Effective Health Care Program

Future Research Needs Paper
Number 17

Future Research Needs for Prevention and Treatment of *Clostridium difficile* Infection

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Number 17

Future Research Needs for Prevention and Treatment of *Clostridium difficile* Infection

Identification of Future Research Needs From Comparative Effectiveness Review No. 31

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Addendum added October 2012

Addendum
October 26, 2012

The report Future Research Needs for Prevention and Treatment of *Clostridium difficile* Infection was posed for public comment from May 29, 2012, to June 26, 2012.

In response to the comments received the authors add the following discussion points:

- Standardized definitions in a number of areas will be critical to address in future research of prevention and treatment of CDI. These include clinically relevant definitions of disease, disease severity and disease resolution.
- Absent a consensus on a definition of standard of care, methodological transparency will be essential to defining the intervention and comparator in an era where infection control bundles are ubiquitous. To that end, mathematical modeling may be especially helpful in isolating the relative impact of each bundle element.
- Prevention studies should include the contribution of surveillance, perioperative prophylaxis, hand hygiene, and patient education and engagement, and all studies need to consider relevant functional outcomes, such as mobility and duration of diarrhea in an aging population, along with common patient-centered outcomes such as recurrence.
- Future research priorities should include pediatrics and emerging populations such as pregnant, peripartum, and those with inflammatory bowel disease, and interventions in the ambulatory and critical care settings.

This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies.. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Executive Summary

Background

Clostridium difficile infection (CDI) is a serious healthcare-associated infection and a growing health care problem, especially with the emergence of more virulent strains in the early 2000s.[1] CDI is now the most common cause of nosocomial infectious diarrhea and is increasing in incidence and, in all likelihood, severity.

A comparative effectiveness review (CER) was prepared by the Minnesota Evidence-based Practice Center (EPC) on *Comparative Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection* (December 2011).[1] The purpose of the CER was to provide an overarching assessment of the evidence for comparing the accuracy of diagnostic tests and the effectiveness of prevention and treatment interventions on initial and recurrent CDI-related patient outcomes in adults. The analytical framework that guided the CER is provided in Figure A. The framework lays out the clinical path for patients with the potential to develop CDI, from diagnostic laboratory tests, through their impact on treatment decisions, to implications for prevention strategies.[1] Key Questions (KQs) and CER summary follows (Table A):

Table A. Key questions and summary of results from CER

Key Question	Summary Results
1) How do different methods for detection of toxigenic *Clostridium difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity?	• Immunoassays for toxins A and B: 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. • Gene detection tests versus immunoassays for toxins A and B: 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. • Patient characteristics: Insufficient patient information was provided in reports of comparative data.
2) What are effective prevention strategies?	• Antibiotic use: Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. Harms were not reported. • Gloves: One controlled trial found use of gloves in hospital settings reduced CDI incidence. • Disposable thermometer: Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence. • Handwashing/alcohol gel: 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. • Disinfection: Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills *C. difficile* spores reduced CDI incidence. • Sustainability: No evidence was available. • Risk Factors: 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. • Multiple component strategies: Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data is insufficient to draw conclusions. Harms were not reported.

Table A. Key questions and summary of results from CER (continued)

Key Question	Summary Results
3) What are the comparative effectiveness and harms of different antibiotic treatments?	• Vancomycin versus metronidazole: There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure definitions, especially with regard to stool count and 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. • Severe disease, vancomycin versus metronidazole: One RCT examined a prespecified subgroup of 69 subjects with severe CDI; Improved clinical cure based on per-protocol analysis, but not with strict intention-to-treat analysis. • Fidaxomycin versus vancomycin: One large, high quality RCT demonstrated decreased recurrence among those receiving fidaxomicin. • All other comparisons of standard treatments: 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. • Strain of organism: One RCT (fidaxomicin versus vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain. • Patient characteristics: No comparative data were available. • Resistance of other pathogens: No data were available.
4) What are the effectiveness and harms of nonstandard adjunctive interventions?	• Treating CDI, active control: Probiotics, prebiotics, *C. difficile* immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo. • Treating CDI, placebo: 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. • Treating recurrent CDI: There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year. • Preventing CDI: There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI. • Preventing recurrent CDI: 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.

Limited high-quality evidence was available to support the diagnostic, preventive, and treatment practices for CDI carried out by providers in hospital, long-term care, and outpatient settings.[1] Inconsistency in definitions of diarrhea, severity, resolution of symptoms, recurrence, or cure contributed to the difficulty in drawing conclusions from the evidence.[1] There were a number of important evidence gaps identified in the CER.[1] Table B summarizes the research recommendations from the CER. The objective of this Future Research Needs project was to systematically prioritize evidence gaps on prevention and treatment of CDI, and to develop a list of research questions to address the prioritized gaps. Although different diagnostic methods for toxigenic *Clostridium difficile* were evaluated in the CER, diagnostic methods were not included in this project primarily because polymerase chain reaction testing is rapidly becoming the standard diagnostic test for the infection.

Methods

First, evidence gaps were identified through the Minnesota EPC CER. After the CER was published, the literature search was updated and clinicaltrials.gov was searched to identify any ongoing research studies that might address the evidence gaps. Next, stakeholders were identified and through and iterative process the gaps were shared with and refined by these stakeholders. A group of nine stakeholders (Stakeholder Panel), representing diverse perspectives, including methodological/research expertise, clinical experience, and patient and payer representation, was formed; this group prioritized the refined evidence gaps, and generated research questions. Evidence gaps and subsequent research questions for each gap were generated online by the Stakeholder Panel using SurveyMonkey®, an online survey tool. The list of gaps and research questions was then circulated and discussed at the respective Stakeholder Panel teleconference calls. EPC staff compiled a final list, taking the Panel comments into consideration and paying particular attention to areas where ongoing efforts might overlap with prioritized gaps.

In selecting criteria for prioritization, we drew on our experience from a Future Research Needs project for Localized Prostate Cancer, in which the Effective Health Care (EHC) Program Selection Criteria were modified to be applicable to primary research rather than to systematic reviews of original research. The criteria were used to prioritize gaps and research questions. The modified EHC Program Selection Criteria were distributed to panel members each time they were asked to prioritize evidence gaps or research questions. The research questions were characterized using the PICOTS framework using the population (P), intervention (I), comparison (C), outcomes (O), timing (T), and setting (S). The project team then evaluated potential study designs to address each of the research questions. Prioritization of study designs was handled by the EPC in accordance with the recent Future Research Needs methods report by AHRQ.[2] The Stakeholder Panel provided insight into how future research agendas and proposed studies to address gaps fit within these prespecified criteria.

Figure A. Analytic framework from CER for CDI diagnostic testing, prevention, and treatment

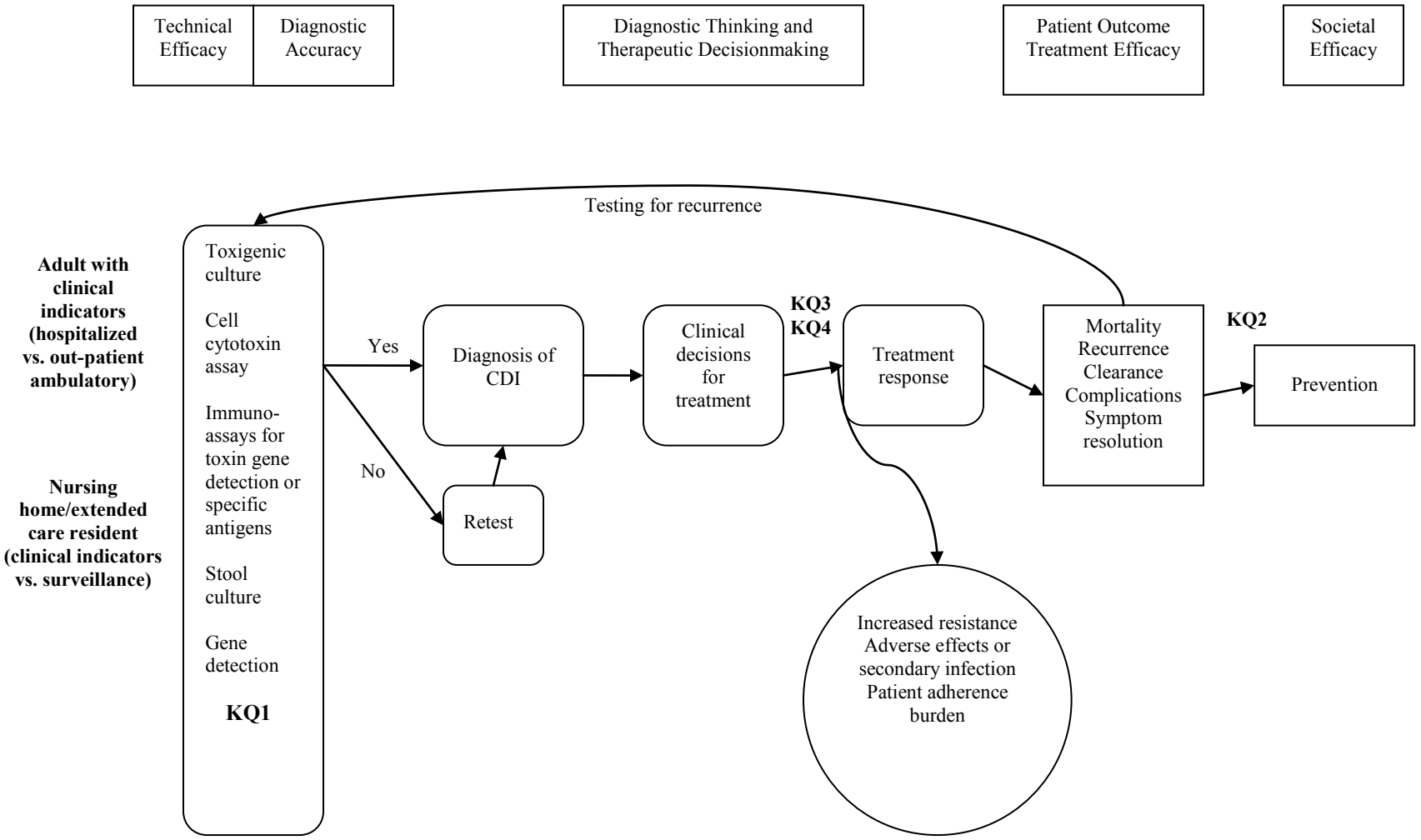

Table B. Future research recommendations from CER[1]

Key Question	Research Gaps	Types of Studies Needed to Answer Questions	Future Research Recommendation
Key Question 1. How do different methods for detection of toxigenic CD compare in their sensitivity, specificity, and predictive values?	• Few comparisons are available • Heterogeneity is an obstacle • Unknown what differences in sensitivity and specificity would alter clinician decisionmaking • Unknown influence of patient and stool characteristics on test sensitivity and specificity	• Comparison of diagnostic tests using same samples, same labs • Multicenter studies with well-documented patient samples	• Document stool sample characteristics, patient selection criteria, patient characteristics, and signs and symptoms of suspected CDI
Key Question 2. What are effective prevention strategies?	• Little evidence available with clinically important outcomes	• High-quality comparative studies evaluating effectiveness and harms of single and/or multi-component prevention strategies, including cleaning, isolation, antibiotic restriction • Discrete simulation models	• Pool data from multiple participating hospital sites • Establish minimum datasets for observational data points that can inform models
Key Question 3. What are the comparative effectiveness and harms of different antibiotic treatments?	• Limited evidence available on whether vancomycin is more effective for severe CDI.	• High-quality comparative studies with adequate power to detect significance in a priori subgroups	• A uniform and clinically relevant definition of severity • Subgroup analysis may include age, gender, comorbid conditions • Explicit reporting of adverse events
Key Question 4. What are the effectiveness and harms of nonstandard adjunctive interventions?	• Probiotics as a treatment adjuvant is not supported. Potential harms to seriously ill patients may outweigh potential benefits for further prevention research • Probiotics as prevention warrants further study • Further research of monoclonal antibodies for prevention is warranted • Further research of fecal transplant is warranted	• High-quality comparative studies with adequate power	• Placebo comparators would contribute indirect evidence to help guide potential combination therapies • Quality research includes power analysis, intention to treat • Multicenter trials are likely needed to achieve adequate samples • Probiotics trials for prevention are well represented in ongoing studies • Patient characteristics for subgroup analysis
Umbrella issues			• Adoption of standard definitions for diarrhea, CDI resolution

