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Canadian Agency for Drugs and Technologies in Health

Vancomycin or Metronidazole for Treatment of *Clostridium difficile* Infection: Clinical and Economic Analyses

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January 2011

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This report is a review of existing literature, studies, materials, and other information and documentation (collectively the "source documentation"), which are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.

Authorship

Christine Perras was the project lead. She contributed to the development of the protocol and participated in the study selection, the quality assessment, and the data extraction and analysis of the clinical review. She was the principal author of the clinical review section, and of the

discussion, the conclusions, and the appendices related to the clinical sections. She also contributed to writing or revising other sections of the report. She responded to peer review comments and made changes to the drafts as required. She approved the final version of the report.

Eva Tsakonas contributed to the development of the protocol and participated in the study selection, the quality assessment, and the data extraction and analysis of the economic review. She was the principal author of the economic review section, the primary economic evaluation, and the budget impact analysis. She authored the discussion, the conclusions, and all appendices related to the economic sections. She also contributed to revising other sections of the report. She responded to peer review comments and made changes to the drafts as required. She approved the final version of the report.

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John Conly contributed to the development of the protocol. He provided clinical expert advice throughout the project. He also revised and provided comments on drafts. He approved the final version of the report.

Louis Valiquette contributed to the development of the protocol. He provided clinical expert advice throughout the project. He also revised and provided comments on drafts. He approved the final version of the report.

Kelly Farrah developed the literature search strategies, performed all searches, and managed the references of the report. She authored the literature search methods sections and its related appendix. She approved the final version of the report for these sections.

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Conflicts of Interest

John Conly has received speaker fees from Janssen-Ortho and Astellas Telavancin Advisory Board.

Louis Valiquette has received funding for investigator-originated research, honoraria for industry-related clinical trials, and speaker fees for lectures and for participation in advisory boards.

EXECUTIVE SUMMARY

The Issue

Clostridium difficile (*C. difficile*) infection is the most common cause of nosocomial infectious diarrhea in adults. The spread of a hypervirulent strain of *C. difficile* has caused recent outbreaks of *C. difficile* infection. Metronidazole and vancomycin are the antibiotics of choice to treat *C. difficile* infection. An assessment was prepared to help guide the choice of therapy for *C. difficile* infection and to inform reimbursement policies in the Canadian publicly funded health care system.

Objectives

The research objectives were to evaluate the relative clinical effectiveness, the relative cost-effectiveness, and the budget impact of using vancomycin or metronidazole in the management of initial episodes of moderate to severe *C. difficile* infection in children or in adults. Clinical practice guidelines recommendations were also reviewed.

Methods

A search for systematic reviews, health technology assessments, randomized controlled trials, and observational studies that compared vancomycin and metronidazole was conducted. An analysis of the clinical studies was completed. A narrative synthesis of economic evaluations was performed. A primary economic analysis and a budget impact analysis were also prepared.

After the literature was searched, it was determined that none of the retrieved studies met the population inclusion criteria. The authors of this report decided to proceed with a systematic review of studies that included patients with an initial or recurrent episode of moderate or severe *C. difficile* infection. Other than this amendment, the original research protocol for the clinical review was followed.

Findings

Clinical

The goal of the clinical review was to compare vancomycin with metronidazole based on the outcomes of cure, recurrences, complications, and serious adverse events in adults or children with moderate or severe *C. difficile* infection.

One randomized controlled trial showed no difference in cure rate when comparing the use of metronidazole and vancomycin by adult patients with initial or recurrent episodes of moderate *C. difficile* infection. In adult patients with initial or recurrent episodes of severe *C. difficile* infection, the use of vancomycin increased the cure rate by 27% (relative risk [RR] 1.27; 95% confidence interval [CI], 1.05 to 1.53) compared with metronidazole in a randomized controlled trial conducted before the outbreak of a hypervirulent strain, NAP1/BI/027 (NAP1). In one randomized controlled trial where a third of patients were infected with NAP1, the use of vancomycin increased the cure rate by 31% (RR 1.31; 95% CI, 1.03 to 1.66) compared with metronidazole in adult patients with initial or recurrent episodes of severe *C. difficile* infection. Other outcomes were reported, but the comparisons between vancomycin and metronidazole

yielded inconclusive findings, or the effect measures were not calculated because the number of events was too small for adequate comparisons.

Clinical Practice Guidelines

The two international clinical practice guidelines that were identified were rigorously developed and clearly presented. Both guidelines recommended the use of oral metronidazole for non-severe initial episodes of *C. difficile* infection. Both guidelines recommended the use of oral vancomycin for severe initial episodes of *C. difficile* infection.

Economic

A primary economic analysis based on the efficacy data from one randomized controlled trial compared the cost-effectiveness of first-line therapy with vancomycin versus metronidazole in patients with severe *C. difficile* infection. It was assumed that there was no difference between vancomycin and metronidazole in the incidence of serious complications. In the economic evaluation, it was estimated that each additional clinical cure that was attained through first-line vancomycin use would occur at an additional cost of $1,161 to the health care system.

Deterministic sensitivity analyses showed that the incremental cost per clinical cure increased during an outbreak of a hypervirulent strain of *C. difficile*. Increasing incremental costs were largely due to high doses of vancomycin being prescribed to an increasing proportion of patients who were initially treated with a lower dose of vancomycin and and whose treatment failed. Another sensitivity analysis suggested that the substitution of oral vancomycin capsules with a lower cost generic intravenous formulation that was administered orally and available only to hospitals could decrease incremental cost-effectiveness ratios. Cost-effectiveness ratios that were estimated based on the assumption that treatment success leads to an earlier discharge suggest that treatment with vancomycin is cost-equivalent to treatment with metronidazole given small reductions in the length of stay among patients taking vancomycin. If serious complications occurred at equal rates among treatment failures, initial treatment with vancomycin may result in net health expenditure reductions to the health care system due to savings in hospital costs. It was also found that these results were sensitive to model assumptions about efficacy rates of initial therapy with metronidazole.

Budget Impact

The budget impact analysis compared the incremental costs of first-line treatment using vancomycin with the costs of first-line treatment using metronidazole in hospitalized patients with severe *C. difficile* infection. The probabilities of treatment success, relapse, failure, complications, and subsequent drug therapy were the same as those used in the base case of the economic evaluation. The results showed annual incremental costs to hospital budgets of $734,826 at the national level, and annual incremental costs to community drug budgets of $398,454 after using vancomycin as first-line treatment.

In sensitivity analyses, the use of a lower-cost, generic intravenous vancomycin that was administered orally and only available to hospitals decreased incremental hospital costs to $72,646 at the national level. In an outbreak of a hypervirulent strain, the incremental costs to hospital budgets increased to $1.74 million, and those of community drug budgets increased to $3.2 million when accounting for a greater number of patients with uncomplicated treatment failures obtaining treatment in the community after hospital discharge. Differing complication

rates between treatment groups resulted in a total incremental cost of $681,258 in hospital budget for first-line treatment using vancomycin. The incremental cost to community drug budget was $712,667. If vancomycin is more effective than metronidazole in reducing the rate of complications in severe disease, its use would result in net savings to hospital budgets of $8.5 million at the national level because of savings in hospital stays.

Generalizability of Findings

Of the RCTs that were found, none included patients with an initial episode of *C. difficile* infection exclusively, and none included children or were conducted in the community. Hence, the findings of the clinical and economic systematic reviews and economic analysis apply to hospitalized adult patients with initial or recurrent episodes of moderate or severe *C. difficile* infection.

Conclusions

Five randomized controlled trials included hospitalized adult patients with initial or recurrent episodes of *C. difficile* infection. Based on the limited data that were obtained from subgroup analyses, the use of metronidazole and of vancomycin leads to a similar clinical cure rate among hospitalized adult patients with initial or recurrent *C. difficile* infection of moderate severity. A higher clinical cure rate is reported after the use of vancomycin by hospitalized adult patients with initial or recurrent severe *C. difficile* infection. Conclusions about the outcomes of recurrences, complications, and serious adverse events cannot be made.

The use of oral vancomycin by patients with severe disease will incur an incremental cost of $1,161 per clinical cure, but the use of vancomycin may reduce net health expenditure, if it has an impact on hospitalization costs through reduced length of stay due to earlier discharge or reductions in serious complications.

The annual incremental costs of using vancomycin as first-line treatment in hospitalized patients with severe *C. difficile* infection are, at the national level, $734,826 for hospitals and $398,454 for community drug budgets.

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ABBREVIATIONS

AGREE	Appraisal of Guidelines for Research and Evaluation
CDAD	*Clostridium difficile*-associated disease
CDI	*Clostridium difficile* infection
C. difficile	*Clostridium difficile*
CI	confidence interval
CNISP	Canadian Nosocomial Infection Surveillance Program
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IV	intravenous
NAP1/BI/027	North American pulsed-field Type 1, with a restriction enzyme analysis type BI and PCR (or polymerase chain reaction) ribotype 027; referred to as NAP1
NNT	numbers needed to treat
OR	odds ratio
PMC	pseudomembranous colitis
RCT	randomized controlled trial
RR	relative risk
RRI	relative risk increase
RRR	relative risk reduction
SHEA	Society for Healthcare Epidemiology of America

GLOSSARY

***Clostridium difficile* infection**: an intestinal infection that occurs when a susceptible host ingests *Clostridium difficile* spores which then colonize the large bowel, germinate, and cause toxin-mediated colitis and diarrhea.[1]

colonization: the presence of microorganisms without tissue invasion or injury.[2]

fungemia: the presence of fungi in the blood.[3]

infection: penetration and multiplication of an infectious agent in tissue, resulting in subclinical or clinical illness.[2]

intracolonic: within the colon.[4]

nasogastric tube: a tube that is inserted through the nose, down the throat, and into the stomach.[5]

nosocomial: pertaining to or originating in a hospital.[6]

probiotics: live microorganisms that have the potential to elicit health benefits when ingested in adequate amounts.[7]

recurrent *Clostridium difficile* infection: occurs because of a relapse or a reinfection.[8]

reinfection: acquisition of a new strain of *Clostridium difficile* from an exogenous source.[8]

relapse: endogenous persistence of the same strain of *Clostridium difficile*.[8]

1 BACKGROUND

1.1 Epidemiology

1.1.1 Pathogenesis and clinical manifestations

Clostridium difficile (*C. difficile*) is an anerobic, gram-positive, spore-forming bacillus.[9] The transmission of *C. difficile* occurs through spores or bacteria in stools or through spores in the environment.[10] Environmental spores are resistant to many disinfectants.[11] They can survive for months or years.[12] Healthy individuals who are colonized with *C. difficile* may be asymptomatic carriers, or they may develop symptoms.[9] Among healthy adults in the community, the colonization rates of *C. difficile* range from 2.4% to 13.0%.[13] Between 40% to 60% of neonates are asymptomatic carriers.[10]

C. difficile infection (CDI), which is also called *C. difficile*-associated disease (CDAD), occurs when toxins are produced by *C. difficile* as a result of disruption of the normal intestinal flora or as a result of ingestion.[10] *C. difficile* produces two toxins, A and B, that lead to intestinal mucosal damage and inflammation.[9] The symptoms range from mild diarrhea to abdominal pain, fever, or leukocytosis, which occur in severe disease.[14] Complications include pseudomembranous colitis (PMC), toxic megacolon, septic shock, bowel perforation, and death.[12]

1.1.2 Diagnosis

The diagnosis of CDI is usually based on the clinical history of episodes of unformed stool combined with the detection of toxin A, toxin B, or both, in a stool sample.[15,16] Most patients also have a history of antibiotic use within the previous eight weeks.[16] Laboratory tests are available for the detection of *C. difficile* or of toxins. The cell culture cytotoxicity assay is the reference standard for the detection of *C. difficile* toxins.[15,16] The turnaround time of cell culture assays is at least 48 hours. Laboratory facilities and technical expertise are needed to perform the cell culture assay. Enzyme immunoassays are more commonly used in Canada than cell culture assays because the technique is simple and the results are available within 24 hours.[17] However, enzyme immunoasssays are less sensitive than cell culture assays. Therefore, two-step testing using enzyme immunoassays for screening and cell culture assays for confirmation has been recommended.[15,16] With a turnaround time of less than four hours and a comparable sensitivity to that of cell culture assays, real−time polymerase chain reaction is a feasible option for the diagnosis of CDI.[18] In patients with a high clinical suspicion of CDI and a negative stool toxin result, endoscopy or abdominal computed tomography may be needed for rapid diagnosis and for rapid treatment.[11] Characteristic findings include thickening of the colonic wall, dilation, and pseudomembrane formation.[19,20] An abdominal computed tomography scan may be used as a diagnostic tool, but it is not adequately sensitive or specific to CDI.[16]

1.1.3 Risk factors

Antibiotic exposure is a risk factor for CDI. All antibiotics can disrupt the normal intestinal flora and cause CDI. The antibiotics with a higher risk include clindamycin, cephalosporins, and fluoroquinolones.[12,21] Advanced age, immunosuppression, surgical procedures, comorbidities,

and hospitalization or residence in a long-term care facility (which may expose patients to a spore-contaminated environment, infected roommates, and inadequate hand hygiene by health care workers) are other risk factors.[22] The use of proton pump inhibitors has been reported as a potential risk factor in some studies,[23-30] but not all.[31-39]

The risk of CDI in patients in the community is lower than that of hospitalized patients.[12] Patients in the community may not have received recent therapy with antibiotics, but they are likely to have had a recent hospitalization.[12,26] Other potential sources of infection in the community include soil, water, animals, meats, and vegetables.[12] There is no evidence that eating food that is contaminated with *C. difficile* will lead to a clinically important infection in humans.[40]

1.1.4 Disease burden

There is a disease burden that is associated with CDI in Canada. In a 1997 prospective surveillance six-week study, liquid or semi-formed stools of inpatients of 19 hospitals were tested for the presence of *C. difficile* cytotoxin.[41] In the presence of the cytotoxin, a practitioner reviewed the patient's chart to determine if the patient met the case definition for CDI. Of 2,062 patients tested, 371 (18%) had a positive result for the presence of the toxin, and 269 (13%) met the case definition. Of the 269 cases, three (1%) experienced a gastrointestinal hemorrhage and needed transfusion, one (0.4%) had bowel perforation, one (0.4%) experienced secondary sepsis, and four (1.5%) died as a result of causes directly or indirectly related to CDI.[41]

From December 2002 to December 2005, outbreaks of CDI cases were reported in Quebec.[42,43] These outbreaks were characterized by a four-fold increase in the incidence of CDI (156.3 per 100,000 in 2003 compared to 35.6 per 100,000 in 1991), a three-fold increase in the proportion of complicated cases (18.2% in 2003 compared to 7.1% in 1991), and a three-fold increase in mortality within 30 days of diagnosis (13.8% in 2003 compared to 4.7% in 1991).[42] Four Quebec hospitals had up to a 20-fold increase in the number of CDI-related emergency colectomies during the epidemic.[44] Between 2003 and 2004, a cumulative attributable mortality of 16.7% was documented in elderly patients at a Quebec hospital. The increase in mortality was attributed to a hypervirulent strain of *C. difficile*.[43] Each case of nosocomial CDI led to 10.7 additional days in hospital.[43]

Outbreaks that were caused by the same strain were subsequently reported in other Canadian provinces.[45] National data are available after prospective surveillance at participating hospitals across Canada (except Prince Edward Island and the territories) as part of the Canadian Nosocomial Infection Surveillance Program (CNISP). From November 1, 2004 to April 30, 2005, 1,842 cases of CDI were reported in 34 hospitals.[46,47] Of the reported cases, 1,745 (94.7%) occurred in adults, and 1,430 (81.9%) of the cases in adults were nosocomial. The overall incidence rate of nosocomial CDI among adults was 4.6 cases per 1,000 patient admissions and 65 per 100,000 patient-days. Quebec reported the most cases of nosocomial CDI and had the highest CDI-related mortality rate. Of the 1,430 adult nosocomial cases of CDI, 12 (0.8%) patients needed colectomies, 31 (2.2%) patients were admitted to the intensive care unit (ICU) for CDI complications, and 82 (5.7%) deaths were directly or indirectly related to CDI. Of the 1,008 patients with infecting strain documentation, 311 (30.8%) were infected with the hypervirulent strain.[46,48] Thirty-nine (12.5%) of these patients experienced a severe outcome

(defined as ICU admission, colectomy, or death).[48] The increased rates of CDI-related complications and mortality that were observed in adults during the epidemic did not appear to occur in the pediatric population.[49,50]

According to CNISP data from 2009, the overall incidence rate of CDI in hospitalized patients one year of age and older was 4.7 cases per 1,000 admissions and 5.8 per 10,000 patient-days. The overall CDI fatality rate was 1.9 per 100 CDI patients (Denise Gravel, Public Health Agency of Canada, Ottawa, ON: personal communication, 2010 November 30).

The hypervirulent *C. difficile* strain that was the most likely cause of the outbreaks across Canada has been identified as North American pulsed-field Type 1, with a restriction enzyme analysis type BI and polymerase chain reaction or PCR ribotype 027 (NAP1/BI/027).[21,40,51,52] This strain produces higher levels of toxin A and toxin B than other strains, and an additional binary toxin with an unclear role.[9,21,40] Its presence has been documented in every Canadian province (no data available for the territories), 40 states in the United States, and many European countries.[40] This strain has been isolated from patients in the community and in hospital. The risk factors for CDI caused by the NAP1/BI/027 (NAP1) strain include advanced patient age, hospitalization, and exposure to antibiotics, particularly fluoroquinolones.[40] A prospective study that was conducted after the outbreaks had subsided noted the predominance of the NAP1 strain in 88 Quebec hospitals.[53]

In a retrospective observational study, the impact of hospital-acquired CDI on in-hospital mortality was evaluated.[54] The study considered inpatient admissions at a tertiary care hospital from July 1, 2002 to March 31, 2009. For all included admissions, data were obtained from a data warehouse (age, gender, dates of admission and discharge, admitting department, ICD-10 code [international classification of disease], and all laboratory tests results) and health care utilization was measured. The main outcome was time to in-hospital death. A total of 136,877 admissions were included (89,086 patients). Hospital-acquired CDI was identified in 1,393 admissions (overall risk 1.02%; 95% CI, 0.97 to 1.06). The median time from CDI diagnosis to death was 14 days (interquartile range 5.5, 31.0). An absolute risk of death of 10% in patients with hospital-acquired CDI was found.[54]

1.1.5 Economic burden

The emergence of the NAP1 strain has increased health care costs due to extended length of hospital stay for the management of complications and re-hospitalization for recurrent episodes.[55] Information on the economic costs of CDI in Canada is limited and precedes the epidemic. Using 1997 surveillance data (before the emergence of the NAP1 strain), one study estimated the minimum cost of CDI readmissions to be approximately C$128,200 per hospital, per year, plus the cost for the management of complications.[41] Another study estimated that the total costs of one year of treatment for CDI (including charges for culture and toxin assay) for 100 patients in one institution ranged from C$3,475 (using oral metronidazole 1.5 g per day for 10 days) to C$48,925 (using oral vancomycin 1 g per day for 10 days).[56]

1.2 Overview of Technologies

If a patient develops CDI during antibiotic therapy — particularly if the antibiotic has been shown to increase the risk of CDI (for example, clindamycin, cephalosporin, or fluoroquinolone) — the antibiotic is discontinued, if possible.[57] Mild cases of CDI may resolve after discontinuation of the antibiotic, but most patients will need treatment.[19] In moderate to severe cases, treatment with an antibiotic that is active against *C. difficile* is administered to resolve the symptoms (including diarrhea), reduce the risk of complications (including gastrointestinal bleeding, sepsis, toxic megacolon, bowel perforation, need for emergency colectomy), and reduce mortality.[58] The treatment of CDI is based on the severity of the disease, but there is no standard validated scoring system that is used to classify disease severity or to predict outcomes.[40]

The two antibiotics that are most commonly used for treating patients with moderate to severe CDI are metronidazole and vancomycin.[59] Both antibiotics are available in Canada (Appendix 1, Tables 1 and 2). The injectable preparation of vancomycin may be taken orally at a lower cost than oral vancomycin capsules.

Recurrent diarrhea has been reported in approximately 5% to 20% of patients after treatment with vancomycin or metronidazole for an initial episode of CDI.[60] Up to 45% of those who have had one recurrent CDI episode will experience more recurrences.[57] There does not appear to be a progression in disease severity with subsequent episodes of CDI.[60] Independent risk factors for recurrent *C. difficile* diarrhea include age greater than 65 years, concomitant administration of antacid medications, and continuation of non-*C. difficile* antibiotic therapy after CDI diagnosis.[61] Almost half of recurrences are caused by reinfection with a different strain.[62,63] Relapse with the same strain that is responsible for the first episode is most likely caused by the intraluminal persistence of *C. difficile* spores rather than antibiotic resistance.[64,65]

In addition to metronidazole and vancomycin, other antibiotics have been investigated for the management of CDI, including rifampin, bacitracin (which needs preparation for oral administration), nitazoxanide, teicoplanin, rifaximin, and fusidic acid.[66] These agents, except rifampin and bacitracin, are unavailable in Canada for systemic therapy.

Additional options for the management of CDI include probiotics (such as lactobacillus species or *Saccharomyces boulardii* [*S. boulardii*]). Two systematic reviews concluded that there is insufficient evidence to support the routine clinical use of probiotics as an adjunct to antibiotic therapy for CDI.[67,68] A more recent randomized controlled trial (RCT) of 255 patients showed a statistically significant decrease in the number of patients testing positive for CDI with the use of probiotics (lactobacillus species) administered concurrently with antibiotherapy.[69] One meta-analysis (two RCTs) on the use of *S. boulardii* administered with vancomycin or metronidazole found a reduction in the recurrence rate of CDI.[70] There are case reports of fungemia developing in patients who have received *S. boulardii* when a probiotic was used to prevent recurrent CDI.[71] No cases of bacteremia or fungemia were reported in the meta-analysis.[70]

Case reports and case series have shown some success with the administration of donor stool by nasogastric tube or colonoscopy in patients with severe and recurrent CDI.[72] Other

investigational treatment options include the use of anion-binding resins such as tolevamer, intravenous (IV) immunoglobulin, *C. difficile* toxoid vaccines, monoclonal antibodies, fidaxomicin (OPT-80), ramoplanin, tigecycline, and whey protein concentrate.[9,21,73]

Expanded infection control has been advocated to prevent and control outbreaks. Environmental cleaning with bleach or vaporized hydrogen peroxide (regular disinfectant does not kill spores), improved hand hygiene (using soap and water instead of alcohol hand gel, or using gloves), the use of individually assigned thermometers, the isolation of infected patients, and targeted antimicrobial restrictions are some recommended measures.[12,74,75]

2 ISSUE

In the past, because of its higher cost and concerns about the emergence of vancomycin- resistant enterococci, the use of vancomycin as a treatment for CDI was reserved for cases of intolerance to or treatment failure with metronidazole,[59,76]or for severe illness.[77] During the outbreak of the hypervirulent strain of *C. difficile*, increased rates of treatment failure were documented in patients receiving metronidazole.[78-80] Pharmacokinetic differences between the two drugs may play a role in treatment failure.[81] In patients receiving oral metronidazole, concentrations of metronidazole are higher in watery stools at the start of treatment, but decrease as diarrhea improves and colonic inflammation subsides.[81] In contrast, stool concentrations of orally administered vancomycin remain high throughout therapy.[14] Studies also suggest that the rates of colonization and persistent overgrowth of vancomycin- resistant enterococci may be equivalent in patients who are treated with oral vancomycin or with oral metronidazole.[82-84] Clinical practice is shifting toward using oral vancomycin, and several best practice documents recommend using oral vancomycin as initial therapy for severe CDI.[85-87]

The concern about drug expenditures on vancomycin compared with metronidazole to manage patients with CDI is increasing. The reimbursement status for vancomycin varies among jurisdictional drug plans in Canada (Table 1). Therefore, an assessment is needed to help guide the choice of therapy for CDI and inform reimbursement policies for vancomycin in the Canadian publicly funded health care system.

Table 1: Formulary Status of Vancomycin and Metronidazole for CDI[88-101]		
Drug	**Jurisdiction**	**Formulary status‡**
Intravenous vancomycin 500 mg or 1g vials*	AB, BC, MB, NB, NS, QC, YK†	Benefit
	SK, YK§	Restricted
	NL, ON, PE	Not covered
Oral vancomycin 125 mg or 250 mg capsules	NB, NL, QC, YK†	Benefit
	MB	Limited
	AB, BC, NS, PE, SK, YK§	Restricted
	ON	Not covered
Oral metronidazole 250 mg tablets	AB, BC, MB, NB, NL, NS, ON, PE, SK, QC, NT, NU, YK†	Benefit
Oral metronidazole 500 mg capsules	BC, NL, ON, QC, NT, NU, YK,SK	Benefit
Intravenous metronidazole 5 mg/mL vial	AB, BC, NB, QC	Benefit

AB = Alberta; BC = British Columbia; CDI = *Clostridium difficile* infection; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; YK = Yukon.
*Intravenous vancomycin 5 g vials also covered in BC, QC; intravenous vancomycin 10 g vials also covered in QC; only intravenous 500 mg vials covered in YK.
†Covered in Pharmacare Program.
‡*Benefit*: indicates that no patient-specific criteria need to be met to receive reimbursement for a drug. *Limited*: indicates that specific criteria set by a plan or program must be met during regular (automated) adjudication processes to receive reimbursement. *Restricted:* indicates that a formal request for coverage must be completed by the prescriber for patient-specific review against the set criteria of a plan or program.
§Restricted in Chronic Disease Program.

3 OBJECTIVES

The research objectives for this technology report are to evaluate the relative clinical effectiveness, the relative cost-effectiveness, and the budget impact of using vancomycin or metronidazole in the management of initial episodes of moderate to severe CDI in children or adults. We also review clinical practice guidelines.

Specific research questions are:

1. What is the clinical effectiveness of vancomycin compared to metronidazole in the treatment of children or adults with an initial episode of moderate to severe CDI?
2. What recommendations on the use of metronidazole and vancomycin are included in current Canadian and international guidelines on the treatment of children or adults with an initial episode of moderate to severe CDI?
3. What is the level and strength of evidence supporting the recommendations on the use of metronidazole and vancomycin in current Canadian and international guidelines?
4. What is the cost-effectiveness of vancomycin compared to metronidazole in the treatment of children or adults with an initial episode of moderate to severe CDI?
5. What is the expected budget impact on Canadian provinces and territories with the provision of metronidazole and vancomycin therapy for children or adults with an initial episode of moderate to severe CDI?

4 CLINICAL REVIEW

4.1 Methods

4.1.1 Literature search

The clinical literature search was performed by an information specialist using a peer-reviewed search strategy.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Biosis Previews, The Cochrane Library, and the Centre for Reviews and Dissemination databases. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were vancomycin, metronidazole, and *C. difficile*. The clinical search was not restricted by publication date, but was restricted to English and French language publications. Methodological filters were applied to limit retrieval to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. See Appendix 2 for the detailed search strategies.

The search was run on October 28, 2009. Regular alerts were established to update the search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, clinical trials registries, and other specialized databases. Appendix 2 shows a list of the main grey literature resources. Google and other Internet search engines were used to search for additional information. These searches were supplemented by handsearching the bibliographies and abstracts of key papers and conference proceedings, and through contacts with appropriate experts and agencies.

Three manufacturers (Sanofi-Aventis Canada Inc., Ferring Pharmaceuticals Canada, and Iroko International LP) were contacted to request unpublished clinical studies.

4.1.2 Selection criteria

To be included, the clinical studies had to meet the criteria shown in Table 2.

Table 2: Selection Criteria for Clinical Review	
Study Design	• systematic reviews • health technology assessments • RCTs • controlled clinical trials • prospective and retrospective controlled observational studies (> 50 participants)
Population	• adults and children • hospitalized or in the community • first episode of moderate to severe CDI
Interventions	• vancomycin • metronidazole
Primary Outcomes	• resolution of symptoms (clinical cure and recurrence rates)
Secondary Outcomes	• complications (PMC, toxic megacolon, septic shock, bowel perforation) • need for emergent colectomy • adverse events • all-cause mortality
Publication Characteristics	• English and French

CDI = *Clostridium difficile* infection; PMC = pseudomembranous colitis; RCTs = randomized controlled trials.

The original research protocol was followed. After the literature was searched, it was determined that none of the retrieved studies met the population inclusion criteria (none of the studies included only patients with an initial episode of moderate or severe CDI). Some studies included patients with moderate or severe CDI in a mixed population of patients, with an initial or recurrent episode of CDI. One study included only patients with an initial episode of CDI, and mild, moderate, or severe disease. It was decided to proceed with a systematic review in which this information could be used. As a result, the original research questions could not be answered. By broadening the scope, the results would apply to a population that included patients with an initial or a recurrent episode of moderate or severe CDI, instead of only patients with an initial episode.

