National Institute for Health and Care Excellence

Draft for consultation

Clostridioides difficile infection: antimicrobial prescribing guideline

Evidence review

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Draft for consultation

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ISBN:

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1 Context

1.1 Background

Diarrhoea is the abnormal passing of loose or liquid stools, with increased frequency and/or increased volume. It can be categorised as persistent (lasting more than 14 days), chronic (lasting more than 4 weeks) or acute (lasting less than 14 days). Acute diarrhoea is defined as 3 or more episodes of diarrhoea per day for less than 14 days with stools taking the shape of the container used to sample it (Public Health England 2015).

Acute infectious diarrhoea can be caused by viral (for example norovirus, sapovirus and rotavirus), bacterial (for example *Salmonella* species, *Campylobacter* species, *Shigella* species, *Escherichia coli* and *Clostridioides difficile [C. difficile]*) or parasitic (for example *Cryptosporidium*, *Giardia*, *Entamoeba histolytica*, and *Cyclospora*) infection, but in 60% of cases no infectious agent is found. Other causes of diarrhoea include medicines, anxiety, food allergy and acute appendicitis (NICE clinical knowledge summary: Diarrhoea - adult's assessment 2018).

Infectious diarrhoea is common affecting 1 in 4 people in the UK each year (NICE clinical knowledge summary: Diarrhoea - adult's assessment 2018). Most infectious diarrhoea is self-limiting with nearly half of episodes lasting less than 1 day, and most cases usually stopping within 5 to 7 days (NHS online).

Diarrhoea is a common consequence of antibiotic treatment occurring in 2 to 25% of people taking antibiotics, depending on the antibiotic prescribed. An estimated 20% to 30% of cases of antibiotic-associated diarrhoea are due to *C. difficile* (NICE clinical knowledge summary: Diarrhoea - antibiotic associated 2019). *C. difficile* are bacteria that exist in the environment and can become established in the colon of healthy people, affecting up to 3% of adults and 66% of babies.

C. difficile infection (CDI) occurs when other harmless bacteria in the colon are disrupted (for example, by taking antibiotics) or when the immune system is compromised, allowing the numbers of *C. difficile* bacteria to increase to high levels. However, an overgrowth of *C. difficile* alone does not cause diarrhoea. *C. difficile* diarrhoea is caused by toxins produced by certain strains of *C. difficile* which damage the lining of the colon. Antibiotics frequently associated with CDI including clindamycin, cephalosporins (especially third and fourth generation), fluoroquinolones, and broad-spectrum penicillins (NICE clinical knowledge summary: Diarrhoea - antibiotic associated 2019). However, all broad-spectrum antibiotics need to be prescribed appropriately and with careful stewardship to reduce the risk of CDI (NICE evidence summary: CDI risk with broad-spectrum antibiotics). The number of *C. difficile* infections in the NHS in England decreased substantially from 2007/08 to 2018/19, falling from 55,498 cases to 12,275 cases (Public Health England 2019). This has been attributed to surveillance programmes, measures to control antibiotic prescribing, and implementation of and compliance with isolation and hygiene protocols.

If CDI is suspected a stool sample is sent for testing (NICE clinical knowledge summary: Diarrhoea - antibiotic associated 2018).

The severity of CDI can be categorised as (Public Health England 2019):

- **mild**: not associated with an increased white cell count (WCC) and less than 3 loose stools (loose enough to take the shape of the container used to sample it) per day)
- **moderate**: associated with an increased WCC but less than 15 x 10^9/L and associated with 3 to 5 loose stools per day

- **severe**: associated with a WCC greater than 15 x 10^9/L, or an acutely increased serum creatinine concentration (greater than 50% increase above baseline), or a temperature higher than 38.5°C, or evidence of severe colitis (abdominal or radiological signs)
- **life-threatening**: signs and symptoms including hypotension, partial or complete ileus, toxic megacolon, or computerised tomography evidence of severe disease.

1.2 Antimicrobial stewardship

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers consider the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.3 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2019 to 2020 reported that antimicrobial prescribing has been decreasing since its peak in 2014, with the total consumption of antibiotics in primary and secondary care (measured in terms of new defined daily doses) declining by 7.5% from 2015 to 2019. This reflected a 12.2% and 19.5% decrease in GP and dental antibiotic prescribing, and a 3.5% increase in secondary care prescribing. In 2019, the most commonly used antibiotic groups were penicillins (37.8%), tetracyclines (26.4%) and macrolides (15.3%).

Over the 5-year period, significant declining trends of use were seen for penicillins (excluding inhibitor combinations), first and second-generation cephalosporins, carbapenems, macrolides, lincosamides and streptogramins, sulfonamides and trimethoprim. In contrast, use of third, fourth and fifth generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

Anti-C. *difficile* agents (oral vancomycin and fidaxomicin) total consumption was unchanged between 2015 and 2019, while use of metronidazole had a significant declining trend in total consumption from 2015 to 2019.

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for *C. difficile* infection.

This evidence review outlines the evidence for the treatment and prevention of *C. Difficile* infection.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for the treatment and prevention of *C. Difficile* infection (see appendix C: literature search strategy for full details). The literature search identified 1768 references. These references were screened using their titles and abstracts and 351 full text references were obtained and assessed for relevance. 59 full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). 10 percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. 18 of the 59 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies). 11 studies were included for treatment and 7 studies were included for prevention. One additional study was identified by the committee which was included in the evidence review.

The 41 references that were not prioritised for inclusion for treatment and prevention are listed in appendix J: studies not prioritised, with reasons for not prioritising the studies. Also see appendix E: evidence prioritisation for more information on study selection.

The literature search was re-run from July 2019 to July 2020 to consider any new published evidence and update the existing evidence review considered by the NICE committee in December 2019. The updated literature search identified 241 additional references. These references were screened using their title and abstracts and 62 full text references were obtained (n=17 had already been identified in the original search and were not considered further) and assessed for relevance. 2 full text references of RCTs were assessed as relevant to the guideline review question and included for full text review. 1 of the 2 references was prioritised by the committee as the best available evidence and was included for prevention (see appendix F: included studies). 12 studies were included for treatment and 8 studies were included for prevention in total.

The 1 reference that was not prioritised for inclusion for prevention is listed in appendix J: studies not prioritised, with reasons for not prioritising the studies.

The remaining 335 references were excluded. These are listed in appendix K: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in table 1 to table 12**.** Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Methods used for modified GRADE assessment for network meta-analysis are included in appendix H. For outcomes reporting odds ratios (OR), a minimal important difference (MID) of 1 (line of no difference) was used to assess effectiveness, this is due to the severe consequences of not treating *C. difficile* infection appropriately.

2.2.1 Treatment

Table 1: Summary of included studies: antibiotic versus placebo

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Nelson et al. 2017 Systematic review	1 RCT N=44	Individuals with postoperative diarrhoea from surgical wards and no previous history of pseudomembranous colitis	Oral vancomycin 125 mg four times a daily for 5 days	Placebo	Symptomatic cure; bacteriological cure
Abbreviations: RCT: randomised control trial					

Table 2: Summary of included studies: antibiotic versus antibiotic

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Beinortas et al. 2018 Network meta-analysis	24 RCTs N=5,361	Adults ≥18 years with confirmed CDI	Fusidic acid, Fidaxomicin, Metronidazole Cadazolid, Rifaximin, Surotomycin, Teicoplanin, Ridinilazole, LFF571, Nitazoxanide, Tolevamer, Bacitracin[1]	Vancomycin (reference treatment)	Sustained symptomatic cure calculated as the number of patients with a primary cure (resolution of diarrhoea) at the end of treatment minus the number of patients with recurrence (recurrence of diarrhoea or requirement for additional treatment) or who died during the follow-up period
Gawronska et al. 2017 Poland	1 RCT N=31	Children and young people ≤18 years with inflammatory bowel disease and CDI	Metronidazole 750mg to 1.5g three times a day for 14 days	Rifaximin 600mg to 1.2g, three times a day for 14 days	CDI cure

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Wolf et al. 2019 Europe, Canada, USA	1 RCT N=148	Children and young people <18 years with CDI	Fidaxomicin 16 mg/kg oral suspension twice a day for those aged 0–<6 years, or 200 mg tablets twice a day for those aged ≥6–<18 years for 10 days	Vancomycin 10 mg/kg oral liquid four times a day for those aged 0 to <6 years, or 125 mg capsules four times a day for those aged ≥6 to <18 years for 10 days	Confirmed clinical response defined as initial clinical response at end of treatment with no further requirement for CDI therapy at 2 days post treatment
Abbreviations: CDI: *Clostridioides difficile* infection; RCT: randomised control trial					
[1] Ridinilazole, cadazolid, surotomycin, nitazoxanide, tolevamer, LFF571 and bacitracin are outside the scope of this guideline because they are not available in the UK					

Table 3: Summary of included studies: antibiotic dose

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Nelson et al. 2017 Systematic review	1 RCT N=56	Individuals with CDI	Vancomycin 125 mg four times a day (mean duration 10.6 days)	Vancomycin dose 500 mg four times a day (mean duration 10.1 days)	Cure; bacteriologic resolution;
Nelson et al. 2017 Systematic review	1 RCT N=48	Individuals with a primary or first relapse of CDI that was mild to moderate	Fidaxomicin 400 mg daily for 10 days	Fidaxomicin 100 mg daily for 10 days Fidaxomicin 200 mg daily for 10 days	Resolution of diarrhoea and abdominal discomfort; relapse
Abbreviations: CDI: *Clostridioides difficile* infection; RCT: randomised controlled trial					

Table 4: Summary of included studies: antibiotic frequency

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Nelson et al. 2017 Systematic review	1 RCT N=92	Individuals with CDI	Teicoplanin 100 mg twice a day	Teicoplanin 50 mg four times a day	Cure; bacteriologic resolution; relapse

Table 5: Summary of included studies: Faecal microbiota transplant (FMT)

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Camacho-Ortiz et al 2017 (initial treatment) RCT Mexico	N=19	Adults ≥18 years hospitalised for any cause and diagnosed with a first CDI episode >48 hours after admission	1 dose FMT – mode of delivery	Vancomycin 250 mg four times a day for 10 to 14 days	CDI resolution
Dubberke et al 2018 RCT USA	N=128	Adults ≥18 years with recurrent CDI and either 2 or more documented recurrences of CDI after a primary episode or 2 or more documented episodes of severe CDI that resulted in hospitalisation. Administration of the first doses FMT commenced 24–48 hours following completion of CDI treatment antibiotics, with the second dose administered 7 ± 2 days thereafter based on the need to control suspected CDI recurrence.	2 doses FMT enema drug candidate (RBX2660)	2 doses placebo enema 1 dose FMT enema drug candidate (RBX2660) and 1 dose placebo enema	Prevention of recurrent CDI
Van Nood et al 2013 RCT Holland	N=42	Adults ≥18 years with a relapse of CDI after at least 1 course of adequate antibiotic therapy	FMT preceded by vancomycin 500 mg four times a day for 4 days and bowel lavage with macrogol	Vancomycin 500 mg four times a day for 14 days Vancomycin 500 mg four times a day for	Resolution of diarrhoea associated with CDI without relapse

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
				14 days with bowel lavage on day 4 or 5	
Hota et al 2017 RCT Canada	N=30	Adults ≥18 years with at least 2 episodes of laboratory or pathology-confirmed CDI who had received at least 1 course of vancomycin	FMT preceded by 14 days of vancomycin 125 mg four times a day	Vancomycin 125 mg four times a day for 14 days, then tapered dose over 4 weeks	Recurrence of symptomatic, laboratory-confirmed CDI
Cammarota et al 2015 RCT	N=128	Adults ≥18 years with a recurrence of CDI after 1 or more courses of specific antibiotic therapy	FMT preceded by vancomycin 125 mg four times a day for 3 days and bowel lavage with macrogol	Vancomycin 125 mg four times a day for 10 days then pulsed vancomycin for at least 3 weeks	Resolution of diarrhoea associated with CDI
Hvas et al 2019 RCT	N=64	Adults ≥18 years with an acute episode of recurrence CDI who had at least 1 previous episode of CDI	FMT preceded by vancomycin 125 mg four times a day for 4 to 10 days	Vancomycin 125 mg four times a day for 10 days Fidaxomicin 200 mg twice a day for 10 days	Combined clinical resolution and a negative CDI test result without the need for rescue FMT preceded by vancomycin or colectomy
Abbreviations: ; CDI, *Clostridioides difficile* infection; RCT, randomised controlled trial					

Table 6: Summary of included studies: prebiotic - oligofructose

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Lewis et al 2005a Double-blind RCT UK	N=142	Adult inpatients with Diarrhoea associated with *Clostridioides difficile* infection;	Metronidazole or vancomycin for 10 days (dose not reported) with 12 g/day oligofructose for 30 days	Metronidazole or vancomycin for 10 days with placebo for 30 days	Development of further diarrhoea
Abbreviations:; RCT: randomised controlled trial					

Table 7: Summary of included studies: probiotics

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Basu et al 2007 RCT India	N=235	Children with a diagnosis of persistent diarrhoea for 14 days or more	Oral rehydration solution plus *Lactobacillus rhamnosus* GG powder (60 million cells) twice a day for a minimum of 7 days	Oral rehydration solution alone twice a day for a minimum of 7 days	Decrease in frequency and duration of diarrhoea and vomiting
Abbreviations: RCT: randomised controlled trial					

2.2.2 Prevention

Table 8: Summary of included studies: Antibiotics versus placebo for prevention of *Clostridioides difficile* infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Mullane et al 2019 RCT USA	N=611	Adults ≥18 years undergoing hematopoietic stem cell transplantation receiving fluoroquinolone prophylaxis during neutropenia	Fidaxomicin 200mg once a day for up to 40 days	Placebo	CDI associated diarrhoea incidence through 30 days after last dose of study medication
Johnson et al 2019 RCT USA	N=100	Adults with high risk of healthcare facility–onset CDI defined as ≥60 years, hospitalized ≥30 days prior to the index hospitalization, and received systemic antibiotics during that prior hospitalization	Vancomycin 125mg once a day whilst receiving systemic antibiotics and continued for 5 days post completion of systemic antibiotics	Placebo	Healthcare facility onset CDI defined as symptoms of loose stools (≥ 3) or diarrhoea in 24-hour period with a positive stool test for *C. Difficile* >72 hours into hospitalisation
Abbreviations: RCT: Randomised Controlled Trial; CDI: *Clostridioides difficile* infection					

Table 9: Summary of included studies: Antibiotics versus placebo for prevention of recurrence of *Clostridioides difficile* infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Major et al 2019 RCT UK	N=151	Adults aged ≥18 years immediately after resolution of CDI through treatment with	Rifaximin 400 mg three times a day for 14 days, reduced to 200 mg three times a	Placebo	Recurrence of CDI within 12 weeks

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		metronidazole or vancomycin.	day for a further 14 days		
Garey et al 2011 RCT USA	N=68	Adults aged ≥18 years with CDI and a Horn's index ≥1	Rifaximin 400mg three times a day for 20 days given immediately after finishing standard anti-CDI antibiotics (metronidazole or vancomycin)	Placebo	Recurrent diarrhoea that included CDI recurrence (return of diarrhoea with a positive toxin test) and patient self-reported return of non-CDI diarrhoea
Abbreviations: RCT: Randomised Controlled Trial; CDI: *Clostridioides difficile* infection					

Table 10: Summary of included studies: Monoclonal antibodies versus placebo for prevention of recurrence of *Clostridioides difficile* infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Wilcox et al 2017 2 RCTs (MODIFY I and MODIFY II) 30 countries	N=2,559	Adults aged >18 years with CDI treated with standard anti-CDI antibiotics (metronidazole, vancomycin or fidaxomicin)	Single intravenous infusion of bezlotoxumab 10mg/kg on study day 1, while receiving standard of care antibiotic therapy	Placebo (0.9% saline) infusion	Recurrence of CDI within 12 weeks
Abbreviations: RCT: Randomised Controlled Trial; CDI: *Clostridioides difficile* infection					

Table 11: Summary of included studies: Probiotic versus placebo for prevention of *Clostridioides difficile* infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Goldenberg et al 2017 Systematic review Multinational	39 RCTs N=9,955	Adults and children receiving antibiotics for any reason	Oral probiotic (drink or capsule, any species)	Placebo, other prophylaxis or no treatment	Incidence of CDI
Kolodziej and Szajewska 2019 RCT Poland	N=247	Hospitalised children <18 years receiving any antibiotic	Oral *Lactobacillus reuteri* drops	Placebo drops	Incidence of diarrhoea
Abbreviations: RCT: Randomised Controlled Trial; CDI: *Clostridioides difficile* infection					

Table 12: Summary of included studies: Prebiotic versus placebo for prevention of *Clostridioides difficile* infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Lewis et al 2005b RCT UK	N=435	Hospitalised adults aged ≥65 years prescribed a broad-spectrum antibiotic within the preceding 24 hours	Oral oligofructose powder (12g /day) during antibiotic treatment and for 7 days after	Oral placebo (sucrose) powder (12g/ day) during antibiotic treatment and for 7 days after	Incidence of antibiotic associated diarrhoea
Abbreviations: RCT: Randomised Controlled Trial; CDI: *Clostridioides difficile* infection					

1

3 Evidence summary

Full details of the evidence are shown in appendix I: GRADE profiles.

The main results are summarised below for adults, young people and children for the prevention and treatment of *C. difficile* infection (CDI).

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNFC) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

Table 13 outlines a summary of the evidence for treatment of CDI.

Table 13: Interventions for treatment of *Clostridioides difficile* infection

Comparison	Adults	Children
Antibiotic prescribing strategies	No evidence identified	No evidence identified
Antibiotic efficacy	Nelson et al. 2017 Wolf et al. 2019	No evidence identified
Antibiotic choice	Beinortas et al. 2018	Gawronska et al. 2017
Antibiotic dose	Nelson et al. 2017	No evidence identified
Antibiotic dose frequency	Nelson et al. 2017	No evidence identified
Antibiotic course length	No evidence identified	No evidence identified
Antibiotic route of administration	No evidence identified	No evidence identified
Faecal microbiota transplant	Camacho-Ortiz et al 2017 Dubberke et al 2018 Van Nood et al 2013 Hota et al 2017 Cammarota et al 2015 Hvas et al 2019	No evidence identified
Prebiotics	No evidence identified	Lewis et al 2005a
Probiotics	Basu et al 2007	No evidence identified

Table 14 outlines a summary of the evidence for prevention of CDI.

Table 14: Interventions for prevention of *Clostridioides difficile* infection

Comparison	Adults	Children
Antibiotic prescribing strategies	No evidence identified	No evidence identified
Antibiotic efficacy	Mullane et al 2019 Johnson et al 2019 Major et al 2019 Garey et al 2011	No evidence identified

Comparison	Adults	Children
Antibiotic choice	No evidence identified	No evidence identified
Antibiotic dose	No evidence identified	No evidence identified
Antibiotic dose frequency	No evidence identified	No evidence identified
Antibiotic course length	No evidence identified	No evidence identified
Antibiotic route of administration	No evidence identified	No evidence identified
Faecal microbiota transplant	No evidence identified	No evidence identified
Bezlotoxumab	Wilcox et al 2017	No evidence identified
Probiotics	Goldenberg et al 2017	Goldenberg et al 2017 Kolodziej and Szajewska 2019
Prebiotics	Lewis et al 2005b	No evidence identified

3.1 Treatment

3.1.1 Antibiotics in adults

3.1.1.1 Efficacy of antibiotic

Vancomycin versus placebo

The evidence for vancomycin versus placebo for the treatment of diarrhoea associated with *Clostridioides difficile* infection (CDI) comes from 1 randomised controlled trial (RCT) of people with post-operative diarrhoea treated for first occurrence of pseudomembranous colitis (n=44) within a systematic review (Nelson et al. 2017). Details of the study population were minimal within the systematic review. However, it divided patients into 3 groups based on stool analysis results and reported on 21 of 44 participants with some evidence of *C. difficile* infection, 16 of which were toxin positive and 5 culture positive. The study was judged to be at high risk of bias within the systematic review due to small sample size and high participant attrition. The primary outcomes were cure and bacteriological resolution. The intervention was oral vancomycin 125 mg four times a day for 5 days compared with placebo.

Vancomycin 125 mg four times a day for 5 days resulted in a significant increase in symptomatic cure (1 RCT, n=44, relative risk [RR] 9.0, 95% confidence interval [CI] 1.24 to 65.16, very low-quality evidence) and bacteriological cure (1 RCT, n=44, RR 10.0, 95% CI 1.40 to 71.62, very low-quality evidence) compared with placebo. Absolute values could not be calculated for this outcome due to the way they are reported in the systematic review.

