Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	For KQ2, especially with regards to antimicrobial stewardship, I am concerned that your search strategy will leave out studies. There are several studies (mostly quasi-experimental) of stewardship interventions that have C diff incidence as one outcome but would not necessarily have this in the title. Specifically, would look at Feazel LM et al. J Antimicrob and Chemother 2014; Aldeyab MA, et al J Antimicrob Chemother (2012) 67 (12): 2988-2996; and Dellit TH, et al Infect Control Hosp Epidemiol (2014) 35(5): 589-90)	The search algorithm looked for "difficile" in any part of the database record, not just the title. We also located articles by handsearching other relevant systematic reviews. However, all three articles mentioned by the reviewer were captured in the searches.
Peer Reviewer #1	Methods	For KQ2, would explicitly state whether each study was done in an outbreak setting or not.	We have added the information to the evidence table G1 in the appendix.
Peer Reviewer #1	Methods	p. 7, line 30: how exactly do you plan on updating the searches and until what date?	The update search, using the same search algorithm and screening methods, was conducted while the report was out for peer and public comment.
Peer Reviewer #2	Methods	The inclusion and exclusion criteria appear to be justifiable. It should be noted, however, that for the intervention section, studies that assessed clinical outcome such as Clostridium difficile infection (CDI) were used. Studies that looked at microbiologic end points such as environmental cultures, etc., seem to be excluded. While such surrogate markers may be unreliable since data are meager relating environmental culture results to clinical outcome, this perhaps should be more explicitly stated. This exclusion also decreases the number of studies evaluated, thus decreasing the overall quality of the data. It is likely this is justifiable, but should be clearly noted (it is seen in the limitations section now, but not explicit before).	We have added environmental swabbing and culture to the exclusion criteria for KQ2.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	The methods described have appropriate inclusion and exclusion criteria. The search strategy listed is logical and clearly described. Appropriate definitions are explicitly stated by the authors. The overall framework for data gathering, analysis and synthesis are appropriate and within stated guidelines.	Thank you for the comment.
Peer Reviewer #4	Methods	The inclusion and exclusion criteria are understandable and justifiable. The search strategies are explicitly stated and logical. The definitions or diagnostic criteria for the outcome measures seem appropriate. I do not claim expert knowledge of statistical methods however those described in this manuscript are understandable and logical.	Thank you for the comment.
Peer Reviewer #5	Methods	no specific comments	NA
Peer Reviewer #6	Methods	There is a terse but detailed methods section including literature search strategy, study selection and data extraction, risk of bias assessment, data synthesis, strengths of evidence with definitions for high, moderate, low and insufficient.	Thank you for the comment.
Peer Reviewer #6	Methods	Although the areas searched seems appropriate Medline and Cochran and then separate clinical trial funding sources, I am wondering if this captured all appropriate. Specifically, AHRQ had funded a s series of HAI prevention projects some of the results presented at their and published together and wondering if would have captured all (recent ICHE and AJIC issues 2014 and AHRQ publication on methodology in 2014- not sure if in in these search engines).	The ICHE and AJIC issues were indexed on Medline and subject to the search algorithm. In addition, we handsearched relevant or related systematic reviews.
Peer Reviewer #6	Methods	It would helpful to elaborate on the applicability section as this type of review may have a wide audience who would not be familiar with PICOTS.	We have added the definition of PICOTS to the section.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Methods	yes. However I would delete the lactoferrin paper, it is a tiny study, and not worth mentioning, and unlikely to be clinically relevant in the future. It's inclusion dilutes the quality of the paper.	The lactoferrin paper meets the inclusion criteria. One of the strengths of systematic review methodology lies in the a priori and transparent decision rules for study selection. Without commenting on the potential scientific merit of lactoferrin as an adjuvant treatment, a decade ago probiotics and fecal transplantation were also on the fringes of scientific inquiry.
TEP Reviewer #1	Methods	Also new paper RCT of FMT for RCDI should be included: Camarotta et al. APT 2015; The role of FMT for RCDI is such an important clinical topic that it must be added as it is the 3d RCT and would likely change the evidence from low to moderate. For clinicians, this is very important information, as the patients with multiple recurrences do not have any other treatment options other than being on vancomycin for life.	Thank you. This paper was picked up with the update bridge search and is included in the final paper.
TEP Reviewer #2	Methods	Metaanalytic methodology is sound. Identified literature for each key question appear to be properly identified as well as appropriately included or excluded.	Thank you for the comment.
TEP Reviewer #3	Methods	Inclusion and exclusion criteria appears well justified. Search strategy well-stated and logical. Statistical methods appear to be appropriate.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Methods	What criteria were used for "sustainability" in KQ2c?	Evidence suggesting that the prevention practice has become part of standard infectious disease prevention practices within the facility beyond the special efforts expended during a research trial or initial program roll-out. As noted in the results section, evidence that studies documented sustained practices over several years suggests the practices had become part of standard procedures and did not required special effort for continuation.
TEP Reviewer #3	Methods	What are health system outcomes for KQ1c?	Unfortunately, no studies with health system outcomes were identified. We would have been open to outcomes such as improved outcomes for patients or measured improvement for health systems (with respect to cost of care, length of stay, or rates of CDI. We have noted this in Table 1.