4.1.3 Selection method

Two reviewers (CP, SN) independently screened the titles and abstracts of all citations that were retrieved in the literature search. Based on the selection criteria that were specified before the research was done, the full text of any articles that met the criteria was ordered. The reviewers then independently reviewed the full text of selected articles, applying the selection criteria, and comparing the included and excluded studies. Disagreements were resolved through discussion until consensus was reached. When consensus could not be reached, a colleague (BH) evaluated the study to determine inclusion. When the full study was retrieved and was deemed not to meet the inclusion criteria, the reason for the exclusion was recorded. Duplicate publications of the same trial were excluded.

4.1.4 Data extraction strategy

A data extraction form was designed before the research was done to document the characteristics and outcomes of the selected studies (Appendix 3). Data were extracted by two independent reviewers (CP, SN), and any disagreement was resolved through discussion until consensus was reached. Where data were insufficient, missing from the research report, or if the study was only available as an abstract or conference proceeding, the corresponding author of the study was contacted to determine if these data could be obtained.

4.1.5 Strategy for validity assessment

A quality assessment of full-text publications of the included studies measuring the clinical effectiveness of vancomycin or metronidazole was independently conducted by two reviewers (CP, SN). The two reviewers resolved any disagreement through discussion until consensus was reached. The methodological quality of the systematic reviews was assessed using the Oxman and Guyatt scale.[102] The methodological quality of RCTs and observational studies was assessed using the Downs and Black checklist.[103] Guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument[104] (Appendix 4).

4.1.6 Data analysis methods

For RCTs, the relative risks (RR) with corresponding 95% CI were calculated using the Confidence Interval Analysis or CIA software.[105] Because of the clinical heterogeneity among studies, a meta-analysis was not performed.

For observational studies, the RRs for prospective studies or the odds ratios (OR) for retrospective studies, with corresponding 95% CI, were calculated using the Confidence Interval Analysis software.[105] These results were used in a narrative review.

The findings were interpreted in light of the heterogeneity of the studies (differences in design, study populations, interventions or exposures, and outcome measures) and the quality assessment (confounding, bias, and external validity).

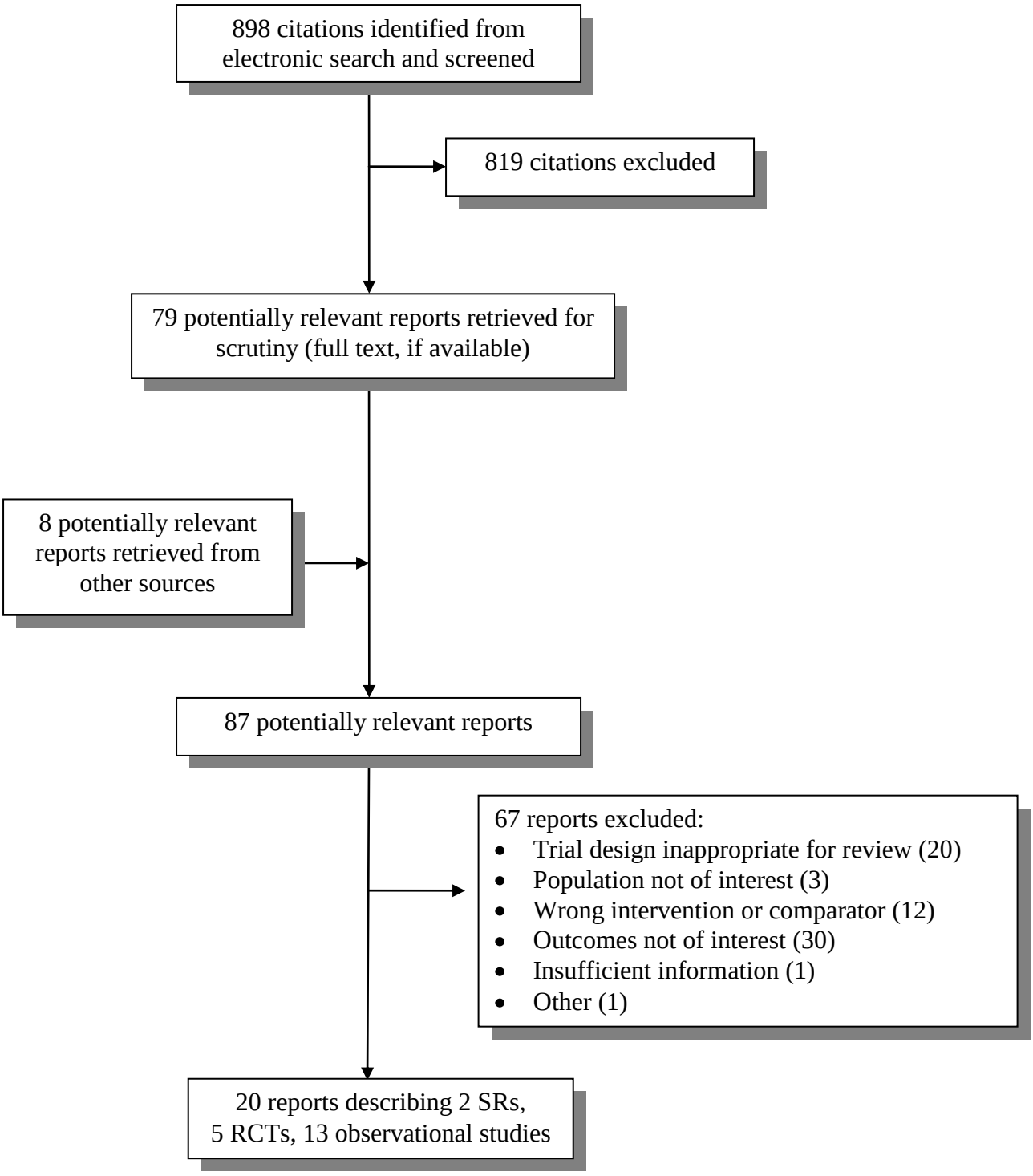
4.2 Results

4.2.1 Quantity of research available

Of the 87 potentially relevant reports that were retrieved for a full text review, 67 were excluded, leaving 20 reports (two systematic reviews, five RCTs, and 13 observational studies) that compared vancomycin and metronidazole in patients with CDI (Figure 1). The excluded clinical studies appear in Appendix 5. None of the 20 reports fully met the original inclusion criteria. Thus, the original research questions could not be answered using the identified literature.

No additional studies were provided from the three manufacturers that were contacted.

Figure 1: Selected Reports



RCTs = randomized controlled trials; SRs = systematic reviews.

4.2.2 Study characteristics

a) Systematic reviews

Two systematic reviews[66,106] evaluated RCTs comparing antibiotics for the treatment of CDI. The population included patients with CDI and was not limited by the number of episodes or the severity of disease. All the included RCTs that compared metronidazole and vancomycin were conducted before the emergence of the NAP1 strain. The details appear in Appendix 6, Tables 1 and 2.

b) Randomized controlled trials

Of the five RCTs that compared vancomycin to metronidazole,[107-111] three were available as full text publications,[107-109]one was available as an abstract,[110] and another was available as a conference poster.[111]Data were extracted from all five.

All five RCTs included a mixed population of patients with first or recurrent episodes of mild, moderate, or severe CDI. One study provided separate data on patients with moderate disease,[111] two RCTs provided data on patients with PMC at diagnosis (a marker for severe disease),[107,108] and two RCTs provided data on patients with severe disease.[109,111] Patients were hospitalized in three studies.[107-109] It was unclear whether or not patients were hospitalized in the other two studies.[110,111] One RCT[111] was conducted during the NAP1 epidemic.

c) Observational studies

Eight retrospective[112-119] and five prospective[120-124] studies compared vancomycin to metronidazole. Five of these studies were available as abstracts,[116,117,122-124] and eight were available as full text publications.[112-115,118-121] Of the thirteen studies, one study[123] presented data on patients with an initial episode of CDI after the emergence of the NAP1 strain, and one study[112] provided data on patients with moderate or severe disease before the NAP1 epidemic.

4.2.3 Data analyses and synthesis

We extracted data from the five RCTs and the 13 observational studies because this had not been previously done systematically. The study characteristics, results, and quality assessments appear in Tables 1 to 5 of Appendix 7 and Tables 1 to 4 of Appendix 8, respectively. The definitions of disease severity and clinical outcomes that were used in the studies appear in Tables 1 and 2 of Appendix 8.

The effectiveness of vancomycin compared to that of metronidazole in the population that was identified in the research question could not be determined based on the selected studies. The data on patients with moderate CDI, severe CDI, or PMC at diagnosis in a mixed population (those with initial and recurrent episodes), and data on adult patients with an initial episode of CDI of varying disease severity, were analysed.

a) Randomized controlled trials

From the RCTs that provided data on patients with moderate and severe disease, we calculated RR, RR reduction (RRR), or RR increase (RRI), and numbers needed to treat (NNT) (Table 3).

Table 3: Effect Measures in Randomized Controlled Trials[*]					
Author	**Cure**	**Recurrence**	**Complications**	**SAEs**	**Death**
Patients with moderate disease					
Louie[111]	v 58/73 (79.5%); m 40/53 (75.5%); RR 1.05 (95% CI : 0.87 to 1.28); RRI 5%	NA	NA	NA	NA
Patients with PMC at diagnosis					
Teasley[107]	v 17/20 (85%); m 13/13 (100%); RR 0.86 (95% CI: 0.7 to 1.07); RRR 14%	v 3/20 (15%); m 0/13 (0%)[†]	NA	0 in each group	NA
Wenisch[108]	v 16/17 (94.1%); m 18/19 (94.7%); RR 0.99 (95% CI: 0.85 to 1.17); RRR 1%	v 1/17 (5.9%); m 2/19 (10.5%)[†]	NA	NA	NA
Patients with severe disease					
Louie[111]	v 28/33 (84.8%); m 37/57 (64.9%); RR 1.31 (95% CI : 1.03 to 1.66); RRI 31%; NNT 5	NA	NA	NA	NA
Zar[109]	v 30/31 (96.8%); m 29/38 (76.3%); RR 1.27 (95% CI : 1.05 to 1.53); RRI 27%; NNT 5	v 3/31 (9.7%); m 6/38 (15.8%); RR 0.61 (95% CI: 0.17 to 2.25); RRR 39%	Colectomy: v 0/31 (0%); m 1/38 (2.6%)[†]	NA	v 0/31 (0%); m 4/38 (10.5%)[†]

CI = confidence interval; m = metronidazole; NA = not available; NNT = numbers needed to treat; PMC = pseudo-membranous colitis; RR = relative risk; RRI = relative risk increase; RRR = relative risk reduction; SAEs = serious adverse events; v = vancomycin.

[*]Includes patients with initial and recurrent episodes.

[†]Relative risks not calculated for outcomes because of small number of events.

Zar et al.[109] stratified patients into mild and severe disease groups based on a severity assessment score that was developed for the study. A total of 69 patients were classified as being in the severe disease group. Louie et al.[111] presented data on clinical success by CDI severity. In this study, 90 patients were classified as having severe CDI. These two studies showed that, in patients with severe CDI, the use of vancomycin increased the cure rate by 27% (RR 1.27 [95% CI, 1.05 to 1.53]; NNT 5)[109] and 31% (RR 1.31 [95% CI, 1.03 to 1.66]; NNT 5)[111] compared

with metronidazole. These results include patients with initial or recurrent CDI. In Louie et al.'s study,[111] more than 70% of patients had an initial episode of CDI.

The results of the severe CDI groups in the Zar and in the Louie studies were not combined in a meta-analysis because the patients in Zar trial were enrolled before the epidemic (1994 to 2002) and the patients in Louie trial were enrolled during the epidemic, with up to a third of the patients testing positive for NAP1 (Thomas Louie, University of Calgary, Calgary, AB: personal communication, 2010 February 24). Furthermore, different criteria were used to define disease severity. In Zar et al.'s trial,[109] patients were included in the severe disease group if they had two of the following: age over 60 years, a temperature greater than 38.3ºC, an albumin level of less than 2.5 mg/dL, or a peripheral white blood cell count greater than 15,000 cells/mm^3 within 48 hours of enrollment; or one of the following: endoscopic evidence of PMC, or treatment in the ICU. In Louie et al.'s trial,[111] patients met the following three criteria to be included in the severe group: 10 or more bowel movements per day, a white blood cell count of greater than 20,000/ mm^3, and severe abdominal pain.

Teasley et al.[107] and Wenisch et al.[108] provided subgroup analyses of patients with PMC, a marker for disease severity. The relative risks of recurrences in patients with PMC at diagnosis were not calculated because of the small number of events.[107,108] Furthermore, Teasley et al.'s and Wenisch et al.'s trials were not combined in a meta-analysis because the two populations were not clinically homogeneous.[107,108] The patients in Teasley et al.'s trial were selected from a veteran's medical centre and were more than 20 years older than the patients in Wenisch et al.'s trial. They had underlying diseases and comorbidities, and more than 80% had undergone surgery during admission compared to less than half of the patients in Wenisch et al.'s trial.

Zar et al.'s RCT[109] reported the incidence of colectomy and all-cause mortality. The relative risks were not calculated for these outcomes because of the small number of events.

Other effect measures were calculated (Table 3), but the comparisons between vancomycin and metronidazole produced inconclusive findings.

The Downs and Black criteria[103] were used to assess study quality and limitations. In Teasley et al.'s study[107] and Zar et al.'s study,[109] a lower dose of metronidazole than that recommended in recent guidelines was used (1 g total daily dose instead of 1.5 g).[19] In Zar et al.'s study,[109] the drop-out rate was 12.8% among all randomized patients and 15.8% among those with severe disease. Among patients with severe CDI, seven patients on vancomycin and six patients on metronidazole did not complete the treatment course and were excluded from the analysis. Of these 13 patients, seven died within five days of therapy. The analysis was not based on intention to treat, and the cure rate may have been overestimated. The drop-out rate was 36.4% among all patients who were randomized in Louie et al.'s trial.[111] When excluding the patients on tolevamer, a drop-out rate of 19.8% in the vancomycin and metronidazole groups combined was reported. Separate drop-out data were not provided for patients with severe disease. Teasley et al.'s study[107] and Wenisch et al.'s study[108] were neither placebo-controlled nor double-blinded, and the concealment of treatment allocation was not described. This may have biased the results (selection and performance biases).

b) Observational studies

The effect measures were calculated for two observational studies,[112,123] but the comparisons between vancomycin and metronidazole yielded inconclusive findings (Table 4).

Talbot et al.'s[112] study is the only one that included children (16 participants) in the study population. No separate information (severity of disease, treatments, or results) was provided for the children.

Table 4: Effect Measures Observational Studies

Author	Population	Recurrence
Lieu[123]	Patients with an initial episode (includes all severity types)	v 5/27 (18.5%); m 5/27 (18.5%); RR 1.00 (95% CI : 0.33 to 3.06); RRR 0%
Talbot[112]	Patients with moderate disease (includes initial and recurrent episodes; may include children)	v 14/52 (26.9%); m 5/24 (20.8%); OR 1.40 (95% CI: 0.44 to 4.47)
	Patients with severe disease (includes initial and recurrent episodes; may include children)	v 4/20 (20%); m 1/6 (16.7%); OR 1.25 (95% CI: 0.11 to 13.92)

CI = confidence interval; m = metronidazole; OR = odds ratio; RR = relative risk; v = vancomycin.

It could not be determined whether or not the identified RCTs and observational studies included patients who were treated with vancomycin or metronidazole as outpatients in the community.

5 Clinical Practice Guidelines

5.1 Methods

5.1.1 Literature search

The guideline literature search was performed by an information specialist using a peer-reviewed search strategy.

The bibliographic databases and grey literature sources that were searched were the same as those for the clinical review (section 4.1.1).

The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was *C. difficile*. A methodological filter was applied to limit retrieval to guidelines. The guideline search was not restricted by publication date, but was restricted to English and French language publications. Appendix 2 shows the detailed search strategies. The search was run on October 28, 2009. Regular alerts were established to update the search until the publication of the final report.

5.1.2 Selection and assessment

Two reviewers (CP, SN) independently selected guidelines that were published in peer-reviewed journals within the last three years.

Each guideline was assessed using the AGREE Instrument.[104] The AGREE Instrument includes a systematic framework to evaluate the key components of guidelines. In total, 23 items are grouped into six domains: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability (organizational and cost implications of implementing guidelines), and editorial independence (potential conflicts of interest from the guidelines development group and source of funding).[104] Appendix 4 section 4.3, summarizes each domain. The items were scored separately on a four-point Likert scale (4 = strongly agree, to 1 = strongly disagree), followed by the domain scores (%) based on the average scores of the items.

The recommendations on the treatment of CDI using vancomycin or metronidazole were summarized. The following data were extracted from the guidelines: objectives of the guideline; practice guidelines or statements on vancomycin and metronidazole when used in the management of moderate or severe CDI; and grade of recommendation. A validity assessment, based on AGREE, and an overall assessment of whether the guideline is to be recommended are provided.

5.2 Results

No Canadian guidelines were identified. Two clinical practice guidelines developed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend the use of oral metronidazole for non-severe initial episodes of CDI and oral vancomycin for severe initial episodes of CDI (Appendix 10, Table 1).[16,19] The ESCMID guidelines recommend that intravenous metronidazole in combination with intracolonic vancomycin with or without vancomycin administered by nasogastric tube be used in severe cases where oral therapy is not possible.[19] The SHEA-IDSA guidelines recommend vancomycin given orally or by nasogastric tube with or without intravenous metronidazole for the treatment of severe, complicated CDI. In the case of complete ileus, rectal vancomycin may be considered.[16] The definition of severity of disease differs between the two guidelines. Recommendations are also made on the treatment of recurrences. The level and strength of the evidence appear in Appendix 10, Table 1.

Using AGREE,[104] most elements of the rigour and development domain, including a systematic search for evidence to support the recommendations, were scored high in the appraisal of both guidelines (Appendix 10, Table 2). However, the methods for the selection of evidence and formulation of recommendations were not clearly described in the SHEA-IDSA guidelines. The ESCMID guidelines did not outline the potential health benefits and risks of adopting the recommendations. Information about an external review process was not clearly described in either guideline. The clarity and presentation domain was scored high in the appraisal of both guidelines. The scoring for stakeholder involvement and applicability were low because of insufficient information. Overall, the recommendations were rigorously developed and clearly presented. Both guidelines could be used to inform clinical practice and reimbursement policies.

6 ECONOMIC REVIEW

6.1 Methods

6.1.1 Literature search

The economic literature search was performed by an information specialist using a peer-reviewed search strategy.

In addition to the bibliographic databases and grey literature sources that were searched for the clinical review (section 4.1.1), parallel searches were run in the Health Economic Evaluations Database (HEED). The economic search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were vancomycin, metronidazole, and *C. difficile*. The economic search was not restricted by publication date, but was restricted to English and French language publications. A methodological filter was applied to limit retrieval to economic studies. Appendix 2 shows the detailed search strategies.

The search was run on October 28, 2009. Regular alerts were established to update the search until the publication of the final report.

In addition to published and grey literature sources, additional unpublished data was obtained from the Canadian Institute for Health Information for the economic evaluation and health services impact section.

6.1.2 Selection criteria

The inclusion criteria for the economic studies were as follows:

Table 5: Selection Criteria for Economic Review	
Study Design	• cost-effectiveness, cost-utility, cost-minimization, cost-benefit, and cost-consequences analyses • costing studies
Population	• adults and children • hospitalized or in the community • first episode of moderate to severe CDI
Interventions	• vancomycin • metronidazole
Outcomes	• quality-adjusted life-years • life-years saved • cure rate • mortality rate • relapse rate • complications (PMC, toxic megacolon, septic shock, intestinal perforation) • need for emergent colectomy • length of hospital stay • length of ICU stay • time to return to work • time to resumption of usual activities

CDI = *Clostridium difficile* infection; ICU = intensive care unit; PMC = pseudomembranous colitis.

6.1.3 Selection method

Two reviewers (ET, SN) independently screened the titles and abstracts of all citations that were retrieved in the literature search. Based on the selection criteria, the reviewers ordered the full text of any articles that seemed to meet the criteria, independently reviewed the full text of selected articles, applied the selection criteria, and compared the independently chosen included and excluded studies. Disagreements were resolved through discussion until consensus was reached.

6.1.4 Data extraction strategy

Data to be used in the economic review were extracted by two reviewers (ET, SN) using a data extraction form. Evidence tables were constructed (ET) using the extracted data. Data that were entered in the evidence tables were verified by a second reviewer (SN). Any discrepancies were resolved through discussion until consensus was reached. The data extraction form that was used for the economic review appears in Appendix 11.

6.1.5 Strategy for validity assessment

Drummond et al.'s checklist for reporting economic evaluations was used to assess the quality of reporting.[125] The information from the retrieved studies was limited because two were abstracts, and one was not primarily reported as an economic study. As a result, the quality of reporting

could not be evaluated. The study characteristics that may affect the quality or validity of evidence were addressed in the qualitative analysis of the retrieved economic studies.

The external validity of each study was evaluated through a series of questions that are formulated based on CADTH's economic guidelines[126] (Appendix 12, Tables 1 and 2). This tool has been used in previous CADTH assessments. The studies were assessed by one reviewer (ET), and the results of the assessment were confirmed by a second reviewer (SN).

6.1.6 Data analysis methods

Given the limitations in the quantity and quality of reporting of the studies that were retrieved for this review, the studies were detailed in a narrative description. The characteristics and main findings of the studies were described, the strength of evidence was assessed, and study limitations were noted.

6.2 Results

6.2.1 Quantity of research available

A total of 183 citations were identified: 174 citations in the economic literature search, five citations from the grey literature, and four citations through the handsearching of selected references. Of these, 170 were excluded in the initial selection. Most of the citations were excluded because they were not economic evaluations or comparisons of metronidazole and vancomycin. The review of the 13 remaining articles resulted in the exclusion of ten. The reasons for exclusion were: not an economic evaluation (seven citations), not a comparative economic evaluation (one citation), metronidazole not a comparator (one citation), and economic results not patient-specific (one citation). A list of the excluded studies appears in Appendix 13.

Of the three economic assessments that were selected for this review, two[116,127] were reported in abstracts and one[115] was reported as a full article. Two studies[116,127] were American and one[115] was conducted by a research group from Northern Ireland.

It was not possible to determine the extent to which the populations in each of the three studies met the inclusion criterion of initial episode of moderate or severe CDI and whether or not children were included because of limitations in data reporting. Although the three evaluations did not meet the inclusion criteria, no other reviews of economic evaluations on CDI were available. Thus, information on the three evaluations is provided.

6.2.2 Study characteristics

A summary of study characteristics appears in Appendix 14, Table 1.

a) Study quality

The quality of reporting could not be assessed because two selected studies were abstracts that contained limited information, and the third study was not primarily reported as a comparative economic evaluation.

b) External validity

The results of the external validity assessment appear in Appendix 14, Table 3. The research questions in Lahue and Davidson's[116] study and in Thomas et al.'s[127] study reflected the issue that was included in this report's research questions. Al-Eidan et al.'s[115] study did so partially. To the extent that there may be similarities in practice patterns between the U.S., Ireland, and Canada in the treatment of CDI, the clinical data that were used in the analysis partially reflected what might be achieved during routine clinical practice in Canada in two studies,[115,116] but were unclear in one study because of a lack of clinical data.[127] The extent to which resource use patterns and relative cost levels were generalizable to Canada was judged to be partial in all three studies. Uncertainty was not considered to be adequately reflected in two studies[115,116] that did not conduct sensitivity analyses and only to some degree in one study.[127]

c) Study design

Lahue and Davidson[116] and Al-Eidan et al.[115] reported the costs and consequences of treatment. Thomas et al.'s study[127] was reported as a cost comparison.

d) Time horizon

The time horizon in Lahue and Davidson's study[116] and in Al-Eidan et al.'s study[115] was the duration of hospital admission. In Lahue and Davidson's study,[116] this duration ranged from 11.5 days to 12.8 days. In Al-Eidan et al.'s study,[115] the mean duration was 11.3 days. The time horizon in Thomas et al.'s study[127] was unstated. The model that was used in this analysis allowed for up to six recurrences of CDI.

e) Study perspective

The study perspective was that of a hospital in Lahue and Davidson's study[116] and in Al-Eidan et al.'s study.[115] The perspective was unclear in Thomas et al.'s study,[127] but based on the included costs and their sources, it may be considered to be from the perspective of a United States third-party payer (Medicare).

f) Study population

Lahue and Davidson[116] did not specify the disease severity of patients. Although the treatment of CDI was identified as first-line, 10.4% of patients using metronidazole and 30.7% of patients using vancomycin had previous CDI hospital admissions. Thomas et al.[127] did not provide information on the clinical data that were used in their model. It was assumed in the model that treatment was first-line. Al-Eidan et al.[115] did not specify whether or not patients were treated for initial episodes of CDI, and it was not possible to determine disease severity using the data that were provided.

The patient data in Lahue and Davidson's study[116] were retrospectively analyzed electronic health records of 32,325 patients (3,420 receiving vancomycin and 28,905 receiving metronidazole) obtained from a national hospital database (Premier Perspective) between January 2004 and June 2005. The included patients were hospitalized, had an ICD9 diagnosis code 008.45, and were receiving metronidazole or vancomycin. Patients who had not received therapy for CDI, who had received initial dual therapy, and who simultaneously received intravenous metronidazole as first-line therapy were excluded. The mean age of patients taking vancomycin was 70.5 years and the mean age of patients taking metronidazole was 70.2 years. A larger proportion of patients taking vancomycin were female (64%) compared to 58% taking

metronidazole. Thirty-one per cent of patients taking vancomycin and 19% of patients taking metronidazole had a principal CDI diagnosis at admission, and 31% and 10% had a prior CDI admission respectively. Of patients taking vancomycin, 53% had received prior acid suppressive therapy. Of patients taking metronidazole, 42% had received prior acid suppressive therapy. The authors used the All Patient Refined Diagnosis Related Groups as a comorbidity proxy measure. Among patients taking vancomycin and those taking metronidazole, 3.4% and 2.4% had minor illness severity, 24.1% and 18.1% had moderate illness severity, 48.5% in both groups had major illness severity, and 24.1% and 30.5% had extreme illness severity, respectively ($P < 0.0001$). The risk of mortality was evaluated to be higher in the metronidazole group ($P < 0.0001$); the estimates were not reported.

Al-Eidan et al.[115] conducted a retrospective chart review of 87 patients at a hospital centre in Northern Ireland over a two-year period. Patients were included if they had a change in bowel habits, with three or more loose stools per day for two or more consecutive days associated with the laboratory-confirmed presence of *C. difficile* toxin A in a fecal sample. Patients were excluded from the study if they were treated empirically for CDI without a positive *C. difficile* assay result. The baseline characteristics of patients were not presented by treatment group, but were based on whether patients were community-admitted or National Health Service-admitted. The mean age of all patients was 71 years (range 33 years to 96 years), and 69% were female. The mean number of days before treatment was 5.1 (range 2 days to 28 days), and the mean number of comorbid illnesses was 1.9 (range 1 to 4). Of the patients, 63% had abdominal pain, 100% had diarrhea, and 43% had fever. Forty-eight (55%) patients were treated with vancomycin, and 39 (45%) were treated with metronidazole. The mean duration of therapy in all patients was 7.4 days (range five days to ten days). Although the figures were not provided, the authors stated that there were no statistically significant differences between patients who were treated with metronidazole and those who were treated with vancomycin in age, gender, outpatient status, comorbidities, symptoms (diarrhea, abdominal pain, and fever), duration of symptoms before the start of treatment, and duration of treatment.

Thomas et al.[127] did not report the source or characteristics of the study population in their analysis.

g) Intervention and comparator

In all three studies, treatment with vancomycin was compared to treatment with metronidazole. The mean dosages and durations of therapy by treatment group were not reported in any of the studies.

h) Economic outcomes

Lahue and Davidson[116] and Al-Eidan et al.[115] presented their results in terms of the costs of treatment, and the clinical and health care utilization consequences of treatment. Lahue and Davidson[116] reported total length of stay, proportion of patients in ICU, duration of ICU stay, colectomy rates, and in-hospital death. Al-Eidan et al.[115] compared patients who were treated using metronidazole to patients who were treated using vancomycin in duration of treatment, length of stay, laboratory results, treatment response time, and mortality. Thomas et al.[127] did not report the clinical or health care utilization consequences of treatment. The ratios of costs to outcomes were not estimated in any of the three studies.

i) Economic costs

Lahue and Davidson[116] considered pharmacy costs and total inpatient costs. Thomas et al.[127] included costs of outpatient clinic visits, antibiotic costs, costs of stool tests, and direct hospital costs. Al-Eidan et al.[115] conducted a cost analysis of all patients and included hospital stay, laboratory tests, and drugs. Only the cost of drug therapy was reported in the analysis (metronidazole compared to vancomycin).

j) Funding sources

The source of funding was not stated by Thomas et al.[127] or by Al-Eidan et al.[115] Lahue and Davidson's[116] study was funded by Genzyme.

k) Base-case results

A summary of study results appears in Appendix 14, Table 2.

