Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection*

Draft review available for public comment from August 24, 2010 to September 24, 2010.

Research Review Citation: Butler M, Bliss D, Drekonja D, Filice G, Rector T, MacDonald R, Wilt T. Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection. Comparative Effectiveness Review No. 31 (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) AHRQ Publication No. 11(12)-EHC051-EF. Rockville, MD. Agency for Healthcare Research and Quality. December 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Title	Title: “Clostridium” should be spelled out and in italics (and “difficile” should be italics).	Correction made
Peer Reviewer #6	Front matter	Page v, line 9: C. difficile should be in italics (C. difficile) here and throughout (as was generally done). It would be standard practice to spell out Clostridium the first time Clostridium difficile is used. Also, here and elsewhere, the nomenclature has recently changed so that C. difficile associated disease (CDAD) is now referred to as C. difficile infection (CDI). I do appreciate the comments about this later in the report. As an aside, when we wrote the original SHEA position paper we intended CDAD to mean C. difficile associated diarrhea (not disease) – since that is the disease – but we did not make that point well and did not even rigidly adhere to it in the guideline.	Correction made. CDI is the accepted term
Peer Reviewer #2	Abstract	The sentences, "For diagnostic testing, commercially available enzyme immunoassays do not differ in sensitivity or specificity. Gene-based testing using PCR appears to be more sensitive without loss of specificity" -- while technically correct, do oversimplify the issues. There are, in fact, substantial differences in sensitivity and specificity between commercial assays, but the authors likely didn't include the articles that describe these differences because the articles didn't meet the authors' specifications. The authors may want to qualify these two sentences somewhat.	REVISED TEXT: For diagnostic testing, direct comparisons of commercially available enzyme immunoassays for *C. difficile* toxins A & B did not find major differences in sensitivity or specificity. Limited comparative evidence suggests that tests for genes related to the production of C. difficile toxins may be more sensitive than immunoassays for toxins A & B. However, estimates of the magnitude of differences in test sensitivities were not very precise. More importantly, studies have not established that any of the possible differences in test accuracy would lead to substantially different patient outcomes in clinical practice.
Peer Reviewer #4	Acknowledgements	Acknowledgements: Please correct my affiliation to: Professor of Medicine, University of Washington School of Medicine.	Our apologies; correction made.
Peer Reviewer #5	Executive Summary	The methods employed for KQ4, although likely similar to KQ3, are not explicitly stated on page 13.	Methods for KQ4 added.
Peer Reviewer #5	Executive Summary	Page 11, line 23: please clarify whether you mean community-associated (e.g. no healthcare exposures in last 12 weeks or greater) or community-onset (symptom onset in the community or within first 3 days after admission).	The reference is community associated as per CDC definitions.

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Peer Reviewer #5	Executive Summary	Page 11 line 28: the sentence about toxigenic strains should be clarified. Strains that produce toxin A and toxin B and strains that produce only toxin B have been described. Strains that produce only toxin A have not been described, but this is not clear from the current wording.	REVISED TEXT: Toxigenic strains are those that make toxin B (a cytotoxin) with or without toxin A (an enterotoxin).
Peer Reviewer #6	Executive Summary	Page 1, line 11 and throughout: Since Gram was a person, many use Gram-positive instead of gram-positive.	Corrected.
Peer Reviewer #6	Executive Summary	Page 1, line 13: I am not aware that there is actually any evidence the C. difficile causes mild diarrhea. It may be best just to eliminate the word mild.	Sentence was revised, and the term “mild” was removed.
Peer Reviewer #6	Executive Summary	Page 1, line 16: I do not think the majority of the literature supports a 7% mortality rate. Most would accept 1-2% as a likely rate.	Sentence was revised to “up to” as per the prevalence study.
Peer Reviewer #6	Executive Summary	Page 1, line 29: There has never been a confirmed toxin A only producing strain so you may wish to reword this sentence. C. difficile makes both toxins, toxin B only, or neither. Also, toxin A is the enterotoxin and B the potent cytotoxin (the reverse from what is written).	REVISED TEXT: Toxigenic strains are those that make toxin B (a cytotoxin) with or without toxin A (an enterotoxin).
Peer Reviewer #6	Executive Summary	Page 1, line 46: Increased toxin production is not consistent in all strains and not accepted as a cause of increased virulence (there are both up and down regulatory genes and the deletion only affects the down regulator).	Sentence was revised.
Peer Reviewer #6	Executive Summary	Page 3, Methods: It may be useful to include the date when the last search was done here as well as in the later section where it is mentioned.	Suggestion accepted.
Peer Reviewer #6	Executive Summary	Pages 3-4, Diagnostics: While I realize you cannot include this, I am also sending you our manuscript that is under review for this topic. It is the largest study done to date and would have met the stated criteria – and compares 80% of the testing used in the US. It is currently under review at Clinical Infectious Diseases and I suppose could go in the table near the end containing additional studies in progress. It was sponsored by BD GeneOhm (San Diego, CA).	ADDED TEXT TO SECTION ABOUT ONGOING STUDIES: More studies that compare toxin gene detection tests to other diagnosistic tests for toxigenic *C. difficile* are forthcoming and will support the notion the the gene-detection tests are generally more sensitive.

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Peer Reviewer #6	Executive Summary	Page 4, lines 15-18: I doubt this has been critically evaluated. In my own experience when a laboratory moves from testing any sample to only testing loose stools the prevalence of positive tests increases between 50 and 100% (from 10% positive to 15-20% positive), which helps test performance. I wonder if this should be reworded as the way it is now stated implies that studies have been done and they show no difference, which could be interpreted that testing formed stool is satisfactory practice and I do not think most experts would concur.	Section has been revised
Peer Reviewer #6	Executive Summary	Page 4, Prevention: I am also including our recent paper on prevention using hypochlorite in the endemic setting should that be helpful. The described program is still ongoing with the outcome sustained.	See response below.
Peer Reviewer #6	Executive Summary	Page 5, Treatment: I believe there was one clinical trial comparing vancomycin to placebo you may wish to look at (difficile was not in the title) – Mogg GA et al. Therapeutic trials of antibiotic-associated colitis. Scand J Infect Dis (suppl 22):41-45, 1980.	Reviewing this paper, we note that the facility, the number of subjects treated with vancomycin and placebo, and the pre-existing conditions documented, are all identical to those reported in another study by the same author group, and are almost certainly the same group of subjects being reported on twice. It would be inappropriate to include this study, since it appears to duplicate data already included in our analysis. We have briefly mentioned why this paper was excluded on page 74/128.
Peer Reviewer #6	Executive Summary	Page 12, Executive Summary Table 1, section 2 (gene detection tests). 1 paper missed was a prospective evaluation of PCR and routine tests (Peterson LR, Manson RU, Paule SM, Hacek DM, Robicsek A, Thomson RB Jr, Kaul KL. Detection of toxigenic Clostridium difficile in stool samples by real-time polymerase chain reaction for the diagnosis of C. difficile-associated diarrhea. Clin Infect Dis. 2007;45:1152-60). PCR was superior to all but culture. I wonder if the search terms were comprehensive enough – I do not think much was missed, but likely some.	Article was reviewed, but not included because the "in-house" gene-detection test did not appear to be commercially available and only one immunoassay for toxins A &B was tested.
Peer Reviewer #6	Executive Summary	Page 12, Executive Summary Table 1, Disinfection. 1 paper missed was a paper on a more endemic state (Hacek DM, Ogle AM, Fisher A, Robicsek A, Peterson LR. Significant impact of terminal room cleaning with bleach on reducing nosocomial Clostridium difficile. Am J Infect Control. 2010;38:350-3). A significant, sustained reduction was seen with bleach cleaning in 3 hospitals.	This paper, published in June, meets criteria with a before-after study design and was added to results and discussion sections.