TEP Reviewer #4	Methods	Yes.	Thank you for the comment.
Peer Reviewer #1	Results	Overall, the presentation of the results is clear and the use of figures and appendices appropriate.	Thank you for the comment.
Peer Reviewer #1	Results	KQ1: This is in the appendix, but would comment as to the fact that the majority of the studies were on unformed stool.	We have added this to the text.
Peer Reviewer #1	Results	KQ1: Would flesh out the algorithms more to state exactly which ones were studied.	There is substantial heterogeneity with respect to the second step (after GDH-EIA) between studies, making this relatively unwieldy to do, and would detract from the key messages.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	You focus a lot on +LR in the bullet points but then later state that sensitivity and —LR are very important parameters clinically (p 23, lines 20-21). Would focus on these parameters, then (e.g. LAMP vs. PCR likely not appreciably different with regards to these).	Thank you for this comment; we attempted to present the bulleted results in a standard fashion in order to make the report as readable as possible. However, we can see how it may appear we focused more on a positive test in the bullets and suggested negatives are more important later. Thus, the order of the wording in the text has been changed.
Peer Reviewer #1	Results	KQ2: It looks like citation 38 is now published in ICHE 2014; 35(10): 1209-28. Also, the same group has published analysis of ASP in the outpatient setting. Please also see my comments in the Methods section above.	We cited the full report produced for the VA evidence synthesis program. The later journal publication was a derivative product and treated as a duplicate article.
Peer Reviewer #1	Results	KQ2, p 14, line 35-36: can you quantify the reduction in CDI? Is this in the outbreak setting or not?	Unfortunately, each of the ASP studies included in the review used different measurement techniques and did not report the numbers in any combinable way. If we reported only those that provided numbers in a useful manner, it may not be representative of the set as a whole.
Peer Reviewer #1	Results	KQ2, Transmission Interruption: Again, would state whether these studies were in an outbreak setting or not.	We noted that no study self-identified as taking place in an outbreak setting.
Peer Reviewer #1	Results	KQ2, p 15, line 25: not clear why cipro versus levo would make a difference with regards to C diff rates. Also, what do you mean by “resulting decline in levofloxacin and quinolone”?	We have removed the sentence from the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	KQ2, p 15, line 48-49: For ASPs, mortality is often reported—would consider this a "harm."	The ASP systematic review reported mortality as a primary outcome. We have added the mortality outcomes for the studies that reported CDI incidence to the harms section. There were not significant differences between comparisons.
Peer Reviewer #1	Results	KQ3: Why not include subgroup analyses?	Data regarding the sub-group of patients with severe disease is presented. We did not feel that the number of available studies allowed for further meaningful subgroup analyses.
Peer Reviewer #1	Results	KQ4, table 7, FMT "refractory CDI" is not a finding	This has been clarified in the table to indicate the findings for the category.
Peer Reviewer #1	Results	KQ4, p 19, line 9, would change "adjunctive treatment" to "prevention" as probiotics are really not studied in the setting of active CDI.	Thank you for the suggestion. We changed the name for the interventions included in this section from the initial review, which referred to them as "nonstandard." The "nonstandard" term was considered likely to cause consternation as new interventions became more standard. However, there remained the possibility that new interventions might be identified that were studied in the setting of active CDI. We have chosen to use the broadest term of "other treatments".
Peer Reviewer #1	Results	KQ4, "Probiotics for CDI" section—you need to put in citations here.	Thank you for the suggestion. We added a sentence reminding the readers to refer to the evidence tables in the appendix for further information.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	KQ4: would consider the addition of Allen Lancet 2013 RCT; also Johnston BC, et al. Ann Int Med 2012; 157: 878-888 and Goldenberg JZ, et al. Cochrane Database of Systematic Reviews 2013, DOI: 10.1002/14651858.CD006095.pub3 meta-analyses.	The Allen article was included in the review. We elected to conduct this part of the update review de novo because of the differences in the key questions and PICOTS, and so did not use the Johnston systematic review (a journal article that was a derivative product of the Goldenberg Cochrane review)..
Peer Reviewer #1	Results	KQ4, "Harms of Adjunctive Therapy," there have been a couple of case reports of norovirus infection after stool transplant.	Thank you for the comment. Case reports were an excluded article category.
Peer Reviewer #2	Results	The results seem clear, concise, and inclusive. While it is always disappointing that better science not available to answer these clinically important questions, it does allow clarity in research needs for the future. As is the case with all reports such as this, literature continues to accumulate while the report is being vetted through concurrence. The report may benefit from indicating the stop date for literature review so the reader is clear what documents may be included (perhaps this is already planned for the final version).	Thank you for the comment. We have updated the search and noted the stop date.