See GRADE: **Table 32**

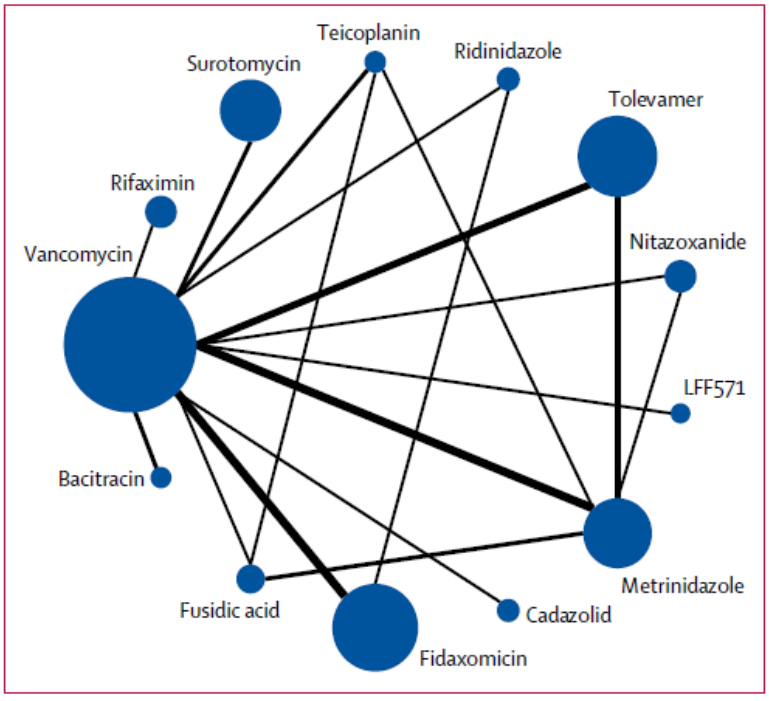
3.1.1.2 Antibiotic versus antibiotic for the treatment of a first episode or first recurrent episode of Clostridioides difficile infection

The evidence for vancomycin versus other antibiotics for the treatment of CDI comes from a random-effects network meta-analysis (NMA) undertaken within a frequentist setting (Beinortas et al. 2018) of adults (mean age 63) with first episode or first recurrent episode CDI (n=5361). Across included studies the mean age of participants ranged from 42 to 75 years and where reported between 0% to 29% of participants previously had a CDI; and 6% to 48% of participants having severe CDI. The NMA included 24 RCTs which investigated indirect and direct comparisons between 13 pharmacological treatments (see figure 1 for the network diagram) with

treatment duration ranging from 4 to 25 days and a median follow-up duration of 28 days (ranging from 21 to 90 days). Vancomycin was selected as the reference treatment by Beinortas et al (2018), as its use is considered widespread and it was a common comparator amongst trials, providing a closed network loop. Other treatments included: fusidic acid, fidaxomicin, metronidazole, cadazolid, surotomycin, teicoplanin, ridinilazole, LFF571, nitazoxanide, tolevamer and bacitracin. Some treatments that were included in the NMA are not in the scope of this review because they are not available in the UK (ridinilazole, cadazolid, surotomycin, nitazoxanide, tolevamer, LFF571 and bacitracin). Whilst these treatments cannot be disaggregated from the study analysis, they are not considered further here. The primary outcome was sustained symptomatic cure calculated as the number of patients with resolution of diarrhoea at the end of treatment, minus the number of patients with recurrence of diarrhoea or who required additional treatment or who died during the follow-up period.

Beinortas et al. (2018) generated a network diagram (see **figure 1**) and a league table of pairwise comparisons for attaining a sustained symptomatic cure (**Table 15**). Based on P scores (higher suggests better) the NMA ranks teicoplanin (P score=0.9386), ridinilazole (P score=0.8280) and fidaxomicin (P score=0.7922) as having the greatest chance of attaining a sustained symptomatic cure. Beinortas et al (2018) note that the effect estimates for teicoplanin are derived from 2 small RCTs (n=55) that were assessed as being at high risk of bias, and should be treated with caution. Overall, the quality of the outcome reported by the NMA was moderate. Sensitivity analysis was undertaken which removed non-blinded trials, studies with <50 patients per trial arm and RCTs published before 2000 from the NMA. See Table 16 for details.

Figure 1 Network diagram (taken from Beinortas et al. 2018)[1]



1 Line width is proportional to the number of trials comparing every pair of treatments. The size of the circle is proportional to the number of patients assigned to receive the treatment

Table 15: League table of pairwise comparisons from a network meta-analysis for attaining a sustained symptomatic cure (shaded boxes indicate significant differences) (adapted from Beinortas et al. 2018)

P=0.9386 Teicoplanin												
0.65, (0.20 to 2.12)	**P=0.8280 Ridinilazole**											
0.55, (0.21 to 1.44)	0.84, (0.41 to 1.74)	**P=0.7922 Fidaxomicin**										
0.53, (0.13 to 2.15(	0.82, (0.23 to 2.86)	0.97, (0.34 to 2.78)	**P=0.6951 Cadazolid**									
0.41, (0.15 to 1.10)	0.63, (0.29 to 1.35)	0.75, (0.53 to 1.06)	0.77, (0.26 to 2.24)	**P=0.5820 Surotomycin**								
0.39, (0.13 to 1.21)	0.60, (0.23 to 1.58)	0.72, (0.37 to 1.41)	0.74, (0.22 to 2.49)	0.96, (0.48 to 1.94)	**P=0.5405 Nitazoxanide**							
0.37, (0.14 to 0.94)	0.57, (0.28 to 1.15)	0.67, (0.55 to 0.82)	0.69, (0.25 to 1.94)	0.90, (0.68 to 1.19)	0.93, (0.49 to 1.78)	**P=0.4850 Vancomycin**						
0.34, (0.11 to 1.01)	0.52, (0.21 to 1.28)	0.62, (0.34 to 1.12)	0.64, (0.20 to 2.06)	0.83, (0.44 to 1.55)	0.86, (0.37 to 2.02)	0.92, (0.53 to 1.61)	**P=0.4296 Rifaximin**					
0.31, (0.11 to 0.89)	0.48, (0.19 to 1.23)	0.57, (0.30 to 1.09)	0.59, (0.18 to 1.95)	0.77, (0.39 to 1.50)	0.80, (0.35 to 1.84)	0.85, (0.47 to 1.57)	0.93, (0.41 to 2.11)	**P=0.3794 Fusidic acid**				
0.29, (0.08 to 1.15)	0.45, (0.13 to 1.52)	0.54, (0.20 to 1.46)	0.55, (0.13 to 2.29)	0.72, (0.26 to 1.99)	0.75 (0.23 to 2.42)	0.80, (0.30 to 2.13)	0.87, (0.28 to 2.68)	0.94, (0.30 to 2.97)	**P=0.3635 LFF571**			
0.27, (0.10 to 0.70)	0.41, (0.19 to 0.88)	0.49, (0.35 to 0.68)	0.51, (0.17 to 1.46)	0.66, (0.45 to 0.97)	0.68, (0.37 to 1.27)	0.73, (0.56 to 0.95)	0.79, (0.43 to 1.47)	0.86, (0.48 to 1.52)	0.92, (0.33 to 2.53)	**P=0.2411 Metronidazole**		
0.22, (0.06 to 0.77)	0.34, (0.11 to 1.00)	0.40, (0.17 to 0.94)	0.42, (0.11 to 1.55)	0.54, (0.23 to 1.28)	0.56, (0.20 to 1.59)	0.60, (0.26 to 1.36)	0.65, (0.24 to 1.76)	0.70, (0.25 to 1.95)	0.75, (0.21 to 2.70)	0.82, (0.35 to 1.94)	**P=0.2006 Bacitracin**	
0.15, (0.06 to 0.39)	0.23, (0.11 to 0.48)	0.27, (0.20 to 0.37)	0.28, (0.10 to 0.80)	0.36, (0.25 to 0.53)	0.38, (0.20 to 0.73)	0.40, (0.32 to 0.51)	0.44, (0.24 to 0.80)	0.47, (0.25 to 0.87)	0.50, (0.18 to 1.39)	0.55, (0.42 to 0.72)	0.67, (0.28 to 1.58)	**P=0.0245 Tolevamer**

Figures are Odds Ratio (OR) with 95% Confidence interval (95%CI)

Table 16: Data for sensitivity analysis from Beinortas et al (2018)

Sensitivity analysis[1]			
	Rank 1	Rank 2	Rank 3
Non-blinded trials	Ridinilazole (P score=0.8566)	Fidaxomicin (P score=0.8266)	Cadazolid (P score=0.7262)
Studies with <50 patients per trial arm	Ridinilazole (P score=0.8742)	Fidaxomicin (P score=0.8484)	Surotomycin (P score=0.6131)
RCTs published before 2000	Teicoplanin (P score=0.9309)	Ridinilazole (P score=0.8192)	Fidaxomicin (P score=0.7798)

1 Findings for treatments ranked highest within the NMA for the greatest chance of achieving a sustained symptomatic cure. The overall quality of Beinortas et al (2018) was assessed in GRADE as moderate (see **table 20**).

Table 17: **Results of the sub-group analysis for sustained symptomatic cure (adapted from Beinortas et al. 2018)**[2]

	Ranked 1	**Ranked 2**	**Ranked 3**	**Ranked 4**	**Ranked 5**	**Ranked 6**	**Ranked 7**	**Ranked 8**
Severe CDI	Ridinilazole (P score= 0.8070)	Fidaxomicin (P score= 0.7830)	Nitazoxanide (P score= 0.6692)	Vancomycin (P score= 0.5385)	Metronidazole (P score= 0.3570)	Surotomycin (P score= 0.2149)	Tolevamer (P score= 0.1305)	n/a
Non-severe CDI	Ridinilazole (P score= 0.8771)	Fidaxomicin (P score= 0.7926)	Surotomycin (P score= 0.6762)	Nitazoxanide (P score= 0.5263)	Vancomycin. (P score= 0.4092)	Metronidazole (P score= 0.2066)	Tolevamer (P score= 0.0121)	n/a
Initial CDI	Ridinilazole (P score= 0.8389)	Fidaxomicin (P score= 0.7816)	Surotomycin (P score= 0.7233)	Nitazoxanide (P score = 0.5757)	Fusidic acid (P score= 0.4989)	Vancomycin (P score= 0.3791)	Metronidazole (P score= 0.1997)	Tolevamer (P score= 0.0029)
Non-initial CDI	Fidaxomicin (P score= 0.8226)	Ridinilazole (P score= 0.7688)	Surotomycin (P score = 0.5897)	Vancomycin (P score= 0.5082)	Nitazoxanide (P score= 0.3879)	Tolevamer (P score= 0.2186)	Metronidazole (P score= 0.2042)	n/a
Aged at least 65 years	Fidaxomicin (P score= 0.9205)	Ridinilazole (P score= 0.6759)	Vancomycin (P score= 0.5676)	Surotomycin (P score= 0.5530)	Metronidazole (P score= 0.2727)	Tolevamer (P score= 0.0104)	n/a	n/a
Younger than 65 years	Ridinilazole (P score= 0.9216)	Surotomycin (P score = 0.7418)	Fidaxomicin (P score= 0.7244)	Vancomycin (P score= 0.376)	Metronidazole (P score= 0.2359)	Tolevamer (P score= 0.0003)	n/a	n/a

2 Comparisons against Vancomycin

Beinortas et al. (2018) undertook additional sub-group analysis (see **Table 17**) which ranged in quality from very low to moderate.

Table 16: Data for sensitivity analysis from Beinortas et al (2018)

Sensitivity analysis[1]			
	Rank 1	Rank 2	Rank 3
Non-blinded trials	Ridinilazole (P score=0.8566)	Fidaxomicin (P score=0.8266)	Cadazolid (P score=0.7262)
Studies with <50 patients per trial arm	Ridinilazole (P score=0.8742)	Fidaxomicin (P score=0.8484)	Surotomycin (P score=0.6131)
RCTs published before 2000	Teicoplanin (P score=0.9309)	Ridinilazole (P score=0.8192)	Fidaxomicin (P score=0.7798)

1 Findings for treatments ranked highest within the NMA for the greatest chance of achieving a sustained symptomatic cure. The overall quality of Beinortas et al (2018) was assessed in GRADE as moderate (see **table 20**).

Table 17 The Beinortas et al (2018) NMA has limitations. The NMA included single-blind studies and industry sponsored RCTs (n=17) which are a source of potential bias. The sub-group analyses for CDI severity did not establish a definition of non-severe or severe CDI among included RCTs. This impacts the reliability of the sub-group analyses for CDI as there may be variation between outcomes within RCTs. The NMA included all treatments as monotherapy against CDI.

See GRADE: **Table 33**

A modified version of the Beinortas et al (2018) NMA was used to inform the treatment efficacy parameters in the health economic model. Details of the changes made and the new results are given in Appendix L:. We would like to thank the authors of Beinortas et al (2018) for supplying us with the raw data to rerun these analyses.

3.1.1.3 Antibiotics versus other antibiotics or interventions for the treatment of recurrent *Clostridioides difficile* infection

The evidence for antibiotics versus other antibiotics or interventions for the treatment of recurrent CDI comes from 2 RCTs in adults with an acute recurrence of CDI (van Nood et al 2013; Hvas et al 2019).

Both RCTs included only adults (aged ≥18 years) with an acute episode of recurrent CDI who had previous episode(s) of CDI. In van Nood et al (2013) the diagnosis of the acute episode required diarrhoea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours). The RCT by Hvas et al (2019) required 3 more liquid stools (Bristol score of 6–7) per day and a positive polymerase chain reaction (PCR) test result for CD toxin A, toxin B, or binary toxin.

In van Nood et al (2013) the inclusion criteria were a life expectancy >3 months and recurrent CDI after ≥1 courses of vancomycin (for at least 10 days at a dose of 125 mg four times daily) or metronidazole (for at least 10 days at a dose of 500 mg three times daily). In the RCT by Hvas et al (2019) the inclusion criteria were a documented recurrence within 8 weeks after stopping treatment for CDI and at least 1 prior treatment course with vancomycin or fidaxomicin.

Both RCTs (van Nood et al 2013; Hvas et al 2019) had 3 arms. van Nood et al (2013) compared a short regimen of oral vancomycin (500 mg four times daily for 4 or 5 days) followed by bowel lavage (colonic irrigation) with 4 L of macrogol solution on

the last day of antibiotic treatment then fresh faecal microbiota transplant (FMT) via a nasoduodenal tube the next day with either a standard oral vancomycin regimen (500 mg four times daily for 14 days) or a standard vancomycin regimen with bowel lavage on day 4 or 5. If recurrent CDI developed after the first donor-faeces infusion, participants were given a second infusion with faeces from a different donor. If antibiotic therapy failed, participants were offered treatment with donor faeces off protocol. Hvas et al (2019) compared a short course of vancomycin (125 mg four times daily for 4 to 10 days) followed by frozen-thawed FMT via nasojejunal tube or colonoscopy with either 10 days of vancomycin (125 mg four times daily) or fidaxomicin (200 mg twice daily). Details of the comparisons with FMT are in section 3.2.

One RCT (van Nood et al 2013) was stopped at the interim analysis phase due to the high rate of relapse in the vancomycin arm(s).

Both RCTs were open label (no blinding). The RCT by van Nood et al (2013) was assessed as at low risk of bias. The RCT by Hvas et al (2019) was assessed as at higher risk of bias due to issues with randomisation and deviations from the intended interventions (see appendix G).

Resolution of CDI diarrhoea

Vancomycin 125 mg four times daily for 10 days was not significantly different to fidaxomicin 200 mg twice daily for 10 days for resolution of diarrhoea (clinical resolution or persistent diarrhoea with a negative CD toxin test) at 8 weeks (1 RCT, n=30, 31.3% versus 54.2%, RR 0.58, 95% CI 0.26 to 1.3; very low-quality evidence).

Vancomycin 500 mg four times daily for 14 days was not significantly different to vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5 for resolution of diarrhoea at 10 weeks (1 RCT, n=26, 30.8% versus 23.1%, RR 1.33, 95% CI 0.37 to 4.82; low-quality evidence).

Clinical resolution of CDI

Vancomycin 125 mg four times daily for 10 days was not significantly different to fidaxomicin 200 mg twice daily for 10 days for clinical resolution and a negative CD toxin test at 1 week (1 RCT, n=40, 12.5% versus 37.5%, RR 0.33, 95% CI 0.08 to 1.35; very low-quality evidence) or at 8 weeks (1 RCT, n=40, 18.8% versus 33.3%, RR 0.56, 95% CI 0.18 to 1.81; very low-quality evidence).

Relapse of CDI at 5 weeks

Vancomycin 500 mg four times daily for 14 days was not significantly different to vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5 for relapse (diarrhoea with a positive stool test) at 5 weeks (1 RCT, n=26, 61.5% versus 53.8%, RR 1.14, 95% CI 0.59 to 2.22; low-quality evidence).

Adverse events

There was no significant difference in the overall number of adverse events with 10 days of vancomycin 125 mg four times daily compared with 10 days of fidaxomicin 200 mg twice daily (1 RCT, n=40, 50% versus 37.5%, RR 1.33, 95% CI 0.65 to 2.72; very low-quality evidence). There was also no significant difference in the number of gastrointestinal (GI) adverse events with vancomycin compared with fidaxomicin (1 RCT, n=40, 12.5% versus 25%, RR 0.50, 95% CI 0.11 to 2.17; very low-quality evidence).

See GRADE: **Table 34**.

3.1.1.4 Dose of antibiotic

Low-dose versus high-dose vancomycin

The evidence for high versus low dose oral vancomycin for the treatment of CDI comes from 1 RCT from 1 systematic review (n=56) (Nelson et al. 2017). Details of the study population were minimal within the systematic review. The study was judged to be at high risk of bias within the systematic review due to a lack of allocation concealment and outcome assessor blinding, incomplete outcome data and selective outcome reporting. The primary outcomes were cure, bacteriological resolution and relapse. The intervention was vancomycin 125 mg four times a day for 5 to 15 days compared with vancomycin 500 mg four times a day for 5 to 15 days.

There was no difference between high-dose vancomycin and low-dose vancomycin for symptomatic cure (1 RCT, n=56, RR 0.95, 95% CI 0.65 to 1.38, very low-quality evidence). The findings for bacteriological resolution or relapse were not reported.

See GRADE: **Table 35**

High-dose versus low-dose fidaxomicin

The evidence for low versus high dose fidaxomicin for the treatment of CDI comes from 1 RCT from 1 systematic review of people of people with mild to moderate CDI with a primary episode or first relapse (n=48) within a systematic review (Nelson et al. 2017). Details of the study population were minimal within the systematic review. The study was judged to be at high risk of bias within the systematic review due to unclear allocation concealment, being an open-label study and the potential impacts of excluding patients with severe disease. The primary outcomes were the resolution of diarrhoea and abdominal discomfort within the treatment period and relapse. Nelson et al (2017) compared 400 mg daily with lower dose fidaxomicin (pooled findings for 100 mg and 200 mg daily) for 10 days.

Fidaxomicin 400 mg daily for 10 days was more effective than a lower daily dose of fidaxomicin (pooled findings for 200 mg and 100 mg daily) for 10 days for symptomatic cure (resolution of diarrhoea and abdominal discomfort) (1 RCT, n=48, RR 1.26, 95% CI 1.03 to 1.54, very low quality evidence). The systematic review did not outline findings for the other fidaxomicin doses or for relapse and it is unclear whether this is an omission from the systematic review or if these outputs were not reported in the primary study.

See GRADE: **Table 36**

3.1.1.5 Antibiotic dose frequency

Teicoplanin 100 mg twice a day versus 50 mg four times a day

The evidence for oral teicoplanin 100 mg twice a day versus 50 mg four times a day for the treatment of CDI comes from 1 RCT from 1 systematic review of people (n=92) with diarrhoea who had recently received antibiotics for an infection other than *C. difficile* (Nelson et al. 2017). Details of the study population were minimal within the systematic review. The study was judged to be at high risk of bias within the systematic review due to unclear randomisation, allocation concealment, and blinding, and a 47% drop out rate in the study. The primary outcomes were symptomatic cure, bacteriological resolution and relapse (none of which are further defined) but only findings for symptomatic cure are reported in the systematic review.

Teicoplanin 100 mg twice a day was not significantly different to teicoplanin 50 mg four times a day for symptomatic cure (1 RCT, n=92, RR 0.57, 95% CI 0.27 to 1.20, very low-quality evidence). The systematic review did not outline findings for bacteriological resolution and relapse.

See GRADE: **Table 37**

3.1.1.6 Antibiotic course length

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.1.7 Antibiotic route of administration

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.2 Faecal microbiota transplant prevention or treatment of recurrence in *Clostridioides difficile* infection in adults

3.1.2.1 Faecal microbiota transplant versus placebo for the prevention of recurrence of *Clostridioides difficile* infection

The evidence for faecal microbiota transplant (FMT) for the prevention of recurrence of *Clostridioides difficile* infection (CDI) comes from 1 randomised, double-blind, placebo-controlled phase 2B 3 arm trial (Dubberke et al 2018). This RCT included adults (aged >18 years) with a diagnosis of recurrent CDI and either 2 or more recurrences of CDI after a primary episode or 2 or more documented episodes of severe CDI that resulted in hospitalisation. Treatment with FMT commenced once antibiotic treatment (either vancomycin, fidaxomicin, or metronidazole) for current CDI had finished. The initial antibiotic treatment for CDI was considered during study randomisation.

The study compared 2 doses of FMT in the form of a microbiota-based drug candidate (RBX2660) enema with either 2 doses of placebo enema or 1 dose of FMT plus 1 dose of placebo. The FMT was a microbiota suspension prepared from human stool, each dose consisting of 150 mL containing $\geq 10^7$ live organisms/mL in a single dose ready to use enema bag. Participants had a history of multiple recurrent CDI and received the first dose of FMT or placebo enema 24-48 hours following completion of antibiotics treatment (either metronidazole or vancomycin) for current CDI episode with the second dose of FMT or placebo administered 5 to 9 days after. The product (and placebo) were transported frozen and thawed for 24 hours before administration. The study was of moderate quality and was limited by its lack of description of allocation sequence and low number of characteristics demonstrating adequate randomisation (see appendix G). The primary outcome of the RCT was the prevention of CDI recurrence at 8 weeks after the second dose of the assigned treatment. However, a longer follow-up period was included with open-label treatment with FMT for any participant who had been previously determined to be a treatment failure in any trial arm.

Recurrence of CDI

Two doses of FMT was not significantly different to placebo for the outcome of recurrence of CDI at 8 weeks (n=85, 61% versus 45.5%, RR 1.34, 95% CI 0.89 to 2.01; low quality evidence). In NICE analysis a single dose of FMT was also not significantly different to placebo for recurrence of CDI at 8 weeks (n=86, 66.7%

versus 45.5%, RR 1.47, 95% CI 1.0 to 2.16; low-quality evidence). However, in the authors analysis using Pearson's X^2 test this was significant (P-value, P = 0.049).