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Peer Reviewer #6	Executive Summary	Page 12, Executive Summary Table 1, Alcohol gel. 1 paper missed was showed less reduction of C. difficile on hands using alcohol gels (Jabbar U, Leischner J, Kasper D, Gerber R, Sambol SP, Parada JP, Johnson S, Gerding DN. Effectiveness of alcohol-based hand rubs for removal of Clostridium difficile spores from hands. Infect Control Hosp Epidemiol. 2010;31:565-70.).	This interesting paper, published in June 2010, tests the effectiveness of handwashing with soap and hand disinfection with alcohol based hand rubs on hand spore counts and transmission of spores through handshaking. It does not measure the impact of hand hygiene on CDI rates and therefore does not meet inclusion criteria for this review.
Peer Reviewer #4	Executive Summary	Page 5, line 30 and elsewhere: Cytotoxin B is the cytotoxin, Toxin A is the enterotoxin.	REVISED TEXT: Toxigenic strains are those that make toxin B (a cytotoxin) with or without toxin A (an enterotoxin).
Peer Reviewer #4	Executive Summary	Page 5,Line 50: Should read "…based on as seen with…"	Corrected.
Peer Reviewer #4	Executive Summary	Page 11, Line 13: The word "pseudo membranous" as in the introduction should be "pseudomembranous" (one word), also Page 27, line 13.	Corrected.
Peer Reviewer #4	Executive Summary	Page 11, Line 32: The sentence "There is a small risk…" The authors probably mean "colonization" since "infection" with a nontoxigenic strain is not suggestive of disease. Moreover the statement that infection is common in healthy individuals is incorrect. Carrier rates are only 1 to 2% in healthy adults. Line 30: I disagree that infection occurs commonly in healthy individuals.	Section has been revised to clarify colonization versus infection.
Peer Reviewer #4/Peer Reviewer #5	Executive Summary	Page 15, Line 20: "metronidazole" is misspelled.	Corrected.
Peer Reviewer #4	Executive Summary	Page 15, Line 35: "nonserious" is not a word; you can say non serious instead.	Word was changed to "not serious"
Peer Reviewer #4	Executive Summary	Page 16, line 6. Which placebo was used?	Information on placebos as identified in the articles was provided in Table 19 in the body of the text.
Peer Reviewer #8	Introduction	Very authoritative statements were made in the introduction which, too, are not well supported and the references quoted are also not always of high quality.	We thank the reviewer for her comment. We have revised the section and responded to the specific comments as below.

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Peer Reviewer #8	Introduction	A single reference is quoted from which it is implied that rates in LTC facilities are higher than in acute hospitals even though the reference describes a single institution in which a range of rates that varied by time and ward location were reported, and the range included 0 (reference 7). This single institution study was compared to a cross Canada study involving many institutions. (page 17 paragraph 1).	Sentence was revised, further references added.
Peer Reviewer #8	Introduction	In paragraph 2 colonization and infection are considered equivalent (line 34) which is not in keeping with the definition listed above by the SHEA/IDSA.	Sentence has been revised to be consistent with colonization definition.
Peer Reviewer #8	Introduction	The statement regarding risk factors, remarks on the controversial data on gastric acid suppressant medications, although conflicting data also exist regarding the other risk factors exist none of these are described as controversial.	Section was revised and references, which are in support of acid suppression as a risk factor, identified with the search update were incorporated.
Peer Reviewer #8	Introduction	The statements regarding antibiotics and the pathophysiology of CDAD with respect to disruption of the colon flora refer to a single report of one patient with antibiotic associated diarrhea who did not have C.difficile (reference 12) and reference 11 demonstrated that more profound changes in bowel flora were observed primarily in patients with recurrent disease rather than primary CDI	Explorations of gut microbiomes are generally reported on a case study or case series basis, although more investigation is ongoing with metagenomic surveys. The cited articles are examples of such research. A comprehensive review of such articles is beyond the scope of this project.
Peer Reviewer #8	Introduction	Diagnosis - Page 18 - paragraph 2 - while the statement concerning the patient selection and stool consistency are important specifically with respect to the PPV of the tests in a low prevalence setting, the statement regarding testing patients with diarrheal stools who have one or more risk factors is referenced by older studies and may not be valid now if indeed newer strains are causing disease in populations not previously thought to be at risk.	Thank you for the comment.
Peer Reviewer #8	Introduction	Page 19 line 26 - "The emergence of the new, more resistant strains of *C. difficile* encourages nonantibiotic approaches to avoid potential future “super resistance.” Is this a relevant statement? Does it differ from other infectious agents such as *S.Aureus*, yet we do not do similar research to find non-antibiotic treatments for other super resistant organisms.	Sentence was deleted.
Peer Reviewer #8	Introduction	Prevention - In the introduction no discussion was given regarding review of strategies to improving patient's resistance to disease if exposed to the organism (a term that is perhaps more accurate than the term used "should infection occur") Page 19 line 40.	Text was added to elaborate on strategies to improve resistance.

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Peer Reviewer #8	Introduction	Scope of the review - page 20 line 24 " The general use of the term C. difficile associated disease, or CDAD, rather than C. difficile infection (CDI) underlines the major impetus of this review, which is concern for the presence of clinical disease, not asymptomatic carriage of the C. difficile organism." This statement as discussed above is not coherent with the guidelines proposed by the SHEA/IDSA statements.	Term has been changed to CDI for document.
Peer Reviewer #8	Introduction	Figure 1 - confusion with the terms colonization and infection - perhaps the term exposed to nontoxigenic and toxigenic strains should be used. Also the risk rates described as very small, moderate and substantial are not well defined or supported. Are there published estimates?	The figure is intended to give a general summary of the pathogenesis. Epidemiological research was not the focus of this review.
Peer Reviewer #8	Introduction	Glossary of terms - the definitions of carrier, CDI, CDAD and colonization should be reviewed.	Definitions have been revised.
Peer Reviewer #8	Introduction	Page 31 -Line 49 - This may also be due to the fact that *S. aureus* and *S. pneumoniae* are not part of the usual gastrointestinal (GI) flora, so there is a plausible biological mechanism to suggest that vancomycin therapy for CDAD may not select for resistance in these clinically important pathogens. This is an inaccurate statement, *S. aureus* is considered part of normal gut flora, MRSA enteritis has been described and this organism was once thought to be the cause of antibiotic associated colitis.	Section has been revised.
Peer Reviewer #8	Introduction	Page 39 - line 23 - there appears to be a consensus that the "gold though imperfect standard" is "Although stool culture is not clinically practical because of its slow turnaround time, the sensitivity and specificity of stool culture followed by identification of a toxigenic isolate (ie, toxigenic culture), as performed by an experienced laboratory, provides the standard against which other clinical test results should be compared **(B-III).** (SHEA/IDSA guidelines, *Infect Control Hosp Epidemiol* 2010; 31(5): 431-455).	REVISED TEXT: None of the reference methods that were used are true gold standards in that they are not 100 percent sensitive or specific for true toxigenic CDI and their accuracies are not all the same.
Peer Reviewer #5	Introduction	KQ1a could use some additional clarification. “Sample characteristics” should be “patient and stool sample characteristics.”	We appreciate the comment. However, as the sentence was a statement of the key question, we were unable to change it.
Peer Reviewer #5	Introduction	Page 19, line 33: this should be clarified; tests that detect the genes of C. difficile toxins, not genes related to toxin production	We believe the current statement to be correct.