Peer Reviewer #3	Results	In general, the results section is well-organized and presents an appropriate amount of detail, summarizing the literature reviewed. Each of the studies are clearly described and specific messages with any important caveats are presented. The breadth of the primary literature that is reviewed as appropriate. All significant topics are reviewed and appropriate detail. Key studies in each of the areas are included. The authors may consider the inclusion of two additional forms of non-antibiotic treatment. The first is to review the use of non-toxigenic C. difficile strains as a preventive method.	Thank you for the comment. The vaccination using non-toxigenic strains was reviewed in the initial review. Since no new studies were identified in the period since the initial review, it was not covered in this update. The vaccination treatment was not included in Table 8 because the initial research was too preliminary.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Second, the use of monoclonal antibodies directed against TcdA and TcdB could be discussed. While the data on both of these therapeutic strategies is somewhat limited, it may be important to briefly discuss them as it is likely that there will be additional information coming out in the next few years and it would be good to alert the readers to this possibility.	The monoclonal antibodies were reviewed in the initial review. Since no new studies were identified in the period since the initial review, it was not covered in this update. The findings for the monoclonal antibodies from the initial report were summarized in Table 8.
Peer Reviewer #4	Results	The amount of detail presented in the results section is appropriate – well summarized and easy to understand. The characteristics of the studies are clearly described. Key messages are explicit and applicable.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	The authors' conclusions on NAAT specificity are absolutely incorrect. Most assay comparisons are fatally flawed because there are no data on the patient. Most patients colonized with C. difficile are asymptomatic carriers. Without clinical data, the studies are not designed to differentiate between CDI and asymptomatic C. difficile colonization. When clinical presentation of the patient and/or patient outcomes are taken into account, the specificity of NAATs for CDI is ~90%, for a positive predictive value of ~60%. So, NAATs are highly sensitive and specific for detecting toxigenic C. difficile, but have poor specificity for CDI. This is a major flaw that must be changed. Conversely, toxin assays in general have specificity >98% and much better positive predictive value. Also, despite the lower sensitivity of toxin assays, the negative predictive value in general is >95%.	Thank you for this comment; you have highlighted the most significant difficulty in evaluating the evidence about the diagnosis of CDI. Since we were primarily evaluating test analytics we opted to use toxigenic culture and/or CCNA as the reference standard and not a consensus standard that included clinical information. However, we only included studies that evaluated specimens from patients at risk for CDI, making asymptomatic colonization less likely. A consensus reference standard would be problematically heterogeneous and make analysis difficult and methodologically problematic. We have added to the text to ensure that the reference standard we used is clear and why the results and conclusions may differ compared to studies that use a clinical/consensus reference standard rather than a positive TC/CCNA in a patient at risk with symptoms.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	When interpreting the results of studies using probiotics for the primary prevention of CDI, the authors must be cognizant of the CDI incidence in the placebo group and the inclusion/exclusion criteria for the studies. One of the highest risk populations for CDI are people >65 years of age that are hospitalized and on antimicrobials. The CDI incidence in this population, including during CDI outbreaks, ranges from <1 to 3%. The incidence of many of the "positive" studies is much higher than this, often also in lower risk populations. This likely biases the study to the positive result, plus calls into question the validity of the results. Another consideration is the type of organism(s) contained in available probiotic preparations do not appear to be the key organism important to protect against CDI based on studies of the microbiome, so biological plausibility of probiotics preventing CDI is increasingly being called into question.	Thank you for the comments. We agree with the reviewer regarding the differences in CDI risk for different populations. Unfortunately, the studies do not report outcomes with enough detail to do a subgroup analysis of people over 65. We have added this as a limitation in the discussion section. The results were assessed as low strength of evidence in part due to the high study limitations, including the issue of possible bias in the positive results from the unusually high incidence rates in the studies. This rating should communicate the possibility of biased effect estimates and results should be interpreted with caution. We had addressed in the research gaps section the need to better understand the role of the human biome in probiotics research.
Peer Reviewer #5	Results	Page 19, line 55: incorrect per above comment on NAATs.	Thank you. We have responded to the comment above. We believe the results as stated are appropriate. We have added more discussion about how the reference standard used strongly influences the results.
Peer Reviewer #5	Results	Page 21, line 8: chlorhexidine is not sporicidal. The findings of the study are likely due to chance more so than actual efficacy of chlorhexidine bathing to prevent CDI. Other studies of chlorexidine bathing have not identified an impact on CDI.	A new study on chlorhexidine was located during the update search and included in the results. Based on the new body of evidence, the strength of evidence was downgraded to insufficient.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	The results section is organized first by the literature search and the by the four questions. The is a nice consort table. Each question section has a nice summary table and some conclusions for each section.	Thank you for the comment.
Peer Reviewer #6	Results	Either by consort table or elsewhere with summaries (maybe even page 21 finding) there should be some breakdown of how many of the studies for treatment antibiotic and non antibiotic are drug company sponsored.	Funding sources for studies are reported in the risk of bias tables provided in the appendix.
Peer Reviewer #6	Results	What was the actual latest date for including studies in the review (see below regarding prevention articles)?	The final search date was added.
Peer Reviewer #6	Results	It would be helpful somewhere in the results section to have the definitions for strength of evidence.	The definitions are provided in the methods section, should readers need to refer to them.
Peer Reviewer #6	Results	It would be helpful to have practical application/ implications from the study. On page 12 the bottom section start with " in short…" is likely meant to do this. However I think this is actually fair confusing.	The summary statements for diagnostic tests have been reorganized.