Two doses of FMT was not significantly different to 1 dose of FMT for recurrence of CDI at 8 weeks (n=83, 61% versus 66.7%, RR 0.91, 95% CI 0.66 to 1.27; low-quality evidence).

When the 2 groups who had received 1 or 2 doses of FMT were pooled and compared to those who received placebo, there was no significant difference in the NICE analysis for recurrence of CDI at 8 weeks (n=127, 63.9% versus 45.5%, RR 1.40, 95% CI 0.98 to 2.02; low-quality evidence), but this was significant in the authors analysis (P=0.047).

Adverse events

There were many adverse events (379 in 82 participants), but no significant differences between the blinded treatment groups. The most common adverse events were gastrointestinal disorders (not further described; 48%), followed by general disorders (not further described; 11%) and infections (not further described; 5.5%) (very low-quality evidence).

Three severe adverse events possibly related to FMT were reported (all in the 2 doses of FMT arm), this included 1 case of recurrent myeloid leukaemia, 1 case of abdominal cramping and pain and 1 case of severe constipation. Nine people across the 3 arms had 14 episodes of *Clostridioides difficile* infection and 35 people had severe adverse events related to pre-existing conditions (no analysis reported and not estimable in NICE analysis; very low-quality evidence).

There were 3 deaths in the 2 doses of FMT arm of the trial (1 related to *MRSA* infection, 1 related to *Clostridioides difficile* disease and 1 related to a pre-existing condition) and also 3 deaths in the 1 dose of FMT arm (all 3 related to pre-existing conditions). There were no deaths in the placebo arm of the trial. There were no significant differences between the groups for the outcome of mortality (very low-quality evidence).

See GRADE: **Table 38**.

3.1.2.2 Faecal microbiota transplant versus oral antibiotic for first presentation of *Clostridioides difficile* infection in adults

The evidence for FMT versus oral antibiotic for CDI at first presentation in adults comes from 1 open-label, 2-arm RCT (Camacho-Ortiz et al 2017). This RCT included hospitalised adults (aged ≥18 years) with no prior history of CDI or prior treatment for the current episode of CDI. Diagnosis of the current episode of CDI was >3 bowel movements during prior 24 hours and Bristol stool scale >5, plus a positive test immunoassay or real-time polymerase chain reaction (PCR) test.

The intervention was frozen-thawed faecal donor-unrelated mix (FMT-FURM) transplantation compared to oral vancomycin (250 mg four times a day 10 to 14 days). Patients in either arm without clinical improvement at 72 hours received a second treatment (FMT-FURM in all cases). The primary outcome from the study was a resolution in clinical symptoms within 72 hours, which was defined as at least 2 of the following criteria: a reduction in Bristol stool scale of at least 2 points, a reduction of at least 50% in the number of bowel movements during the first 72 hours after the FMT-FURM (second treatment), an absence of fever (not ≥38°C) and resolution of abdominal pain.

The study was limited as it was unclear whether symptoms were clinician-assessed or self-reported and the route of administration of FMT-FURM (nasojejunal, superior endoscopy or colonoscopy) was not randomised but based on patient factors and other planned procedures. The study was assessed as being at high risk of bias due to randomisation concerns, deviation from intended interventions, missing data concerns and bias in the measurement of outcome domains (see appendix G).

Resolution of symptoms

FMT-FURM first dose (1 RCT, n=16, 57.1% versus 88.9%, RR 0.64, 95% CI 0.33 to 1.27; very low-quality evidence) or second dose (1 RCT, n=16, 71.4% versus 88.9%, RR 0.80, 95% CI 0.48 to 1.35; very low-quality evidence) were not significantly different compared with vancomycin for resolution of clinical symptoms after 72 hours.

Treatment failure

FMT-FURM first dose was not significantly different to vancomycin for treatment failure at 72 hours (≥3 of the resolution criteria not met) (1 RCT, n=16, 28.6% versus 11.1%, RR 2.57, 95% CI 0.29 to 22.93; very low-quality evidence).

Mortality

FMT-FURM was not significantly different to vancomycin for all-cause mortality at 30 days (1 RCT, n=16, 28.6% versus 44.4%, RR 0.64, 95% CI 0.16 to 2.56; very low-quality evidence) or CDI-attributable mortality at 30 days (1 RCT, n=16, 14.3% versus 11.1%, RR 1.29, 95% CI 0.1 to 17.14; very low-quality evidence).

Length of stay

The median length of stay and range for each arm was presented but no analyses were undertaken. Median length of stay (range) in the FMT-FURM arm was 7 days (4 to 19 days) and in the vancomycin arm was 9 days (6 to 36 days) (very low-quality evidence).

See GRADE: **Table 39**.

3.1.2.3 Antibiotics followed by faecal microbiota transplant for the treatment of recurrent CDI

Oral vancomycin followed by faecal microbiota transplant versus other antibiotic regimens or interventions for the treatment of recurrent CDI

The evidence for FMT for the treatment of recurrent CDI comes from 4 RCTs in adults with an acute recurrence of CDI (van Nood et al 2013; Cammarota et al 2015; Hota et al 2017 and Hvas et al 2019).

All 4 RCTs included only adults (aged ≥18 years) with an acute episode of recurrent CDI who had previous episode(s) of CDI. In 2 RCTs (van Nood et al 2013; Cammarota et al 2015) the diagnosis of the acute episode was similar requiring diarrhoea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours) and a positive stool test for *C. difficile* toxin (in Cammarota et al (2015) the positivity in the *C. difficile* toxin stool test was within 10 weeks from the end of the previous antibiotic treatment). In Hota et al (2017) symptoms of CDI were self-reported and confirmed by study physicians. Enzymatic immunoassay or PCR for *C. difficile* toxin or gene was accepted for laboratory

confirmation. The RCT by Hvas et al (2019) required ≥3 liquid stools (Bristol score of 6–7) per day and a positive PCR test result for *C. difficile* toxin A, toxin B, or binary toxin.

In 2 RCTs (van Nood et al 2013; Cammarota et al 2015) the inclusion criteria were the same: a life expectancy >3 months and a recurrent CDI episode after at least 1 course of vancomycin (at least 10 days at a dose of 125 mg four times daily) or metronidazole (at least 10 days at a dose of 500 mg three times daily). In Hvas et al (2019) the inclusion criteria were a documented recurrence within 8 weeks after stopping CDI treatment and at least 1 prior course of vancomycin or fidaxomicin. Hota et al (2017) required a history of at least 2 episodes of laboratory or pathology confirmed CDI and at least 1 course of vancomycin (10 days of 500 mg total daily dose).

Two of the RCTs were 2 arm trials (Cammarota et al 2015; Hota et al 2017). Cammarota et al (2015) compared a short regimen of oral vancomycin (125 mg four times daily for 3 days) and bowel cleaning (4 L macrogol [an oral osmotic laxative preparation]) on the last 1 or 2 days of antibiotic treatment followed by fresh FMT delivered by colonoscopy the next day compared with oral vancomycin treatment of 125 mg four times daily for 10 days followed by a pulse regimen (125–500 mg/day every 2–3 days) for at least 3 weeks. If recurrent CDI developed after the first faecal infusion, participants were given a second infusion of faeces within 1 week.

Hota et al (2017) compared 14 days of oral vancomycin 125 mg four times daily followed by 1 fresh FMT dose by enema 48 hours after stopping vancomycin with a regimen of tapered doses of oral vancomycin (14 days of vancomycin 125 mg four times daily followed by a taper over 4 weeks: vancomycin 125 mg twice daily for 1 week; then, vancomycin 125 mg once daily for 1 week; then, vancomycin 125 mg every second day for 1 week; then, vancomycin 125 mg every third day for 1 week). Participants who experienced recurrent CDI were offered crossover to the alternative study treatment.

The remaining 2 RCTs (van Nood et al 2013; Hvas et al 2019) both had 3 arms. van Nood et al (2013) compared a short regimen of oral vancomycin (500 mg four times daily for 4 or 5 days) followed by bowel lavage (colonic irrigation) with 4 L of macrogol solution on the last day of antibiotic treatment then fresh FMT via a nasoduodenal tube the next day with either a standard oral vancomycin regimen (500 mg four times daily for 14 days) or a standard vancomycin regimen with bowel lavage on day 4 or 5. If recurrent CDI developed after the first donor-faeces infusion, participants were given a second infusion with faeces from a different donor. Participants in whom antibiotic therapy failed were offered treatment with donor faeces off protocol.

Hvas et al (2019) compared a short course of oral vancomycin (125 mg four times daily for 4 to 10 days) followed by frozen-thawed FMT via either nasojejunal tube or colonoscopy with either 10 days of oral vancomycin (125 mg four times daily) or oral fidaxomicin (200 mg twice daily). Participants with recurrent CDI after the primary allocated treatment were offered rescue treatment with FMT.

Three of the 4 RCTs (Cammarota et al 2015; Hota et al 2017 and van Nood et al 2013) were stopped at the interim analysis phase. 2 RCTs were stopped due to either the significant effect of FMT (Cammarota et al 2015) or the high rate of relapse in the vancomycin arm(s) (van Nood et al 2013). One RCT was stopped following a futility analysis which showed the trial would be unlikely to show an effect between interventions and comparator (Hota et al 2017).

All 4 RCTs were open-label (no blinding). Two RCTs were assessed to be at low risk of bias (van Nood et al 2013; Cammarota et al 2015). The remaining 2 RCTs were both assessed as at higher risk of bias due to issues with randomisation and deviations from the intended interventions (see Appendix G.6). Data were largely not meta-analysed due to the heterogeneity of the interventions and follow-up time periods.

Clinical resolution of symptoms

A short course of vancomycin followed by FMT significantly increased clinical resolution of symptoms and negative CD toxin test at 1 week compared with 10 days of vancomycin (1 RCT, n=40, 54.2% versus 12.5%, RR 4.33, 95% CI 1.13 to 16.68; NNT 3, 95% CI 2 to 7; very low-quality evidence) but not compared with 10 days of fidaxomicin (1 RCT, n=48, 54.2% versus 37.5%, RR 1.44, 95% CI 0.77 to 2.72; very low-quality evidence).

A short course of vancomycin followed by FMT significantly increased clinical resolution of symptoms and negative CD toxin test at 8 weeks compared with either 10 days of vancomycin (1 RCT, n=40, 70.8% versus 18.8%, RR 3.78, 95% CI 1.32 to 10.82, NNT 2, 95% CI 2 to 4; low-quality evidence) or 10 days of fidaxomicin (1 RCT, n=48, 70.8% versus 33.3%, RR 2.13, 95% CI 1.14 to 3.96, NNT 3 (95% CI 2 to 9); low-quality evidence).

Resolution of diarrhoea

A short course of vancomycin followed by FMT significantly increased resolution of *Clostridioides difficile* -associated diarrhoea (resolution of diarrhoea or persistent diarrhoea with a negative CD toxin test) at 8 weeks compared with either 10 days of vancomycin (1 RCT, n=40, 91.7% versus 31.3%, RR 2.93, 95% CI 1.4 to 6.13, NNT 2 (95% CI 2 to 3); moderate quality evidence) or 10 days of fidaxomicin (1 RCT, n=48, 91.7% versus 54.2%, RR 1.69, 95% CI 1.15 to 2.49, NNT 3 (95% CI 2 to 7); low-quality evidence).

A short course of vancomycin plus bowel lavage followed by FMT significantly increased resolution of diarrhoea at 10 weeks compared with either 14 days of vancomycin (1 RCT, n=29, 93.8% versus 30.8%, RR 3.05, 95% CI 1.34 to 6.95, NNT 2 (95% CI 2 to 3); moderate quality evidence) or 14 days of vancomycin plus bowel lavage at days 4 to 5 (1 RCT, n=29, 93.8% versus 23.1%, RR 4.06, 95% CI 1.49 to 11.05, NNT 2 (95% CI 1 to 3); moderate quality evidence).

A short course of vancomycin followed by FMT significantly increased resolution of diarrhoea at 10 weeks compared with standard then pulsed vancomycin (1 RCT, n=39, 90% versus 26.3%, RR 3.42, 95% CI 1.59 to 7.36, NNT 2 (95% CI 2 to 3); moderate quality evidence).

Relapse of diarrhoea

A short course of vancomycin plus bowel lavage followed by FMT significantly reduced relapse of diarrhoea (diarrhoea with a positive stool test for *C. difficile* toxin) at 5 weeks compared with either 14 days of vancomycin (1 RCT, n=29, 6.3% versus 61.5%, RR 0.10, 95% CI 0.01 to 0.71, NNT 3 (95% CI 2 to 6); high quality evidence) or 14 days of vancomycin plus bowel lavage at days 4 to 5 (1 RCT, n=29, 6.3% versus 53.8%, RR 0.12, 95% CI 0.02 to 0.83, NNT 3 (95% CI 2 to 8); moderate quality evidence).

Mortality

Vancomycin followed by FMT (and bowel lavage in 1 RCT) was not significantly different to vancomycin alone (there were no deaths in the other arms of the included studies) for all-cause mortality at the end of follow up (4 RCTs, n=136, 2.8% versus 10.9%, RR 0.31, 95% CI 0.08 to 1.17; low-quality evidence) or for CDI-related mortality (1 RCT, n=39, 10% versus 10.5%, RR 0.95, 95% CI 0.15 to 6.08; low-quality evidence).

Adverse events

There was no significant difference in the overall number of adverse events with a short course of vancomycin followed by FMT compared with either 10 days of vancomycin (1 RCT, n=40, 50% versus 50%, RR 1.00, 95% CI 0.53 to 1.88; very low-quality evidence) or 10 days of fidaxomicin (1 RCT, n=48, 50% versus 37.5%, RR 1.33, 95% CI 0.69 to 2.56; very low-quality evidence).

A short course of vancomycin followed by FMT was not significantly different for the number of gastrointestinal adverse events compared with either 10 days of vancomycin (1 RCT, n=30, 25% versus 12.5%, RR 2.00, 95% CI 0.46 to 8.7; very low-quality evidence) or 10 days of fidaxomicin (1 RCT, n=48, 25% versus 25%, RR 1.00, 95% CI 0.38 to 2.66; very low-quality of evidence).

A short course of vancomycin followed by FMT or bowel lavage plus FMT significantly increased treatment-related diarrhoea (2 RCTs, n=80, 94.4% versus 0%, RR 41.62, 95% CI 5.97 to 289.87, number needed to harm [NNH] 2 (95% CI 1 to 1); low-quality evidence) and treatment-related bloating or cramping (2 RCTs, n=80, 47.2% versus 0%, RR 20.77, 95%CI 2.8 to 153.91, NNH 3 (95% CI 1 to 3); moderate quality evidence) compared with standard then pulsed vancomycin or vancomycin with or without lavage.

A short course of vancomycin followed by bowel lavage plus FMT was not significantly different to vancomycin with or without lavage for treatment-related constipation (1 RCT, n=41, 18.8% versus 0%, RR 10.71, 95% CI 0.59 to 194.46; low-quality evidence).

There was a significantly lower mean number of days of diarrhoea experienced during follow up with vancomycin followed by FMT compared with standard the tapered vancomycin (1 RCT, n=28, mean (standard deviation [SD]) 0.8(0.8) versus 1.7(0.4), mean difference [MD] −0.90, 95% CI −1.35 to −0.45; moderate quality evidence).

Serious adverse events

Hvas et al (2019) reported a serious adverse event (sepsis like symptoms) possibly related to FMT in 1 participant. In the RCT by Hota et al (2017), 3 serious adverse events were reported, but none were thought to be related to study interventions.

See GRADE: **Table 40**.

3.1.3 Probiotics in adults

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.4 Prebiotics in adults

3.1.4.1 Oligofructose to prevent relapse of diarrhoea in Clostridium difficile infection

The evidence for the prebiotic oligofructose to prevent relapse of diarrhoea in CDI comes from 1 double-blind RCT of hospital inpatients (>65 years) with diarrhoea associated with confirmed *C. difficile* (n=142) (Lewis et al 2005a). The primary outcome was relapse of diarrhoea. The study compared 12 g/day oligofructose (taken as soon as possible after diagnosis and for 30 days after diarrhoea stopped) with placebo in people also taking antibiotic treatment with metronidazole or vancomycin (dose and frequency not outlined) for 10 days to treat diarrhoea associated with CDI.

The addition of oligofructose to antibiotic treatment resulted in significantly fewer relapses of diarrhoea after initial CDAD compared with placebo (1 RCT, n=142, 8.3% versus 34.3%, RR 0.24 95% CI 0.11 to 0.56, number needed to treat (NNT) 4 (95%CI 3 to 8) moderate quality evidence. There was no difference between treatments for mortality (1 RCT, n=142, 12.5% versus 14.3%, RR 0.88 95% CI 0.38 to 2.02, very low-quality evidence). Lewis et al (2005a) outlined that side effects (abdominal pain, defecatory frequency and bloating) were reported and were not significant, but no data was presented in the study.

See GRADE: **Table 41**

3.1.5 Antibiotics in children and young people

3.1.5.1 Choice of antibiotic in children and young people

Oral metronidazole versus oral rifaximin

The evidence for metronidazole compared with rifaximin for the treatment of first incidence of CDI in children and young people comes from 1 single-blind RCT in children and young people (≤18 years) with inflammatory bowel disease (IBD) (n=31) (Gawronska et al. 2017). The children and young people had CDI confirmed by a positive enzyme immunoassay (EIA) stool test and mild to moderate symptoms. The RCT was stopped early due to changes in dosing and guidelines used for the included antibiotics and changes in definition of severity. The primary outcome was CDI cure rates 4 weeks after the end of treatment. Gawronska et al (2017) also reported on CDI recurrence rates, and CDI cure rates in children with either Crohn's disease and ulcerative colitis. The intervention was oral metronidazole with dose varying by body weight from 750 mg to 1.5 g three times a day for 14 days compared with oral rifaximin with dose varying by body weight from 600 mg to 1.2 g three times a day for 14 days.

Metronidazole was not significantly different to rifaximin for CDI cure rates 4 weeks after treatment (1 RCT, n=31, 70.6% versus 78.6%, RR 0.90 95% CI 0.60 to 1.36, very low-quality evidence) or recurrent CDI (1 RCT, n=23, 16.7% versus 0%, RR 4.62 95% CI 0.25 to 86.72, very low-quality evidence). There were no significant differences between metronidazole and rifaximin for CDI cure rates in children with Crohn's disease (1 RCT, n=12, 66.7% versus 100%, RR 0.69, 95% CI 0.38 to 1.25, very low-quality evidence) or ulcerative colitis (1 RCT, n=19, 72.7% versus 62.5%, RR 1.16 95% CI 0.61 to 2.22, very low-quality evidence).

See GRADE: **Table 42**

Oral fidaxomicin versus oral vancomycin

The evidence for fidaxomicin compared with vancomycin for the treatment of confirmed CDI in children and young people comes from 1 single blind-RCT in children and young people (<18 years) (Wolf et al. 2019). Participants had CDI confirmed by the presence of watery diarrhoea in those <2 years, or ≥3 unformed bowel movements for those ≥2 years within 24 hours before screening. Participants also underwent a test for toxin A/B or toxigenic *C. Difficile* in stools within 24 hours prior to screening. The primary outcome was confirmed clinical response at the end of treatment with no further requirement for CDI treatment 2 days after the end of treatment. Other outcomes reported were CDI recurrence, resolution of diarrhoea or global cure (confirmed clinical response without CDI recurrence at up to 30 days after the end of treatment) and treatment-emergent adverse events (which included pyrexia and diarrhoea).

The intervention was oral fidaxomicin with those aged 0 to <6 years receiving 16 mg/kg oral suspension twice daily (maximum 400 mg/day) and those aged ≥6 to <18 years receiving 200 mg tablets twice daily for 10 days compared with oral vancomycin with those aged 0–<6 years receiving 10 mg/kg oral liquid four times daily [maximum 500 mg/day], and those aged ≥6 to <18 receiving 125 mg capsules four times daily for 10 days.

There was no significant difference between fidaxomicin and vancomycin for the resolution of diarrhoea at 30 days (1 RCT, n=142, 75.5% versus 72.7%, RR 1.04, 95%CI 0.84 to 1.28, low-quality evidence). Fidaxomicin was not significantly different to vancomycin for confirmed clinical response (1 RCT, n=142, 77.6% versus 70.5%, RR 1.10, 95% CI 0.88 to 1.37, very low-quality evidence). Wolf et al (2019) stratified results by those <2 years, ≥2 years and those ≥2 years with a positive toxin test; in both analyses there was no significant difference between treatments for confirmed clinical cure.

Fidaxomicin was not significantly different to vancomycin for global cure at the end of study (1 RCT, n=142, 68.4% versus 50.0%, RR 1.37, 95%CI 0.99 to 1.89, low quality evidence). The findings for this outcome were stratified by age and fidaxomicin significantly increased global cure by the end of study compared with vancomycin in those aged ≥2 (1 RCT, n=112, 71.8% versus 44.1%, RR 1.63, 95%CI 1.09 to 2.44; NNT 4, 95% CI 2 to 12, low-quality evidence) and in those aged ≥2 with a positive toxin test (1 RCT, n=50, 75% versus 38.9%, RR 1.93, 95%CI 1.05 to 3.56, low-quality evidence) but not in those <2 years (1 RCT, n=30, 55.0% versus 70.0%, RR 0.79, 95%CI 0.45 to 1.39, very low-quality evidence).