Lahue and Davidson[116] reported a statistically significantly higher mean total length of stay (12.8 days compared to 11.5 days, $P < 0.0001$) and a statistically significantly higher proportion of patients in the ICU (23.2% compared to 17.7%, $P < 0.0001$) in the metronidazole group. The mean lengths of ICU stay in the vancomycin and metronidazole groups were 6.6 days and 6.8 days ($P = 0.37$), respectively. The colectomy rates were comparable in the two groups (vancomycin 0.8%, metronidazole 1.0%; $P = 0.37$). The rate of in-hospital death was statistically significantly higher in the metronidazole group (7.9% versus 6.8%, $P < 0.02$). The mean CDI therapy costs were higher in the vancomycin group ($375 versus $90, $P < 0.0001$). The total pharmacy costs were comparable (vancomycin $2,492, metronidazole $2,439; $P = 0.52$). The mean hospitalization costs were higher in the metronidazole group ($16,953) than in the vancomycin group ($14,718; $P < 0.0001$).

Thomas et al.[127] reported average treatment costs only. In the vancomycin group, the average treatment costs were $910, and in the metronidazole group, the costs were $561.

The mean length of stay of all patients in Al-Eidan et al.'s study[115] was 17 days (range nine days to 34 days). The mortality of all patients was 10%. There were no statistically significant differences between patients who were treated with metronidazole and vancomycin in duration of treatment, length of stay, laboratory results, or mortality (data not provided). There was no difference between treatment groups in response time (vancomycin 3.1 ± 1.4 days, metronidazole 2.8 ± 1.1 days). The average cost of drug therapy was £162.5 in the vancomycin group and £1.60 in the metronidazole group.

l) Sensitivity analysis results

Lahue and Davidson[116] and Al-Eidan et al.[115] did not report sensitivity analyses. Thomas et al.[127] reported that the equivalent costs between groups were attained when the resistance rates of metronidazole approached 75%, and that the cost of vancomycin would need to be reduced by 88% to achieve economic superiority to metronidazole.

7 PRIMARY ECONOMIC ANALYSIS

The economic review did not provide evidence on the relative cost-effectiveness of vancomycin and metronidazole in moderate to severe CDI that would be relevant in a Canadian context, and a primary economic evaluation was undertaken.

7.1 Methods

The clinical review did not reveal evidence on the differences in efficacy between metronidazole and vancomycin in patients with moderate CDI.[111] Two RCTs[109,111] reported statistically significantly higher cure rates with the use of vancomycin by patients with severe CDI. Zar et al.'s trial[109] was conducted before the NAP1 outbreak, and approximately a third of patients in Louie et al.'s trial[111] were infected with the NAP1 strain. While the sample sizes were small in both studies, the findings were clinically and statistically significant in patients with severe disease. The efficacy rates of both drugs were higher in Zar et al.'s trial[109] than those reported in Louie et al.'s trial.[111] Neither trial considered quality-of-life as an outcome. The findings on mortality or other serious complications between treatment groups were inconclusive. Both trials had inclusion criteria that may have excluded patients who are more likely to experience complications (for example, the presence of non–life-threatening medical conditions). Zar et al.'s trial[109] had a dropout rate of 12.8% among all randomized patients and a dropout rate of 15.8% among those with severe disease. Among patients who were randomized to receive vancomycin or metronidazole in Louie et al.'s trial,[111] the dropout rate was close to 20% (data were not provided on patients with severe disease).

Data from Pépin et al.'s observational study,[118] which was conducted at a teaching hospital in Quebec, suggest that patients receiving vancomycin as initial therapy were less likely to experience serious complications (all-cause mortality included) than those receiving metronidazole in the pre-NAP1 (1991 to 2002). This benefit was no longer apparent during the epidemic (2003 to 2006). It cannot be determined if this finding was due to a bias present during the NAP1 outbreak that could not be controlled for in the analysis, or if the dynamics of toxin production in NAP1 made vancomycin less effective. Other large observational studies[116,117] were unable to provide evidence about relative complication and mortality rates.

The rate of complications in Zar et al.'s trial[109] was lower than the estimates that were obtained through special tabulations from the Canadian Institute for Health Information, Ottawa, Ontario, Canada, Discharge Abstract Database. According to these data, 8.25% of all patients who were hospitalized with a diagnosis of *C. difficile* infection (ICD10 Code A04.7) in fiscal year 2008 to 2009 also experienced at least one of the following serious complications: toxic megacolon, colonic perforation, sepsis, or colectomy. The cases of death from all causes were not identified in these data, but it was assumed that patients who died as a direct result of their complications would be included in this estimate. We could not determine, based on these data, if all the complications (for example, sepsis) were directly related to CDI. Data from Pépin's study[118] suggest that these complications occur in at least 3% to 4% of patients who were hospitalized with CDI (all-cause mortality excluded). To estimate the rate of serious complications in a population of patients with severe CDI, the authors of this report first assumed that the distribution of disease severity in Louie et al.'s trial[111] (25% mild cases, 41% moderate cases,

and 34% severe cases) was representative of the CDI population. We then assumed that most of the serious complications occur in those with severe disease. Applying the range of complication rates that was obtained from Pépin et al.[118] and from the Canadian Institute for Health Information (3.5% and 8.25% of all severities of CDI combined, respectively) to the proportion of cases of CDI that were assumed to be severe (34%), it was estimated that between 10% and 24% of patients with severe CDI experience serious complications directly related to their infection. Most of the patients in the Pépin study were initially given metronidazole. Earlier data that were reported by Pépin et al.[42] indicate that, from 1991 to 2002, these complications occurred in approximately 25% of patients who also had high leukocyte counts, creatinine levels, or both. In 2003, they occurred in approximately 40% of these cases. These data do not provide information on specific complications by treatment. Pépin et al.[118] provided information on complication rates by treatment group in a later study, but not on specific complications, and all-cause mortality was included in these rates.

These data suggest that the complication rates in severe disease are higher in the general population than in the populations in trials. It is biologically plausible that the reduction in treatment failure with vancomycin compared with metronidazole in both trials[109,111] would result in fewer serious complications. However, there is no evidence to support this hypothesis.

For these reasons, it was decided that the base-case economic evaluation would rely solely on relative cure rates, and no assumptions about relative serious complication rates and mortality would be made. A deterministic sensitivity analysis would be used to explore the potential impact of a range of complication rates among patients whose initial therapy with metronidazole and vancomycin failed. In these sensitivity analyses, it was assumed that the probability of complication after a failure of initial therapy would be the same in both treatment groups. Because of the lack of reliable data, the potential relative impact of treatment with metronidazole and vancomycin on mortality is not estimated.

The data from Louie et al.'s trial[111] are used in the base-case analysis, because these are the only data available that included patients known to be infected with the NAP1 strain.

7.1.1 Type of economic evaluation

During the clinical review, no evidence was found on the differences in quality of life or mortality among patients with CDI taking metronidazole and vancomycin. The evidence from two RCTs[109,111] showed a difference between treatment groups in the cure rates of severe CDI. Based on these data, a cost-effectiveness analysis was conducted.

7.1.2 Target population

Louie et al.[111] defined patients with severe CDI as those having ten or more bowel movements a day, a white blood cell count greater than 20,000/mm^2, and severe abdominal pain due to CDI.

7.1.3 Comparators

Oral metronidazole 375 mg four times daily for 10 days was compared to oral vancomycin 125 mg four times daily for 10 days. In the base case, initial therapy using both comparators was assumed to be given as capsules, because this formulation was used in Louie et al.'s study.[111]

7.1.4 Perspective

The target audience and recommended perspective for economic evaluations that are conducted by CADTH are that of the publicly funded health care system.[126] Among the costs that are accounted for in this perspective are direct costs to the publicly funded health care system (for example, hospital costs, physician payments, fees for diagnostic tests) and direct costs to patients and their families (for example, out-of-pocket copayments), both of which were relevant to this analysis.

7.1.5 Effectiveness

The measure of effectiveness is clinical success (Zar et al.[109] used the term "cure"), which is defined as the resolution and absence of severe abdominal discomfort due to CDI for two contiguous days (the definition in Louie et al.'s trial[111] appears in Appendix 9). Patients who did not achieve clinical success were assumed to have undergone a treatment that failed. Treatment failure was defined as persistent diarrhea (not defined in Louie et al.'s trial[111] but defined in other RCTs in Appendix 9).

7.1.6 Time horizon

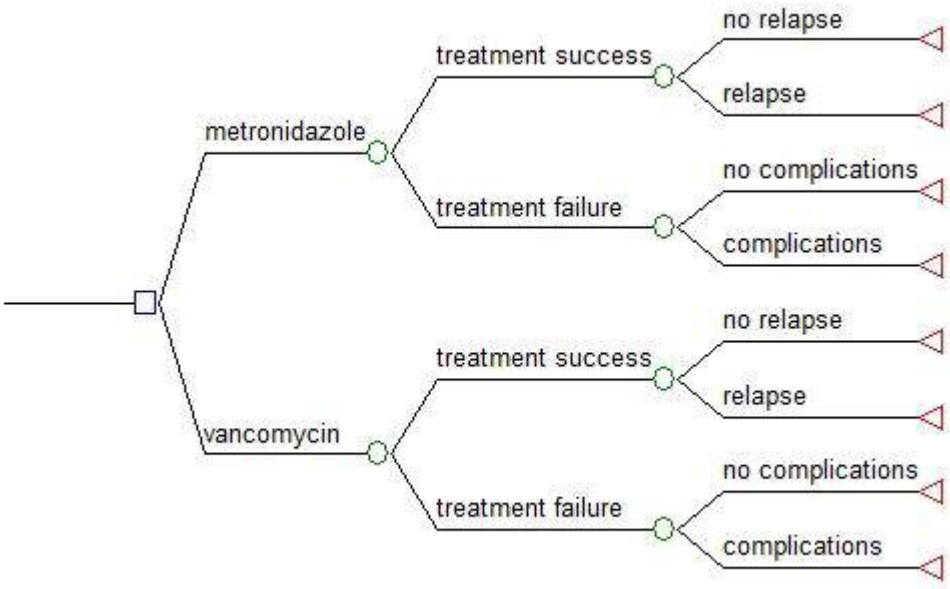
Patients are followed up to 50 days from the time of hospital admission. This duration was determined based on the duration of initial therapy, the expected time to relapse, and the expected duration of treatment for relapse.

7.1.7 Modelling

Analyses were based on a decision-analytic model and were conducted in Microsoft Excel 2002 Service Pack 3[128] and in TreeAge Pro Suite 2009, version 1.0.2.[129] The model structure and its inputs were discussed with the co-authors and clinical experts when the protocol was written, and during the research to find the evidence that was used to populate the models. An internal validation of the models was conducted by varying the parameters to extreme values and verifying the feasibility of the resulting estimates.

A diagram of the model that was used for all analyses appears in Figure 2.

Figure 2: Decision-Analytic Model for Economic Evaluation of Metronidazole Compared to Vancomycin in CDI



In the model, it is assumed that patients will have an onset of symptoms by the eleventh day after admission.[47] Patients who receive initial therapy with metronidazole or vancomycin will experience a treatment success or failure, which will be evaluated on the fifth day of treatment. Patients who are treated successfully will have no relapse or a relapse 14.5 days after completing the initial course of therapy.[8] Patients who have a relapse will be assigned another course of drug therapy, and it is assumed that this treatment occurs in the community. One relapse after initial therapy is considered in this model. Patients with treatment failures may or may not have complications. Patients with treatment failures are assigned another drug therapy and are assessed for colectomy. Complications include toxic megacolon, colonic perforation, sepsis, or colectomy.

7.1.8 Valuing outcomes

Efficacy data from Louie et al.'s trial[111] were used for the base-case analysis. In this trial, approximately a third of patients were infected with the NAP1 strain. The clinical success rates among patients with severe disease who were given metronidazole and vancomycin were 64.9% (37/57) and 84.8% (28/33), respectively. Expert opinion states that the rate of relapse after initial treatment ranges between 10% and 20% for metronidazole and vancomycin, and that the rate would be higher with more virulent strains of *C.difficile*. Given that the patients in Louie et al.'s trial[111] were a mix of those with NAP1 and those with non-NAP1, a relapse rate of 15% was assumed for metronidazole and vancomycin in the base-case. The complication rates were assumed to be equal in the two treatment groups and were estimated based on data that were reported by Pépin et al.[118] to be 3.5% in the general CDI population. Assuming that most of these complications occur in severe disease and that 34% of all CDI cases are severe,[111] a complication

rate of 10.3% was estimated in severe patients for both treatment groups. Colectomy was estimated to occur in 41% of complicated cases.[118] Approximately 30% of cases in Louie et al.'s trial[111] were recurrences, and it is assumed in the model that the observed efficacy rates are for initial episodes. It is also assumed that recurrences in Louie et al.'s trial[111] were equally distributed by treatment group through the randomization process.

7.1.9 Resource use and costs

a) Medication

The treatment regimens in the model were based on those in Louie et al.'s trial[111] and on those in current practice guidelines.[16,19] Patients initially received treatment with one oral vancomycin 125 mg capsule four times daily for 10 days or one oral metronidazole 500 mg capsule three times daily for 10 days. Patients who were initially on metronidazole and whose treatment failed (without complication) or who experienced a relapse were placed on one oral vancomycin 125 mg capsule four times daily for 10 to 14 days. Patients who were initially placed on vancomycin and whose treatment failed (without complication) were given oral vancomycin 500 mg (the IV formulation administered orally to hospitalized patients and the capsule form administered to patients who were discharged in the community) four times daily for 10 to 14 days. Patients initially given vancomycin and who experienced a recurrence were prescribed one oral vancomycin 125 mg capsule four times daily for 10 to 14 days. Patients from either treatment group whose therapy failed and who had complications were prescribed IV metronidazole 500 mg every eight hours plus orally administered IV vancomycin 500 mg four times per day. For patients requiring subsequent treatment because of failure or relapses, it was assumed that the treatment with vancomycin in the hospital was an IV formulation that is administered orally because of the higher doses that were needed. Vancomycin that was received in the community was in capsule form (250 mg).

The costs of medication were obtained from three provincial drug formularies,[88,97,98] as well as from one hospital centre in Quebec (Benoit Cossette, Pharmacist, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC: personal communication, 2010 August 31). The estimated average cost of 1,500 mg oral metronidazole (three 500 mg capsules) is $0.36, and that of 500 mg oral vancomycin (four 125 mg capsules) is $31.22. Intravenous metronidazole 500 mg/100 mL costs $1.31. One 1,000 mg of injectable vancomycin costs $6.85.

A description of the drugs that are used at each stage in the model and the estimated daily costs appears in Appendix 15, Table 1.

b) Hospitalization

Special tabulations from the Canadian Institute for Health Information's Discharge Abstract Database were used to estimate lengths of stay and hospital costs. All patients who were admitted to hospital with the ICD10 code for enterocolitis due to *C. difficile* (A04.7) were stratified by whether or not they had any one of the following complications: toxic megacolon, colonic perforation, colectomy, or sepsis. The average length of stay for patients without complications was 16.8 days, and the average length of stay for patients with complications was estimated to be 29.1 days. Per diem rates for patients without complications was estimated to be $1,916 and with complications, $2,283.

c) Procedures and professional fees

The two procedures that were considered in this analysis were likely to have the greatest impact on total costs because of high frequency (colonoscopy) or high unit cost (colectomy). Patients whose initial therapy failed were assumed to undergo colonoscopy and surgical consult. The costs of these procedures were obtained from the Ontario Schedule of Benefits for Physician Services.[130] The cost of a colonoscopy (gastroenterologist fees) was $91.60 per procedure. A subsequent surgical consult was $89.30. The cost of a total colectomy, including surgical assistant fees, anesthesiologist fees, and surgeon fees was estimated to be $1,700.46 per procedure.

Patients who received their prescriptions in the community (relapse or failure without complication) were seen by a family practitioner for one visit. The cost of a consultation with a family practitioner was $62.65.[130]

All costs are reported in 2010 Canadian dollars. The costs that were obtained from sources dating before 2010 were inflated using the Canadian Consumer Price Index (All- items, 326-0021).[131]

7.1.10 Discount rate

Because the follow-up for this analysis is less than one year, the cost and outcomes were not discounted.

7.1.11 Variability and uncertainty

Deterministic sensitivity analyses were used to explore the potential impact of five factors on the base-case results: expected efficacy rates of metronidazole and vancomycin in pre-epidemic and epidemic periods, the substitution of a lower-cost generic IV vancomycin that is used orally in hospital instead of vancomycin capsules, shorter hospital length of stay among those with treatment successes, the potential impact of a range of complication rates among those with treatment failures, and higher efficacy rates of metronidazole.

The cost-effectiveness of vancomycin compared to metronidazole in the pre-epidemic period was assessed based on Zar et al.'s[109] efficacy data. In this trial, the treatment success rates among patients with severe CDI taking metronidazole and vancomycin were 76.3% (29/38) and 96.8% (30/31), respectively. A relapse rate of 10% for metronidazole and vancomycin was assumed. The complication rates were the same as those in the base case.

No trial data were available for a population that was only infected with the NAP1 strain. To estimate what efficacy rates might be like in such a population, the authors of this report assumed that the difference in the efficacy rates that was observed between Louie et al.'s trial[111] and Zar et al.'s trial[109] was due to a third of patients being infected with the hypervirulent strain in Louie et al.'s study. Using the data from Zar et al.'s study to stratify the results from Louie et al.'s study, it was estimated that the patients who were infected with the NAP1 strain in Louie et al.'s study would have efficacy rates of 42% (metronidazole) and 61% (vancomycin). The relapse rate in this population was assumed to be 20% for both treatment groups. The base case complication rates were assumed.

A lower-cost generic IV formulation of vancomycin is available to hospitals.[132] An analysis was done using the base-case model with the assumptions that all vancomycin that is used in hospitals would be the IV formulation, and that the efficacy of the IV formulation used orally and that of the capsules is similar in patients with severe CDI.

Although no data indicate a shorter length of stay among patients experiencing treatment success with initial therapy, this assumption was considered plausible, and its impact on the incremental cost-effectiveness ratio was explored.

The possibility that lower rates of treatment failure may result in fewer overall complications was explored. A range of probabilities for complication in cases of treatment failure were considered (0% to 100%). It was estimated with the base-case model that a probability of complication given a treatment failure rate of 33% would give rise to the complication rates that were observed in Pépin et al.'s trial[118] (approximately 3.5% of all CDI cases).

In the base-case analysis, it was assumed that all patients received therapy for a first occurence, and that the results that were reported by Louie et al.[111] were representative of the efficacy in initial infection. However, this trial included patients who had experienced recurrent disease (approximately 30% of patients). Given the proportion of patients who had initial infections (approximately 70%), the high efficacy rate among patients receiving vancomycin (85%) suggests that this therapy was effective in initial and recurrent disease. However, this assumption is brought into question in metronidazole therapy with an efficacy rate of 65%. We considered the possibility that metronizadole may be more effective in actual first occurences than what was reported by Louie et al., and estimated this potential impact on the base-case incremental cost-effectiveness ratio.

The probabilistic sensitivity analyses using Monte-Carlo simulation were conducted to estimate the uncertainty in the the incremental cost-effectiveness ratio. Analyses were done using the base-case model and a model that assumed a 33% complication rate among those with treatment failures. The results of these analyses were expressed in 95% CIs around incremental costs and incremental treatment effectiveness. The probability that treatment with vancomycin is more costly than metronidazole for each additional clinical cure was also estimated. The probabilities that were used in the model were assumed to follow a beta distribution. It was assumed that drug costs had a fixed distribution and that other health care resource costs followed a gamma distribution, with standard errors estimated at 50% of the mean.[133] The parameters that were used in the probabilistic sensitivity analysis of both models appear in Appendix 15, Tables 2 and 3.

7.2 Results

7.2.1 Analysis and results

Table 6 shows the costs of treatment with metronidazole or vancomycin in the base-case model. The hospital costs are the largest component of total costs, but they have no impact on the analysis because it is assumed that the two treatment groups have the same complication rates. Similarly, there is no incremental difference in costs between groups for colectomy.

Table 6: Base-case Average and Incremental Costs for Treatment with Metronidazole Compared with Treatment with Vancomycin in Patients with *Clostridium difficile* Infection			
Resource	**Average Cost Per Patient**		
	Metronidazole	**Vancomycin**	**Increment**
Drugs	$147	$425	$278
Hospital	$35,714	$35,714	$0
Colonoscopy	$32	$14	−$18
Surgical consult	$31	$14	−$17
Colectomy	$72	$72	$0
Family practitioner	$22	$11	−$11
Total	**$36,018**	**$36,250**	**$232**

Total average costs for treatment with metronidazole and vancomycin were $36,018 and $36,250 per patient, respectively. The incremental costs were $232, and treatment with vancomycin was more expensive. The incremental benefit (in cure rates) of vancomycin compared with metronidazole for severe CDI that was reported in Louie et al.'s study[111] was 19.9%. The incremental cost-effectiveness ratio (ICER) for the base-case analysis is $1,161 per clinical cure, meaning that each additional clinical cure resulting from the first-line use of vancomycin over metronidazole is attained at an additional cost of $1,161 to the health care system.

7.2.2 Results of variability analysis

a) Sensitivity Analysis 1: Clostridium difficile infection populations

In this analysis, the base-case assumptions in two patient populations are considered: a pre-NAP1 population that is represented by Zar et al.'s data,[109] and a population of patients with NAP1, the efficacy rates of which were estimated using data from Zar et al.'s trial[109] and Louie et al.'s trial.[111] The incremental difference in costs increases as the efficacy of both drugs decreases (Table 7). Incremental costs are largely attributed to drug costs. Incremental costs increase as drug efficacy decreases, because more patients experience treatment failure with initial vancomycin and need higher doses.

Table 7: Cost-effectiveness of Vancomycin Compared with Metronidazole in Three CDI Populations					
Population		**Metronidazole**	**Vancomycin**	**Increment**	**ICER**
Zar*[109]	Average cost	$33,476	$33,669	$193	$946/clinical cure
	Effectiveness	0.763	0.968	0.205	
Louie†[111]	Average cost	$36,018	$36,250	$232	$1,161/clinical cure
	Effectiveness	0.649	0.848	0.199	
NAP1‡	Average cost	$36,146	$36,660	$454	$2,413/clinical cure
	Effectiveness	0.421	0.609	0.188	

ICER=incremental cost-effectiveness ratio; NAP1 = more virulent strain of *Clostridium difficile*.
*Population in Zar et al.'s trial[109] assumed to be pre-NAP1.
†Approximately 30% of patients from Louie et al.'s trial[111] had NAP1 strain. Results for population in Louie et al.'s trial are base case.
‡NAP1 effectiveness estimated using data from Louie et al.'s trial[111] and Zar et al.'s trial[109] (section 6.1.11).

b) Sensitivity Analysis 2: Generic intravenous vancomycin administered orally as initial therapy in-hospital

In this analysis, it is assumed that patients are given a generic orally administered IV vancomycin for all in-hospital use of this drug. All three patient populations were considered, assuming that there is no difference in complication rates, and that IV vancomycin administered orally has the same effectiveness as vancomycin capsules administered orally. The results of this analysis (Table 8) show decreases in the incremental cost-effectiveness ratios for all three patient populations compared with the results in Table 7.

Table 8: Cost-effectiveness of Vancomycin Compared with Metronidazole in Three CDI Populations, Using Generic IV Vancomycin In-hospital

Population		Metronidazole	Vancomycin	Increment	ICER
Zar[109]	Average cost	$33,476	$33,504	$28	$135/clinical cure
	Effectiveness	0.763	0.968	0.205	
Louie[111]	Average cost	$36,018	$36,087	$69	$346/clinical cure
	Effectiveness	0.649	0.848	0.199	
NAP1	Average cost	$36,147	$36,445	$278	$1,584/clinical cure
	Effectiveness	0.421	0.609	0.188	

CDI = *Clostridium difficile* infection; ICER = incremental cost-effectiveness ratio; IV = intravenous; NAP1 = more virulent strain of *Clostridium difficile*.

c) Sensitivity Analysis 3: Shorter length of stay with successful initial therapy

The length of hospital stay among patients experiencing clinical success with initial therapy was varied to determine the reduction that was needed to make the incremental costs of vancomycin equal to those of metronidazole. The required reductions in length of stay in the Zar,[109] Louie[111] and NAP1 populations were 0.5 days, 0.6 days, and 1.25 days, respectively (data not shown).

d) Sensitivity Analysis 4: Complications based on treatment failure

The costs in Table 9 were estimated using data from Louie et al.'s trial,[111] assuming that the probability of complication among cases of treatment failure in either group would be 33%. This probability was chosen because it was estimated that this probability would have given rise to the complication rates that were seen in Pépin et al.'s trial[118] if the drug efficacy rates were the same in that population. The results show negative total incremental costs for the use of oral vancomycin, with this difference largely attributed to decreased average hospitalization costs driven by a lower length of stay (average between-group difference in lengths of stay was 1.15 days).

Table 9: Average and Incremental Costs in Metronidazole and Vancomycin-treated Patients, Assuming Complication Rates are Related to Treatment Failure			
Resource	**Average Cost Per Patient**		
	Metronidazole	**Vancomycin**	**Increment**
Drugs	$145	$487	$342
Hospital	$36,154	$33,901	−$2,253
Colonoscopy	$32	$14	−$18
Surgical consult	$31	$14	−$17
Colectomy	$81	$35	−$46
Family practitioner	$21	$14	−$7
Total	**$36,464**	**$34,465**	**−$1,999**

Because of uncertainty about the actual probability of complication in cases of treatment failure, a range of probabilities was considered in each of the three patient populations (pre-NAP1, mixed, and NAP1) (Appendix 15, Tables 4, 5, and 6). The results in these tables show that a probability of complication given treatment failure as low as 10% would result in net expenditure reductions for inital therapy with oral (capsule form) vancomycin in each patient population.

e) Sensitivity Analysis 5: Higher efficacy rates in initial therapy with metronidazole

We increased the efficacy rate of initial therapy with metronidazole in the base-case model from 65% by 5% increments, up to 85%. At 70% efficacy for metronidazole, the estimated ICER for initial therapy with vancomycin over metronidazole increased from $1,611 per clinical cure to $1,738 per clinical cure. At 75% efficacy, the ICER was $2,286 per clinical cure, and at 85% it was $6,402 per clinical cure (data not shown).

7.2.3 Results of uncertainty analysis

a) Base-case model

The 95% CI around the incremental cost of using vancomycin first-line ($232 per patient) was −$6,345 to $7,665, with most of this variation attributed to the variation in hospital costs. The 95% CI around incremental effectiveness (0.199) was 0.018 to 0.370. Initial therapy with vancomycin was more expensive than initial therapy with metronidazole in 60.1% of simulations.

b) Model with 33% complication rate among treatment failures

The 95% CI for the incremental cost of using vancomycin first line (−$1,999 per patient) was −$11,375 to $3,460. As with the base-case analysis, most of this variation was due to a variation in hospital costs. The 95% CI for incremental effectiveness was estimated to be 0.019 to 0.361, and initial therapy with vancomycin was more expensive than initial therapy with metronidazole in 31.1% of cases.

8 HEALTH SERVICES IMPACT

8.1 Population Impact

The annual incidence of CDI in Canadian hospitals (except Quebec) was obtained from the Canadian Institute for Health Information's Discharge Abstract Database for 2008-2009 (special tabulations). All patients who were admitted to hospital with the ICD10 code for enterocolitis due to *Clostridium difficile* (A04.7) were identified by province and territory. Data on Quebec were obtained from published data on hospital admissions in Quebec for 2008-2009[134] and the reported rates of CDI infection in Quebec hospitals for 2008-2009.[135] The estimated incidence of CDI in Canadian hospitals was 5.2 cases per 1,000 admissions. The rate obtained from CNISP for the same time period was 4.7 cases per 1,000 admissions (Denise Gravel, Public Health Agency of Canada, Ottawa, ON: personal communication, 2010 November 30). To estimate the number of CDI cases that were hospital-acquired initial infections, these figures were adjusted by an estimated proportion of hospitalized CDI cases that are community-acquired (19%)[46] and a rate of re-hospitalization of 7%.[41]

The number of cases were then distributed by disease severity, which was determined using the distribution that was reported by Louie et al.[111] Patients with severe CDI were categorized into those with uncomplicated and those with complicated disease cases. The proportion of complicated disease cases was estimated using the reported rates of CDI-related complications in Pépin et al.'s trial.[118] The distribution of disease severity by mild, moderate, severe without complications, and severe with complications was estimated to be 25%, 41%, 30.5%, and 3.5%, respectively. All-cause mortality was not included as a complication, and it was assumed that patients who would die as a direct result of their CDI-related complications would be included among the cases of severe and complicated CDI. The resulting estimates appear in Table 10.