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Peer Reviewer #5	Introduction	Page 28, line 27: very few labs in the US use toxin EIAs to detect toxin from culture isolates. Almost all use them directly on stool. This sentence seems to imply testing of isolates, and therefore culture for C. difficile, is common	REVISED TEXT; Greater than 90 percent of labs in the United States use one of the commercially available immunoassays to detect toxins in stool samples because they are fast, inexpensive, and technically easier to perform. However, the use of toxin gene-detection tests has increased in recent years.
Peer Reviewer #1	Introduction	Page 29, LINE 52: Change "hospital acquired infections" to 'healthcare-associated infections'	Suggestion adopted.
Peer Reviewer #1	Introduction	Page 29, LINE 53: Do not capitalize methicillin and italicize Staphylococcus aureus	Corrected.
Peer Reviewer #1	Introduction	PAGE 32: Figure 1: Change 'Risk of resolution' to 'Probability of resolution'	Corrected.
Peer Reviewer #1	Introduction	PAGE 36, LINE 14: 'sessation' should be 'cessation'	Corrected.
Peer Reviewer #1	Introduction	PAGE 37, LINE 44: 'Association for Professional Infection Control and Epidemiology' should be Association for Professionals in Infection Control and Epidemiology, Inc	Corrected.
Peer Reviewer #6	Introduction	Page 18, line 14: Pseudomembranous should be 1 word.	Corrected
Peer Reviewer #6	Introduction	Page 18, lines 16-19: It should also be mentioned that culture for toxigenic organisms and direct detection of cytotoxicity from stool have considerably different sensitivity (and specificity). Culture has better sensitivity and cytotoxin better specificity.	ADDED TEXT: Some of the variation is due to differences in the accuracy of the reference tests that are not 100% sensitive or specific. Toxigenic culture can be more sensitive than cytotoxicity assays that can be more specific. When a new test is evaluated using a more sensitive reference test, the estimate of its sensitivity may be lower.

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Peer Reviewer #6	Introduction	Page 18, lines 24-28: It would be worth discussing that the choice of comparator affects the performance of the evaluated tests. Lower sensitivity of the reference comparator (e.g., stool cytotoxicity) improves the sensitivity of the evaluated tests.	See response above. Both tests are being compared to the same imperfect reference test, thus the extent of this problem should be the same for both tests being compared and have no effect on the estimates of differences between tests. The text was not revised.
Peer Reviewer #6	Introduction	Pages 18-19, Treatment: In my review of the literature there seems to be evidence that treatment for less than 10 days leads to increased relapse rates and that 10-14 days should be given. If you agree, this should be stated – I can send you my review and reference, but it was only published in France after a closed symposium.	Among the 10 included standard treatment trials, only 2 (Young 1985[69], Keighly 1978[70]) used a duration other than 10 days (7 and 5, respectively). The relapse rates was not reported in one (Keighly), and was 37% in the other. Based on this limited amount of data, we do not feel that further speculation on the consequences of treatment for < 10 days is warranted, but have highlighted the fact that the most frequently studied therapy duration was 10 days. (Page 74 of 127 in draft document)
Peer Reviewer #6	Introduction	Page 25, CDI definition: I do like your definition but there will not be consensus on it as some experts will argue this means clinical disease.	We thank you for the compliment. However, we have changed the definitions as noted above.
Peer Reviewer #6	Introduction	Page 28, last sentence: I would reword to state it is important rather than it might be important.	Suggestion adopted.
Peer Reviewer #4	Introduction	Page 20 and page 84, line 54: The “fecal biomass transplant” term should be replaced by “fecal flora reconstitution.” There are several recent papers which could be included (Khoruts et al, J Clin Gastro 2010, 44:354-360; Rohlke et al, J Clin Gastro 2010; 14:567-570; Silverman et al, Clin Gastro Hep 2010; 8:471-473; Yoon et al, J CLin Gastro 2010; 44:562-566. Moreover, the use of fecal biomass should be clarified that this is used for recurrent C. difficile disease and not for primary therapy.	The term “fecal flora reconstitution” has been substituted through the document. Additional text was added to briefly mention the multitude of terms available in the literature.
Peer Reviewer #4	Introduction	Page 20: Sentence should add yeast Saccharomyces boulardii as an additional probiotic.	The introduction section does not list specific organisms studied as probiotics. The text does refer to either bacteria or yeast as potential probiotics.

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Peer Reviewer #4	Introduction	Page 23: In the papers on this topic, treatment of recurrent Clostridium difficile and prevention of recurrent Clostridium difficile are the same thing. That is, the outcome is prevention of further recurrences. They are not analyzing response to the therapy (resolution of diarrhea) itself since that is not the issue. The probiotic Saccharomyces boulardii should be added to studies of prevention of recurrences. There is low to moderate evidence for its efficacy in decreasing recurrences. You also need to separate out bacteria from the yeast Saccharomyces boulardii.	The designs of the studies have the probiotic administered concurrently with the standard antibiotic; resolution of CDI is not determined before the probiotic is given. Therefore, it is not possible to know that the probiotic did not a have some treatment effect and it is not possible to separate its effects as being for prevention of recurrence.
Peer Reviewer #4	Introduction	Page 24: Clarify antibiotic-associated diarrhea versus Clostridium difficile disease. Moreover, "Trials of probiotics for prevention are well represented in ongoing studies." I disagree with this because most of the trials are to prevent antibiotic-associated diarrhea with C. difficile as a secondary outcome and only a few have really been specifically to prevent C. difficile as a primary outcome.	See comment below. There are 12 studies of prevention of AAD and only 5 do not seem to include C. diff. Donna
Peer Reviewer #4	Introduction	Page 28. Stool culture is not a standard reference test because this cannot differentiate disease from carriers. Moreover Toxin A-negative and B-positive strains should be identified.	REVISED TEXT; Culturing C. difficile organism in stool specimens followed by testing grown colonies for toxins (toxigenic culture) and cultured cell cytotoxicity assays of the stool specimens are historically held as the standard reference tests;