Fidaxomicin significantly reduced CDI recurrence by the end of study compared with vancomycin in the whole study population (1 RCT, n=108, 11.8% versus 29%, RR 0.41, 95%CI 0.18 to 0.93, low-quality evidence). The findings for this outcome were stratified by age; fidaxomicin significantly reduced CDI recurrence by the end of study compared with vancomycin in those aged ≥2 (1 RCT, n=85, 11.1% versus 31.8%, RR 0.35, 95%CI 0.14 to 0.88, low-quality evidence) and in those aged ≥2 with a positive toxin test (1 RCT, n=34, 4.3% versus 36.4%, RR 0.12, 95%CI 0.02 to 0.95, low-quality evidence) but not in those <2 years (1 RCT, n=22, 15.4% versus 22.2%, RR 0.69, 95%CI 0.12 to 4.05, very low-quality evidence).

Fidaxomicin was not significantly different to vancomycin for treatment-emergent adverse events, serious treatment-emergent adverse events, drug-related serious treatment-emergent adverse events, treatment-emergent adverse events leading to death or treatment-emergent adverse events leading to withdrawal from treatment. See GRADE: **Table 43**

3.1.5.2 Antibiotic dose frequency

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.5.3 Antibiotic course length

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.6 Probiotics in children and young people

Oral rehydration solution with probiotic versus oral rehydration solution alone

The evidence for oral rehydration solution (ORS) with the probiotic *Lactobacillus rhamnosus* GG (LGG) versus ORS alone for the treatment of persistent diarrhoea in children and young people comes from 1 double-blind RCT (Basu et al 2007) in children with persistent diarrhoea. The children were on average between 4.1 and 4.2 years of age across study arms and were diagnosed with diarrhoea persisting for 14 days or more without remission. The intervention was 100 ml ORS with LGG (60 million cells) powder twice daily for 7 days or until diarrhoea stopped compared with 100 ml ORS twice daily for 7 days or until diarrhoea stopped.

For children with a positive *C. difficile* stool culture, ORS with LGG resulted in a significantly lower mean number of days duration of diarrhoea compared with ORS alone (1 RCT, n=14, mean difference -4.80 95%CI -7.53 to -2.07, low-quality evidence). There was no significant difference between ORS with LGG and ORS alone for mean number of days duration of vomiting in children with a positive *C. difficile* stool culture (1 RCT, n=14, mean difference 0.20 95%CI -0.77 to 1.17, very low-quality evidence).

See GRADE: **Table 44**

3.1.7 Prebiotics in children

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2 Prevention

3.2.1 Antibiotics in adults

3.2.1.1 Efficacy of antibiotic

3.2.1.1.1 Antibiotics versus placebo for the prevention of Clostridioides difficile infection

The evidence for prophylactic antibiotics versus placebo for the prevention of *Clostridioides difficile* infection (CDI) in people without CDI comes from 2 RCTs in adults (Mullane et al 2019; Johnson et al 2019).

Mullane et al (2019) included adults over 18 undergoing autologous or allogenic, hematopoietic stem cell transplantation (n=600) who received fluoroquinolone prophylaxis during neutropenia. Participants were excluded if they had active CDI or were receiving treatment for CDI. Study participants were stratified by transplant type (autologous versus allogeneic stem cells) before randomisation.

Mullane et al (2019) compared oral fidaxomicin 200 mg once daily for up to 40 days with placebo for the incidence of diarrhoea associated with CDI at 30 days post treatment. Both groups also received fluoroquinolone prophylaxis (regimen not outlined), and dosing of study medication began within 2 days of starting fluoroquinolone prophylaxis and continued until 7 days after neutrophil engraftment or completion of fluoroquinolone prophylaxis. Incidence of diarrhoea associated with CDI was also evaluated at 2 secondary time points: up to 60 days after last dose and up to 70 days after the first dose.

A modified intention-to treat-analysis (mITT) was used for the efficacy analysis.

Johnson et al (2019) included adults 60 years and over, hospitalised for up to 30 days prior to their current hospitalisation and receiving more than one dose of a systemic antibiotic. Participants were excluded if they had a known or suspected active CDI, unable to swallow oral vancomycin, were receiving concurrent treatment with metronidazole or probiotics, were allergic to vancomycin or had a contraindication for use of oral vancomycin.

Johnson et al (2019) compared oral vancomycin 125 mg once daily (as solution) with placebo in people whilst taking, and up to 5 days after completion of systemic antibiotics. Outcomes were the incidence of 'healthcare facility-onset CDI' defined as ≥3 symptoms of loose stools or diarrhoea in a 24-hour period >72 hours into hospitalisation. The regimens for systemic antibiotics taken by participants were not specified, but they were categorised as high risk (clindamycin, cephalosporin, carbapenems and fluoroquinolones) and moderate risk (aztreonam, macrolides, penicillins and sulfamethoxazole/trimethoprim) for CDI infection. The incidence of community-onset healthcare facility-associated CDI after hospital discharge defined as patient-reported symptoms with CDI diagnosis by a medical provider or charted diagnosis of CDI with symptoms was also evaluated via patient phone call 28 to 32 days post hospital discharge and medical record reviews at up to 3 months post-discharge.

3.2.1.2 Prophylaxis failure

Mullane et al (2019) reports its primary outcome as 'prophylaxis failure' which combines confirmed diarrhoea associated with CDI, use of antibiotics potentially effective against confirmed diarrhoea associated with CDI, or missing assessment for confirmed diarrhoea associated with CDI due to death or adverse events.

Prophylaxis failure included outcomes that are not necessarily diarrhoea associated with CDI, for example missing data due to death or adverse events. This evidence review reports outcomes for confirmed diarrhoea associated with CDI. These are explored further in the stratified findings and additional pre-specified sensitivity analysis.

There was no difference in prophylactic failure at 30 days or 60 days after the end of treatment between oral fidaxomicin 200 mg once daily for up to 40 days and placebo (1 RCT, n=600, 28.6% versus 30.8%, RR 0.93, 95% CI 0.73 to 1.19; low-quality evidence; 1 RCT, n=600, 35.2% versus 35.8%, RR 0.98, 95% CI 0.79 to 1.22; moderate quality evidence, respectively); or at 70 days after the start of treatment (1 RCT, n=600, 29.2% versus 31.1%, RR 0.94, 95% CI 0.74 to 1.20; low-quality evidence).

3.2.1.3 Confirmed diarrhoea associated with CDI

Johnson et al (2019) reports that there was no difference between oral vancomycin 125 mg once daily for up to up to 5 days post-completion of systemic antibiotics and placebo for healthcare facility-onset CDI (1 RCT, n=100, 0% versus 12%, RR 0.08, 95% CI 0.00 to 1.33, very low-quality evidence) or community-onset healthcare facility-associated CDI after hospital discharge (1 RCT, n=100, 0% versus 4%, RR 0.20, 95% CI 0.01 to 4.06, very low-quality evidence)

A sensitivity analysis was undertaken using the data from Mullane et al (2020) restricted to participants with confirmed diarrhoea associated with CDI only. Confirmed diarrhoea associated with CDI was defined as >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests for CDI. Oral fidaxomicin 200 mg once daily for up to 40 days was more effective than placebo for confirmed diarrhoea associated with CDI at 30 days (1 RCT, n=600, 4.3% versus 10.7%, RR 0.40, 95% CI 0.22 to 0.75; NNT 16, 95% CI 9 to 45; low-quality evidence) and 60 days (1 RCT, n=600, 5.6% versus 10.7%, RR 0.53, 95% CI 0.30 to 0.93; NNT 20, 95% CI 11 to 132 low-quality evidence) after the end of treatment; and at 70 days after the start of treatment (1 RCT, n=600, 4.7% versus 10.7%, RR 0.43, 95% CI 0.24 to 0.80; NNT 17, 95% CI 10 to 55; low-quality evidence).

3.2.1.4 Adverse events

There were no difference between oral fidaxomicin 200 mg once daily for up to 40 days and placebo for the number of people experiencing treatment emergent adverse events (1 RCT, n=600, 99.0% versus 99.7%, RR 0.99, 95% CI 0.98 to 1.01; moderate quality evidence), a moderate or severe adverse events (1 RCT, n=600, 87.3% versus 87.3%, RR 1.00, 95% CI 0.94 to 1.06; moderate quality evidence), serious adverse events (1 RCT, n=600, 32.7% versus 30.7%, RR 1.07, 95% CI 0.84 to 1.35; low-quality evidence), adverse events leading to death (1 RCT, n=600, 4.3% versus 4.7%, RR 0.93, 95% CI 0.44 to 1.94; very low-quality evidence), diarrhoea (1 RCT, n=600, 6% versus 10.3%, RR 0.58, 95% CI 0.33 to 1.01; very low-quality evidence) and vomiting (1 RCT, n=600, 4% versus 5%, RR 0.80, 95% CI 0.38 to 1.68; very low-quality evidence).

3.2.1.5 Time to onset of confirmed diarrhoea associated with CDI

Mullane et al (2019) assessed the incidence of diarrhoea associated with CDI over time via the Kaplan-Meier survival analysis method. This showed a significant increase in time to onset of diarrhoea associated with CDI with oral fidaxomicin 200 mg once daily for up to 40 days compared with placebo (1 RCT, hazard ratio [HR] 1.95, 95% CI 1.08 to 3.50, p=0.027; very low-quality evidence).

See GRADE: **Table 45** and **Table 46**

3.2.1.6 Antibiotics versus placebo for prevention of recurrence of *Clostridioides difficile* infection

The evidence for antibiotics versus placebo for prevention of recurrence of CDI comes from 2 RCTs in adults aged ≥18 years (Major et al 2019; Garey et al 2011).

Major et al (2019) included adults with a confirmed primary, recurrent or multiple-recurrent CDI that was successfully treated with metronidazole or vancomycin. CDI was defined as an episode of loose stools in the presence of a positive stool assay for glutamate dehydrogenase and enzyme immunoassay for *C. difficile* toxins with or

without a positive *C. difficile* culture. Endoscopic evidence of pseudomembranous colitis could substitute for toxin positivity.

Major et al (2019) randomised participants within 5 days of the last dose of metronidazole or vancomycin to receive oral rifaximin (400 mg three times a day for 14 days reduced to 200 mg three times a day for a further 14 days) or placebo. All participants continued to receive standard care, which is not clearly defined but does include antibiotic treatment for indications other than CDI. The primary outcome was CDI recurrence (defined as 3 or more loose stools for 2 or more days in conjunction with a positive stool toxin assay) at 4 and 12 weeks after the start of the intervention. Participants were followed up at 2 weeks, 8 weeks and 6 months by telephone, for secondary outcomes including: recurrence of CDI within 6 months; rehospitalisation for CDI within 6 months; and adverse events.

Garey et al (2011) included adults with CDI and a Horn's index of moderate or above who had diarrhoea (3 or more unformed stools per day for at least 2 days, or more than 6 unformed stools in 1 day) associated with a positive stool test for *C. difficile* toxin (via a stool cytotoxicity assay). Participants had been treated with oral vancomycin or metronidazole (dose not outlined) for 10 to 14 days and were excluded if they had a history of more than 1 recurrence of CDI.

Garey et al (2011) randomised participants immediately after finishing their initial 10 to 14 days of antibiotic treatment to either oral rifaximin 400 mg three times a day or placebo for 20 days and they were followed-up for up to 3 months after the discontinuation of treatment. The primary outcome was recurrent diarrhoea, which included recurrent CDI (defined as return of diarrhoea with a positive toxin test after resolution of the initial CDI diarrheal episode after study medication had been started) and patient self-reported return of non-CDI diarrhoea (defined as diarrhoea without a positive toxin test). The authors only considered the first episode of CDI recurrence within the efficacy assessments.

3.2.1.7 CDI recurrence

Major et al (2019) indicated no significant difference between oral rifaximin and placebo for CDI recurrence within 12 weeks (1 RCT, n=130, 15.9% versus 29.5%, RR 0.54, 95% CI 0.28 to 1.05; low-quality evidence), CDI recurrence within 6 months (1 RCT, n=127, 21.2% versus 32.8%, RR 0.65, 95% CI 0.36 to 1.16; low-quality evidence) or rehospitalisation for CDI within 6 months (1 RCT, n=127, 13.6% versus 13.1%, RR 1.04, 95% CI 0.43 to 2.52; very low-quality evidence).

Major et al (2019) undertook a prespecified sub-group analysis that considered the influence of either metronidazole or vancomycin to treat the initial incidence of CDI prior to treatment with oral rifaximin or placebo. In both cases there was no significant difference between rifaximin and placebo in CDI recurrence in participants initially treated with metronidazole (1 RCT, n=50; 23.8% vs 13.8%, Risk difference -10.2%, 95%CI -32.4% to 12.1%) or vancomycin (1 RCT, n=80; 32.5% vs 17.5%, Risk difference -15.1%, 95%CI -33.9% to 3.7%). The authors also undertook a post-hoc analysis that considered participant history of CDI on CDI recurrence, and found no significant differences between rifaximin and placebo when participants had no previous diagnosis of CDI, when participants had previously diagnosed with CDI, or when previous CDI history was unknown.

Garey et al (2011) indicated that oral rifaximin 400 mg three times a day for 20 days was more effective than placebo at up to 3 months for reducing recurrent diarrhoea (which is a combination of both recurrent CDI confirmed diarrhoea and recurrent self-reported non-CDI confirmed diarrhoea) (1 RCT, n=68, 21.2% versus 48.6%, RR 0.44,

95% CI 0.21 to 0.92; NNT 4, 95% CI 2 to 18; moderate quality evidence). There was no significant difference between oral rifaximin and placebo at up to 3 months for recurrent CDI confirmed diarrhoea (1 RCT, n=68, 15.2% versus 31.4%, RR 0.48, 95% CI 0.19 to 1.24; moderate quality evidence) or for recurrent self-reported non-CDI confirmed diarrhoea (1 RCT, n=68, 6.1% versus 17.1%, RR 0.35, 95% CI 0.08 to 1.68; low-quality evidence).

Garey et al (2011) undertook a Kaplan-Meier analysis which showed a significant increase in time to recurrent diarrhoea for oral rifaximin compared with placebo (1 RCT, HR = 2.72, 95% CI 1.1 to 6.6, p=0.010; low-quality evidence). However, there was no significant difference for time to recurrent CDI confirmed diarrhoea (1 RCT, HR 2.4, 95% CI 0.82 to 7.1, p=0.11; low-quality evidence) or time to recurrent self-reported non-CDI confirmed diarrhoea (1 RCT, HR 3.5, 95% CI 0.08 to 1.68; p=0.13; low-quality evidence).

3.2.1.8 Adverse events

Major et al (2019) did not identify any significant differences between rifaximin and placebo for serious adverse events (1 RCT, n=151, 15.6% versus 23%, RR 0.68, 95% CI 0.35 to 2.65; very low-quality evidence) and non-serious adverse events (1 RCT, n=151, 23.4% versus 29.7%, RR 0.79, 95% CI 0.46 to 1.34; very low-quality evidence). There were a total of 18 deaths in the study (9 in the rifaximin arm and 9 in the placebo arm) but this finding should be treated with caution because these figures are not consistent within the published paper.

See GRADE: **Table 47**

No systematic reviews or RCTs met the inclusion criteria for dose of antibiotics, antibiotic dose frequency, antibiotic course length, antibiotic route of administration, choice pf antibiotic in children and young people, antibiotic dose frequency in children and young people or antibiotic course length in children and young people

3.2.2 Monoclonal antibodies for prevention of recurrence of *Clostridioides difficile* infection adults

The evidence for monoclonal antibodies versus placebo for CDI comes from 1 published paper reporting 2 RCTs, MODIFY I and MODIFY II (Wilcox et al 2017). Both RCTs were double-blind, placebo-controlled trials conducted at 322 sites in 30 countries.

The population in both RCTs was very similar, adults with primary or recurrent CDI. There were 2,559 adults in the modified intention-to-treat (mITT) population; which was defined as all randomly assigned participants who received the study infusion, had a baseline stool test that was positive for toxigenic *C. difficile*, and began receiving standard-of-care treatment for CDI before or within 1 day after receiving the monoclonal antibodies. Of the participants 27.5% had ≥1 episodes of CDI in the previous 6 months and 14.2% had ≥2 previous episodes of CDI ever, with 16.4% having more severe CDI (defined as a Zar score of 2 or more). All participants were receiving standard-of-care oral antibiotics (metronidazole [46.7%], vancomycin [47.7%] or fidaxomicin [3.6%] for 10 to 14 days) which was chosen by the treating physician (no doses, frequency of administration or routes of administration were reported). Over half of the participants were aged ≥65 years (53.1%) and 56.4% were females, and most were hospital inpatients (67.6%).

The intervention was a single, 60-minute intravenous infusion of the assigned monoclonal antibody (bezlotoxumab (10 mg/kg of body weight), actoxumab [in

MODIFY I only], or actoxumab-bezlotoxumab) or placebo infusion of 0.9% saline on study day 1 while they were receiving standard-of-care antibiotics. Actoxumab is not licensed for any indication in the UK, therefore only the results of bezlotoxumab compared with placebo are presented in this evidence review.

The primary outcome of the RCTs was CDI recurrence at 12 weeks follow-up. The authors also undertook several pre-planned subgroup analyses for the outcome of recurrence of CDI at 12 weeks for risk factors (age, CDI history, immune status, CDI severity, and CD strain) for CDI and by trial stratification variables (inpatient, outpatient, and standard-of-care antibiotic). The RCTs are limited by under reporting of allocation concealment and sequencing; additionally, potential diagnostic detection bias, particularly in the MODIFY II trial, cannot be excluded. The analysis of certain outcomes, including adverse events, was limited by only pooled data (rather than individual trial data) being available.

3.2.2.1 Bezlotoxumab versus placebo for CDI

3.2.2.1.1 Initial clinical cure

Bezlotoxumab was not significantly different to placebo for initial clinical cure at 2 days (2 RCTs, n=1,554, 80% versus 80.3%, relative risk [RR] 1.00, 95% confidence interval [CI] 0.88 to 1.13; low-quality evidence).

3.2.2.1.2 Recurrence of CDI

Bezlotoxumab significantly reduced recurrence of CDI at 12 weeks compared with placebo (2 RCTs, n=1,554, 16.5% versus 26.6%, RR 0.62, 95% CI 0.51 to 0.76, number needed to treat [NNT] 10, 95%CI 7 to 17; low-quality evidence), with Kaplan-Meier rate estimates showing differences in the time to recurrence favoring bezlotoxumab of 12% at weeks 4 and 8 follow-up and 13% at week 12 follow-up, although it is unclear if these differences are statistically significant (very low-quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in participants with initial clinical cure at day 2 compared with placebo at 12 weeks follow-up (2 RCTs, n=1,246, 20.6% versus 33.2%, RR 0.62, 95% CI 0.52 to 0.76, NNT 8, 95% CI 6 to 14; low quality evidence).

3.2.2.1.3 Recurrence of diarrhoea

Bezlotoxumab significantly reduced recurrence of diarrhoea (regardless of whether it was associated with a positive toxin test) compared with placebo, follow-up time point not reported (2 RCTs, n=1,554, 27.3% versus 37.5%, RR 0.73, 95% CI 0.63 to 0.84, NNT 10, 95% CI 7 to 18; low-quality evidence).

3.2.2.1.4 Sustained cure

Bezlotoxumab significantly increased sustained cure (initial clinical cure without recurrence) at 12 weeks compared with placebo (2 RCTs, n=1,554, 63.5% versus 53.7%, RR 1.18, 95% CI 1.01 to 1.39, NNT 11, 95% CI 7 to 21; very low-quality evidence).

3.2.2.1.5 Mortality

Bezlotoxumab was not significantly different for all-cause mortality compared with placebo at either 4 weeks (2 RCTs, n=1,567, 4.1% versus 4.1%, RR 0.99, 95% CI 0.61 to 1.61; very low-quality evidence) or 12 weeks (2 RCTs, n=1,567, 7.1% versus 7.6%, RR 0.94, 95% CI 0.66 to 1.34; very low-quality evidence).

3.2.2.1.6 *Subgroup analyses for CDI risk factors: recurrence of CDI*

Bezlotoxumab significantly reduced recurrence of CDI in adults aged 65 years or over compared with placebo at 12 weeks follow-up (2 RCTs, n=795, 15.4% versus 31.4%, RR 0.49, 95% CI 0.37 to 0.65, NNT 7, 95% CI 5 to 10; moderate quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in adults with no previous history of CDI in the past 6 months compared with placebo at 12 weeks follow-up (2 RCTs, n=1,101, 13.5% versus 20.9%, RR 0.65, 95% CI 0.5 to 0.84, NNT 14, 95% CI 9 to 34; low-quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in adults with 1 or more episodes of CDI in the past 6 months compared with placebo at 12 weeks follow-up (2 RCTs, n=435, 25% versus 41.4%, RR 0.61, 95% CI 0.46 to 0.8, NNT 7, 95% CI 4 to 14; low-quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in adults with 2 or more episodes of CDI ever compared with placebo at 12 weeks follow-up (2 RCTs, n=226, 29% versus 42.1%, RR 0.68, 95% CI 0.47 to 0.98, NNT 8, 95% CI 4 to 148; low-quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in immunocompromised adults (based on medical history or use of immunosuppressive therapy) compared with placebo at 12 weeks follow-up (2 RCTs, n=331, 14.6% versus 27.5%, RR 0.55, 95% CI 0.35 to 0.84, NNT 8, 95% CI 5 to 25; low-quality evidence).

Bezlotoxumab significantly reduced recurrence of CDI in adults with more severe CDI (Zar score of ≥2) compared with placebo at 12 weeks follow-up (2 RCTs, n=247, 10.7% versus 22.4%, RR 0.47, 95% CI 0.26 to 0.87, NNT 9, 95% CI 5 to 39; low-quality evidence).

Bezlotoxumab was not significantly different for recurrence of CDI in adults with CDI strains 027, 078 or 244 (2 RCTs, n=217, 21.6% versus 32.2%, RR 0.65, 95% CI 0.41 to 1.04; low-quality evidence) or strain 027 alone (2 RCTs, n=189, 23.6% versus 34%, RR 0.68, 95% CI 0.42 to 1.08; low-quality evidence) compared with placebo at 12 weeks follow-up.