Peer Reviewer #6	Results	The prevention section yielded few articles. It is likely that this is correct, however. There was a recent AHRQ funded study role ASP on CDI. Even if not included in final analysis do not see in excluded list either, thus this raises concern that other prevent studies could have been excluded.	The AHRQ-funded studies published in the recent 2014 ICHE and AJIC issues were picked up by the search algorithm. We did not include relevant systematic reviews in the bibliography of excluded studies; only primary studies that were excluded are listed.
Peer Reviewer #6	Results	The categories for prevention seem odd- usually breakdown into infection prevention & control, environmental cleaning and transmission, antibiotic prescribing/ stewardship and bundled approaches- either multiple components at once or sequentially	Thank you. The categories used were brought forward from the initial review that this review was updating.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	For the antibiotic treatment section, the harms do not address antibiotic resistance (including VRE) and costs (or at least that these are not mentioned). On page 17 listing nephrotoxicity for vancomycin seems irrelevant since this is a discussion about vancomycin that should not be absorbed and is unrelated to nephrotoxicity.	We have added language indicating that antimicrobial resistance harms were not assessed, Regarding nephrotoxicity: although we agree that oral vancomycin is not absorbed and thus may not directly cause nephrotoxicity, the observed rates are what was reported, and it could be argued that perhaps slower resolution of infection could lead to a longer duration of diarrhea, leading to volume losses resulting in the observed nephrotoxicity.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Results	This is where I have my major concern and is in the nonantibiotic section. Initially this seemed like a reasonable way to divide the topics, but now that I see the results, I believe it makes it confusing. The organization of the treatment section is incorrect, that is for clinicians, and should be modified. There are several major problems (1): FMT is both a treatment for RCDI as well as a prevention of further RCDI. Nothing else is as effective for the patient who has had multiple recurrences. Its role is very different than probiotics. It does change the microbiome. (2). Probiotics have no role in therapy of CDI, and a minor role in prevention of RCDI and this should be made much clearer. Most of the probiotic studies are not adjunct to treatment, they are adjunct to antibiotics to prevent AAD and CDI< and the Placide study really casts doubt on their overall efficacy. The S boulardii studies to prevent RCDI belong in a separate section. —it should be very clear that probiotics have no role in treatment of CDI first episodes or sever episodes, especially since they are not without risk. Fungemia is mentioned as a risk but bacteremia should also be mentioned as cases have been reported, and deaths have also been noted in transplant patients. Before FMT, probiotics such as S boulardii had a role on treatment of RCDI but with FMT being so much more successful, the role of probiotics should be minimized unless there is better evidence for safety and efficacy. Also, there is not much evidence that probiotics change the microbiome, in contrast to FMT. 3. Rifaximin is an antibiotic, and should be included with antibiotics. In short, I feel that the role of FMT is under-emphasized, and the role of probiotics is over-emphasized. This means that the abstract and conclusions should be changed.	Thank you for your suggestions. Based on the overall trend of reviewer comments, we have retained the original organization. To help with the presentation, we have clarified that FMT is usually administered after initial treatment with antimicrobials has reduced or eliminated acute symptoms of CDI, and that the goal of treatment is largely to prevent subsequent recurrence.We have also noted in Table 7 the inability to separate patients by CDI symptom relief versus recurrent CDI patients. Similarly, rifaximin is described and used as an adjunct therapy (albeit one that is an antibiotic), given after an initial course of treatment with vancomycin,

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	The just published sytematic review of FMT should be included in this review: Drekonja D et al Ann Int Med 2015, 162:630-638	Thank you for the suggestion. Since the publication was after our review, we did not use it to replace our de novo review process. We have mentioned the article in the discussion section.
TEP Reviewer #3	Results	Table 5 p 14 line 6-7 appears that they took the strength of evidence report from another systematic review (overlapping authors with this review), not as described in the methods.	Thank you for the comment. The strength of evidence process used for the published review used the strength of evidence methods developed by the AHRQ EPC program as were reported in our methods section.
TEP Reviewer #4	Results	Yes	Thank you for the comment.
TEP Reviewer #3	Results	The detail seems reasonable, and I do not know of any studies that should have been included and were not.	Thank you for the comment.
Public Reviewer NASPGHAN	Results	The report states an important finding is continuing moderate-strength evidence that fidaxomicin is similar to vancomycin for the initial cure of CDI, and increased strength of evidence for fidaxomicin as superior for the prevention of recurrent CDI. We agree the desired outcome with CDI treatment is cure of the initial illness without subsequent recurrence, and that the review findings ought to prompt consideration of fidaxomicin for the initial treatment of CDI. However, we wish to bring to the Agency's attention that evidence is lacking to suggest fidaxomicin is effective as first line therapy after multiple recurrent CDI. Consequently, research of treatment for multiple recurrent CDI where traditional medical therapies have failed is of significant importance.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer NASPGHAN	Results	As a result of the review, the report also states the strength of evidence has been increased from moderate to high for vancomycin as a more effective agent than metronidazole for CDI, with moderate-strength evidence of the effect regardless of severity. While the report notes decreased concern about the emergence of vancomycin-resistant enterococci during oral vancomycin therapy, we suggest the long-term consequences of the drug's use are still largely unknown.	Thank you for the suggestion. We have added language to reflect this concern
Public Reviewer NASPGHAN	Results	The report states low-strength evidence supports FMT as a promising therapy for recurrent CDI. However, we want to emphasize that even though the data to support FMT for recurrent CDI provide only a low strength of evidence, FMT is an important treatment option for patients with multiple recurrent CDI. While there is the need for additional controlled studies of FMT, current guidelines, both United States and abroad, support the use of FMT and/or its consideration for recurrent or refractory CDI.	Thank you for the comment.