At the national level, the (adjusted) rate of hospital-acquired initial CDI cases per 1,000 admissions was 4.0, with a range of 0.9 cases per 1,000 admissions in the territories, to 6.0 cases per 1,000 admissions in British Columbia.

Table 10: Annual Incidence of Hospital-acquired Initial CDI in Canadian Hospitals, 2008-2009							
Region	**All Admissions**	**Rate of Hospital-acquired Initial CDI per 1,000 Admissions**	**Cases by Disease Severity**				**Total Cases**
			Mild	**Moderate**	**Severe without Comp.**	**Severe with Comp.**	
NL	55,446	1.2	17	27	20	2	66
PE	15,914	1.2	5	8	6	1	19
NS	91,789	3.2	74	122	91	10	298
NB	93,173	2.4	56	91	68	8	223
QC	644,640	4.1	662	1,086	808	93	2,649
ON	1,085,025	4.4	1,192	1,955	1,455	167	4,769
MB	133,191	2.3	76	124	93	11	304
SK	135,710	1.8	60	99	74	8	241
AB	355,773	2.6	234	384	286	33	937
BC	409,143	6.0	617	1,011	752	86	2,466
Territories	11,128	0.9	2	4	3	0	10
Canada	**3,030,932**	**4.0**	**2,996**	**4,913**	**3,655**	**419**	**11,982**

AB = Alberta; BC = British Columbia; CDI = *Clostridium difficile* infection; comp = complications ; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

a) Outbreaks

National surveillance data[47] indicate that the rate of infection in Quebec hospitals reached 12.8 per 1,000 admissions in 2004-2005, with similar rates reported in 2003-2004.[136] Adjusting this rate for community-acquired cases and for readmissions results in a rate of 9.6 initial hospital-acquired cases per 1,000 hospital admissions. The potential population impact of similar outbreak rates of infection on each province and in the territories appears in Table 11.

Table 11: Estimated Annual Incidence of CDI in Canadian Hospitals, Assuming Outbreak Rate of Infection							
Region	**All Admissions**	**Rate of Hospital-acquired Initial CDI per 1,000 Admissions**	**Cases by Disease Severity**				**Total Cases**
			Mild	**Moderate**	**Severe without Comp.**	**Severe with Comp.**	
NL	55,446	9.6	134	219	163	19	535
PE	15,914	9.6	38	63	47	5	153
NS	91,789	9.6	221	363	270	31	885
NB	93,173	9.6	225	368	274	31	898
QC	644,640	9.6	1,554	2,548	1,895	218	6,214
ON	1,085,025	9.6	2,615	4,288	2,190	366	10,460
MB	133,191	9.6	321	526	392	45	1,284
SK	135,710	9.6	327	536	399	46	1,308
AB	355,773	9.6	857	1,406	1,046	120	3,430
BC	409,143	9.6	986	1,617	1,203	138	3,944
Territories	11,128	9.6	27	44	33	4	107
Canada	**3,030,932**	**9.6**	**7,305**	**11,979**	**8,912**	**1,023**	**29,218**

AB = Alberta; BC = British Columbia; CDI = *Clostridium difficile* infection; comp = complications ; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

These estimates did not assume higher rates of hospitalization due to concurrent outbreak in the community, and assumed the same distribution of disease severity. Although higher rates of all-cause mortality have been observed during outbreak periods, the rates of specific disease-related complications remain relatively constant.[118]

8.2 Budget Impact

The potential budget impact of treatment with vancomycin compared with metronidazole was considered for severe disease only. Current guidelines[16,19] do not recommend the use of vancomycin in initial episodes of moderate disease. Furthermore, the clinical review did not reveal any evidence to suggest a better efficacy of vancomycin in this patient population.

Although therapy for hospital-acquired CDI begins in hospital, a part of that therapy will occur in the community. As a result, this patient population will have an impact on two public budgets (hospitals and government-sponsored drug plans), and both these types of budgets are considered in this analysis. Because a recommended perspective for budget impact analyses is that of the budget holder,[137] an analysis from a hospital perspective also includes the impacts of the decision to use a treatment alternative on other hospital resources and on the overall budget. In this analysis, the decision to use vancomycin first line over metronidazole in severe CDI will have no impact on other hospital resouces in the base case, because it is assumed that there is no difference in complication rates between the two treatments. The base-case hospital budget impact represents a hospital's drug budget. However, the potential impacts on other hospital resources due to the differences in complication rates will be considered in the sensitivity analysis. Furthermore, it is acknowledged that some of the community drug expediture that is

estimated in this analysis may be borne by private payers. However, given that the average age of Canadian hospitalized patients with CDI is 70 years,[46] it is likely that most of the estimated community drug budget costs will be paid by public drug plans.

The population data on severe disease, with and without complications (Table 10), were used in the base-case analysis. The incremental costs of initially treating patients with severe disease with one oral vancomycin 125 mg capsule four times per day for 10 days compared with one oral metronidazole 500 mg capsule three times per day for 10 days were estimated. The treatment after relapse or failure was also considered and has been previously described in Section 7.1.9. Recurrences due to re-infection and the impacts were not considered in this analysis. Estimation of the portion of treatment that is covered in hospital budgets and in community drug budgets required information about length of stay, time to appearance of symptoms, and average time to first relapse. The length of stay data that were obtained from the Canadian Institute for Health Information's Discharge Abstract Database indicate that the mean lengths of stay in uncomplicated and complicated disease are 16.8 days and 29.1 days, respectively. An estimate of 11 days time to the appearance of CDI symptoms while in hospital was obtained from the literature.[47] The average time to first relapse that was obtained from the literature[8] was 14.5 days. Using this information, it was estimated that patients with uncomplicated disease would receive the first six days of therapy for an initial episode in hospital, and the remainder would be received in the community. The treatment of relapses would be received in the community, and the treatment after failures of therapy would be started in hospital and completed in the community. Patients with severe and complicated disease would receive the full course of therapy in hospital. The efficacy rates for metronidazole and vancomycin were assumed to be those reported by Louie et al.[111] The relapse and complication rates were the same as those that were used in the base case of the economic evaluation (Section 7.1.8). The drug costs were obtained from provincial formularies,[88,97,98] and a university hospital centre in Quebec (Section 7.1.9 and Appendix 15 Table 1).

The total and incremental costs of the treatment alternatives in hospital and community drug budgets appear in Table 12.

Table 12: Total and Incremental Annual Costs of First-line Therapy with Metronidazole or Vancomycin in Hospital and Community Drug Budgets, by Province						
Region	**Hospital Budget**			**Community Drug Budget**		
	First-line Metronidazole	**First-line Vancomycin**	**Increment**	**First-line Metronidazole**	**First-line Vancomycin**	**Increment**
NL	$555	$4,621	$4,065	$2,762	$4,966	$2,204
PE	$158	$1,313	$1,155	$785	$1,411	$626
NS	$2,493	$20,741	$18,248	$12,397	$22,292	$9,895
NB	$1,868	$15,543	$13,674	$9,290	$16,705	$7,415
QC	$22,191	$184,615	$162,424	$110,344	$198,418	$88,073
ON	$39,959	$332,435	$292,476	$196,697	$357,290	$158,593
MB	$2,544	$21,161	$18,618	$12,648	$22,743	$10,095
SK	$2,020	$16,803	$14,783	$10,043	$18,059	$8,016
AB	$7,852	$65,321	$57,470	$39,043	$70,205	$31,162
BC	$20,864	$171,915	$151,251	$102,754	$184,768	$82,014
Territories	$82	$683	$601	$408	$734	$326
Canada	**$100,393**	**$835,219**	**$734,826**	**$499,211**	**$897,665**	**$398,454**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

These data show that a larger proportion of annual incremental costs for using vancomycin as first-line therapy occur in hospital budgets ($734,826 in Canada). The annual incremental cost to community drug budgets at the national level was $398,454. The higher costs of vancomycin in community drug budgets were largely due to patients who were treated successfully with initial therapy and completed their prescription in the community.

Sensitivity analyses were done to consider the budget impact of using low-cost IV vancomycin during an outbreak of a hypervirulent strain (for example NAP1) and with differing complication rates.

The potential budget impact of using IV vancomycin (administered orally) as initial therapy was estimated (Table 13). This analysis assumes a similar efficacy of the capsule and IV formulation taken orally. This approach reduces the incremental cost to hospital budgets by $662,180 at the national level.

Table 13: Total and Incremental Annual Costs of First-line Therapy with Metronidazole or Vancomycin (with Intravenous Vancomycin Administered Orally In Hospital) in Hospital and Community Budgets, by Province

Region	Hospital Budget			Community Drug Budget		
	First-line Metronidazole	First-line Vancomycin	Increment	First-line Metronidazole	First-line Vancomycin	Increment
NL	$555	$957	$402	$2,762	$4,966	$2,204
PE	$158	$272	$114	$785	$1,411	$626
NS	$2,493	$4,297	$1,804	$12,397	$22,292	$9,895
NB	$1,868	$3,220	$1,352	$9,290	$16,705	$7,415
QC	$22,191	$38,248	$16,057	$110,344	$198,418	$88,073
ON	$39,959	$68,873	$28,915	$196,697	$357,290	$158,593
MB	$2,544	$4,384	$1,841	$12,648	$22,743	$10,095
SK	$2,020	$3,481	$1,461	$10,043	$18,059	$8,016
AB	$7,852	$13,533	$5,682	$39,043	$70,205	$31,162
BC	$20,864	$35,617	$14,953	$102,754	$184,768	$82,014
Territories	$82	$141	$59	$408	$734	$326
Canada	**$100,393**	**$173,039**	**$72,646**	**$499,211**	**$897,665**	**$398,454**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

The potential budget impact of first-line treatment of severe CDI with vancomycin during an outbreak of a hypervirulent strain of CDI was estimated. Population data from Table 11 were used. The estimation of outcomes for the NAP1 scenario was described in Section 7.1.8. The estimated impact to hospital budget and community drug budget with a NAP1 scenario appears in Table 14.

Table 14: Total and Incremental Annual Costs of First-line Therapy with Metronidazole or Vancomycin in Hospital and Community Budgets in an Outbreak Scenario, by Province

Region	Hospital Budget			Community Drug Budget		
	First-line Metronidazole	First-line Vancomycin	Increment	First-line Metronidazole	First-line Vancomycin	Increment
NL	$4,606	$36,495	$31,890	$35,546	$93,995	$58,449
PE	$1,322	$10,475	$9,153	$10,202	$96,978	$16,776
NS	$7,625	$60,417	$52,792	$58,846	$155,606	$96,761
NB	$7,740	$61,328	$53,588	$59,733	$157,953	$98,219
QC	$53,548	$424,312	$370,764	$413,278	$1,092,833	$679,555
ON	$90,130	$714,180	$624,050	$695,608	$1,839,401	$1,143,793
MB	$11,064	$87,668	$76,605	$85,389	$225,794	$140,405
SK	$11,273	$89,326	$78,053	$87,003	$230,064	$143,060
AB	$29,553	$234,175	$204,622	$228,086	$603,128	$375,043
BC	$33,986	$269,304	$235,318	$262,301	$693,604	$431,303
Territories	$924	$7,325	$6,400	$7,134	$18,865	$11,731
Canada	**$251,770**	**$1,995,005**	**$1,743,235**	**$1,934,126**	**$5,138,221**	**$3,195,095**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

The annual incremental budget impact of first-line treatment with vancomycin is $1.74 million at the national level in hospital budgets, with most of this higher marginal cost due to an increase in the volume of cases. The incremental budget impact of first-line treatment with vancomycin on community drug budgets is $3.20 million per year at the national level. The greater impact of first-line vancomycin on community drug budgets in this scenario was largely attributed to a larger proportion of those with uncomplicated treatment failures receiving higher doses of vancomycin in the community.

The potential budget impact of first-line therapy with vancomycin in severe CDI, assuming that treatment with vancomycin results in fewer complications, was also assessed. The assumptions in this scenario have been described in Sections 7.1.8 and 7.2.2. The results of this scenario appear in Table 15.

Table 15: Total and Incremental Annual Costs of First-line Therapy with Metronidazole or Vancomycin in Hospital and Community Budgets, Assuming Differing Complication Rates, by Province

Region	Hospital Budget			Community Drug Budget		
	First-line Metronidazole	First-line Vancomycin	Increment	First-line Metronidazole	First-line Vancomycin	Increment
NL	$616	$4,385	$3,769	$2,662	$6,605	$3,943
PE	$175	$1,246	$1,071	$756	$1,876	$1,120
NS	$2,764	$19,681	$16,918	$11,951	$29,648	$17,698
NB	$2,071	$14,749	$12,678	$8,955	$22,218	$13,262
QC	$24,599	$175,182	$150,584	$106,373	$263,899	$157,526
ON	$44,295	$315,450	$271,155	$191,545	$475,201	$283,656
MB	$2,820	$20,080	$17,260	$12,193	$30,249	$18,056
SK	$2,239	$15,944	$13,706	$9,682	$24,019	$14,337
AB	$8,704	$61,984	$53,280	$37,637	$93,374	$55,737
BC	$22,906	$163,131	$140,224	$99,055	$245,744	$146,689
Territories	$91	$648	$557	$393	$976	$582
Canada	**$111,287**	**$792,545**	**$681,258**	**$481,242**	**$1,193,909**	**$712,667**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NF = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

Compared with the base case where complications are assumed to be the same in the two treatment groups, this analysis shows lower incremental costs in hospital budgets after first-line therapy with vancomycin ($681,258 per year at the national level) and higher incremental costs in community drug budgets after first-line therapy with vancomycin ($712,667 per year at the national level). The higher costs to the community drug budgets were largely attributed to a lower complication rate among patients with treatment failure who were taking vancomycin. Thus, more patients with treatment failure were discharged into the community sooner and received therapy with vancomycin in capsule form in the community.

To consider the potential impact of first-line vancomycin treatment in severe CDI on the overall hospital budget, the potential savings from reductions in hospital stay were applied to the number of severe cases, with and without complications (Table 10). This was done for the scenario

where treatment with vancomycin would result in fewer complications (Table 9). The average reduction in hospitalization costs resulting from first-line treatment with vancomycin was estimated to be $2,253 per case. This incremental hospital cost corresponded to a difference of 1.15 days in average length of stay. The results of this analysis appear in Table 16.

Table 16: Annual Impact on Hospital Budgets of Lower Average Hospital Costs Due to First-line Therapy with Vancomycin

Region	Incremental Drug Costs to Hospital Budgets with First-line Vancomycin	Savings in Hospital Costs	Net Impact to Hospital Budgets with First-line Vancomycin
NL	$3,769	−$50,781	−$47,012
PE	$1,071	−$14,426	−$13,356
NS	$16,918	−$227,938	−$211,020
NB	$12,678	−$170,809	−$158,132
QC	$150,584	−$2,028,859	−$1,878,275
ON	$271,155	−$3,653,354	−$3,382,199
MB	$17,260	−$232,554	−$215,294
SK	$13,706	−$184,659	−$170,953
AB	$53,280	−$717,880	−$664,580
BC	$140,224	−$1,889,288	−$1,749,063
Territories	$557	−$7,502	−$6,945
Canada	**$681,258**	**−$9,178,797**	**−$8,497,539**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; QC = Quebec; SK = Saskatchewan; Territories = include Nunavut, Northwest Territories, and Yukon.

Decreased hospital costs that were attributed to fewer complications and shorter average length of stay among patients taking vancomycin first line resulted in net savings to hospital budgets ($8,497,539 per year at the national level).

8.3 Planning, Implementation, Utilization, and Legal or Regulatory Considerations

Vancomycin and metronidazole have been approved for use in Canada for years. Three RCTs that were included in our analysis were conducted in hospitalized patients. The formulary status of vancomycin and metronidazole is a consideration when hospitalized patients are discharged into the community. A review of formulary listings of vancomycin and metronidazole revealed no consensus on the reimbursement policies for vancomycin among publicly funded drug programs. The vancomycin capsule is a full benefit in four publicly funded drug programs. In other programs, the vancomycin capsule is of limited or restricted use, or is not covered. The listing of injectable vancomycin has full benefit coverage in seven jursidictions, has restricted use in two provinces, and has no coverage in three jurisdictions. Metronidazole 250 mg tablet (but not the 500 mg capsule) is a full benefit in all jurisdictions. Thus, a patient who received vancomycin while hospitalized may not have drug coverage when discharged in the community or may have reimbursement limited to metronidazole only. The ability to pay for antibiotic therapy may be a limiting factor in continuing vancomycin treatment in the community. In these

patients, it is unknown if switching from vancomycin to metronidazole has an impact on patient care and long-term outcomes such as recurrences.

The impact of our findings may be greater for health care institutions where cases of severe disease are diagnosed and treated. The base-case analysis shows that the incremental cost of using oral vancomycin is $232 per patient (95% CI, −$6,345 to $7,665). This translates to an incremental cost-effectiveness ratio of $1,161 per clinical cure. In sensitivity analyses, the incremental cost-effectiveness ratios vary from $135 per clinical cure (for generic IV vancomycin that is used by non-NAP1 patients) to $2,413 per clinical cure (for patients who are treated with oral vancomycin capsules and who are infected with the NAP1 strain). Sensitivity analyses that assumed fewer complications among patients treated with vancomycin first line found that this treatment option resulted in reduced health care costs.

9 DISCUSSION

C. difficile infection is the most common cause of nosocomial infectious diarrhea in adults. CDI rates have increased and the spread of a hypervirulent strain has caused outbreaks of the disease. Metronidazole and vancomycin have remained the two main alternatives to treat CDI. Traditionally, the use of vancomycin was reserved for cases of intolerance to or treatment failure with metronidazole because of its higher cost and concerns about the emergence of vancomycin-resistant enterococci. However, clinical practice has shifted toward using oral vancomycin in severe CDI. Therefore, this assessment was done to help guide the choice of therapy for CDI and to inform drug reimbursement policies in the Canadian publicly funded health care system.

9.1 Summary of Results

9.1.1 Clinical review

The goal of the clinical review was to compare vancomycin to metronidazole for the outcomes of cure, recurrences, complications, and serious adverse events (including all-cause mortality) in adults or children hospitalized or in the community, with an initial episode of moderate or severe CDI. The literature search was not limited by publication date. The original research protocol was followed, but in the search for systematic reviews, RCTs, and observational studies, no reports that met the eligibility criteria were retrieved. A decision was made to expand the population of interest to include patients with initial or recurrent episodes of moderate or severe CDI.

In adult patients with initial or recurrent episodes of severe CDI, vancomycin increased the cure rate by 27% in a RCT conducted before the epidemic.[109] Caution is needed in interpreting this finding because the dose of metronidazole was lower than that recommended in recent guidelines, and the analysis was not intention to treat. In one trial where a third of patients were infected with NAP1, the use of vancomycin increased cure rate by 31% compared with metronidazole in adult patients with initial or recurrent episodes of severe CDI.[111]

Based on one RCT, there was no difference in cure rate when comparing metronidazole and vancomycin in patients with initial or recurrent episodes of moderate CDI.[111]

Other outcomes were reported, but comparisons between vancomycin and metronidazole yielded inconclusive findings, or effect measures were not calculated because the number of events was too small for adequate comparisons.

It could not be determined if any of the trials included patients who were treated in the community.

One observational study[112] included adult patients and children aged three months to 13 years. However, a subgroup analysis of the pediatric patients was not performed.

The quality of the studies was assessed using the Downs and Black checklist.[103] One RCT met all but two quality criteria (external validity and selection bias). Patients in this study were administered a lower dose of metronidazole.[109] A quality assessment was not done for the other RCT because it was available as a conference poster.[111] None of the observational studies consistently met the quality criteria. In addition, the observational studies had insufficient power to detect a clinically important effect, and all effect measures were inconclusive.

9.1.2 Clinical practice guidelines

During a search for guidelines to inform clinical practice about the initial treatment of moderate to severe CDI in children and in adult patients, a 2009 document that was developed by ESCMID[19] and a 2010 publication by SHEA-IDSA[16] were found. The guidelines recommended oral vancomycin as the treatment of choice for severe initial episodes of CDI. Oral metronidazole was recommended for non-severe initial episodes. These evidence-based recommendations may be considered to be the new standard of care for the treatment of CDI.

9.1.3 Economic review

During the economic literature review, three economic assessments[115,116,127] of vancomycin compared to metronidazole in CDI were found. It could not be determined whether or not they met the inclusion criterion for an initial episode of moderate or severe CDI. The study quality could not be assessed in two studies that were reported in an abstract format.[116,127] The studies differed in the costs that were included in the analyses, and two studies[115,116] reported outcomes. Two studies were based on retrospectively analyzed data,[115,116] and the source data for the third study[116] was unspecified. The relevance of the three studies to a Canadian context in patient populations, health care resource use, and costs was limited.

9.1.4 Economic model

A primary economic analysis of vancomycin compared to metronidazole in patients with severe CDI was conducted using efficacy data from Louie et al.'s study.[111] It was assumed that there was no difference between vancomycin and metronidazole in the incidence of serious complications. In the economic evaluation, it was estimated that each additional clinical cure that

was attained through first-line vancomycin use would cost an additional $1,161 to the health care system.

Approximately a third of the population in Louie et al.'s trial[111] was infected with a NAP1 strain of *C. difficile.* The probabilistic sensitivity analysis of this model showed variability in incremental costs for treatment with vancomycin over metronidazole. This was largely due to the variability in hospital costs. In this base-case scenario, treatment with vancomycin was more costly than treatment with metronidazole in 60.1% of cases. Deterministic sensitivity analyses showed that the incremental cost per clinical cure increased as *C. difficile* strains became more virulent. This was largely due to high doses of vancomycin being prescribed to an increasing proportion of patients who were initially treated with vancomycin and whose treatment was failing.

Another sensitivity analysis suggested that treatment with a lower-cost generic IV vancomycin that was available to hospitals could decrease incremental cost-effectiveness ratios, assuming IV vancomycin used orally and vancomycin capsules have similar efficacy.

The possibility that clinical cure may lead to an earlier discharge from hospital was explored in the model, and the results suggested that a decrease of more than 0.6 days (range 0.5 days to 1.25 days, depending on the patient population) could make vancomycin less costly than metronidazole.

Finally, a sensitivity analysis that considered the possibility serious complications would occur in equal rates among those with treatment failures, and which estimated this rate to be approximately 30%, suggested that initial treatment with vancomycin resulted in net expenditure reductions to the health care system, largely because of savings in hospital costs. More analysis on the probability of complication in cases of treatment failure suggested that these cost reductions would be attained with a probability of as low as 10%.

The base-case findings depend on the assumption that the efficacy rates observed in Louie et al.'s trial[111] represent the treatment of initial occurences of severe CDI. The testing of this assumption found the results to be sensitive to higher efficacy rates with first-line metronidazole.

In probabilistic sensitivity analyses of this second model, it was estimated that initial treatment with vancomycin was more expensive than initial therapy with metronidazole in 31.1% of cases.

9.1.5 Health services impact

In the population impact analysis, it was estimated that almost 12,000 cases of initial hospital-acquired *C. difficile* infections occurred in Canada in 2008-2009, and 75% of these cases were moderate to severe. If we were to assume extreme rates of infection such as those seen in Quebec in 2004-2005, the number of total cases of CDI would be 29,218 in Canada.

The budget impact analysis compared the incremental costs of first-line vancomycin with those of first-line metronidazole in severe CDI. The probabilities of cure, relapse, failure, and complication, and subsequent drug therapy after these outcomes, were the same as those that were used in the base case of the economic evaluation. Hospital budgets and community drug

budgets were considered in this analysis. The results showed that annual incremental costs to hospital budgets were $734,826 at the national level, and annual incremental costs to community drug budgets were $398,454.

The use of lower-cost generic IV vancomycin in-hospital decreased annual incremental costs, to hospitals, to $72,646 at the national level.

In an outbreak scenario, the incremental costs to hospital budgets increase to $1.74 million per year, and those of community drug budgets increase to $3.2 million per year. The proportionally greater increase in community drug budgets is due to a greater number of those with uncomplicated treatment failures obtaining treatment in the community after hospital discharge.

The consideration of differing complication rates between treatment groups resulted in total incremental costs for first-line vancomycin use to hospital budgets of $681,258 per year, and incremental costs to community drug budgets of $712,667 per year. Compared with the base case, the increase in costs to the community drug budgets was largely attributed to lower complication rates among those with treatment failures in the vancomycin group, with more patients receiving subsequent therapy in the community. If vancomycin were to have an impact on complications in severe disease (compared with metronidazole), its use may result in annual net savings to hospital budgets of $8.5 million at the national level because of savings in hospital stays.

9.2 Strengths and Weaknesses of this Assessment

Our review is a comprehensive examination of clinical and economic studies that compared vancomycin and metronidazole in moderate or severe CDI, and includes a primary economic analysis. The methods were robust and met CADTH's standards for systematic reviews and economic analysis.

9.2.1 Clinical review

None of the clinical studies met the inclusion criteria that were set before the research was done. Limited data were available for inclusion in our systematic review. As a result, we decided to review all studies that compared vancomyin and metronidazole in patients with moderate or severe CDI. A meta-analysis could not be undertaken because of the heterogeneity of patient populations and outcomes. The strength of the conclusions of the systematic review depends on the quality of the primary literature, which had the following limitations:

- Two RCTs and one observational study that were used in our analysis were available in abstract or poster form only.
- The cure rates were derived from small sample sizes. The effect measures of other outcomes were not calculated because the number of events that occurred during treatment was too small for adequate comparisons or were not reported.
- The RCTs may have included a population with less chance of relapse and with complications compared to what is typical of clinical practice. The result may not be generalizable to a real-world setting.
- In the RCTs, the longest follow-up was one month.

- Two RCTs were stratified for disease severity. In one of these studies, a lower than recommended dose of metronidazole was used.
- One RCT was conducted during the epidemic, with approximately a third of the patients being infected with NAP1.
- No RCTs included children in the study population.
- Most of the observational studies were retrospective, and many included small sample sizes.
- Some observational studies lacked information about treatment dosing and duration, disease course and severity, and baseline risk factors.
- The definitions of disease severity and clinical outcomes differed among the included studies.
- Because strain typing was not done, it is unclear whether the recurrent episodes in the trials were due to relapse or reinfection.
- A meta-analysis was not done because the patient populations that were included in the studies were not clinically similar.

9.2.2 Primary economic analyses

The base-case economic evaluation was based on clinical data that included Canadian patients. The health care resources use and costs were obtained from Canadian sources. The models for all analyses were constructed in consultation with clinical experts, and the internal validation of models was conducted. Deterministic and probabilistic sensitivity analyses were done to explore alternative scenarios and assumptions, and to assess uncertainty in the models.

In the evaluation, death was not considered as an outcome. Death is an outcome in CDI, but the relative impact of vancomycin and metronidazole on this outcome is unclear. Any assumptions and estimations for a model in which mortality is considered would be complicated by the fact that published estimates of mortality in CDI are often all-cause. For these reasons, the authors of this report did not estimate the potential drug impacts on mortality in the sensitivity analyses.

The base-case analysis of the economic model was based on clinical data that included recurrent episodes. It was assumed that the observed clinical cure rates were for initial episodes. It is difficult to determine how clinical cure rates in Louie et al.'s trial[111] would have differed if all cases were first-time infections. However, analyses suggest that the base-case cost-effectiveness ratio is sensitive to higher efficacy rates with metronidazole.

The long-term health care costs of complications were not considered in this evaluation. The long-term health care utilization and costs in CDI are poorly documented. Quantifying these costs in elderly patients who are discharged to long-term care facilities with comorbid conditions also poses some difficulty. The omission of these costs would have little impact in the base-case analysis, where it was assumed that both treatment groups had an equal probability of serious complications. In the sensitivity analysis that considered the possibility of fewer complications among patients receiving first-line therapy with vancomycin, the inclusion of longer-term health care costs that are associated with complications would likely have been in favour of vancomycin.

The cost of some tests and examinations that were conducted in-hospital (for example, laboratory tests) may not be accounted for in the estimated hospital costs. This omission would likely lead

to an overestimate of the incremental cost of initial treatment with vancomycin. However, based on the observed impact of other tests and professional fees on incremental costs, the effect of such an omission is likely to be small.

Re-hospitalization due to relapse was not included in the evaluation. Re-hospitalization rates of 7% for diarrhea symptoms have been reported in Canadian data that were collected before the NAP1 outbreak.[41] However, we do not know how these readmissions are distributed between relapses versus re-infections, by disease severity, or by treatment, and they would be difficult to estimate.

