adults with recurrent CDI ( $\geq 3$ mild to moderate episodes or $\geq 2$ severe), median age 65, 45% women	20 FMT (capsules) Followup: 6 months	Resolution of diarrhea or symptoms, adverse events	No serious adverse events deemed treatment-related; abdominal cramping and bloating (n=4, 20%)
Youngster 2014 <sup>42</sup> United States	Open-label RCT Government, University	People aged 7-90 with recurrent CDI ( $\geq 3$ mild to moderate episodes or $\geq 2$ severe), mean age 54, 55% women, race/ethnicity NR	20 FMT: 10 colonoscopic, 10 nasogastric Followup: 8 weeks (n=20), 6 months (n=15)	Resolution of diarrhea without relapse within 8 weeks, adverse events	No serious adverse events; abdominal cramping and bloating (n=6, 30%), which resolved within 72 hours
Emanuelsson, 2014 <sup>43</sup> Sweden	Retrospective review No funding	Adults with recurrent CDI (median 3 recurrences, range 1-5), median age 69, 61% female, race/ethnicity NR	31 FMT Followup: median 18 months (range 0-201)	Resolution of diarrhea and symptoms, adverse events	No significant adverse events on the day of microbiota infusion
Patel, 2013 <sup>44</sup> United States	Retrospective review Funding NR	Adults with with CDI who experienced $\geq 2$ relapses, mean age 61, 55% women, race/ethnicity NR	31 FMT Followup: 1 week and 1 month (n=30), 3 months (n=23), 1 year (n=6)	Resolution of diarrhea or symptoms, recurrence, adverse events, death	No serious adverse events; microperforation caused by a biopsy during the FMT procedure (n=1)

Author, Year, Country,	Design, Funding Source	Population, Age, % Women, Race/ethnicity	Sample Size, Intervention(s), Control(s), Study Duration	Outcomes	Harms
Pathak, 2014 <sup>45</sup> United States	Retrospective review Funding NR	Adults with CDI who experienced relapses or treatment failure (inclusion criteria based on severity), age range 37-92, 67% women, race/ethnicity NR	12 FMT followed by 2 months of <i>S. boulardii</i> Followup: range 2-30 months	Resolution of diarrhea or symptoms	NR
Rubin, 2013 <sup>46</sup> United States	Retrospective review Health organization	Adults with CDI who experienced $\geq 2$ relapses, mean age 63, 65% women, race/ethnicity NR	74 FMT Followup: 60 days	Resolution of diarrhea, recurrence, adverse events	None
van Nood, 2013 <sup>47</sup> The Netherlands	Open-label randomized trial Government	Adults with CDI relapse (with positive stool test) after antibiotics (vancomycin or metronidazole), mean age 70, 43% women, race/ethnicity NR	43 randomized 17 vancomycin (500 mg 4 times/day for 4 days), bowel lavage, FMT 13 vancomycin, bowel lavage 13 vancomycin Followup: 10 weeks	Resolution of diarrhea, CDI, adverse events	No serious adverse events; immediately after procedure, resolved within 3 hours: diarrhea (94%), cramping (31%) belching (19%); during followup: constipation (19%)
Brandt, 2012 <sup>48</sup> United States	Survey No funding	Adults who experienced recurrent CDI unresponsive to standard therapy and had undergone FMT $\geq 3$ months before data gathering, mean age 65, 73% women, race/ethnicity NR	77 FMT Followup: mean 17 months (range 3-68)	Resolution of diarrhea or symptoms, recurrence, adverse events	None directly attributed to FMT; n=4 developed new disorders after FMT (peripheral neuropathy, Sjogren ' s disease, idiopathic thrombocytopenic purpura, rheumatoid arthritis)
Hamilton, 2012 <sup>49</sup> United States	Case series Foundation, government	Adults with CDI who experienced $\geq 2$ relapses, mean age 59, 72% women, race/ethnicity NR	43 FMT Followup: NR	Resolution of diarrhea, CDI (not tested if asymptomatic), recurrence, adverse events	No serious adverse events; irregularity of bowel movements and excessive flatulence (approximately one third of patients), which resolved
Jorup-Ronstrom, 2012 <sup>50</sup> Sweden	Case series Funding NR	Adults with CDI who experienced $\geq 3$ relapses, median age 75 (range 27-94), 62.5% women, race/ethnicity NR	32 FMT (cultured for 10 years) Followup: median 26 months (range 1-68)	Cure ("if no relapse occurred"), improvement, recurrence, adverse events	None

<b>Author, Year, Country,</b>	<b>Design, Funding Source</b>	<b>Population, Age, % Women, Race/ethnicity</b>	<b>Sample Size, Intervention(s), Control(s), Study Duration</b>	<b>Outcomes</b>	<b>Harms</b>
Kelly, 2012 <sup>51</sup> United States	Case series Funding NR	Adults with CDI who experienced $\geq 3$ relapses, mean age 59 (range 19-86) 92% women, 100% white	26 FMT Followup: mean 11 months (range 2-30)	Resolution of diarrhea, CDI, recurrence	NR
Mattila, 2012 <sup>52</sup> Finland	Retrospective review Foundation	Adults with recurrent CDI, mean age 73 (range 22-90), 60% women, race/ethnicity NR	70 FMT Followup: 12 weeks and 1 year	Resolution of symptoms, recurrence, adverse events, death	No serious adverse events
Mellow, 2011 <sup>53</sup> United States	Case Series Funding NR	Adults with recurrent ( $\geq 3$ episodes, n=12) or refractory (n=1) CDI Mean age 67 (range 32-87), 46% women, race/ethnicity NR	13 FMT Followup: mean 5 months (range 3-24)	Resolution of diarrhea, recurrence, stool test for CDI (n=10), death	NR
Garborg, 2010 <sup>54</sup> Norway	Retrospective review Funding NR	Adults with confirmed or suspected (n=2) CDI, mean age 75 (range 53-94), 53% women	39 FMT Followup: 80 days based on records (no systematic follow-up)	Resolution of diarrhea, adverse events	None
Aas, 2003 <sup>55</sup> United States	Retrospective review Health organization	Adults with recurrent CDI who experienced $\geq 2$ relapses, mean age 73 (range 51–88), 72% women, race/ethnicity NR	18 FMT Followup: 90 days	Resolution of diarrhea, stool test for CDI (n=14), recurrence, adverse events, death	None
<b>Previously identified studies</b>					
Rohlke, 2010 <sup>56</sup> United States	Retrospective review No funding	Adults with recurrent CDI, mean age 49, 89% women, race/ethnicity NR	19 FMT Followup: mean 27 months (range 6-65)	Resolution of symptoms, recurrence	NR
Yoon, 2010 <sup>57</sup> United States	Case series No funding	Adults with recurrent or refractory CDI, mean age 66 (range 30-86), 75% women,	12 FMT Followup: range 3 weeks to 8 years	Resolution of symptoms, adverse events	None
MacConnachie, 2009 <sup>58</sup> United Kingdom	Retrospective review Funding NR	Adults with recurrent CDI, mean age 82 (range 68-95), 93% women, race/ethnicity NR	15 FMT Followup: median 16 weeks (range 4-24)	Resolution of symptoms, adverse events	No adverse events related to FMT

CDI=C. difficile infection; FMT=fecal microbiota transplant; NR=not reported

**Appendix Table E5. Included studies for probiotic nonstandard treatments**

Author, Year, Country, Funding Source	Population, Age	Sample Size, Intervention(s), Control(s), Study Duration	Adverse Events*
<b>Newly identified randomized trials</b>			
Allen, 2013 <sup>59</sup> United Kingdom Government	2981 adult inpatients aged 65 years and older, mean age 77.2, exposed to one or more parenteral antibiotics	Multistrain preparation of <i>lactobacilli</i> and <i>bifidobacteria</i> , $6 \times 10^{10}$ organisms for 21 days (n=1493) Placebo (n=1488) Followup: 8 weeks after recruitment, chart review at 12 weeks	No serious adverse events attributed to participation in the trial
Selinger, 2013 <sup>60</sup> United Kingdom Industry, government	229 adult hospital inpatients, mean age 58 exposed to systemic antibiotics	VSL#3 probiotic, $450 \times 10^9$ cfu/day (n=117) Placebo (n=112) Treatment duration: antibiotic duration plus 7 days Followup: 28 days	Treatment group: 14/117 Placebo: 16/112
Pozzoni, 2012 <sup>61</sup> Italy Hospital	275 adult hospital inpatients exposed to antibiotics without ongoing diarrhea or recent use of probiotics, mean age 72	<i>S. boulardii</i> , within 48 hours of starting antibiotic therapy (n=141) Placebo (n=134) Treatment duration: antibiotic duration plus 7 days Followup: 12 weeks	Treatment group: 52/141 Placebo: 42/135
Gao, 2010 <sup>62</sup> China Industry	255 adult inpatients exposed to antibiotics, aged 50-70, without active diarrhea or CDI within 3 months, mean age 60	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> LBC80R, $100 \times 10^9$ CFU/day (n=86) <i>L. acidophilus</i> CL1285 and <i>L. casei</i> , LBC80R, $50 \times 10^9$ cfu/day (n=85) within 36 hours of starting antibiotic therapy until 5 days after discontinuation; antibiotic duration 3-14 days Placebo (n=85) Followup: 21 days after last study drug dose	Treatment group: 1/171 Placebo: 2/84
Lonnermark, 2010 <sup>63</sup> Sweden Funding NR	239 adults (137 inpatients) treated for infections, mean age 45	<i>L. plantarum</i> 299v, $10 \times 10^9$ cfu/day, within 48 hours of starting antibiotic therapy until 7 days after discontinuation (n=118) Placebo (n=121) Followup: $\geq 1$ week after last study drug dose	Treatment group: 3/80 Placebo: 3/83
Psaradellis, 2010 <sup>64</sup> Canada Industry	437 adults (248 inpatients) prescribed antibiotics, mean age 59	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> , $25 \times 10^9$ CFU/day, for 2 days then $50 \times 10^9$ cfu/day until 5 days after discontinuation of antibiotic (n=233) Placebo (n=239) Followup: 21 days after last study drug dose	Treatment group: 87/216 Placebo: 99/221
Safdar, 2008 <sup>65</sup> United States Industry NR	40 adult inpatients, elderly US veterans exposed to antibiotics, mean age 69	<i>L. acidophilus</i> , $60 \times 10^9$ cfu/day during and 14 days after antibiotic course (n=23) Placebo (n=17) Follow-up: NR	Treatment group: 2/23 Placebo: 5/17

Author, Year, Country, Funding Source	Population, Age	Sample Size, Intervention(s), Control(s), Study Duration	Adverse Events*
Beausoleil, 2007 <sup>66</sup> Canada Industry	89 adult inpatients who were anticipated to take systemic antibiotics, mean age 71	<i>L. acidophilus</i> CL1285 and <i>L. casei</i> , 25 x 10 <sup>9</sup> cfu/day for 2 days, then 50 x 10 <sup>9</sup> CFU/day for antibiotic duration (n=44) Placebo (n=45) Followup: 21 days after last study drug dose	Treatment group: 21/44 Placebo: 20/45
Duman, 2005 Turkey <sup>67</sup> Funding NR	204 adults who received 14 days triple therapy for <i>Helicobacter pylori</i> eradication, mean age 45	<i>S. boulardii</i> , 30 x 10 <sup>9</sup> cfu/day for antibiotic duration (14 days) (n=204) No treatment (n=185) Followup: 4 weeks after last study drug dose	Treatment group: 3/196 No treatment: 4/180
<b>Newly identified observational study</b>			
Maziade, 2013 <sup>68</sup> Canada Open prospective Hospital	31,832 hospitalized patients receiving antibiotics, mean age NR	Standard care (n=1580) Standard care plus <i>L. acidophilus</i> CL1285 and <i>L. casei</i> LBC80R 50-60 x 10 <sup>9</sup> cfu/day (n= 4968) Treatment duration: minimum 30 days or antibiotic duration Study duration: 6 years	No serious adverse events
<b>Previously identified trials</b>			
Hickson, 2007 <sup>69</sup> United Kingdom Foundation	135 adult inpatients, mean age 74	<i>L. casei immunitas</i> DN-114 001, 19 x 10 <sup>9</sup> CFU/day; <i>L. bulgaris</i> , 1.9 x 10 <sup>9</sup> cfu/day; and <i>S.thermophiles</i> , 19 x 10 <sup>9</sup> cfu/day within 48 hours of starting antibiotic therapy until 7 days after discontinuation (n=69) Placebo (n=66) Followup: 4 weeks after last antibiotic or study drug dose	Treatment group: 0/56 Placebo: 0/53
Can, 2006 <sup>70</sup> Turkey Funding NR	151 adult inpatients aged 25-50, mean age NR	<i>S. boulardii</i> , lyophilized 20 x 10 <sup>9</sup> cfu/day ≤48 hours of antibiotic start dose (duration of study drug course NR) (n=73) Placebo (n=78) Followup: 4 weeks after last antibiotic dose	No serious adverse events
Plummer, 2004 <sup>71</sup> United Kingdom Funding NR	150 older adult inpatients	<i>L. acidophilus</i> and <i>Bifidobacterium bifidum</i> , 20 x 10 <sup>9</sup> cfu/day within 36 hours of starting antibiotic therapy, for 20 days (n=69) Placebo (n=69) Followup: Last day of study drug dose	NR
Thomas, 2001 <sup>72</sup> United States Industry	302 adult inpatients, mean age 56	<i>L. rhamnosus</i> GG, 20 x 10 <sup>9</sup> cfu/day within 24 hours of starting antibiotic therapy, for 14 days (n=152) Placebo (n=150) Followup: 7 days after last study drug dose	Treatment group: 37/133 Placebo: 52/134

Author, Year, Country, Funding Source	Population, Age	Sample Size, Intervention(s), Control(s), Study Duration	Adverse Events*
Lewis, 1998 <sup>73</sup> United Kingdom Health organization	72 older adult inpatients, mean age 74 (range 70-85)	<i>S. boulardii</i> , 113 mg (n=33) Placebo (n=36)	NR
McFarland, 1995 <sup>74</sup> United States	193 adult inpatients, mean age 41	<i>S. boulardii</i> lyophilized, 30 x 10 <sup>9</sup> cfu/day within 72 hours of starting antibiotic therapy until 3 days after discontinuation (n=97) Placebo (n=96) Followup: 7 weeks after last study drug dose	Treatment group: 0/93 Placebo: 12/92
Surawicz, 1989 <sup>75</sup> United States Industry	318 adults inpatients (n=138 had CDI tested), mean age 48	<i>S. boulardii</i> lyophilized, 20 x 10 <sup>9</sup> cfu/day within 48 hours of starting antibiotic therapy until 2 weeks after discontinuation (n=212) Placebo (n=106) Followup: mean 17 days	Treatment group: 0/116 Placebo: 0/64

CDI=C. difficile infection; FMT=fecal microbiota transplant; mITT=modified intention-to-treat; NR=not reported

\* No serious adverse events reported that were attributed to probiotic treatment.

