Evidence-based Practice Center Systematic Review Protocol

Project Title: *Effectiveness of Screening and Treatment of C. difficile Infections*

I. Background and Objectives for the Systematic Review

Clostridium difficile associated disease (CDAD) rates in the United States (and globally) have increased in the last decade, along with associated morbidity and mortality, particularly among elderly persons. The Medicaid Medical Directors Learning Network (MMDLN) requested the topic to assist the MMDLN in understanding best practices for hospitals to diagnose and prevent CDAD. It was also noted during the topic triage process that the topic has arisen in a number of Agency for Healthcare Research and Quality (AHRQ) venues recently, suggesting a broader concern and potential audience.

Clostridium difficile is a gram-positive, anaerobic bacterium that is generally acquired through ingestion. Various strains of the bacteria may produce disease generating enterotoxin A and cytotoxin B, as well as the lesser understood binary toxin. Use of the term CDAD indicates the major focus of this review is on the presence of clinical disease, not asymptomatic carriage of *C. difficile* organism. CDAD symptoms can range from mild diarrhea to severe cases including pseudomembranous colitis and toxic megacolon. Mortality from CDAD is estimated at 7 percent of cases.[1]

Distribution of CDAD in the population is bimodal, with the largest incidence in elderly individuals, and a considerably smaller peak in children under age 10. The vast majority of severe morbidity and mortality is experienced in the elderly population.[2-4] Residents of long term care facilities (LTC) are at high risk, with up to 26.2 cases per 10,000 resident days in LTC versus 6.5 cases per 10,000 patient days in hospitals.[5,6] Incidence rates may increase by four or five fold during outbreaks.[7] Community associated CDAD rates are generally much lower, accounting for 27 percent of cases in a recent prevalence study,[8] but is also on the rise.[7]

New, more virulent strains of *C. difficile* have emerged since 2000 which affect a wider population, often with a lack of standard risk profiles such as previous hospitalization or antibiotic use, including children, pregnant women, and other healthy adults.[9] Characteristics associated with hypervirulent strains include increased toxin production, an additional "binary" toxin, hypersporulation, and high-level resistance to fluoroquinolone antibiotics.[10] The time from symptom development to septic shock may be reduced in the hypervirulent strains, making quick diagnosis and proactive treatment regimens critical for positive outcomes. The hypervirulent strain accounts for 51 percent of *C. difficile* infections, compared to only 17 percent of historical isolates.[11,12]

Once a patient has acquired *C. difficile*, the likelihood of developing CDAD is dependent on a number of factors that allow colonization and toxin production, including failure of the immune defenses and use of antibiotics, particularly broad-spectrum or multiple antibiotics. In addition to eliminating, where possible, the offending antibiotic, and environmental and infection control strategies, recent prevention efforts at the patient level have also focused on improving immune defenses through healthy digestive function and gut flora, and nutritional status.[16] Other risk factors include increasing age, female gender, comorbidities, and use of gastric acid suppressant medications (although this last is still controversial). Risk profiles for recurrent

CDAD are similar.[17] One study which statistically modeled CDAD within the hospital setting suggested that reducing patient susceptibility to infection is more effective in reducing CDAD cases than lowering transmission rates.[18]

Effective prevention and treatment of CDAD is dependent on swift and accurate diagnosis. There are increasing numbers of diagnostic tests designed to detect either the presence of the organism, or toxins A and/or B, with a variety of sensitivities, specificities, predictive values, biotechnologies used, costs, and time-to-results. No single commercial test offers both sufficient sensitivity and specificity together with fast turn-around time.[19,20] Greater than 90 percent of labs in the U.S. use enzyme immunoassay because it is fast, inexpensive, and technically easy to perform.[19] Some diagnostic tests rely on two-step procedures, making use of inexpensive, fast screening tests for the presence of the organism followed by a second test for toxins if the first step test is positive. Physicians may not always be sufficiently educated as to which diagnostic test is best to use and how best to resolve a suspected false negative result (e.g., evidence suggests retesting with the same test is common practice, yet not recommended).