CDI = *Clostridium difficile* infection

Results

A total of 18 evidence gaps were identified through a combination of the CER findings and conversations with the Stakeholder Panel. These gaps were grouped based on the three key questions addressed in the CER (i.e., prevention, antibiotic treatments, and nonstandard adjunctive interventions). Through an iterative process, the Stakeholder Panel identified and prioritized evidence gaps. The EPC generated the final ranking of four evidence gaps taking all Stakeholder Panel comments into account. The final four research gaps are stated below:

1. Effectiveness and harms of single and/or multi-component prevention strategies for CDI
2. Effectiveness and harms of different strategies for recurrent CDI treatment and prevention
3. Effectiveness and harms of antibiotic treatments for first episode of CDI
4. Effectiveness and harms of fecal transplantation for management of CDI

These four evidence gaps were considered a priority in need of further research primarily given that the information at present is insufficient or imprecise that precludes conclusions from being made about each gap. The Panel then generated and prioritized a list of potential research questions to address these gaps. The final prioritized list of research gaps and research questions accompanied by PICOTS elements are stated in Table C. For the assessment of study designs, EPC staff evaluated the appropriateness of various designs (i.e., randomized controlled trial, nonrandomized comparative trial, prospective cohort, retrospective cohort, nested case-control, case-control, before-after study, modeling) for each prioritized research question.

Discussion

This Future Research Needs project was built from the Minnesota EPC CER. We used a multidisciplinary Stakeholder Panel of nine participants using an 11-step process to identify and prioritize evidence gaps and key research questions across the selected gaps. The final research questions, reflecting the breadth of the original key questions on prevention and treatment of CDI, address a variety of interventions and outcomes for the initial disease and of CDI recurrence. Through this process, we propose a final list of four evidence gaps and seven associated research questions.

It should be noted that the Stakeholder Panel highlighted evidence gaps that were outside the CER scope, such as the need for more research into the epidemiology of CDI and basic science to understand the microbiology. Gaps in the existing epidemiologic knowledge base should be identified with corresponding research projects targeted to fill those gaps. We used multiple techniques to engage stakeholders, including individual interviews, online surveys and conference calls. The literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials to which further research would add the greatest value.

Table C. Prioritized list of evidence gaps and research questions

Evidence Gap	Research Question	Population	Intervention	Comparator	Outcomes	Timing	Setting
Effectiveness and harms of single and/or multi-component prevention strategies for CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Not the right information (results not applicable to setting of interest).	**1.1** What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings? **1.2** What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?	Hospital inpatients, ambulatory care patients, residents of any healthcare facility without symptoms/ diagnosis of CDI on admission	Novel strategy (+ standard care) e.g., intensified environmental cleaning	Standard care alone	Primary: change in acquisition incidence of CDI, adverse events; secondary: changes in antibiotic usage, antimicrobial resistance, length of stay, barriers to implementation, mortality	Defined *a priori*	Hospital, ambulatory care, nursing home
Effectiveness and harms of different strategies for recurrent CDI treatment and prevention Reason(s) for Gap: Insufficient or imprecise information (limited number of studies).	**2.1** What is the comparative effectiveness of different treatment options for recurrent CDI?	Patients with laboratory confirmed recurrence of CDI of any disease severity	Novel therapy e.g., monoclonal antibody, drug ACT-179811	different treatment options (standard care)	Primary: initial response to therapy (e.g., mean days to resolution of diarrhea, clearance of toxin, persistence of the organism), harms; secondary: recent antibiotic history, sustained response, mortality.	Duration of followup of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence (for prospective studies)	Hospital, outpatient clinics
	2.2 What are the factors/determinants that make for better recurrence prevention for CDI?	The PICOTS on this question will depend on study question and design					
	2.3 To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?	Patients being treated for CDI or who have completed CDI treatment	Concomitant antibiotic administered either during or after CDI therapy	No concomitant antibiotic or an alternative concomitant antibiotic	Initial response rate and sustained response rate for CDI, harms, time to initial response, duration of CDI therapy, mortality	A few weeks	Any healthcare setting

Table C. Prioritized list of evidence gaps and research questions (continued)

Evidence Gap	Research Question	Population	Intervention	Comparator	Outcomes	Timing	Setting
Effectiveness and harms of antibiotic treatments for first episode of CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Not the right information (optimal/most important outcomes not addressed)	**3.1** What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?	Patients diagnosed with CDI	Novel therapy e.g., modified release metronidazole, fixadomycin with vancomycin	Vancomycin or metronidazole	Primary: Initial response e.g. resolution of diarrhea at end of treatment (~10 days), harms, recent antibiotic history; secondary: sustained response (i.e. initial response without recurrence), mean days to resolution of diarrhea, death	Variable but likely a few weeks	Hospital, nursing home, long-term care facility, community
Effectiveness and harms of fecal transplantation for management of CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Information at risk of bias (major methodological limitations in studies)	**4.1** What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?	Patients with laboratory confirmed recurrence of CDI of any disease severity	Fecal transplantation	Vancomycin or metronidazole	Primary- initial response to therapy (e.g., mean days to resolution of diarrhea, clearance of toxin, persistence of the organism), harms; secondary: recent antibiotic history, sustained response, mortality.	Duration of followup of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence (for prospective studies)	Hospital, outpatient clinics

One of the major challenges we encountered in our process was to maintain the focus on the key questions (and scope) addressed in the original CER. It was important on being very explicit about the original scope of the CER as well as the scope of this future research needs effort. There also were several ways to combine/categorize many of the proposed topics; there was crossover and overlap between the various evidence gaps, and the key underlying research questions were addressed within the top-ranked four gaps. In addition, during discussions on research questions, outcomes of interest for certain questions were deemed to be difficult to address in future studies.

Conclusions

The following four prioritized evidence gaps and seven research questions were identified (Table D).

Table D. Prioritized evidence gaps and research questions

Evidence Gap	Research Question
Effectiveness and harms of single and/or multi-component prevention strategies for CDI	1.1 What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings? 1.2 What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?
Effectiveness and harms of different strategies for recurrent CDI treatment and prevention	2.1 What is the comparative effectiveness of different treatment options for recurrent CDI? 2.2 What are the factors/determinants that make for better recurrence prevention for CDI? 2.3 To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?
Effectiveness and harms of antibiotic treatments for first episode of CDI	3.1 What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?
Effectiveness and harms of fecal transplantation for management of CDI	4.1 What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?

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2. Carey T, Sanders GD, Viswanathan M, Trikalinos TA, Kato E, Chang S. Framework for Considering Study Designs for Future Research Needs. Methods Future Research Needs Paper No. 8 (Prepared by the RTI–UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC048-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012.

Introduction

Background

Context

Clostridium difficile infection (CDI) is a serious healthcare-associated infection and a growing health care problem, especially with the emergence of more virulent strains in the early 2000s.[1] *Clostridium difficile* was first recognized as having the ability to cause pseudomembranous colitis in the late 1970s.[2] CDI is now the most common cause of nosocomial infectious diarrhea. Asymptomatic colonization in healthy adults has been observed in only 3 percent of persons, while the prevalence of such colonization among residents in long-term-care facilities approaches 50 percent.[3] Individuals colonized with *Clostridium difficile* serve as a reservoir for infection by contaminating the environment with *Clostridium difficile* spores, thus leading to the spread of the organism on the hands of health care workers or via use of medical equipment. CDI is increasing in incidence and, in all likelihood, severity. The number of cases diagnosed among patients discharged from hospitals increased from 31 per 100,000 persons in 1996 to 84 per 100,000 persons in 2005.[4] Infection due to a relatively new strain of *Clostridium difficile*, termed "North American pulsed-field gel electrophoresis type 1" (NAP1), is felt to be at least partially responsible for this increased incidence of CDI as well as for the increased severity of clinical illness. The NAP1 strain is capable of producing more than 15 times the quantity of both toxins A and B, which are directly responsible for the damage to the intestinal tract of infected patients. Hence, CDI is not only now more common, but also more severe, leading to an attributable mortality of up to 16 percent of all deaths.[5]

A comparative effectiveness review (CER) was prepared by the Minnesota Evidence-based Practice Center (EPC) on *Comparative Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection* (December 2011).[1] The purpose of the CER was to provide an overarching assessment of the evidence for comparing the accuracy of diagnostic tests and the effectiveness of prevention and treatment interventions on initial and recurrent CDI-related patient outcomes in adults. Key informants, provided input to the EPC on the scope of the CER, agreed that its greatest contribution to the field could be to have an independent organization provide a comprehensive review of the major concerns of the field for both clinicians and researchers.[1]

The major impetus underlying the SR was a concern about the presence of clinical disease, not asymptomatic carriage of the *Clostridium difficile* organism.[1] Molecular epidemiological studies whose main purpose was to identify the strains of *Clostridium difficile* present in the population were outside the scope of the CER. The CER focused on adult patients as they, particularly elderly adults, carry the most of the morbidity and mortality burden.[1]

The CER addressed the following Key Questions (KQs):

1. How do different methods for detection of toxigenic *Clostridium difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity?
    a. Do the differences in performance measures vary with sample characteristics?
2. What are effective prevention strategies?
    a. What is the effectiveness of current prevention strategies?
    b. What are the harms associated with prevention strategies?

c. How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?

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?
4. What are the effectiveness and harms of nonstandard adjunctive interventions?
   a. In patients with relapse/recurrent CDI?[1]

Limited high-quality evidence was available to support the diagnostic, preventive, and treatment practices for CDI carried out by providers in hospital, long-term care, and outpatient settings.[1] The KQ s and summary of results from the CER are presented in Table 1 below. Appendix A provides further details on the findings presented in the CER. Inconsistency in definitions of diarrhea, severity, resolution of symptoms, recurrence, or cure contributed to the difficulty in drawing conclusions from the evidence.[1]

Table 1. Key questions and summary of results from CER

Key Question	Summary Results
1) How do different methods for detection of toxigenic *Clostridium difficile* to assist with diagnosis of CDI compare in their sensitivity and specificity?	• Immunoassays for toxins A and B: 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. • Gene detection tests versus immunoassays for toxins A and B: 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. • Patient characteristics: Insufficient patient information was provided in reports of comparative data.
2) What are effective prevention strategies?	• Antibiotic use: Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. Harms were not reported. • Gloves: One controlled trial found use of gloves in hospital settings reduced CDI incidence. • Disposable thermometer: Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence. • Handwashing/ alcohol gel: 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. • Disinfection: Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills *C. difficile* spores reduced CDI incidence. • Sustainability: No evidence was available. • Risk Factors: 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. • Multiple component strategies: Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data is insufficient to draw conclusions. Harms were not reported.

Table 1. Key questions and summary of results from CER (continued)

Key Question	Summary Results
3) What are the comparative effectiveness and harms of different antibiotic treatments?	• Vancomycin versus metronidazole: There were 3 head-to-head trials with a total of 335 subjects. Trials used various definitions of CDI patient and cure definitions, especially with regard to stool count and 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. • Severe disease, vancomycin versus metronidazole: One RCT examined a prespecified subgroup of 69 subjects with severe CDI; Improved clinical cure based on per-protocol analysis, but not with strict intention-to-treat analysis. • Fidaxomycin versus vancomycin: One large, high quality RCT demonstrated decreased recurrence among those receiving fidaxomicin. • All other comparisons of standard treatments: 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. • Strain of organism: One RCT (fidaxomicin versus vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain. • Patient characteristics: No comparative data were available. • Resistance of other pathogens: No data were available.
4) What are the effectiveness and harms of nonstandard adjunctive interventions?	• Treating CDI, active control: Probiotics, prebiotics, *C. difficile* immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo. • Treating CDI, placebo: 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. • Treating recurrent CDI: There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year. • Preventing CDI: There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI. • Preventing recurrent CDI: 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.