**Appendix Table E6. Included RCTs for other nonstandard treatments**

Author, Year, Country, Funding Source	Population, Age	Sample Size, Intervention(s), Control(s), Study Duration
Garey, 2011 <sup>76</sup>	68 adult inpatients treated for CDI and no longer symptomatic, 50% female, Mean age 61	Rifaximin 400 mg 3 times/day for 20 days immediately after finishing standard anti-CDI antibiotics (n=39 randomized, 33 treated) Placebo (n=40 randomized, 35 treated) Followup: 3 months following 20 day treatment To prevent relapse
Laffan, 2011 <sup>77</sup>	30 longterm care facility residents, 64% female, mean age 62, 32%	Recombinant lactoferrin 5mg/mL in 600 mL saline solution for 8 weeks (n=13) Placebo (n=9)  (30 participants randomized but initial randomization of the 8 patients excluded from analysis unclear; 6 were from lactoferrin group and 2 were from unknown group)  Followup: 14, 42, and 56 days To prevent occurrence or relapse

CDI=C. difficile infection

## Appendix F. Risk-of-Bias and Study Quality

### KQ1 - Diagnostics

We used an updated rubric for assessing the quality of included studies (QUADAS-2). Overall, 12 of 31 studies were “low risk of bias” in all 4 QUADAS-2 domains (patient selection, index test, reference standard, and flow and timing). In keeping with the previous report, most studies that were included in this report that were not included in the original report enrolled samples from patients at risk for or with symptoms consistent with CDI. However, some studies included enrolled unformed specimens only irrespective of whether testing for CDI was requested by the patients’ clinician. The clinical characteristics of the patients from whom fecal samples were obtained for inclusion in the included studies were generally not described, making determination of applicability of findings problematic. While the characteristics of patients from whom fecal specimens were obtained for inclusion in the study were often not described, most studies (22) included only unformed stools samples while two studies contained both formed and unformed specimens and seven studies did not specify whether samples were formed or unformed. Nineteen studies did not include repeat samples from a single patient, but 12 studies included more samples than patients or did not specify the number of patients.

In contrast to the previous report, we included studies that prospectively enrolled samples from a patient population with a “baseline” pre-test probability of CDI without modification of the probability of disease by a screening test. The prevalence of CDI in the studies varied widely, between 6 percent and 48 percent. While this variability may not have an impact on sensitivity and specificity, the positive and negative predictive values of included tests are not applicable to a population with different prevalence than the prevalence of CDI in an included study. Fifteen studies enrolled a random or consecutive sample of samples, 14 studies did not specify if a consecutive or random sample of patients was included, and three studies did not include a random or consecutive sample of specimens. The impact of enrolling nonconsecutive samples on the measured operating characteristics of a certain diagnostic test is unclear. We cannot exclude the possibility that a study that had a nonconsecutive sample of patients could systematically entrain bias if there were characteristics of that led to samples being included and others excluded, such as volume of stool, variability of testing practices in certain wards, or other characteristics.

Similar to the previous report, we found that there were few concerns in the conduct and interpretation of index tests with respect to risk of bias. However, there was significant heterogeneity in the studies and the source of this heterogeneity in observed operating characteristics for the included studies is not completely clear. Many studies did not apply different tests to the exact same number of patients and the reasons for these differences were not often specified. There was some variability in how invalid or inconclusive index test(s) were interpreted and if the index test(s) were repeated on invalid or inconclusive specimens. The previous report included studies with a combination of reference standards including cell cytotoxicity test, cell cytotoxicity test in conjunction with toxigenic culture, one used a toxin immunoassay in conjunction with toxigenic culture, multiple immunoassays for toxins A and B in conjunction with toxigenic culture, and in-house gene detection tests. In the current update report, we used a more stringent reference standard of the cell cytotoxicity assay, toxigenic culture, or a combination thereof. A few studies used enriched toxigenic culture as the reference standard which is likely a more sensitive reference standard than typical toxigenic culture or cytotoxicity assay; the logical consequence is that index tests may appear less sensitive when

compared against a more sensitive reference standard. Twenty-five studies used toxigenic culture as the reference standard, four studies used a composite reference standard of cell cytotoxicity assay and/or toxigenic culture, and two studies used cell cytotoxicity assays as the reference standard. Although regarded as an acceptable reference standard, toxigenic culture, cell cytotoxicity assay or a combination thereof are not perfectly accurate. In the majority of included studies the diagnostic tests were performed independently although it was usually not explicitly stated whether or not the tests were evaluated without knowledge of the other tests. However, it was inferred that most index tests (which are more rapid than the reference standards that take 24-48 hours) were interpreted prior to the results of the reference test being available.

Fifteen studies were “high risk of bias” with respect to flow and timing, mostly due to not all samples being included in the analysis. While the number of indeterminate results was generally small, small changes in a 2x2 table for a certain study can have marked changes in the calculated operating characteristics. As in the previous report, the handling of indeterminate or inconclusive results is problematic. One approach many investigators used was to exclude the inconclusive tests from the calculation of the operating characteristics of a certain test, while others repeated the index test and used the second result (if positive or negative) as the result used in the calculation of operating characteristics. The former approach may lead to an overestimation or underestimation of the sensitivity and specificity of a test depending on whether the reference standard result of the excluded samples is positive or negative. Further, this approach also may lead to the body of samples included being no longer consecutive or random. The latter approach may also lead a misestimation of the operating characteristics as the approach to inconclusive results likely varies significantly between laboratories.

**Appendix Table F1. Diagnostic study quality**

Author	Year	Patient Selection	Index Test	Reference Standard	Flow and Timing	Test Class Examined
Barkin, 2012 <sup>1</sup>	2012	Low	Low	Low	High	A/B, GDH, LAMP
Bruins, 2012 <sup>2</sup>	2012	Low	Unclear	Low	Unclear	PCR, A/B, GDH, LAMP
Buchan, 2012 <sup>3</sup>	2012	Unclear	Low	Low	High	LAMP
Calderaro, 2012 <sup>4</sup>	2012	Low	Low	Low	Low	GDH, LAMP
Carroll, 2013 <sup>5</sup>	2013	Unclear	Low	Low	High	PCR
Dalpke, 2013 <sup>6</sup>	2013	Unclear	Low	Low	Low	PCR
de Boer, 2010 <sup>7</sup>	2010	Low	Low	Low	Low	PCR
de Jong, 2012 <sup>8</sup>	2012	Low	Low	Low	Low	A/B
Herrera, 2010 <sup>9</sup>	2010	Low	Unclear	Low	Unclear	A/B
Hirvonen, 2013 <sup>10</sup>	2013	Low	Low	Low	Low	PCR
Hoegh, 2012 <sup>11</sup>	2012	Low	Low	Low	High	A/B
Humphries, 2013 <sup>12</sup>	2013	High	Unclear	High	Unclear	A/B, LAMP
Kim, 2012 <sup>13</sup>	2012	Low	Low	Low	High	PCR, A/B
Knetsch, 2011 <sup>14</sup>	2011	Low	Low	Low	High	PCR
Lalande, 2011 <sup>15</sup>	2011	Low	Low	Low	Low	LAMP
Le Guern, 2012 <sup>16</sup>	2012	Low	Low	Low	Low	PCR
Leitner, 2013 <sup>17</sup>	2013	Low	Low	Low	Low	PCR, A/B
Mattner, 2012 <sup>18</sup>	2012	Low	Low	Low	Low	A/B
Noren, 2011 <sup>19</sup>	2011	Low	Low	Low	Low	LAMP
Noren, 2014 <sup>20</sup>	2013	Low	Low	Low	High	A/B, LAMP
Planche, 2013 <sup>21</sup>	2013	Low	High	Low	High	A/B, GDH, TA
Qutub, 2011 <sup>22</sup>	2011	Low	Low	Low	Low	GDH
Reller, 2010 <sup>23</sup>	2010	Unclear	Low	Low	Low	A/B, GDH
Rene, 2011 <sup>24</sup>	2012	Low	Low	Low	High	A/B
Shin, 2012 <sup>25</sup>	2012	Low	Low	Low	Low	PCR, A/B
Shin, 2012 <sup>26</sup>	2012	Low	Low	Low	High	PCR
Strachan, 2013 <sup>27</sup>	2013	Low	Low	Low	Low	A/B
Viala, 2012 <sup>28</sup>	2012	Low	Low	Low	High	PCR, LAMP
Walkty, 2013 <sup>29</sup>	2013	Low	Low	Low	High	A/B, GDH, LAMP, TA
Ylisiurua, 2013 <sup>29</sup>	2013	Low	Low	Low	High	PCR, A/B, LAMP
Zidaric, 2011 <sup>30</sup>	2011	Low	Low	Low	High	PCR

## KQ2 - Prevention

Appendix Table F2. Prevention study risk-of-bias

Author, Year Country	Study Design	Overall Summary Score	Comments
<b>Transmission Interruption</b>			
Filice, 2013 <sup>78</sup> United States	Systematic review	Low	Publication bias not assessed – fewer than 10 relevant studies for CDI outcome. English language only, but focused on interventions in systems similar to the U.S.
Rupp, 2012 <sup>79</sup> United States	Quasi-experimental staged introduction trial, 19 months followed by 4 month wash-out	Moderate	Cohorts, not matched concurrent control. Tested for effect of compliance on change in CDI rates. Change in diagnostic testing would conservatively increase CDI rate. Limited information on regression models.
Levin, 2013 <sup>80</sup> United States	Pre/post single site. 1 year followup	High	No concurrent control. Change in antibiotic formulary during study period.
Manian, 2013 <sup>81</sup> United States	Retrospective Pre/post single site. 1 year followup	High	No concurrent control
Passaretti 2013 <sup>82</sup> United States	Prospective cohort intervention in 3 cohorts. 1 year, 6 month followup	High	No concurrent control. No information on CDI definition.
Stone, 2012 <sup>83</sup> United Kingdom	Prospective, ecological, interrupted time series, 3 year followup after roll-out	Moderate	CDI incidence estimated because mandatory reporting database does not include patient age as variable. Limited information on regression models. Analysis reported evidence of selection bias- trusts missing data for soap had lower rates of CDI.
Didiodato, 2013 <sup>84</sup> Canada	Prospective, ecological, interrupted time series, 3 year followup	High	Limited information on regression models, imputation for missing data, limited confounding variables captured in the patient safety indicator database.
Bearman, 2010 <sup>85</sup> United States	Prospective pre/post single site. 6 month followup	High	No concurrent control
<b>Multicomponent</b>			
Brakovich, 2013 <sup>86</sup> United States	Prospective pre/post single site design. 2 year followup	High	No concurrent control
Bishop, 2013 <sup>87</sup> United States	Prospective pre/post single site design. 3 year followup	High	No concurrent control
Mermel, 2013 <sup>88</sup> United States	Time series single site design. 6 year, 9 month followup	High	Unclear timing for data collection, switch to PCR (more sensitive test) during intervention period confounds change in CDI, limited information on regression model
Price, 2010 <sup>89</sup> United Kingdom	Interrupted time series single site design; 12 months pre, 15 months post. Retrospective	High	Retrospective data, no information on <i>C. difficile</i> diagnostic testing methods, other than no changes except for reduced from 7 to 5 days per week, limited information on regression model.