Peer Reviewer #1	Discussion	Discussion/ Conclusion: This section is clear and well thought out. I would make a couple of additional suggestions:	Thank you for the comment.
Peer Reviewer #1	Discussion	Consider discussion of fidaxomicin being used in certain populations at highest risk—e.g. studying specific subgroups	This has been mentioned under the research gaps section.
Peer Reviewer #1	Discussion	Consider discussion of cost	The discussion section includes a brief mention of a cost-benefit analysis for fidaxomycin.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion	p. 26, line 48-49: see Bakken JS CID 2014; 59: 858-61.	Thank you for the comment. The Bakken article was found with the update search and added to the review. However, since it was a case series for probiotics, which has a considerable RCT-based body of evidence, we did not comment further on the study.
Peer Reviewer #1	Discussion	Some additional future directions to consider: FMT for prevention and approach to the patient needing ongoing systemic antibiotics/ concomitant antibiotics	Thank you for the comment, we have added the suggestion to the future research areas.
Peer Reviewer #2	Discussion	The implications of the major findings are clearly stated. Unfortunately, the report may leave readers unsatisfied since the data do not allow for simplistic planning for all components of a Clostridium difficile medication plan. On the other hand, in the context of a local facility or healthcare system, knowledge of the data and the quality of the data can allow for rational planning despite data that do not definitively answer all the questions that are pertinent to local operational needs. Of specific note, the authors comment on the nonalignment of the current CDI treatment guidelines with the outcome of this review. This will have the advantage of enhancing the conversation with regard to optimal initial treatment with the fewest recurrences. The research gaps section of the document seems clear and reasonable.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion	The implications of the major findings of this systematic review are clearly stated. The authors do a laudable job in helping interpret some of the major findings for their audience. Their opinions are clearly stated as such and are logically presented. In particular, the discussion of the current state of diagnostic testing appropriately highlights some of the areas of controversy and needed study going forward. I agree with the early statement (page 22, line 47) regarding the lack of studies that focus on the impact of diagnostic tests on individual or health system outcomes.	Thank you for the comment.
Peer Reviewer #3	Discussion	One area that is not discussed explicitly is some of the controversy regarding the association of specific C. difficile ribotypes with disease severity. This is a difficult area to discuss and perhaps the authors chose not to discuss this in detail given the ongoing nature of this debate. However they do cite in the introduction that specific record types have been associated with the increasing overall severity of this disease.	Thank you for the comment. The reviewer is correct in our decision to not pursue this subtopic, given the lack of trials investigating differential effects of treatments by ribotype.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion	The reviewers appropriately discuss controversies over diagnostic testing with regards to a Bayesian standpoint. Especially since the authors explicitly state that the review is focused on patients with clinical disease, the potential of detecting asymptomatic carriage (or perhaps even transient passage) with C. difficile using the highly sensitive nucleic acid methods is important to discuss. This is discussed on page 24. The authors may consider to bring up this caveat earlier in the review. In the initial summary of the review the authors point out that the use of NAAT was associated with "high" evidence. It may be useful to consider suggesting that there are caveats to using this testing modality in that section to avoid suggesting that this is the preferred method for testing. Although not explicitly stated as such, it could be interpreted that this will be the recommended testing modality. The authors clearly state research gaps in this section could be easily translated into areas for further research.	Thank you for this helpful comment. Text has been added to the discussion to address this point.
Peer Reviewer #4	Discussion	Implications of the major findings are clearly stated. Limitations of the review/studies are clearly & adequately described. I am not aware of any important literature that was omitted. Future research section clearly identifies topics for future research; the descriptions of gaps in knowledge or opportunities for future research should easily translate to new research. Hopefully there will be new research related to the prevention of CDI, specifically to clarify or separate out the role of various environmental factors in transmission & studies with higher strength of evidence to support strategies & interventions to prevent CDI.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Discussion	Page 32, line 4: the update of the clinical guidelines has been ongoing, and the experts involved in that process have been aware of the inferiority of metronidazole for several years. Although guideline panel has been informally advocating a low threshold for use of vancomycin in preference of metronidazole at educational venues, the guideline process is quite cumbersome and ongoing for quite some time. It is the preference of this reviewer that the authors re-word this sentence in such a fashion as to not imply this review was the prompt to change the treatment guidelines (as they will be changing, consistent with the results of this review).	Thank you for the comments. We have adopted the suggestion and rephrased the sentence to state the review findings would be consistent with a reconsideration of the preferred agent.