There are a number of treatment algorithms available in the literature.[7,21-23] Treatment for mild to moderate CDAD appears to have a fairly good clinical consensus for the use of metronidazole, in part because of the concern that overuse of vancomycin may contribute to increasing pathogen resistance. Consensus also exists for treatment of severe initial incident CDAD with vancomycin. Surgery may be life-saving in patients with fulminant, or acute severe, colitis. Pepin[24] suggests that both vancomycin and metronidazole are implicated in increased frequency of vancomycin-resistant enterococci. Surgery may be life-saving in patients with fulminant colitis.

Treatment for relapsed or recurrent *C. difficile* infections, however, is much more problematic. CDAD recurs in 15 to 35 percent of patients with one previous episode and 33 to 65 percent of patients who have had more than two episodes.[22] Currently, clinicians choose from a number of antibiotics and dosing protocols and adjunctive treatments such as the use of antimicrobials, probiotics, fecal transplant, toxin-binding agents, and immune-system enhancing agents.[25-27]

Preventing the spread of *C. difficile* within institutional settings is dependent on staff compliance with national guidelines and standards[13] and locally determined hygiene protocols. Unfortunately, protocols for targeted hospital acquired infections are not always congruent. For example, the availability of alcohol hand rubs improved physician compliance and reduced methicillin-resistant *Staphylococcus aureus* infections,[14] yet *C. difficile* produces spores that can withstand hostile environments and are resistant to alcohol hand rubs and other routine antiseptics. Spores may be best removed by handwashing. Other institutional prevention strategies may be required as *C. difficile* transmission knowledge develops. For example, a recent study isolated *C. difficile* spores from air samples in a United Kingdom hospital, 4 to 7 weeks after the last confirmed CDAD case in the ward, and successfully cultured bacterium.[15]

Community-acquired and community-onset *C. difficile* infection, where CDAD occurs outside the institutional setting, complicates measuring the effectiveness of prevention within an institutional setting. The pathogenesis of CDAD is complex and incompletely understood, and on-set may occur as late as several months after hospitalization or antibiotic use.

Increasing morbidity and mortality of *C. difficile* infection, the limited therapeutic options and difficulty treating recurrent cases, and the associated economic costs all argue for increased attention to hospital acquired infections. The U.S. Centers for Medicare and Medicaid Services is

considering adding CDAD to the inpatient prospective payment system, and reimbursing hospitals at a lower rate for CDAD if it is acquired during the hospital stay.

II. The Key Questions

Question 1: How do different methods for detection of toxigenic *C. difficile* to assist with diagnosis of CDAD compare in their sensitivity, specificity, and predictive values?
   a. Overall
   b. Do performance measures vary with sample characteristics?

Question 2: What are effective prevention strategies?
   a. What is the effectiveness of current prevention strategies?
   b. What are the harms associated with prevention strategies?
   c. How sustainable are prevention practices in health care (outpatient, hospital inpatient, extended care) and community settings?

Question 3: What is 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, co-morbidity, hospital vs. community acquired setting?
   c. How do prevention and treatment of CDAD affect resistance of other pathogens?

Question 4: What are the effectiveness and harms of non-antibiotic adjunctive interventions?
   a. Overall
   b. In patients with relapse/recurrent CDAD.

- **Population(s):**

Diagnosis: Adults with clinical signs consistent with CDAD.
Treatment: Adults with clinical signs consistent with CDAD.
Prevention: Adults at risk for *C. difficile* infection.

- **Interventions:**

Diagnostic tests: tests for toxin producing *C. difficile*, such as enzyme immunoassays, enzyme-linked immunosorbent assay, immunochromatography assay, polymerase chain reaction.

Standard antibiotics treatments: metronidazole, rifampicin, rifaxamin, vancomycin.

Non-antibiotic adjunctive treatments: fecal transplant, immunoglobulin, prebiotics, probiotics, steroids, toxin binding agents, other new treatments.

Prevention: antibiotic stewardship, contact barriers, dedicated medical equipment, education, environmental cleaning, handcleansing, patient isolation, prebiotics or probiotics used as preventive measure.

- **Comparators:**

Diagnostic tests: cell cytotoxicity assay with or without stool culture (excludes in-house laboratory tests), other diagnostic test interventions listed above.

Antibiotics: active treatments such as metronidazole or vancomycin.

Non-antibiotic adjunctive treatments: placebo, active controls such as vancomycin, metronidazole, usual care.

Prevention: placebo or active controls for probiotics used as preventive measure. Usual prevention practices for other prevention strategies.