**Appendix Table F3. Quality of previous systematic reviews**

Study	A priori Study Design	Dual Study Selection and Data Abstraction	Comprehensive literature search	Publication Status	Lists of Included and Excluded Studies Provided?	Scientific Quality of Included Studies Assessed and Documented?	Scientific Quality of Included Studies Used Appropriately in Formulating Conclusions?	Methods of Combining Studies Appropriate?	Likelihood of Publication Bias Assessed?	Conflict of Interest Stated?	Overall Quality
Filice, 2013 <sup>78</sup>	yes	yes	yes	yes	yes	yes	yes	yes	Unclear	yes	good

## KQ3 – Standard Treatment

**Appendix Table F4. Standard treatment study risk-of-bias**

Study ID	Design	Funding source	Overall Summary	Comments
Johnson 2014 <sup>31</sup>	RCT- 3 arms, tolevamer vs. metronidazole vs. vancomycin	Genzyme (tolevamer maker)	Low risk of bias	No reason to downgrade.
Cornely 2012 <sup>32</sup>	RCT- Vancomycin vs. fidaxomicin	Optimer pharmaceutical (fidaxomicin maker)	Low risk of bias	No reason to downgrade.
Wenisch 2012 <sup>33</sup>	Prospective Cohort - oral metronidazole vs. IV metronidazole vs. oral vancomycin	"No financial support was received for this study"	High risk of bias	Downgraded for: "no" answers to sequence generation, allocation concealment, blinding, and other (non-RCT). Unclear for incomplete outcome data

## KQ4 – Nonstandard Treatment

Appendix Table F5. FMT adjunctive treatments study risk-of-bias

Study Country Funding	Type of Study	Overall Risk of Bias Assessment	Rationale
<b>Newly identified studies</b>			
Dutta, 2014 <sup>38</sup> United States Health organization, University	Prospective	High	Case series, inadequate sample size
Khan, 2014 <sup>39</sup> United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size, CDI assessed based on symptoms only, population inclusion criteria (“recurrent CDI”) not defined
Weingarden, 2014 <sup>40</sup> United States Government, University	Observational	High	Case series, inadequate sample size, population inclusion criteria (“recurrent CDI”) not defined, adverse events not reported
Youngster 2014 <sup>42</sup> United States Health organization	Open-label feasibility study	High	Inadequate sample size, no comparison group
Youngster 2014 <sup>41</sup> United States Government, University	Open-label RCT	High	Inadequate sample size, no non-FMT comparison group, attrition
Emanuelsson, 2013 <sup>43</sup> Sweden No funding	Retrospective review	High	Retrospective, case series, inadequate sample size, lack of systematic followup (n=5 patients with 0-1 months follow-up)
Patel, 2013 <sup>44</sup> United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size, attrition
Pathak, 2013 <sup>45</sup> United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size
Rubin, 2013 <sup>46</sup> United States Health organization	Retrospective review	High	Retrospective, case series
van Nood, 2013 <sup>47</sup> The Netherlands Government	Open-label randomized trial	High	Inadequate sample size (n=43 randomized, n=13-17 per arm)
Brandt, 2012 <sup>48</sup> United States No funding	Survey	High	Retrospective, survey design
Hamilton, 2012 <sup>49</sup> United States Foundation, government	Case series	High	Case series, followup not reported
Jorup-Ronstrom, 2012 <sup>50</sup> Sweden Funding NR	Observational	High	Retrospective, case series, inadequate sample size, outcomes not clearly defined
Kelly, 2012 <sup>51</sup> United States Funding NR	Case series	High	Case series, inadequate sample size, adverse events not reported
Mattila, 2012 <sup>52</sup> Finland Foundation	Retrospective review	High	Retrospective, case series
Mellow, 2011 <sup>53</sup> United States Funding NR	Observational	High	Case series, inadequate sample size, selective CDI testing

<b>Study Country Funding</b>	<b>Type of Study</b>	<b>Overall Risk of Bias Assessment</b>	<b>Rationale</b>
Garborg, <sup>54</sup> 2010 <sup>54</sup> Norway Funding NR	Retrospective review	High	Retrospective, case series, heterogeneous sample (confirmed or suspected CDI), lack of systematic followup
Aas, 2003 <sup>55</sup> United States Health organization	Retrospective review	High	Retrospective, case series, inadequate sample size, selective CDI testing
<b><i>Previously identified studies</i></b>			
Rohlke, 2010 <sup>56</sup> United States No funding	Retrospective review	High	Retrospective, case series, inadequate sample size, population inclusion criteria ("recurrent CDI") not defined, adverse events not reported
Yoon, 2010 <sup>57</sup> United States No funding	Case series	High	Retrospective, case series, inadequate sample size
MacConnachie, 2009 <sup>58</sup> United Kingdom Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size

**Appendix Table F6. Probiotic adjunctive treatments study risk-of-bias**

<b>Study Country Funding</b>	<b>Overall Risk of Bias Assessment</b>	<b>Rationale</b>
<b><i>Newly identified randomized trials</i></b>		
Allen, 2013 <sup>59</sup> United Kingdom Government	High	Underpowered for event rate, limited followup duration
Selinger, 2013 <sup>60</sup> United Kingdom Industry, government	High	Underpowered for event rate, 45% did not complete study, trial stopped early due to low incidence of CDI
Pozzoni, 2012 <sup>61</sup> Italy Hospital	High	Possible attrition bias, selective CDI testing, underpowered for event rate
Gao, 2010 <sup>62</sup> China Industry	Moderate	Selective CDI testing.
Lonnermark, 2010 <sup>63</sup> Sweden Funding NR	High	Possible attrition bias, selective CDI testing, limited followup duration, underpowered for event rate
Psaradellis, 2010 <sup>64</sup> Canada Industry	High	Unclear randomization process and allocation concealment, possible attrition bias, selective CDI testing, underpowered for event rate, outcomes not reported by recurrence (heterogeneous population)
Safdar, 2008 <sup>65</sup> United States Industry, NR	High	Underpowered for event rate
Beausoleil, 2007 <sup>66</sup> Canada Industry	High	Unclear randomization process and allocation concealment, selective CDI testing, underpowered for event rate
Duman, 2005 <sup>67</sup> Turkey Funding NR	High	Unclear randomization process and allocation concealment, open label, possible attrition bias, underpowered for event rate
<b><i>Newly identified observational study</i></b>		
Maziade, 2013 <sup>68</sup> Canada Open prospective Hospital	High	Observational design, unclear details of treatment/comparison groups
<b><i>Previously identified trials</i></b>		
Hickson, 2007 <sup>69</sup> United Kingdom Foundation	High	Possible attrition bias, selective CDI testing, underpowered for event rate
Can, 2006 <sup>70</sup> Turkey Funding NR	High	Unclear randomization process and allocation concealment, blinding patient or assessors; possible attrition bias, underpowered for event rate
Plummer, 2004 <sup>71</sup> United Kingdom Funding NR	High	Unclear randomization process and allocation concealment, selective CDI testing, underpowered for event rate, outcomes not reported by carrier status (heterogeneous population)
Thomas, 2001 <sup>72</sup> United States Industry	High	Possible attrition bias, selective CDI testing, CDI assessment by retrospective chart review, underpowered for event rate
Lewis, 1998 <sup>73</sup> United Kingdom Health organization	High	Unclear randomization process and allocation concealment, unclear followup duration, underpowered for event rate
McFarland, 1995 <sup>74</sup> United States	High	Unclear randomization process and allocation concealment, attrition bias, underpowered for event rate

<b>Study Country Funding</b>	<b>Overall Risk of Bias Assessment</b>	<b>Rationale</b>
Surawicz, 1989 <sup>b</sup> United States Industry	High	Unclear allocation concealment, attrition bias, underpowered for event rate, outcomes not reported by carrier status (heterogeneous population)

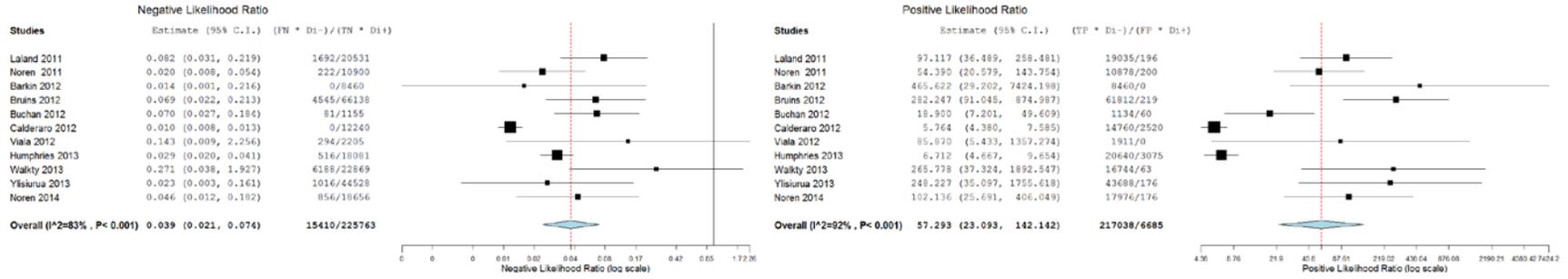
**Appendix Table F7. Other adjunctive treatments study risk-of-bias**

<b>Study Country Funding</b>	<b>Type of Study</b>	<b>Overall Risk of Bias Assessment</b>	<b>Rationale</b>
<b><i>Newly identified studies</i></b>			
Garey 2011 <sup>76</sup> United States Industry	Randomized trial	High	Trial stopped early; unusually low cure rate for established comparator.
Laffan, 2011 <sup>77</sup> United States Industry	Randomized trial	High	Inadequate sample size

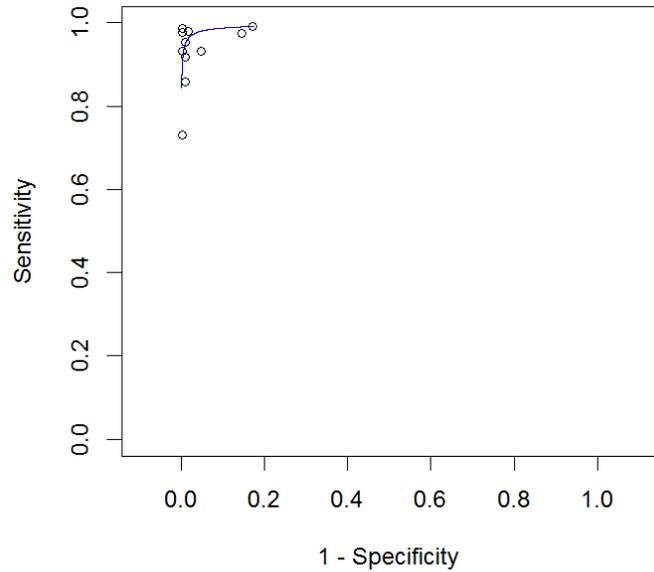
# Appendix G. Detailed Analyses

## KQ1 Diagnostics

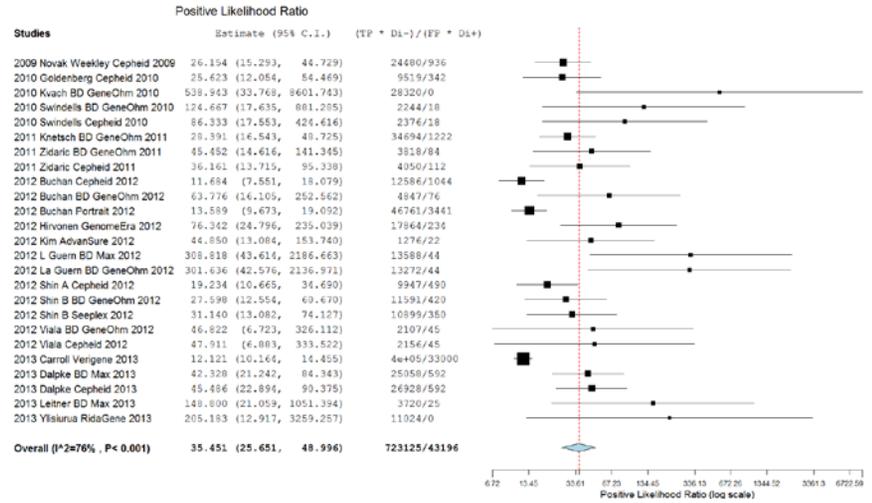
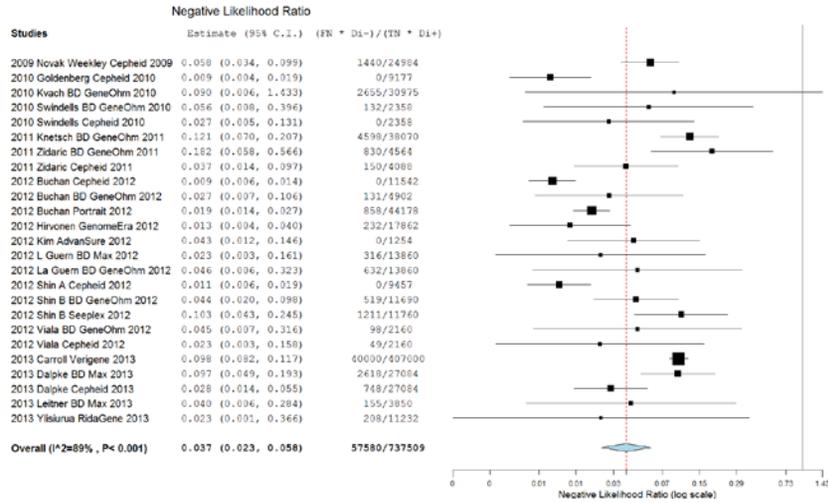
Appendix Figure G1. LAMP Likelihood Ratios