Peer Reviewer #5	Discussion	Page 34, line 40: the most clinically relevant tests are toxin assays.	We understand this comment in the context of the previous discussion about the definition of CDI. However, given the findings of our review we respectfully disagree but have removed the parenthetical statement.
Peer Reviewer #5	Discussion	conclusion on assays is incorrect.	Thank you for the comment. We believe the findings are appropriate.
Peer Reviewer #6	Discussion	There is a nice table including findings from original and update. This table is the meat of the review and should be able to somewhat stand on its own. There are some important points made in the discussion that would be lost. Perhaps the summary/ conclusions/ comments box could be used better. For example- the last paragraph of the testing section is important.	Thank you for the suggestion. It is difficult to create a table that fully incorporates all pertinent and important points that doesn't simultaneously lose the reader in dense text. We have left the table format as is.
Peer Reviewer #6	Discussion	For the testing section there should be some acknowledgement that the choice of test may also be altered by the type of lab available. Some facilities have also gone with mixed methods due to costs of running the more complex test such as NAAT or pcr.	This has been added to the text.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion	For the standard treatment, on pages 24-25 the authors make statements about less resistance and less cost and that vancomycin should be reconsidered for all treatment. This certainly can be brought to the professional societies.	Thank you for the comment.
Peer Reviewer #6	Discussion	However the statements seem too strong that facilities may change their practice---what is missing is…The authors did not comment that a few of the studies used very high doses of po vancomycin 500mg (which is not the standard dose used of 125mg). In addition where is the evidence regarding resistance such as VRE. High doses such as 500mg have been theoretically thought to disrupt much more of the flora and be the reason why universal use of vancomycin has been a concern. The cost issue may be somewhat resolved in inpatients settings where the pharmacy can make po vanc solutions. This still requires labor. In the outpatient setting there is still much higher cots with vancomycin. Thus these factors would still need to be looked at before deciding that this one review with a handful of articles should change practice for a common condition.	Thank you for the comment. We agree with the reviewer that there are many issues to weigh when considering changing the guidelines, but such detailed discussion is beyond the scope of this review. We have changed the sentence to read that the review findings are consistent with reconsidering the preferred agent.
Peer Reviewer #6	Discussion	The authors do a better job addressing how fidaxomicin may be used given costs on page 25. They do not address that most of the studies with these drug exclude those patients with severe diseases or those who cannot take po meds.	The fidaxomicin studies did not exclude patients with severe disease and provided specific definitions for disease severity as a category.
Peer Reviewer #6	Discussion	The research gaps and limitation are important sections. Given that there were few studies for the prevention section but this is important, if the authors use less rigor are there any strategies or finding that might be helpful for future?	Thank you for the comment. We have already allowed as included studies study designs of far less rigorous methods in order to capture what is available. However, there does need to be a certain amount of rigor in order to be able to draw conclusions.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Discussion	Discussion/ Conclusion: I feel that the role of FMT is under-emphasized, and the role of probiotics is over-emphasized. I suggest the following organization: 1. Diagnosis 2. Prevention - Add probiotics here 3. Treatment CDI – Antibiotics- 4. Treatment of RCDI which includes prevention of RCDI further episodes - Antibiotics including rifaximin - FMT - Probiotics	Thank you for the suggestion. Given the overall trend of the review comments, we have retained the original organization. We have noted in Table 7 the inability to separate patients by CDI symptom relief versus recurrent CDI patients.
TEP Reviewer #2	Discussion	There are numerous subgroup analyses which are needed to better guide CDI management and treatment choices. One example--Patients treated with fidoxomycin has lower recurrence rates overall compared with vancomycin, but are these rates the same in patients with "standard" c difficile and in those with the hypervirulent strain? Should that guide our treatment choice? If this data is not available, then it should be listed as areas in need of future research	Thank you for the comment. We have added the suggestion.
TEP Reviewer #3	Discussion	Implications are well-stated. Comparison table with prior review is helpful.	Thank you for the comment.
TEP Reviewer #3	Discussion	Future research directions are ok but mostly just say this is a challenging area for research. Suggestions for future pragmatic trials would be helpful, especially for multicomponent prevention interventions vs usual care. May want to make specific suggestions about studies in long-term care settings.	Thank you for the comment. We have added the suggestions.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion	p. 23, line 20-21 appears to be a key point, but then is detracted from with later comments about ROC curves etc, on lines 51-55. If this is a key point, then many of the distinctions between the tests are less crucial (since 3 have sensitivity of 0.94-0.95 and similar negative likelihood ratios. The ROC curve comments seem to diverge from corresponding curves in Appendix G, which are not impressively different.	Thank you for this comment. We have changed the ROC discussion.
TEP Reviewer #3	Discussion	p. 25, lines 21-24, need more details about the CMS new technology add-on payment, such as the amount and years it will be in effect. Cost/economic data are conspicuously lacking in the report.	Thank you for the suggestion. We have discussed some cost issues for fidaxomicin, as a newly approved but costly treatment. However, the main purpose of the review is the clinical information derived from the systematic review.
TEP Reviewer #3	Discussion	p. 27, lines 23-24 is confusing. Conceivably a reference standard could use positive and negative controls, although that was not done here. Also, the explanation of reference standards seemed much clearer earlier in he report.	This has been altered in the text to read more clearly.