Evidence Gaps

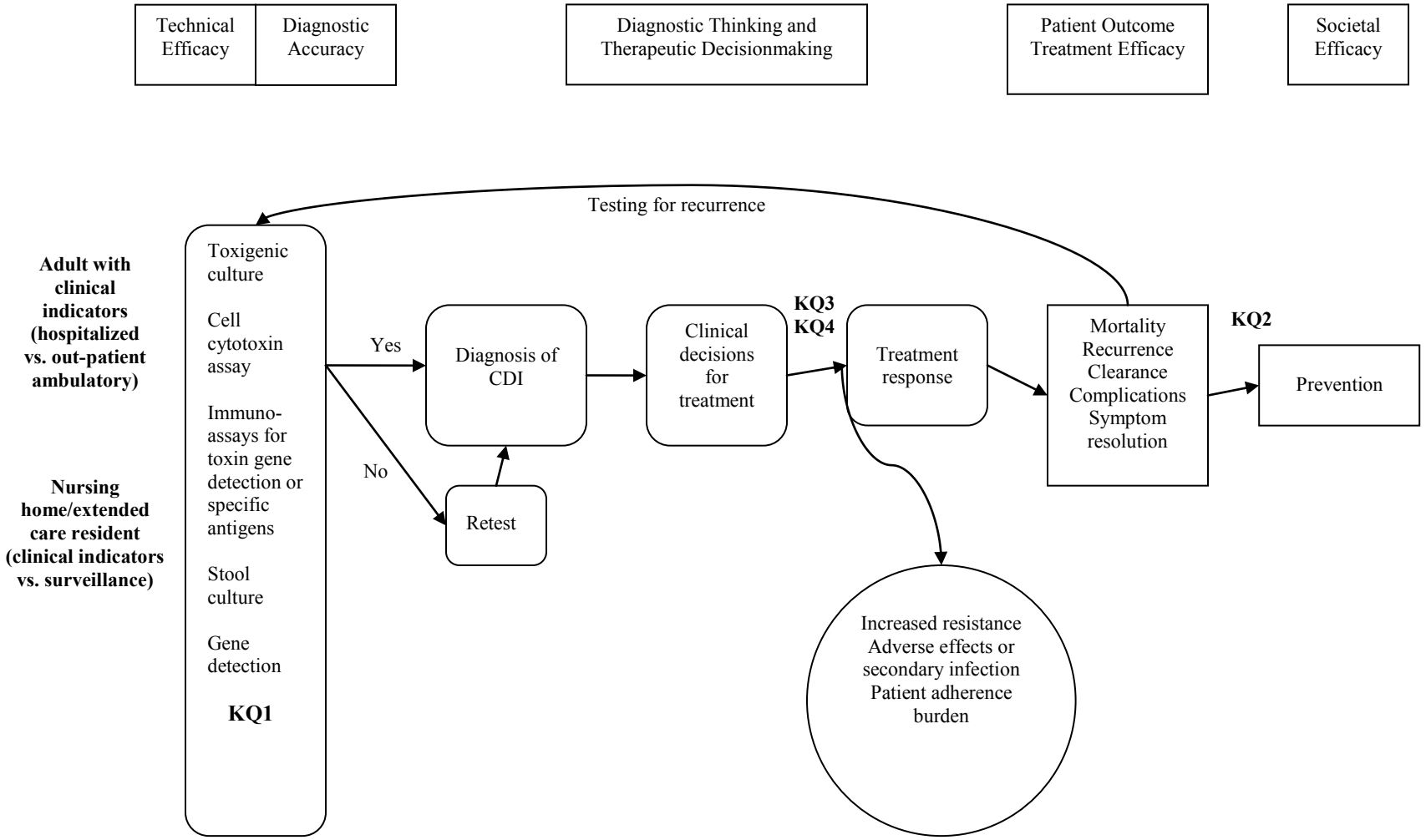
There were a number of important evidence gaps identified in the CER.[1] Table 2 summarizes the research recommendations from the CER. The analytical framework that guided the CER is provided in Figure 1. The framework lays out the clinical path for patients with the potential to develop CDI, from diagnostic laboratory tests, through their impact on treatment decisions, to implications for prevention strategies.[1] The CER Key Questions are identified within the framework (Figure 1).

Table 2. Future research recommendations from comparative effectiveness review

Key Question	Research Gaps	Types of Studies Needed to Answer Questions	Future Research Recommendation
Key Question 1. How do different methods for detection of toxigenic CD compare in their sensitivity, specificity, and predictive values?	• Few comparisons are available • Heterogeneity is an obstacle • Unknown what differences in sensitivity and specificity would alter clinician decisionmaking • Unknown influence of patient and stool characteristics on test sensitivity and specificity	• Comparison of diagnostic tests using same samples, same labs • Multicenter studies with well-documented patient samples	• Document stool sample characteristics, patient selection criteria, patient characteristics, and signs and symptoms of suspected CDI
Key Question 2. What are effective prevention strategies?	• Little evidence available with clinically important outcomes	• High-quality comparative studies evaluating effectiveness and harms of single and/or multi-component prevention strategies, including cleaning, isolation, antibiotic restriction • Discrete simulation models	• Pool data from multiple participating hospital sites • Establish minimum datasets for observational data points that can inform models
Key Question 3. What are the comparative effectiveness and harms of different antibiotic treatments?	• Limited evidence available on whether vancomycin is more effective for severe CDI.	• High-quality comparative studies with adequate power to detect significance in a priori subgroups	• A uniform and clinically relevant definition of severity • Subgroup analysis may include age, gender, comorbid conditions • Explicit reporting of adverse events
Key Question 4. What are the effectiveness and harms of nonstandard adjunctive interventions?	• Probiotics as a treatment adjuvant is not supported. Potential harms to seriously ill patients may outweigh potential benefits for further prevention research • Probiotics as prevention warrants further study • Further research of monoclonal antibodies for prevention is warranted • Further research of fecal transplant is warranted	• High-quality comparative studies with adequate power	• Placebo comparators would contribute indirect evidence to help guide potential combination therapies • Quality research includes power analysis, intention to treat • Multicenter trials are likely needed to achieve adequate samples • Probiotics trials for prevention are well represented in ongoing studies • Patient characteristics for subgroup analysis
Umbrella issues			• Adoption of standard definitions for diarrhea, CDI resolution

CDI = Clostridium difficile infection

Figure 1. Analytic framework from CER for CDI diagnostic testing, prevention, and treatment



Methods

Identification of Evidence Gaps

Figure 2 outlines the process steps of this Future Research Needs project. The details are described in the text. First, evidence gaps were identified through the Minnesota EPC CER. After the CER was published, the literature search was updated and ClinicalTrials.gov was searched to identify any ongoing research studies that might address the evidence gaps. Next, stakeholders were identified and through and iterative process the gaps were shared with and refined by these stakeholders (see section on engagement of stakeholders, researchers and funders). A group of nine stakeholders (Stakeholder Panel) representing diverse perspectives was formed; this group prioritized the refined evidence gaps, and generated research questions (see sections on criteria for prioritization, and research question development). Gaps were prioritized through the Web using the SurveyMonkey® Web site. Finally, the exploration of various research designs was conducted by the EPC. Details of these steps follow.

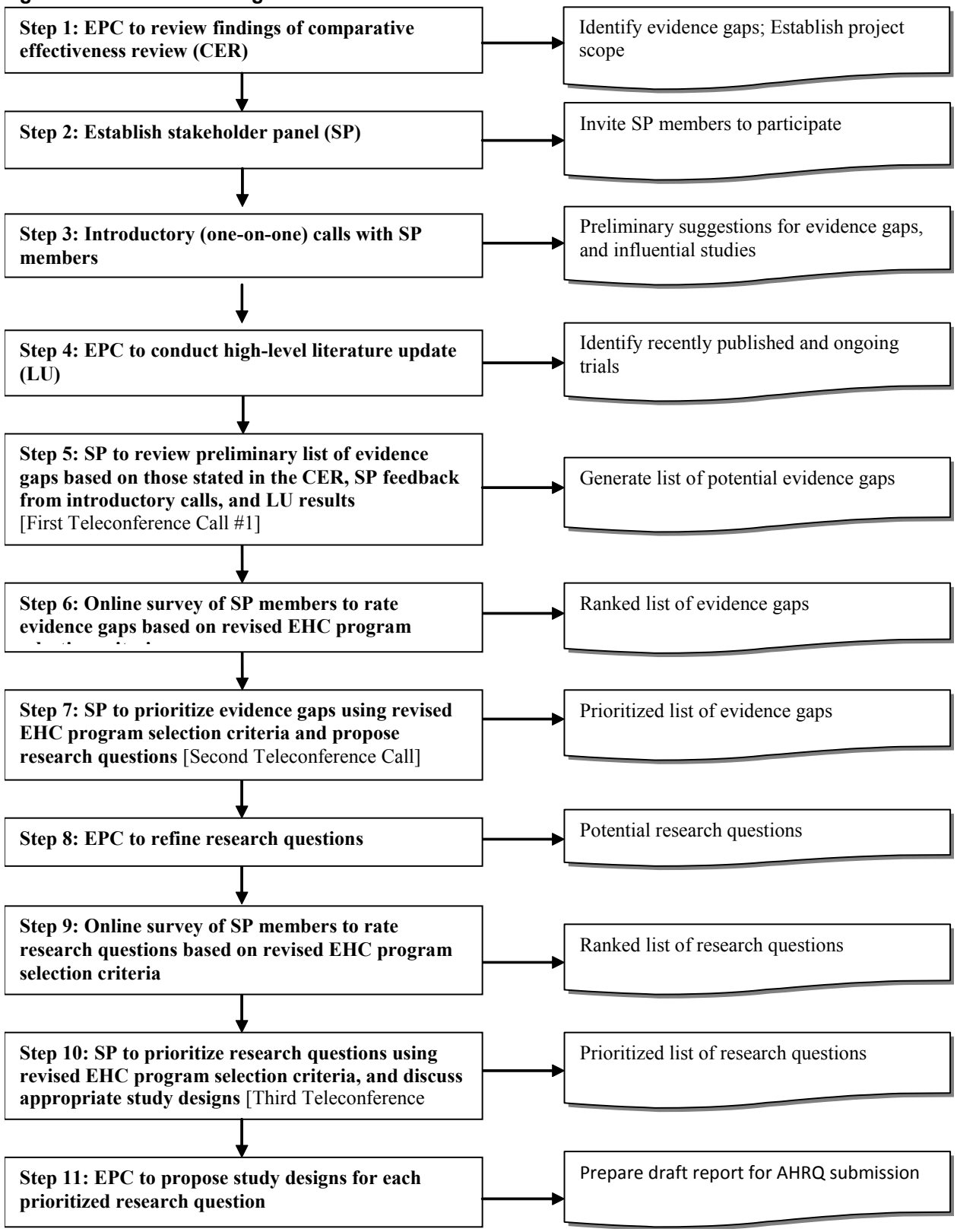
Project Scope

The project team held multiple meetings to discuss the Future Research Needs project scope including dialogue with the lead investigator of the CER. Through these discussions, the project team focused the project on CDI prevention and treatment, including antibiotic therapy, immunotherapy, and reconstitution or manipulation of the gut microflora (i.e., probiotics, fecal transplant, etc.), and other novel and "nonstandard" adjunctive interventions. This Future Research Needs project addresses the appropriateness and effectiveness of varied preventive and therapeutic interventions are in patient subgroups. Although different diagnostic methods for toxigenic *Clostridium difficile* were evaluated in the CER, diagnostic methods were not included in this project primarily because polymerase chain reaction testing is rapidly becoming the standard diagnostic test for the infection.