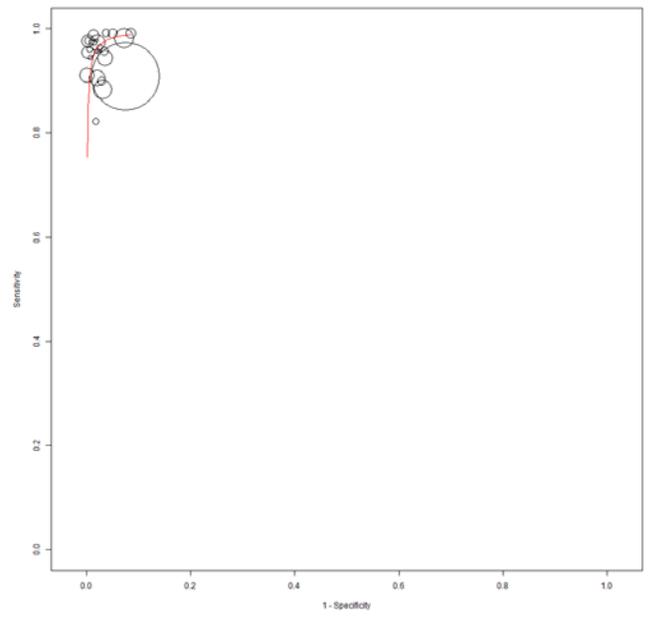
Appendix Figure G2. LAMP SROC



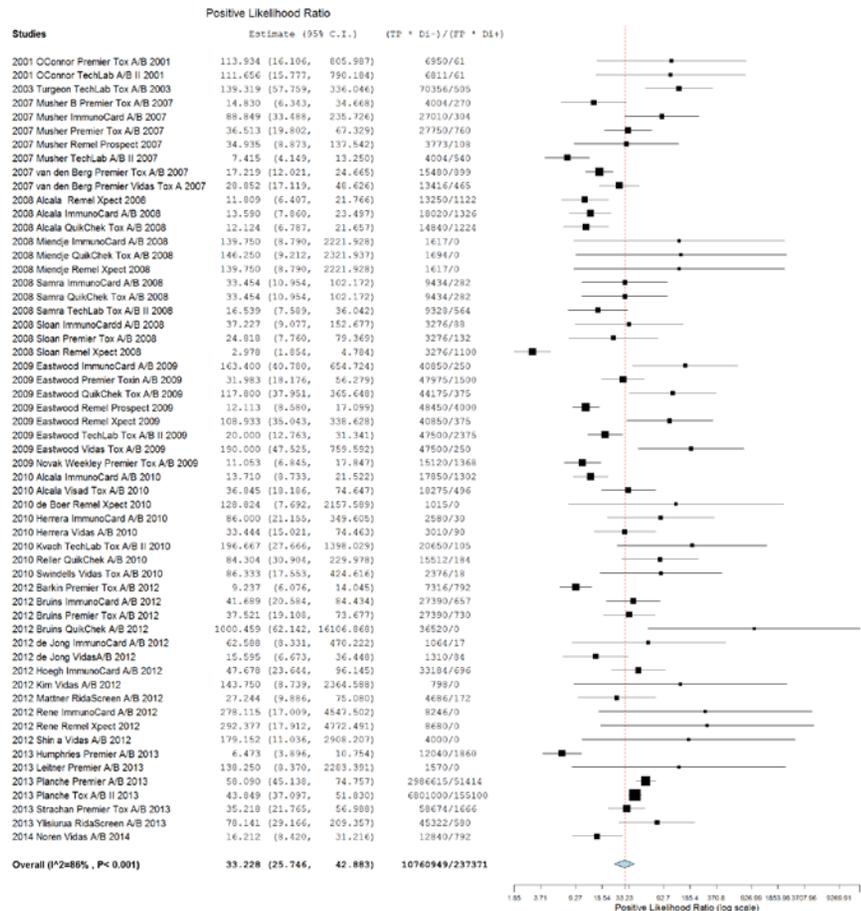
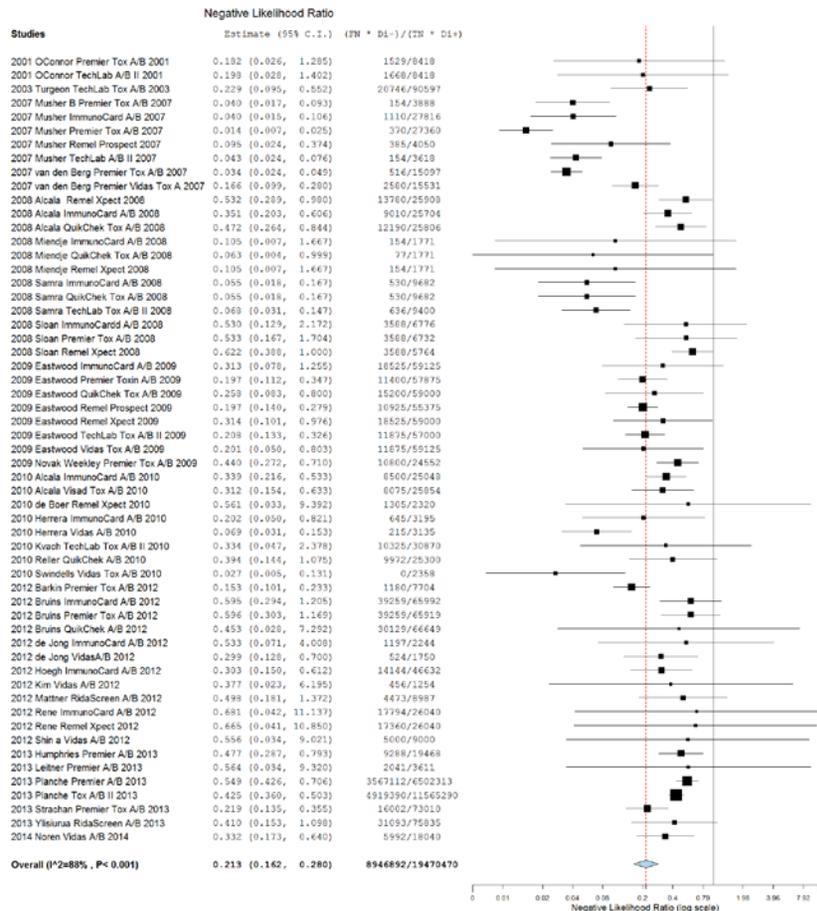
### Appendix Figure G3. PCR Likelihood Ratios



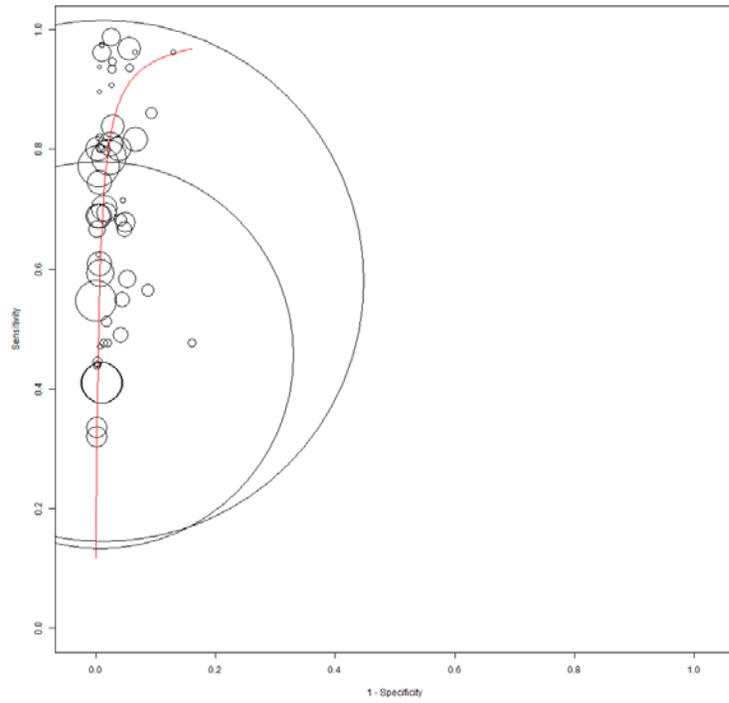
### Appendix Figure G4. PCR SROC



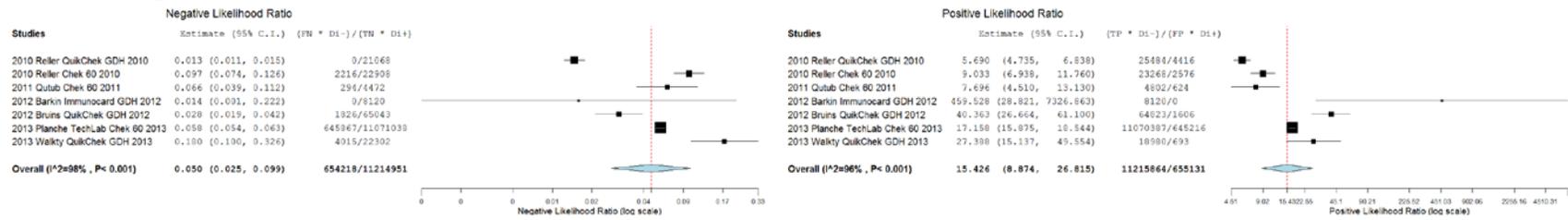
# Appendix Figure G5. Toxin A/B Likelihood Ratios



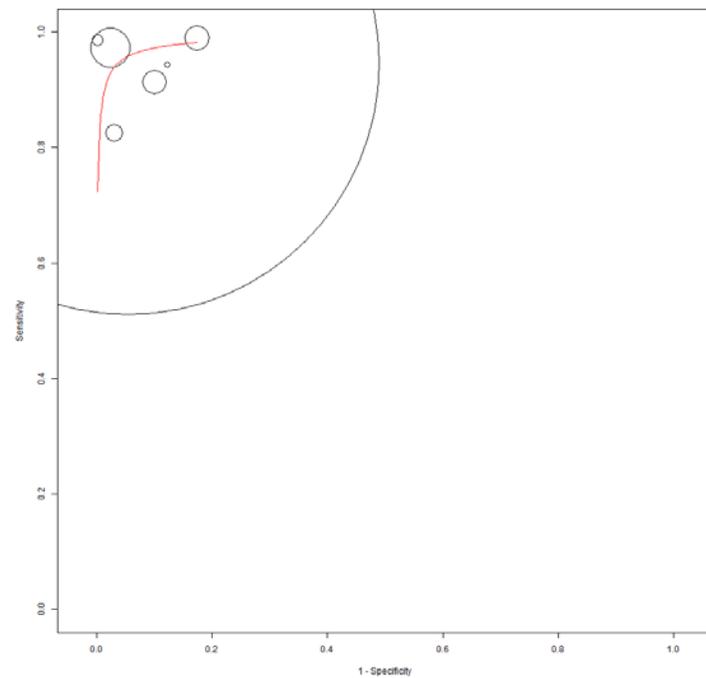
Appendix Figure G6. Toxin A/B SROC



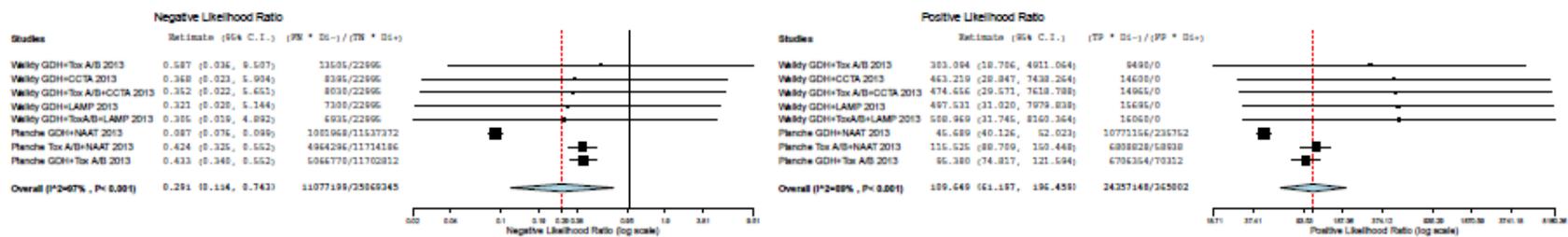
## Appendix Figure G7. GDH Likelihood Ratios



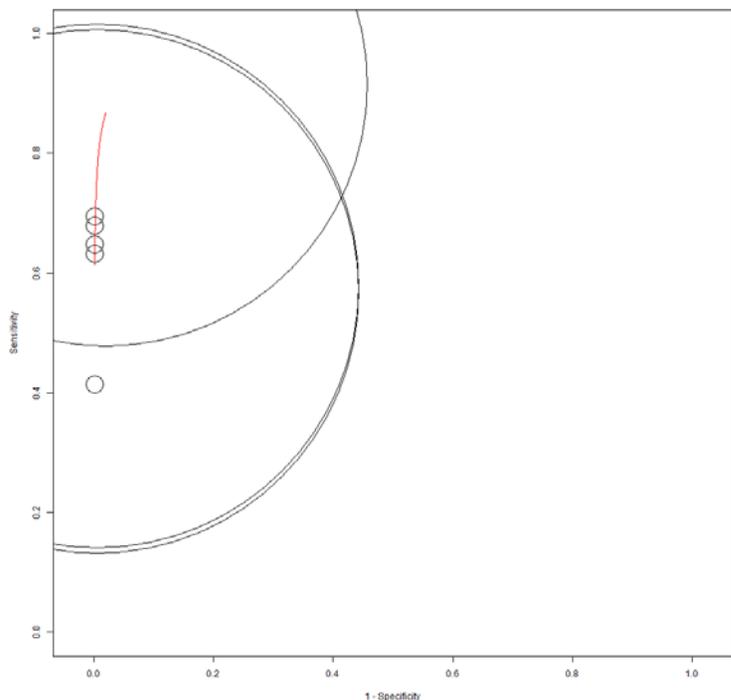
## Appendix Figure G8. GDH SROC



### Appendix Figure G9. All Test Algorithms Likelihood Ratios



### Appendix Figure G10. All Test Algorithms SROC



## KQ2 Prevention

**Appendix Table G1. Prevention interventions, all with CDI incidence as outcome**

Author, Year Country	Study Design	Population Setting	CDI Definition Timing Testing	Intervention	Study Findings
<b>Antibiotic Stewardship</b>					
Filice, 2013 <sup>78</sup> United States	Systematic review 37 included studies  1 RCT, 5 interrupted time series (one of which overlapped with the original report) relevant to CDI incidence	Patients at risk for CDI Inpatient settings, not pediatric	Defined: based on individual study Timing: NA Testing: NA	Inpatient antimicrobial stewardship programs	Low strength evidence from 3 moderate and 3 high risk of bias studies that broad range of antimicrobial stewardship programs reduce CDI incidence (qualitative synthesis)
<b>Transmission Interruption</b>					
Rupp, 2012 <sup>9</sup> United States	Quasi- experimental staged introduction trial in 3 cohorts, 19 months followed by 4 month wash- out	Patients at risk for CDI 689 bed academic medical center (not pediatric)	Defined: CDC NHSN criteria Timing: NR Testing: NR	Chlorhexidine gluconate (CHG) bathing 3 days per week or daily	CDI RR 0.41 (95% CI, 0.29 to 0.59) for daily bathing, 0.71 (95%, CI 0.57 to 0.89) for 3 times per week, and 1.85 (95% CI, 1.38 to 2.53) for CDI in washout period compared with daily bathing. Daily more effective than 3 times per week  Adverse Events: no events reported
Manian, 2013 <sup>81,1.90</sup> United States	Retrospective Pre/post single site. 1 year followup.	Patients at risk for CDI (not pediatric or rehabilitation) 900-bed teaching hospital, St. Louis, MO	Defined: diarrhea with positive test for toxin A/B Timing: 3 days after admission or 7 days after discharge Test: EIA (Meridian)	Hydrogen peroxide vapor in sealed room	CDI incidence rate dropped from 0.88/1000 patient days to 0.55/1000 patient days (0.63. 95% CI, 0.50 to 0.79)  Adverse Events: Reported no events related to cleaning
Passaretti, 2013 <sup>82</sup> United States	Prospective cohort intervention in 3 cohorts. 1 year, 6 month followup	Patients at risk for CDI 994-bed tertiary hospital	Defined: Not reported Timing: 48 hours after admission Test: Not reported	Hydrogen peroxide vapor in sealed room	Trend in reduced rate but no statistical difference in CDI incidence rate.  Adverse Events: Reported no events related to cleaning