TEP Reviewer #4	Discussion	Yes	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer NASPGHAN	Discussion	The report highlights the unique scientific and regulatory issues associated with FMT and cites the lack of standard formulations, methods of quantifying, or assessing safety of stool. In a July 2013, NASPGHAN and other national medical societies sent a letter to the FDA recommending establishment a protocol for FMT that balances appropriate oversight of this effective, yet not fully understood, therapy with reasonable access for patients with recurrent CDI, to whom few alternatives are available. The communication offered suggestions for guidance on donor selection and screening, serum testing, and stool testing.	Thank you for the comment.
Peer Reviewer #1	Clarity/ Usability	The report is overall well structured and organized. The conclusions can be used to inform policy and practice.	Thank you for the comment.
Peer Reviewer #2	Clarity/ Usability	The document is clear and useful. While the conclusions are limited by the quality of the data, it still will inform policy and planning.	Thank you for the comment.
Peer Reviewer #3	Clarity/ Usability	Overall, the report is well structured and organized. The authors take care to clearly present the main points, stressing key points several times within the review. Areas of continued question/concern are highlighted and areas where there is more consensus at this time are also pointed out. The latter could be used to inform policy and practice decisions.	Thank you for the comments.
Peer Reviewer #4	Clarity/ Usability	The report is well structured and organized in a manner that is both clear and highly usable. The conclusions can be incorporated into decision-making processes to drive policy and/or practice decisions. The sections on diagnostic testing and treatment are especially helpful in clarifying such decisions.	Thank you for the comments.
Peer Reviewer #5	Clarity/ Usability	please see results. The section on diagnostic assays is highly problematic	Thank you for your comments. We have addressed these above.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Clarity/ Usability	The overall questions are important - Unfortunately the most useful would be the sub questions that could not be addressed - I am still unclear the audience, perhaps some better context and challenges in clinical practice would make more clear - The review is systematic but the presentation is choppy and redundant. The abstract and initial results need to stand on their own. As written they seem to be missing some of the important details. Especially with the suggestion for po vancomycin as first line for all CDI. - The tables, forrest plots are small, dense and if the audience is to be useful for clinical practice or decision makers at a facility level some better presentation/ explanation would help.	Thank you for the comments. We agree it is unfortunate that we could not address important subgroups. We have added a sentence regarding the report audience. We have revised the abstract, but word count limitations make it challenging to write for such a comprehensive review. We placed the majority of tables and forrest plots in the appendix in order to focus the text into a shorter, more readable report for readers who are less interested in the finer details.
TEP Reviewer #2	Clarity/ Usability	The report delivers high quality review of relevant literature. The questions are appropriate, dividing the overall 'management' of CDI into categories that reflect the day to day challenges and decision making in practice.	Thank you for the comment.
TEP Reviewer #2	Clarity/ Usability	My concern relates to how the results are delivered. The format utilized appropriately provides conclusions tied to the level of evidence. The statements however are not sufficiently clear or compelling to change clinical practice. Clinicians continue to order testing for the wrong reasons, treat with less effective or more expensive medication and offer adjunctive treatment that may have no benefit. If this report is to have direct impact on clinical practice, restating in stronger clinical terms (when supported by the level of evidence) may have greater impact on day to day clinical decision making.	Thank you for the comment. The purpose of the review is to assess the literature. While we report findings, we do not make clinical recommendations.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity/ Usability	The authors could consider adopting primary and secondary prevention concepts that are in practice within the medical community, for this report.	Thank you for the comment. There are numerous ways to organize the material. We believe the current format is sufficient to the topic.
TEP Reviewer #3	Clarity/ Usability	The comments on p. 23, lines 39-45 appear to be recommending against CDI screening, although that was not formally considered in this report. Screening considerations typically also include cost, patient acceptability, speed of results, in addition to some of the elements of this report (available effective treatment that prevents adverse health outcomes).	Thank you for the comment. The report does not make clinical recommendations, but instead presents the evidence around a clinical question.
TEP Reviewer #4	Clarity/ Usability	Yes	Thank you for the comment.
Peer Reviewer #6	Figures	The forrest plots and figures are small and difficult to see.	We are sorry for that. Given the amount of information packaged into the pictures, it is hard to get the plots to fit to a standard 8X11 page.
Peer Reviewer #1	General	Overall, this report is a useful overview and update of the recent literature on Clostridium difficile. The target audience is well-defined. I think the authors could highlight the target population in a bit more detail. The key questions are on target and very clearly stated.	Thank you for the comment. We have added a sentence regarding the potential audience.
Peer Reviewer #1	General	I do wish that you explained exactly why you chose to avoid discussion of treatment effectiveness for subgroups of patients, such as those with recurrent disease, concomitant antibiotics, etc.	Thank you for the comment. We were disappointed that the literature was too sparse to allow exploring subgroups of interest. This is noted as a future research suggestion.