- **Outcomes for each question:**

Diagnostic Test Outcomes

1. Sensitivity
2. Specificity
3. Predictive values
4. Time to results

Treatment Outcomes

1. Mortality
2. Recurrence
3. Clearance
4. Complications
5. CDAD-related colectomy rate
6. Symptom resolution

Prevention Outcomes

1. CDAD incidence rates
2. CDAD complication rates
3. CDAD mortality rates

Prevention Intermediate Process Measures/Outcomes

1. Appropriate antibiotic usage
2. Positive environmental cultures
3. Days to resolution of symptoms (faster resolution may mean shorter window for transmission)
4. Other prevention strategy-related process variables that demonstrate prevention strategy was taken up.

- **Timing:**

Diagnostic testing: time to test

Antibiotic and non-standard treatments: variable, generally ranging from 4 weeks to several months

Prevention: variable, generally from 6 months up to 2 years

- **Settings:**

Health care facilities: outpatient, inpatient, extended care

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III. Analytic Framework

Figure 1. Provisional framework for diagnostic testing and treatment

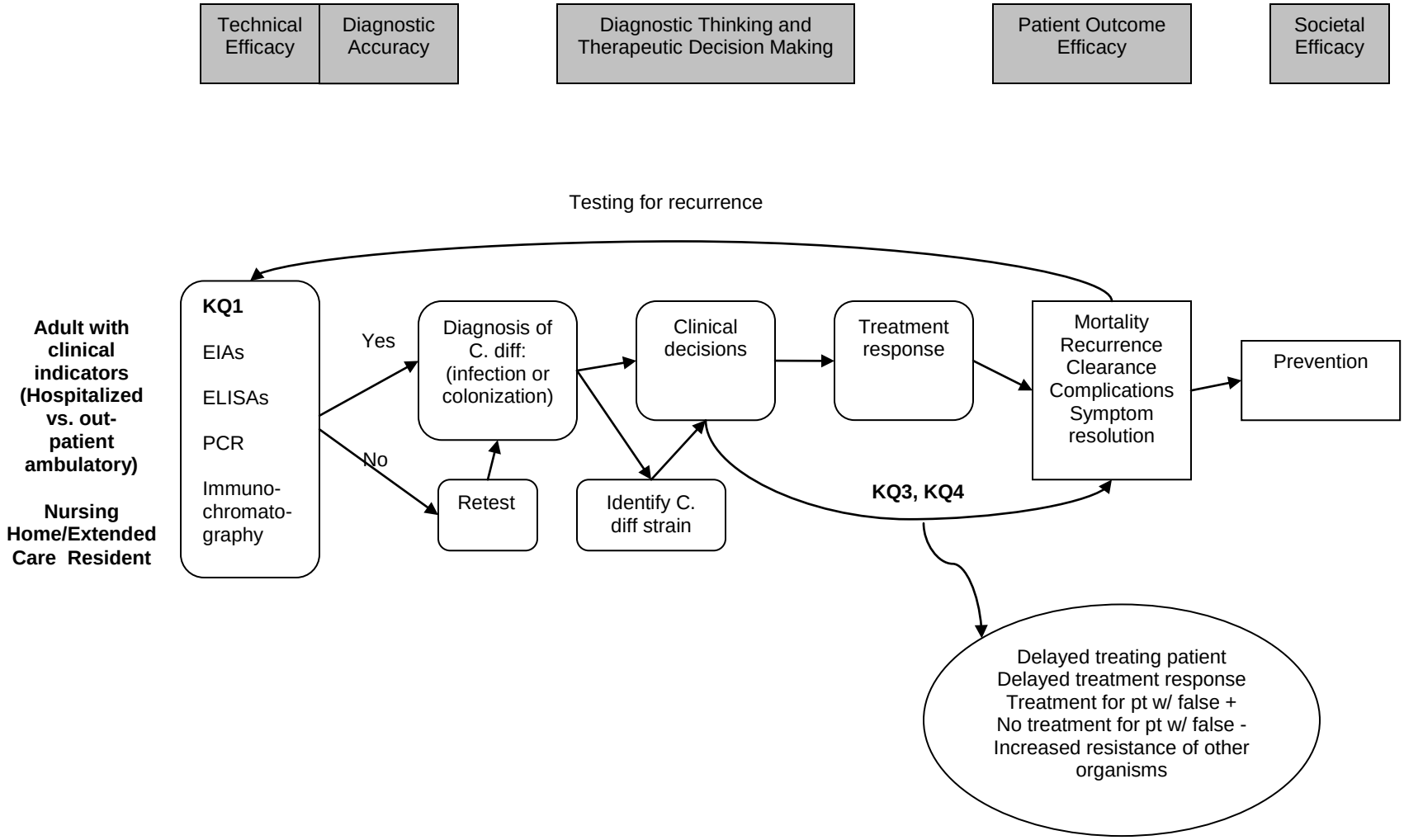

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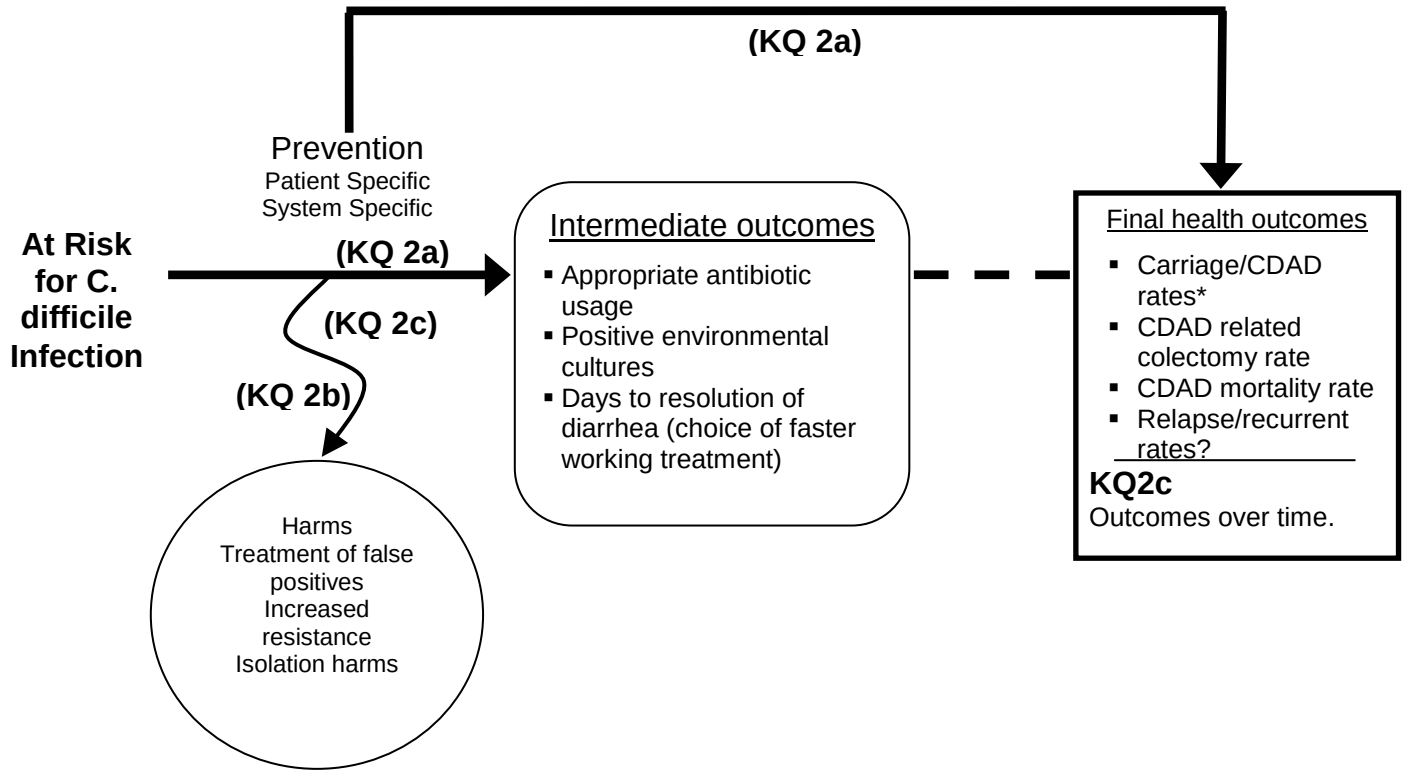
Figure 2. Provisional analytic framework for CDAD prevention.