Bezlotoxumab significantly reduced recurrence of CDI in adults with 1 or more risk factors (≥65 years, no CDI in the past 6 months, ≥1 CDI episodes in the past 6 months, ≥2 previous episodes of CDI ever, immunocompromised, severe CDI or strains 027, 078 or 244) compared with placebo, follow-up time period not reported and this outcome was a *post hoc* analysis (2 RCTs [separate RCT data not available], n=1,175, 16.9% versus 29.8%, RR 0.57, 95% CI 0.46 to 0.7, NNT 8, 95% CI 6 to 13; low-quality evidence).

3.2.2.1.7 *Subgroup analysis by stratification variable: recurrence of CDI*

Bezlotoxumab significantly reduced recurrence of CDI in adult inpatients (2 RCTs, n=1,050, 13.8% versus 23.1%, RR 0.60, 95% CI 0.46 to 0.78, NNT 11, 95% CI 8 to 22; low-quality evidence) and outpatients (2 RCTs, n=504, 22.3% versus 34%, RR 0.66, 95% CI 0.49 to 0.87, NNT 9, 95% CI 6 to 26; low-quality evidence) compared with placebo at 12 weeks follow-up.

Bezlotoxumab significantly reduced recurrence of CDI in adults whose standard-of-care antibiotic was metronidazole (2 RCTs, n=753, 14.8% versus 22.7%, RR 0.65, 95% CI 0.48 to 0.88, NNT 13, 95% CI 8 to 42; low-quality evidence) or vancomycin (2 RCTs, n=745, 18% versus 30.6%, RR 0.59, 95% CI 0.45 to 0.77, NNT 8, 95% CI 6

to 16; low-quality evidence) compared with placebo at 12 weeks follow-up. However, there was no significant difference between bezlotoxumab and placebo when the standard-of-care antibiotic was fidaxomicin (2 RCTs, n=56, 20% versus 26.9%, RR 0.75, 95% CI 0.29 to 1.94; very low-quality evidence).

3.2.2.1.8 Adverse events

Bezlotoxumab was not significantly different to placebo for infusion specific adverse events (mostly mild nausea, headache, dizziness, fatigue or pyrexia) occurring within 24 hours of drug administration (2 RCTs, n=1,567, 10.3% versus 7.6%, RR 1.36, 95% CI 0.99 to 1.88; very low-quality evidence) or for adverse events leading to treatment being stopped (2 RCTs, n=1,567, 0.13% versus 0%, RR 2.98, 95% CI 0.12 to 73.06; low-quality evidence) at 24 hours follow-up.

Bezlotoxumab was not significantly different to placebo for adverse events, most commonly abdominal pain, diarrhoea, nausea, vomiting, fatigue, pyrexia, serious *C. difficile*, urinary tract infection or headache, (2 RCTs, n=1,567, 61.7% versus 61.2%, RR 1.01, 95% CI 0.93 to 1.09; low-quality evidence) or for drug related adverse events (2 RCTs, n=1,567, 7.5% versus 5.9%, RR 1.27, 95% CI 0.88 to 1.85; very low-quality evidence) occurring during the 4 weeks after infusion.

Bezlotoxumab was not significantly different to placebo for serious adverse events (2 RCTs, n=1,567, 19.8% versus 21.4%, RR 0.93, 95% CI 0.76 to 1.13; low-quality evidence) or for drug related serious adverse events (2 RCTs, n=1,567, 0.51% versus 0.26%, RR 1.99, 95% CI 0.37 to 10.82; very low-quality evidence) occurring during the 4 weeks after infusion compared to placebo. Bezlotoxumab was not significantly different for serious adverse events at 12 weeks (2 RCTs, n=1,567, 29.4% versus 32.7%, RR 0.90, 95% CI 0.78 to 1.04; low-quality evidence).

See GRADE: **Table 48**.

3.2.3 Prebiotics in adults

The evidence for the prebiotic oligofructose comes from 1 RCT (n=435) of consecutive inpatients aged 65 years or over prescribed a broad-spectrum antibiotic (ampicillin, amoxicillin, co-amoxiclav, cephalosporins, clarithromycin, ciprofloxacin or doxycycline) within the preceding 24 hours (Lewis et al 2005b).

The study excluded adults who had taken an antibiotic in the previous 6 weeks, those who were immunocompromised or had gastrointestinal disease, or those with diabetes (because the placebo arm was sucrose). The median age of the included population was 77 years (IQR ranging from 70 to 84 years). Participants were taking on average 2 antibiotics at study enrollment. Only 2.3% (n=10) of participants had *C. difficile* toxin at study entry, although 12.4% (n=54) had growth of *C. difficile*.

The intervention was a powder of oligofructose (12 g per day) taken orally; it is unclear if the oligofructose was taken as a single dose or split throughout the day. The comparator was sucrose (12 g per day). Study medications were started within a few hours of being prescribed antibiotics and taken throughout the period in which antibiotics were prescribed (phase 1) and taken for a further 7 days after antibiotics were stopped (phase 2). Outcomes were assessed 1 week after the end of the intervention (phase 3).

The primary outcome of the study was the incidence of antibiotic-associated diarrhoea. The study has several limitations: an unvalidated scoring tool was used for stool assessment (although in assessment by NICE the categories used would map

to a validated scoring tool such as the Bristol stool chart) and study blinding and allocation concealment are poorly described.

Results

Oligofructose was not significantly different to placebo at end of follow up for:

- incidence of diarrhoea (1 RCT, n=435, 26% versus 27.3%, RR 0.96, 95% CI 0.70 to 1.30; very low-quality evidence)
- incidence of significant diarrhoea, ≥3 loose stools in a 24-hour period (1 RCT, n=435, 16.7% versus 16.8%, RR 1.00, 95% CI 0.66 to 1.51; very low-quality evidence)
- incidence of non-significant diarrhoea, 1 or 2 loose stools in a 24-hour period (1 RCT, n=435, 9.3% versus 10.5%, RR 0.89, 0.50 to 1.57; very low-quality evidence)
- incidence of *C. difficile* associated diarrhoea (1 RCT, n=435, 10.2% versus 12.3%, RR 0.83, 95% CI 0.49 to 1.42; very low-quality evidence)
- incidence of *C. difficile* associated significant diarrhoea (1 RCT, n=435, 8.8% versus 9.5%, RR 0.93, 95% CI 0.51 to 1.67; very low-quality evidence)
- all-cause mortality (1 RCT, n=435, 1.9% versus 0.91%, RR 2.05, 95% CI 0.38 to 11.06; very low-quality evidence). Of the 6 deaths that occurred during the RCT, 3 participants who died had had no diarrhoea, 2 participants had significant diarrhoea (both of whom were *C. difficile* positive) and 1 participant had non-significant diarrhoea (*C. difficile* negative).

In the oligofructose group, the median (interquartile range) length of hospital stay was 17 days (13 to 22) compared with 15 days (11 to 18) in the placebo group. The authors state that no significant difference was noted.

See GRADE: **Table 49**

3.2.4 Probiotics in adults

The evidence for probiotics in the prevention of CDI in adults comes from 1 systematic review of 39 RCTs, of which 31 RCTs were included in a quantitative synthesis. 25 RCTs were in an adult population (Goldenberg et al 2017).

The population in the included studies were adults aged >18 years receiving antibiotic treatment for any reason. The settings of the RCTs varied, but most (20) were conducted in hospital settings, with only 3 RCTs in an outpatient setting and 3 in a mixed setting (inpatient and outpatient); in the remaining 7 RCTs the setting was unclear. The intervention was any probiotic (any strain or dose) compared with placebo (27 RCTs), no treatment (5 RCTs) and 1 RCT had an unclear comparator, for the outcome of prevention of *C. difficile* associated diarrhoea (CDAD). It was unclear in most studies if participants could have previous episodes of CDAD. Two RCTs included with adults had participants aged 15 or 17 years or older and 1 further RCT had an unclear population age. The analyses in the systematic review compared the intervention to any comparator.

3.2.4.1 Incidence of CDI

Probiotics significantly reduced the incidence of CDI compared with any comparator in adults, follow-up time point not reported, (24 RCTs, n=7,687, 1.37% versus 3.25%, RR 0.40, 95% CI 0.30 to 0.54, NNT 54, 95% CI 40 to 83; moderate quality evidence).

3.2.4.2 Incidence of CDAD

Probiotics significantly reduced the incidence of CDAD compared with any comparator in adult inpatients (19 RCTs, n=6,488, 1.6% versus 3.7%, RR 0.40, 95% CI 0.29 to 0.54, NNT 47, 95% CI 35 to 75; moderate quality evidence) but not in adult outpatients (2 RCTs, n=462, 0% versus 0.44%, RR 0.31, 95% CI 0.01 to 7.47; very low-quality evidence) or adults in mixed settings studies (2 RCTs, n=600, 0.67% versus 1.31%, RR 0.57, 95% CI 0.12 to 2.66; very low-quality evidence), follow-up time points not reported.

3.2.4.3 Incidence of CDI – confirmed by *C. Difficile* in stool

Probiotics were not significantly different compared with any comparator in adults for the outcome of incidence of *C. difficile* infection, determined by detection of *C. difficile* in stool (13 RCTs, n=961, 12.6% versus 12.7%, RR 0.85, 95% CI 0.61 to 1.17; low-quality evidence), follow-up time point not reported. Probiotics were also not significantly different compared with any comparator in adults for this outcome, regardless of setting (inpatients: 6 RCTs, n=617, 16.4% versus 16%, RR 0.86, 95% CI 0.60 to 1.23; very low-quality evidence; outpatients: 4 RCTs, n=112, 5.4% versus 12.5%, RR 0.46, 95% CI 0.14 to 1.53; very low-quality evidence; or mixed study settings: 1 RCT, n=150, 4.1% versus 3.9%, RR 1.03, 95% CI 0.21 to 4.93; very low-quality evidence), follow-up time points not reported.

3.2.4.4 Hospital length of stay

Probiotics were not significantly different compared with any comparator for hospital length of stay in adults (4 RCTs, n=3,484, mean difference [MD] −0.17 days, 95% CI −1.03 to 0.68 days; moderate quality evidence).

3.2.4.5 Adverse events

Probiotics significantly reduced the number of adverse events in adults compared with any comparator, follow-up time point not reported (28 RCTs, n=7,417, 15.9% versus 19.2%, RR 0.90, 95% CI 0.82 to 0.98; low-quality evidence). Details of the adverse events were not reported.

3.2.4.6 Sensitivity analysis

The systematic review authors undertook several prespecified and *post hoc* sensitivity analyses in order to explore the impact of missing data of efficacy (incidence of CDAD) and safety (adverse events) in the overall review population (adults and children). Missing data did not affect incidence of CDAD when replaced at any control event rate (1.5:1, 2:1, 3:1 and 5:1). Sensitivity analyses of RCTs analysed according to study risk of bias (low or high/unclear) made no difference to incidence of CDAD.

In a *post hoc* analysis of RCTs analysed by baseline risk in the control group (0 to 2%, 3 to 5% and over 5%) only studies at over 5% baseline risk of CDI in the control group were found to be statistically significant (favoring probiotic compared to any comparator) for incidence of CDAD (in both low and high/unclear risk of bias studies). Incidence of infection remained non-statistically significant under all sensitivity analyses. More adverse events occurred in the control group in studies at high/unclear risk of bias ($p<0.05$) but not for low risk bias studies; sensitivity analyses by missing data and care setting did not affect adverse effects.

See GRADE: **Table 50**

3.2.5 Prebiotics in children

No systematic reviews or RCTs met the inclusion criteria.

3.2.6 Probiotics in children and young people

The evidence for probiotics in the prevention of CDI in children and young people comes from 1 systematic review of 31 RCTs in a quantitative synthesis, of which 6 RCTs were in children receiving antibiotic treatment for any reason (Goldenberg et al 2017) and 1 additional RCT of probiotic compared with placebo in hospitalised children receiving antibiotics (Kolodziej and Szajewska 2019).

The population in the included RCTs were children (aged <18 years) receiving antibiotic treatment for any reason. The settings of the RCTs varied, 4 RCTs were conducted in hospital settings and 3 RCTs in outpatient settings. The intervention was any probiotic compared with placebo (in 6 RCTs) or no treatment (1 RCT) for the outcome of prevention of *C. difficile* associated diarrhoea (CDAD). In all RCTs it was unclear if participants with previous CDAD were excluded. The analyses in the systematic review compared the intervention to any of the comparators combined, and the outcomes from the single RCT (Kolodziej and Szajewska 2019) were combined where appropriate with these. For sensitivity analyses please see the section on probiotics in adults.

3.2.6.1 Incidence of CDAD

Probiotics significantly reduced the incidence of CDAD compared with any comparator in children, follow-up time point not reported (7 RCTs, n=1,388, 2.0% versus 6.3%, RR 0.33, 95% CI 0.19 to 0.59, NNT 24, 95% CI 16 to 46; moderate quality evidence).

Probiotics significantly reduced the incidence of CDAD compared with any comparator in child inpatients (4 RCTs, n=783, 1.8% versus 6.6%, RR 0.29, 95% CI 0.13 to 0.62, NNT 21, 95% CI 14 to 50; moderate quality evidence) or in children in mixed settings studies (3 RCTs, n=605, 2.3% versus 5.9%, RR 0.40, 95% CI 0.17 to 0.94, NNT 29, 95% CI 15 to 239; moderate quality evidence), follow-up time points not reported.

Probiotics were not significantly different compared with any comparator in child inpatients for the outcome of incidence of *C. difficile* infection, determined by detection of *C. difficile* in stool (2 RCTs, n=253, 26.8% versus 32.5%, RR 0.82, 95% CI 0.56 to 1.21; moderate quality evidence), follow-up time point not reported.

3.2.6.2 Adverse events

Probiotics were not significantly different compared with any comparator in children for the outcome of adverse events, follow-up time point not reported (5 RCTs, n=1,135, 0.53% versus 1.2%, RR 0.43, 95% CI 0.11 to 1.63; very low-quality evidence).

See GRADE: **Table 51.**

3.3 Economic model

As part of the development of this guideline, NICE commissioned York Health Economics Consortium (YHEC), as part of its role as the Economic and Methodological Unit, to develop a cost-effectiveness model for the treatment of CDI.

This model set out to find the most cost-effective sequence of antibiotic treatment options for:

- A population with the characteristics of the 'average' CDI patient (base-case population)
- An 'at increased risk' population which is older, and with a higher risk of more severe recurrences.
- An 'at decreased risk' population which is younger, and with a lower risk of more severe recurrences.

This model evaluates the cost-effectiveness of different treatment sequences for the treatment of CDI in the NHS healthcare system. Costs were applied from the perspective of the NHS, outcomes were quantified in terms of quality-adjusted life years (QALYs) and both costs and QALYs were discounted at 3.5% per annum in line with the NICE Reference Case. The model population was a cohort of 1,000 patients who entered the model after diagnosis of a CDI.

The full methods and results of this model are presented in Appendix M:.

4 Terms used in the guideline

Bristol Stool Scale: A 7-point rating scale designed to classify the form of human faeces, it is used in clinical practice and research, developed by Lewis & Heaton 1997.

Cochran's Q: A test to find differences in matched sets of three or more frequencies or proportions. It is used in Beinortas et al (2018) to test for heterogeneity within its network meta-analysis.

Frequentist network meta-analysis: An approach to network meta-analysis that adopts a frequentist interpretation of probability which defines the probability of an event occurring in terms of how frequently it occurs in a process for example an experiment

Haematopoietic stem cell transplantation: involves replacement of the patient's stem cells with healthy donor cells; patients receive conditioning chemotherapy followed by an infusion of stem cells (the transplant) from the donor (Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning 2018). Transplantation can be 'autologous' (using a patient's own stem cells) or 'allogenic' (using stem cells from a different donor) (NHS England 2015). The success of a stem cell transplant is measured by neutrophil engraftment, which is defined in Mullane et al (2019) as absolute neutrophil count ≥500 cells/mm^3 for 3 consecutive days or white blood cell count >1000 cells/mm^3 for 2 consecutive days.

Horn's index: is a severity score based on underlying clinical illness, which predicts patients at high risk of CDI.

Kaplan-Meier survival analysis: A survival curve in which the survival probability is plotted against the time from baseline. It is used when exact times to reach the endpoint are known (Petrie & Sabin 2009)

Neutropenia: is a condition that causes a low white blood cell count and can increase the risk of infection.

P score: P scores are used to rank treatments within network meta-analyses that adopt a frequentist approach. They measure the mean extent of certainty that a treatment is better than the competing treatments. They are based solely on the point estimates and standard errors of the frequentist network meta-analysis estimates under normality assumption and can easily be calculated as means of one-sided p-values.

Prebiotic oligofructose: is a food additive metabolized by bifidobacteria which is thought to lead to increases in their numbers and through competition a decrease in the number of C. difficile bacteria.

Zar score: is a CDI severity assessment score developed by Zar et al 2007. People with ≥2 points were considered to have severe diarrhoea associated with CDI. One point each was given for: age >60 years; temperature 138.3°C; albumin level <2.5 mg/dL; or peripheral WBC count >115,000 cells/mm3 within 48 h of enrolment onto the Zar et al (2019) study. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit.

Appendices

Appendix A: **Evidence sources**

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• Public Health England: Infectious diarrhoea: microbiological examination of faeces guide for primary care (2015) • NICE clinical knowledge summary: Diarrhoea - adult's assessment (2018) • NICE Evidence summary [ES13] Preventing recurrence of Clostridium difficile infection: bezlotoxumab (2017) • NICE evidence summary: CDI risk with broad-spectrum antibiotics (2015)
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG51: Sepsis: recognition, diagnosis and early management on sepsis (2017) • NICE guideline NG143: Fever in under 5s: assessment and initial management (2019)NICE clinical knowledge summary: diarrhoea – antibiotic associated (2019) • NICE guideline CG 183: drug allergy: diagnosis and management (2014) • BNF September 2020 • NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • CMO report 2011

Key area	Key question(s)	Evidence sources
		• NICE guideline NG63: antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • CMO report 2011 • ESPAUR report (2019)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff • BNF September 2020
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see Appendix F: for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see Appendix F: for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see Appendix F: for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see Appendix F: for included studies

Key area	Key question(s)	Evidence sources
		• BNF September 2020 • BNF for children (BNF-C) September 2020 • Summary of product characteristics

Appendix B: **Review protocol**

Review question	What antimicrobial pharmacological interventions, non-antimicrobial pharmacological interventions and non-pharmacological interventions are effective in treating or preventing *Clostridioides difficile* infection?
Types of review question	Intervention questions will primarily be addressed through the search.
Objective of the review	To determine the effectiveness of antimicrobial, non-antimicrobial and non-pharmacological interventions in treating or preventing acute infectious diarrhoea where *Clostridioides difficile* infection is confirmed or suspected, in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/ disease/ condition/ issue/domain	Population: For the treatment of Clostridioides difficile: Adults and children (aged 72 hours and older) with acute infectious diarrhoea where *Clostridioides difficile* infection is confirmed or suspected[1] Or, For the prevention (or prevention of recurrence) of Clostridioides difficile: Adults and children receiving antibiotic therapy for any reason.
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	Interventions will include: • Antimicrobial interventions[2] • Non-antimicrobial interventions (bezlotoxumab and intravenous immunoglobulin only) • Non-pharmacological interventions[3] (probiotics, prebiotics, faecal transplant, and stopping current antibiotic or proton pump inhibitor treatment only).

[1] From PHE 2019: Clostridium difficile infection is confirmed or suspected when there is diarrhoea AND one of the following: positive C. difficile toxin test OR results of C. difficile toxin test pending AND clinical suspicion of C. difficile infection (Mild severity: not associated with a raised WCC, typically associated with <3 stools of type 5–7 on the Bristol Stool Chart per day; Moderate severity: associated with a raised WCC that is $<15\times10^9$/L, typically associated with 3–5 stools per day; Severe severity: associated with a WCC $>15\times10^9$/L, or an acute rising serum creatinine (i.e. >50% increase above baseline), or a temperature of >38.5°C, or evidence of severe colitis (abdominal or radiological signs), the number of stools may be a less reliable indicator of severity; Life-threatening: includes hypotension, partial or complete ileus or toxic megacolon, or CT evidence of severe disease.)

[2] Antimicrobial interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance plus other antibiotics agreed by the committee.

[3] Within class comparisons will not be undertaken for non-pharmacological interventions, there will be no analysis of route, dose or type of preparation undertaken for these interventions.

	For treating or preventing acute infectious diarrhoea where *Clostridioides difficile* infection is confirmed or suspected as outlined above, in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction)
Eligibility criteria – comparator(s)/ control or reference (gold) standard	Interventions will be compared to any of the comparators listed below: • Placebo or no treatment • fluid management • nutritional management • anti-diarrhoea medications • any other active treatment
Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment (including surgery for pseudomembranous colitis, post-infectious irritable bowel syndrome) • relapse or reinfection (together called recurrence) • safety, tolerability, and adverse effects. b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d) Ability to carry out activities of daily living. e) Service user experience. f) Health and social care related quality of life, including long-term harm or disability. g) Health and social care utilisation (including length of stay, planned and unplanned contacts). The committee considered which outcomes and the time points at which they reported were clinically important.
Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs • Network meta-analysis (NMA) If insufficient evidence is available progress to: • Non-randomised controlled trials • Systematic reviews of non-randomised controlled trials • Cohort studies • Pre and post intervention studies (before and after) • Interrupted time series studies

Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • vaccinations • infection prevention and control measures • general good antimicrobial stewardship issues to prevent C. difficile infection (such as duration of antibiotic use, inappropriate use of broad-spectrum antibiotics etc). This will be cross-referred to existing NICE AMS guidelines. • fluid management as an intervention • nutritional management as an intervention • anti-diarrhoea medications (such as oral rehydration therapy, anti-motility medicines and other anti-diarrhoeal medicines) and other active treatments as intervention
Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, children (those under 18 years of age), older adults and people with characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.
Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. The Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.
Data management (software)	Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process (including Daily Update and Epub Ahead of Print) via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage.