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Peer Reviewer #4	Introduction	Page 29. Where is the data that vancomycin and metronidazole is ineffective in treating 25 to 30 percent of patients with CDAD? Is this referring to epidemics? Moreover, while C. difficile initially recurs in 20 percent of patients, it goes up to 40 to 60 percent of these patients who then spiral into multiple recurrences. Also please clarify the sentence." the emergence of new more resistant strains." What do the authors mean by "resistant," are they referring to in vitro the clindamycin and quinolone resistance or is there actual evidence of resistance to the treating antibiotics or more that there is increased severity of disease?	25-30% was thought representative of the proportion failing to achieve initial cure in standard treatment trials. The full range of subjects not initially cured in the included trials with vancomycin or metronidazole was 6% (Wenisch, 1996[65]) to 36% (Musher, 2006[64]). Accordingly, we have edited the text to reflect the uncertainty regarding in what percentage of patients treatment is ineffective. We agree that recurrence is more frequent among subjects having recurred once already; we addressed this by stating that "a subset of recurrent patients spiral into several subsequent recurrences". Because our review did not go into details of this subset of patients with multiple recurrences, we do not think that adding specific percentages adds substantially to the point being made, Regarding the comment on resistance: we agree that this is an imprecise sentence which added little context, and have deleted it from the manuscript.
Peer Reviewer #4	Introduction	Page 32, Figure 1: The word "infection" in the first box should be changed to "colonization with nontoxigenic strains"	Suggestion adopted.
Peer Reviewer #4	Introduction	Page 33, Figure 2. "Identify organism strain." This is not done except in evaluation of epidemics and is not feasible clinically.	Box removed from figure; it was not essential to the report.
Peer Reviewer #4	Introduction	Page 35, Line 55: "Non-standard therapy" - Why not just say non-antibiotic therapies?	Nonstandard was retained as the term. This key question was interested in treatments or therapies under investigation, whether through controlled trials or reported as case studies/series, that may become standard treatments over time should they prove efficacious and effective. Off-label use of tigecycline and the new OPT-80 are examples.

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Peer Reviewer #4	Introduction	Page 35, Glossary of Terms: CDI, I disagree with the use of colonization and infection. This must be clarified.	Definitions have been revised.
Peer Reviewer #4	Introduction	Page 36, Line 11: "Probiotics" - The standard definition of a probiotic is "a living substance which, when administered to the host improves their health."	The World Health Organization probiotics definition was used: "live microorganisms which when administered in adequate amounts confer a health benefit on the host" which is what most people use
Peer Reviewer #4	Introduction	Page 37, line 32: Address A positive strains.	Suggestion adopted.
Peer Reviewer #8/Peer Reviewer #5/ Peer Reviewer #2	Introduction	Line 27, page 27, should read, "... the 1980's.	Corrected.
Peer Reviewer #8	Methods	The selection of papers included and excluded does not always appear to be consistent. The inclusion criteria for " good quality studies" that identified specific risk factors were "(1) prospective study design; (2) the methods for the risk factor analysis were specified; (3) the study included a clearly defined control group; (4) the study was of risk for CDAD, not C. difficile infection or colonization; and (5) the CDAD definition included diarrhea and a positive test for C. difficile toxin. " yet in Table 7 Page 60, the first study by Sundrom quoted is retrospective, the second study by Walbrown is also retrospective and mainly looks at a pharmacy database and no other risk factors, and the study by Peled was limited to patients with antibiotic associated diarrhea. The study by Munoz was limited to heart transplant recipients and is not generalizable. As studies that did not meet their inclusion criteria were excluded, it is hard to justify their reasons for excluding other studies.	Sundram, Walbrown were removed – retrospective studies. Munoz for heart patient population. Peled was retained: Peled looked at CDI and toxin positive. Risk factors for CDI was not formally part of the scope of the CER. It was a supplemental issue we addressed within the framework of the narrative review.

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Peer Reviewer #8	Methods	It is also not clear how data from systematic reviews are incorporated. For example some of the studies from the systematic review by Planche on diagnostic tests are reviewed separately and included in the list of 10, but not others, the systematic review is also quoted in a different table. For the risk factors, only studies published after the systematic review by Bignardi are selected for review.	No systematic reviews were incorporated into analysis. Rather, results of this review were compared to other relevant systematic reviews for consistency of findings. The one somewhat exception to this was the Bignardi review. The risk factor question was a second order question, not directly answering the key question but providing information about which future prevention targets might be useful. Thus, the Bignardi review was used as a cut-off date and only literature published after the Bignardi review was examined. The Planche systematic review itself was referenced to make a point. Articles therein had to meet our specific criteria to be included.
Peer Reviewer #8	Methods	It is not clear how data from meta-analyses and systematic reviews are combined to produce the summary statements, perhaps this could also be clarified	As stated above, no previous systematic review was combined with a meta-analysis. Both the Planche and Bricker reviews were discussed, but only the articles which met inclusion criteria were included, abstracted, and entered meta-analysis at that point.
Peer Reviewer #5	Methods	KQ1 The target population should be expanded to include hospital epidemiologists and infection prevention and control specialists in addition to clinicians and researchers.	We believe this comment is intended to point out potential readership audiences for the report.
Peer Reviewer #5	Methods	Page 40, line 27-28: toxigenic C. difficile (not CDI)	Corrected.
Peer Reviewer #5	Methods	Page 41, line 38: additional variables have been associated with severity of CDI than those listed. Either expand list or clarify list is not all inclusive.	We have clarified that the list is not all-inclusive.
Peer Reviewer #5	Methods	Page 41, line 49: additional reasons include extremely high fecal levels of vancomycin would likely still prevent growth of Staph and strep with reduced sensitivity to vancomycin and also the mechanisms for vancomycin resistance is very complex and requires several genes, not a single point mutation.	We have incorporated these additional reasons into our manuscript.