Literature Search Update

To identify published and ongoing studies addressing the CDI evidence gaps, we conducted searches using MEDLINE® (via PubMed®), the Cochrane Library, and the ClinicalTrials.gov databases. The search captured studies published since January 2012 for the evidence gaps identified in the CER. As the time frame was short and retrieval was expected to be quite small, an initial search was undertaken for all ongoing CDI studies (Appendix B).

Figure 2. Process flow diagram



Criteria for Prioritization

In criteria for prioritization, we drew on our experience from a Future Research Needs project for localized prostate cancer,[6] in which the Effective Health Care (EHC) Program Selection Criteria were modified to be applicable to primary research rather than to systematic reviews of original research.[7] The criteria were used to prioritize gaps and research questions (Table 3). The modified EHC Program Selection Criteria were distributed to panel members each time they were asked to prioritize evidence gaps or research questions. Prioritization of study designs was handled by the EPC in accordance with the recent FRN methods report by AHRQ.[8] The Stakeholder Panel provided insight into how future research agendas and proposed studies to address gaps fit within these prespecified criteria.

Table 3. Prioritization criteria for evidence gaps and proposed research studies

Category	Criterion
Current importance	• Incorporates both clinical benefits and harms • Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care • Addresses high costs to consumers, patients, health-care systems, or payers • Utility of available evidence limited by changes in practice, for example disease detection

Potential for significant health impact	• Potential for significant health impact:
	  ○ To improve health outcomes
	  ○ To reduce significant variation related to quality of care
	  ○ To reduce unnecessary burden on those with health-care problems
	• Potential for significant economic impact, reducing unnecessary or excessive costs.
	• Potential for evidence-based change.
	• Potential risk from inaction, for example lack of evidence for decisionmaking produces unintended harms
	• Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value	• Adds useful new information to existing portfolio of research on topic OR • Validates existing research when body of evidence is scant.
Feasibility	*Factors to be considered:* • Interest among researchers • Duration • Cost • Methodological complexity (e.g., do existing methods need to be refined?) • Implementation difficulty • Facilitating factors • Potential funders

Methods for Ranking Research Gaps

Evidence gaps were ranked via the SurveyMonkey® Web site. The Stakeholder Panel was sent a link to the Web site where they ranked the research gaps from 1 to 5 and generated research questions for each gap. The survey allowed each rank to be used only once. Points were assigned to each gap: 1 point for a ranking of fifth, up to 5 points for a ranking of first. The gap with the largest number of points was assigned the highest priority. The gaps were presented in a random order for the survey. The comments received from the Stakeholder Panel were reviewed by EPC staff and incorporated where necessary. In addition to the modified EHC Program Selection Criteria, special attention was paid to where evidence gaps overlapped with existing research. The reasons for each evidence gap were categorized based on a classification scheme created by the Johns Hopkins University EPC on behalf of AHRQ.[9]

Engagement of Stakeholders, Researchers, Funders

Central to the methodology of this report was the use of the Stakeholder Panel to identify and prioritize evidence gaps. A single multidisciplinary Stakeholder Panel was convened to provide input on this project. The Panel included individuals interested in comparative effectiveness research and knowledgeable about current research on CDI. They consisted of nine participants (including the lead investigator of the CER) representing diverse perspectives, including methodological/research expertise, clinical experience (from infectious diseases, epidemiology, gastroenterology), and patient and payer representation. The Stakeholder Panel brought forth specific expertise on prevention and treatment of CDI, including antibiotic therapy, immunotherapy, and reconstitution or manipulation of the gut microflora (e.g., fecal transplantation, probiotics).

The Stakeholder Panel was asked to recommend important studies published since the Minnesota EPC completed the CER,[1] revise and prioritize the evidence gaps listed in the CER and gathered throughout this project, and develop and prioritize a list of potential research questions to address those gaps. As proscribed by AHRQ, conflict of interest forms were completed by all panel members and staff on this project. The multidisciplinary character of the Stakeholder Panel and their varied affiliations enriched the process.

The Stakeholder Panel was asked to participate in three conference calls (1 hour each) over the project duration, and some interim communications by email. In addition, a brief introductory call (30 minutes) was scheduled separately with each individual member, to provide an overview of the project, to discuss the role of the Stakeholder Panel, and to solicit preliminary suggestions on further evidence gaps. The First Call was held on February 7, 2012. During this call, the members were asked to review the preliminary list of evidence gaps. This list was a synthesis of evidence gaps from the CER, those proposed by panel members during the individual introductory calls, and results of the literature search update. Following the first call, the Stakeholder Panel members were asked to rank, via an online survey, their top 5 evidence gaps from 1 to 5 with 1 having the highest priority and 5 the lowest. Panel members rated these evidence gaps based on revised EHC program selection criteria (Appendix C). The Second Call was scheduled on February 28, 2012. During the second call, Stakeholder Panel members were invited to review the prioritized list of research gaps and "brainstorm" research questions to address each evidence gap.

The Third Call was convened on March 30, 2012 for prioritization of research questions. A list of potential research questions were sent to members via electronic mail prior to this

teleconference call. The Stakeholder Panel was asked to prioritize the research questions via an online survey instrument (using SurveyMonkey™) similar to that used for selection of evidence gaps. As with the online survey for evidence gaps, members were asked to rank their top 5 research questions from 1 to 5 with 1 having the highest priority and 5 the lowest (Appendix D). The project team collated the "votes" and reported the results at the third Panel meeting held via teleconference. The meeting participants reviewed the results and further discuss the importance of the research questions to patients and clinical decisionmaking. These discussions formed the basis for the final prioritized list of research questions submitted to AHRQ. Alternate calls were scheduled as necessary with members who were unable to participate during the panel calls, in accordance with the collective preferences of the panel members and the project team. All teleconference call materials were distributed a few days prior to scheduled calls. To enhance public engagement, AHRQ will solicit broader input on this document by making it available for public input, which will be incorporated and reflected in the final report.

Research Question Development and Study Design Considerations

Key research questions for each evidence gap were generated through an online survey instrument and discussions by the Stakeholder Panel (discussed previously). The project team compiled a final list of research questions taking the feedback of the Panel into consideration. The research questions were characterized using the PICOTS framework using the population (P), intervention (I), comparison (C), outcomes (O), timing (T), and setting (S). The project team evaluated potential study designs to address each of the key research questions. This approach is consistent with the guidance published by AHRQ.[8] The appropriateness of any one study design to address an evidence gap was further evaluated using the following criteria:

- Advantages of the study design for producing a valid result
- Resource use, size, and duration
- Ethical, legal, and social issues
- Availability of data or ability to recruit

The project team relied on this framework[8] as a guide during discussions of the least biased study design that was likely to be feasible and affordable. Public comments received after the document is posted will be incorporated into the final report.

Results

Research Needs

As stated in the Methods section, we had the Stakeholder Panel rank the research gaps and generate research questions online prior to the second and third teleconference calls, respectively. The results of the first survey ranking the importance of these evidence gaps are found in Appendix E, and those of the second survey ranking the importance of research questions are found in Appendix F.

A total of 18 evidence gaps were identified through a combination of the CER findings and conversations with the Stakeholder Panel (Appendix E). These gaps were grouped based on the three Key Questions addressed in the CER (i.e., prevention, antibiotic treatments, and adjunctive nonstandard interventions). The response rate was 100 percent (n=9); 16 (of 18) evidence gaps received votes (Appendix E).

The EPC generated the final ranking of evidence gaps taking all Stakeholder Panel comments into account. Several top-ranked gaps (Appendix E) brought forth through Panel discussions related to research into the epidemiology of CDI and basic science to understand the microbiology. Increased understanding of the basic science underlying CDI (and *Clostridium difficile*) was brought forth by the Stakeholder Panel to be critical for informing prevention efforts. Panel members highlighted the need for future studies on these aspects including further understanding of the gut microbiome, mapping of CDI, and modes of transmission of *Clostridium difficile*. These research areas related to the basic science and epidemiology of CDI were considered outside the original scope of the CER (i.e., the literature in these areas was not submitted to any systematic analysis) and thus not prioritized with the remaining evidence gaps for this Future Research Needs project. The evidence gaps outside the scope are highlighted in Appendix E.

The Stakeholder Panel also discussed the implications of the published studies and ongoing trials identified through the literature search update; these were not considered 'groundbreaking' from a prevention and treatment standpoint to impact the list of evidence gaps. Panel members proposed regrouping and rearrangement of the top-ranked evidence gaps as some of these gaps addressed similar issues. The final four research gaps are stated in Table 4.

Table 4. Prioritized list of evidence gaps

1	Effectiveness and harms of single and/or multi-component prevention strategies for CDI
2	Effectiveness and harms of different strategies for recurrent CDI treatment and prevention
3	Effectiveness and harms of antibiotic treatments for first episode of CDI
4	Effectiveness and harms of fecal transplantation for management of CDI

The prioritized list of evidence gaps, accompanied by preliminary research questions drafted by the EPC across each gap, was submitted for feedback to panel members via email following the second Stakeholder Panel call. Following this feedback, the second survey of research questions was submitted to Panel members for ranking prior to the third Stakeholder Panel call. As with the evidence gaps, the research questions were presented in a random order for the survey. The response rate was 100 percent (n=9); all questions received votes (Appendix F). Panel members discussed the importance and usefulness of future studies on the top-ranked questions based on the voting results at the third Stakeholder Panel call; eight (of 9) members were present on the third Stakeholder Panel call and an alternate call was held with one member

unable to participate on this call. Panel members reiterated the need for more basic epidemiologic data to address these questions especially for those related to prevention strategies. There was discussion on the appropriate threshold with respect to a short-list of research questions; further combining some of the overlapping topics on the list into key categories would be of benefit in this regard.

Panel members discussed the different weights given to the selection criteria when prioritizing research questions (e.g., potential health impact vs. feasibility), and other aspects including the role of entities which may fund this research to the short-list of research questions (e.g., likelihood of future studies for each of the research questions being sponsored by industry as opposed to funding by Federal or other non-profit sources). There also was further discussion for any redundancies around the research questions in light of the respective ongoing trials. Panel members reviewed the results of the literature search update; MEDLINE® yielded no new studies, neither did The Cochrane Library, yet 35 studies emerged from ClinicalTrials.gov that fell into this short update period. After careful review 15 studies appeared to address five (of 11) research questions (Appendix F). These discussions formed the basis for the final prioritized list of seven research questions below (Table 5; in order of priority).

Table 5. Prioritized list of research questions

1	What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings?
2	What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?
3	What is the comparative effectiveness of different treatment options for recurrent CDI?
4	What are the factors/ determinants that make for better recurrence prevention for CDI?
5	What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?
6	What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?
7	To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?

The final prioritized list of evidence gaps and research questions with details (PICOTS information and considerations of pros and cons of various research designs (developed after the second round of ranking) are stated in Table 6. The specific research projects to address each evidence gap and research questions are described in more detail in the following section.