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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Diagnostic studies: tests of diagnostic accuracy for enzyme immunoassays, enzyme-linked immunosorbent assay, toxin-related polymerase chain reaction tests, immunochromatography assay will be included. Tests for technical feasibility and cost characteristics will be excluded. Tests must be approved by the U.S. Food and Drug Administration and in current use. Studies which used in-house laboratory cell cytotoxicity tests will be excluded. Stool samples must be from patients with suspected *C. difficile* infection. The focus of the review is the clinical population, and the presence of toxinogenic organisms is of most relevance.

Treatment studies: Randomized controlled trials (RCTs) and high quality quasi-experimental observational studies of adult populations in United States health care settings. Studies for standard treatments which include non-U.S. approved treatments will be retained if the treatment is compared to US approved treatments, whether on or off label. Non-standard treatments from international settings will be included.

Prevention studies: RCTs and high quality quasi-experimental observational studies of adult populations in U.S. health care settings. Included prevention studies will focus on primary and secondary prevention strategies related to breaking routes of transmission. Prebiotic and probiotic treatments aimed at preventing CDAD from occurring/recurring will be included.

Systematic reviews will be included if the research question is deemed relevant using methods outlined in Chapter 12 of the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*

All studies will be subject to further exclusion criteria of non English publication or non human or pediatric test subjects. Only full articles or dissertations will be used. The search will be limited to studies published after 1970. We do not plan to review grey literature. We may contact the authors to clarify unreported quality components or ambiguous data.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will search several databases, such as MEDLINE, Cochrane Database of Systematic Reviews and randomized controlled clinical trials, ClinicalTrials.gov, and Scirus. A preliminary search of the literature in MEDLINE established a keyword search for ‘difficile’ was highly specific yet sensitive to *C. difficile* related articles. Excluding non human, pediatric, and non research publications, the set of possible related articles is only 2563 as of June 10, 2009. We will use tested search strings to establish subsets of articles databases for RCTs, observational studies, and diagnostic tests. However, the entire difficile set will be screened by one reviewer for potentially includable articles. We will update the literature search in May 2009.

We will review abstracts against pre-established inclusion/exclusion criteria to determine potential eligibility for inclusion in the evidence synthesis. An unknown number of these will not have a useable abstract available electronically. For these articles, we will retrieve abstracts from the original articles. The project manager, together with the expert clinical abstractors, will review all the abstracts to determine the eligibility of the articles for inclusion in the literature synthesis. To ensure consistency, all abstractors will attend a training session prior to beginning

the abstract review step in which the inclusion/exclusion criteria will be presented and discussed. In addition, the project team, including the expert clinical abstractors, will meet after reviewing the first 25 abstracts, review their current status, discuss and minimize disagreements, and develop a standardized reviewing approach. The project director and project manager will re-review all abstracts that were determined to be ineligible after the initial review as a quality step. In addition, we will randomly select a 10 percent sample of abstracts determined to be eligible for inclusion and subject them to re-review by the project director or project manager. Generally speaking, for all abstracts, we will err on the side on inclusion rather than exclusion.

Articles passing the initial screening will be retrieved, read, and abstracted onto evidence tables by an expert clinical abstractor. The project director or project manager will then re-read the articles and check the abstracted information against the original article. The project director or project manager will read and verify the exclusion of any articles that were subsequently found to excludable based on the full article. We will develop a coding scheme to account for reasons for exclusion for later documentation.

C. Data Abstraction and Data Management

We will develop data collection forms for each research question to evaluate quality of the study and abstract relevant information regarding study, patient, conditions, intervention characteristics, and outcomes. Evidence tables will be subjected to quality checks. Evidence tables will be created following PICOT elements.

As reviews are conducted, study search coordinators will track the status of each article. The search coordinators will have a master list of all the retrieved articles that indicates who was assigned the initial review and abstraction, its status in the review and abstraction process, the results of the review (e.g., whether it was selected for a full review or the reason why it was not, the date the initial review and abstraction was completed, and the date it was reviewed and checked by the project director or project manager).