The efficacy of metronidazole and vancomycin in a NAP1/BI/027 population was estimated by using data from two RCTs[109,111] that had some differences, including metronidazole dose and definition of clinical success. An assumption was made that the differences in efficacy seen in the two trials were mainly due to the presence of NAP1 infection in one trial. The resulting estimations were also based on a small sample size. Although the limitations with this approach are clear, these were the only available data for estimating the relative efficacy of metronidazole and vancomycin in a NAP1 population. The results of analyses that are conducted based on these estimations are to be considered with caution.

9.3 Generalizability of Findings

We did not find studies that were conducted only in children or in adults with an initial episode of CDI. Hence, the findings of the clinical and economic systematic reviews and economic analysis apply to hospitalized adult patients with initial or recurrent episodes of moderate or severe CDI. The generalizability of the results to other patient populations remains unknown.

9.4 Knowledge Gaps

Our systematic review showed that few studies addressed the relative effectiveness of vancomycin and metronidazole for CDI. The identified studies included mixed patient populations in terms of disease severity and recurrence. Larger studies are needed to compare the relative efficacy of vancomycin and metronidazole for key clinical outcomes in different patient populations.

Study power: Although a clinically and statistically significant difference in cure rate was seen in two RCTs for patients with severe CDI, conclusions could not be made for other outcomes because of small sample sizes and small number of events that were reported in the included studies.

Disease severity: The included studies had different definitions of moderate or severe disease. This may be due to the fact that there is no validated prognostic instrument to define disease severity. Research is needed to develop consistent and uniform definitions to be used in future studies.

Initial CDI compared to recurrent CDI: Would patients with an initial episode of CDI have higher cure rates than patients with a recurrence? Would one of the two drugs under review

perform better in a patient population that only included initial episodes of CDI? Research is needed to determine the relative effectiveness of vancomycin and metronidazole for patients with an initial episode of CDI. Approximately 70% of patients in Louie et al.'s trial[111] were experiencing an initial episode of CDI, and 30% of patients had a recurrence. Although our results showed that patients with severe disease had a higher treatment cure rate with vancomycin than metronidazole, it is unclear if these results apply to patients with a first episode of CDI.

Adults compared to children: The RCTs that were retrieved in this systematic review included adult patients only. Trials that include children are needed to determine the relative effectiveness of vancomycin and metronidazole in this population.

Patients treated in the community compared to patients treated in hospital: Research is needed to determine the relative effectiveness of vancomycin and metronidazole in community patients. Studies have focused on hospitalized patients who may have been sicker because of characteristics such as advanced age and comorbidities, and the results may not be generalizable to patients who are treated in the community.

Patients with NAP1 strain compared to non-NAP1: The RCTs did not identify the infecting strain of *C. difficile*. One observational study suggested that the superiority of vancomycin over metronidazole for the prevention of CDI-related complications was lost during the epidemic.[118] Research is needed to determine the relative effectiveness of vancomycin and metronidazole in different *C. difficile* strains, including NAP1, and during outbreaks.

Outcomes: Studies have included rates of cure and recurrence. It was impossible to determine whether recurrences were due to a relapse or to a re-infection. Cure and recurrence definitions were not uniform across studies. The relative effectiveness of vancomycin and metronidazole for preventing complications, serious adverse events, and mortality remains unclear.

Length of treatment: Prospective RCTs compared treatment regimens that were administered for 10 days. Some patients may respond slowly and need a longer course of treatment such as 14 days, as recommended in the SHEA-IDSA guidelines. Research is needed to determine if length of treatment has an impact on outcomes.

10 CONCLUSIONS

A health technology assessment was conducted to determine the relative clinical effectiveness and cost-effectiveness of vancomycin and metronidazole in children or adults with an initial episode of moderate or severe CDI. Given the evidence that was retrieved, we could not answer all the initial research questions because the studies included patients with initial or recurrent episodes of CDI, or did not separate the data according to disease severity. The review was expanded to include patients with initial or recurrent episodes of moderate or severe CDI.

In our clinical review, we could only determine the cure rates of metronidazole and vancomycin in groups of patients with moderate or severe CDI. Conclusions could not be made for other

outcomes (for example, the relative effectiveness of the two antibiotics on complications and mortality) or for other populations (for example, for patients with initial CDI only, for children, or for patients in the community).

We found higher cure rates with vancomycin compared to metronidazole in adult patients with initial or recurrent severe CDI. This finding was based on groups of 69 patients and 90 patients from two RCTs. For moderate CDI, metronidazole and vancomycin had similar cure rates. The non-validation of severity criteria makes it difficult to draw definite conclusions and formulate recommendations.

Our clinical findings are congruent with the recommendations that are included in two sets of international guidelines except on one point. The guidelines recommended the use of vancomycin in patients with an initial episode of severe CDI, yet this recommendation is based on studies that included patients with initial or recurrent disease.

Unanswered questions remain on the relative effectiveness of using metronidazole and vancomycin in patients with an initial episode of CDI, in children, among patients in the community, and in patients infected with NAP1; and on the rates of complications, serious adverse events, and mortality after using either antibiotic.

Given the limitations in the clinical data and with the absence of evidence on complication rates, the primary economic analysis suggests that the incremental health care cost for each additional clinical cure after first-line use of vancomycin over metronidazole is $1,161. The incremental costs may increase as *C. difficile* strains increase in virulence. The use of orally administered generic IV vancomycin in hospital decreases overall health care costs assuming an efficacy that is similar to that of vancomycin capsules. If we assume that complications occur among those with treatment failures, complication rates as small as 10% among these patients may result in cost savings with the first-line use of vancomycin because of savings in hospital costs.

Approximately 12,000 Canadian patients acquired a new CDI in hospital, in fiscal year 2008-2009, and an estimated 75% of these infections were moderate to severe. In an extreme outbreak scenario, this number could increase to 29,000 cases per year. The incremental cost of first-line treatment of CDI with vancomycin compared to metronidazole is $1.13 million per year at the national level, with 65% of these marginal costs paid for from hospital drug budgets. The total and marginal costs for hospital and community drug budgets increase as the *C. difficile* strain becomes more virulent and treatments become less effective, with more patients needing additional and more costly drug therapy. If complication rates are different in both treatment groups and are related to treatment failure, the use of vancomycin as first-line therapy may result in cost reductions for overall hospital budgets because of decreased hospitalization costs.

In conclusion, the use of metronidazole or vancomycin produces a similar clinical cure rate in patients with initial or recurrent moderate CDI. A higher clinical cure rate is reported with vancomycin in patients with initial or recurrent severe CDI. The use of oral vancomycin by patients with severe disease will incur an incremental cost of $1,161 per clinical cure. However, this cost-effectiveness ratio may be lower if generic IV vancomycin is used in hospitals ($346 per clinical cure), and the use of vancomycin may result in net health expenditure reductions if it

has an impact on complication rates and reduces hospitalization costs. These findings are to be interpreted in consideration of the study limitations and the assumptions that are made in the primary economic model.

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APPENDIX 1: AVAILABILITY OF PRODUCTS IN CANADA

Table 1: Metronidazole[138]		
Product name	**DIN**	**Manufacturer**
Apo-Metronidazole tablet 250 mg	00545066	Apotex Incorporated
Apo-Metronidazole capsule 500 mg	02248562	
Flagyl capsule 500 mg	01926853	Sanofi-Aventis Canada Inc.
Florazole ER 750 mg extended-release tablet	02244405	Ferring Inc.
Metronidazole 5 mg/mL solution for injection	00870420	Baxter Corporation
Metronidazole 5 mg/mL solution for injection	00649074	Hospira Healthcare Corporation
Metronidazole tablet 250 mg	00420409	Pro Doc Limitée
Novo-Nidazol tablet 250 mg	00021555	Novopharm Limited
PMS-Metronidazole tablet 250 mg	00584339	Pharmascience Inc.
PMS- Metronidazole tablet 500 mg	00783137	

Table 2: Vancomycin[138]		
Product Name	**DIN**	**Manufacturer**
PMS-Vancomycin 1 g powder for injectable solution	02241821	Pharmascience Inc
PMS-Vancomycin 500 mg powder for injectable solution	02241820	
Sterile Vancomycin 500 mg powder for injectable solution	02139375	Pharmaceutical Partners of Canada, Inc.
Sterile Vancomycin 1 g powder for injectable solution	02139383	
Sterile Vancomycin 5 g powder for injectable solution	02139243	
Sterile Vancomycin 10 g powder for injectable solution	02241807	
Sterile Vancomycin 1 g powder for injectable solution	02230192	Hospira Healthcare Corporation
Sterile Vancomycin 500 mg powder for injectable solution	02230191	
Vancocin capsule 250 mg	00788716	Iroko International LP
Vancocin capsule 125 mg	00800430	

APPENDIX 2: SEARCH STRATEGIES

OVERVIEW	
Interface:	Ovid
Databases:	BIOSIS Previews <1989 to 2009 Week 46 > EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2009 > EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009 > EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2009 > EBM Reviews - Health Technology Assessment <4th Quarter 2009 > EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2009 > EMBASE <1980 to 2009 Week 43 > Ovid MEDLINE(R) <1950 to October Week 3 2009 > Ovid MEDLINE(R) <In-Process & Other Non-Indexed Citations (October 27, 2009)> **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 28, 2009
Alerts:	Monthly search updates began October 28, 2009 and were run until the publication of the final report.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; epidemiologic studies; prospective studies, retrospective studies, also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	Publication years – no date limits; English or French language only

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.mp	Mapped word
.jw	Journal word

MULTI-DATABASE STRATEGY	
Line #	**Searches**
	Clostridium Difficile Concept
1	Clostridium difficile/
2	(clostrid* adj2 difficil*).ti,ab.
3	(bacillus difficilis or "c. diff" or "c.diff" or "c diff" or "c. difficil*" or "c.difficil*" or "c difficil*" or "CDF/cdf" or CDAD).ti,ab.
4	or/1-3
	Vancomycin Concept
5	Vancomycin/
6	1404-90-6.rn.
7	(vancomycin* or vancomicin* or Diatracin or vanco azupharma or VANCO-cell or Vanco-saar or Vancocin* or Vancocine or Vancomicina Chiesi).ti,ab.
8	(Fabomicina or icoplax or rivervan or vancomax or vancotenk or varedet or vancoled or biovancomin or vanclomin or lyphocin).ti,ab.
	Metronidazole Conept
9	Metronidazole/
10	443-48-1.rn.
11	(metronidazol* or 2-Methyl-5-nitroimidazole-1-ethanol or Satric or Trichazol or Clont or Danizol or Flagyl or Gineflavir or Metric or Metrodzhil or Metrogel or Metrogyl or Trichopol or Trivazol or Vagilen or Bayer 5360).ti,ab.
12	(Florazole or metrocream or nidagel or noritate or novo-nidazol or trikacide or metronide or rozex or elyzol or flagyl or rosiced or rozacreme or rozagel or acea or anabact or metrolyl or metrosa or metrotop or metrozol or noritate or norzol or vaginyl or zadstat or zidoval or zyomet or metro).ti,ab.
13	or/5-12
14	4 and 13
	Meta-analysis/Systematic Review/Health Technology Assessment Filter
15	meta-analysis.pt.
16	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
17	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.

18	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
19	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
20	(data synthes* or data extraction* or data abstraction*).ti,ab.
21	(handsearch* or hand search*).ti,ab.
22	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
23	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
24	(meta regression* or metaregression* or mega regression*).ti,ab.
25	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
26	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
27	(cochrane or health technology assessment or evidence report).jw.
28	or/15-27
	Randomized Controlled Trial/Controlled Clinical Trial Filter
29	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
30	Randomized Controlled Trial/
31	Randomized Controlled Trials as Topic/
32	Controlled Clinical Trial/
33	Controlled Clinical Trials as Topic/
34	Randomization/
35	Random Allocation/
36	Double-Blind Method/
37	Double Blind Procedure/
38	Double-Blind Studies/
39	Single-Blind Method/
40	Single Blind Procedure/
41	Single-Blind Studies/
42	Placebos/
43	Placebo/

44	Control Groups/
45	Control Group/
46	(random* or sham or placebo*).ti,ab,hw.
47	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
48	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
49	(control* adj3 (study or studies or trial*)).ti,ab,hw.
50	(Nonrandom* or non random* or non-random* or quasi-random*).ti,ab,hw.
51	(allocated adj1 to).ti,ab,hw.
52	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
53	or/29-52
	Observational Studies Filter
54	epidemiologic methods.sh.
55	epidemiologic studies.sh.
56	cohort studies/
57	cohort analysis/
58	longitudinal studies/
59	longitudinal study/
60	prospective studies/
61	prospective study/
62	follow-up studies/
63	follow up/
64	followup studies/
65	retrospective studies/
66	retrospective study/
67	case-control studies/
68	exp case control study/
69	cross-sectional study/
70	observational study/

71	quasi experimental study/
72	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
73	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.
74	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab,hw.
75	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,hw.
76	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab,hw.
77	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab,hw.
78	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
79	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
80	(population adj3 (study or studies or analysis or analyses)).ti,ab.
81	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
82	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
83	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,hw.
84	((natural adj experiment) or (natural adj experiments)).ti,ab,hw.
85	(quasi adj (experiment or experiments or experimental)).ti,ab,hw.
86	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,hw.
87	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,hw.
88	or/54-87
	Clinical Search Results
89	or/28,53,88
90	14 and 89
91	14 use cctr,coch,clhta,dare
92	90 or 91
93	limit 92 to (english or french) [Limit not valid in DARE,CLEED,CCTR,CDSR; records were retained]
94	remove duplicates from 93
	Economic Filter
95	*Economics/

96	*Economics, Medical/
97	*Economics, Pharmaceutical/
98	exp "Costs and Cost Analysis"/
99	exp Health Care Costs/
100	exp decision support techniques/
101	exp models, economic/
102	markov chains.sh.
103	monte carlo method.sh.
104	uncertainty.sh.
105	quality of life.sh.
106	quality-adjusted life years.sh.
107	exp health economics/
108	exp economic evaluation/
109	exp pharmacoeconomics/
110	exp economic aspect/
111	quality adjusted life year/
112	quality of life/
113	exp "costs and cost analyses"/
114	(economic impact or economic value or pharmacoeconomics or health care cost or economic factors or cost analysis or economic analysis or cost or cost-effectiveness or cost effectiveness or costs or health care cost or cost savings or cost-benefit analysis or hospital costs or medical costs or quality-of-life).sh.
115	(economy* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).ti,ab.
116	(cost* adj1 (util* or effective* or efficacy* or benefit* or consequence* or analy* or minimi* or saving* or breakdown or lowering or estimate* or variable* or allocation or control or illness or sharing or life or lives or affordabl* or instrument* or technolog* or day* or fee or fees or charge or charges)).ti,ab.
117	(decision adj1 (tree* or analy* or model*)).ti,ab.
118	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).ti,ab.

119	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.
120	(sensitivity analys?s or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).ti,ab.
121	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).ti,ab.
122	(decision adj1 (tree* or analy* or model*)).ti,ab.
123	or/95-122
	Economic Search Results
124	14 and 123
125	14 use cleed
126	124 or 125
127	limit 126 to (english or french) [Limit not valid in DARE,CLEED,CCTR,CDSR; records were retained]
128	remove duplicates from 127
	Guideline Filter
129	Guidelines as topic/
130	Guideline/
131	Practice guideline/
132	exp Consensus Development Conference/
133	Consensus Development.sh.
134	Health Planning Guidelines/
135	Practice Guidelines as Topic/
136	Clinical Protocols/
137	(Guideline or Practice Guideline or Consensus Development Conference).pt.
138	Standards.fs.
139	Clinical Protocol/
140	(guideline* or standards or best practice).ti.
141	(expert consensus or consensus statement or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).ti,ab.
142	or/129-141

	Guideline Search Results
143	4 and 142
144	limit 143 to (english or french) [Limit not valid in DARE,CLEED,CCTR,CDSR; records were retained]
145	remove duplicates from 144

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Health Economic Evaluations Database (HEED)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for HEED database.

GREY LITERATURE	
Dates for Search:	November 2009 [limited update: August 2010]
Keywords:	clostridium difficile, c difficile, c. difficile, c.difficile, c diff, c. diff, c.diff, vancomycin, metronidazole
Limits:	English or French language. Conferences: publication date 2007-2009 (if available)

NOTE: This section lists the main agencies, organizations, and websites searched**; it is not a complete list.** For a complete list of sources searched, contact CADTH (http://www.cadth.ca).

Health Technology Assessment Agencies

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec
http://www.aetmis.gouv.qc.ca

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Centre for Evaluation of Medicines. Father Sean O'Sullivan Research Centre,
St.Joseph's Healthcare, Hamilton, and McMaster University, Faculty of Health Sciences. Hamilton, Ontario
http://www.thecem.net/

Centre for Health Services and Policy Research, University of British Columbia
http://www.chspr.ubc.ca/cgi-bin/pub

Health Quality Council. Saskatchewan.
http://www.hqc.sk.ca/

Institute for Clinical Evaluative Sciences (ICES). Ontario
http://www.ices.on.ca/

Institute of Health Economics (IHE). Alberta
http://www.ihe.ca/

Manitoba Centre for Health Policy (MCHP)
http://umanitoba.ca/medicine/units/mchp/

Ontario Ministry of Health and Long Term Care. Health Technology Analyses and Recommendations
http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas_mn.html

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/

Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia
http://www.ti.ubc.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network for Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

WHO Health Evidence Network
http://www.euro.who.int/HEN

NPS RADAR (National Prescribing Service Ltd.)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

Institute of Technology Assessment (ITA)
http://www.oeaw.ac.at/ita/welcome.htm

Federal Kenniscentrum voor de Gezendheidszorg
http://www.kenniscentrum.fgov.be

Danish Centre for Evaluation and Health Technology Assessment (DCEHTA). National Board of Health
http://www.dihta.dk/

Finnish Office for Health Care Technology and Assessment (FinOHTA). National Research and Development Centre for Welfare and Health
http://finohta.stakes.fi/EN/index.htm

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)
http://cedit.aphp.fr/english/index_present.html

German Institute for Medical Documentation and Information (DIMDI). Federal Ministry of Health
http://www.dimdi.de/dynamic/en/hta/db/index.htm

Norwegian Knowledge Centre for the Health Services (NOKC)
http://www.kunnskapssenteret.no/

Catalan Agency for Health Technology Assessment and Research (CAHTA)
http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

Swedish Council on Technology Assessment in Health Care (SBU)
http://www.sbu.se/en/

Swiss Network for Health Technology Assessment
http://www.snhta.ch/

European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre
http://www.euroscan.bham.ac.uk

National Horizon Scanning Centre (NHSC)
http://www.pcpoh.bham.ac.uk/publichealth/horizon

NIHR Health Technology Assessment programme, Coordinating Centre for Health Technology Assessment (NCCHTA)
http://www.hta.ac.uk/

NHS National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk

NHS Quality Improvement Scotland
http://www.nhshealthquality.org

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

Health Service Executive
http://www.hse.ie/eng/

Dept. of Veterans Affairs Research & Development
http://www.research.va.gov/resources/pubs/default.cfm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

Institute for Clinical Systems Improvement
http://www.icsi.org/index.asp

Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC)
http://www.bcbs.com/blueresources/tec/

University HealthSystem Consortium (UHC)
http://www.uhc.edu/

Health Economics

Centre for Health Economics and Policy Analysis (CHEPA). Dept. of Clinical Epidemiology and Biostatistics. Faculty of Health Sciences. McMaster University, Canada
http://www.chepa.org

Health Economics Research Group (HERG). Brunel University, U.K.
http://www.brunel.ac.uk/about/acad/herg

Health Economics Research Unit (HERU). University of Aberdeen
http://www.abdn.ac.uk/heru/

The Hospital for Sick Children (Toronto). PEDE Database
http://pede.ccb.sickkids.ca/pede/search.jsp

University of Connecticut. Department of Economics. RePEc database
http://ideas.repec.org

Clinical Trials

U.S. National Institutes of Health. Clinical Trials Database
http://clinicaltrials.gov/

World Health Organization. International clinical trials registry search portal (ICTRP)
http://www.who.int/trialsearch/

UK Clinical Research Network . NIHR Clinical Research Network (UKCRN)
http://www.ukcrc-ctu.org.uk/resourcefinder/Pages/DetailedSearch.aspx

Conferences and Meetings

49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2009)
http://www.icaac.org/index.php?option=com_content&view=category&id=49&Itemid=95

47th Annual Meeting of the Infectious Diseases Society of America (IDSA 2009)
http://www.idsociety.org/IDSA2009.htm

48th Annual ICAAC/IDSA 46th Annual Meeting. A Joint Meeting of the American Society for Microbiology and the Infectious Diseases Society of America. October 25 - 28, 2008; Washington, DC (ICAAC/IDSA 2008)

19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2009)
http://www.congrex.ch/ECCMID2009/

18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2008)
http://www.congrex.ch/eccmid2008/

Second International Clostridium difficile Symposium (2007) http://www.clostridia.net/IcdsAbstract%20Book.pdf

Organizations
Society for Healthcare Epidemiology of America (SHEA)
http://www.shea-online.org

Infectious Diseases Society of America (IDSA)
http://www.idsociety.org

Search Engines

Google
http://www.google.ca/

Bing
http://www.bing.com

APPENDIX 3: DATA EXTRACTION FORM FOR CLINICAL STUDIES

Date	**Reviewer initials**
Study	
First author, year, publication type	
Study characteristics	
Population	
Geographic location	
Number of Centres	
Time period	
Setting *(for example, hospital-based, clinic-based, community-based, referral criteria/process, other)*	
Declared conflict of interest of one or more author or investigator	
Source(s) of funding	
Design *(RCT, CCT, controlled observational study)*	
Inclusion criteria	
Exclusion criteria	
Duration of follow-up	
Sampling method *(cohort studies only)*	
Method used to collect or report adverse event data	
C.Difficile Strain(s) *(if available)* (proportion NAP1)	

Intervention, Comparator	**vancomycin**	**metronidazole**	**Other**
Dose*(*s) Route of administration Duration of treatment			
Co-interventions for treatment of CDI *(frequency, dose)*			
Other treatments including patients continuing antibiotics for other indications *(frequency, dose)*			
Other *(specify)*			

Definitions	
Primary outcomes	
Secondary outcomes	
CDI diagnostic criteria	
Disease severity	
Treatment cure	
Treatment failure	
Relapse	
Treatment intolerance	
Treatment compliance	

Baseline Characteristics	**vancomycin**	**metronidazole**	**other**	**Total, all groups**
Age *(years) mean, SD*				
Gender *(male) n, %*				
Number who received previous antibiotic therapy *(n, %)*				
Disease course *(initial, recurrent) (n, %)*				
Disease severity *(mild, moderate, or severe) (n, %)*				
Number with colonic evidence of pseudomembranous colitis *(n, %)*				
Number of bowel movements *(mean, SD)*				
Other relevant patient characteristics *(specify)*				
Study Population	**vancomycin**	**metronidazole**	**other**	**Total, all groups**
Number of patients assessed				
Number randomized				
Number included in ITT analysis				
Number included in per-protocol analysis				
Number of withdrawals and reason				

Outcomes				
Please extract data for all outcomes including sample size, point and variance estimates, units of measure, and p-values for comparisons across groups				
Outcomes*	**Timing of assessment**	**vancomycin n=**	**metronidazole n=**	**other n=**
Number of treatment cures *(n, %)*				
Time to resolution of diarrhea *(days) mean, SD*				
Number of relapses *(n, %)*				
Number developing serious complications *(e.g. pseudomembranous colitis, toxic megacolon, septic shock, bowel perforation) (n, %)*				
Number requiring emergent colectomy *(n, %)*				
Number of deaths *(n, %)*				
Number of patients with AE				
Number of patients with SAE				
Number of SAE				
HRQL measure (specify)				
Length of hospital stay *(days)* †				
Length of ICU stay *(days)* †				

*report drug, dose, and total number of patients per group. If number of patients with data for a specific outcome is different from the sample size, indicate total number with each outcome measure.
†specify mean, median, IQR, range, SD, SE

APPENDIX 4: QUALITY ASSESSMENT INSTRUMENTS FOR CLINICAL STUDIES

4.1 Quality assessment form for systematic reviews, Oxman and Guyatt Scale[102]

1. Were the search methods that were used to find evidence (original research) on the primary question (s) stated?

- ☐ yes
- ☐ partially
- ☐ no

2. Was the search for evidence reasonably comprehensive?

- ☐ yes
- ☐ can't tell
- ☐ no

3. Were the criteria that were used for deciding which studies to include in the overview reported?

- ☐ yes
- ☐ partially
- ☐ no

4. Was bias in the selection of studies avoided?

- ☐ yes
- ☐ can't tell
- ☐ no

5. Were the criteria that were used for assessing the validity of the included studies reported?

- ☐ yes
- ☐ partially
- ☐ no

6. Was the validity of all studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?

- ☐ yes
- ☐ can't tell
- ☐ no

7. Were the methods that were used to combine the findings of the relevant studies (to reach a conclusion) reported?

- ☐ yes
- ☐ partially
- ☐ no

8. Were the findings of the relevant studies combined appropriately relative to the primary question that the overview addresses?

- ☐ yes
- ☐ can't tell
- ☐ no

For question 8, if no attempt was made to combine findings, and no statement is made about the inappropriateness of combining findings, check "no". If a summary (general) estimate is given in the abstract, the discussion, or the summary of the paper, and it is not reported how the estimate was derived, mark "no" even if there is a statement about the limitations of combining the findings of the studies that are reviewed. If in doubt mark "can't tell".

9. Were the conclusions made by the author(s) supported by the data or analysis that was reported in the overview?

☐ yes
☐ partially
☐ no

For an overview to be scored as "yes" on question 9, data (not just citations) must be reported to support the main conclusions about the primary questions (s) that the overview addresses.

10. How would you rate the scientific quality of the overview?

Extensive Flaws		Major Flaws		Minor Flaws		Minimal Flaws
☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7

The score for question 10, the overall scientific quality, is based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score. If the "can't tell" option is used one or more times on the preceding questions, a review is likely to have minor flaws at best, and it is difficult to rule out major flaws (a score of 4 or lower). If the "no" option is used on question 2, 4, 6, or 8, the review is likely to have major flaws (a score of 3 or less, depending on the number and degree of the flaws).

4.2 Quality assessment form for randomized controlled trials and observational studies, Downs and Black Checklist[103]

Criteria	Yes	No	Unable to determine	Comments
Reporting				
1. Is hypothesis, aim, or objective of study clearly described?				
2. Are main outcomes to be measured clearly described in Introduction or Methods?				
3. Are characteristics of patients included in study clearly described?				
4. Are interventions of interest clearly described?				
5. Are distributions of principal confounders in each group of patients to be compared clearly described?				
6. Are main findings of the clearly described?				
7. Does study provide estimates of random variability in data for main outcomes?				

8. Have all important adverse events that may be a consequence of intervention been reported?				
9. Have characteristics of patients lost to follow-up been described?				
10. Have actual probability values been reported (e.g. 0.035 instead of <0.05) for main outcomes except where probability value <0.001?				
External validity				
11. Were patients asked to participate in study representative of entire population from which they were recruited?				
12. Were those patients who were prepared to participate representative of entire population from which they were recruited?				
13. Were staff, places and facilities where patients were treated, representative of treatment majority of patients receive?				
Internal validity-bias				
14. Was an attempt made to blind study patients to intervention they have received?				
15. Was an attempt made to blind those measuring main outcomes of intervention?				
16. If any results of study were based on "data dredging", was this made clear?				
17. In trials and cohort studies, do analyses adjust for different lengths of follow-up of patients, or in case-control studies, is period between intervention and outcome same for cases and controls?				
18. Were statistical tests used to assess main outcomes appropriate?				
19. Was compliance with intervention(s) reliable?				
20. Were main outcome measures used accurate (valid and reliable)?				
Internal validity-confounding (selection bias)				
21. Were patients in different intervention groups (trials and cohort studies) or were cases and controls (case-control studies) recruited from same population?				
22. Were study patients in different intervention groups (trials and cohort studies) or were cases and controls (case-control studies) recruited over same period?				
23. Were study patients randomized to				

intervention groups?				
24. Was randomized intervention assignment concealed from patients and health care staff until recruitment was complete and irrevocable?				
25. Was there adequate adjustment for confounding in the analysis from which main findings were drawn?				
26. Were losses of patients to follow-up taken into account?				
Power				
27. Did study have sufficient power to detect a clinically important effect where probability value for a difference being due to chance is <5%?				