Table 6. Prioritized list of evidence gaps and research questions

Evidence Gap	Research Question	Population	Intervention	Comparator	Outcomes	Timing	Setting
Effectiveness and harms of single and/or multi-component prevention strategies for CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Not the right information (results not applicable to setting of interest).	**1.1** What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings? **1.2** What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?	Hospital inpatients, ambulatory care patients, residents of any healthcare facility without symptoms/ diagnosis of CDI on admission	Novel strategy (+ standard care) e.g., intensified environmental cleaning	Standard care alone	Primary: change in acquisition incidence of CDI, adverse events; secondary: changes in antibiotic usage, antimicrobial resistance, length of stay, barriers to implementation, mortality	Defined *a priori*	Hospital, ambulatory care, nursing home
Effectiveness and harms of different strategies for recurrent CDI treatment and prevention Reason(s) for Gap: Insufficient or imprecise information (limited number of studies).	**2.1** What is the comparative effectiveness of different treatment options for recurrent CDI?	Patients with laboratory confirmed recurrence of CDI of any disease severity	Novel therapy e.g., monoclonal antibody, drug ACT-179811	Different treatment options (standard care)	Primary: initial response to therapy (e.g., mean days to resolution of diarrhea, clearance of toxin, persistence of the organism), harms; secondary: recent antibiotic history, sustained response, mortality.	Duration of followup of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence (for prospective studies)	Hospital, outpatient clinics
	2.2 What are the factors/determinants that make for better recurrence prevention for CDI?	The PICOTS on this question will depend on study question and design					
	2.3 To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?	Patients being treated for CDI or who have completed CDI treatment	Concomitant antibiotic administered either during or after CDI therapy	No concomitant antibiotic or an alternative concomitant antibiotic	Initial response rate and sustained response rate for CDI, harms, time to initial response, duration of CDI therapy, mortality	A few weeks	Any healthcare setting

Table 6. Prioritized list of evidence gaps and research questions (continued)

Evidence Gap	Research Question	Population	Intervention	Comparator	Outcomes	Timing	Setting
Effectiveness and harms of antibiotic treatments for first episode of CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Not the right information (optimal/most important outcomes not addressed)	**3.1** What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?	Patients diagnosed with CDI	Novel therapy e.g., modified release metronidazole, fixadomycin with vancomycin	Vancomycin or metronidazole	Primary: Initial response e.g. resolution of diarrhea at end of treatment (~10 days), harms, recent antibiotic history; secondary: sustained response (i.e. initial response without recurrence), mean days to resolution of diarrhea, death	Variable but likely a few weeks	Hospital, nursing home, long-term care facility, community
Effectiveness and harms of fecal transplantation for management of CDI Reason(s) for Gap: Insufficient or imprecise information (limited number of studies); Information at Risk of Bias (major methodological limitations in studies)	**4.1** What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?	Patients with laboratory confirmed recurrence of CDI of any disease severity	Fecal transplantation	Vancomycin or metronidazole	Primary- initial response to therapy (e.g., mean days to resolution of diarrhea, clearance of toxin, persistence of the organism), harms; secondary: recent antibiotic history, sustained response, mortality.	Duration of followup of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence (for prospective studies)	Hospital, outpatient clinics

Research Question Number 1.1

What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings?

Research Question Number 1.2

What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?

The study design evaluations for research questions 1.1 and 1.2 were combined as they would require the same design and face similar challenges (Table 7). Based on the CER, the focus of these questions is on the contribution of preventive strategies aimed at interrupting transmission of *Clostridium difficile* and reducing susceptibility to CDI in non-outbreak settings; this would include non-acute care facilities, which is an understudied setting. Onset in the majority of CDI cases occurs outside of the hospital setting, as relatively few cases can be traced back to other CDI cases in the hospital. Results may need to be stratified by preintervention *Clostridium difficile* acquisition incidence, as CDI incidence may be too low to use. Prevention measures may be evaluated individually or as bundled strategies, and may need to account for other institutional infection control practices already in place (referred to as standard care in Table 7), using higher quality comparative effectiveness research approaches.[10] Information on barriers to implementation and sustainability of such programs should be obtained.

Table 7. Study design evaluations for Research Questions 1.1 and 1.2

Study design considerations	Randomized controlled trial (RCT)	Quasi-experimental: before-after study (variations)	Modeling
Description of design	Individuals or groups randomly assigned to receive novel strategy or standard care. Patients and potentially staff are followed during implementation for incidence of CDI and other adverse events. Longer follow-up post implementation may be required if sustainability is a desired outcome. Cluster RCTs that randomize at a hospital or ward level may be more suitable for population-level strategies in non-outbreak settings when outcomes for individuals from a given unit are not independent. If pooling data across institutions is required, consensus on outcome measures, minimum datasets and follow-up periods would be needed.	Incidence of CDI compared in a group of individuals before and after exposure to the preventive strategy. Investigator controls timing of measurement(s) and variables (e.g. baseline disease severity) measured, but not all intervention variables are in the control of the investigator. If pooling data across institutions is required, consensus on outcome measures, minimum datasets and follow-up periods would be needed.	Simulation model developed and validated to assess the value of individual strategies or individual components of bundled strategies across a range of populations, settings and conditions. Use of agent based modeling for tracking CD transmission would allow for assessing the impact of different interventions.
Advantages of study design for producing a valid result	Best method to control for selection bias but potentially at the cost of generalizability. It should produce the most valid results. Requires planning to balance baseline characteristics and sample size considerations.	Simple design with generalizable results. May be best option if randomization is not possible. Highly susceptible to confounding variables, regression to the mean and maturation effects. Internal validity may be strengthened by use of a concurrent non-randomized comparison group that is not exposed to the preventive strategy, by multiple pre-intervention observations and by replication in different groups at multiple times. These studies must have adequate statistical methods to control for confounding and secular trend, otherwise no causal inference can be made.	May be the best option to use when questions cannot be addressed using conventional clinical trial methods or existing data analysis. May inform and help focus future clinical trials and data collection. Models can be tailored to multiple end users/perspectives, conditions and settings to enhance generalizability of findings and to help target interventions (different situations may call for different interventions). Other forms of modeling (e.g. compartment based, decision tree, etc.) can be informative but will require more assumptions and thus greater variability with less confidence in the results.
Resource use, size and duration	Depending on the strategy and desired effect size, costs, sample size and staff time needed for recruitment and implementation could be high. Recruitment of individuals or unit “clusters” willing to be randomized may be a constraint on sample size. Duration likely to be brief which may keep costs down, but if sustainability is a desired outcome, then longer follow-up will be required.	Generally less resource intensive than an experimental design. Otherwise, size and duration issues would be similar to RCT.	May require substantial personnel time but is generally less resource intensive than primary studies. Once agent based modeling identifies the transmission chains of CD, other modeling studies (e.g. decision tree) can be performed, but may require primary data collection to inform components if reliable estimates cannot be obtained from the literature, empiric studies or experts.

Table 7. Study design evaluations for Research Questions 1.1 and 1.2 (continued)

Study design considerations	Randomized controlled trial (RCT)	Quasi-experimental: before-after study (variations)	Modeling
Ethical, legal, and social issues	Ethical issues are moderate as the effectiveness may be uncertain. For cluster RCTs, a waiver of informed consent would be required. Otherwise a cluster RCT would not be possible if individuals have the ability to drop out. Legal mandates or clinical culture may impede randomization to novel interventions or supersede trial objectives.	Ethical issues are moderate as the effectiveness may be uncertain. A waiver of informed consent may be required if comparisons are at a unit level. Legal mandates or clinical culture may supersede trial objectives.	Ethical issues are moderate. To obtain data needed to do agent based modeling, ideally would need waiver of informed consent would be needed, as missed CD carriers could significantly bias the data.
Availability of data or ability to recruit	Cluster RCTs require collaborative network of sites willing to participate. Strategies implemented at the unit level require participation of all individuals within that unit, which could affect recruitment.	Recruitment is generally feasible, particularly where randomization is unacceptable. Strategies implemented at the unit level require participation of all individuals within that unit, which could affect recruitment.	Data would be obtained primarily from published sources, proprietary institutional databases, and expert opinion. The enrollment or consent process may be challenging particularly among sicker patients. As above, a waiver of informed consent would be needed, as missed CD carriers could significantly bias the data.

Research Question Number 2.1

What is the comparative effectiveness of different treatment options for recurrent CDI? The study design evaluations for this question was combined with research question number 4.1 as they would require the same design and face similar challenges. The considerations associated with the study designs addressing this question are discussed under research question number 4.1 below.

Research Question Number 2.2

What are the factors/determinants that make for better recurrence prevention for CDI?

Considerations: Based on Stakeholder Panel discussions, there was uncertainty on how best to address this question. Significant research exists on factors associated with recurrence, except for what can be associated with the first treatment. This question could possibly be combined with other questions of treatment effectiveness and look for less-studied hypothesized risk factors (e.g., procalcitonin in the stool or spore counts) as well as some known factors. Definitions of a number of patient characteristics and outcomes would need to be formulated *a priori*. Any study type must include a comparison of harms and should attempt to stratify by disease severity with adequate sample sizes to detect meaningful differences (Table 8).

Table 8. Study design evaluations for Research Question 2.2

Study design considerations	Randomized controlled trial (RCT)	Prospective cohort study	Nested case-control study	Case-control study
Description of design	Individuals with CDI randomly assigned to novel therapy versus standard therapy and followed prospectively for a defined period. Data gathered on risk factors of interest.	Individuals with CDI non-randomly assigned treatment by physician and followed prospectively for a defined period. Data gathered on effectiveness and risk factors of interest.	A sampling of patients who have been treated for CDI and developed recurrence (cases) or did not develop recurrence (controls) are included from a prospective cohort and followed prospectively for a defined period. Data on risk factors collected retrospectively. May be nested within prospective studies of treatment effectiveness.	Patients who have been treated for CDI and developed recurrence (cases) or did not develop recurrence (controls) are included. Data on treatment exposure and risk factors of interest collected retrospectively.
Advantages of study design for producing a valid result	This design is feasible and should provide the most valid results, as important characteristics should be balanced between the two groups.	May be optimal if random assignment is impractical. Less valid than RCT as baseline characteristics may not be balanced, but may be more generalizable.	Usually more valid than case-control study but balance of baseline characteristics is largely dependent on the original cohort.	Relatively quick to collect data, but has multiple threats to validity. Sample should accurately reflect population of interest and sampling method should be clearly described.
Resource use, size and duration	Likely to require substantial resources to collect epidemiological data of interest and to recruit adequate sample sizes, and multiple sites may be needed. Duration of follow-up of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence.	Resources and duration would be similar to RCTs.	Resources are low as it uses existing data and fewer subjects. Duration may be shorter than prospective studies.	Same as nested case control study.
Ethical, legal, and social issues	Ethical issues are high, as the effectiveness of one or more interventions is uncertain. Enrollment and consent of critically ill patients could be an issue.	Ethical issues are lower than with RCT because of non-randomized assignment.	Minimal since data are already collected.	Minimal since data are already collected.
Availability of data or ability to recruit	Recruitment could be an issue due to willingness to be randomized. Recruitment may be slow at any one site, and multiple centers may be needed.	This design is generally more acceptable to participants. Recruitment issues are similar to RCT.	Availability of data should be high, since study samples data already collected.	Same as nested case control study.

Research Question Number 2.3

To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?

Considerations: Studies should include sufficient correction for confounders such as severe underlying disease, advanced age, etc. The Stakeholder Panel emphasized the need for further retrospective analyses to look at the epidemiology of the population before hospital admission (e.g., examine the data with these larger numbers of patients to determine some of the factors for poor outcomes, for concomitant antibiotics, and to determine which patients will do poorly with their infection, the relationship between number of days on antibiotic therapy and relapse rates.) However, epidemiological studies were not addressed in the scope of the CER, yet such data would inform this question and others (Table 9).