The project manager will also monitor the progress of reviews. Weekly during the review phase of the study, the research coordinators will report the number of abstracts and articles out for review to the project and scientific directors, contact reviewers to determine progress and collect completed reviews, and assess evidence table entries for completeness. Periodically, the project staff will meet to discuss the results and progress to date; review cases that have been particularly difficult to classify, abstract, interpret, or adjudicate; and address any question the review team may have. In addition, all abstractors and other project team members will routinely use email to communicate any concerns or questions arising during the course of the reviews.

We will develop mock evidence tables for each key question and discuss draft tables with team and Technical Expert Panel (TEP) members. In addition, we will develop summary tables to accompany the results chapter of the report itself. These will be organized according to key questions.

D. Assessment of Methodological Quality of Individual Studies

We will rate the quality of studies according to recommendations from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Quality of interventional studies will use criteria from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* l including randomization, adequacy of randomization and allocation concealment, masking of the treatment status, intention to treat principles, and

justification of the sample size. For observational study quality, we will use the AHRQ tools to assess quality of observational studies. The draft of the AHRQ guidance for evaluation of diagnostic tests will also be used.

We will use the following ratings of quality of individual studies:

Well designed (good/low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups, appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low drop out rate; and clear reporting of dropouts.

Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amount of missing information; or discrepancies in reporting.

E. Data Synthesis

We will summarize articles and results in evidence and summary tables with qualitative analysis of the results by study applicability and internal validity. We may calculate odds ratio with 95 percent confidence interval or absolute risk differences from the reported number of events in randomized controlled clinical trials as well as the number needed to treat to achieve one event of the outcome. We also may calculate diagnostic predictive value of the diagnostic tests for *C. difficile* when false and true positive and negative cases were reported. All additional calculations will be documented and performed at 95 percent confidence intervals. We will investigate the possibility of pooled analysis where appropriate.

F. Grading the Evidence for Each Key Question

On the basis of the quality checklist(s) developed for the articles relevant to the various key questions, the abstractor will assign a single quality score to each article. Assessment of the strength of the evidence will be based on GRADE Working Group methods.

V. References

1. Loo VG, Poirier L, Miller MA, , et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005;353(23):2442-9.
2. Brandt LJ, Kosche KA, Greenwald DA, et al. Clostridium difficile-associated diarrhea in the elderly. *Am J Gastroenterol*. 1999;94(11):3263-6.
3. Hebuterne X. Gut changes attributed to ageing: effects on intestinal microflora. Curr Opin Clin Nutr Metab Care. 2003;6(1):49-54.
4. Kim J, Smathers SA, Prasad P, et al. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics*. 2008;122(6):1266-70.
5. Laffan AM, Bellantoni MF, Greenough WB, et al. Burden of Clostridium difficile-associated diarrhea in a long-term care facility. *J Am Geriatr Soc*. 2006 ;54(7):1068-73.
6. Gravel D, Miller M, Simor A, , et al. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. *Clin Infect Dis*. 2009;48(5):568-76.
7. McFarland LV. Renewed interest in a difficult disease: Clostridium difficile infections--epidemiology and current treatment strategies. *Curr Opin Gastroenterol*. 2009;25(1):24-35.
8. Jarvis WR, Scholsser J, Jarvis AA, Chinn RY. National point prevalence of Clostridium difficile in US health care facility inpatients, 2008. 2009;37(4): 263-70.
9. United States Centers for disease Control and Prevention. Severe Clostridium difficile Associated Disease in Populations Previously at Low Risk – Four States, 2005. *MMWR*. 2005; 54(47): 1201-1205.
10. Gerding DN, Muto CA, Owens RC, Jr. Measures to control and prevent Clostridium difficile infection. *Clin Infect Dis*. 2008;46 Suppl 1:S43-9.
11. Hubert B, Loo VG, Bourgault A-M, et al. A portrait of the geographic dissemination of the Clostridium difficile North American pulsed-field type 1 strain and the epidemiology of C. difficile-associated disease in Quebec. *Clin Infect Dis*. 2007;44(2):238-44.
12. Karpa KD. Probiotics for Clostridium difficile diarrhea: putting it into perspective. *Ann Pharmacother*. 2007; 41(7):1284-7.
13. Dubberke ER, Gerding DN, Classen D, et al. Strategies to prevent clostridium difficile infections in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008; 29 Suppl 1:S81-92.
14. Gordin FM, Schultz ME, Huber RA, et al. Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. *Infect Control Hosp Epidemiol*. 2005; 26(7):650-3
15. Roberts K, Smith CF, Snelling AM, et al. Aerial dissemination of Clostridium difficile spores. *BMC Infect Dis*. 2008; 8:7.
16. Owens RC, Jr., Donskey CJ, Gaynes RP, et al. Antimicrobial-associated risk factors for Clostridium difficile infection. *Clin Infect Dis.* 2008; 46 Suppl 1:S19-31.
17. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. *J Hosp Infect.* 2008; 70(4):298-304.

