

# ***AHRQ Comparative Effectiveness Review Surveillance Program***

## **CER #31:**

### **Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection**

#### **Original release date:**

**December 2011**

#### **Surveillance Report:**

**October 2012**

#### **Key Findings:**

- One of three conclusions for Key Question 1, two of eight conclusions for Key Question 2, one of three conclusions for Key Question 3, and one of five conclusions for Key Question 4 are possibly out of date.
- There are no new significant safety concerns.

### **Summary Decision**

This CER's priority for updating is **Low**

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# Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection

## 1. Introduction

Comparative Effectiveness Review (CER) #31, Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection<sup>1</sup>, was released in December 2011. It was therefore due for a surveillance assessment in June, 2012.

## 2. Methods

### 2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010 to June 5, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Clinical Infectious Diseases, Journal of Gastroenterology, Journal of Hospital Infection, Journal of Clinical Microbiology, and Infection Control and Hospital Epidemiology). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

### 2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

### 2.3 Expert Opinion

We shared the conclusions of the original report with 6 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; three subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

### 2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.<sup>2,3</sup>

<b>Ottawa Method</b>	
<b>Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence</b>	
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
<b>Criteria for Signals of Major Changes in Evidence</b>	
A4	Important changes in effectiveness short of “opposing findings”
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
<b>Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence</b>	
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
<b>RAND Method Indications for the Need for an Update</b>	
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

## 2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that

might change the conclusion, then we classified the CER conclusion as probably out of date.

- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

## **2.6 Determining Priority for Updating**

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

## **3. Results**

### **3.1 Search**

The literature search identified 128 titles. After title and abstract review, 105 titles were rejected because they were editorials or letters or did not include topics of interest or did not address the key question. The remaining 23 journal articles went on for further review. Four additional articles were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 27 articles went on to full text review. Of these, 20 articles were rejected because they were did not include a comparison of interest or did not meet the inclusion criteria. One article was the journal article of the original report. Thus, 7 articles were abstracted into an evidence table (Appendix B).

The FDA MedWatch searches identified no notifications of relevance.

### **3.2 Expert Opinion**

In general, expert opinion thought that the conclusions were either almost certainly supported by the evidence or did not know.

### **3.3 Identifying qualitative and quantitative signals**

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the

Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

**Table 1: Summary Table**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<b>Key Question 1: How do different methods for detection of toxigenic <i>C. difficile</i> to assist with diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?</b>				
<p><b>Immunoassays for toxins A and B</b>  <b>Level of Evidence:</b> Low to moderate</p> <ul style="list-style-type: none"> <li>•Ten studies directly compared at least 2 immunoassays for toxins A and B, providing 16 pairwise comparisons of 7 different immunoassays. Comparative data were not found for many currently used tests.</li> <li>•There were no statistical differences between the sensitivities of immunoassays that were compared; however, the estimates of the differences in sensitivity were not very precise and could not rule out substantial differences.</li> <li>•Substantial differences in false positives, that is, specificity, were not found among the tests that were compared.</li> </ul>	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<p><b>Gene detection tests versus immunoassays for toxins A and B</b>  <b>Level of Evidence:</b> Low to moderate</p> <ul style="list-style-type: none"> <li>•Four studies compared at least one toxin gene detection test to at least one immunoassay for toxins A and B, providing a total of nine direct comparisons. Comparative data were not always available for the three currently available gene detection tests.</li> <li>•The gene detection tests could be substantially more sensitive than many immunoassays for toxins A and B, with no or relatively modest loss of specificity.</li> </ul>	<p>One study<sup>4</sup> found that adding clinical symptoms (such as diarrhea severity) had minimal change on sensitivity but significantly lowered specificity.</p> <p>A meta-analysis of 19 studies<sup>5</sup> found that PCR (all variants) has a high sensitivity and specificity to confirm CDI.</p>	No new data.	<p>One expert agreed that this conclusion was almost certainly still supported by the evidence.</p> <p>One expert thought this was out of date.</p> <p>One expert did not know.</p>	Original conclusion is possibly out of date and this portion of the original report may need updating
<p><b>Patient characteristics</b>  <b>Level of Evidence:</b> Insufficient</p>	No new data.	No new data.	Two experts agreed that this conclusion	Conclusion is still valid and this