Author, Year Country	Study Design	Population Setting	CDI Definition Timing Testing	Intervention	Study Findings
Levin, 2013 <sup>80</sup> United States	Pre/post single site. 1 year followup	Patients at risk for CDI 140-bed community hospital, Western MA	Defined: CDC NHSN criteria Timing: not reported Test: PCR and Immunocard Toxins A and B	Portable pulsed xenon ultraviolet light used in 3 7-minute sessions per patient room. Device operated remotely by cleaning personel. Safety feature turns off light if door opens.	CDI rates declined from 9.46 per 10,000 in 2010 to 4.45 per 10,000 in 2011, a 53% reduction. Declines also in deaths, from 6 to 1, and colectomies, from 3 to 0.
Stone, 2012 <sup>83</sup> United Kingdom	Prospective, ecological, interrupted time series. 3 year followup after roll-out	Patients 65+ years at risk for CDI 187 hospital trusts in England	Defined: Not reported Timing: 48 hours after admission Test: Not reported	Clean your hands campaign: alcohol rub at bedside, reminder posters, compliance audit and feedback, materials to patients empowering them to remind healthcare workers to clean their hands	CDI fell from peak of 16.75 to 9.49 cases per 10,000 bed days. Soap use independently associated with reduced CDI. CDI was not associated with alcohol gel in multivariate analysis.
DiDiodato, 2013 <sup>84</sup> Canada	Prospective, ecological, interrupted time series. 3 years	Patients at risk for CDI 166 acute care hospitals, Ontario	Defined: Not reported Timing: 72 hours after admission Test: Not reported	Ontario Just Clean Your Hands patient safety initiative. Education and training program. Mandated hand hygiene audits and public reporting	No statistical differences found
Bearman, 2010 <sup>85</sup> United States	Prospective Pre/post single site. 6 month followup	Patients at risk for CDI 18 bed surgical intensive care unit (820-bed academic medical center)	Defined: Not reported Timing: Not reported Test: Not reported	Universal gloving with emollient-impregnated gloves	No significant differences in CDI incidence
<b>Multicomponent</b>					
Brakovich, 2013 <sup>86</sup> United States	Prospective Pre/post single site design. 2 year followup	Patients at risk for CDI 50-bed long-term acute care hospital, southeastern United States	Defined: unclear Timing: first event at least 3 days after admission Test: for antigen marker, <i>C. diff</i> glutamate dehydrogenase, toxins A and B	Tiered approach: Cleaning education plan developed based on empiric test of site terminal cleaning Microfiber mops Hydrogen peroxide vapor equipment/services Bleach Contact isolation Hand hygiene Antimicrobial stewardship plan Quarterly feedback	CDI incidence rate: 44.25% decrease in cumulative rate, sustained over 2 years. (Cumulative rate drop from 56.52 to 31.51)

Author, Year Country	Study Design	Population Setting	CDI Definition Timing Testing	Intervention	Study Findings
Bishop, 2013 <sup>87</sup> United States	Prospective pre/post single site design. 3 year followup	Surgical patients at risk for CDI Connecticut community hospital (Stamford Hospital)	Defined: CDC NHSN criteria Timing: within 30 days of hospital exposure Test: EIA (2007-2008) PCR (2009-2010)	Resident rounding protocol Antibiotic stewardship Restriction of gastric acid suppression Contact isolation Hand hygiene (Terminal cleaning previously introduced)	CDI incidence rate: 41% decrease in annual rate, sustained over 3 year 64% decrease in patient days. (2.8/1000 vs 1.8/1000)
Mermel, 2013 <sup>88</sup> United States	Time series single site design. 6 year, 9 month followup. Prospective monitoring	Patients at risk for CDI 719-bed Rhode Island tertiary care hospital (Rhode Island Hospital)	Defined: CDC NHSN criteria Timing: includes patients with 30 day readmit with diarrhea and confirmed toxin present. Test: PCR	Progressive roll-out of elements of CDI control plan based on risk assessment Monitor CDI morbidity/mortality Improve testing using PCR Enhance environmental cleaning CDI treatment plans Other interventions	CDI incidence rate: drop from 12.2/1000 to 3.6/1000. Annual mortality drop from 52 to 19
Price, 2010 <sup>89</sup> United Kingdom	Interrupted time series single site design; 12 months pre, 15 months post. Retrospective	Patients at risk for CDI 820-bed teaching hospital and tertiary services (Brighton and Sussex University Hospital NHS Trust)	Defined: Liquid stool and positive test for Toxins A or B Timing: More than 3 days after admission or before 3 days after discharge Test: Not Reported	Restrictive antibiotic use and isolation or cohorting active cases	Increase in the CDI reduction rate from 3% to 8% per month.

CDI=*C. difficile* infection; CDC NHSN-Centers for Disease Control and Prevention National Healthcare Safety Network; SHEA=Society for Healthcare Epidemiology of America

## KQ3 – Standard Treatment

### Initial Cure

A single new RCT comparing metronidazole, vancomycin, and tolevamer was published in 2014.<sup>31</sup> Tolevamer was inferior to both metronidazole and vancomycin, and is not discussed further since it is not licensed by the U.S. Food and Drug Administration. The results of the metronidazole and vancomycin arms (n = 537) showed that vancomycin led to a significant increase in subjects achieving initial cure (81.1% vs. 72.7%; P = .02). When combined with the three previous RCTs comparing metronidazole to vancomycin,<sup>35-37</sup> the percentage of subjects achieving initial cure was significantly higher among those receiving vancomycin (83.9% vs. 75.7%; RR 1.08, 95% CI 1.02 – 1.15).

The second RCT identified in our update is a trial of fidaxomicin versus vancomycin (n = 509).<sup>32</sup> This study is the second of two studies that led to the approval of fidaxomicin for the treatment of CDI in the United States. Consistent with the first study, which was included in our original review, fidaxomicin performed similarly to vancomycin for the outcome of initial cure. Specifically, the percentage of subjects meeting initial cure did not differ significantly by treatment received (87.7% for fidaxomicin versus 86.8% for vancomycin; P = .79). Combining these results with those from the first study of fidaxomicin versus vancomycin<sup>34</sup> led to a similar finding of no significant difference in initial cure when stratified by treatment received (87.6% vs. 85.6%; RR 1.02, 95% CI 0.98 – 1.07).

### Recurrent CDI

The newly identified trial of metronidazole versus vancomycin<sup>31</sup> demonstrated no difference between the two agents for the outcome of recurrent CDI (20.6% vs. 23.0%; P = .64). Similarly, when data from this study were pooled with the three previous RCTs comparing metronidazole versus vancomycin, no significant differences were observed (16.5% vs. 18.7%; RR 0.89, 95% CI 0.65 – 1.23).

In contrast, the trial of fidaxomicin versus vancomycin demonstrated that use of fidaxomicin led to significantly fewer subjects having recurrent CDI (12.7% vs. 26.9%; P = .002). Similarly, when pooled with the data from the prior study of fidaxomicin and vancomycin,<sup>34</sup> recurrence remained less likely after fidaxomicin treatment (14.1% vs. 26.1%; RR 0.55, 95% CI 0.42 – 0.71).

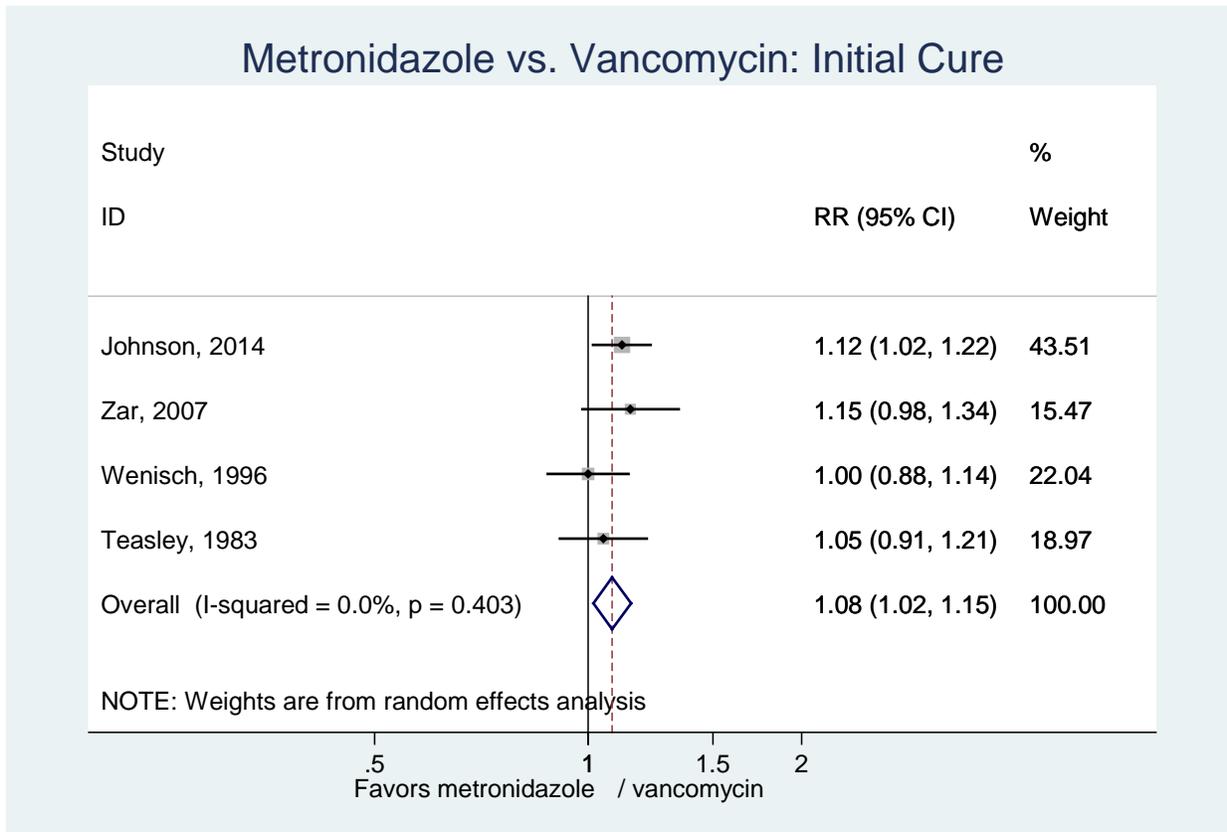
Finally, the observational study noted similar recurrence rates after oral metronidazole and vancomycin (20.6% and 19.0%, respectively), but higher rates after intravenous metronidazole (50.0%; P = .007).