4.3 Summary of AGREE instrument[104]

Domain	Description
Scope and purpose	Focuses on overall aim of guideline, specific clinical questions, and target patient population.
Stakeholder involvement	Focuses on extent to which guideline represents views of its intended users. Guideline development involves all stakeholders whose activities are likely to be covered in proposed guideline. This also includes patient groups.
Rigour of development	Relates to process used to collect and synthesise evidence, methods to formulate recommendations and to update guideline. Includes information about literature searches, criteria used to select evidence, and methods used to formulate recommendations. Recommendations explicitly linked to supporting evidence. Guideline reviewed externally before publication and contains a clear statement about procedure for updating.
Clarity and presentation	Deals with language and format of guidelines. Because main role of guidelines is to help clinicians and patients make better decisions, busy clinicians need simple, patient-specific, user-friendly guidelines that are easy to understand. A good guideline presents clear information about management options available and likely consequences of each.
Applicability	Pertains to likely organizational and cost implications of applying guideline. Guidelines should be feasible to use in current organization of care and must fit in routine practice and time constraints of jobs. In addition, review criteria should be derived from key recommendations.
Editorial independence	Focuses on independence of recommendations and acknowledgement of possible conflict of interest from guidelines development group. Increasing number of guidelines are funded, directly or indirectly, by external funding. Those who fund guidelines may have a vested interest. There is an explicit statement that views or interests of funding body have not influenced final recommendations.

APPENDIX 5: EXCLUDED CLINICAL STUDIES

Excluded based on study design

Bartlett JG. Treatment of Clostridium difficile colitis. Gastroenterology. 1985 Nov;89(5):1192-5.

Bishara J, Wattad M, Paul M. Vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea [letter]. Clin Infect Dis [Internet]. 2007 Dec 15 [cited 2009 Mar 2];45(12):1646-7. Available from: http://www.journals.uchicago.edu/doi/pdf/10.1086/523719?cookieSet=1

Butterworth SA, Koppert E, Clarke A, Wiggs B, MacFarlane JK. Recent trends in diagnosis and treatment of Clostridium difficile in a tertiary care facility. Am J Surg. 1998 May;175(5):403-7.

Chevrel B. The treatment of pseudomembranous colitis. The effect of vancomycin on Clostridium difficile. Med Chir Dig. 1991;20(2):121-8.

Fraisse A, Croix C, Maniere D, Pfitzenmeyer P. Diarrhee a Clostridium difficile chez le sujet tres age: Particularites cliniques et evolutives de 21 cas. Presse Medicale. 1999;28(32):1748-52.

Goldstein EJ, Polonsky J, Touzani M, Citron DM. C. difficile infection (CDI) in a long-term acute care facility (LTAC). Anaerobe. 2009 Dec;15(6):241-3.

Hu MY, Katchar K, Kyne L, Maroo S, Tummala S, Dreisbach V, et al. Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent Clostridium difficile Infection. Gastroenterology. 2009;136(4):1206-14.

Huggan PJ, Murdoch DR. Vancomycin therapy for severe Clostridium difficile-associated diarrhea [letter]. Clin Infect Dis [Internet]. 2007 Dec 15 [cited 2009 Mar 2];45(12):1647-8. Available from: http://www.journals.uchicago.edu/doi/pdf/10.1086/523719?cookieSet=1

Johnson S, Peterson LR, Gerding DN. Intravenous metronidazole and Clostridium difficile-associated diarrhea or colitis. J Infect Dis. 1989 Dec;160(6):1087-8.

Keven K, Basu A, Re L, Tan H, Marcos A, Fung JJ, et al. Clostridium difficile colitis in patients after kidney and pancreas-kidney transplantation. Transpl Infect Dis. 2004;6(1):10-4.

Lawrence SJ, Dubberke ER, Johnson S, Gerding DN. Clostridium difficile-associated disease treatment response depends on definition of cure [letter]. Clin Infect Dis. 2007 Dec 15;45(12):1648-51.

McFarland LV. Update on the changing epidemiology of Clostridium difficile-associated disease. Nat Clin Pract Gastroenterol Hepatol. 2008 Jan;5(1):40-8.

Nair S, Yadav D, Corpuz M, Pitchumoni CS. Clostridium difficile colitis: factors influencing treatment failure and relapse--a prospective evaluation. Am J Gastroenterol. 1998 Oct;93(10):1873-6.

Pepin J. Vancomycin for the treatment of Clostridium difficile infection: for whom is this expensive bullet really magic? Clin Infect Dis. 2008 May 15;46(10):1493-8.

Pupaibool J, Khantipong M, Suankratay C. A study of Clostridium difficile-associated disease at King Chulalongkorn Memorial Hospital, Thailand. J Med Assoc Thai. 2008 Jan;91(1):37-43.

Riley TV, Cooper M, Bell B, Golledge CL. Community-acquired Clostridium difficile-associated diarrhea. Clin Infect Dis. 1995 Jun;20 Suppl 2:S263-5.

Rosenberg JM, Walker M, Welch JP, Mullany L. Clostridium difficile colitis in surgical patients. Am J Surg. 1984 Apr;147(4):486-91.

Salgado CD, Giannetta ET, Farr BM. Failure to Develop Vancomycin-Resistant Enterococcus with Oral Vancomycin Treatment of Clostridium difficile. Infect Control Hosp Epidemiol. 2004;25(5):413-7.

Williams OM, Spencer RC. The management of Clostridium difficile infection. Br Med Bull. 2009;91:87-110.

Zar FA, Davis MB. Reply to Bishara et al., Huggan et al., and Lawrence et al. Clin Infect Dis. 2007;45(12):1649-51.

Excluded based on population

Bartlett JG. Treatment of antibiotic-associated pseudomembranous colitis. Rev Infect Dis. 1984 Mar;6 Suppl 1:S235-41.

Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis. 1997 Mar;24(3):324-33.

McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol. 2002 Jul;97(7):1769-75.

Excluded based on intervention or comparator

Anand G, Fernandez AA, Sorondo BM, Friedenberg FK. Predicting failure of metronidazole therapy in patients with clostridium difficile-associated diarrhea. Gastroenterology. 2003 Apr;124(4 Supp 1):A145.

Berman L, Carling T, Fitzgerald TN, Bell RL, Duffy AJ, Longo WE, et al. Defining surgical therapy for pseudomembranous colitis with toxic megacolon. J Clin Gastroenterol. 2008;42(5):476-80.

Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: Effect on the incidence of Clostridium difficile-associated diarrhea and cost. Ann Intern Med. 1998;128(12 PART 1):989-95.

Fernandez A, Anand G, Friedenberg F. Factors associated with failure of metronidazole in Clostridium difficile-associated disease. J Clin Gastroenterol. 2004 May;38(5):414-8.

Friedenberg F, Fernandez A, Kaul V, Niami P, Levine GM. Intravenous metronidazole for the treatment of Clostridium difficile colitis. Dis Colon Rectum. 2001 Aug;44(8):1176-80.

Hu MY, Maroo S, Kyne L, Cloud J, Tummala S, Katchar K, et al. A prospective study of risk factors and historical trends in metronidazole failure for Clostridium difficile infection. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1354-60.

Hu M, Maroo S, Cloud J, Tummala S, Katchar K, Dreisbach V, et al. Failure of metromidazole therapy for C-difficile - Associated disease (CDAD): Risk factors and historical trends [abstract]. Gastroenterology. 2008;134(4 Suppl 1):A670, APR.

Kenneally C, Rosini JM, Skrupky LP, Doherty JA, Hollands JM, Martinez E, et al. Analysis of 30-day mortality for Clostridium difficile-associated disease in the ICU setting. Chest [Internet]. 2007;132(2):418-24. Available from: http://chestjournal.chestpubs.org/content/132/2/418.full.pdf+html

Lawrence SJ, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. Clostridium difficile in the intensive care unit: epidemiology, costs, and colonization pressure. Infect Control Hosp Epidemiol. 2007 Feb;28(2):123-30.

Martin H, Willey B, Low DE, Staempfli HR, McGeer A, Boerlin P, et al. Characterization of Clostridium difficile strains isolated from patients in Ontario, Canada, from 2004 to 2006. J Clin Microbiol [Internet]. 2008 Sep [cited 2009 Aug 25];46(9):2999-3004. Available from: http://jcm.asm.org/cgi/reprint/46/9/2999

Musher DM, Aslam S, Logan N, Nallacheru S, Bhaila I, Borchert F, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. Clin Infect Dis. 2005 Jun 1;40(11):1586-90.

Vasa CV, Glatt AE. Effectiveness and appropriateness of empiric metronidazole for Clostridium difficile-associated diarrhea. Am J Gastroenterol. 2003 Feb;98(2):354-8.

Excluded based on outcomes

Al-Nassir WN, Sethi AK, Li Y, Pultz MJ, Riggs MM, Donskey CJ. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of Clostridium difficile-associated disease. Antimicrob Agents Chemother. 2008 Jul;52(7):2403-6.

Cloud J, Noddin L, Pressman A, Hu M, Kelly C. Clostridium difficile Strain NAP-1 Is Not Associated With Severe Disease in a Nonepidemic Setting. Clin Gastroenterol Hepatol. 2009;7(8):868-73.

Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. CMAJ [Internet]. 2008 Oct 7 [cited 2009 Aug 13];179(8):767-72. Available from: http://www.cmaj.ca/cgi/reprint/179/8/767

Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of Clostridium difficile-associated disease in nonsurgical inpatients. Clin Infect Dis. 2008 Feb 15;46(4):497-504.

Fenner L, Frei R, Gregory M, Dangel M, Stranden A, Widmer AF. Epidemiology of Clostridium difficile-associated disease at University Hospital Basel including molecular characterisation of the isolates 2006-2007. Eur J Clin Microbiol Infect Dis. 2008 Dec;27(12):1201-7.

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

Gerding DN. Is there a relationship between vancomycin-resistant enterococcal infection and Clostridium difficile infection? Clin Infect Dis. 1997 Sep;25 Suppl 2:S206-10.

Grundfest-Broniatowski S, Quader M, Alexander F, Walsh RM, Lavery I, Milsom J. Clostridium difficile colitis in the critically ill. Dis Colon Rectum. 1996 Jun;39(6):619-23.

Hubert B, Loo VG, Bourgault AM, Poirier L, Dascal A, Fortin E, 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.

Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. 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.

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med [Internet]. 2005 Dec 8 [cited 2009 Aug 13];353(23):2442-9. Available from: http://content.nejm.org/cgi/reprint/353/23/2442.pdf

Marra AR, Edmond MB, Wenzel RP, Bearman GM. Hospital-acquired Clostridium difficile-associated disease in the intensive care unit setting: epidemiology, clinical course and outcome. BMC Infect Dis [Internet]. 2007 [cited 2009 Nov 11];7:42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1888698/pdf/1471-2334-7-42.pdf

McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent Clostridium difficile disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999 Jan;20(1):43-50.

McGraw MA, Chan-Tompkins NH, Herbert C, Sahud A. Combination Therapy vs. Monotherapy for the Treatment of Nosocomial Clostridium difficile Infection (CDI). Abstract presented at: 47th Annual Meeting of the Infectious Diseases Society of America. 2009 Oct 29 - Nov 1; Philadelphia, PA.

McMahon D, Langridge S, Danziger L. Evaluation of empiric and definitive treatment of *Clostridium difficile*-associated diarrhea. Abstract presented at: 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious-Diseases-Society-of-America. 2008 Oct 25-28; Washington DC. Abstract no. K-519.

Morinville V, McDonald J. Clostridium difficile-associated diarrhea in 200 Canadian children. Can J Gastroenterol. 2005 Aug;19(8):497-501.

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APPENDIX 6: SYSTEMATIC REVIEWS

Table 1: Nelson's[66] Systematic Review	
Country	UK
Funding source	Cochrane Collaboration
Objectives of systematic review	To establish efficacy of antibiotic therapy for *C.difficile*-associated diarrhea (CDAD); to identify most effective antibiotic treatment for CDAD in adults; and to determine need for stopping causative antibiotic during therapy.
Inclusion and exclusion criteria of studies	
Study design	Randomized controlled trials (RCTs)
Population	Inclusion • patients with diarrhea: various definitions describing consistency of stool, number of bowel movements per day, duration of symptoms, and volume of stool • patients with *C. difficile* in stool identified by stool culture positive for *C. difficile,* or by stool positive for *C. difficile* cytotoxin, or both • patients who had received prior antibiotic therapy for an infection other than *C. difficile*; and • patients ≥ 18 years. Exclusion Patients did not have diarrhea or if there was no evidence of *C. difficile* infection.
Interventions and Comparators	Antibiotic therapy for CDAD (comparisons among antibiotics, between different doses of same antibiotic, or between antibiotic therapy and placebo). Excluded studies with probiotics and *C. difficile* cytotoxin absorbing resins.
Outcome measures	Initial resolution of diarrhea; initial conversion of stool to *C. difficile* cytotoxin, or stool culture negative, or both; recurrence of diarrhea; recurrence of fecal *C. difficile* cytotoxin or positive stool culture or both; patient response to cessation of prior antibiotic therapy; sepsis; emergent surgery (fecal diversion or colectomy); and death.
Methods for identification of studies	
Search strategy	Databases searched: MEDLINE (1966 to 2006), EMBASE (1980 to 2006), Cochrane Central Database of Controlled Trials, and Cochrane IBD Review Group Specialized Trial Register. Text search terms: "pseudomembranous colitis and randomized trial": "*Clostridium difficile* and randomized trial"; "antibiotic associated diarrhea and randomized trial".
Data collection and analysis	
Study selection	Trial selection performed independently by 2 reviewers. Disagreements about trial inclusion resolved by group discussion.
Data extraction	Data extraction performed independently by 2 reviewers. Results compared between 2 reviewers. Studies presented for group discussion among 6 investigators.
Data analysis	Data analyzed using Review Manager 4.2.7. For dichotomous outcomes, relative risks (RR) and 95% confidence intervals (CI) were derived. Results were combined, where appropriate, using a fixed effects model. When heterogeneity was detected, a random effects model was used.
Quality assessment and validity	Quality assessment performed independently by 2 reviewers for random allocation, allocation concealment, number of withdrawals and dropouts, intention to treat analysis, blinding of participants and assessors.

Results	
Included studies	12 studies of which 2 compared vancomycin and metronidazole: (Teasley[107] and Wenisch[108])
Quality assessment* of included studies: vancomycin versus metronidazole	Teasley[107]: allocation concealment unclear Wenisch[108]: allocation concealment adequate Studies did not exclude presence of other pathogens in the stool as a cause of diarrhea; did not state how many patients had offending antibiotic discontinued; unclear if researchers and subjects were blinded.
Results: vancomycin versus metronidazole	All findings were inconclusive symptomatic initial response: RR=0.97 (95% CI: 0.88, 1.07), n=163 symptomatic cure: RR=1.01 (95% CI: 0.87, 1.18), n=163 bacteriologic initial cure: RR=0.96 (95% CI: 0.70, 1.30), n=62 bacteriologic cure: RR=0.74 (95% CI: 0.53, 1.03), n=174 symptomatic recurrence: RR=0.64 (95% CI: 0.26, 1.55), n=170 bacteriologic recurrence: RR=1.0 (95% CI: 0.46, 2.18), n=62
Conclusions	8 antibiotics included in review. In paired comparisons, no antibiotic clearly superior to others.
Quality assessment of systematic review Rating 5 (minor flaws) according to Oxman and Guyatt Scale.[102] Authors of this systematic review made no attempt to search grey literature. They could have expanded their search terms.	

*as determined by Nelson et al.

Table 2: Zimmerman *et al.'s*[106] Systematic Review	
Country	Australia and Canada
Funding source	not stated
Objectives of systematic review	To review efficacy of different treatments of symptomatic *C. difficile* intestinal disease.
Inclusion and exclusion criteria of studies	
Study design	Randomized controlled trials
Population	Patients with symptomatic *C.difficile* intestinal disease
Interventions and Comparators	not stated
Outcome measures	Primary end-points: rate of clinical resolution; treatment failure. Secondary end-points: rate of clinical relapse; rate of clearance of *C. difficile* form stool cultures; clearance of *C. difficile* toxin from stool samples; treatment toxicity, and adverse events.
Methods for identification of studies	
Search strategy	Databases searched: MEDLINE and EMBASE (January 1978 to June 1996). Hand-searching index of abstracts from American Gastroenterology Association meetings (1990 to 1996). Reviewing references cited in published reviews and editorials on *C. difficile* and references cited in papers found. Direct communication with trial authors. Search terms: *Clostridium difficile*, *Clostridium difficile* diarrhea, pseudomembranous colitis, *Clostridium difficile* enterocolitis, *Clostridium difficile* colitis, antibiotic-associated diarrhea, antibiotic-associated pseudomembraenous colitis, antibiotic-associated colitis, therapy and treatment.
Data collection and analysis	
Study selection	not stated
Data extraction	Data extraction performed independently by 2 reviewers. Differences resolved

	through consensus and arbitration by third reviewer.
Data analysis	Data analyzed using Review Manager. For dichotomous outcomes, odds ratios (OR) and 95% confidence intervals (CI) were derived.
Quality assessment and validity	not stated
Results	
Included studies	9 studies of which 2 compared vancomycin and metronidazole (Teasley[107] and Wenisch[108])
Quality assessment* of included studies: vancomycin versus metronidazole	Teasley[107] did not report blinding status. Wenisch[108] had randomization but no concealment of allocation or blinding; no washout period between discontinuing offending antibiotic, and starting *C. difficile* treatment (efficacy of interventions may have been overestimated). Studies underpowered to detect small differences (would required 232 patients per treatment arm). None of the studies stratified patients according to *C. difficile* severity or co-morbidities.
Results: vancomycin versus metronidazole	All findings inconclusive: Teasley[107] clinical resolution: OR 0.28 (95% CI: 0.04, 2.09) clinical relapse: OR 0.44 (95% CI: 0.10, 1.91) Wenisch[108] clinical resolution: OR 1.00 (95% CI: 0.13, 7.46) clinical relapse: OR 1.00 (95% CI: 0.20, 3.82) clearance of toxin: OR 0.73 (95% CI: 0.24, 2.18) Pooled results (from abstract[139]) clinical resolution: OR 0.53 (95% CI: 0.13, 2.19) clinical relapse: OR 0.69 (95% CI: 0.26, 1.85)
Conclusions	No antibiotic showed clear therapeutic superiority.
Quality assessment of systematic review Rating 4 (minor flaws) based on Oxman and Guyatt Scale.[102] Zimmerman et al did not report methods used for study selection or criteria used to assess validity of studies.	

*as determined by Zimmerman et al.

APPENDIX 7: RANDOMIZED CONTROLLED TRIALS – STUDY CHARACTERISTICS, RESULTS, AND QUALITY ASSESSMENT

Table 1: Characteristics of the randomized controlled trials

Author, Country, Funding	CDI Diagnostic Criteria	Population	Interventions	Time period and Follow-up post-treatment	Total number patients and withdrawals
Teasley, 1983[107] US Funded by the US Veterans' Administration and Searle Laboratories	≥1 positive results from 3 diagnostic tests (culture for *C. difficile*, cytotoxin assay for *C. difficile*, or endoscopic/ biopsy evidence of PMC).	Inpatients had the Minneapolis Veterans Administration Medical Centre who had passed unformed stools at least 6 times over a period of 36 h	vancomycin 500 mg po QID for 10 days metronidazole 250 mg po QID for 10 days	January 1982 to January 1983; 21 days	randomized: 101 analyzed: 94 total withdrawn: 7
Wenisch, 1996[108] Austria	Results of *C. difficile* toxin assay and/ or endoscopic evidence of typical colitis, with granulocytes in stool	All patients who developed diarrhea during their stay at the University Hospital of Vienna, hospitalized for a minimum of 5 days	vancomycin 500 mg capsule po TID for 10 days fusidic acid 500 mg tablet po TID for 10 days teicoplanin 400 mg in tea po BID for 10 days metronidazole 500 mg tablet po TID for 10 days	January 1993 to April 1995; 10 and 30 days	randomized: 126 analyzed: 119 total withdrawn: 7
Zar, 2007[109] US	NA	Inpatients with diarrhea who had stool assay performed for *C. difficile* toxin because of clinical suspicion of CDAD	vancomycin 125 mg liquid po QID + placebo tablet for 10 days metronidazole 250 mg tablet po QID + placebo liquid for 10 days	October 1994 to June 2002; 21 days	randomized: 90 mild 82 severe analyzed: 81 mild 69 severe withdrawn: 9 mild 13 severe

Table 1: Characteristics of the randomized controlled trials					
Author, Country, Funding	**CDI Diagnostic Criteria**	**Population**	**Interventions**	**Time period and Follow-up post-treatment**	**Total number patients and withdrawals**
Bouza, 2008[110] Europe, Australia, Canada *abstract*	NA	Adult patients with acute CDAD	tolevamer 9 g loading dose then 3 g po TID for 14 days vancomycin 125 mg po QID for 10 days metronidazole 375 mg po QID for 10 days	not specified; 4 weeks	randomized: 528 (ITT) withdrawn: NA
Louie, 2009[111] US and Canada *poster*	≥3 BM in a 24 hour period with an average consistency of loose or watery, with a positive *C. difficile* toxin assay or PM on endoscopy	Patients with primary or recurrent CDAD	tolevamer 9 g loading dose then 3 g liquid po TID for 14 days vancomycin 125 mg capsule po QID for 10 days metronidazole 375 mg capsule po QID for 10 days + placebo for all groups	not specified; 4 weeks	randomized: 574 analyzed: 543 per protocol: 471 completed treatment: 365

BID=twice daily; BM=bowel movement; CDAD= *Clostridium difficile* associated disease
CDI=*Clostridium difficile* infection; h=hour; ITT=intention-to-treat; NA=not available;
PM=pseudomembranes; PMC=pseudomembranous colitis; po=orally; QID=four times daily; TID=three times daily

Table 2: Study Withdrawals			
Author	**Treatment**	**Withdrawn (n, %)**	**Reasons (n, %)**
Teasley, 1983[107]	vancomycin	4 (7.1%)	death (2, 3.6%); protocol violation (2, 3.6%)
	metronidazole	3 (6.7%)	misdiagnosis (2, 4.4%); protocol violation (1, 2.2%)
Wenisch, 1996[108] NB: Data only available for both patient groups combined	vancomycin	7 (5.6%)	death (3, 2.4%); protocol violation (4, 3.2%)
	metronidazole		
Zar, 2007[109]	Vancomycin	11 (13.4%)	death within 5 days of therapy (3, 3.7%); non-compliance (3, 3.7%); drug intolerance (2, 2.4%); lost to follow-up (3, 3.7%)
	metronidazole	11 (12.2%)	death within 5 days of therapy (5, 5.6%); non-compliance (1, 1.1%); lost to follow-up (4, 4.4%); drug intolerance (1, 1.1%)
Zar, 2007[109] NB: Data for patients with severe disease	Vancomycin	7 (18.4%)	death within 5 days of therapy (3, 7.9%); non-compliance (2, 5.3%); drug intolerance (1, 2.6%); lost to follow-up (1, 2.6%)
	metronidazole	6 (13.6%)	death within 5 days of therapy (4, 9.1%); non-compliance (1, 2.3%); lost to follow-up (1, 2.3%)
Bouza, 2008[110]	vancomycin	NA	NA
	metronidazole	NA	NA
Louie, 2009[111]	vancomycin	21 (15.0%)	non-response (8, 5.7%); adverse event (5, 3.6%); death (2, 1.4%); patient withdrew (1, 0.7%); physician decision (1, 0.7%); protocol violation (4, 2.9%)
	metronidazole	39 (26.2%)	non-response (8, 5.4%); adverse event (8, 5.4%); death (2, 1.3%); patient withdrew (16, 10.7%); physician decision (4, 2.7%); protocol violation (1, 0.7%)

NA=not available

Table 3: Baseline Characteristics of Study Participants							
Author and Intervention	**Age (mean years ± sd or range); Male (n, %)**	**Patients receiving previous antibiotic (n, %)**	**Disease course (n, %)**	**Disease severity (n, %)**	**Patients with PMC at diagnosis (n, %)**	**BM (mean± sd)**	**Other**
Teasley, 1983[107]							
vancomycin n=52	65.5 (19-92)	52 (100%)	NA	NA	20/38 (52.6%)	NA	NA
metronidazole n=42	63.6 (33-92)	42 (100%)	NA	NA	13/29 (44.8%)	NA	NA
Wenisch, 1996[108]							
vancomycin n=31	38±17; male, n=17 (54.8%)	31 (100%)	NA	NA	17/21 (80.9%)	5±2	100% hospital-acquired CDI
metronidazole n=31	44±17; male, n=16 (51.6%)	31 (100%)	NA	NA	19/21 (90.5%)	7±2	
Zar, 2007[109]							
vancomycin n=71	<u>mild:</u> 56.8± 11.5; male, n=19 (47.5%) <u>severe:</u> 61.9± 16.4; male, n=20 (64.5%)	<u>mild:</u> 40 (100%) <u>severe:</u> 31 (100%)	NA	<u>mild:</u> 40 (56.3%) <u>severe:</u> 31 (43.7%)	<u>mild:</u> 0 <u>severe:</u> 5 (16.1%)*	<u>mild:</u> 6±1 <u>severe:</u> 6±1	<u>mild:</u> hospitalized in ICU 0 <u>severe:</u> hospitalized in ICU 2 (6.5%)
metronidazole n=79	<u>mild:</u> 57.9± 16.8; male, n=25 (61.0%) <u>severe:</u> 57.5± 9.5; male, n=18 (47.4%)	<u>mild:</u> 41 (100%) <u>severe:</u> 38 (100%)	NA	<u>mild:</u> 41 (51.9%) <u>severe</u>: 38 (48.1%)	<u>mild:</u> 0 <u>severe:</u> 6 (15.8%)*	<u>mild:</u> 5±1 <u>severe:</u> 5±1	<u>mild:</u> hospitalized in ICU 0 <u>severe:</u> hospitalized in ICU 3 (7.9%)

Bouza, 2008[110]							
vancomycin n=125	NA	NA	no prior episode: 216 (83%) recurrent episode: 44 (17%)	mild: 81 (31 %) moderate:112 (43%) severe: 65 (25 %)	NA	NA	NA
metronidazole n=135	NA	NA			NA	NA	NA
Louie, 2009[111]							
vancomycin n=140	62± 17.2; male, n=75 (53.6%)	NA	no prior episode: 108 (77.1%) 1 or more than 1 prior episode: 32 (22.9%)	mild: 28 (20.1 %) moderate: 76 (54.7 %) severe: 35 (25.2 %)	NA	NA	NA
metronidazole n=149	63± 17.7; male, n=69 (46.3%)	NA	no prior episode: 104 (70.0 %) 1 or more than 1 prior episode: 45 (30.2%)	mild: 34 (22.8 %) moderate: 57 (38.3 %) severe: 58 (38.9 %)	NA	NA	NA

*based on total population
BM=bowel movement; CDI=C. *difficile* infection; NA=not available; PMC=pseudomembranous colitis; sd=standard deviation

Table 4: Study Results					
Author	**Treatment cures and failures (n,%)**	**Time to resolution of diarrhea (mean days ± sd)**	**Recurrence* (n, %)**	**Complications (n, %)**	**Adverse events (n, %)**
Teasley, 1983[107]					
vancomycin n=52	cure: 45 (86.5%) failure: 0	2.8 ± 1.8	6/51 (11.8%)	NA	drug intolerance: 1 (1.9%)
metronidazole n=42	cure: 37 (88.0%) failure: 2 (4.8%)	2.4 ± 1.9	2/39 (5.1%)	NA	drug intolerance: 1 (2.4%)
Teasley, 1983[107] – data for patients with PMC at diagnosis					
vancomycin n=20	cure: 17 (85.0%) failure: 0	NA	3 (15.0%)	NA	0
metronidazole n=13	cure: 13 (100%) failure: 0	NA	0	NA	0
Wenisch, 1996[108]					
vancomycin n=31	cure: 29 (93.5%)	3.1 ± 1.1	5 (16.1%)	NA	0
metronidazole n=31	cure: 29 (93.5%)	3.2 ± 1.8	5 (16.1%)	NA	GI: 3 (9.7%)
Wenisch, 1996[108] – data for patients with PMC at diagnosis					
vancomycin n=17	cure: 16 (94.1%)	NA	1 (5.9%)	NA	NA
metronidazole n=19	cure: 18 (94.7%)	NA	2 (10.5%)	NA	NA
Zar, 2007[109]					
vancomycin n=71	<u>cure:</u> <u>mild:</u> 39/40 (97.5%) <u>severe:</u> 30/31 (96.8%)	NA	<u>mild:</u> 2/40 (5.0%) <u>severe:</u> 3/31 (9.7%)	<u>mild:</u> death or colectomy: 0[140] <u>severe:</u> death or colectomy: 0[140]	GI: 1 (1.4%)

metronidazole n=79	cure: mild: 37/41 (90.2%) severe: 29/38 (76.3%) p=0.02	NA	mild: 3/41 (7.3%) severe: 6/38 (15.8%)	mild: death or colectomy: 0[140] severe: colectomy: 1 (2.6%)[140] death: 4 (10.5%)[140]	GI: 1 (1.3%)
Bouza, 2008[110]					
vancomycin n=125	cure: 101 (80.8%)	NA	23 (18.4%)	NA	NA
metronidazole n=135	cure: 99 (73.3%)	NA	26 (19.2%)	NA	NA
Louie, 2009[111]					
vancomycin n=133	cure: mild: 23/27 (85.2 %) moderate: 58/73 (79.5 %) severe: 28/33 (84.8%)	median: 5 days	25/107 (23.4%)	death: 7/136 (5.0%) sepsis: 0 (0%)	serious AE: 28/136 (20.6%) C.*difficile* colitis: 8/136 (5.9%) #AEs: GI: 94 hypokalemia: 19 increased WBC: 4 altered taste: 3
metronidazole n=143	cure: mild: 26/33 (78.8 %) moderate: 40/53 (75.5 %) severe: 37/57 (64.9 %) p=0.04 for severe disease	median: 5 days	29/107 (27.1%)	death: 5/146 (3.4%) sepsis: 2/146 (1.4%)	serious AE: 29/146 (19.9%) C.*difficile* colitis: 4/146 (2.7%) #AEs: GI: 96 hypokalemia: 22 increased WBC: 6 altered taste: 13

AE=adverse events; GI=gastrointestinal; PMC=pseudomembranous colitis; sd=standard deviation; WBC=white blood cell count

*Recurrence may include patients with a re-infection, a relapse or both. Appendix 9 lists specific definitions.