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Peer Reviewer #1	Methods	PAGE 39, LINE 10: 'The topic for this report was nominated in a public process.' This sentence seems to deserve more explanation.	Sentence amended to document the nomination was received on AHRQs website for public nominations.
Peer Reviewer #1	Methods	PAGE 43, LINE 19: 'These criteria for include' Correct typo (remove 'for')	Corrected.
Peer Reviewer #1	Methods	PAGE 45, LINE 53: 'Grey literature'. Is that a sufficiently universal term so that it does not need a definition?	The term is well established in the systematic review field.
Peer Reviewer #1	Methods	PAGE 46, LINE 8: 'New York Academy of Medicine's Grey Literature'. Fix typo	Corrected.
Peer Reviewer #7	Methods	Inclusion and exclusion criteria are too strict and not always based upon deep subject matter understanding and clinical impact.	We appreciate the comment. However, it is a broad and general statement, thus difficult to respond to. The investigative team worked with the Technical Expert Panel through the course of the review and solicited feedback on the criteria and PICOT.
Peer Reviewer #4	Methods	Line 40: "use of gastric acid suppressant medications" although this is still controversial, this is becoming less so with more evidence suggesting an increased risk of enteric infections, including Clostridium difficile, with the suppression of stomach acid.	Statement has been reworded, with new references added.
Peer Reviewer #4	Methods	Page 43. "Cytotoxin testing is not standardized." This was a standardized test and is relatively accurate. The authors should clarify what they mean by "not standardized or perfectly accurate."	REVISED TEXT; Cytotoxicity testing is not a perfectly accurate gold standard. Methodological differences in the time to process and dilution of stool samples, the age and type of cultured test cells being used for the test, the antitoxins, and in the interpretation of results all can cause cytotoxicity assay results to vary. Toxins can degrade or be inactivated depending on how long stool specimens are stored before being tested and the storage temperature. Nevertheless, the imperfect cytotoxicity assay is often used as the reference test in the evaluation of other diagnostic tests for toxigenic *C. difficile*.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	One could argue that the summary of the Methods (page 13)should be longer, and/or contain more detail, but in reading and re-reading that section I'm not convinced that lengthening it would add much to their clarity	Thank you for the comment.
Peer Reviewer #8	Results	The numbers do not add up - 69 included studies plus 26 from hand searching and 3 from testing - adds up to 98, in the flow diagram - it is listed as 109 yet when broken down by key question , the number of included studies 10 (KQ1) , 38 (KQ2) , 12 for (KQ3) and 35 for (KQ4) adds up to 95. Perhaps this could be clarified.	Figures have been updated to include June update search.
Peer Reviewer #8	Results	Based on the 13 studies included for the risk factors, all of the studies which examined acid suppression, found a positive association, none of the studies which did not find an association are included , yet in their summary, they quote that there is conflicting data for acid suppression. It is not clear why some of those studies were excluded, or if the systematic review on these agents was not incorporated.	Summary was revised. See comments above.
Peer Reviewer #8	Results	Conflicting data on why certain studies show significant variation in specific antibiotic risks is not discussed, neither is the lack of a coherent explanation as to why all classes of antibiotics, irrespective of resistance pattern with respect to C. difficile spectrum of organisms, have been associated with CDI.	A discussion at this level was deemed outside the scope of this review. There are so many important questions and details relevant to C. difficile, but we are limited in report size, available time, and associated costs. Since risk factors were being treated as a second order question for Key Question 2, we felt a brief overview was the limit to what we could reasonably provide in this report.
Peer Reviewer #8	Results	The tables on the preventative studies appear complete, although non-antibiotic preventative treatment studies perhaps could have been included here. This would be more in keeping with the way the key questions were posed. For KQ4 - emphasis was made on these adjuvant therapies as treatments, yet in the results section prevention with these agents are discussed.	Since nonstandard interventions have been investigated as both treatments and prevention measures, they were grouped into a separate key question. The prevention key question, then, was constrained to actions that did not include giving a substance to a patient, regardless of the method, e.g. orally, injection, etc. A paragraph was added to the introduction that briefly discusses the types of nonstandard interventions under investigation for prevention.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	Page 59, line 43: The wording here appears to differentiate this study from other before/after studies, but this study has the same limitations. Although the CDI incidence declines after the introduction of the vapor system, the CDI incidence after the outbreak was not different from before the outbreak despite continued use of the vapor system. (see figure with monthly CDI incidence: only higher during outbreak period)	Section has been reworded.
Peer Reviewer #5	Results	Page 77, line 20: The clinical relevance of clearance of toxin and persistence of the organism are not clear, and if anything appears to not be predictive of response to therapy or risk of relapse. This should be noted.	We have noted that the significance is uncertain.
Peer Reviewer #5	Results	Page 77, table 16: Musher, 2006 should be metronidazole and nitizoxanide.	Corrected
Peer Reviewer #5	Results	Page 78, line 7: In response to several letters to the editor, there were two patients in the severe CDI group miscategorized as treatment failures, one in each treatment group, and data are provided for an intention to treat analysis. Inclusion of how the results change with these corrections should be considered.	We have included a discussion regarding the re-classification, and the modified intention-to-treat analysis provided in the letters to the editor and the responses. Additionally, we analyze the data using a strict intention-to-treat analysis, where all randomized subjects are included. The authors did not include subjects who were lost to follow-up, noncompliant, or intolerant of therapy.
Peer Reviewer #5	Results	Page 79, table 18, line 39: Musher, 2006 should be metronidazole and nitizoxanide.	Corrected