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Insufficient patient information was provided in reports of comparative data.			was almost certainly still supported by the evidence. One expert did not know.	portion of the CER does not need updating.
<b>Key Question 2. What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? 3 (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?</b>				
<b>Antibiotic use</b> <b>Level of Evidence:</b> Low •Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. •Harms were not reported.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Gloves</b> <b>Level of Evidence:</b> Low One controlled trial found use of gloves in hospital settings reduced CDI incidence.	One prospective before-after study <sup>6</sup> found no difference in CDI rates in a trial of universal gloving with emollient-impregnated gloves	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Original conclusion is possibly out of date and this portion of the original report may need updating.
<b>Disposable thermometer</b> <b>Level of Evidence:</b> Low Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Handwashing/alcohol gel</b> <b>Level of Evidence:</b> Low •No study examined whether handwashing reduced CDI incidence. •Two studies, one controlled trial and one before–after study, of use of alcohol gel to reduce MRSA transmission did not find significant differences in CDI incidence.	No new data.	No new data.	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Disinfection</b> <b>Level of Evidence:</b> Low Thirteen before–after studies of	One study <sup>7</sup> found no change in the incidence of <i>C. difficile</i> hospital acquired infection	No new data.	Two experts agreed that this conclusion was almost certainly	Original conclusion is possibly out of

<b>Conclusions From CER Executive Summary</b>	<b>RAND Literature Search</b>	<b>FDA/ Health Canada/MHRA (UK)</b>	<b>Expert Opinion EPC Investigator Other Experts</b>	<b>Conclusion from SCEPC</b>
outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills <i>C. difficile</i> spores reduced CDI incidence.	among general medical patients with chlorhexadine bathing.		still supported by the evidence. One expert did not know.	date and this portion of the original report may need updating
<b>Sustainability</b> <b>Level of Evidence:</b> Insufficient No evidence was available.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Risk Factors</b> <b>Level of Evidence:</b> Low •Ten observational studies found evidence that antibiotic use, whether specific or general, increased risk of CDI. •Severe underlying disease, acid suppression, and age are indicated as risk factors. A number of other potential factors may be indicated in single studies.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Multiple component strategies</b> <b>Level of Evidence:</b> Insufficient •Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data are insufficient to draw conclusions. •Harms were not reported.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Key Question 3: What are the comparative effectiveness and harms of different antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?</b>				
<b>Vancomycin versus metronidazole</b> <b>Level of Evidence:</b> Moderate for clinical cure, low for all other outcomes •There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>cure, especially with regard to stool count and consistency.</p> <ul style="list-style-type: none"> <li>•No significant differences in outcomes, including initial cure, clinical recurrence, and mean days to resolved diarrhea, were found.</li> <li>•Our results build upon, and are consistent with, the Cochrane Reviews search completed by Bricker et al.<sup>1</sup></li> </ul>				
<p><b>Severe disease, vancomycin versus metronidazole</b>  <b>Level of Evidence:</b> Insufficient  One RCT examined a prespecified subgroup of 69 subjects with severe CDI; improved clinical cure was based on per-protocol analysis, but not with strict intention-to-treat analysis</p>	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<p><b>Fidaxomicin versus vancomycin</b>  <b>Level of Evidence:</b> Moderate  One large, high-quality RCT demonstrated decreased recurrence among those receiving fidaxomicin.</p>	One meta-analysis of two recently completed phase three trials <sup>8</sup> showed that fidaxomicin reduced persistent diarrhea, recurrence or death compared with vancomycin. A subgroup analysis <sup>9</sup> found that fidaxomicin was more effective than vancomycin in achieving clinical cure in the presence of concomitant antibiotics.	No new data.	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.	Original conclusion is possibly out of date and this portion of the original report may need updating
<p><b>All other comparisons of standard treatments</b>  <b>Level of Evidence:</b> Moderate for vancomycin versus fidaxomicin, low for all other comparisons</p>	No new data.	No new data.	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two	Conclusion is still valid and this portion of the CER does not need updating.