Peer Reviewer #1	General	One additional topic that could be considered, though there lacks direct data, is the possibility of C diff coming from the food source. If this is the case, then prevention efforts focused on this may be appropriate. Perhaps this is just an area for future research.	Thank you for the comment. The topic of community-associated CDI is outside the scope of this review.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The topic of this review is very important in that it deals with a clinically relevant condition that causes misery, morbidity, mortality. The key questions are sound and relevant. The review will be relevant to multiple audiences since it deals with a broad-spectrum of activities related to Clostridium difficile.	Thank you for the comment.
Peer Reviewer #3	General	The report entitled, "Early Diagnosis, Prevention, And Treatment of C. difficile: Update" is a timely and clinically meaningful review of the diagnosis and therapy of this important nosocomial infection. It is explicitly stated that this report is targeted for the use of patients, clinicians and health policy makers. With such a broad audience, there are necessarily some compromises that need to be made. However, the information contained in the report should be useful to a variety of individuals who are interested in CDI, with a particular emphasis for clinicians. The key questions listed by the authors are explicitly stated. The four key questions are appropriate for considering the current state of CDI in terms of diagnosis, prevention and therapy. Therapy is divided into both antibiotic and non-antibiotic strategies, both of which are of significant current interest.	Thank you for the comment.
Peer Reviewer #3	General	While the questions themselves are stated clearly the sub questions under each are somewhat "telegraphic" and could be expanded to give the reader a better idea of what will be discussed.	Thank you for the comment. The key questions were posted for public comment prior to conducting the systematic review.
Peer Reviewer #4	General	Yes, the report is clinically meaningful and the target populations and audience are identified. The key questions are very appropriate and are explicitly stated. These are the questions that the clinicians in my facility are asking.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	In general this is a well done and written review. However, there are some incorrect statements and conclusions, likely owing to a lack of C. difficile expertise among the authors.	Thank you for the comment.
Peer Reviewer #6	General	This is an updated systematic review sponsored by AHRQ through its Evidence –based Practice Centers on C. difficile (CDI). The review addresses four questions: diagnostic testing, prevention strategies, antibiotic treatments for CDI and non-antibiotic adjunctive interventions. These are clinically meaningful as the best test, the right treatment and how we can prevent CDI is important. This especially timely since this CDI has been increasing and resilient to many of the strategies that have improved other HAIs such as CA-BSI. In addition local and national regulatory agencies are asking facilities to report their CDI rates with the hopes of showing improvement.	Thank you for the comment.
Peer Reviewer #6	General	A few issues to raise regarding this review are: - The audience is not explicated defined	Thank you, we have added a statement regarding the audience.
Peer Reviewer #6	General	- The abstract is short as needed, but having some of the results so terse could have ramifications as may be taken by stakeholders without looking at the data and all the potential mitigating factors. This could translate a large change in care for patients and facilities-specifically the statement about vancomycin being superior to metronidazole is one where the potential down sides seems not given much weight (will address below).	Thank you for the comment. We have made some revisions to the abstract, but the reviewer is correct that word count is a limiting factor.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	- The review if 116 pages. I worry given the size and that things are presented in a choppy fashion. The conclusions that are suggested in the abstract and main section of the results 11-20 and the discussion 24-29 need to be more cohesive.	Thank you for the comment. We have attempted to smooth the sections and improve cohesion with the revision. However, we have chosen to prioritize focus on the main key messages over fine detail in order to keep the report readable and accessible to the broad audience.
Peer Reviewer #6	General	- Some recent studies may be missing (methods)- specifically some recent HAI prevention- although agree data in this area insufficient	Thank you. We believe the search algorithm was sensitive to prevention studies.
Peer Reviewer #6	General	- The strong conclusions for vancomycin and to a lesser degree for fidaxomicin without some disclaimer that these results are from the few studies in this systematic review cannot necessarily be generalized (given cost and other considerations) to all patients and facilities. As it is written without this, the conclusions seem too strong. This is especially since many of the sub questions had to be deleted, as data did not exist to support. This is a very important issue that needs to be addressed	Thank you for the comment. We have added an applicability statement to the discussion section to make clear the review was unable to speak to subgroup questions.
TEP Reviewer #1	General	This is a very good report, and could be excellent with some minor revisions. The section on diagnosis is excellent as is the section on treatment. The main objection that I have is that the nonantibiotic section is too disparate in content, and thus confuses the issues that are relevant to patient care. As a clinician who has cared for many patients with recurrent C difficile infection, I feel that this section is very important and should be revised in order to be clinically relevant and not misleading . I will elaborate below.	Thank you for the comment. Based on the overall trend of review comments, we have left the report organization as is.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	This report is important guidance for societies, organizations and hospitals/health systems in identifying new findings that are of sufficient quality to warrant changes to guidelines or policies. It also provides clear direction for future research. It is of limited value to clinicians in daily practice.	Thank you for the comment.
TEP Reviewer #3	General	Overall quite well done, through and informative.	Thank you for the comment.
TEP Reviewer #4	General	yes in terms of treatment. In terms of diagnostics the questions do not address clinical diagnosis, only analytic test performance	This is definitely a limitation of the review; however, a consensus standard to determine the presence or absence of CDI is methodologically problematic and would lead to significant incorporation bias
Public Reviewer NASPGHAN	General	Overall, we believe the comparative effectiveness review is well presented in the report.	Thank you for the comment.