18. Starr JM, Campbell A, Renshaw E, et al. Spatio-temporal stochastic modelling of Clostridium difficile. *J Hosp Infect.* 2009; 71(1):49-56.
19. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis. 2008; 46 Suppl 1:S12-8.
20. Planche T, Aghaizu A, Holliman R, et al. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. *Lancet Infect Dis.* 2008; 8(12):777-84.
21. Fekety R. Guidelines for the diagnosis and management of Clostridium difficile-associated diarrhea and colitis. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 1997; 92(5):739-50.
22. Gerding DN, Muto CA, Owens RC, Jr. Treatment of Clostridium difficile infection. *Clin Infect Dis*. 2008; 46 Suppl 1:S32-42.
23. Jaber MR, Olafsson S, Fung WL, et al. Clinical review of the management of fulminant clostridium difficile infection. *Am J Gastroenterol.* 2008; 103(12):3195-203.
24. Pepin J. Vancomycin for the treatment of Clostridium difficile Infection: for whom is this expensive bullet really magic? *Clin Infect Dis.* 2008; 46(10):1493-8.
25. Jodlowski TZ, Oehler R, Kam LW, et al. Emerging therapies in the treatment of Clostridium difficile-associated disease. *Ann Pharmacother.* 2006; 40(12):2164-9.
26. Stepan C, Surawicz CM. Treatment strategies for C. difficile associated diarrhea. *Acta Gastroenterol Latinoam.* 2007; 37(3):183-91.
27. Halsey J. Current and future treatment modalities for Clostridium difficile-associated disease. *Am J Health-Syst Pharm.* 2008; 65(8):705-15.

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Bignardi GE. Risk factors for Clostridium difficile infection. *J Hosp Infect.* 1998;40(1):1-15.

Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev.* 2005(4):CD003543.

Dendukuri N, Costa V, McGregor M, et al. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. *CMAJ* 2005;173(2):167-70.

Eddins C, Gray M. Are probiotic or synbiotic preparations effective for the management of clostridium difficile-associated or radiation-induced diarrhea? *J Wound Ostomy Continence Nurs*. 2008;35(1):50-8.

Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. *J Hosp Infect.* 2008;70(4):298-304.

Koo HL, Koo DC, Musher DM, et al. Antimotility agents for the treatment of Clostridium difficile diarrhea and colitis. *Clin Infect Dis.* 2009;48(5):598-605.

Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. 2006;6:130.

Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol.* 2007;102(9):2047-56.

Nelson R. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults.[update of Cochrane Database Syst Rev. 2005;(1):CD004610; PMID: 15674956]. *Cochrane Database Syst Rev.* 2007(3):CD004610.

Pillai A, Nelson R. Probiotics for treatment of Clostridium difficile-associated colitis in adults. *Cochrane Database Syst Rev.* 2008(1):CD004611.

Segarra-Newnham M. Probiotics for Clostridium difficile-associated diarrhea: focus on Lactobacillus rhamnosus GG and Saccharomyces boulardii.[see comment]. *Ann Pharmacother.* 2007;41(7):1212-21.

Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. *J Antimicrob Chemother.* 2003;51(6):1339-50.

Zimmerman MJ, Bak A, Sutherland LR. Review article: treatment of Clostridium difficile infection. *Aliment Pharmacol Ther.* 1997 ;11(6):1003-12.

VI. Definition of Terms – N/A

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review (*Standard Language*)

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

XII. Conflict of Interest Mitigation

We will steer all technical guidance queries to minimize any potential for perceived undue influence by TEP members during the review process. In particular, TEP member Dr. Dale Gerding's participation will not include areas that involve preventive or secondary treatment with non-toxigenic *C. difficile* strains.

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