**Appendix Table G2. Initial clinical cure: # subjects / # randomized (%) for vancomycin versus metronidazole**

Study	Vancomycin	Metronidazole	RR [95% CI]
Johnson, 2014 <sup>31</sup>	210/259 (81)	202/278 (73)	1.12 [1.02 to 1.22]
Zar, 2007	69/82 (84)	66/90 (73)	1.15 [0.98 to 1.34]
Wenisch, 1996	29/31 (94)	29/31 (94)	1.00 [0.88 to 1.14]
Teasley, 1983	51/56 (91)	39/45 (87)	1.05 [0.91 to 1.21]
Totals	359/428 (84)	336/444 (76)	1.08 [1.01 to 1.15]

CI = confidence interval; RR = relative risk

**Appendix Figure G11. Initial clinical cure: for vancomycin versus metronidazole**

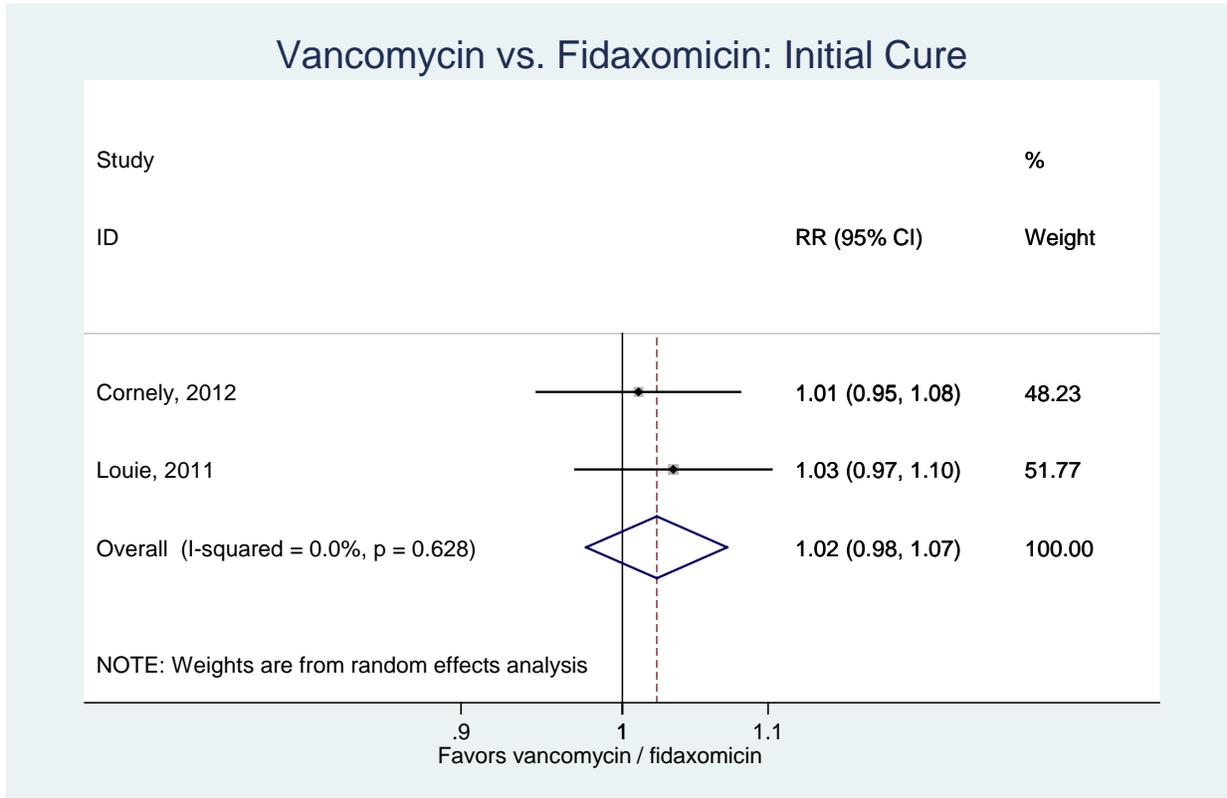


**Appendix Table G3. Initial clinical cure: # subjects / # randomized (%) for fidaxomicin versus vancomycin**

Study	Fidaxomicin	Vancomycin	RR [95% CI]
Cornely, 2012 <sup>32</sup>	221/252 (88)	223/257 (87)	1.01 [0.95 to 1.08]
Louie, 2011	253/289 (88)	265/313 (85)	1.03 [0.97 to 1.10]
Totals	474/541 (88)	488/570 (86)	1.02 [0.98 to 1.07]

CI = confidence interval; RR = relative risk

**Appendix Figure G12. Initial clinical cure: vancomycin versus fidaxomicin**

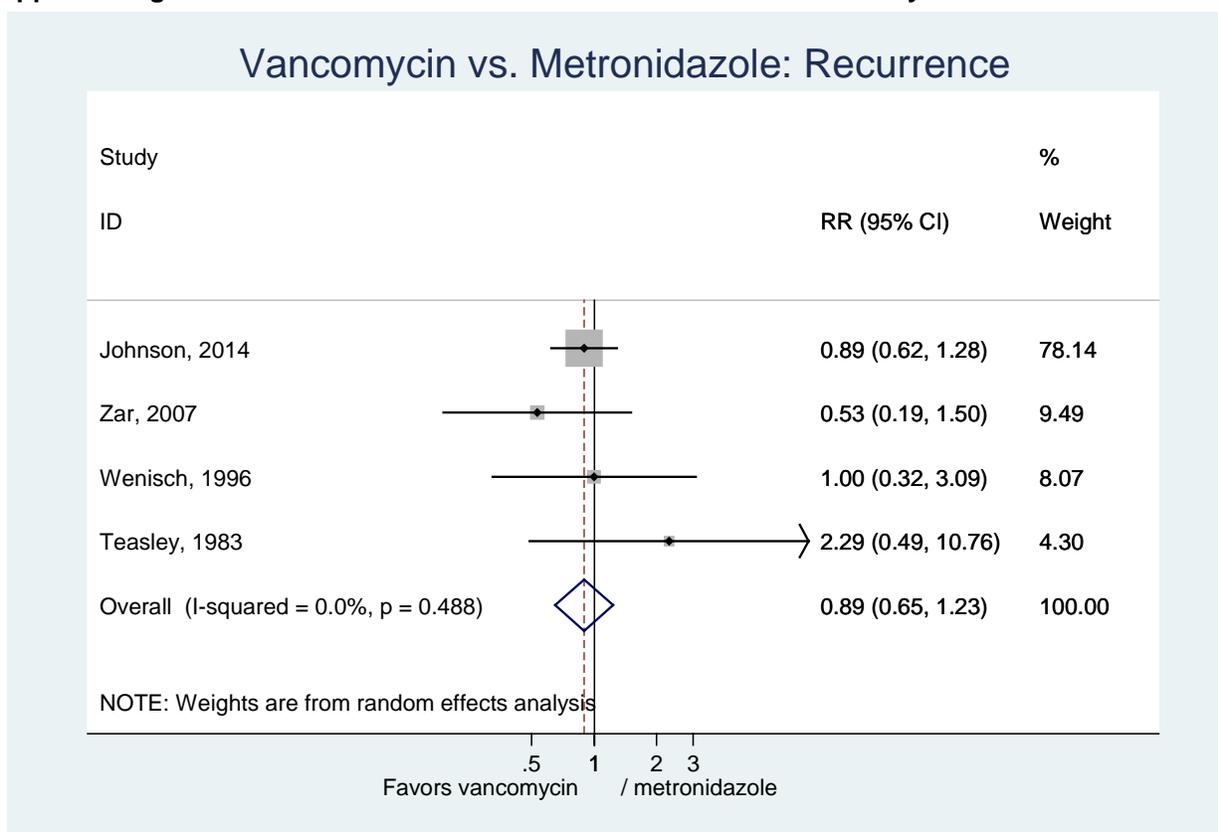


**Appendix Table G4. Clinical recurrence: # subjects / # initially cured (%) for vancomycin versus metronidazole**

Study	Vancomycin	Metronidazole	Relative Risk [95% CI]
Johnson, 2014 <sup>31</sup>	43/209 (21)	49/213 (23)	0.89 [0.62 to 1.28]
Zar, 2007	5/69 (7)	9/66 (14)	0.53 [0.19 to 1.50]
Wenisch, 1996	5/29 (17)	5/29 (17)	1.00 [0.32 to 3.09]
Teasley, 1983	6/51 (12)	2/39 (5)	2.29 [0.49 to 10.76]
Totals	59/358 (16)	65/347 (19)	0.89 [0.65 to 1.23]

CI = confidence interval

**Appendix Figure G13. Recurrence of CDI: metronidazole versus vancomycin**

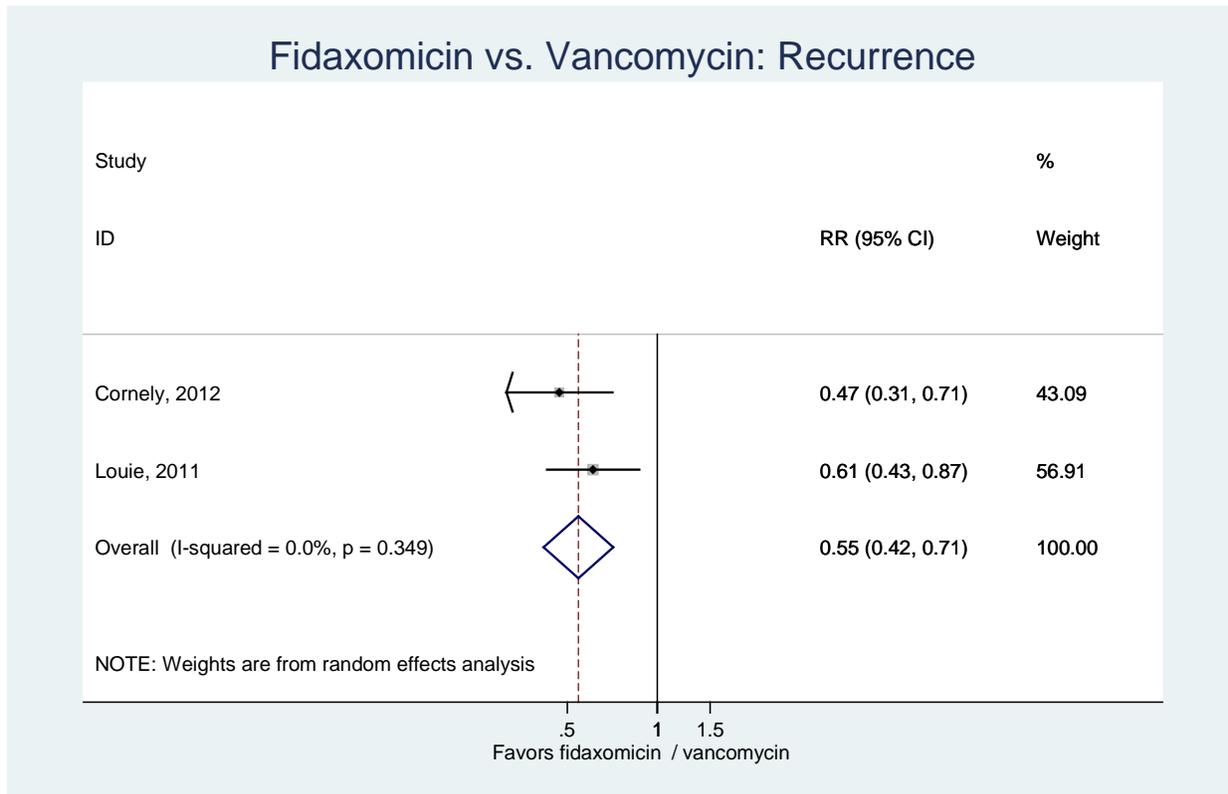


**Appendix Table G5. Clinical recurrence: # subjects / # initially cured (%) for fidaxomicin versus vancomycin**

Study	Fidaxomicin	Vancomycin	Relative Risk [95% CI]
Cornely, 2012 <sup>32</sup>	28/221 (13)	60/223 (27)	0.47 [0.31 to 0.71]
Louie, 2011	39/253 (15)	67/265 (25)	0.61 [0.43 to 0.87]
Totals	67/474 (14)	127/488 (26)	0.55 [0.42 to 0.71]

CI = confidence interval

**Appendix Figure G14. Recurrence of CDI: for vancomycin versus fidaxomicin**



**Appendix Table G6. Severe disease: # subjects / # (%)**

Study	Fidaxomicin	Vancomycin	Metronidazole	Finding
Cornely, 2012 <sup>32</sup> initial cure	48/63 (76)	43/61 (71)		RR 0.81 [CI 0.45-1.45]
Cornely, 2012 <sup>32</sup> recurrence	4/48 (8)	14/43 (33)		RR 0.26 [CI 0.09-0.72] results fragile to missing or reassignment
Johnson, 2014 Initial cure		50/64 (79)	61/92 (66)	RR 0.65 [CI 0.38-1.12]
Zar 2007 Initial cure		24/31 (78)	25/38 (66)	RR 1.20 [CI 0.92-1.57]