	A summary of the proposed search strategy is given in the appendix below. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2000 to the present day The results will be downloaded in the following sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results See appendix B for further details on the search strategy. Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.
Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Study checklists were used to critically appraise individual studies. For details please see appendix H of Developing NICE guidelines: the manual (2020) The following checklists will be used: • Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist • Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool • Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I.

	• Risk of bias of single-arm observational studies will be assessed using the IHE Quality Appraisal Checklist for Case Series Studies. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	Results reported by individual studies will be reported in the evidence review in narrative format and in GRADE tables in appendix H of the evidence review. If systematic reviews are identified as being sufficiently applicable and high quality, they will be used as the primary source of data, rather than extracting information from primary studies. Where appropriate, meta-analyses may be conducted to combine the results of quantitative studies for each outcome, for example: • if there is concern about the reported data (for example, if statistical significance has not been reported or inappropriate methods have been used for meta-analysis), • if more than one study reports the same comparison and outcomes
Methods for analysis – combining studies and exploring (in)consistency	Where meta-anaysis is undertaken they will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) and they will be performed in Cochrane Review Manager. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks will be presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials). Fixed- and random-effects models (der Simonian and Laird) will be used, with the choice of model based on the degree of heterogeneity for the results of each outcome. Fixed-effects models are the preferred choice, but in situations where the assumptions of a shared mean for fixed-effects model are clearly not met, random-effects results will be presented. Random-effects models will be selected for analysis if significant statistical heterogeneity is identified in the meta-analysis, defined as $I^2 \geq 50\%$. Network meta-analysis (NMA) will not be carried out for antimicrobial prescribing guidelines. If a study that is included in the review has undertaken an NMA and reports these results, they will be reported verbatim in the evidence review.
Meta-bias assessment – publication bias, selective reporting bias	Where meta-analysis is undertaken, please see Developing NICE guidelines: the manual (2018) for details.
Assessment of confidence in	Where meta-analysis is undertaken, please see Developing NICE guidelines: the manual (2018) for details.

cumulative evidence	Information on medicines safety data and antimicrobial resistance will not be quality assessed.
Rationale/ context – Current management	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the Developing NICE guidelines: the manual (2018). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis where appropriate and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	Developed and funded by NICE.
Name of sponsor	Developed and funded by NICE.
Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.

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Appendix C: **Literature search strategy**

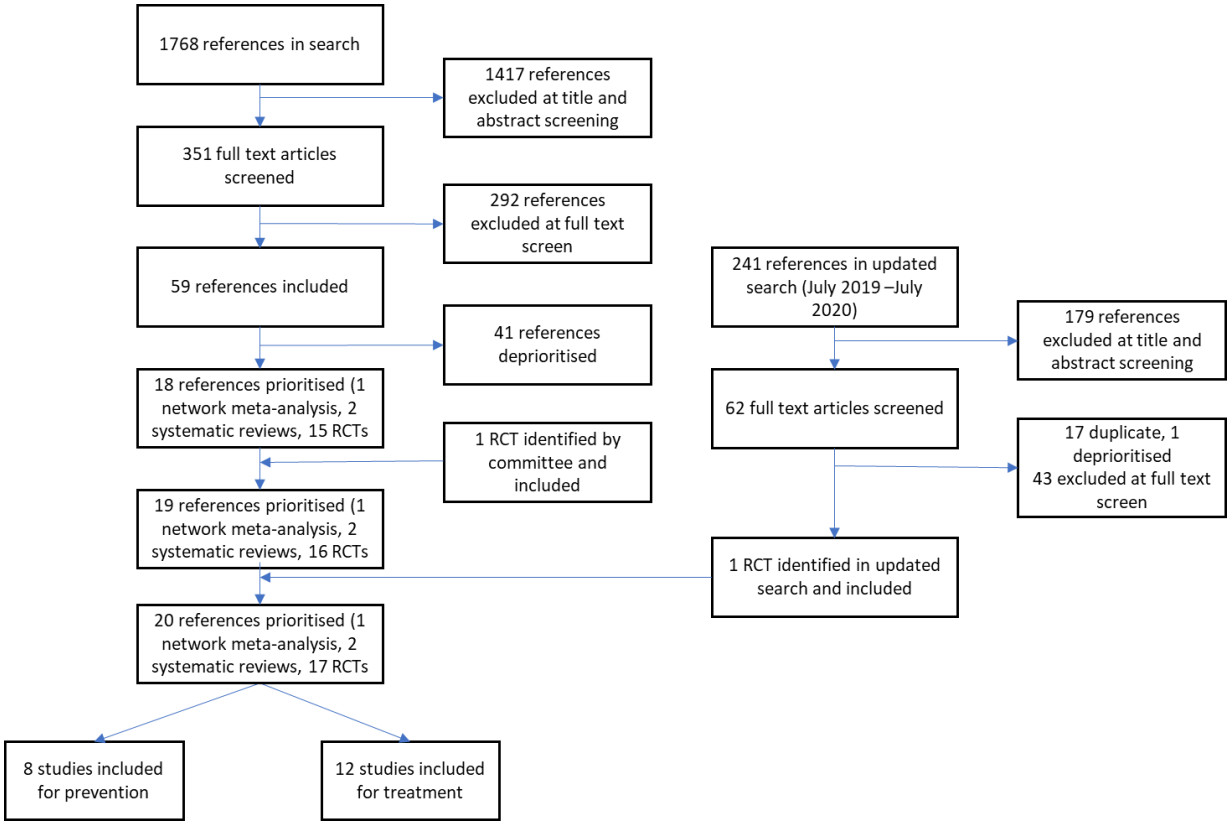
Main concepts	Concept	Proposed search terms
Condition	Clostridium difficile	Clostridium difficile/ ((Clostridium or Clostridioides) adj2 difficile*).ti,ab. C diff*.ti,ab. or/1-3 exp Clostridium Infections/ Diarrhea/ (Diarrhea or diarrhoea).ti,ab. or/6-7 4 and 8 5 or 9
Named Antibiotics	Metronidazole	Metronidazole/ (metronidazole* or flagyl*).ti,ab.
	Vancomycin	Vancomycin/ (Vancomycin* or Vancomicin* or Vancocin*).ti,ab
	Fidaxomicin	Fidaxomicin/ (fidaxomicin or Dificid or Dificlir).ti,ab.
	Fusidic Acid	Fusidic Acid/ Fusidic acid*.ti,ab.
	Rifampin/	Rifampin/ (Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab.
	Rifaximin	Rifaximin/ rifaximin.ti,ab
	Tigecycline	Tigecycline/ Tigecycline*.ti,ab.
	Nitazoxanide	nitazoxanide*.ti,ab.

	Bacitracin	Bacitracin/ (bacitracin or baciguent).ti,ab.
	Teicoplanin	Teicoplanin/ (Teicoplanin* or Targocid*).ti,ab.
Interventions – specific probiotics	Lactobacillus	Lactobacillus/ (lactobacillus* or saccharomyc*).ti,ab.
	Saccharomyces	Saccharomyces boulardii/ Saccharomyces/
Interventions – general probiotic terms		exp Probiotics/ exp Synbiotics/ (probiotic* or synbiotic*).ti,ab.
Interventions – specific prebiotics	Xylitol	Xylitol/ (xylitol* or oligofructose or oligosaccharide*).ti,ab.
	Oligofructose	Oligosaccharides/
Interventions – general prebiotic terms		exp Prebiotics/
Non-antibiotic pharma interventions	Bezlotoxumab	Bezlotoxumab*.ti,ab,kw.
	Intravenous Immunoglobulin	Immunoglobulins, Intravenous/ ((Intravenous or IV or pool*) adj3 immunoglobulin*).ti,ab.
Non-antibiotic non-pharma interventions	Fecal Microbiota Transplantation	Fecal Microbiota Transplantation/ ((Fecal or faecal) adj4 transplant*).ti,ab. FMT.ti,ab.
	Stopping current antibiotic or proton pump inhibitor treatment	((causativ* or stop* or withdraw*) adj2 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab. ((causativ* or stop* or withdraw*) adj2 (PPI or proton pump inhibitor*)).ti,ab

Prescribing strategies	Active surveillance No intervention Watchful waiting	watchful waiting/ "no intervention*".ti,ab (watchful* adj2 wait*).ti,ab. (wait adj2 see).ti,ab (expectant* adj2 manage*).ti,ab (active* adj2 surveillance*).ti,ab
	Prescribing times Delayed treatment Prophylaxis	Inappropriate prescribing/ ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab ((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab. ((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misus* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Standard search filter
Randomised Controlled Trials	Controlled Clinical Trials Cross over studies Randomised controlled trials (rcts)	Standard search filter
Observational Studies	Case-Control Studies Cohort Studies Controlled Before-After Studies	Standard search filter

	Cross-Sectional Studies Epidemiologic Studies Observational Study	
Limits	Exclude experiments on animals Exclude letters, editorials and letters Limit date to 2000 - Current	Standard search limits

Appendix D: **Study flow diagram**



Appendix E: **Evidence prioritisation**

E.1 Treatment

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Are antimicrobial pharmacological interventions effective for the treatment of acute infectious Clostridioides difficile associated diarrhoea in adults, children and young people?						
Antibiotic vs placebo						
Nelson et al 2017	Systematic review	Vancomycin	Placebo	Presence or absence of *C. difficile* in the stool during treatment; symptomatic and bacteriological cure	Prioritised	Only study identified that compares antibiotic versus placebo
Which antimicrobial pharmacological interventions is most effective for the treatment of acute infectious Clostridioides difficile associated diarrhoea in adults, children and young people?						
Antibiotics compared with another antibiotic						
Beinortas et al. 2018	Network meta-analysis	Fusidic acid	Vancomycin (reference treatment)	Sustained symptomatic cure	Prioritised	Most comprehensive and high quality review identified for this comparison that consider the majority of RCTs identified in other systematic reviews identified.
		Fidaxomicin				
		Metronidazole				
		Cadazolid				
		Rifaximin				
		Surotomycin				
		Teicoplanin				
		Ridinilazole				
		LFF571				
		Nitazoxanide				
		Tolevamer				

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
		Bacitracin				
Gawronska et al 2017	RCT	Metronidazole	Rifaximin	*C. Difficile* cure rate	Prioritised	Not included in Beinortas et al (2018) and considers children
Wolf et al 2019	RCT	Fidaxomicin	Vancomycin	Confirmed clinical response	Prioritised	Not included in Beinortas et al (2018) and considers children
Sridharan et al 2019	Systematic review	Vancomycin	Vancomycin	Symptomatic and bacteriological cure	Deprioritised	Lower quality evidence than the Beinortas et al. (2018) network meta-analysis based on synthesis and findings
		Metronidazole	Metronidazole			
		Teicoplanin	Teicoplanin			
		Fusidic acid	Fusidic acid,			
		Bacitracin	Bacitracin,			
		Fidaxomicin	Fidaxomicin,			
		Nitazoxanide	Nitazoxanide,			
		Ridinilazole	Ridinilazole,			
		Surotomycin	Surotomycin,			
		LFF 571	LFF 571,			
		Cadazolid	Cadazolid,			
		metronidazole/ rifampicin combination	metronidazole/ rifampicin combination			
Nelson et al 2017	Systematic review	Vancomycin	Vancomycin	Presence or absence of *C. difficile* in the stool; symptomatic and bacteriological cure	Deprioritised	For this question Nelson et al (2017) was of lower quality than the Beinortas et al. (2018) network meta-analysis based on synthesis and findings
		Metronidazole				
		fusidic acid	Teicoplanin			
		Nitazoxanide				
		Teicoplanin	Metronidazole			
		Rifampin				
		Rifaximin				

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
		Bacitracin	Metronidazole plus rifampin			
		Cadazolid	Fidaxomicin (OPT 80)			
		LFF517				
		Surotomycin	Nitazoxanide			
		Fidaxomicin (OPT 80)	Bacitracin			
Al Momani et al 2018	Systematic review	Fidaxomicin	Vancomycin	Clinical cure rate and rate of recurrence	Deprioritised	Lower quality evidence than the Beinortas et al. (2018) network meta-analysis based on study eligibility criteria; identification and selection of studies; synthesis and findings
Li et al 2015	Systematic review	Metronidazole	Vancomycin,	Clinical cure rate; CDI recurrence rate	Deprioritised	Lower quality evidence than the Beinortas et al. (2018) network meta-analysis based on study eligibility criteria; identification and selection of studies; synthesis and findings
			Vancomycin plus metronidazole,			
			Vancomycin plus rifampin			
Ng et al 2019	Systematic review	Rifaximin	Metronidazole	Treatment of and reducing CDI recurrence	Deprioritised	Lower quality evidence than the Beinortas et al. (2018) network meta-analysis based on study eligibility criteria; identification and selection of studies; synthesis and findings
			Rifaximin			
			Vancomycin/ metronidazole or a combination,			
Igarashi et al 2018	Systematic review	Vancomycin	Metronidazole	Clinical cure of CDI	Deprioritised	Lower quality evidence than the Beinortas et al. (2018) network

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						meta-analysis based on identification and selection of studies; synthesis and findings
Housman et al 2016	RCT	Fidaxomicin	Vancomycin	Bacteriological cure and clinical failure	Deprioritised	Lower quality RCT and better-quality evidence was available to address antibiotic choice question based on potential bias arising from the randomisation process
What is the optimal dose for the antimicrobial pharmacological treatment of acute infectious Clostridioides difficile associated diarrhoea in adults, children and young people?						
Antibiotic Dose and/or frequency						
Nelson et al 2017	Systematic review	Vancomycin 500 mg four times daily	Vancomycin dose study 125 mg four times daily	Symptomatic Cure, Bacteriologic resolution and rate of Relapse	Prioritised	Only study identified that assesses the efficacy of different Vancomycin doses
Nelson et al 2017	Systematic review	Fidaxomicin (OPT 80) dose 200 mg and 400 mg	Fidaxomicin (OPT 80) dose 100 mg	Resolution of diarrhoea and abdominal discomfort	Prioritised	Only study identified that assesses the efficacy of different Fidaxomicin doses
What non-antimicrobial pharmacological interventions and non-pharmacological interventions are effective in treating Clostridioides difficile infection?						
Prebiotics with antibiotics compared with placebo with antibiotics						
Lewis 2005a	RCT	Metronidazole or vancomycin with oligofructose	Metronidazole or vancomycin with placebo	Development of further diarrhoea	Prioritised	Only study identified that assesses the efficacy prebiotics with antibiotics versus placebo with antibiotics for treatment
Probiotic with antibiotics vs placebo with antibiotic						

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Basu et al 2007	RCT	Oral rehydration solution	Oral rehydration solution plus Lactobacillus rhamnosus GG powder	Decrease in frequency and duration of diarrhoea and vomiting.	Prioritised	Only study identified that assesses the efficacy probiotics with antibiotics versus placebo with antibiotics for treatment
Wullt et al 2007	RCT	Metronidazole and Lactobacillus plantarum 299v	Metronidazole and placebo	Clinical recurrence rate and bacteriological effect	Deprioritised	Lower quality RCT and better quality evidence was available to address probiotic efficacy. Sources of bias arising from the randomisation process, risk of bias due to deviations from the intended interventions, and bias due to missing outcome data.
Faecal microbiota transplant (FMT) vs antibiotic or placebo: Treatment – initial treatment of CDI						
Camacho-Ortiz et al 2017	RCT	Vancomycin	FMT	CDI resolution	Prioritised	Only study identified that assesses the efficacy of antibiotics compared to FMT for treatment of first episode of CDI
Faecal microbiota transplant (FMT) vs antibiotic or placebo: Treatment – recurrent CDI						
Dubberke et al 2018	RCT	FMT (RBX2660) - 2 doses	Placebo	Prevention of recurrent CDI	Prioritised	Only study identified that assesses the efficacy of FMT compared to placebo for treatment of recurrent CDI
			FMT (RBX2660) – 1 dose and placebo			
Van Nood et al 2013	RCT	Vancomycin plus FMT	Vancomycin	Cure without relapse	Prioritised	Study identified in Rokkas et al 2019 – which was subsequently deprioritised (see below). On review the study

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						represents the highest quality evidence identified (Low risk of bias and directly applicable) to assesses the efficacy of FMT compared to antibiotic for the treatment of recurrent CDI and is combined in a NICE conducted meta-analysis.
Hota et al 2017	RCT	Vancomycin plus FMT	Vancomycin	Recurrence of symptomatic, laboratory-confirmed CDI	Prioritised	Study identified in Rokkas et al 2019 – which was subsequently deprioritised (see below). On review was directly applicable but at moderate to high risk of bias due to poor reporting of allocation sequencing and deviation from intended interventions. It has been included in a NICE conducted meta-analysis for completeness to assesses the efficacy of FMT compared to antibiotic for the treatment of recurrent CDI.
Cammarota et al 2015	RCT	Vancomycin plus FMT	Vancomycin	Resolution of diarrhoea associated with CDI	Prioritised	Study identified in Rokkas et al 2019 – which was subsequently deprioritised (see below). On review the study represents the highest quality evidence identified (Low risk of bias and directly applicable) to assesses the efficacy of FMT compared to antibiotic for the treatment of recurrent CDI and

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						is combined in a NICE conducted meta-analysis.
Hvas et al 2019	RCT	FMT plus vancomycin	fidaxomicin vancomycin	Clinical resolution and a negative result from a polymerase chain reaction test for Clostridium difficile	Prioritised	Study identified in Rokkas et al 2019 – which was subsequently deprioritised (see below). This study provides the only evidence for FMT plus vancomycin compared to fidaxomicin. On review the study represents the highest quality evidence identified (Low risk of bias and directly applicable) to assesses the efficacy of FMT compared to antibiotic for the treatment of recurrent CDI and is combined in a NICE conducted meta-analysis.
Rokkas et al 2019	Network meta-analysis	FMT plus vancomycin or FMT only	Vancomycin or fidaxomicin or FMT	Resolution of CDI-related symptoms, without the need for additional CDI treatment during the follow-up period	Deprioritised	There was insufficient transitivity between studies included in the NMA – indicating that studies had been inappropriately included in the NMA. It was also not clear what outcome was reported in the NMA.
Khan et al 2018	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review meta-analysis undertaken was considered inappropriate due to heterogeneity between studies.