Table 5: Consolidated quality assessment of RCTs* that meet Downs and Black criteria[103]			
Criterion	**Yes**	**No**	**Unclear**
Reporting			
Objective of study clearly stated	Teasley[107] Wenisch[108] Zar[109]		
Main outcomes clearly described in Introduction or Methods section	Teasley[107] Wenisch[108] Zar[109]		
Characteristics of patients included in study clearly described (inclusion and exclusion criteria provided)	Teasley[107] Wenisch[108] Zar[109]		
Interventions of interest clearly stated	Teasley[107] Wenisch[108] Zar[109]		
Distribution of principal confounders in each group of patients to be compared clearly stated	Teasley[107] Wenisch[108] Zar[109]		
Main study findings clearly described	Teasley[107] Wenisch[108] Zar[109]		
Estimates of random variability in data for main outcomes provided	Teasley[107] Wenisch[108] Zar[109]		
Important adverse events reported	Teasley[107] Wenisch[108] Zar[109]		
Number of patients lost to follow-up provided	Wenisch[108] Teasley[107] Zar**[109]		
Actual probability values reported except where probability value <0.001 reported	Teasley[107] Wenisch[108] Zar[109]		
External validity			
Patients asked to participate in study representative of entire population from which they were recruited	Teasley[107] Wenisch[108] Zar[109]		
Patients who were prepared to participate representative of entire population from which they were recruited			Teasley[107] Wenisch[108] Zar[109]
Staff, places and facilities where patients were treated were representative of	Teasley[107] Wenisch[108] Zar[109]		

Table 5: Consolidated quality assessment of RCTs* that meet Downs and Black criteria[103]			
Criterion	**Yes**	**No**	**Unclear**
treatment patients receive			
Internal validity			
Attempt made to blind study patients to intervention received	Zar[109]	Teasley[107] Wenisch[108]	
Attempt made to blind those measuring main outcomes of intervention	Zar[109]	Teasley[107] Wenisch[108]	
Study results from "data dredging" clearly described (sub-group analyses determined a priori)	Teasley[107] Wenisch[108] Zar[109]		
Period between intervention and outcome same for intervention and control groups	Teasley[107] Wenisch[108] Zar[109]		
Statistical tests used to assess main outcomes appropriate	Teasley[107] Wenisch[108] Zar[109]		
Compliance with intervention reliable	Zar[109] Wenisch[108]		Teasley[107]
Main outcome measures used accurate	Teasley[107] Wenisch[108] Zar[109]		
Internal validity-confounding (selection bias)			
Patients in different intervention groups recruited from same population	Teasley[107] Wenisch[108] Zar[109]		
Study patients in different intervention groups recruited over same period	Teasley[107] Wenisch[108] Zar[109]		
Study patients randomized to intervention groups (method of randomization ensures random allocation)	Wenisch[108] Zar[109]		Teasley[107]
Randomized intervention assignment concealed from patients and health care staff until recruitment complete and irrevocable	Zar[109]		Teasley[107] Wenisch[108]
Adequate adjustment for confounding in analysis from which main findings were drawn (intention to treat analysis)		Teasley[107] Wenisch[108] Zar[109]	
Patient lost to follow-up taken	Teasley[107]		

Table 5: Consolidated quality assessment of RCTs* that meet Downs and Black criteria[103]			
Criterion	**Yes**	**No**	**Unclear**
into account	Wenisch[108] Zar[109]		
Power			
Study had sufficient power to detect clinically important effect where probability value for difference due to chance <5% (sample size calculated to detect difference)	Zar[109]	Teasley[107] Wenisch[108]	

*studies published as abstracts[110,111] not evaluated for quality

**22 patients withdrawn from study before completion of 10 days of treatment

APPENDIX 8: OBSERVATIONAL STUDIES – STUDY CHARACTERISTICS, RESULTS, AND QUALITY ASSESSMENT

Table 1: Characteristics of the Observational studies

Author, Country, Funding	Study design	Time period	Population	Interventions and Sample size	Diagnostic/ Inclusion criteria
Talbot, 1986[112] US	retrospective study (medical records)	July 1982 to June 1984	patients with CTAC hospitalized at the Mayo Clinic	vancomycin (n=102) metronidazole (n=38) bacitracin (n=4) no antibiotic (n=46) duration of treatment=10 to 14 days	NA
Marts, 1993[113] US	retrospective study (computerized medical records)	1990 to 1992 (18 months)	patients with CDC at a tertiary care medical facility (7% developed symptoms outside of the hospital)	vancomycin (n=53) metronidazole (n=19) sequential vancomycin and metronidazole (n=8) no antibiotic (n=10) duration of treatment=9 days (range 1 to 16 days)	positive fecal cytotoxin assay for *C.difficile*

Table 1: Characteristics of the Observational studies					
Author, Country, Funding	**Study design**	**Time period**	**Population**	**Interventions and Sample size**	**Diagnostic/ Inclusion criteria**
Olson, 1994[120] US funded by the Dept. of Veterans Affairs	prospective study	January 1982 to December 1991	patients with CDAD at a Veterans Affairs Medical Center (93% of cases acquired nosocomially)	oral vancomycin for median of 10 days, range 8 to 14 (n=122) oral metronidazole for median of 10 days, range 6 to 18 (n=632) no antibiotic (n=154)	diarrhea plus a positive culture or cytotoxin for *C.difficile*; or a positive endoscopy, biopsy, or autopsy for pseudo-membranes
Wilcox, 1995[114] UK funded by Eli Lilly	retrospective study (medical records)	1991 to 1993	adult inpatients with diarrhea possibly caused by *C. difficile* from 2 hospitals (1 geriatric and 1university teaching hospital)	vancomycin 125 mg po QID, 125 mg po TID, or 250 mg po TID for mean of 7.6 days, range 3 to 12 (n=26) metronidazole 400 mg po TID for mean of 8.1 days, range 2 to 16 (n=32)	diarrhea (≥2 loose stools per day) in which *C.difficile* toxin detected
Al-Eidan 2000[115] Ireland	retrospective study (medical records)	2-year period	hospitalized adult patients who developed CDAD during their hospitalization at a teaching hospital	vancomycin 125 mg, 250 mg, or 500 mg po Q6H (n=48) metronidazole 400 mg po Q8H (n=39) duration of treatment= 7.5 days, range 5 to 10	patients with a change in bowel habits with ≥3 loose stools per day for ≥2 consecutive days associated with lab-confirmed *C.difficile* toxin A in feces
Lahue, 2007[116]	retrospective study (national	January 2004 to June	inpatients with CDAD	oral vancomycin (n=3,420)	patients with ICD-9 code of

Table 1: Characteristics of the Observational studies					
Author, Country, Funding	**Study design**	**Time period**	**Population**	**Interventions and Sample size**	**Diagnostic/ Inclusion criteria**
US study funded by Genzyme *abstract*	US hospital database)	2005		oral metronidazole (n=28,905)	*C.difficile*
Lahue, 2007[117] US study funded by Genzyme *abstract*	retrospective study (national US hospital database)	July 2005 to June 2006	inpatients with CDAD	oral vancomycin (n=3,326) oral metronidazole (n=21,646)	patients with ICD-9 code of *C.difficile*
Pépin, 2007[118] Canada university funding	retrospective cohort study (hospital computerized medical records or from hospital discharge summaries)	January 1991 to August 2006	patients with CDAD at a tertiary care teaching hospital	oral/intrarectal vancomcycin (1991 to 2002, n=74; 2003 to 2006, n=145) oral/iv metronidazole (1991 to 2002, n=689; 2003 to 2006, n=671) combination metronidazole and vancomycin (1991 to 2002, n=10; 2003 to 2006, n=27)	patients with a positive *C.difficile* assay results; or with endoscopic evidence of PMC; or histopathologic evidence of PMC on a specimen obtained during endoscopy, colectomy or autopsy
Al-Nassir, 2008[121] US funded by Viropharm Ltd. and the Dept. of Veteran's Affairs	prospective observational study	November 2006 to July 2007 (follow-up, 9 months)	patients with CDAD at a Veterans Affairs Medical Center	vancomycin (n=18) metronidazole (n=34)	diarrhea (≥3 unformed stools in 24 h for 2 days) and *C.difficile* toxin in stool
Cober, 2009[119] US funded by Viropharm Ltd, Veteran's Affairs and others	retrospective study (medical records)	January 2006 to December 2006	patients aged 80 years and older with CDI at a tertiary care facility (34.3% of cases acquired nosocomially)	vancomycin (n=2) metronidazole (n=65) no antibiotic (n=3)	positive assay for *C.difficile* cytotoxin A or B and a clinical course consistent with CDI

Table 1: Characteristics of the Observational studies					
Author, Country, Funding	**Study design**	**Time period**	**Population**	**Interventions and Sample size**	**Diagnostic/ Inclusion criteria**
Le, 2009[122] US *abstract*	prospective cohort study	NA (follow-up, 7 days)	patients with CDI at a university-affiliated teaching hospital	oral vancomycin (n=16) oral metronidazole (n=128)	patients assessed for severity of illness based on: ICU admission; PMC at endoscopy; and 2 of: age>60 years, temperature> 101º F, albumin<2.5 mg/dL, or WBC>15,000/µL
Lieu, 2009[123] US *abstract*	prospective study	October 1 2008 to December 31 2008	patients with CDI and any of the following risk factors: age ≥ 60 years, previous history of CDI, or comorbidities	short course (14 days) vancomycin (n=27) 6-week taper vancomycin (n=73) metronidazole (n=27)	patients positive for *C.difficile* toxin
Leitner, 2010[124] Austria *abstract*	prospective study	November 2008 to August 2009	hospitalized patients with CDI	oral metronidazole (n=47) iv metronidazole (n=11) oral vancomycin (n=5)	patients fulfilling the case definition given by ESCD with the need for antimicrobial therapy

CDAD=*C.difficile*-associated disease; CDC=*C.difficile* colitis; CDI=*C.difficile* infection; CTAC=*C.difficile* toxin-associated colitis; ESCD=not defined in abstract; ICU=intensive care unit; iv=intravenous; PMC=pseudomembranous colitis; po=orally; Q6H= every six hours; Q8H=every eight hours; QID=four times daily; TID=three times daily; WBC=white blood cell

Table 2: Baseline Characteristics of Study Participants						
Author and Intervention	**Age (mean years ± sd or range), Male (n, %)**	**Patients on previous antibiotic (n, %)**	**Patients stopping previous antibiotic**	**Disease course (n, %)**	**Disease severity (n, %)**	**Other**
Talbot, 1986[112]						**PMC at diagnosis****
vancomycin	male*, n=83 (43.7%) also included are children aged 3 months to 13 years, n=16 (8.4%)	151/170* (88.8%)	NA	NA	asymptomatic: 5 (4.9%) mild: 25 (24.5%) moderate: 52 (51%) severe: 20 (19.6%)	39/98 (39.8%)
metronidazole			NA	NA	asymptomatic: 3 (7.9%) mild: 5 (13.2%) moderate: 24 (63.2%) severe: 6 (15.8%)	
Marts, 1993[113]						**PMC at diagnosis****
vancomycin or metronidazole or both	58 years* (17-92); male*, n=49 (54.4%)	80/90* (88.9%)	cessation of precipitating antibiotic was done when possible	initial: 89 (98.9%) recurrence: 1 (1.1%)	NA	1/4 (25%)
Olson, 1994[120]						**PMC at diagnosis****
vancomycin or metronidazole	NA	679/705* (96.3%) within 14 days; 100% within 3 months	100%	NA	NA	80/196 (40.8%)
Wilcox, 1995[114]						**drop-outs**
vancomycin	69 (19 to 91); male, n=12/22 (54.5%)	11/22 (50%)	7/22 (31.8%)	NA	NA	4 (2 due to diarrhea from other cause; 2 due to death)

Table 2: Baseline Characteristics of Study Participants						
Author and Intervention	**Age (mean years ± sd or range), Male (n, %)**	**Patients on previous antibiotic (n, %)**	**Patients stopping previous antibiotic**	**Disease course (n, %)**	**Disease severity (n, %)**	**Other**
metronidazole	74.9 (51 to 93); male, n=16/28 (57.1%)	15/28 (53.6%)	12/28 (42.9%)	NA	NA	4 (2 due to diarrhea from other cause; 1 death; and 1 insufficient data)
Al-Eidan, 2000[115]						**PMC at diagnosis****
vancomycin	NA	NA	NA	NA	NA	8/8(100%)
metronidazole	NA	NA	NA	NA	NA	
Lahue, 2007[116]						**history of PPI**
vancomycin	70.5; male, n=1,276 (37.3%)	NA	NA	prior CDAD admission:1,050 (30.7%)	minor: 116 (3.4%) moderate: 824 (24.1%) major: 1,659 (48.5%) extreme: 824 (24.1%)	1,816/ 3,420 (53.1%)
metronidazole	70.2; male, n=12,169 (42.1%)	NA	NA	prior CDAD admission: 3,006 (10.4%)	minor: 694 (2.4%) moderate: 5,405 (18.7%) major: 14,019 (48.5%) extreme: 8,816 (30.5%)	12,169/ 28,905 (42.1%)
Lahue, 2007[117]						**history of PPI**

Table 2: Baseline Characteristics of Study Participants						
Author and Intervention	**Age (mean years ± sd or range), Male (n, %)**	**Patients on previous antibiotic (n, %)**	**Patients stopping previous antibiotic**	**Disease course (n, %)**	**Disease severity (n, %)**	**Other**
vancomycin	70.9; male, n=1,330 (40%)	NA	NA	history of CDAD: 1,098 (33%)	mild: 100 (3.0%) moderate: 698 (21.0%) severe: 1,563 (47.0%) extreme: 931 (28.0%) unknown: 7 (0.2%)	1,796 (54%)
metronidazole	70.4; male, n=9,091 (42%)	NA	NA	history of CDAD: 2,381 (11%)	mild: 433 (2.0%) moderate: 3,680 (17.0%) severe: 10,174 (47.0%) extreme: 7,143 (33.0%) unknown: 43 (0.2%)	9,308 (43%)
Pépin, 2007[118]						**hospital-acquired**
vancomycin 1991 to 2002	64 (39 to 75); male, n=26 (35.1%)	NA	NA	history of CDAD: 5/74 (6.8%)	NA	41/74 (55.4%)
metronidazole 1991 to 2002	61 (37 to 74); male, n=311 (45.1%)	NA	NA	history of CDAD: 29/688 (4.2%)	NA	344/686 (50.1%)
vancomycin 2003 to 2006	78 (65 to 83); male, n=73 (50.3%)	NA	NA	history of CDAD: 15/145 (10.3%)	NA	126/145 (86.9%)

Table 2: Baseline Characteristics of Study Participants						
Author and Intervention	**Age (mean years ± sd or range), Male (n, %)**	**Patients on previous antibiotic (n, %)**	**Patients stopping previous antibiotic**	**Disease course (n, %)**	**Disease severity (n, %)**	**Other**
metronidazole 2003 to 2006	73 (58 to 81); male, n=315 (46.9%)	NA	NA	initial	NA	535 (79.7%)
Al-Nassir, 2008[121]						**epidemic strain**
vancomycin	65 (56 to 77)	NA	NA	previous CDAD: 7 (38.9%)	severe: 5 (27.8%)	11 (61.1%)
metronidazole	75.5 (63 to 79)	NA	NA	previous CDAD: 1 (2.9%)	severe: 7 (20.6%)	20 (58.8%)
Cober, 2009[119]						**on PPI**
vancomycin	84±4.1* (80 to 94); male*, n=29 (41.1%)	57/70* (81.4%)	NA	NA	NA	41* (58.5%)
metronidazole			NA	NA	NA	
Le, 2009[122]						
vancomycin	63±17 year; male, n=76 (53%)	NA	NA	NA	mild: 85 (59%) severe: 59 (41%)	NA
metronidazole		NA	NA	NA		NA
Lieu, 2009[123]						
vancomycin	NA	NA	NA	initial episode: 127 (100%)	NA	NA
metronidazole	NA	NA	NA		NA	NA
Leitner, 2010[124]						
vancomycin	NA	NA	NA	NA	NA	NA
metronidazole	NA	NA	NA	NA	NA	NA

PPI=proton pump inhibitor
*data for total population
**based on the total number of patients who received endoscopy

Table 3: Study Results					
Author	**Treatment failures (n,%)**	**Time to resolution of diarrhea (mean, ± sd or range)**	**Recurrence† (n, %)**	**Complications (n, %)**	**Adverse events (n, %)**
Talbot, 1986[112]					
vancomycin n= 102	NA	NA	mild: 3/25 (12%) moderate: 14/52 (26.9%) severe: 4/20 (20%)	NA	NA
metronidazole n= 38	NA	NA	mild: 3/5 (60%) moderate: 5/24 (20.8%) severe: 1/6 (16.7%)	NA	NA
Marts, 1993[113]					
vancomycin n= 53	NA	NA	0 (0%)	deaths: 14 (15.6%). Cause 3 sepsis; 4 cardiac failure; 3 respiratory failure; 4 multi-organ failure (no cases of toxic magacolon or colonic perforation)	NA
metronidazole n= 19	NA	NA	1 (5.3%)		NA
sequential vancomycin and metronidazole n=8	NA	NA	0 (0%)		NA
Olson, 1994[120]					
vancomycin n=122	1 (0.82%)	NA	12 (9.8%)	19 (2.5%) treated patients died; 52 (6.9%) cases of ileus; PMC reported, but we don't know if these were treated patients	1 (0.8%) vomiting
metronidazole n=632	14 (2.2%)	NA	39 (6.2%)		7 (1.1%) including 4 rash; 2 vomiting; 1seizure
Wilcox, 1995[114]					
vancomycin n=22	NA	3.0 (1 to 7)	1 (4.5%)	death: 2 (9.1%)	NA
metronidazole n=28	NA	4.65 (1 to 16), p<0.01	1 (3.6%)	death: 1 (3.6%)	NA
Al-Eidan, 2000[115]					
vancomycin (n=48)	NA	3.2±1.4 days	NA	NA	NA

Table 3: Study Results					
Author	**Treatment failures (n,%)**	**Time to resolution of diarrhea (mean, ± sd or range)**	**Recurrence† (n, %)**	**Complications (n, %)**	**Adverse events (n, %)**
metronidazole (n=39)	NA	2.8±1.1 days	NA	NA	NA
Lahue*, 2007[116]					
vancomycin n=3,420	NA	NA	NA	colon resection: 27 (0.8%) death: 233 (6.8%)	NA
metronidazole n=28,905	NA	NA	NA	colon resection: 289 (1.0%) death: 2,283 (7.9%), p<0.0001	NA
Lahue*, 2007[117]					
vancomycin n=3,326	NA	NA	NA	colon resection: 30 (0.9%) death: 220 (6.6%)	NA
metronidazole n=21,646	NA	NA	NA	colon resection: 216 (1.0%) death: 1,688 (7.8%), p=0.01	NA
Pépin, 2007[118]					
vancomycin 1991 to 2002 n=64	NA	NA	13 (20.0%)	4/74 (5.4%)**	NA
metronidazole 1991 to 2002 n=551	NA	NA	108 (19.6%)	75/689 (10.9%)	NA
vancomycin 2003 to 2004 n=75	NA	NA	29 (38.6%)	31/145 (21.4%)	NA
vancomycin 2005 to 2006 n=51	NA	NA	12 (23.0%)		NA
metronidazole 2003 to 2004 n=352	NA	NA	157 (44.6%)	90/671 (13.4%)	NA
metronidazole 2005 to 2006 n=103	NA	NA	36 (34.5%)		NA
Al-Nassir, 2008[121]					
vancomycin n=18	1 (5.6%)	NA	2 (11.1%)	death: 4 (22.2%)	NA
metronidazole n=34	4 (11.8%)	NA	4 (11.8%)	death:10 (29.4%)	NA

Table 3: Study Results					
Author	**Treatment failures (n,%)**	**Time to resolution of diarrhea (mean, ± sd or range)**	**Recurrence† (n, %)**	**Complications (n, %)**	**Adverse events (n, %)**
Cober, 2009[119]					
vancomycin n=2	0	NA	0 (0%)	death: 1 (50%)	NA
metronidazole n=65	18 (27.7%)	NA	12 (18.5%)	death: 11 (16.9%)	NA
Le, 2009[122]					
vancomycin n=16	NA	NA	0 (0%)	NA	NA
metronidazole n=128	NA	NA	47 (37%), p=0.04	NA	NA
Lieu, 2009[123]					
vancomycin n=27	NA	NA	5 (18.5%)	NA	NA
vancomycin taper n=73	NA	NA	6 (8.2%)	NA	NA
metronidazole n=27	NA	NA	5 (18.5%)	NA	NA
Leitner, 2010[124]					
vancomcycin n=5	2 (40.0%)	13.4 (7-21)	0	death: 0	NA
metronidazole oral n=47	8 (17.0%)	14 (1-82)	2 (4.3%)	death: 3 (6.4%)	NA
metronidazole iv n=11	1 (9.1%)	8.4 (3-24)	1 (9.1%)	death: 4 (36.4%)	NA

CDI=C.*difficile* infection; PMC=pseudomembranous colitis
*LOS and ICU LOS or stay also reported for both groups
**reported as number of patients developing severe and complicated *Clostridium difficile*-Associated Disease including septic shock, megacolon, perforation, requiring colectomy, or death.
†Recurrence may include patients with a re-infection, a relapse or both. Appendix 9 lists specific definitions.

Table 4: Consolidated quality assessment of observational studies* that meet Downs and Black criteria[103]				
Criterion	**Yes**	**No**	**Unclear**	**Not Applicable**
Reporting				
Objective of study clearly stated	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]			
Main outcomes clearly described in Introduction or Methods section	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Pépin[118] Talbot[112] Wilcox[114]	Marts[113]		
Characteristics of patients included in study clearly described (inclusion and exclusion criteria given)	Al-Eidan[115] Al-Nassir[121] Cober[119] Marts[113] Pépin[118]	Olson[120] Talbot[112] Wilcox[114]		
Interventions of interest clearly stated	Wilcox[114] Al-Eidan[115]	Al- Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112]		
Distribution of principal confounders in each group of patients to be compared clearly stated	Al-Nassir[121] Pépin[118] Wilcox[114]	Al-Eidan[115] Cober[119] Olson[120] Marts[113] Talbot[112]		
Main study findings clearly described	Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]	Al-Eidan[115]		

Table 4: Consolidated quality assessment of observational studies* that meet Downs and Black criteria[103]				
Criterion	**Yes**	**No**	**Unclear**	**Not Applicable**
Estimates of random variability in data for main outcomes provided	Al-Eidan[115] Al-Nassir[121] Cober[119] Pépin[118] Wilcox[114]	Marts[113] Olson[120] Talbot[112]		
Important adverse events reported	Marts[113] Olson[120]	Al-Eidan[115] Al-Nassir[121] Cober[119] Pépin[118] Talbot[112] Wilcox[114]		
Number of patients lost to follow-up provided	Al-Nassir[121] Olson[120] Wilcox[114]			Al-Eidan[115] Cober[119] Marts[113] Pépin[118] Talbot[112]
Actual probability values reported except where probability value <0.001 reported	Al-Eidan[115] Al-Nassir[121] Cober[119] Pépin[118]	Marts[113] Olson[120] Talbot[112] Wilcox[114]		
External validity				
Patients asked to participate in study representative of entire population from which they were recruited	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]			
Patients who were prepared to participate representative of entire population from which they were recruited			Al-Nassir[121] Olson[120]	Al-Eidan[115] Cober[119] Marts[113] Pépin[118] Talbot[112] Wilcox[114]
Staff, places, and facilities where patients were treated were representative of treatment patients receive	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]			

Table 4: Consolidated quality assessment of observational studies* that meet Downs and Black criteria[103]				
Criterion	**Yes**	**No**	**Unclear**	**Not Applicable**
Internal validity				
Attempt made to blind study patients to intervention received				Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]
Attempt made to blind those measuring main outcomes of intervention				Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]
Study results from "data dredging" clearly described (sub-group analyses determined a priori)	Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]	Al-Eidan[115]		
Period between intervention and outcome same for intervention and control groups	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]			
Statistical tests used to assess main outcomes appropriate	Al-Eidan[115] Al-Nassir[121] Cober[119] Pépin[118] Wilcox[114]		Olson[120] Marts[113] Talbot[112]	
Compliance with intervention reliable			Al-Nassir[121] Olson[120]	Al-Eidan[115] Cober[119] Marts[113] Pépin[118] Talbot[112] Wilcox[114]

Table 4: Consolidated quality assessment of observational studies* that meet Downs and Black criteria[103]				
Criterion	**Yes**	**No**	**Unclear**	**Not Applicable**
Main outcome measures used accurate	Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Wilcox[114]		Talbot[112]	
Internal validity-confounding (selection bias)				
Patients in different intervention groups recruited from same population	Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]		Al-Eidan[115]	
Study patients in different intervention groups recruited over same period	Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]		Al-Eidan[115]	
Study patients randomized to intervention groups				Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]
Randomized intervention assignment concealed from patients and health care staff until recruitment complete and irrevocable				Al-Eidan[115] Al-Nassir[121] Cober[119] Olson[120] Marts[113] Pépin[118] Talbot[112] Wilcox[114]
Adequate adjustment for confounding in analysis from which main findings were drawn	Al-Nassir[121] Cober[119] Pépin[118]	Al-Eidan[115]	Olson[120] Marts[113] Talbot[112] Wilcox[114]	

Table 4: Consolidated quality assessment of observational studies* that meet Downs and Black criteria[103]				
Criterion	**Yes**	**No**	**Unclear**	**Not Applicable**
Patient lost to follow-up taken into account	Al-Nassir[121] Olson[120] Wilcox[114]			Al-Eidan[115] Cober[119] Marts[113] Pépin[118] Talbot[112]
Power				
Study had sufficient power to detect clinically important effect where probability value for difference due to chance <5%		Al-Eidan[115] Al-Nassir[121] Cober[119] Marts[113] Olson[120] Pépin[118] Talbot[112] Wilcox[114]		

*studies published as abstracts[116,117,122-124] not evaluated for quality

APPENDIX 9: DEFINITIONS USED IN STUDIES

Table 1: Definitions - randomized controlled trials		
Study	**Data Element**	**Definition**
Teasley[107]	severity of disease	judged by frequency of fever, abdominal pain, and duration of diarrhea
	Cure	diarrhea resolved (no stools or <2 formed stools per day) within 6 days of treatment; treatment course tolerated; no relapse of symptoms in 21-day follow-up
	treatment failure	persistence of watery stools ≥4 times per day after 6 days of treatment
	relapse	recurrence within 21 days of diarrhea (watery stools ≥4 times per day for minimum of 48 hours) in patient who had completed 10 days of treatment, had normal stools at end of treatment period, and had not received additional antibiotics after treatment period; new evidence of presence of *C. difficile* by stool culture or cytotoxin assay or presence of pseudomembranes at endoscopy measured at completion of therapy and 21 days after therapy
	intolerance	inability or refusal to continue medication because of side effects (rash, nausea, vomiting)
Wenisch[108]	severity of disease	based on number and shape of stools, body temperature, serum levels of C-reactive protein, blood leukocyte count, and erythrocyte sedimentation rate
	clinical cure	lack of symptoms (no loose stools, gastrointestinal symptoms, or fever and normalization of serum levels of C-reactive protein and leukocyte counts)
	clinical failure	persistence of diarrhea after 6 days of treatment
	clinical relapse	reappearance of CDAD and other symptoms during follow-up (10 to 30 days after treatment discontinuation)
Zar[109]	severity of disease	patients with ≥2 points considered to have severe CDAD: 1 point each for age >60 years, temperature >38.3ºC, albumin level <2.5 mg/dL, or peripheral WBC count >15,000 cells/mm^3 within 48 hours of enrolment; 2 points for endoscopic evidence of PMC or treatment in ICU
	Cure	resolution of diarrhea by day 6 of treatment and negative result of C. *difficile* toxin A assay at days 6 and 10 of treatment
	treatment failure	persistence of diarrhea, or a positive result, or both of C. *difficile* toxin A assay after 6 days of treatment; need for colectomy; or death after 5 days of therapy
	relapse	recurrence of C. *difficile* toxin A positive-diarrhea by day 21 after initial cure
	intolerance	inability or refusal to continue medication because of adverse reactions
	noncompliance	missing >3 doses of study medication during 10 days of therapy for reasons other than intolerance