Table 9. Study design evaluations for Research Question 2.3

Study design considerations	Prospective cohort	Retrospective cohort study	Modeling
Description of design	Patients classified according to whether they are on concomitant therapy either during or after CDI treatment and followed prospectively for a defined period. Data on desired outcomes are compared.	Patients who were treated for CDI are classified according to concomitant antibiotic status and followed to a pre-specified endpoint. Desired outcomes between intervention and comparison groups are compared.	Simulation model designed to assess impact of concomitant antibiotics for a range of subpopulations, settings and conditions. May be used to define factors (covariates) impacting response rate and other outcomes (e.g., role of concomitant antibiotics, role of carriers, reducing antibiotics by X amount, age, severity of underlying diseases)
Advantages of study design for producing a valid result	This design may be optimal and should provide the most valid results, as randomization would not be feasible. Baseline clinical characteristics (e.g. indication for treatment, disease severity) may not be balanced between the two groups. Consensus on definitions of a number of patient characteristics (e.g. disease severity) and outcomes would be needed to enhance generalizability to a non-breakout setting.	Uses existing data, but design is subject to selection bias and imbalance of baseline clinical characteristics. Generalizability may be impacted by the population studied.	May be the best option to use when questions cannot be addressed using conventional clinical trial methods. May inform and help focus future clinical trials. Models can be tailored to multiple end users, conditions and settings to enhance generalizability of findings.
Resource use, size and duration	Willingness to participate is high since patients would not be randomized. Likely to require substantial resources to recruit adequate sample sizes, as multiple sites may be needed. Duration of follow-up would likely be short (a few weeks).	Duration is generally shorter than a prospective analysis. Sample size may need to be large for subgroup analyses stratified by disease severity, age, et cetera.	May require substantial personnel time but is generally less resource intensive than primary studies. May require some primary data collection to inform components of the analysis if reliable estimates cannot be obtained from the literature or experts.
Ethical, legal, and social issues	Ethical issues are low, since patients/providers select treatment. May require a waiver for informed consent for population-level analyses, as drop outs would be an issue.	No major legal or ethical issues.	Ethical issues are low. Few administration approvals would be needed to access confidential information. If primary data collection is needed, human subjects protections will be needed for enrollment/consent.
Availability of data or ability to recruit	Recruitment may be slow at any one site, and multiple centers may be needed. Definitions of a number of patient characteristics and outcomes would need to be defined *a priori*.	No major issues other than obtaining approval for access to data, as the data have been collected. Heterogeneity of definitions of patient characteristics and outcomes could be a problem.	Data would be obtained primarily from published sources, proprietary institutional databases, and expert opinion, so patient recruitment issues would not exist. If primary data collection is needed to inform elements of the model, the enrollment or consent process may be challenging particularly among sicker patients.

Research Question Number 3.1
What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?

Considerations: Based on the CER, the focus of this question is on comparing the effectiveness of novel antibiotics to the most frequently used antibiotics (vancomycin and metronidazole) for treating an initial episode of CDI, using higher quality comparative effectiveness research approaches. Any study type must include a comparison of harms and attempt to stratify by baseline disease severity with adequate sample sizes to detect meaningful differences. No data were available to assess the importance of general patient characteristics or the strain of organism on the effectiveness of an antimicrobial and it is unclear at this time how clinically relevant it would be to collect these data (Table 10).

Table 10. Study design evaluations for Research Question 3.1

Study design considerations	Randomized controlled trial (RCT)	Nonrandomized comparative study	Retrospective cohort
Description of design	Individuals with CDI randomly assigned to novel therapy versus standard therapy and followed prospectively for a defined period. Data collected on harms, initial clinical cure, clinical recurrence, mean days to resolution of diarrhea and death.	Individuals diagnosed with CDI are assigned to novel therapy or standard care based on physician choice or purposive sampling and followed prospectively for a defined period. Data collected on harms, initial clinical cure, clinical recurrence, mean days to resolution of diarrhea and death.	Individuals with CDI who were treated with novel therapy or standard care are included and followed for a specified period of time. Data collected on recent antibiotic history, potential risk factors, harms, initial clinical cure, clinical recurrence, mean days to resolution of diarrhea and death.
Advantages of study design for producing a valid result	This design is feasible and should provide the most valid results, as clinical characteristics (e.g. indication for treatment, disease severity) should be balanced between the two groups. Consensus would be needed on definitions and reporting of outcomes, and a clinically relevant definition of disease severity to enhance generalizability to a non-breakout setting.	Design is susceptible to selection bias, but may be an optimal design if required sample size is large and the patient or their practitioner finds random assignment unacceptable. Statistical techniques may partially control for confounders.	Uses available data sources. Significant risk of selection bias and incomplete data. Generalizability will depend on population sample. May produce less valid results than an RCT, but may be a more feasible way of estimating effectiveness of new drugs for which some evidence of safety and efficacy exists.
Resource use, size and duration	Recruitment could be an issue due to willingness to be randomized. Likely to require substantial resources to recruit adequate sample sizes. Multiple sites may be needed to reach adequate sample sizes. Duration of follow-up of 2 weeks should be sufficient for initial response and 6-8 for sustained response without recurrence, as late recurrences after 8 weeks are rare.	Likely to require similar resources as RCT. Multiple sites may be needed to reach adequate sample sizes. Duration of follow-up would be short (a few weeks).	Less resource intensive and shorter than a prospective study. There may be costs associated with using data.
Ethical, legal, and social issues	Ethical issues are moderate, as the effectiveness of the intervention is uncertain, but the perception may be that patient safety is being compromised by withholding an intervention considered standard care while exposing a patient to an uncertain intervention. Enrollment and consent of critically ill patients could be an issue.	Ethical issues are lower because assignment is not random, but the effectiveness of the novel intervention is still uncertain. Enrollment and consent of critically ill patients could be an issue.	No major ethical or legal issues, unless multiple databases are linked then confidentiality and privacy issues may require patient approvals.
Availability of data or ability to recruit	Recruitment may be slow at any one site, and multiple centers may be needed. Definitions of a number of patient characteristics and outcomes would need to be formulated *a priori*.	Generally more acceptable to potential subjects than random assignment. Severity of patient condition and practitioner preferences may affect consent and enrollment.	May require multiple sites to obtain adequate sample sizes for subgroup analyses and agreement with proprietors of data sources. Obtaining clinical data outside the hospital may be difficult. Lack of uniformity in definition of severity and in reporting of outcomes and adverse events may impede data collection.

Research Question Number 4.1

What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI? The study design evaluations for this question was combined with research question number 2.1 as they would require the same design and face similar challenges.

Considerations: Based on the CER, these questions address the effectiveness of various treatment options, including antibiotics and nonstandard fecal transplantation as adjunctive or alternative therapy, compared with the most frequently used antibiotics (vancomycin and metronidazole) for treating recurrence of CDI, using higher quality comparative effectiveness research approaches. Both questions can be addressed using similar study designs. The CER did not identify any evidence for comparative effectiveness stratified by general patient characteristics such as age, gender, or treatment setting. No data were available to assess the importance of general patient characteristics or the strain of organism on the effectiveness of an antimicrobial and it is unclear at this time how clinically relevant it would be to collect these data. Consensus will be needed on frequency and duration of novel treatment, when to stop treatment, duration of follow-up, and definitions of initial cure, recurrence, disease severity and outcomes. Any study type must include a comparison of harms and should attempt to stratify by disease severity with adequate sample sizes to detect meaningful differences (Table 11).

Table 11. Study design evaluations for Research Questions 2.1 and 4.1

Study design considerations	Randomized controlled trial (RCT)	Prospective cohort	Retrospective cohort
Description of design	Individuals with CDI recurrence diagnosed with toxin test randomly assigned to novel therapy versus standard therapy and followed prospectively for a defined period. May include a crossover design if first assigned treatment fails. Data collected on outcomes.	Individuals with CDI recurrence are assigned to novel therapy or standard care by physician and followed prospectively for a defined period. Data collected on outcomes.	Individuals with CDI recurrence who were treated with novel therapy or standard care are included and followed for a specified period of time. Data collected on outcomes.
Advantages of study design for producing a valid result	This design is feasible and should provide the most valid results, as clinical characteristics should be balanced between the two groups. Crossover design may be more acceptable to physician and patient, reduce influence of covariate imbalance, and improve study efficiency, but treatment order may affect results.	Design is susceptible to selection bias, but may be an optimal design if required sample size is large and the patient or their practitioner finds random assignment unacceptable. Statistical techniques may partially control for confounders.	Uses available data sources. Significant risk of selection bias and incomplete data. Generalizability will depend on population sample. May produce less valid results than an RCT, but may be a more feasible way of estimating effectiveness of novel treatments for which some evidence of safety and efficacy may exist.
Resource use, size and duration	Recruitment could be an issue due to willingness to be randomized. Multiple sites may be needed to reach adequate sample sizes, but crossover design may help reduce numbers needed.	Likely to require similar resources as RCT. Multiple sites may be needed to reach adequate sample sizes. Duration of follow-up would be same as RCT.	Less resource intensive and shorter than a prospective study. There may be costs associated with using data.
Ethical, legal, and social issues	Ethical issues are moderate, as the effectiveness of the novel intervention is uncertain, yet standard care has also been ineffective. Patients' attitudes toward novel therapies may inhibit enrollment; alternatively they may be open to new, "natural" options.	Ethical and social issues are similar to RCT.	No major ethical or legal issues, unless multiple databases are linked then confidentiality and privacy issues may require patient approvals.
Availability of data or ability to recruit	Recruitment may be slow at any one site, and multiple centers may be needed. May require significant education of patients and physicians. Definitions of a number of patient characteristics and outcomes would need to be formulated *a priori*.	Similar to RCT, but may be more acceptable to potential subjects and practitioners than random assignment. Severity of patient condition and practitioner preferences may affect consent and enrollment.	May require multiple sites to obtain adequate sample sizes for subgroup analyses and agreement with proprietors of data sources. Obtaining clinical data outside the hospital setting may be difficult. Lack of uniformity in patient variables and in reporting of outcomes and adverse events may impede data collection.

Discussion

Using the 2011 Minnesota EPC evidence report on the *Comparative Effectiveness of Early Diagnosis, Prevention, and Treatment of Clostridium difficile Infection*[1], we developed an 11-step process for identifying and prioritizing clinically important evidence gaps and research questions, with key input from a diverse group of stakeholders. The final research questions, reflecting the breadth of the original Key Questions on prevention and treatment of CDI, address a variety of interventions and outcomes for the initial disease and of CDI recurrence. Through this process, we propose a final list of four evidence gaps and seven associated research questions.

It should be noted that the Stakeholder Panel highlighted evidence gaps that were outside the scope of the original review, such as the need for more research into the epidemiology of CDI and basic science to understand the microbiology. While these are important areas of interest, the state of the evidence on these aspects was not examined in the CER, and research may have been conducted in this area. There was agreement among the Panel members as to the importance of these issues that current limitations in the published literature, while not reviewed here, provide an opportunity for advancement in the field. Research into the epidemiology and the microbiology (e.g., understanding the gut microbiome) of CDI may be broadened. Gaps in the existing epidemiologic knowledge base should be identified with corresponding research projects targeted to fill those gaps.

There are several strengths to our process. First, it is important that Panel members came forth from a wide range of relevant disciplines to ensure a balanced and broad perspective on research needs that addressed the Key Questions from the CER on prevention and treatment of CDI. Each stakeholder was highly interested and committed. There were high levels of participation at each step. One Panel member was part of the Technical Expert Panel for the original CER. In addition, we had the lead investigator of the CER on our Panel; her insight into the report and the future research recommendations provided "first-hand" knowledge of the content of the CER. The consumer perspective was especially useful in drawing attention to ways in which patients experience care and the impact of illness on other aspects of their lives (e.g., work). The consumer representative particularly addressed prioritizing patient-centered outcomes of interest including the need for more awareness and knowledge on the available treatment options for CDI and further efforts towards better patient reporting and education strategies.

Second, given the breadth of potential topics, the introductory one-on-one calls with panelists helped establish the preliminary list of evidence gaps. This made the first conference call with the stakeholder panel more productive. Third, the literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials to which further research would add the greatest value. Given the large scope of the project, it was helpful to the project team to organize the literature search update and stakeholder information according to broader themes that evolved into specific categories (prevention, treatment). These themes allowed the team to cover more comprehensively aspects of prevention and disease management along the continuum of care, care settings, and populations. The project team also sought feedback from the stakeholders to identify key published studies and ongoing trials across the short-list of evidence gaps.

Finally, the Internet surveys were very successful in prioritizing issues across a broad range of categories. When provided with information on available research, rankings by the Stakeholder Panel appeared to be based on the amenability to CER. A number of stakeholders

were complimentary of our process. The Panel members agreed that the final list of evidence gaps and research questions covered key topics for future study in the area of prevention and treatment of CDI. All Panel members, for example, agreed that it is important to address gaps in the existing knowledge base of current infection control practices for CDI in health care institutions.