## KQ4 – Nonstandard Treatment

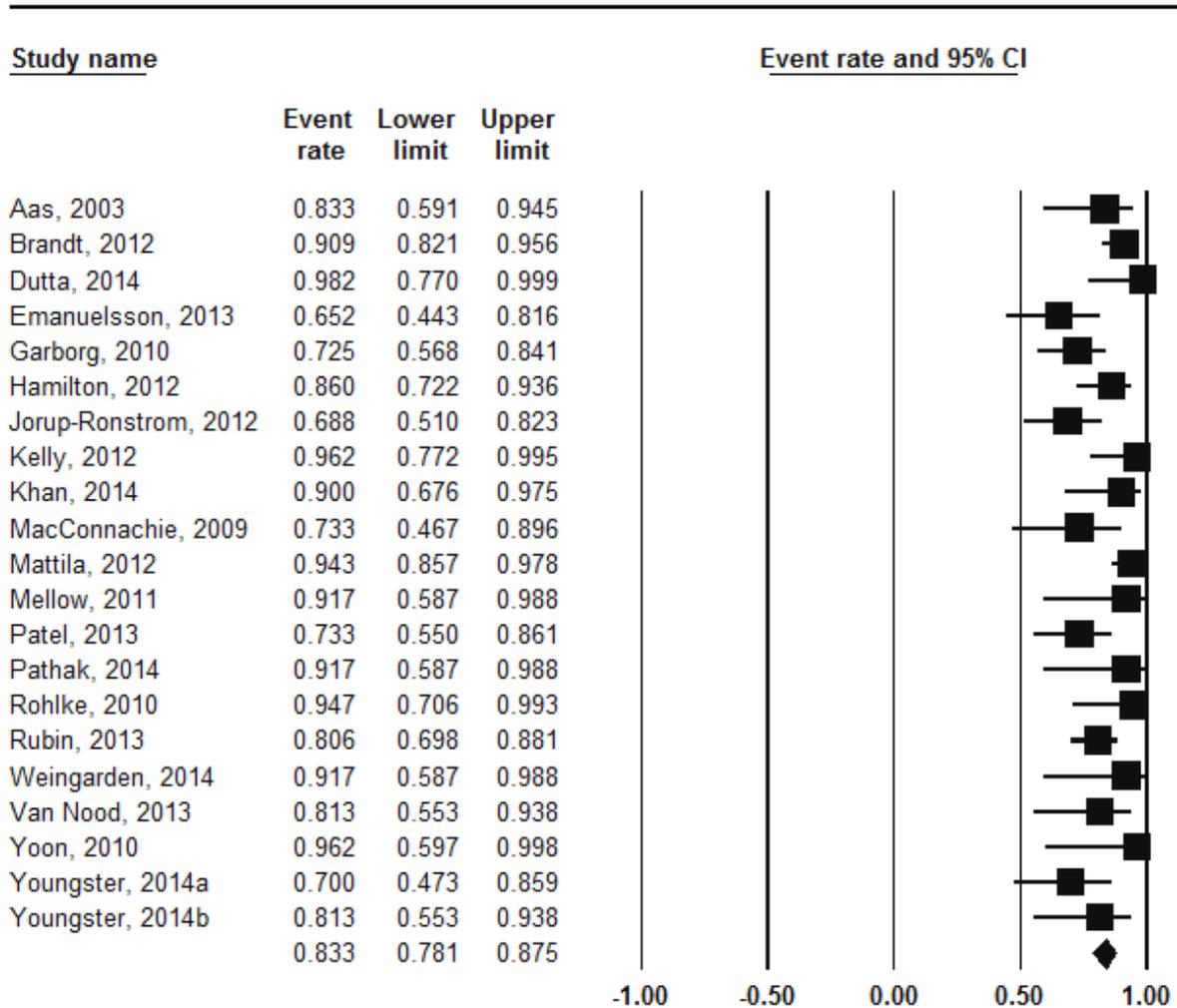
### FMT for Recurrent CDI

We identified 19 studies that addressed FMT for recurrent CDI of which two were small size RCTs and the remaining were observational. We identified two studies that included both recurrent and active CDI.<sup>45,57</sup> The inclusion criteria were  $\geq 3$  episodes of recurrent CDI in six studies,<sup>38,43,48,50,51,53</sup>  $\geq 2$  episodes of recurrent CDI in four studies,<sup>44,46,49,55</sup> while the remaining studies did not specify number of recurrent episodes. The studies included individuals between the ages of 7 and 90 years, with mean or median age of 65 years. In 18 of the 21 studies,  $>55$  percent of the participants were women. Two studies reported race and ethnicity distribution.<sup>38,51</sup> One of these studies enrolled 21 individuals for FMT of which 74% percent were white, 22 percent black, and 4 percent Asian.<sup>38</sup> The other study enrolled 26 individuals, 100 percent of whom were white.<sup>51</sup> Most studies were small, enrolling 12 to 70 individuals. Followup was variable, and ranged from 3 weeks to 8 years. Outcomes reported were resolution of diarrhea or symptoms, recurrence, and adverse events.

The two RCTs are noteworthy. One unblinded, three-arm RCT, conducted in the Netherlands, enrolled 43 adults with recurrent CDI with mean age of 70, 43 percent women.<sup>47</sup> Patients were randomized to oral vancomycin, FMT, or vancomycin plus bowel lavage. Followup was 10 weeks and the endpoint was resolution of diarrhea. The study was stopped early due to a large difference in the FMT and comparator groups (81% vs. 31% and 23%). FMT was administered via nasoduodenal tube. However, the CDI rate in the comparator groups was unusually low.

Youngster and colleagues conducted an unblinded RCT that randomized 20 individuals with recurrent CDI, with mean age of 54, to colonoscopic or nasogastric administration of FMT.<sup>42</sup> The study endpoint was resolution of diarrhea without relapse within 8 weeks. The authors found no difference between the two modalities of FMT administration.

Appendix Figure G15. Resolution of symptoms after initial FMT for recurrent CDI, all routes



**Appendix Table G7. Resolution of symptoms after initial FMT for recurrent CDI**

Study	Events / sample size (event rate)	95% CI lower limit	95% CI upper limit
Aas, 2003	15/18 (83)	0.591	0.945
Brandt, 2012	70/77 (91)	0.821	0.956
Dutta, 2014	27/27 (98)*	0.770	0.999
Emanuelsson, 2013	15/23 (65)	0.443	0.816
Garborg, 2010	29/40 (73)	0.568	0.841
Hamilton, 2012	37/43 (86)	0.722	0.936
Jorup-Ronstrom, 2012	22/32 (69)	0.510	0.823
Kelly, 2012	25/26 (96)	0.772	0.995
Khan, 2014	18/20 (90)	0.676	0.975
MacConnachie, 2009	11/15 (73)	0.467	0.896
Mattila, 2012	66/70 (94)	0.857	0.978
Mellow, 2011	11/12 (92)	0.587	0.988
Patel, 2013	22/30 (73)	0.550	0.861
Pathak, 2014	11/12 (92)	0.587	0.988
Rohlke, 2010	18/19 (95)	0.706	0.993
Rubin, 2013	58/72 (81)	0.698	0.881
Weingarden, 2014	11/12 (92)	0.587	0.988
Van Nood, 2013	13/16 (81)	0.553	0.938
Yoon, 2010	12/12 (96)*	0.597	0.998
Youngster, 2014a	14/20 (70)	0.473	0.859
Youngster, 2014b	13/16 (81)	0.553	0.938
Total	518/612 (85)	0.781	0.875

CI=confidence interval

\*Due to small sample sizes in 2 studies that reported 100% success (Dutta, 2014 and Yoon, 2010) the software used to generate confidence intervals lowered the estimates for these studies from 100% to 98% and 96%, respectively, to allow the upper limit of the 95% CI to be <1.0.

## FMT for Refractory CDI

Two studies reported outcomes for FMT in individuals with refractory CDI (defined as an episode that did not respond to antibiotic treatment). Both were from case series, totaling five individuals.<sup>41,53</sup> Overall, there was insufficient strength of evidence supporting the role of FMT in refractory CDI. Unfortunately few FMT studies provided detailed patient information to identify whether included patients could be considered refractory.

**Appendix Table G8. Resolution of symptoms after initial FMT for recurrent CDI**

Study	Refractory Sample	Cleared of CDI
Mellow, 2011 <sup>53</sup>	1	1/1
Youngster, 2014 (oral) <sup>41</sup>	4	2/4

## Probiotics for CDI

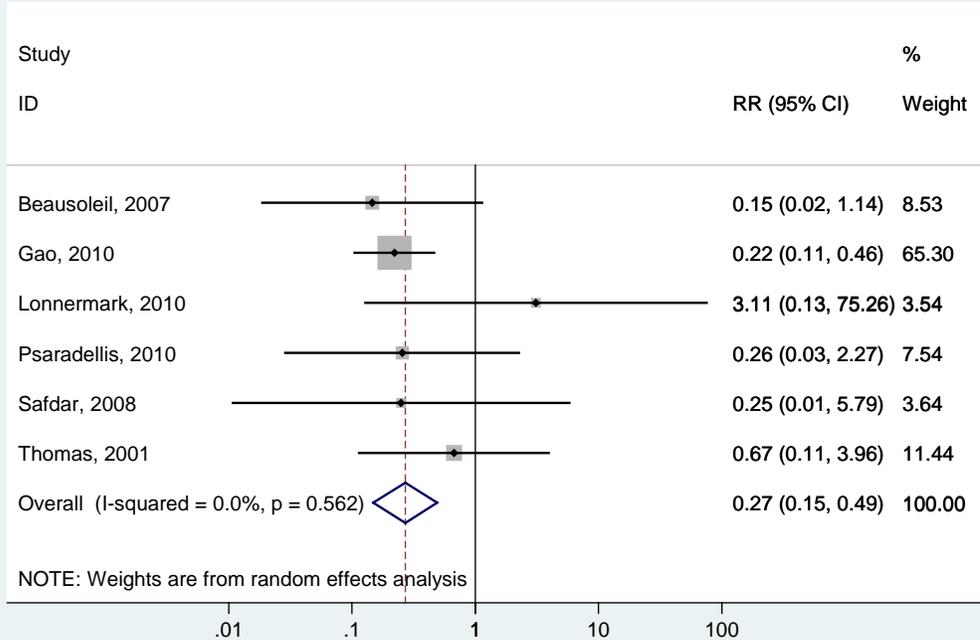
We identified a total of 17 studies that reported use of probiotics as adjunctive treatment for CDI: nine RCTs and one observational study were newly identified, while seven RCTs were included in the prior report. With the plethora of RCTs to provide a best evidence base, the observational study will not be discussed further.

Probiotics were administered as an adjunct to standard antibiotic treatment for CDI in all the studies. All studies included adult with mean reported age of 55 to 76 years. The studies enrolled 40 to 2981 subjects. The probiotics tested were lactobacilli species in seven studies, sacchomyces species (*S. boulardii*) in six studies, both lactobacillus and sacchomyces species in one study, lactobacillus and bifidobacterium in two studies, and VSL#3 in one study. VSL#3 contained *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, and *Streptococcus thermophiles*. The comparator was placebo in 15 studies and standard care or no treatment in one study each. In four studies (beausoleil, duman, mazide, can) the probiotic was continued for the duration of antiobiotic therapy,<sup>66-68,70</sup> while in the others, the probiotic was continued for 3 to 21 days beyond antibiotic administration. Study endpoint was diagnosis of CDI and followup variable, ranging from 7 days to 21 days after probiotic administration.

For quantitative analysis, we categorized probiotics as those containing single organism strains, such as only lactobacillus species, only *S.boulardii*, and those that contained multiple organisms. Overall, we found moderate-strength evidence that probiotics containing only lactobacillus organisms are more effective than placebo in preventing an acute episode of CDI. We found low-strength evidence that probiotics containing single organism (lactobacillus species) or *S.boulardii* given as adjunct to standard antimicrobial therapy, are comparable with placebo in preventing an episode of CDI. We also found moderate-strength evidence that the multiorganisms tested did not perform differently than placebo.

**Appendix Figure G16. Single organism probiotics for prevention of CDI-associated diarrhea**

Single organism probiotics for prevention of CDI-associated diarrhea

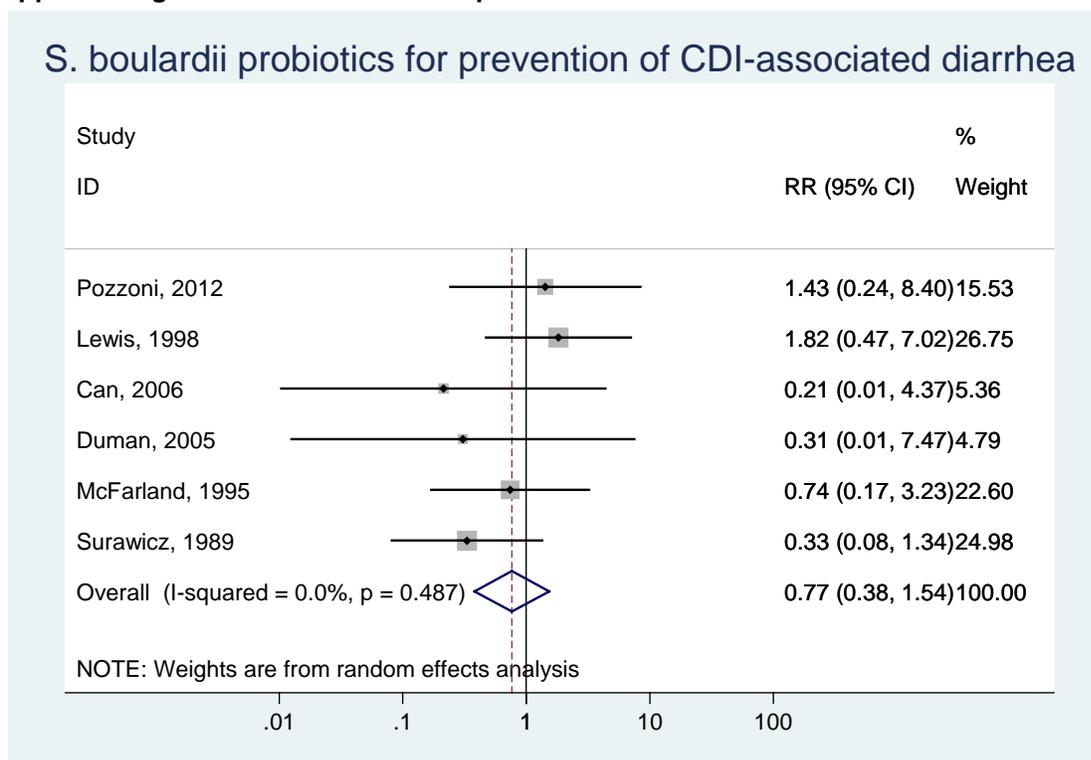


**Appendix Table G9. Single organism probiotics for prevention of CDI-associated diarrhea**

Study	Treatment CDI events (percent)	Control CDI events (percent)	Relative Risk [95% CI]
Beausoleil, 2007	1/44 (2)	7/45 (16)	0.15 [0.02 to 1.14]
Gao, 2010	9/171 (5)	20/84 (24)	0.22 [0.11 to 0.46]
Lonnermark, 2010	1/80 (1)	0/83 (0)	3.11 [0.13 to 75.26]
Psaradellis, 2010	1/216 (0.5)	4/221 (2)	0.26 [0.03 to 2.27]
Safdar, 2008	0/23 (0)	1/17 (6)	0.25 [0.01 to 5.79]
Thomas, 2001	2/133 (2)	3/134 (2)	0.67 [0.11 to 3.96]
Totals	14/667 (2)	35/584 (6)	0.27 [0.15 to 0.49]