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						All included studies (n=3) were identified and have been prioritised
Moayyedi et al 2017	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review meta-analysis undertaken was considered inappropriate due to heterogeneity between studies. All included studies (n=3) were identified and have been prioritised
Health Quality Ontario 2016	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review meta-analysis undertaken was considered inappropriate due to heterogeneity between studies. All included studies (n=3) were identified and have been prioritised
O'Horo et al 2014	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review no meta-analysis undertaken. Mainly observational studies. RCT's identified have already been included
Butler et al 2014	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review no meta-analysis undertaken. Mainly observational studies. RCT's identified have already been included
Chapman et al 2016	Systematic review	FMT plus vancomycin	Vancomycin	Cure of recurrent CDI	Deprioritised	On review no meta-analysis undertaken. Mainly observational studies. RCT's

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						identified have already been included

[1] See appendix F for full references of included studies
[2] See appendix J for full references of not-prioritised studies, with reasons for not prioritising these studies

E.2 Prevention

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Are antimicrobial pharmacological interventions effective for the treatment of acute infectious Clostridioides difficile associated diarrhoea in adults, children and young people?						
Prophylactic antibiotic versus prophylactic antibiotic for prevention of Clostridioides difficile infection						
Mullane et al 2019	RCT	Fluoroquinolone prophylaxis and once-daily oral fidaxomicin (200 mg).	Fluoroquinolone prophylaxis and placebo.	CDI associated diarrhoea incidence through 30 days after study medication	Prioritised	Only study identified that compares prophylactic fluoroquinolone versus placebo
Johnson et al 2019	RCT	Vancomycin 125mg once a day whilst receiving systemic antibiotics and continued for 5 days post completion of systemic antibiotics	Placebo	Healthcare facility onset CDI loose stools (≥ 3) or diarrhoea in 24-hour period (for patients with concurrent confirmed CDI) or >72 hours into hospitalisation	Prioritised	Only study identified that compares prophylactic vancomycin versus placebo
Antibiotics versus placebo for prevention of recurrence of Clostridioides difficile infection						

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Major et al 2019	RCT	Rifaximin 400 mg three times a day for 14 days, reduced to 200 mg three times a day for a further 14 days	Placebo	Recurrence of CDI within 12 weeks of trial entry	Prioritised	Directly addresses the question and more recent study not considered in Nelson et al (2017)
Garey et al 2011	RCT	Rifaximin 400 mg three times daily for 20 days given immediately after finishing standard anti-CDI antibiotics	Placebo	Recurrent diarrhoea that included CDI recurrence (return of diarrhoea with a positive toxin test); patient self-reported return of non-CDI diarrhoea after a period of wellness.	Prioritised	Directly addresses the question and provides additional detail not included in Nelson et al (2017)
Nelson et al 2017	Systematic review	Vancomycin	Vancomycin	Presence or absence of *C. difficile* in the stool; symptomatic and bacteriological cure	Deprioritised	For this question Nelson et al (2017) does not address the prevention of recurrence question fully.
		Metronidazole				
		fusidic acid	Teicoplanin			
		Nitazoxanide				
		Teicoplanin	Metronidazole			
		Rifampin				
		Rifaximin	Metronidazole plus rifampin			
		Bacitracin				
		Cadazolid	Fidaxomicin (OPT 80)			
		LFF517				
		Surotomycin	Nitazoxanide			
		Fidaxomicin (OPT 80)	Bacitracin			

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Which non-antimicrobial pharmacological interventions is most effective for the prevention of the recurrence of Clostridioides difficile associated diarrhoea in adults, children and young people?						
Monoclonal antibodies versus placebo for prevention of Clostridioides difficile infection						
Wilcox et al 2017	2 RCTs (MODIFY I and MODIFY II)	A single intravenous infusion of bezlotoxumab (10 mg per Kg of body weight)	Placebo	Prevention of recurrent CDI	Prioritised	This is the original publication in this area. All other identified studies in this area were post-hoc analysis of Wilcox et al (2017).
What non-antimicrobial pharmacological interventions and non-pharmacological interventions are effective in preventing Clostridioides difficile infection?						
Probiotic with antibiotics vs placebo with antibiotic						
Goldenberg et al 2017	Systematic review (39 RCTs)	Oral probiotic (drink or capsule, any species).	Placebo, other prophylaxis or no treatment.	Incidence of CDI	Prioritised	Only study identified that assesses the efficacy prebiotics with antibiotics versus placebo with antibiotics for treatment
Kolodziej and Szajewska 2019	RCT	Oral Lactobacillus reuteri drink	Placebo drink	Incidence of diarrhoea	Prioritised	Additional study not identified within the Goldenberg et al 2017
Cai et al 2018	Systematic review (51 studies)	Oral probiotics, with any duration and dose 10 different probiotic therapies	Active or placebo control	Incidence of diarrhoea, and the efficacy of probiotics on antibiotic associated diarrhoea and CDI rate	Deprioritised	Goldenberg et al (2017) provided more detail of relevance in line with research protocols including sub-groups for age, severity. Furthermore, primary outcome is AAD, not Diarrhoea associated with CDI, and reported 21 studies in contrast to Goldenberg et al

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						(2017) which has Diarrhoea associated with CDI as primary outcome and includes 31studie reporting this outcome
Avadhani et al 2011	Systematic review (8 RCTs)	Probiotic	Active or placebo	Incidence of CDI associated disease	Deprioritised	All included studies are identified in Goldenberg et al (2017)
Allen et al (2013)	RCT	Probiotic	Placebo	Preventing antibiotic associated diarrhoea and CDI associated diarrhoea	Deprioritised	Higher quality evidence was available to address the probiotic efficacy question
Johnston et al 2018	Systematic review (18 RCTs)	Probiotics prophylaxis	Placebo	Incidence of CDI associated disease	Deprioritised	Higher quality evidence was available to address the probiotic efficacy question
Johnston et al 2012	Systematic review (22 RCTs)	Probiotics	Placebo	Incidence of CDI associated disease	Deprioritised	Higher quality evidence was available to address the probiotic efficacy question
McFarland et al 2015	Systematic review (3 RCTs)	Bio k+	placebo	Incidence of CDI	Deprioritised	All included studies are identified in Goldenberg et al (2017)
Shen et al 2017	Systematic review (19 RCTs)	Probiotics (any route or dose)	Placebo or no treatment	incidence of CDI	Deprioritised	All included studies are identified in Goldenberg et al (2017)
Sinclair et al 2016	Systematic review (10 RCTs)	Lactobacillus probiotics	Placebo	incidence of CDI	Deprioritised	Higher quality evidence was available to address probiotic efficacy

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Sinclair et al 2011	Systematic review (11 RCTs)	Lactobacillus probiotics	Placebo	Antibiotic associated diarrhoea and CDI associated Diarrhoea	Deprioritised	Goldenberg et al (2017) provided more detail of relevance in line with research protocols
Szajewska et al 2015	Systematic review (21 RCTs)	S. boulardii	Placebo or no treatment	Antibiotic associated diarrhoea and CDI associated Diarrhoea	Deprioritised	Goldenberg et al (2017) provided more detail of relevance in line with research protocols
McFarland et al 2015	Systematic review (21 RCTs)	Any strain or dose of a specified probiotic	Placebo or "no intervention" control group	Incidence and recurrence of C Diff	Deprioritised	Higher quality evidence was available to address probiotic efficacy based on Bias arising from the randomisation process, Risk of bias due to deviations from the intended interventions, Bias due to missing outcome data
McFarland et al 2006	Systematic review (31 RCTs)	Any strain or dose of a specified probiotic	Placebo, active treatment currently used as standard practice, or no treatment control.	Prevention of Antibiotic associated diarrhoea and treatment of CDI associated Diarrhoea Adults and children	Deprioritised	Higher quality systematic review was selected to address the efficacy of probiotic question
Pattani et al 2013	Systematic review (16 RCTs)	Receiving antibiotics and co-administration of probiotics	Usual care, with or without the use of placebo	Incidence of CDI	Deprioritised	Higher quality evidence was available to address the probiotic efficacy question
Butler et al 2016	Systematic review	Single and Multi-organism probiotics	Placebo	Prevent CDI	Deprioritised	Contains a meta-analysis of 2 RCTs, both RCTs were prioritised for inclusion

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
D'Souza et al 2002	Systematic review (9 RCTs)	Probiotic plus antibiotics	Placebo	Prevention of Antibiotic associated diarrhoea and narrative outline of treatment of CDI associated Diarrhoea Adults and children	Deprioritised	Goldenberg et al (2017) provided more detail of relevance in line with research protocols
Dendukuri et al 2005	Systematic review (8 RCTs)	Probiotic	Placebo	CDI associated disease	Deprioritised	Goldenberg et al (2017) provided more detail of relevance in line with research protocols
Ritchie et al 2012	Systematic review (6 RCTs)	Probiotics	Placebo	Prevention in overall symptoms or treatment of the gastrointestinal diseases reports CDD outcome	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Vernaya et al 2017	Systematic review (5 RCTs)	Probiotics	Placebo	incidence or relapse of CDAD.	Deprioritised	Higher quality evidence was available to better addresses the probiotic efficacy question
Tung et al 2019	Systematic review (6 RCTs)	Probiotics including Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and Bacillusdalone or in combination	Placebo	antibiotic-associated diarrhoea (AAD) and Clostridium difficile diarrhoea (CDD)	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Wu et al 2013	Systematic review (7 RCTs)	Lactobacillus probiotic	Placebo and ORS	Lactobacillus probiotic	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Song et al 2010	RCT	Probiotic Lactobacillus - Lacidofil cap	Placebo	Development of Antibiotic Associated Diarrhoea within 14 days of enrolment	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Helps et al 2015	RCT	Probiotic fermented milk drink containing Lactobacillus casei Shirota	Placebo	Antibiotic-associated diarrhoea (AAD) and Clostridium difficile-associated disease (CDAD) on renal unit inpatients	Deprioritised	The study is smaller than an RCT of the same intervention in the same population already included within a systematic review.
Lau et al 2016	Systematic review (26 RCTs)	Probiotics	Placebo	Incidence of Clostridium difficile-associated diarrhoea	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Salari et al 2012	Systematic review (19 RCTs)	Probiotics	Placebo	Treatment of diarrhoea	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Rajkumar et al 2020	RCT	Lactobacillus casei DN114001 (combined as a drink with two regular yoghurt cultures, Lactobacillus bulgaricus and Streptococcus thermophilus)	Placebo	Incidence of antibiotic associated diarrhoea	Deprioritised	Higher quality evidence was available to better address the probiotic efficacy question
Prebiotic versus placebo for prevention of Clostridioides difficile infection						
Lewis et al 2005b	RCT	Oral oligofructose powder (12g /day) during antibiotic	Oral placebo (sucrose) powder (12 g/ day) during antibiotic therapy	Development of CDI.	Prioritised	Only study identified that assesses the efficacy probiotics with antibiotics

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
		therapy and for 7 days after	and for 7 days after			versus placebo with antibiotics for prevention

[1] See appendix F for full references of included studies
[2] See appendix J for full references of not-prioritised studies, with reasons for not prioritising these studies

Appendix F: **Included studies**

F.1 Treatment

Basu, S, Chatterjee, M, Ganguly, S et al. (2007) Effect of Lactobacillus rhamnosus GG in persistent diarrhea in Indian children: a randomized controlled trial. *Journal of clinical gastroenterology* 41(8): 756-60

Beinortas, Tumas, Burr, Nicholas E, Wilcox, Mark H et al. (2018) Comparative efficacy of treatments for Clostridium difficile infection: a systematic review and network meta-analysis. The Lancet. Infectious diseases 18(9): 1035-1044

Camacho-Ortiz, A; Gutierrez-Delgado, EM; Garcia-Mazcorro, JF *et al*. (2017) Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial *Clostridium difficile* infection in intestinal microbiome. *PloS one* 12(12): e0189768

Cammarota, G; Masucci, L; Ianiro, G *et al* (2015) Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Alimentary pharmacology & therapeutics*; vol. 41 (no. 9); 835-43

Dubberke E.R., Lee C.H., Orenstein R. et al. (2018) Results from a Randomized, Placebo-Controlled Clinical Trial of a RBX2660 - A Microbiota-Based Drug for the Prevention of Recurrent *Clostridium difficile* Infection. Clinical Infectious Diseases 67(8): 1198-1204

Gawronska, Agnieszka, Banasiuk, Marcin, Lachowicz, Dominika et al. (2017) Metronidazole or Rifaximin for Treatment of *Clostridium difficile* in Pediatric Patients with Inflammatory Bowel Disease: A Randomized Clinical Trial. *Inflammatory bowel diseases* 23(12): 2209-2214

Hota, SS; Sales, V; Tomlinson, G *et al* (2017) Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial. *Clinical infectious diseases*: an official publication of the Infectious Diseases Society of America; vol. 64 (no. 3); 265-271

Hvas, CL; Dahl J, Simon M *et al* (2019) Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection. *Gastroenterology*; vol. 156 (no. 5); 1324-1332e3

Lewis, S; Burmeister, S; Brazier, J (2005) Effect of the prebiotic oligofructose on relapse of *Clostridium difficile*-associated diarrhea: a randomized, controlled study. Clinical gastroenterology and hepatology: the official clinical practice *journal of the American Gastroenterological Association* 3(5): 442-8

Nelson, R L; Suda, K J; Evans, C T (2017) Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. The Cochrane database of systematic reviews 3: cd004610

van Nood, E; Vrieze, A; Nieuwdorp, M *et al* (2013) Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *The New England journal of medicine*; vol. 368 (no. 5); 407-15

Wolf, J; Kalocsai, K; Fortuny, C *et al* (2019) Safety and efficacy of fidaxomicin and vancomycin in children and adolescents with Clostridioides (Clostridium) difficile

infection: a phase 3, multicenter, randomized, single-blind clinical trial (SUNSHINE). *Clinical Infectious Diseases, ciz1149*, https://doi.org/10.1093/cid/ciz1149

F.2 Prevention

Garey, Kevin W, Ghantoji, Shashank S, Shah, Dhara N et al. (2011) A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with *Clostridium difficile* infection. *The Journal of antimicrobial chemotherapy* 66(12): 2850-5

Goldenberg, J Z, Yap, C, Lytvyn, L et al. (2017) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. The Cochrane database of systematic reviews 12: cd006095

Johnson, S W, Brown, S V, Priest, D H (2019) Effectiveness of Oral Vancomycin for Prevention of Healthcare Facility-Onset Clostridioides difficile Infection in Targeted Patients During Systemic Antibiotic Exposure. *Clin Infect Dis. 2020 Aug 22;71(5):1133-1139.*

Kolodziej M. and Szajewska H. (2019) Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: a randomized clinical trial. *Clinical Microbiology and Infection* 25(6): 699-704

Lewis, S, Burmeister, S, Cohen, S et al. (2005) Failure of dietary oligofructose to prevent antibiotic-associated diarrhoea. *Alimentary pharmacology & therapeutics* 21(4): 469-77

Major G., Bradshaw L., Boota N. et al. (2019) Follow-on RifAximin for the Prevention of recurrence following standard treatment of Infection with *Clostridium Difficile* (RAPID): A randomised placebo controlled trial. *Gut* 68(7): 1224-1231

Mullane K.M., Winston D.J., Nooka A. et al. (2019) A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of *Clostridium difficile*-associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation. *Clinical Infectious Diseases* 68(2): 196-203

Wilcox, Mark H, Gerding, Dale N, Poxton, Ian R et al. (2017) Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection. *The New England journal of medicine* 376(4): 305-317

Appendix G: **Quality assessment of included studies**

G.1 Treatment

G.1.1 Antibiotic prescribing strategy in adults, young people and children

No evidence identified

G.1.2 Antibiotic efficacy in adults, young people and children

Table 18: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	**Nelson et al 2017**
DOMAIN 1: IDENTIFYING CONCERNS WITH THE REVIEW PROCESS: *Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:*	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y – Appendix 1 (separate document outlines full strategy) in document outlines clear eligibility criteria and PICO outlined.
1.2 Were the eligibility criteria appropriate for the review question?	Y – Research protocol restricted by RCT and was aligned with Cochrane methods and process.
1.3 Were eligibility criteria unambiguous?	N – The study clearly outlined and focused on C.Diff associated diarrhoea in adults focused on assessing antibiotic treatment for CDI; clearly outlined inclusion criteria, population and intervention of interest.
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	N – Study criteria restricted by RCT and was aligned with Cochrane methods and process. This is clearly outlined. Not all studies featured in the subsequent analysis. No restrictions by date, study sample size, study quality or outcome measures
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	NI – No information was provided regarding restrictions in eligibility criteria based on sources of information
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES - Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y – An appropriate range of databases were searched including MEDLINE, EMBASE, CENTRAL and the Cochrane IBD Group Specialized Trials Register

	which were searched from inception to 26 January 2017. Also searched clinicaltrials.gov and clinicaltrialsregister.eu for ongoing trials. Restriction to RCT and SR meant unpublished reports not considered
2.2 Were methods additional to database searching used to identify relevant reports?	Y – Clinical trial registers including clinicaltrials.gov and clinicaltrialsregister.eu were searched for ongoing trials
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y – Nelson et al (2017) updates previous systematic review. A full and comprehensive search strategy was available as appendix. Search terms were appropriate and searches run up to 2017
2.4 Were restrictions based on date, publication format, or language appropriate?	Y - The systematic review does not include any data restrictions, and restrictions by participants, intervention, outcome measures align with the review question and pre-established outcomes
2.5 Were efforts made to minimise error in selection of studies?	Y - The review had strategies in place to minimise errors in study selection including at least two authors examining all the citations and abstracts derived from the electronic search strategy who independently selected trials to be included
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL - Describe methods of study identification and selection (e.g. number of reviewers involved):	
3.1 Were efforts made to minimise error in data collection?	Y - Data extraction was performed independently by at least two authors. Results were compared between reviewers and all studies were presented for group discussion. Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PN – Not all studies feature in meta-analysis and those that did not the characteristics of included studies section did not provide enough detail with which to understand how the results were generated for example antibiotic versus placebo – This did not detract from the comparison of the efficacy of antibiotics treatment for *C. difficile*-associated diarrhoea (CDAD), or CDI.
3.3 Were all relevant study results collected for use in the synthesis?	N – The review categorises some studies as contributing to 'main findings' (antibiotics vs antibiotics); Antibiotics vs placebo, Rifaximin versus Vancomycin (small study n=20); Fusidic acid versus vancomycin; Nitazoxanide versus vancomycin; Metronidazole versus Nitazoxanide; Metronidazole versus Metronidazole and Rifampin; Metronidazole versus Teicoplanin; Metronidazole versus Teicoplanin; Metronidazole versus Fusidic Acid; Teicoplanin versus Fusidic Acid; dose; dose timing; Rifaximin to diminish relapse risk; Cadazolid versus Vancomycin; LFF517 versus vancomycin; Surotomycin versus vancomycin do not feature in meta-analysis but are narratively outlined

3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).	
3.5 Were efforts made to minimise error in risk of bias assessment?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).	
DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:		
4.1 Did the synthesis include all studies that it should?	PY – The rationale for not including studies was outlined and centred around poor quality, small study size and singular RCTs; All synthesis undertaken addresses the primary research question.	
4.2 Were all pre-defined analyses reported or departures explained?	Y – This systematic review sought to investigate the efficacy and safety of antibiotic therapy for CDI, to identify the most effective antibiotic treatment for CDAD in adults and to determine the need for stopping the causative antibiotic during therapy; This is a Cochrane review and follows its methods and process	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y – The synthesis included all RCT, dichotomous outcomes and utilised a random-effects meta-analysis to account for differences across studies for example in antibiotic treatments	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	N – Heterogeneity was defined as significant if I^2 >60% or Chi^2 <0.10 - two meta-analysis had I^2 >40% but not >60% and two had Chi^2 <0.10 which none of the synthesis reached indicating high heterogeneity. The quality of the included RCT's was categorised as low.	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y – Funnel plot was planned but does not appear to be undertaken; The study highlights issues with bias in included RCTs and being of very low to low quality. However the method and process are clear and findings are limited but based on robust process	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	PN – The authors flag the very low to low quality and bias of the evidence. Authors state that they changed outcome assessment to reduce the risk of bias but it's not clear how – also it's not clear when this change occurred.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Low	The review method and process are clear and outlined. There was no information for assessment criteria 1.5 but all other aspects indicate low concern for risk of bias from study eligibility.
2. Concerns regarding methods used to identify and/or select studies	Low	The review clearly outlines its identification and selection of studies process and the methods

		and process underpinning this are clearly outlined and robust.
3. Concerns regarding methods used to collect data and appraise studies	Low	The review does not include all studies within the meta-analysis undertaken. Despite the absence of some studies in these synthesis the methods and process for the collection and appraisal of RCTs was consistent and clear. Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.
4. Concerns regarding the synthesis and findings	High	The study outlines the synthesis of some studies narratively and only provides limited data regarding these making fuller assessment of these findings within this study difficult. There was significant heterogeneity in the meta-analysis undertaken (assessed with Chi^2 or I^2). There was an absence of narrative explaining issues regarding bias in studies and the very low to low quality of studies was addressed.
RISK OF BIAS IN THE REVIEW: Describe whether conclusions were supported by the evidence:		
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PY – There were no issues raised across domains 1-4, apart from 4.6. However, the authors outline the limitations of the findings in discussion and conclusions section which addressed concerns raised.	
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y – The review utilised Cochrane methods and process, undertook adequate searching and appraisal processes. The studies identified were of low quality but applicable to the review research question	
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y - The authors flag the limitations of the findings outlining the high heterogeneity in the meta-analysis, very low to low quality evidence and identified bias in studies	
Risk of bias in the review RISK: Rationale for risk:	Low/Moderate There were issues raised regarding the synthesis undertaken and the lack of narrative to explain how the low to very low quality of studies were addressed or accounted for within the review. However, the method and process underpinning	

	the review are clear and robust and the issues with the identified studies are outlined

Table 19: Overall risk of bias/quality assessment – network meta-analysis (NMA checklist)

Study reference	Beinortas et al. 2018
Domain 1: Background	
Has the rationale for the review been described in context?	Y – The NMA outlined the study context and a rationale which included no NMAs in the area and no review of indirect comparisons
Domain 2: Study selection	
2.1. Have the study characteristics used as criteria for eligibility been specified, with rationale given for the choices made?	Y – The NMA outlines clear PICO, the length of follow-up and report characteristics with rationales outlined explaining eligibility
2.2. Have eligible treatments included in the treatment network been clearly described?	Y – The antibiotics included are described with rationales outlined for inclusion.
2.3. Has it been noted whether any treatments have been clustered or merged into the same node (with justification)?	N - Node merging /clustering not present in NMA - all treatments outlined. Identification of the potential influence of Fusidic acid in combination with teicoplanin or metronidazole where differing results were outlined
Domain 3: Methods for data handling and statistics	
3.1. Have the methods used to explore the geometry of the treatment network and potential biases related to it been described?	Y – The network is well described and graphically presented, relationships between direct and indirect comparisons are outlined. Quality appraisal undertaken using PRISMA and Cochrane RoB; GRADE undertaken; A funnel plot did not demonstrate any small trial or publication bias
3.2. Have the summary measures (e.g., risk ratio, difference in means) been described?	Y – The sub-group analysis and pairwise comparisons outlined as odds ratios
3.3. Has the methodology for data handling been described?	Y - Most trials were pairwise comparisons with Cochrane RoB tools used to assess bias. The code underpinning the NMA not outlined in the study. Narrative outlines that data linked is linked to identified RCTs. A random-effects frequentist NMA has been undertaken and the between study variance is defined with a generalised methods-of-moments estimate.