<sup>1</sup>Abougergi MS, Broor A, Cui W, et al. Intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis: an observational study and review of the literature. J Hosp Med 2010 Jan; 5(1):E1–9.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
There were eight trials examining: vancomycin versus bacitracin (two trials), vancomycin versus fidaxomicin, vancomycin versus nitazoxanide, vancomycin high versus low dose, vancomycin versus placebo, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin (one each). No differences.			experts did not know.	
<b>Strain of organism</b> <b>Level of Evidence:</b> Low One RCT (fidaxomicin vs. vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain.	No new data.	No new data.	One expert agreed that this conclusion was almost certainly still supported by the evidence. Two experts did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Patient characteristics</b> <b>Level of Evidence:</b> Insufficient No comparative data were available.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Resistance of other pathogens</b> <b>Level of Evidence:</b> Insufficient No data were available.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?</b>				
<b>Treating CDI, active control</b> <b>Level of Evidence:</b> Low Probiotics, prebiotics, <i>C. difficile</i> immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence.  One expert cited new evidence of an additional harm.	Conclusion is still valid and this portion of the CER does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<b>Treating CDI, placebo</b> <b>Level of Evidence:</b> Low Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Treating recurrent CDI</b> <b>Level of Evidence:</b> Low There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.	No new data.	One systematic review <sup>10</sup> found intestinal microbiota transplantation to be highly effective with disease resolution in 92% of cases.	Three experts agreed that this conclusion was almost certainly still supported by the evidence.	Original conclusion is possibly out of date and this portion of the original report may need updating
<b>Preventing CDI</b> <b>Level of Evidence:</b> Low There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.
<b>Preventing recurrent CDI</b> <b>Level of Evidence:</b> Low to moderate •There is limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics. •There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.	No new data.	No new data.	Two experts agreed that this conclusion was almost certainly still supported by the evidence. One expert did not know.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: *C. difficile* = *Clostridium difficile*; CDI = *Clostridium difficile* Infection; SCEPC Southern California Evidence-based Practice Center

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1002.22002980

# **Appendices**

**Appendix A: Search Methodology**

**Appendix B: Evidence Table**

**Appendix C: Questionnaire Matrix**

## Appendix A. Search Methodology

### SEARCH #1:

#### DATABASE SEARCHED & TIME PERIOD COVERED:

Medline on OVID – 2010-6/5/2012

#### LANGUAGE:

English

#### SEARCH STRATEGY:

difficile.mp.

AND

randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab. OR Cohort studies/ or comparative study/ or follow-up studies/ or prospective studies/ or risk factors/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp.

NOT

addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits OR comment or historical article

NOT

(animals not (humans and animals)).sh.

**NUMBER OF RESULTS AFTER REMOVAL OF DUPLICATES: 595**

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### SEARCH #2 (DIAGNOSTIC ACCURACY)

#### DATABASE SEARCHED & TIME PERIOD COVERED:

Medline on OVID – 2010-6/6/2012

#### LANGUAGE:

English

#### SEARCH STRATEGY:

difficile.mp.

AND

diagnostic accuracy.mp. OR (enzyme adj2 immunoassay\$).mp OR Immunoenzyme techniques/ OR enzyme linked immunosorbent assay/ OR feces/ OR faeces analysis.mp. OR fecal.mp. OR stool culture.mp. OR exp "Sensitivity and Specificity" OR cytotoxicity test, immunologic/ OR cell cytotoxicity assay.mp. OR pcr.mp. or polymerase chain reaction/ OR immunochromatography.mp.

NOT

(animals not (humans and animals)).sh.