CI = confidence interval

**Appendix Figure G17. *S. boulardii* for prevention of CDI-associated diarrhea**

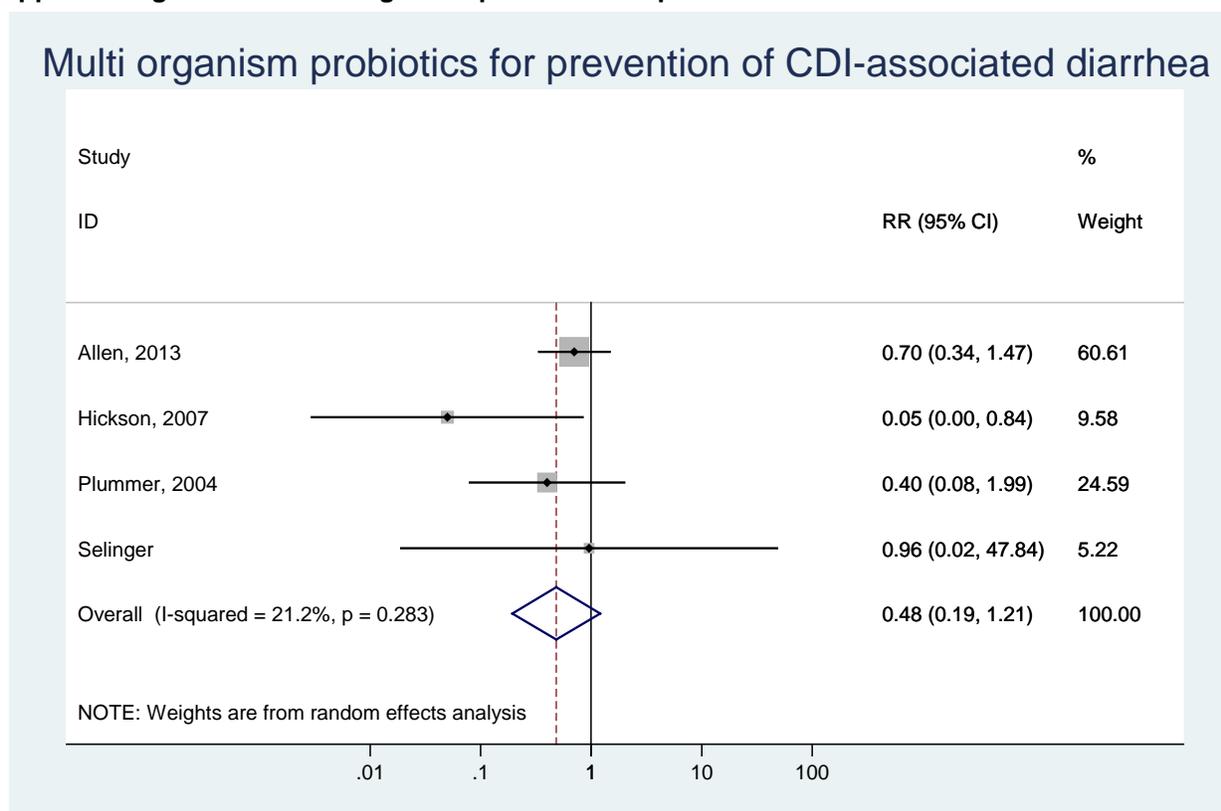


**Appendix Table G10. *S. boulardii* probiotics for prevention of CDI-associated diarrhea**

Study	Treatment CDI events (percent)	Control CDI events (percent)	Relative Risk [95% CI]
Pozzoni, 2012	3/141 (2)	2/134 (1)	1.43 [0.24 to 8.40]
Lewis, 1998	5/33 (15)	3/36 (8)	1.82 [0.47 to 7.02]
Can, 2006	0/73 (0)	2/78 (3)	0.21 [0.01 to 4.37]
Duman, 2005	0/196 (0)	1/180 (0.5)	0.31 [0.01 to 7.47]
McFarland, 1995	3/97 (3)	4/96 (4)	0.74 [0.17 to 3.23]
Surawicz, 1989	3/116 (3)	5/64 (8)	0.33 [0.08 to 1.34]
Totals	14/656 (2)	17/588 (3)	0.77 [0.38 to 1.54]

CI = confidence interval

**Appendix Figure G18. Multi-organism probiotics for prevention of CDI-associated diarrhea**



**Appendix Table G11. Multi organism probiotics for prevention of CDI-associated diarrhea**

Study	Treatment CDI events (percent)	Control CDI events (percent)	Relative Risk [95% CI]
Allen, 2013	12/1493 (0.8)	17/1488 (1)	0.70 [0.34 to 1.47]
Hickson, 2007	0/56 (0)	9/53 (17)	0.05 [0.00 to 0.84]
Plummer, 2004	2/69 (3)	5/69 (7)	0.40 [0.08 to 1.99]
Selinger, 2013	0.5/117 (0.4)*	0.5/112 (0.4)*	0.96 [0.02 to 47.84]
Totals	67/474 (0.8)	127/488 (2)	0.48 [0.19 to 1.21]

CI = confidence interval

\*Adjusted from 0 to 0.5 to facilitate analysis.

## Appendix H. Strength of Evidence

**Appendix Table H1. Strength of evidence assessments**

Comparison	Outcomes	Finding	Study Limitations	Directness	Precision	Consistency	Evidence Rating
<b>Diagnostics</b>							
LAMP (1 test, 11 arms)		Can serve as stand- alone test (both sensitive and specific)	Low	Direct	Precise	Consistent	High (unable to detect reporting bias)
	Sensitivity Specificity	0.945, 95% CI .0891-0.973 0.984, 95% CI 0.957-0.994					
PCR (9 tests, 25 arms)		Can serve as stand- alone test (both sensitive and specific)	Low	Direct	Precise	Consistent	High (unable to detect reporting bias)
	Sensitivity Specificity	0.943, 95% CI 0.924-0.958 0.974, 95% CI (0.963-0.981)					
Toxin A/B (8 tests, 57 arms)		Cannot serve as stand- alone test (specific but insensitive)	Low	Direct	Imprecise	Consistent	Moderate (unable to detect reporting bias)
	Sensitivity Specificity	0.711, 95% CI 0.667-0.752 0.98, 95% CI 0.974-0.985					
GDH (4 tests, 7 arms)		Cannot serve as stand- alone test (sensitive but not specific)	Moderate	Direct	Precise	Consistent	Moderate (unable to detect reporting bias)
	Sensitivity Specificity	0.937, 95% CI 0.887-0.966 0.939, 95% CI 0.894-0.966					
Test Algorithms (8 tests, 8arms)		Specific but insensitive	Moderate	Direct	Imprecise	Consistent	Low
	Sensitivity Specificity	0.684, 95% CI 0.547-0.795 0.995, 95% CI 0.989-0.998					
<b>Prevention</b>							
Antibiotic Stewardship (1 systematic review, 6 studies)	CDI Incidence						Low, per systematic review
Bathing (2 studies)	CDI Incidence		Moderate	Direct	Imprecise	Single Study	Low
Hydrogen Peroxide Vapor (3 studies)	CDI Incidence		High	Direct	Imprecise	Consistent	Insufficient

Comparison	Outcomes	Finding	Study Limitations	Directness	Precision	Consistency	Evidence Rating
Pulsed ultraviolet light (1 study)	CDI Incidence		High	Direct	Imprecise	Unknown	Insufficient
Handwashing campaigns (1 moderate risk of bias study as best evidence)	CDI Incidence		Moderate	Direct	Imprecise	Single Study	Low
<b>Treatment</b>							
Vancomycin vs. Metronidazole 4 RCT  N=872 initial N=705 recur	Initial cure	83.9% vs. 75.7%; RR 1.08, 95% CI 1.02 – 1.15	Moderate (high old base, low new larger)	Direct	Precise	Consistent	High (reporting bias undetected)
	Recurrent CDI	16.5% vs. 18.7%; RR 0.89, 95% CI 0.65 – 1.23	Moderate (high old base, low new larger)	Direct	Imprecise	Consistent	Moderate (reporting bias undetected)
Fidaxomicin vs. Vancomycin  2 RCT  N=1,111 initial N=962 recur	Initial cure	RR 1.02, 95% CI 0.98-1.07	Low (low both old and new)	Direct	Imprecise	Consistent	Moderate (reporting bias undetected)
	Recurrent CDI	RR 0.55, 95% CI 0.42-0.71	Low (low both old and new)	Direct	Precise	Consistent	High (reporting bias undetected)
Effect by Disease Severity – any antibiotic	Initial cure	NS	Moderate to High (high old base, moderate to high new)	Direct	Imprecise	Consistent	Low
FMT  2 RCT, 19 case series  N=516		Resolves diarrhea and prevents relapse in patients with recurrent CDI	High (case series except 2 high risk of bias trials)	Direct	Imprecise, but numerous trials	Consistent	Low (unable to detect reporting bias)
		Resolves diarrhea in patients with refractory CDI	High (all case series)	Direct	Imprecise, only 2 trials	Unknown	Insufficient
Multi-organism Probiotics vs placebo  4 RCT  N=1723	Primary prevention	RR 0.48, 95%, CI 0.19-1.21	High (dominated by Allen)	Direct	Imprecise (small number of events possible for small samples)	Consistent	Low (unable to detect reporting bias)

<b>Comparison</b>	<b>Outcomes</b>	<b>Finding</b>	<b>Study Limitations</b>	<b>Directness</b>	<b>Precision</b>	<b>Consistency</b>	<b>Evidence Rating</b>
S. boulardii vs placebo  6 RCT  N=588	Primary prevention	RR 0.77, 05% CI 0.38-1.54	High (not dominated)	Direct	Imprecise (small number of events possible for small samples)	Consistent	Low (unable to detect reporting bias)
Single strain lactobacillus  6 RCT  N=584	Primary prevention	RR 0.27, 95% CI 0.15-0.49	Moderate to high (dominated by Gao)	Direct	Imprecise (small number of events possible for small samples)	Inconsistent	Low

RR = relative risk [95 percent confidence intervals]; NS = No statistically significant difference.

## Appendix I. Ongoing Studies

**Table I1. Ongoing phase 3 or phase 4 studies**

<b>NCT Number</b>	<b>Title</b>	<b>Population</b>	<b>Interventions</b>	<b>Study Designs</b>
<b>Vaccines</b>				
NCT01887912	Study of a Candidate Clostridium Difficile Toxoid Vaccine in Subjects at Risk for C. Difficile Infection	Subjects >50 age at risk for CDI and substantial unmet medical need	Vaccine	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Single Blind (Outcomes Assessor) Primary Purpose: Prevention
<b>Antibiotics</b>				
NCT02200328	Efficacy of Metronidazole Prophylaxis Against Clostridium Difficile-Associated Diarrhea in High Risk Adult Patients	Inpatients 55 years and older at risk for CDI	Metronidazole vs placebo	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Single Blind (Caregiver) Primary Purpose: Prevention
NCT02237859	Vancomycin Prophylaxis in Recurrent Clostridium Difficile Infection	Adult inpatients with history of CDI within 16 weeks and treated with Flagyl or Vancomycin, or at risk	Vancomycin vs fruit juice/placebo	Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Double Blind (Subject, Caregiver, Investigator) Primary Purpose: Prevention
NCT01597505	Study of CB-183,315 in Patients with Clostridium Difficile Associated Diarrhea	Adults with CDI	Surotomycin vs oral vancomycin	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Treatment
NCT02179658	A Study to Compare Safety and Efficacy of Fidaxomicin with Vancomycin in Subjects with Clostridium Difficile-associated Diarrhea (CDAD)	Japanese adult inpatients with CDI	Fidaxomicin vs vancomycin	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Treatment
NCT02254967	Study to Compare The Efficacy of Vancomycin Therapy to Extended Duration of Fidaxomicin Therapy in the Clinical Cure of CDI in and Older Population (EXTEND)	Adults >60 with CDI	Fidaxomicin vs vancomycin	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment
NCT01987895	Phase 3 Study with Cadazolid in CDAD	Adults with CDI	Cadazolid vs vancomycin	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Investigator) Primary Purpose: Treatment

<b>NCT Number</b>	<b>Title</b>	<b>Population</b>	<b>Interventions</b>	<b>Study Designs</b>
<b>FMT</b>				
NCT02326636 Recruiting	Fecal Microbiota Transplant for Recurrent Clostridium Difficile Infection	Adult patients referred for recurrent CDI	Fecal Microbiota Transplant	Observational Model: Cohort Time Perspective: Prospective
NCT01958463 Recruiting	Transplantation of Fecal Microbiota for Clostridium Difficile Infection	Adult patients with recurrence within 6 months, or not responding to treatment	Fecal microbiota transplant	Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment
NCT02301000 Recruiting	IMT for Primary Clostridium Difficile Infection	Adults with primary CDI	Intestinal microbiota therapy vs metronidazole	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Single Blind (Outcomes Assessor) Primary Purpose: Treatment
<b>Probiotics</b>				
NCT01687543 Recruiting	Probiotics for Reduction of Infections with Clostridium Difficile in Critically Ill Patients (ProbiEnt)	Adult inpatient ICU	Dietary Supplement: L. plantarym 229 and L. plantarum 229v (+maltodextrin) vs matodextrin	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator) Primary Purpose: Prevention
NCT01873872 Recruiting	Evaluation of Probiotics and the Development of Clostridium Difficile Associated Diarrhea in Patients Receiving Antibiotics	Adult inpatients at risk for CDI due to antibiotic use	Theralac probiotic vs culturelle probiotic vs placebo	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Prevention
NCT02076438 Recruiting	Probiotics for Prevention of Antibiotic Associated Diarrhea and Clostridium Difficile Associated Disease	Adult inpatients with CDI	Probiotics: Culturelle (Lactobacillus Rhamnosus GG) vs placebo	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator) Primary Purpose: Prevention

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