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	The description for the detailed analysis for KQ4 (p82-83) and accompanying tables 19 and 20 can use some clarification. Non-antibiotic treatments when studied for recurrent CDI are not administered to improve response to treatment for that recurrent episode, but rather to prevent future recurrences. The reason for enrolling only patients with recurrent CDI is these patients are at greatest risk for future CDI recurrences (versus patients with a first episode of CDI). It would be better to break this section up into 1) treatment of CDI, 2) prevention of recurrent CDI, and 3) primary prophylaxis. Tables 19 and 20 are confusing because they include many of the same studies, and the descriptions of the studies are not always identical when they appear in both tables. I suggest these tables be split into non-antibiotic treatments for treatment of CDI and to prevent recurrences, and primary prophylaxis.	Regardless of the intent of the investigators, in those studies of recurrent CDI, a probiotic was administered concurrently with an antibiotic to subjects with active recurrent CDI. It is not possible to determine that the probiotic had no effect on treatment of CDI and that its effect was limited to preventing recurrence. (See details below in response to Surawicz). Therefore, there are 4 categories of outcomes, treatment of CDI, 2) treatment of recurrent CDI, 3) prevention of initial CDI and 4) prevention of recurrent CDI. We debated on the organization of the tables. They are organized into the broad categories of treatment and prevention per the recommendation of the TEP. Each is further subdivided into prevention or treatment of initial or recurrent CDI. The reorganization suggested with only 3 categories of studies is based on the idea that probitoics were not part of treatment of recurrent CDI, which we noted is the case. The descriptions of the sample, groups, and parts of the methods are not identical because there is different information about prevention vs. treatment in the same study. The table information is specific to either treatment or prevention. We can add a subheading within the table to designate studies of initial vs. recurrent CDI to improve clarity.
Peer Reviewer #5	Results	Page 82, line 25 and page 15, line 55: immune whey does not enhance the immune response to C. difficile toxins, rather this is another attempt to bind the toxin with passive immunization.	This was revised accordingly.
Peer Reviewer #5	Results	Pages 91 and 95: Surawicz articles, all patients enrolled in this trial had recurrent CDI.	We reworded the sample description to clarify that all subjects had recurrent CDI.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	PAGE 47: Figure 3 categorizes each paper into one discrete category. Weren't there some papers that overlapped categories (e.g. comparing standard and non-standard treatments)?	Papers were categorized according to relevant comparisons.
Peer Reviewer #1	Results	PAGE 49, LINE 39: 'interdeterminate'. Fix typo	Corrected.
Peer Reviewer #1	Results	PAGE 55, LINE 44: Do not italicize 'spores'	Corrected.
Peer Reviewer #1	Results	PAGE 56, LINE 19: 'examined if disinfections' To what does 'disinfections' refer?	Sentence referred to environmental disinfection. Sentence was revised for clarity.
Peer Reviewer #1	Results	FIGURES: PAGE 58, LINE 24: 'Since alcohol does not kill C. difficile spores….'. This statement is misleading, implying that alcohol will not kill spores but soap will. In fact, no soap kills spores either. The reason that handwashing is recommending when C diff is present is because of the theoretical idea that spores will be removed by mechanical friction, not killed. Reword this statement.	Section has been revised.
Peer Reviewer #7	Results KQ1	Another example is in dealing with Question 1 where there is the conclusion that there is only "low-quality" evidence that nucleic acid amplification tests are more sensitive than the toxin EIAs. Not only does this not really appear the correct categorization when one looks at the detailed description of comparisons (seems as though it should at least be "moderate-quality") there is also the fact that other studies have compared home brew PCR to commercial EIAs that have bearing on the fact that the technology is fundamentally more sensitive owing to the fact that it bypasses variation in gene expression and temperature lability of the toxin at room temperature. The summary conclusion in Table 1 where evidence is said to be "low to moderate" is right on, somehow this clarity is lost in the text.	As explained in Table C-2 and the text, the evidence was judged to be low quality because mostly single studies or heterogeneity in the estimates from multiple studies, imprecise confidence intervals on differences, and no evidence that the differences would lead to differences in patient outcomes. The focus was on widely accessible commercially available tests because we did not want to generalize results from expert in-house use of non-commercial tests.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	Page 39, lines 15-41. These 2 paragraphs lay at the heart of the problem of the diagnostic testing problem, as commented upon earlier. One needs to realize that the laboratory cannot diagnose toxigenic CDI, all the laboratory can do is determine if any given specimen contains toxigenic C. difficile and then the diagnosis of toxigenic CDI is made by pairing that information with the clinical scenario. All would agree that anaerobic culture for toxigenic C. difficile is the most sensitive available assay and for the sake of comparison that is really the only true gold standard for sensitivity. The FDA is now realizing that in their clinical trial requirements. In that case it seems you really only have 2 papers published to use for comparison. An important comment also in here is that most do not mention if any specimen result blinding was done during comparative trials. From a practical point, as long as all testing is done concurrently, the investigators will be blind to culture results - particularly if a broth enrichment technique is used and isolate toxigenicity is confirmed, since well done culture takes a week or more to complete.	AGREE –Changed text referring to diagnostic tests to always refer to toxigenic C. difficile, not toxigenic CDI. The fact that culture is most sensitive is mentioned on page 26, next to last sentence. Of course culture alone is insufficient and needs to be combined with a test for toxins. Reference tests are discussed on page 39, lines 9 to15 and page 89, last sentence of the penultimate paragraph. We didn't want to exclude studies that used other reasonable reference tests. Since both tests being compared were compared to the same imperfect reference test, the impact of using a less sensitive references test on the estimated differences in test sensitivities should be minimized. The blinding is discussed on page 39, line 16-20 in the section on quality of studies and is summarized for each study in the evidence table in Appendix C. Our assessment of blinding did consider the sequence and timing of the tests.
Peer Reviewer #6	Results	Page 67, Table 17: There is a brief comment on relapse here. As noted, my sense of all the literature is that there is a trend to more relapse when therapy is less than 10 days. If there are any recommendations that can be made regarding duration of treatment that would be very helpful for this document.	As discussed above, only 2 of 10 studies used treatment duration < 10 days, and one did not report relapse. Accordingly, we do not think that further comment can be made regarding risk of relapse with shorter-duration therapy.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Most of the papers quoted did not have prevention of C. difficile disease as a primary outcome. The authors should note that these studies were done as prevention of antibiotic-associated diarrhea and there is no evidence that preventing antibiotic-associated diarrhea will also prevent C. difficile disease. For many of these there is some data on C. difficile but this is a secondary outcome and thus is not so strong.	Most studies did not specify that CDI was a "secondary" outcome. 7 manuscripts (Surawicz 1989, McFarland 1995, Lewis 1998, Thomas 2001, Lewis 2005 Alim Pharmacol Ther, Can 2006 and Hickson 2007) identified antibiotic-associated diarrhea (AAD) as a focus of the study in their titles and or purpose statement and 5 identified CDI as focus. We have added a statement that 5 of 13 studies seemed to analyze CDAD as a secondary outcome but the lack of a power analysis or having an underpowered study made it impossible to determine if the CDI outcome was weaker than the AAD outcomes.
Peer Reviewer #4	Results	Page 72, Line 48: "metronidazole" is misspelled	Corrected
Peer Reviewer #4	Results	Pages 74, 75, 76 Tables 10, 12 and 14. These are confusing. Please clarify what is treatment 1 and treatment 2, i.e. which is treatment and which is control.	We have attempted to clarify the specified tables.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Pages 74, 75, 76, Tables 10, 12 and 14. Again I disagree with the separation of treatment of recurrent C. difficile disease and prevention of recurrences. There is no evidence that there is a decrease in responsiveness to metronidazole or vancomycin with recurrent C. difficile. Rather, the goals of these studies were to prevent recurrences. Therefore, analyzing treatment of RCDI is a category which doesn't exist. The probiotics used in these studies were to prevent recurrences and not for the treatment of the recurrent C. difficile disease (S. boulardii, Lactobacillus plantarum). The statement on line 36 that all subjects were hospitalized inpatients in three studies is incorrect, many patients were outpatients in reference 71.	There were 3 studies that reported using a probiotic to treat recurrent CDI. In the study by McFarland ((JAMA 1994), 60 of the 124 subjects in the study had recurrent CDI at the start of the intervention. These subjects received the probiotic along with the antibiotic treatment. CDI was not shown to be resolved before the probiotic was given to consider the probiotic a preventive treatment. Therefore, these subjects were determined to receive a probiotic as treatment of recurrent CDI. The reference to treatment of recurrent CDI is appropriately limited to these subjects in the report. In the study by Surawicz (Clin Infect Dis 2001), the sample is described as patients with recurrent CDI both in the Methods section and in Table 1. Subjects received the probiotic along with a standard antibiotic. Because the antibiotic treatment was not completed and CDI was not shown to be resolved before the probiotic was given, it is not possible to conclude that the probiotic was for prevention of recurrence only and had no role in treatment. In the study by Wullt (Scn J Inf Dis 2003), the title and purpose of the study indicates that the probiotic was used for the treatment of recurrent CDI. The sample consisted of subjects who had recurrent CDI. Therefore, we classified the probiotic as a treatment and not a prevention of recurrent CDI. We thank the reviewer for pointing out the misclassification for Reference 71; it has been removed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Page 84, Line 32: Reference 75 should be added as well as to the following sentence. Three studies investigated a probiotic. In addition on line 42 there was a significant difference in studies 71 and 75 in recurrence rates in the patients taking S. boulardii in 2 subgroups.	In the tables, we do indicate a significant difference in recurrence for ref 71 (Surawicz 2001) but the p value for ref 75 (McFarland 1994) =.05 which is not <.05 or significant. We added the paper by McFarland JAMA 1994 (ref 75) to Table 20 and text related to the report in the section under prevention of recurrent CDI. CDI recurrence rate for the antibiotic-only group was reported in 2 separate subgroups (those with CDI at the start of study 22/34 and those without CDI at the start of study 8/33) which I added to table. They did not calculate the rate of recurrence for those with initial vs. recurrent CDI at the start of study like they did for the placebo-antibiotic-only group. They reported findings for prevention of recurrent CDI in the probiotic + antibiotic group as a percent of the entire sample of 124 pts = 41.3%, which I added to table. They also did not compare this finding with recurrence in the group receiving placebo-antibiotic-only. No statistical testing between groups was conducted.
Peer Reviewer #4	Results	Page 87. Table 19. Surawicz study – All the patients had recurrent C. difficile disease. The subset of 32 patients were those treated with high dose vancomycin. There was only a benefit of the adjunct probiotic in that subgroup.	We reworded the sample description to clarify that all subjects had recurrent CDI
Peer Reviewer #4	Results	Page 88: The Wullt study is also a study of recurrences and this should be noted	Results of prevention of recurrences are presented in a separate table than those of treatment. Findings about recurrences from the Wullt are reported in Table 20.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Page 88. The McFarland study from JAMA again is misinterpreted as the outcome was preventing a first or subsequent recurrences and not resolution of CDI	McFarland (JAMA 1994) enrolled patients with an initial episode of CDD and reported results for resolution of initial CDI as well as the recurrence of CDI.