We encountered several challenges to our process. First, one of the major challenges was to maintain the focus on the key questions (and scope) addressed in the original CER. It was important on being very explicit about the original scope of the CER as well as the scope of this FRN effort. The evidence gaps were grouped by categories that could be linked back to the CER scope, as the team had the evidence reviews and the updated literature search to back the findings. Second, there were several ways to combine/categorize many of the proposed topics. There was crossover and overlap between the various evidence gaps, and the key underlying research questions were addressed within the top-ranked four gaps. The categorization was dependent on how the Stakeholder Panel wanted to approach different topic areas. For example, the proposed topics could be categorized as prevention of *Clostridium difficile* colonization or infection, treatment of the initial disease, and then treatment of recurrence. Furthermore, the questions in the latter category could be further divided into those addressing prevention/treatment of first recurrence, or of multiple recurrences. Other options discussed earlier in the process were to group the research questions into short or intermediate goals (e.g., understanding the gut microbiome is a long-term type of endeavor which has the potential to lead to new therapeutics, but in the interim, they are critical needs for immediate therapeutic options and prevention).

Finally, during discussions on research questions, outcomes of interest for certain questions were deemed to be difficult to address in future studies. For example, despite its importance, it would be difficult to study the comparative effectiveness of specific infection control measures to control and prevent CDI in non-outbreak settings (question #1) given the multiple (and varied) interventions adopted by institutions. It is essential in this context to ensure that the appropriate controls are set in place in order to assess the impact of these interventions. Much effort will be required to tease out the incremental impact of bundled components, which include predominantly multiple infection control measures and antibiotic stewardship. The utility of decision modeling (as an alternate study design) was discussed to address strategies for prevention of CDI as a way to determine the efficacy of current and future prevention programs.

Conclusions

This Future Research Needs project was built from the Minnesota EPC CER. We used a multidisciplinary stakeholder panel of nine participants using an 11-step process to identify and prioritize evidence gaps and key research questions across the selected gaps. The results of this process are the four prioritized evidence gaps and seven research questions in Table 12.

Table 12. Prioritized evidence gaps and research questions

Evidence Gap	Research Question
Effectiveness and harms of single and/or multi-component prevention strategies for CDI	1.1 What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings? 1.2 What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?
Effectiveness and harms of different strategies for recurrent CDI treatment and prevention	2.1 What is the comparative effectiveness of different treatment options for recurrent CDI? 2.2 What are the factors/determinants that make for better recurrence prevention for CDI? 2.3 To what extent do concomitant antibiotics administered during or after CDI therapy contribute to lower/delayed initial response rates and sustained response rates?
Effectiveness and harms of antibiotic treatments for first episode of CDI	3.1 What is the comparative effectiveness of new antibiotic interventions compared with standard therapy (metronidazole, vancomycin) for management of CDI?
Effectiveness and harms of fecal transplantation for management of CDI	4.1 What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CD	*Clostridium difficile*
CDI	*Clostridium difficile* infection
CER	Comparative effectiveness review
EHC	Effective Health Care
EPC	Evidence-based Practice Center
FRN	Future research needs
KI	Key informants
KQs	Key Questions
LU	Literature update
NAP1	North American pulsed-field gel electrophoresis type 1
PCR	Polymerase chain reaction
RCT	Randomized controlled trial

Appendix A. Summary of Evidence from Comparative Effectiveness Review

Appendix Table A1. Key Question 1 – Diagnostics

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Immunoassays for toxins A and 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.
Gene detection tests versus immunoassays for toxins A and 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.
Patient characteristics	Insufficient	Insufficient patient information was provided in reports of comparative data.

Appendix Table A2. Key Question 2 – Prevention

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Antibiotic use	Low	Sixteen studies, including six bundled prevention practice studies, found appropriate prescribing practices are associated with decreased CDI incidence. Harms were not reported.
Gloves	Low	One controlled trial found use of gloves in hospital settings reduced CDI incidence.
Disposable thermometer	Low	Three time series/before–after studies, two with controls, found use of disposable thermometers in hospital settings reduced CDI incidence.
Handwashing/ alcohol gel	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
Disinfection	Low	Thirteen before–after studies of outbreaks or endemic hospital settings found intensive disinfection with a chemical compound that kills *C. difficile* spores reduced CDI incidence.
Sustainability	Insufficient	No evidence was available.
Risk factors	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.
Multiple component strategies	Insufficient	Eleven time series/before–after studies examined bundles of prevention components in a single intervention. Data is insufficient to draw conclusions. Harms were not reported.

Appendix Table A3. Key Question 3 - Antibiotic Treatment

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Vancomycin versus metronidazole	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 definitions, especially with regard to stool count and 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.[109]
Severe disease, vancomycin versus metronidazole	Insufficient	One RCT examined a prespecified subgroup of 69 subjects with severe CDI; Improved clinical cure based on per-protocol analysis, but not with strict intention-to-treat analysis
Fidaxomycin versus vancomycin	Moderate	One large, high quality RCT demonstrated decreased recurrence among those receiving fidaxomicin.
All other comparisons of standard treatments	Moderate for vancomycin vs. 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.
Strain of organism	Low	One RCT (fidaxomicin versus vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain.
Patient characteristics	Insufficient	No comparative data were available.
Resistance of other pathogens	Insufficient	No data were available.

Appendix Table A4. Key Question 4 - Nonstandard Treatment

Key Questions	Level of Evidence	Summary/Conclusion/Comments
Treating CDI, active control	Low	Probiotics, prebiotics, *C. difficile* immune whey, and colestipol are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole or placebo.
Treating CDI, placebo	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.
Treating recurrent CDI	Low	There is limited evidence from two case series that fecal flora reconstitution is effective in treating recurrent CDI for up to 1 year.
Preventing CDI	Low	There is limited evidence that the nonstandard interventions in this review are not more effective than placebo for primary prevention of CDI.
Preventing recurrent CDI	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.

CDI = *Clostridium difficile* infection; RCT = randomized controlled trial

Appendix B. Search Strategy for Ongoing Studies

MEDLINE®/PubMed

1. (clostridium difficile infection) OR difficile [tiab] OR c-difficile[tiab] OR clostridium difficile [mesh]

2. clostridium[title] OR (c diff*) OR (c difficile) OR difficile

3. (randomized controlled trial*) OR (comparative study) OR (controlled clinical trial) OR RCT[title] OR randomized[tiab] OR placebo[tiab] OR trial[tiab]

4. (1 OR 2) AND 3

January 2012 to Present

Cochrane Library

1. (clostridium difficile infection) OR difficile [tiab] OR c-difficile[tiab] OR clostridium difficile [mesh]

2. clostridium[title] OR (c diff*) OR (c difficile) OR difficile

3. 3. (randomized controlled trial*) OR (comparative study) OR (controlled clinical trial) OR RCT[title] OR randomized [title] OR placebo[title, abstr] OR trial[title]

4. (1 OR 2) AND 3

Limit to: CCTR

January 2012 to Present

ClinicalTrials.Gov

1. (clostridium difficile infection) OR difficile OR c-difficile OR clostridium difficile OR clostridium OR c-diff*

4. 1 AND 2

Ongoing Trials

Appendix C. Survey Tool Used to Rate Research Gaps

Instructions to fill the survey

The objective is to rate the evidence gaps based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 18 evidence gaps
- Each panel member has been allotted a total of 5 votes.
- Choose and rank gaps in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

• Current importance
• Potential for significant health impact
• Incremental value
• Feasibility

You can review these criteria in detail [below].
Prioritization Criteria for Evidence Gaps
Current importance
• Incorporates both clinical benefits and harms
• Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
• Addresses high costs to consumers, patients, health-care systems, or payers
• Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact
• Potential for significant health impact:
o To improve health outcomes
o To reduce significant variation related to quality of care
o To reduce unnecessary burden on those with health-care problems
• Potential for significant economic impact, reducing unnecessary or excessive costs
• Potential for evidence-based change
• Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
• Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)
Incremental value
• Adds useful new information to existing portfolio of research on topic OR
• Validates existing research when body of evidence is scant

Feasibility

• Factors to be considered:

o Interest among researchers

o Duration

o Cost

o Methodological complexity (e.g., do existing methods need to be refined?)

o Implementation difficulty

o Facilitating factors

o Potential funders

(Modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

<u>*Please rank your top 5 evidence gaps from 1 to 5 with 1 having the highest priority and 5 the lowest.</u>

1. Mapping of CDI (from antibiotic exposures to disruption of microbiota to risk for C. difficile)
2. Effectiveness of probiotics for prevention and management of CDI
3. Factors/determinants that make for better recurrence prevention for CDI
4. Effectiveness of vaccines for the primary prevention of CDI
5. Epidemiology of CDI (e.g., sources of C. difficile in the community, exposure to antibiotics in different settings, typing of different strains)
6. Effectiveness of fecal transplantation for management of CDI
7. Modes of transmission of C. difficile in the health care setting (e.g., food, asymptomatic carriers, beddings/linens)
8. Effectiveness of different treatment options for high-risk patients and relapse/ recurrent patients
9. Effectiveness of monoclonal antibodies for the primary prevention of CDI
10. Duration of treatment with concomitant antibiotics
11. Role of increased knowledge of GI microflora and the microbiome towards impact of disease prevention and management strategies for CDI
12. Effectiveness of different patient education strategies to increase awareness of CDI
13. Effectiveness of new antibiotic interventions for prevention and management of CDI?
14. Effectiveness of antibiotic treatments for severe CDI
15. Role of non-antibiotic interventions (e.g., PPIs) and physiological factors (e.g., intestinal microbiota) towards increased incidence of CDI
16. Effectiveness of novel interventions for management of CDI (e.g., toxin binders, immunotherapies)
17. Effectiveness of single and/or multi-component prevention strategies (e.g., cleaning, isolation, antibiotic stewardship) on reducing CDI rates in non-outbreak settings
18. Role of different patient characteristics (e.g., immunodeficiency) that impact CDI?

If you have any further comments please give them below:

Appendix D. Survey Tool Used to Rate Research Questions

Instructions to fill the survey

The objective is to rate the research questions based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 11 research questions
- Each panel member has been allotted a total of 5 votes.
- Choose and rank questions in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

• Current importance
• Potential for significant health impact
• Incremental value
• Feasibility

You can review these criteria in detail [below].

Prioritization Criteria for Research Questions

Current importance

• Incorporates both clinical benefits and harms
• Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
• Addresses high costs to consumers, patients, health-care systems, or payers
• Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact

• Potential for significant health impact:
o To improve health outcomes
o To reduce significant variation related to quality of care
o To reduce unnecessary burden on those with health-care problems
• Potential for significant economic impact, reducing unnecessary or excessive costs
• Potential for evidence-based change
• Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
• Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value

• Adds useful new information to existing portfolio of research on topic OR

• Validates existing research when body of evidence is scant

Feasibility
• Factors to be considered:
o Interest among researchers
o Duration
o Cost
o Methodological complexity (e.g., do existing methods need to be refined?)
o Implementation difficulty
o Facilitating factors
o Potential funders

(Modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

<u>*Please rank your top 5 research questions from 1 to 5 with 1 having the highest priority and 5 the lowest.</u>

1. What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?
2. What are the factors/determinants that make for better recurrence prevention for CDI?
3. What is the safest and most effective strategy to perform fecal transplantation (i.e., enema, endoscopic delivery via upper or lower gastrointestinal tract, enteric coated capsules, delivery via nasogastric tube) to obtain the desired effects/benefits?
4. What is the optimal duration of treatment of CDI with concomitant antibiotic usage?
5. What is the comparative effectiveness of vancomycin vs. other antibiotic regimens for severe CDI?
6. What is the appropriate protocol for donor screening in fecal transplantation for safety?
7. What is the comparative effectiveness of new antibiotic interventions compared to standard therapy (metronidazole, vancomycin) for management of CDI?
8. What is the comparative effectiveness of different treatment options for recurrent CDI?
9. What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?
10. What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings?
11. What is the impact of regular antibiotics use on rates for C. difficile re-infection?