NOT

addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits

NOT

in vitro

**NUMBER OF RESULTS: 417**

**RESULTS LIMITED TO THE FOLLOWING JOURNALS:**

Annals of Internal Medicine

BMJ

JAMA

Lancet

New England Journal of Medicine

Clinical Infectious Disease

Gastroenterology

Journal of Hospital Infection

Journal of Clinical Microbiology

Infection Control and Hospital Epidemiology

**NUMBER OF RESULTS AFTER FILTERING FOR SPECIFIED JOURNALS: 128**

## Appendix B. Evidence Table

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
<b>Key Question 1: How do different methods for detection of toxigenic <i>C. difficile</i> to assist with diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?</b>						
Dubberke, 2011 <sup>4</sup>	Not applicable	n = 150	-Median age = 60 yrs -50.7% Female -70.0% White	Sensitivity, specificity and predictive values of assays to diagnose CDI with and without including patient characteristics compared with reference of stool culture.	Specimens collected over 6 month period	Minimal changes in sensitivity, but lower specificity for assays Tox A/B II, C. diff Chek-60, BD GeneOhm Cdiff, Xpert C. difficile, and Illumigene C. difficile; p<0.01
Deshpande, 2011 <sup>5</sup>	Meta-analysis	19 studies; 7392 samples	Not reported	Sensitivity and specificity of CDI	Not reported	Real-time PCR has 90% sensitivity and 96% specificity for diagnosing CDI compared with cell culture cytotoxicity neutralization assays or anaerobic toxigenic culture.
<b>Key Question 2. What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? 3 (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?</b>						
Bearman, 2010 <sup>6</sup>	Prospective before-after	Standard precautions: 3486 patient days Universal gloving: 4392 patient days	Surgical ICU academic medical center	Compliance rates, device-related infection, CDI	Standard precautions: 3486 patient days Universal gloving: 4392 patient days	No difference between standard precautions and universal gloving with emollient-impregnated gloves (p = 0.53)
Kassakian, 2011 <sup>7</sup>	Quasi-experimental	Control: n = 7102 Intervention n = 7699	-Patients at an academic hospital in a general medical ward -Mean age control: 61.5 yrs; intervention: 60.7 yrs	Composite incidence of MRSA and VRE hospital acquired infections	Patient-days control: 34,800; intervention: 36,185	No change in the incidence of <i>C. difficile</i> hospital acquired infections (p = 0.6)
<b>Key Question 3: What are the comparative effectiveness and harms of different antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?</b>						

Crook, 2012 <sup>8</sup>	Meta-analysis of 2 phase three RCCT	n = 1164	-Fidaxomicin 200 mg twice daily for 10 days -Vancomycin 125 mg four times daily for 10 days	Persistent diarrhea, recurrence of CDI, or death	36-40 days after randomization.	Compared with vancomycin, fidaxomicin reduced persistent diarrhea, CDI recurrence, and death by 40% (p<0.001)
Mullane, 2011 <sup>9</sup>	Meta-analysis of 2 phase three RCCT	n = 192 -Fidaxomicin = 90 - Vancomycin = 102	-Fidaxomicin 200 mg twice daily for 10 days -Vancomycin 125 mg four times daily for 10 days	Recurrence, clinical cure	36-40 days after randomization	Cure rate 90% for fidaxomicin a,d 79.4% for vancomycin (p = 0.04); Fidaxomicin had 12.3 fewer recurrences compared with vancomycin (p = 0.48).
<b>Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?</b>						
Gough, 2011 <sup>10</sup>	Case series	Patients = 317 Case series and reports = 27	-Average age = 53 yrs -61% Female	Disease resolution	Range: 36 hours-5 yrs	92% of patients experienced resolution.

Legend: Yrs = years; CDI = *Clostridium difficile*; PCR = polymerase chain reaction; MRSA = methicillin resistant staphylococcus aureus; VRE = vancomycin resistant enterococcus

## Appendix C. Questionnaire Matrix

### Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

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

**Your Name:** \_\_\_\_\_

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<p><b>Key Question 1:</b> How do different methods for detection of toxigenic <i>C. difficile</i> to assist with diagnosis of CDI compare in their sensitivity and specificity? (a) Do the differences in performance measures vary with sample characteristics?</p>			
<p><b>Immunoassays for toxins A and B</b>  <b>Level of Evidence:</b> Low to moderate            •Ten studies directly compared at least 2 immunoassays for toxins A and B, providing 16 pairwise comparisons of 7 different immunoassays. Comparative data were not found for many currently used tests.            •There were no statistical differences between the sensitivities of immunoassays that were compared; however, the estimates of the differences in sensitivity were not very precise and could not rule out substantial differences.            •Substantial differences in false positives, that is, specificity, were not found among the tests that were compared.</p>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<p><b>Gene detection tests versus immunoassays for toxins A and B</b>  <b>Level of Evidence:</b> Low to moderate  •Four studies compared at least one toxin gene detection test to at least one immunoassay for toxins A and B, providing a total of nine direct comparisons. Comparative data were not always available for the three currently available gene detection tests.  •The gene detection tests could be substantially more sensitive than many immunoassays for toxins A and B, with no or relatively modest loss of specificity.</p>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<p><b>Patient characteristics</b>  <b>Level of Evidence:</b> Insufficient  Insufficient patient information was provided in reports of comparative data.</p>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<p><b>Key Question 2. What are effective prevention strategies? (a) What is the effectiveness of current prevention strategies? (b) What are the harms associated with prevention strategies? 3 (c) How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?</b></p>			