Peer Reviewer #4	Results	Page 91, Table 20: These are studies of prevention of antibiotic diarrhea. This is not necessarily the same as prevention of C. difficile disease.	In studies of prevention of antibiotic diarrhea, results about prevention of CDI were reported and these are the results included in Table 20. Results of prevention of antibiotic diarrhea were not included as they were not the focus of this review.
Peer Reviewer #4	Results	Page 98, Table 21: Should be "Treatment of C. difficile or recurrent Clostridium difficile infection."	Table has been revised (and moved to Appendix).
Peer Reviewer #4	Results	Page 105, Line 30: Realistically, caretakers washing their hands will always be in the patient's room. I doubt many hospitals would have separate sinks outside of the patient rooms in order for separate hand washing.	Section has been revised to more general statement regarding possibility of recontamination within a CDI patient's room.
Peer Reviewer #4	Results	Page 105 Line 40: "..use of gastric acid suppressant medications" although this is still controversial, this is becoming less so with more evidence suggesting an increased risk of enteric infections, including Clostridium difficile, with the suppression of stomach acid.	See comments above – new literature on acid suppression has been added.
Peer Reviewer #4	Results	Page 106, Line 44: "Prevention of C. difficile disease, initial and recurrent cases" this needs to be clarified as mentioned previously.	See comments above.
Peer Reviewer #4	Results	Page 112, Table 22: "Treating Recurrent C. diffiicle disease" as mentioned, I would delete category and should be included with "prevention of further recurrences in patients who already have recurrent C. difficile infection"	See comments above.
Peer Reviewer #2	Results KQ1	The section on diagnostic tests is a bit confusing, but that unfortunately is the nature of laboratory comparisons of assays.	Thank you for the comment.
Peer Reviewer #8	Discussion	In the nonantibiotic interventions no studies on IV gamma-globulin were included.	Articles identified in the literature update have been added.
Peer Reviewer #5	Discussion	For KQ2 future research, minimum datasets should be defined. Another approach to addressing lack of data to support prevention recommendations are to conduct studies that model C. difficile transmission and the impact the intervention has on interrupting transmission. This may have the additional benefit of identifying new, potentially more effective methods to prevent transmission as well.	Suggestion adopted and section has been revised. The work by SHEA/IDSA in defining a minimum dataset for surveillance was cited as an example.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion	PAGE 105, LINE 3: 'suggesting the possibility that providers and hospital staff did not substitute alcohol gel for hand washing' This is only one of several explanations and should not be suggested as the only one.	Sentence was removed, section revised.
Peer Reviewer #1	Discussion	PAGE 105, LINE 24: 'It is very difficult, if not often impossible, to tease out the relative contributions of single components to the overall multiple component bundle of prevention strategies.' This statement is presented primarily as a 'negative'. Perhaps the authors should suggest that it may be also possible that single interventions will NOT work and only a bundle of interventions will be effective.	From an evidence standpoint, we do not believe the evidence allows us to make the suggestion that only bundles will work. However, we agree with the general perspective that it is a possibility and revised the section to reflect more neutral, rather than negative, language and instead focus on the difficulty of designing research for such studies.
Peer Reviewer #1	Discussion	PAGE 107, LINE 43: 'There are a number of important questions to be addressed regarding: (1) how to control, both infections and outbreak'. Remove comma after 'control'. Also infections are also part of outbreaks. Reword sentence	Sentence has been reworded.
Peer Reviewer #8	General	The organization and structure of the report is fair. With the major finding that there is very little good evidence to guide many of the present practices, it is not clear how it can inform policy and/or practice.	Thank you for the comment.
Peer Reviewer #8	General	Confusion of terms used in the document, in particular CDAD, CDI and the definitions used for infection versus colonization. Recent publications by experts in the field have defined C.difficile infection as "Summary Definition of CDI - A case definition of CDI should include the presence of symptoms (usually diarrhea) and either a stool test result positive for C. difficile toxins or toxigenic C. difficile, or colonoscopic findings demonstrating pseudomembranous colitis. (SHEA/IDSA guidelines, Infect Control Hosp Epidemiol 2010; 31(5): 431-455). In the document what others term as infection is instead called CDAD and what most clinicians would call colonization is referred to as infection. (page 22 - Pathogenesis of CDAD). Also the terms CDAD and CDI have been used interchangeably. (Page 30 - lines 7 and 11). This should be clarified and as there appears to be a gathering consensus that CDI replace the older term CDAD which included the differing states, from colonization to diarrhea to colitis and the severest form pseudomembranous colitis, perhaps the definition proposed in the SHEA/IDSA document should be used.	Definitions have been revised.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	General	The target population and audience are defined but some of the issues raised in the conclusion especially with respect to stakeholders and whether the infection as hospital acquired or not, were not really addressed in the document.	Thank you for the comment.
Peer Reviewer #8	General	The key questions are appropriate and clearly stated but as some of the non-antibiotic treatments are used as preventative measure perhaps those sections could have been discussed in Key question 2. Also the somewhat limited review of risk factors either should be done more completely or not included.	Thank you for the comments. See comment above to the reviewer regarding nonstandard interventions as a separate key question. As also stated above, risk factors were provided as information for potential future prevention research focus. It was a second order question. While not the primary focus of the review, we feel there is still some merit in providing the information.
Peer Reviewer #8	General	It also appears that the work is dated as many studies and guidelines have been published since March 2010 by important groups some of the statements made in the report are in contradiction with guidelines produced by medical opinion leaders in the field and may not significantly add much to those guidelines.	Thank you for the comment. As per standard procedure, we updated the literature search during the comments period, that is, June, 2010. Any relevant literature identified in that search was added to the review. Guidelines and expert opinion are not accepted input to systematic reviews. We appreciate the difference between systematic reviews and guidelines and feel that systematic reviews conducted by independent bodies can provide a useful contribution to the field.
Peer Reviewer #5	General	I strongly disagree with the definitions provided for CDI and CDAD. In the current C. difficile literature, CDI and CDAD are interchangeable to designate symptomatic infection due to C. difficile, and CDI is currently the preferred term. The definition for CDI in this review, to include asymptomatic colonization, has the potential to cause significant confusion we reviewing the current medical literature (in fact I have already heard it has caused confusion after this was posted for public comment!!!). When referring to C. difficile colonization to include symptomatic and asymptomatic states, then it should be referred to as C. difficile colonization (and not CDI). Areas where this must be changed include, but may not be limited to, page 11, line 30; page 12, line 24; page 25, line8; page 29, line 40; page 30, line 24; page 32, figure 1; page 34, figure 3; page 35, line 8; page 41, line 14;	Definitions have been changed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	Although it is mentioned there are several potential explanations for why CDI incidence has not increased when switching from soap and water to alcohol hand hygiene products, in numerous occasions it states a possible explanation is healthcare workers continued to use soap and water after caring for a patient with CDI in the alcohol hand hygiene product period without providing other explanations. This is repeated so often it appears the reviewers feel this is a foregone conclusion. However there are many potential explanations, some of which are more likely: glove use prevents colonization of hands when used properly, a typical 20% to 40% compliance with soap and water (even if performed correctly which most often it is not) may not be high enough to impact C. difficile transmission, rubbing hands when using alcohol hand hygiene products may push C. difficile spores to surfaces of the hand less likely to come in contact with a patient, there is a risk of recontamination of hands after removing gloves and then using the sink in a patient room, soap and water may not remove a sufficient number of C. difficile spores. Although the sample size is extremely small, the 1989 NEJM article by McFarland et al found contamination of healthcare worker hands after caring for a patient with CDI if gloves were not worn was no different whether or not the healthcare worker washed his/her hands. Conversely C. difficile was not recovered from the hands of any of the healthcare workers who wore gloves. If not apparent at this point, I feel the assumption about continued use of soap and water as a potential explanation for lack of increase in CDI during periods when alcohol hand hygiene products were used should either be removed, or other potential explanations be included each time. Places where this occur include, but may not be limited to, page 17, line 42; page 29, line 57; page 55, line 39; page 58, line 32; page 105, line 1	Suggestion adopted. Changes made in indicated areas.
Peer Reviewer #5	General	The report is well structured and organized. It will be useful for guiding future research to eliminate our current gaps in CDI diagnosis, prevention and treatment. It will not be useful for guiding policy or practice decisions. However, this is due to the well documented lack of data to support policy or practice decisions and not a criticism of the document.	Thank you for the comment.
Peer Reviewer #1	General	Each chapter ends rather abruptly without a concluding or summarizing statement. It may be too redundant to have a summary again, but just commenting.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	The overall report is very meaningful from the standpoint of pointing out current evidentiary shortcomings. The target population, although not explicitly defined where I could find it, seems clear to be policy makers and other guideline writers, unlikely (as written) to penetrate to the level of providers/clinicians. Key question are appropriate and explicit. However, it suffers, like many strict evidentiary reviews, by not being as clinically useful as it could be. For example, in the question of evidence to support oral vancomycin is one of the most important questions addressed and yet, because results have not yet appeared in print (delayed because there is not a funding source that is pushing from behind because the pharmaceutical company, Genzyme, missed the endpoint for their 3rd arm study drug), authors have missed strong evidence confirming findings of the Zar study. These results have been reported in abstract form: Louie T, Gerson M, Grimard D, et al. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with Clostridium difficile–associated diarrhea (CDAD). In: Proceedings of the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; 2007; Chicago, IL. Washington, DC: ASM Press; 2007. Abstract K-425a	We highlight the fact that this work has been presented in abstract form, and that if/when it is published it could add to the body of evidence with which the comparison between vancomycin and metronidazole could be made. See pages 74 and 109 of 128.
Peer Reviewer #7	General	Report is useful to research and policymakers. Not useful clinically.	Thank you for the comment.
Peer Reviewer #4	General	The inclusion of trials of prevention of RCDAD are analyzed for treatment of RCDAD. In my opinion, this is a misinterpretation of these studies.	See details of studies and our rationale above re: treatment of recurrent CDI.
Peer Reviewer #2	General	the Introduction (and some of the rest of the document) contains phrases such as "exceedingly low" or "profound alterations" -- the terms are too strong for a publication of this type.	Thank you for the comment. Revisions to terminology have been made.
Peer Reviewer #2	General	The section on diagnostic tests is a bit confusing, but that unfortunately is the nature of laboratory comparisons of assays.	Thank you for the comment. Some revisions have been made, although it is uncertain whether they were enough to remove all potential confusion.