If you have any further comments please give them below:

Appendix E. Survey Results of Evidence Gaps with List of Preliminary Research Questions

Note: The evidence gaps considered outside the original scope of the CER are shaded.

Rank	Evidence Gap	Total Votes	Weighted Total	Preliminary research questions/issues
1	Effectiveness of single and/or multi-component prevention strategies (e.g., cleaning, isolation, antibiotic stewardship) on reducing CDI rates in non-outbreak settings	6	22	• What is the effectiveness of hand-washing (with or without alcohol-based gel or other prophylaxis) as a measure to control and prevent CDI? • What is the incremental impact of various prevention strategies (especially antibiotic stewardship) and the different transmission interruption measures? • From a payer perspective what are the most effective strategies that can decrease morbidity (and decrease costs)?
2	Role of increased knowledge of GI microflora and the microbiome towards impact of disease prevention and management strategies for CDI	6	21	• What is the metagenomic signature of the intestinal microbiotia that predisposes to *C. difficile?* • Role of colonization resistance in holding *C. difficile* in check and understanding through the metagenomics how this is working and the mechanisms through which this works
3	Mapping of CDI (from antibiotic exposures to disruption of microbiota to risk for C. difficile)	4	17	• *To be defined*
4	Epidemiology of CDI (e.g., sources of C. difficile in the community, exposure to antibiotics in different settings, typing of different strains)	5	14	• Longitudinal studies of the epidemiology of the population outside the hospital setting • How the exposure to antibiotics in one setting affects the risk in another setting • Typing of different strains
5	Effectiveness of different treatment options for high-risk patients and relapse/recurrent patients	4	12	• Which treatment choices impact a second episode (relapse or recurrence) with *C. difficile?*
6	Effectiveness of new antibiotic interventions for prevention and management of CDI?	3	11	• What is the impact of regular antibiotics use on rates for *C. difficile* re-infection?

Rank	Evidence Gap	Total Votes	Weighted Total	Preliminary research questions/issues
7	Effectiveness of fecal transplantation for management of CDI	4	8	• How invasive do fecal transplantation procedures need to be to obtain the desired effects/benefits? • What is the appropriate protocol for donor screening in fecal transplantation for CDI (e.g., preparation, procedure)*?* • Can the fecal transplantation procedure be standardized by consensus until we have more randomized, controlled trials?
8	Effectiveness of vaccines for the primary prevention of CDI	3	8	• *What is the effectiveness of* vaccines for the primary prevention of CDI in special populations (i.e., nursing homes)?
9	Effectiveness of antibiotic treatments for severe CDI	2	6	• *To be defined*
10	Role of different patient characteristics (e.g., immunodeficiency) that impact CDI?	1	5	• What factors are associated with poor outcomes (e.g., concomitant antibiotics) for CDI?
11	Effectiveness of novel interventions for management of CDI (e.g., toxin binders, immunotherapies)	1	3	• What is the efficacy of toxin binders as a secondary prophylaxis? • There is a need for more literature on the subject of immune response (e.g., protective epitopes) which could prevent colonization or disease • What is the role of adjuvant interventions in patients with severe, progressive, or advanced disease
12	Effectiveness of probiotics for prevention and management of CDI	1	2	• What is the effectiveness of probiotics vs. fecal transplant as treatments for recurrent CDI? • Which selective probiotics can be used to prevent re-infection? • Can combination probiotics be used to create a polymicrobial environment similar to fecal transplantation?
13	Modes of transmission of C. difficile in the health care setting (e.g., food, asymptomatic carriers, beddings/linens)	2	2	• What is the contribution of asymptomatic carriers to *C. difficile* transmission in long-term care patients (which asymptomatic patients are at most risk for transmission)? • Among asymptomatic carriers what environmental hygiene measures can reduce transmission rates? • Need to better understand the transmission dynamics of *C. diff.* which in turn will inform the effectiveness of prevention strategies and treatment strategies
14	Duration of treatment with concomitant antibiotics	1	2	• How long patients need to be treated if they require concomitant antibiotics
15	Factors/determinants that make for better	1	1	• *To be defined*

Rank	Evidence Gap	Total Votes	Weighted Total	Preliminary research questions/issues
	recurrence prevention for CDI			
16	Effectiveness of monoclonal antibodies for the primary prevention of CDI	1	1	• *To be defined*
17	Effectiveness of different patient education strategies to increase awareness of CDI	0	0	• How can reporting of CDI be improved with regard to accuracy and availability to the public? • Since more CDI are occurring in the community then before, how can patient education be improved to increase awareness of the disease?
18	Role of non-antibiotic interventions (e.g., PPIs) and physiological factors (e.g., intestinal microbiota) towards increased incidence of CDI	0	0	• *To be defined* (20% of people with *C. diff* are getting it without previous antibiotics)

Appendix F. Survey Results of Research Questions with List of Ongoing Studies

Rank	Research Questions	Total Votes	Weighted Score	Ongoing Trials (ClinicalTrials.Gov)
1	What is the comparative effectiveness of infection control measures to control and prevent CDI in non-outbreak settings?	7	27	1. Hospital Design and Risk of Nosocomial Infections: A Prospective Controlled Trial. NCT00563186. 2009; Recruiting (Hospital-Acquired Infection With Clostridium Difficile / Hospital-Acquired VRE Infection or Colonization / Hospital-Acquired MRSA Infection or Colonization). Epub March 6, 2009. http://ClinicalTrials.gov/show/NCT00563186 2. A Randomized Trial Comparing Matt and Antimicrobial Cellomed Laminates. NCT01245829. 2011; Not yet recruiting (Cross Infection / Infection Control). Epub November 22, 2010. http://ClinicalTrials.gov/show/NCT01245829
2	What is the comparative effectiveness of fecal transplantation as an adjunctive or alternative therapy versus antibiotics for management of recurrent CDI?	6	17	1. Oral Vancomycin Followed by Fecal Transplant Versus Tapering Oral Vancomycin. NCT01226992. 2013; Recruiting (Recurrent Clostridium Difficile Infection / Lab or Pathology Confirmed Clostridium Difficile). Last Updated: October 22, 2010. http://ClinicalTrials.gov/show/NCT01226992 2. A Randomized Trial of Fecal Transplantation Versus Oral Vancomycin for Recurrent Clostridium Difficile Infection. NCT01398969. 2013; Not yet recruiting (Clostridium Difficile Infection). Last Updated: July 20, 2011. http://ClinicalTrials.gov/show/NCT01398969
3	What is the comparative effectiveness of different treatment options for recurrent CDI?	5	17	1. Optimal Surgical Treatment Of Fulminant Clostridium Difficile Colitis. NCT01441271. 2013; Not yet recruiting (Clostridium Difficile Colitis). Last Updated: September 23, 2011. http://ClinicalTrials.gov/show/NCT01441271 2. Intracolonic Vancomycin Therapy in Severe C. Diff Colitis. NCT01346059. 2012; Recruiting (Colitis). Last Updated: April 29, 2011. http://ClinicalTrials.gov/show/NCT01346059 3. A Safety, Tolerability and Pharmacokinetic Study of Two Formulations of Metronidazole Versus Immediate Release Metronidazole in Patient With C. Difficile Colitis. NCT01559545. 2012; Not yet recruiting (Clostridium Difficile Associated Diarrhea). Last Updated: March 20, 2012.

Rank	Research Questions	Total Votes	Weighted Score	Ongoing Trials (ClinicalTrials.Gov)
				http://ClinicalTrials.gov/show/NCT01559545 4. ACT-179811 in Patients With Clostridium Difficile Infection. NCT01222702. 2012; Recruiting (Clostridium Difficile Infection). Last Updated: January 11, 2012. http://ClinicalTrials.gov/show/NCT01222702 5. A Study of MK-6072 and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-002). NCT01513239. 2014; Recruiting (Clostridium Difficile Infection). Last Updated: February 29, 2012. http://ClinicalTrials.gov/show/NCT01513239 6. A Study of MK-3415, MK-6072, and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-001 AM2). NCT01241552. 2014; Recruiting (Clostridium Difficile Infection). Last Updated: February 29, 2012. http://ClinicalTrials.gov/show/NCT01241552
3	What are the factors/ determinants that make for better recurrence prevention for CDI?	5	17	1. Fidaxomicin to Prevent Clostridium Difficile Colonization. NCT01552668. 2013; Not yet recruiting (Clostridium Difficile Infection). Last Updated: March 12, 2012. http://ClinicalTrials.gov/show/NCT01552668 2. Study of a Clostridium Difficile Toxoid Vaccine (ACAM-CDIFF™) in Subjects With Clostridium Difficile Infection. NCT00772343. 2011; Active, not recruiting (Diarrhea / Clostridium Difficile Infection). Last Updated: October 5, 2011. http://ClinicalTrials.gov/show/NCT00772343 3. A Study of MK-6072 and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-002). NCT01513239. 2014; Recruiting (Clostridium Difficile Infection). Last Updated: February 29, 2012. http://ClinicalTrials.gov/show/NCT01513239 4. A Study of MK-3415, MK-6072, and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-001 AM2). NCT01241552. 2014; Recruiting (Clostridium Difficile Infection). Last Updated: February 29, 2012. http://ClinicalTrials.gov/show/NCT01241552

Rank	Research Questions	Total Votes	Weighted Score	Ongoing Trials (ClinicalTrials.Gov)
				5. Safety and Efficacy Study of VP20621 for Prevention of Recurrent Clostridium Difficile Infection. NCT01259726. 2012; Recruiting (Clostridium Difficile Infection). Last Updated: October 5, 2011. http://ClinicalTrials.gov/show/NCT01259726 6. Role of Probiotics in Preventing Antibiotic Associated Diarrhoea Including c.Difficile. NCT01087892. 2011; Recruiting (Antibiotic Associated Diarrhoea Including c.Difficile). Last Updated: July 20, 2010. http://ClinicalTrials.gov/show/NCT01087892
5	What is the comparative effectiveness of new antibiotic interventions compared to standard therapy (metronidazole, vancomycin) for management of CDI?	5	15	1. A Safety, Tolerability and Pharmacokinetic Study of Two Formulations of Metronidazole Versus Immediate Release Metronidazole in Patient With C. Difficile Colitis. NCT01559545. 2012; Not yet recruiting (Clostridium Difficile Associated Diarrhea). Last Updated: March 20, 2012. http://ClinicalTrials.gov/show/NCT01559545 2. ACT-179811 in Patients With Clostridium Difficile Infection. NCT01222702. 2012; Recruiting (Clostridium Difficile Infection). Last Updated: January 11, 2012. http://ClinicalTrials.gov/show/NCT01222702 3. Safety and Efficacy of Multiple Daily Dosing of Oral LFF571 in Patients With Moderate Clostridium Difficile Infections. NCT01232595. 2011; Recruiting (Moderate Clostridium Difficile Infection). Last Updated: April 5, 2011. http://ClinicalTrials.gov/show/NCT01232595
6	What is the incremental impact of various strategies to reduce antibiotic usage, such as antibiotic stewardship programs, on clinical outcomes in non-outbreak settings?	5	13	None identified
7	What is the optimal duration of treatment of CDI with	3	9	None identified

Rank	Research Questions	Total Votes	Weighted Score	Ongoing Trials (ClinicalTrials.Gov)
	concomitant antibiotic usage?			
8	What is the comparative effectiveness of vancomycin vs. other antibiotic regimens for severe CDI?	3	8	None identified
9	What is the safest and most effective strategy to perform fecal transplantation (i.e., enema, endoscopic delivery via upper or lower gastrointestinal tract, enteric coated capsules, delivery via nasogastric tube) to obtain the desired effects/benefits?	3	6	None identified
10	What is the impact of regular antibiotics use on rates for *C. difficile* re-infection?	2	4	None identified
11	What is the appropriate protocol for donor screening in fecal transplantation for safety?	1	2	None identified