Bouza[110]	clinical success	resolution of diarrhea and absence of severe abdominal discomfort due to CDAD on day 10
Louie[111]	severity of disease	mild CDAD 3 to 5 BM/day; WBC ≤ 15,000/mm^3; mild abdominal pain due to CDAD moderate CDAD 6 to 9 BM/day; WBC 15,001 to 20,000 mm^3; moderate abdominal pain due to CDAD severe CDAD ≥10 BM/ day; WBC ≥20,001/ mm^3; severe abdominal pain due to CDAD
	clinical success	resolution and absence of severe abdominal discomfort due to CDAD for 2 consecutive days including day 10 (if a patients discontinued because of a non-response, he was not considered a clinical success)
	time to resolution of diarrhea	time to resolution sustained through active treatment
	recurrence	positive toxin assay or endoscopy with no other suspected etiology in patients with resolution of diarrhea after treatment

BM=bowel movement; CDAD= C. *difficile*-associated diarrhea; ICU=intensive care unit; PMC=pseudomembranous colitis; WBC=white blood cells

Table 2: Definitions - observational studies*		
Study	**Data Element**	**Definition**
Talbot[112]	severity of disease	colitis graded as asymptomatic if stool frequency no more than twice daily, mild if 2 to 5 times per day, moderate if 6 to 10 times per day, and severe if >10 times per day or associated with abdominal pain, swelling, or fever
Olsen[120]	treatment failure	persistence of watery stools ≥4 times per day after 7 days of treatment with oral medication
	relapse	recurrence of C. *difficile*-associated diarrhea after successful treatment in which antimicrobials discontinued, oral medication for treatment of CDAD given, patient was producing normal stools, and no new antimicrobials had been given
	drug intolerance	inability to continue medication because of side effects (rash, nausea, vomiting, seizure)
Wilcox[114]	response	cessation of loose stools and other related symptoms such as abdominal pain and fever (temperature ≥38ºC)
	relapse	symptoms recurring within 1 month after end of treatment, associated with positive cytotoxin test
Al-Eidan[115]	treatment response	return to normal bowel frequency (≤2 bowel movements of formed stool per day), and improvement of related symptoms such as resolution of fever and abdominal pain

Pépin[42,118]	recurrence	episode of CDAD occurring within 2 months of prior episode
	complication	patient died within 30 days after diagnosis of CDAD or if any of following occurred: megacolon, perforation, colectomy, or shock requiring vasopressor therapy
Al-Nassir[121]	severity of disease	patients classified as having severe disease if they had ICU admission because of CDAD, toxic megacolon, colectomy necessitated by CDAD, or ≥3 of following criteria: age >65, WBC count of ≥15,000 cells/mm^3, >7 loose bowel movements per day or ileus, fever (temperature >38.5ºC) or hypothermia (temperature <35.4ºC), albumin level <2.5 g/ dL, and acute renal failure
	recurrence	subsequent CDAD within 2 months after resolution of previous episode
Cober[119]	failure of initial agent	lack of clinical improvement after 5 days or change in treatment regimen because of lack of clinical response
	relapse	any recurrence of CDI within 90-day period after initial presentation
	death	all-cause mortality within 90 days of presentation
Le[122]	severity of illness	patients assessed for severity of illness based on ICU admission, PMC at endoscopy, or any 2 of the following: age >60 years, temperature >101ºF, albumin <2.5mg/dL, or peripheral WBC count >15,000/μL
Lieu[123]	relapse	recurrent diarrhea with positive C. *difficile* toxin within 3 months of treatment course
Lahue[117]	recurrence	readmission within 60 days coded with principal or secondary CDAD diagnosis
Leitner[124]	treatment failure	change to an alternative antibiotic regimen
	recurrence	recurrent episode occurring at least two weeks following a previous episode

*No definitions provided for Marts[113] and Lahue[116]
CDAD=C. *difficile*-associated diarrhea; CDI=C. *difficile* infection; ICU=intensive care unit; PMC=pseudomembranous colitis; WBC=white blood cell

APPENDIX 10: CLINICAL PRACTICE GUIDELINES – RECOMMENDATIONS AND QUALITY ASSESSMENT

Table 1: Clinical Practice Guidelines – Recommendations and strength of the evidence*

SHEA-IDSA[16]	ESCMID[19]
Objectives	
To improve the diagnosis and management of CDI in adult patients by updating recommendations regarding epidemiology, diagnosis, treatment, infection control and environmental management.	To evaluate the available evidence regarding the treatment of CDI and formulate recommendations for treatment.
Treatment of Non-Severe Initial Episode	
Metronidazole 500 mg po tid for 10 to 14 days (**A-I)**	If oral therapy possible: Metronidazole 500 mg po tid for 10 days (**A-I)** If oral therapy not possible: Metronidazole 500 mg iv tid for 10 days **(A-III)**
Criteria for Severe Disease	
Leukocytosis with a white blood cell count ≥15,000 cells/μL Serum creatinine level ≥ 1.5 times the premorbid level **(based on expert opinion)**	CDI is judged to be severe when one or more of the markers of severe colitis is present: <u>Physical examination</u> -fever (core body temperature >38.5°C) -rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature) -haemodynamic instability including signs of vasodilatory or septic shock -signs of peritonitis, including decreased bowel sounds, abdominal tenderness, rebound tenderness and guarding -signs of ileus including vomiting and absent passage of stool <u>Laboratory investigations</u> -marked leukocytosis (leukocyte count >15 X 109/L) -marked left shift (band neutrophils >20% of leukocytes) -rise in serum creatinine (>50% above the baseline) -elevated serum lactate <u>Colonoscopy or sigmoidoscopy</u> -pseudomembranous colitis <u>Imaging</u> -distension of large intestine -colonic wall thickening including low-attenuation mural thickening -pericolonic fat stranding -ascites not explained by other causes

Table 1: Clinical Practice Guidelines – Recommendations and strength of the evidence*	
SHEA-IDSA[16]	**ESCMID[19]**
	It is unclear whether moderate disease in a patient with other unfavourable prognostic factors such as advanced age (≥65 years), comorbidity, ICU admission, and immunodeficiency should be regarded as severe.
Treatment of Severe Initial Episode	
Vancomycin 125 mg po qid for 10 to 14 days (**B-I)**	If oral therapy possible: Vancomycin 125 mg po qid for 10 days (**A-I)** If oral therapy not possible: Metronidazole 500 mg iv tid for 10 days **(A-III)** + intracolonic vancomycin 500 mg in 100 mL of ns every 4 to 12 h **(C-III)** and/ or vancomycin 500 mg qid by nasogastric tube **(C-III)**
Criteria for Severe, Complicated Disease	
Hypotension or shock, ileus, megacolon **(based on expert opinion)**	NR
Treatment of Severe, Complicated Initial Episode	
Vancomycin 500 g qid po or by nasogastic tube with or without metronidazole 500 mg iv every 8 h. Consider adding rectal installation of vancomycin 500 mg in 100 mL ns every 6 h in cases of complete ileus **(C-III)**	NR
Treatment of first recurrent episode	
Same as initial episode **(A-II)** but should be stratified based on disease severity **(C-III)**	Treat a first recurrence as a first episode, unless the disease has progressed from non-severe to severe **(not rated for strength)**
Treatment of subsequent recurrent episodes	
Vancomycin in a tapered and/or pulsed regimen **(B-III)**	If oral therapy is possible: Vancomycin 125 mg po qid for 10 days **(B-II)** Consider a taper strategy (decreasing daily dose by 125 mg every 3 days) or a pulse strategy (a dose of 125 mg every 3 days for 3 weeks) **(B-II)** If oral therapy is not possible: Metronidazole 500 mg iv tid for 10 to 14 days **(A-III)** + retention enema of vancomycin 500 mg in 100 mL of ns every 4 to 12 h **(C-III)** and/or vancomycin 500 mg qid by nasogastric tube **(C-III)**
Other Recommendations	
Metronidazole is not recommended beyond the first recurrence or for long-term chronic therapy due to cumulative neurotoxicity **(B-II)**	In all of the above cases, vacomycin may be replaced by teicoplanin 100 mg bid (not available in Canada) **(not rated for strength)**

Table 1: Clinical Practice Guidelines – Recommendations and strength of the evidence*	
SHEA-IDSA[16]	**ESCMID[19]**
	There is no evidence that various genotypes of C. *difficile* should be treated differently if disease severity does not differ.

bid= twice daily; CDI= *C. difficile* infection; ESCMID= European Society of Clinical Microbiology and Infectious Diseases; h= hour; iv= intravenous; NR= not reported; ns= normal saline; po= orally; qid= four times daily; SHEA-IDSA= Society for Healthcare Epidemiology of America-Infectious Diseases Society of America; tid= three times daily

*according to the Canadian Task Force on Preventative Health Care
Strength of recommendation
A: Good evidence to support a recommendation
B: Moderate evidence to support a recommendation
C: Poor evidence to support a recommendation

Quality of the Evidence
I: Evidence from ≥ one properly randomized controlled trial
II: Evidence from ≥ one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one centre); from multiple time-series; or from dramatic results from uncontrolled experiments
III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Table 2: AGREE[104] scores – ESCMID guidelines		
Criteria	**Standardized domain score***	
	SHEA-IDSA[16]	**ESCMID[19]**
Scope and purpose		
The overall objective(s) of the guideline is (are) specifically described	83.3%	22.2%
The clinical question(s) covered by the guideline is(are) specifically described		
The patients to whom the guideline is meant to apply are specifically described		
Stakeholder involvement		
The guideline development group includes individuals from all the relevant professional groups	4.2%	20.8%
The patients' views and preferences have been sought		
The target users of the guideline are clearly defined		
The guideline has been piloted among target users		
Rigor of development		
Systematic methods were used to search for evidence	64.3%	50.0%
The criteria for selecting the evidence are clearly described		
The methods used for formulating the recommendations are clearly described		
The health benefits, side effects, and risks have been considered in formulating the recommendations		

There is an explicit link between the recommendations and the supporting evidence		
The guideline has been externally reviewed by experts prior to its publication		
A procedure for updating the guideline is provided		
Clarity and presentation		
The recommendations are specific and unambiguous	91.7%	91.7%
The different options for management of the condition are clearly presented		
Key recommendations are easily identifiable		
The guideline is supported with tools for application		
Applicability		
The potential organizational barriers in applying the recommendations have been discussed	33.3%	11.1%
The potential cost implications of applying the recommendations have been considered		
The guideline presents key review criteria for monitoring and/or audit purposes		
Editorial independence		
The guideline is editorially independent from the funding body	100%	33.3%
Conflicts of interest of guideline development members have been recorded		

*Standardized domain score = $\frac{\text{obtained score – minimum possible score}}{\text{maximum possible score – minimum possible score}}$

ESCMID=European Society of Clinical Microbiology and Infectious Diseases; SHEA-IDSA= Society for Healthcare Epidemiology of America-Infectious Diseases Society of America

APPENDIX 11: DATA EXTRACTION FORM FOR ECONOMIC STUDIES

Reference ID	
Author, title, journal, publication date	
Study characteristics	1. Study question or objective
	2. Study indication
	3. Study population selection criteria
	4. Study population characteristics
	5. Disease risk of included study population
	6. Study intervention
	7, Study comparator
	8. Type of economic analytic techniques
	9. Analysis type
	10. Currency and year
	11, Care setting or study geographic location
	12, Study perspective
	13. Discounting rate and justification
	14. Analysis time horizon
Source of data	15. Source of effectiveness data
	16. Source of cost data
Method for estimation of benefits and costs	17. Health outcomes
	18. If CBA study, status of outcomes or benefits
	19. Valuation for clinical effectiveness of intervention
	20, Approach for health state assessment
	21, Content of cost considered in study
	22, Cost estimation approach
	23. Modelling (if model used)
	24. Sensitivity analysis type
	25. Key parameters on which sensitivity analysis was done on
	26. Statistical analysis
	27. Sub-group analysis (if applicable)
	28. Regression analysis (if applicable)
Results and analysis	29. Clinical outcome and benefits
	30. Costs
	31. Synthesis of costs and benefits
	32. Health related quality of life benefits
	33. Statistical analysis results
	34. Sensitivity analysis results
	35. Sub-group analysis results
	36. Regression analysis results
Conclusion	37. Conclusion
	38. Limitations
	39. Funding source (if applicable)

APPENDIX 12: VALIDITY ASSESSMENT FOR ECONOMIC STUDIES

Table 1: BMJ Checklist for quality of reporting of economic studies
Study design
1 Research question is stated
2. Economic importance of research question is stated
3. Viewpoints of analysis are clearly stated and justified
4. Rationale for choosing alternative programs or interventions compared is stated.
5. Alternatives being compared are clearly described
6. Form of economic evaluation used is stated.
7. Choice of form of economic evaluation is justified in relation to questions addressed.
Data collection
8. Sources of effectiveness estimates used are stated.
9. Details of design and results of effectiveness study are given (if based on one study).
10. Details of method of synthesis or meta-analysis of estimates are given (if based on overview of a number of effectiveness studies)
11. Primary outcome measure for economic evaluation is clearly stated.
12. Methods to value health states and other benefits are stated.
13. Details of patients from whom valuations were obtained are given.
14. Productivity chances (if included) are reported separately.
15. Relevance of productivity changes to study question is discussed.
16. Quantities of resources are reported separately from their unit costs.
17. Methods for estimation of quantities and unit costs are described.
18. Currency and price data are recorded.
19. Details of currency of price adjustments for inflation or currency conversion are given.
20. Details of any model used are given.
21. Choice of model used and key parameters on which it is based are justified.
Analysis and interpretation of results
22. Time horizon of costs and benefits is stated.
23. Discount rate(s) is stated.
24. Choice of rate(s) is justified.
25. Explanation is given if costs or benefits are not discounted.
26. Details of statistical tests and confidence intervals are given for stochastic data.
27. Approach to sensitivity analysis is given.
28. Choice of variables for sensitivity analysis is justified.
29. Range over which variables are varied is stated.
30. Relevant alternatives are compared.
31. Incremental analysis is reported.
32. Major outcomes are presented in disaggregated and aggregated form.
33. Answer to study question is given.
34. Conclusions follow from data reported.
35. Conclusions are accompanied by appropriate caveats.

Table 2: Checklist for assessing external validity of included economic studies (yes, no, partial)
Does research question reflect issue?
Did clinical data used in analysis reflect what might be achieved in routine clinical practice in Canada?
Are resource use pattern and relative unit cost levels generalizable to Canada?
Is uncertainty adequately reflected in analysis?

APPENDIX 13: EXCLUDED ECONOMIC STUDIES

Excluded based on study design

Clostridium difficile - Associated diarrhoea is costly. Drugs Ther Perspect. 1997;9(3):13-6.

Bartlett JG. The case for vancomycin as the preferred drug for treatment of Clostridium difficile infection. Clin Infect Dis [Internet]. 2008 May 15 [cited 2009 Nov 11];46(10):1489-92. Available from: http://www.journals.uchicago.edu/doi/pdf/10.1086/587654

Burnakis TG. Metronidazole versus vancomycin for antimicrobial-associated pseudomembranous colitis: The question of cost-effectiveness. Hosp Pharm. 1985;20(10):742-7.

Janka J, O'Grady NP. Clostridium difficile infection: Current perspectives. Curr Opin Crit Care. 2009;15(2):149-53.

Pakyz AL, Carroll N, Harpe S, Oinonen M, Polk R. Economic Impact of Hospital-Acquired Clostridium difficile Infection (HA-CDI) in US University Teaching Hospitals [abstract]. Abstr Interscience Conf Antimicrob Agents Chemother. 2008;48:577. (Presented at 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious-Diseases-Society-of-America, Washington, DC, USA).

Remington H, Standing VF. Cost of vancomycin [letter]. Lancet. 1983;2(8361):1259.

Riley TV. Antibiotic-associated diarrhoea: A costly problem. Pharmacoeconomics. 1996;10(1):1-3.

Soice S, Fradette M, Valji T. Cost-effective approaches for the treatment of Clostridium difficile colitis. Hosp Pharm. 1991;26(7):660-1.

Excluded based on population

Butterworth SA, Koppert E, Clarke A, Wiggs B, MacFarlane JK. Recent trends in diagnosis and treatment of Clostridium difficile in a tertiary care facility. Am J Surg. 1998 May;175(5):403-7.

Excluded based on intervention or comparator

Abad F, Calbo F, Zapater P, Rodriguez-Vilanova F, Garcia-Perez L, Sacristan JA. Comparative pharmacoeconomic study of vancomycin and teicoplanin in intensive care patients. Int J Antimicrob Agents. 2000 Jun;15(1):65-71.

APPENDIX 14: ECONOMIC REVIEW – STUDY CHARACTERISTICS AND VALIDITY ASSESSMENT

Table 1: Methods used in the included economic studies on CDI

Author, Country, Setting	Intervention and comparator	Type of economic evaluation, Perspective, Time Horizon	Clinical data sources	Economic data sources and costs included in analysis	Currency and year for cost evaluation
Lahue 2007[116] United States, inpatient	vancomycin and metronidazole	Cost-consequences Hospital Duration of hospital stay (11.5 to 12.8 days)	Retrospectively analyzed electronic health records of 32,325 patients (3,420 receiving vancomycin and 28,905 receiving metronidazole) from a national hospital database (Premier Perspective) between January 2004 and June 2005	Premier Perspective hospital database Pharmacy costs and hospitalization costs	US dollars, year not stated, but may be 2004-2005 based on years of data collection from database
Thomas 2007[127] United States, inpatient and outpatient	vancomycin and metronidazole	Costing Unclear but may be Medicare population Not stated. Model allows for up to six recurrences and follows patients until they are either cured or die (intervals between recurrences and duration of follow-up not specified)	Not reported	Medicare database for direct outpatient costs; Medicare diagnosis related groups for direct hospital costs Direct outpatient costs included clinic visits, antibiotics (vancomycin or metronidazole), stool tests; direct hospital costs included	US dollars, year not stated

				those for enteritis and complications	
Al-Eidan 2000[115] Ireland, inpatient	not a comparative study (however analyses on outcomes and some costs conducted on patients taking vancomycin versus those taking metronidazole)	Costing Hospital Duration of hospital stay (mean 16.9±6.3 days)	Retrospective chart review over two-year period from single hospital in Ireland	Utilization data from chart review but source of costs not stated Only drug costs were reported by treatment group	British pounds, year not stated

CDI=*Clostridium difficile* infection

Table 2: Results reported in the included economic studies on CDI

Author	Cost outcomes	Results of sensitivity analysis	Conclusion	Limitations
Lahue 2007[116]	CDI therapy cost: v $375 m $90, p<0.0001 Total pharmacy costs: v $2,492 m $2,439, p=0.52 Hospitalization costs: v $14,718 m $16,953, p<0.0001	NA	Most CDI patients received metronidazole, and modifications to initial therapy occurred in similar proportions of metronidazole and vancomycin cases. Compared to initial therapy with vancomycin, those receiving metronidazole had higher rates of poor discharge outcomes and higher total costs, however comparisons do not adjust for comorbidities.	Information for this reference was obtained from an abstract and a presentation and was thus limited in detail; clinical and economic data obtained retrospectively; No adjustment for comorbidities and patients on metronidazole may have been sicker; sensitivity analyses not conducted.
Thomas 2007[127]	Average treatment cost: v $910 m $561	Probabilistic and deterministic Equivalent costs	Despite increasing resistance rates of CDI to metronidazole,	Information for this reference was obtained from an abstract

		between groups were attained only once resistance rates of metronidazole approached 75%. Vancomycin expense would need to be reduced by 88% to achieve superiority to metronidazole.	metronidazole outperforms vancomycin as first-line therapy in the treatment of CDI largely due to the expense of vancomycin. First line therapy for CDI should remain as metronidazole unless resistance rates become substantial or the cost of vancomycin is significantly reduced.	and was thus limited in detail; Source of clinical data and patient characteristics not given; time horizon not specified; indirect costs not considered in model.
Al-Eidan 2000[115]	Cost of drug therapy: v £162.5 m £1.60, p<0.001	NA	Treatment of CDI with oral metronidazole and oral vancomycin gives rise to similar response times and efficacy.	Not a cost analysis of a treatment comparative study; retrospective; Based on one study from a single location; small sample size; limited costing with regards to comparative treatments (drug costs only); source and date of costing information not specified; sensitivity analysis not conducted.

CDI=*Clostridium difficile* infection; NA=not applicable

Table 3: External validity checklist for the economic review			
Criterion	**Lahue 2007 (abstract)[116]**	**Thomas 2007 (abstract)[127]**	**Al-Eidan 2000[115]**
Does the research question reflect the issue presently concerned?	Yes	Yes	Partial
Did the clinical data used in the analysis reflect what might be achieved in the routine clinical practice in Canada?	Partial	Uncertain - clinical data were not described	Partial
Are resource use pattern and relative unit cost levels generalizable to Canada?	Partial	Partial	Partial
Is uncertainty adequately reflected in the analysis?	No	Partial	No

APPENDIX 15: PRIMARY ECONOMIC EVALUATION — DRUG USE AND PRICES, PARAMETERS FOR PROBABILISTIC SENSITIVITY ANALYSES, AND RESULTS FOR SENSITIVITY ANALYSES ON COMPLICATION RATES

Table 1: Drug use and prices in economic evaluation

Treatment Group	Indication			
	Initial Therapy	**Relapse**	**Failure without complication**	**Failure with complication**
metronidazole	metronidazole capsule given orally, in hospital and community, 500 mg tid, daily cost $0.36.[88,97,98] Initial therapy is given up to 10 days, with treatment failures being evaluated and changing therapy after 5th day.	vancomycin, capsule given orally, in community, 125 mg qid 10-14 days, daily cost $31.22[88,97,98]	vancomycin, capsule given orally in community, 125 mg qid, daily cost $31.22[88,97,98]; or vancomycin IV formulation given orally in hospital, 500 mg/day, daily cost $3.43*. Therapy given for 10-14 days	metronidazole IV, 500 mg every 8 hours, daily cost $3.93*; plus vancomycin IV 500 mg qid, daily cost $13.70*; both drugs administered in hospital Therapy given for 10-14 days
vancomycin	Basecase: vancomycin, capsule given orally, in hospital and community, 125 mg qid, daily cost $31.22[88,97,98]; Sensitivity analysis: vancomycin given in hospital as IV formulation given orally, 500 mg/day, daily cost $3.43*. Initial therapy is given up to 10 days, with treatment failures being evaluated and changing therapy after 5th day.	vancomycin, capsule given orally, in community, 500 mg qid, 10-14 days, daily cost $124.87[88,97,98]	vancomycin, capsule given orally in community, 500 mg qid, daily cost $124.87[88,97,98]; or vancomycin IV formulation given orally in hospital, 500 mg qid, daily cost $13.70*. Therapy given for 10-14 days	

*Daily cost of therapy estimated from prices obtained from Mr. Benoit Cossette, Pharmacist, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC: personal communication, 2010 August 31
qid=four times daily; tid=three times daily

Table 2: Distribution of probabilities* used in probabilistic sensitivity analysis				
Model	**Parameter**	**alpha**	**beta**	**probability**
Base case	**Metronidazole**			
	P(success)	37	20	.6491
	P(relapse|success)	5.55	31.45	.1500
	P(no relapse|success)	31.45	5.55	.8500
	P(failure)	20	37	.3509
	P(complication|failure)	5.871	14.129	.2936
	P(no complication|failure)	14.129	5.871	.7065
	P(colectomy|complication)	2.407	3.464	.4100
	Vancomycin			
	P(success)	28	5	.8485
	P(relapse|success)	4.2	23.8	.1500
	P(no relapse|success)	23.8	4.2	.8500
	P(failure)	5	28	.1515
	P(complication|failure)	3.399	1.601	.6798
	P(no complication|failure)	1.601	3.399	.3202
	P(colectomy|complication)	1.394	2.005	.4100
Complication rate of 33% among clinical failures	**Metronidazole**			
	P(success)	37	20	.6491
	P(relapse|success)	5.55	31.45	.1500
	P(no relapse|success)	31.45	5.55	.8500
	P(failure)	20	37	.3509
	P(complication|failure)	6.6	13.4	.3300
	P(no complication|failure)	13.4	6.6	.6700
	P(colectomy|complication)	2.706	3.894	.4100
	Vancomycin			
	P(success)	28	5	.8485
	P(relapse|success)	4.2	23.8	.1500
	P(no relapse|success)	23.8	4.2	.8500
	P(failure)	5	28	.1515
	P(complication|failure)	1.65	3.35	.3300
	P(no complication|failure)	3.35	1.65	.6700
	P(colectomy|complication)	0.677	0.974	.4100
*All probabilities assumed to follow beta distribution.				

Table 3: Distribution of costs in probabilistic sensitivity analyses					
Parameter	**Distribution**	**Mean**	**SE**	**alpha**	**beta**
Metronidazole					
1500 mg/d in capsule	Fixed	0.357	-	-	-
1500 mg/d IV	Fixed	3.93	-	-	-
Vancomycin					
500 mg/d in capsule	Fixed	31.22	-	-	-
2000 mg/d IV given orally	Fixed	13.70	-	-	-
2000 mg/d in capsule	Fixed	127.84	-	-	-
Hospital per diem					
No complications	Gamma	1916	958	4	0.00209
Complications	Gamma	2283	1141	4	0.00175
Procedures					
Colectomy	Gamma	1700.46	850.23	4	0.00235
Colonoscopy	Gamma	91.6	45.80	4	0.04367
Physician consultations					
Surgical	Gamma	89.30	44.65	4	0.04479
Family physician	Gamma	62.65	32.33	4	0.06385

Table 4: Sensitivity analysis on complication rates in patient population from Louie et al.[111]			
Probability of complication given treatment failure	**Average total patient costs**		
	Metronidazole	**Vancomycin**	**Increment**
0.0	$32,441	$32,780	$339
0.1	$33,660	$33,290	-$370
0.2	$34,879	$33,801	-$1,078
0.3	$36,098	$34,312	-$1,786
0.4	$37,318	$34,823	-$2,495
0.5	$38,537	$35,334	-$3,203
0.6	$39,756	$35,844	-$3,912
0.7	$40,975	$36,355	-$4,620
0.8	$42,195	$36,866	-$5,329
0.9	$43,414	$37,376	-$6,038
1.0	$44,633	$37,887	-$6,746

Incremental effectiveness of vancomycin versus metronidazole in Louie et al.[111] was 0.199.
Approximately one-third of patient population in Louie et al. was infected with the NAP1 strain.

Table 5: Sensitivity analysis on complication rates in patient population from Zar et al.[109]			
Probability of complication given treatment failure	**Average total patient costs**		
	Metronidazole	**Vancomycin**	**Increment**
0.0	$32,364	$32,591	$227
0.1	$33,187	$32,700	-$487
0.2	$34,010	$32,808	-$1,202
0.3	$34,833	$32,917	-$1,916
0.4	$35,656	$33,026	-$2,630
0.5	$36,478	$33,134	-$3,344
0.6	$37,301	$33,243	-$4,058
0.7	$38,125	$33,352	-$4,773
0.8	$38,948	$33,461	-$5,487
0.9	$39,770	$33,569	-$6,201
1.0	$40,593	$33,678	-$6,915

Incremental effectiveness of vancomycin versus metronidazole in Zar et al.[109] was 0.205. Patient population in Zar et al. is considered to be pre-NAP1

Table 6: Sensitivity analysis on complication rates in NAP1* patient population			
Probability of complication given treatment failure	**Average total patient costs**		
	Metronidazole	**Vancomycin**	**Increment**
0.0	$33,570	$33,131	$561
0.1	$34,581	$34,448	-$133
0.2	$36,593	$35,766	-$857
0.3	$38,604	$37,083	-$1,521
0.4	$40,616	$38,401	-$2,215
0.5	$42,628	$39,719	-$2,909
0.6	$44,639	$41,036	-$3,603
0.7	$46,651	$42,354	-$4,297
0.8	$48,663	$43,671	-$4,992
0.9	$50,674	$44,989	-$5,685
1.0	$52,686	$46,306	-$6,380

* Incremental effectiveness of vancomycin versus metronidazole in NAP1 population estimated using data from Louie et al.[111] and Zar et al.[109] was 0.188.