Commentator & Affiliation	Section	Comment	Response
Public Comment	General	My comment is general. I don't believe you have asked a key question about diagnosis. Because this is a hospital-acquired infection that can take time to manifest itself, it may only be discovered in the PCP environment. If they wait for patients to give a full list of symptoms, it may never be diagnosed at all. My father had c. difficile for two years before it was identified and by then he had, in essence, digested his organs. He was losing weight and had no appetite. I believe he failed to report diarrhea as one of his symptoms, being a stubborn, private individual who hated most medical care, especially antibiotics. You could perform a service if you focused also on the practical side of identification and diagnosis in the PCP office in a flowchart method – IF patient presents with weight loss AND had surgery in the past year, THEN ask about other symptoms of c.div. (such as diarrhea).	Thank you for the comment. While it is outside the scope of these systematic reviews to provide practice guidelines, the comment is an important one. The discussion section has been revised to include mention of the importance of clinical diagnosis in outpatient settings since CDI can manifest several months after hospital exposure or antibiotic use.
Peer Reviewer #8	Appendix	**Appendix Table C3. Description of studies evaluating risk factors for *Clostridium difficile* associated diarrhea (CDAD)**Walbrown, is described as being a prospective observational multicenter cohort study, while the methods section of the paper has the following statement "The study consisted of (1) an assessment of the incidence rates of CDAD per 1,000 days of antibiotic therapy and (2) a retrospective electronic medical record review of patients with a positive *C. difficile* toxin." The only risk factor that was examined was a formulary change.	Article has been removed from risk factor table.
Peer Reviewer #2	Appendix	authors should use the same font type and size throughout	Thank you for the comment. The appendix has undergone editorial review according to the required style guidelines.