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<b>Antibiotic use</b> <b>Level of Evidence:</b> Low •Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. •Harms were not reported.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Gloves</b> <b>Level of Evidence:</b> Low One controlled trial found use of gloves in hospital settings reduced CDI incidence.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Disposable thermometer</b> <b>Level of Evidence:</b> Low Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Handwashing/alcohol gel</b> <b>Level of Evidence:</b> Low •No study examined whether handwashing reduced CDI incidence. •Two studies, one controlled trial and one before–after study, of use of alcohol gel to reduce MRSA transmission did not find significant differences in CDI incidence.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Disinfection</b> <b>Level of Evidence:</b> Low Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills <i>C. difficile</i> spores	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
reduced CDI incidence.			
<b>Sustainability</b> <b>Level of Evidence:</b> Insufficient No evidence was available.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Risk Factors</b> <b>Level of Evidence:</b> Low •Ten observational studies found evidence that antibiotic use, whether specific or general, increased risk of CDI. •Severe underlying disease, acid suppression, and age are indicated as risk factors. A number of other potential factors may be indicated in single studies.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Multiple component strategies</b> <b>Level of Evidence:</b> Insufficient •Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data are insufficient to draw conclusions. •Harms were not reported.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Key Question 3: What are the comparative effectiveness and harms of different antibiotic treatments? (a) Does effectiveness vary by disease severity or strain? (b) Does effectiveness vary by patient characteristics: age, gender, comorbidity, hospital versus community-acquired setting? (c) How do prevention and treatment of CDI affect resistance of other pathogens?</b>			
<b>Vancomycin versus metronidazole</b> <b>Level of Evidence:</b> Moderate for clinical cure, low for all other outcomes •There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure, especially with regard to stool count and	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
consistency. •No significant differences in outcomes, including initial cure, clinical recurrence, and mean days to resolved diarrhea, were found. •Our results build upon, and are consistent with, the Cochrane Reviews search completed by Bricker et al. <sup>2</sup>			
<b>Severe disease, vancomycin versus metronidazole</b> <b>Level of Evidence:</b> Insufficient One RCT examined a prespecified subgroup of 69 subjects with severe CDI; improved clinical cure was based on per-protocol analysis, but not with strict intention-to-treat analysis	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Fidaxomicin versus vancomycin</b> <b>Level of Evidence:</b> Moderate One large, high-quality RCT demonstrated decreased recurrence among those receiving fidaxomicin.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>All other comparisons of standard treatments</b> <b>Level of Evidence:</b> Moderate for vancomycin versus fidaxomicin, low for all other comparisons There were eight trials examining: vancomycin versus bacitracin (two trials), vancomycin versus fidaxomicin, vancomycin versus nitazoxanide, vancomycin high versus low dose, vancomycin versus placebo, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin (one each). No differences.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

<sup>2</sup> Abougergi MS, Broor A, Cui W, et al. Intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis: an observational study and review of the literature. J Hosp Med 2010 Jan; 5(1):E1–9.

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<b>Strain of organism</b> <b>Level of Evidence:</b> Low One RCT (fidaxomicin vs. vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Patient characteristics</b> <b>Level of Evidence:</b> Insufficient No comparative data were available.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Resistance of other pathogens</b> <b>Level of Evidence:</b> Insufficient No data were available.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Key Question 4: What are the effectiveness and harms of nonstandard adjunctive interventions? (a) In patients with relapse/recurrent CDI?</b>			
<b>Treating CDI, active control</b> <b>Level of Evidence:</b> Low Probiotics, prebiotics, <i>C. difficile</i> immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<b>Treating CDI, placebo</b> <b>Level of Evidence:</b> Low Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Treating recurrent CDI</b> <b>Level of Evidence:</b> Low There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Preventing CDI</b> <b>Level of Evidence:</b> Low There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Preventing recurrent CDI</b> <b>Level of Evidence:</b> Low to moderate <ul style="list-style-type: none"> <li>•There is limited evidence from one subgroup analysis that a prebiotic may reduce diarrhea recurrence in patients treated for CDI more so than placebo with standard antibiotics.</li> <li>•There is limited moderate-strength evidence from one study that monoclonal antibodies are effective in preventing recurrence of CDI.</li> </ul>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Are there new data that could inform the key questions that might not be addressed in the conclusions?</b>			

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>