3.4. Have the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied been described?	Y – The consistency between direct and indirect evidence checked by use of node-splitting. A p value of less than 0·10 was considered to be significant in inconsistency assessments.
3.5. Has a description of subgroup, sensitivity and meta-regression analyses been provided, where applicable?	Y – A prespecified subgroup analyses and individual network meta-analyses for patients with severe and mild to moderate infections with C difficile, first and singly recurrent infections with C difficile, and patients aged younger than 65 years and 65 years or older) were undertaken. Additional sensitivity analysis was undertaken that excluded studies with sample sizes <50 per arm, studies published before 2000 and non-blinded studies.
Domain 4. Reporting of results and discussion	
4.1 Is a network diagram presented?	Y – A network diagram is presented within the study
4.2 Are the characteristics of the treatment network described?	Y – A narrative overview of pairwise findings, treatments and the findings of the network itself are outlined alongside a league table of the most effective treatments and sub-group analysis. Heterogeneity and bias were assessed and outlined.
4.3 Have the results, including confidence/credible intervals, of each pairwise meta-analysis carried out been presented?	Y – The study presents a league table of pairwise comparisons in network meta-analysis for attaining a sustained symptomatic cure presented with ORs and 95%CIs
4.4 Have investigations of inconsistency been carried out?	Y - A network heat plot was used to visualise and identify the nodes of single-design inconsistency. The study checked the consistency between direct and indirect evidence by using node-splitting. A p-value of >0.10 was considered to be significant in inconsistency assessments.
4.5 Have the results been presented for any additional analyses (e.g. sensitivity or subgroup analyses, meta-regression analyses) if done?	Y – A Summary of subgroup analyses for sustained symptomatic cure vs vancomycin presented; 3 sensitivity analysis undertaken (non-blinded trials excluded; trials published before 2000 excluded; studies with fewer than 50 participants in each study group excluded, to test for small study effects)
4.6 Is there a discussion of the limitations of the NMA study?	Y – The study outlines the limitations of the NMA. Sensitivity analysis undertaken to account for single-blind trials identified and included in the NMA. Study highlights the inclusions of industry sponsored RCTs but outlines that their exclusion would have removed majority of studies from the analysis. The study outlines that all treatments included as mono-therapies which does not reflect current practice and also included treatments not in clinical development for *C. diff* or licence restricted.
Overall quality and applicability	
Overall quality	High

Applicability as a source of data	Fully applicable

Table 20: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Gawronska et al 2017	Wolf et al 2019
Domain 1: Bias arising from the randomisation process		
1.1. Was the allocation sequence random	Y – The authors outline that patients were randomly allocated to treatment arms, based on a computer-generated bock randomization	Y - Following screening, patients were randomized 2:1 to 10 days of treatment Randomization was stratified by age group and conducted using interactive response technology
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y – The authors outline that a nurse who was not involved in the study assigned consecutive randomization numbers to participants	N - Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, while patients, their guardians and other site staff were not blinded to treatment allocation
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N – The authors outline that there were no significant differences between patient arms regarding median age (14.5 versus 15 years, respectively, P=0.8), median disease activity (10 [7.5–30] points versus 10 [5–25] points, respectively, P=0.6), and immunosuppressive treatment (75% versus 63.2%, respectively, P=0.6).	PN - No statistical tests for differences between arms; numerically greater proportion of participants in the fidaxomicin arm had a confirmed CDI 3 months prior to screening (28.6% vs 22.7%)and higher median age (60 months) compared to those in the vancomycin arm; Greater infections in Vancomycin arm than Fidaxomicin (68.2% vs. 52%)

Risk of bias judgement for the randomisation process	Low	Some concerns - Allocation concealment was not fully blinded; Some differences in relevant baseline factors such as infection and diarrhoea 3 months before screening
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	Y – The study is a single blind trial and patients were not blinded to the treatment they received	Y - Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, while patients, their guardians and other site staff were not blinded to treatment allocation)
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N – The author outlines that researchers, outcome assessors, and a person responsible for the statistical analysis were masked to the intervention until the completion of the study	N - Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, while patients, their guardians and other site staff were not blinded to treatment allocation
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	Y/PY - The study was stopped due to changes in metronidazole prescribing guidelines for CDI. The authors also outline that rifaxamicin may be a continuation therapy post vancomycin but it is unclear how this impacted the finding of this study	Y/PY - The majority of patients (122/142; 85.9%) had no protocol deviations during the study; 11 (11.2%) in the fidaxomicin arm and nine (20.5%) in the vancomycin arm
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Y – The authors outline that deviations from the intended intervention were balanced between groups with no statistical differences outlined	N - Numerically similar but given the 2:1 randomisation there is a 10% difference between arms 11 (11.2%) in

		the fidaxomicin arm and nine (20.5%) in the vancomycin arm
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable	PN - Reasons for deviation were receipt of excluded concomitant treatment (eight [8.2%] in the fidaxomicin and two [4.5%] in the vancomycin arm; receipt of incorrect treatment or dose (two [2.0%] and five [11.4%]) and deviation from the entry criteria (one [1.0%] and two [4.5%])
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y – The effect of assignment to intervention was considered via a modified intention to treat analysis undertaken.	PY - Not titled ITT/mITT but All patients, including those who discontinued study treatment early, were followed for safety and efficacy until 30 days after EOT (end of study, EOS), unless consent was withdrawn
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	Not applicable
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns – The study is a single blind trial where patients were aware of the treatment received and issues regarding change in study protocol mid-study are both potential risk of bias.	Some concerns - Lack of participant blinding, 10-20% deviation from study protocols between arms that were not balanced raised some concerns
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	PY – The authors outline processes for blinding and randomization but as a single blind study it is assumed that participants (children) were not blinded as a clear description	Y - Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, while patients, their guardians and

	of assessor and those involved in the delivery of the intervention and its assessment are outlined.	other site staff were not blinded to treatment allocation.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N – The author outline that those delivering the intervention were subject to blinding and randomization	N - Investigators and site staff involved in the assessment of study outcomes were blinded to treatment allocation, while patients, their guardians and other site staff were not blinded to treatment allocation
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	NI – The authors did not outline any information regarding co-interventions within the study.	N - receipt of excluded concomitant treatment (eight [8.2%] in the fidaxomicin and two [4.5%] in the vancomycin arm
2.4. Could failures in implementing the intervention have affected the outcome?	Y – The authors outlined that the study was stopped early leading to under powering. A total of n=112 required and only n=31 included in study.	PN - The majority of patients (122/142; 85.9%) had no protocol deviations during the study
2.5. Did study participants adhere to the assigned intervention regimen?	Y – The authors outline and flow of participants diagram presented that indicate all participants accounted for in each arm	N - Approximately 15% of total randomised participants deviated from the protocol
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y – The study outlines the use of an intention to treat approach (ITT) to its statistical analysis.	PY - Not titled ITT/mITT but All patients, including those who discontinued study treatment early, were followed for safety and efficacy until 30 days after EOT (end of study, EOS), unless consent was withdrawn

Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns – The study was stopped early leading to possible study under-powering.	Some concerns - Lack of participant blinding, 10-20% deviation from study protocols between arms that were not balanced raised some concerns
Domain 3. Bias due to missing outcome data:		
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y – The study outlines that all data for all participants for the primary outcome are accounted for.	Y - 142/148 of those randomised provided outcome data for primary and secondary outcomes
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	Not applicable
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable	Not applicable
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	Not applicable
Risk-of-bias judgement for missing outcome data	Low – The study accounts for all data from all participants	Low - No concerns; data was available for most participants for primary outcome of interest
Domain 4. Bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	N – The authors outlined the use of a stool test for Clostridium difficile toxins A and B measured at 4 weeks after the end of treatment	N - Confirmed clinical response Initial clinical response at EOT with no further requirement for CDI therapy at 2 days after EOT, calculated as a proportion of all patients in the FAS; Initial clinical response Absence of watery diarrhea (patients <2 years of age) or improvement in the number and character of bowel movements as determined by <3 UBMs (patients ≥2 years of

		age) for 2 consecutive days during treatment and remaining well until EOT, or until study drug discontinuation in the case of early termination
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	N – The authors outline a clear process for participant assessment that was applied across study arms.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	N – The authors outline that researchers, outcome assessors, and a person responsible for the statistical analysis were blinded to the intervention until the completion of the study	N - Evidence of assessor blinding
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Not applicable
Risk-of-bias judgement for measurement of the outcome	Low	Low
Domain 5. Bias in selection of the reported result		
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	PY – The results of the study reflect the pre-specified analytical plan.	Y - Registered on clinical trials identifier
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN – In the study there are no indications of selective reporting and all pre-specified outcomes are reported.	N/PN - All outcomes outlined in the pre-specified plan were reported
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN – In the study there are no indications of selective reporting and all pre-specified outcomes are reported.	N/PN - All outcomes outlined in the pre-specified plan were reported
Risk-of-bias judgement for selection of the reported result	Low	Low
Overall bias and Directness		

Risk of bias judgement	Some concerns – The study was stopped early resulting in study under-powering for primary outcome. The study is single blind with participants aware of the treatment they received which could be a source of bias.	Some concerns – The study's allocation concealment was not fully blinded and there were some differences in relevant baseline factors such as infection and diarrhoea 3 months before screening. The study did not initiate participant blinding, and there was a 10-20% deviation from study protocols between arms that were not balanced.
Overall Directness	Directly applicable	Directly applicable

G.1.3 Antibiotic dose in adults

Table 21: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	**Nelson et al 2017**
DOMAIN 1: IDENTIFYING CONCERNS WITH THE REVIEW PROCESS: *Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:*	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y – Appendix 1 (separate document outlines full strategy) in document outlines clear eligibility criteria and PICO outlined.
1.2 Were the eligibility criteria appropriate for the review question?	Y – Research protocol restricted by RCT and was aligned with Cochrane methods and process.
1.3 Were eligibility criteria unambiguous?	N – The study clearly outlined and focused on C.Diff associated diarrhoea in adults focused on assessing antibiotic treatment for CDI; clearly outlined inclusion criteria, population and intervention of interest.
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	N – Study criteria restricted by RCT and was aligned with Cochrane methods and process. This is clearly outlined. Not all studies featured in the subsequent analysis. No restrictions by date, study sample size, study quality or outcome measures

1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	NI – No information was provided regarding restrictions in eligibility criteria based on sources of information
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES - Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y – An appropriate range of databases were searched including MEDLINE, EMBASE, CENTRAL and the Cochrane IBD Group Specialized Trials Register which were searched from inception to 26 January 2017. Also searched clinicaltrials.gov and clinicaltrialsregister.eu for ongoing trials. Restriction to RCT and SR meant unpublished reports not considered
2.2 Were methods additional to database searching used to identify relevant reports?	Y – Clinical trial registers including clinicaltrials.gov and clinicaltrialsregister.eu were searched for ongoing trials
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y – Nelson et al (2017) updates previous systematic review. A full and comprehensive search strategy was available as appendix. Search terms were appropriate and searches run up to 2017
2.4 Were restrictions based on date, publication format, or language appropriate?	Y - The systematic review does not include any data restrictions, and restrictions by participants, intervention, outcome measures align with the review question and pre-established outcomes
2.5 Were efforts made to minimise error in selection of studies?	Y - The review had strategies in place to minimise errors in study selection including at least two authors examining all the citations and abstracts derived from the electronic search strategy who independently selected trials to be included
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL - Describe methods of study identification and selection (e.g. number of reviewers involved):	
3.1 Were efforts made to minimise error in data collection?	Y - Data extraction was performed independently by at least two authors. Results were compared between reviewers and all studies were presented for group discussion. Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PN – Not all studies feature in meta-analysis and those that did not the characteristics of included studies section did not provide enough detail with which to understand how the results were generated for example antibiotic versus placebo – This did not detract from the comparison of the efficacy of antibiotics treatment for *C. difficile*-associated diarrhoea (CDAD), or CDI.
3.3 Were all relevant study results collected for use in the synthesis?	N – The review categorises some studies as contributing to ‘main findings’ (antibiotics vs antibiotics); Antibiotics vs placebo, Rifaximin versus Vancomycin

	(small study n=20); Fusidic acid versus vancomycin; Nitazoxanide versus vancomycin; Metronidazole versus Nitazoxanide; Metronidazole versus Metronidazole and Rifampin; Metronidazole versus Teicoplanin; Metronidazole versus Teicoplanin; Metronidazole versus Fusidic Acid; Teicoplanin versus Fusidic Acid; dose; dose timing; Rifaximin to diminish relapse risk; Cadazolid versus Vancomycin; LFF517 versus vancomycin; Surotomycin versus vancomycin do not feature in meta-analysis but are narratively outlined	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).	
3.5 Were efforts made to minimise error in risk of bias assessment?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).	
DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:		
4.1 Did the synthesis include all studies that it should?	PY – The rationale for not including studies was outlined and centred around poor quality, small study size and singular RCTs; All synthesis undertaken addresses the primary research question.	
4.2 Were all pre-defined analyses reported or departures explained?	Y – This systematic review sought to investigate the efficacy and safety of antibiotic therapy for CDI, to identify the most effective antibiotic treatment for CDAD in adults and to determine the need for stopping the causative antibiotic during therapy; This is a Cochrane review and follows its methods and process	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y – The synthesis included all RCT, dichotomous outcomes and utilised a random-effects meta-analysis to account for differences across studies for example in antibiotic treatments	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	N – Heterogeneity was defined as significant if I^2 >60% or Chi^2 <0.10 - two meta-analysis had I^2 >40% but not >60% and two had Chi^2 <0.10 which none of the synthesis reached indicating high heterogeneity. The quality of the included RCT's was categorised as low.	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y – Funnel plot was planned but does not appear to be undertaken; The study highlights issues with bias in included RCTs and being of very low to low quality. However, the method and process are clear and findings are limited but based on robust process	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	PN – The authors flag the very low to low quality and bias of the evidence. Authors state that they changed outcome assessment to reduce the risk of bias but it's not clear how – also it's not clear when this change occurred.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern

1. Concerns regarding specification of study eligibility criteria	Low	The review method and process are clear and outlined. There was no information for assessment criteria 1.5 but all other aspects indicate low concern for risk of bias from study eligibility.
2. Concerns regarding methods used to identify and/or select studies	Low	The review clearly outlines its identification and selection of studies process and the methods and process underpinning this are clearly outlined and robust.
3. Concerns regarding methods used to collect data and appraise studies	Low	The review does not include all studies within the meta-analysis undertaken. Despite the absence of some studies in these synthesis the methods and process for the collection and appraisal of RCTs was consistent and clear. Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.
4. Concerns regarding the synthesis and findings	High	The study outlines the synthesis of some studies narratively and only provides limited data regarding these making fuller assessment of these findings within this study difficult. There was significant heterogeneity in the meta-analysis undertaken (assessed with Chi^2 or I^2). There was an absence of narrative explaining issues regarding bias in studies and the very low to low quality of studies was addressed.
RISK OF BIAS IN THE REVIEW: Describe whether conclusions were supported by the evidence:		
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PY – There were no issues raised across domains 1-4, apart from 4.6. However, the authors outline the limitations of the findings in discussion and conclusions section which addressed concerns raised.	
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y – The review utilised Cochrane methods and process, undertook adequate searching and appraisal processes. The studies identified were of low quality but applicable to the review research question	

C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y - The authors flag the limitations of the findings outlining the high heterogeneity in the meta-analysis, very low to low quality evidence and identified bias in studies
Risk of bias in the review RISK: Rationale for risk:	Low/Moderate There were issues raised regarding the synthesis undertaken and the lack of narrative to explain how the low to very low quality of studies were addressed or accounted for within the review. However, the method and process underpinning the review are clear and robust and the issues with the identified studies are outlined

G.1.4 Antibiotic course length in adults, young people and children

No evidence identified

G.1.5 Antibiotic route of administration in adults, young people and children

No evidence identified

G.1.6 Faecal microbiota transplantation FMT in adults, young people and children

Table 22: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Camacho-Ortiz et al 2017	Dubberke et al 2018	van Nood et al 2013
Domain 1: Bias arising from the randomisation process			
1.1. Was the allocation sequence random	PY - Simple randomisation using a closed envelope method generated by the research coordinator in a 1:1 ratio	PY - Although no exact method of the process for randomisation is set out the authors states that participants were randomized using permuted blocks within 3 strata based on the antibiotic regimen for the enrolling episode (vancomycin, fidaxomicin,	NI - No information was given by the authors regarding allocation sequencing.

		or metronidazole) and assigned 1 of 3 treatments (group A, B, or C) at a 1:1:1 ratio.	
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI - Unclear, from the evidence provided in the study, it is not stated if the envelopes were sealed or opaque or who opened the envelopes or if more than 1 person was present when the envelopes were opened.	NI - Allocation and concealment are not described, the ability to predict assignments successfully based on previous assignment (can occur when block randomisation is used) cannot be excluded.	NI - No information was given by the authors about allocation sequencing.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	NI - Unclear, 17 characteristics were assessed (only 1 leukocytes was significantly different), however the study was significantly underpowered so a failure to detect any difference between the groups cannot be excluded.	NI - Insufficient information available as only 6 characteristics of the population are presented (age, gender, race, antibiotic at screening and median number and duration of CDI episodes). No significance test was applied to test if any significant differences and randomisation was stratified according to antibiotic at screening.	N - There were no significant differences in the assessed baseline characteristics.
Risk of bias judgement for the randomisation process	Some concerns - Very little information was given about randomisation and allocation concealment in the study. Although some efforts at both were attempted.	High - There is a significant concern over the lack of adequate description of allocation concealment. Additionally, there are absences from the key characteristics assessed to that would be expected to	Low - Despite inadequate information from the authors about the allocation sequence there were no significant differences between groups in baseline characteristics.

		be reported (such as co-morbidity score and prior use of proton pump inhibitors for example).	
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)			
2.1. Were participants aware of their assigned intervention during the trial?	Y - This was an open label RCT.	N - The RCT is described as double blind. Study participants were blinded to assignment and study drug administration.	Y - This was an open label RCT.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y - This was an open trial only the laboratory investigators (for microbiological outcomes) were blinded to treatment allocation.	N - The RCT is described as double blinded, study and site personnel were blinded to assignment and study drug administration.	Y - This was an open label RCT.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	N/PN - The study was a per protocol analysis, deviations from the intended intervention were handled by exclusion from the analysis.	N/ PN - There were no significant deviations from the intended intervention reported.	N/ PN - The authors do not describe any deviations from the intended intervention except in 1 participant who developed a rapid deterioration in renal-graft function and was given high-dose prednisolone after randomisation but before treatment.
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	PN - 3 participants were removed from the trial (2 in the intervention arm (1 death and 1 medication error affecting protocol) and 1 in the comparator arm (removed from the trial after randomisation at the	Not applicable	Not applicable

	treating clinicians request, no further details were given).		
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Y - The trial was very small and though it achieved its recruitment, the exclusion of 3 participants meant that it was underpowered.	Not applicable	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N - The analysis was naive per-protocol. To further complicate matters all treatment failures at 72 hours were treated with the experimental treatment (FMT-FURM) and most participants (5/9 in the comparator arm and 5/7 in the experimental treatment arm also received systemic antibiotics).	Y - Analysis was by intention to treat on all participants who received at least 1 assigned blinded treatment.	Y - All analyses were conducted on a modified intention to treat basis.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN - It is likely that the study analyse is more affected by the small sample size (inadequate power).	PN - 6 participants (4.5%) withdrew from the study. Only 1 was questionable as they were withdrawn having experienced anxiety during attempted treatment. This participant data should probably have been included as a treatment failure as acceptability of treatment is a valid outcome for enema (intimate and personal therapy). However, it is unlikely that this would	PN - It is unlikely that the single trial exclusion would have a substantial impact on the result.

		have substantial impact on the trial outcome.	
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High - Because this was an open trial with participants and carers aware of their treatment allocation and the confounding of the interventions.	Low - This RCT has a low risk of bias arising from deviation from intended interventions. The study was randomised and double blind without substantial deviation from intended intervention.	Low - The open label nature of the trial and the single exclusion from the study are unlikely to lead to deviations from the intended intervention.
2.1. Were participants aware of their assigned intervention during the trial?	Y - This was an open label RCT.	N - This was a double blinded randomised trial.	Y - This was an open label RCT.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y - This was an open label RCT.	N - This was a double blinded randomised trial.	Y - This was an open label RCT.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	PN - Most of the participants were described as receiving systemic antibiotics but it is unclear if this was before treatment for clostridium difficile, during treatment or after treatment. The groups were unbalanced in receipt of this intervention.	Not applicable	PY - The authors balanced the use of a co-intervention (bowel lavage) using a 3-arm trial to see if lavage + FMT, lavage + vancomycin or vancomycin alone was efficacious.
2.4. Could failures in implementing the intervention have affected the outcome?	Y - The study describes that the intervention (FMT-FURM) was given by a choice of routes (nasojejunal, superior endoscopy or colonoscopy) this was clinician assigned (not randomised) the success of delivery	PN - There were no reports of patients switching or receiving additional treatments.	N - The intervention was successfully delivered in nearly all participants

	between methods was not tested.		
2.5. Did study participants adhere to the assigned intervention regimen?	PY - The study was per protocol so non-adherence was dealt with by removal from the analysis. However, the trial protocol stated that in the event of treatment failure (at 72 hours) in either trial arm that a dose of FMT-FURM would be administered. One participant in the comparator arm had treatment failure but it is unclear if the intended FMT-FURM dose was given.	PY - There were a small number of withdrawals from the RCT. But the majority of participants received the intended intervention.	PY - The authors report only 1 withdrawal after randomisation (due to deterioration) and 1 death after randomisation in a patient who had broken study protocol.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	PN - The study used an inappropriate method to assess this (per protocol analysis).	Y - The RCT used an ITT analysis.	Y - The study used a modified intention to treat analysis.
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High - Due to the lack of blinding in the trial (participants, carers) and the analysis method used and the inadequate description of adherence to the treatment described in the trial protocol.	Low - The RCT was at low risk of bias due to deviation from intended interventions. It was a well conducted double-blind trial with an appropriate ITT analysis and a low withdrawal rate.	Low - Despite the open label nature of the trial, the cointerventions were balanced and an appropriate method of analysis was used. Therefore, the study was assessed to be at low risk of bias due to deviations from intended intervention.
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	N - Data for patient excluded from the per	Y - Outcome data for nearly all randomised patients	Y - Outcome data was available for 41 of 43

	protocol analysis not presented.	(>95%) was available for analysis.	participants who started the trial (>95%).
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NI - Insufficient data from the study on any missing data or how this was assessed and dealt with.	PY - There was little missing data, related only to withdrawal all other data was included and analysed appropriately.	NI - The exclusions from the trial were clinically driven, no further information is given about corrections for missing data.
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y - For 1 patient removed from the trial at the request of the clinician in the comparator arm, it is possible that this could have been due to the participants health status.	Y - In 1 case the missing data was due to withdrawal due to a failure in acceptability of the intervention. This should probably have been included as a treatment failure.	PN - As stated the missing data was based on clinical trial exclusions.
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	N - There were only 3 losses to follow-up, however, from a small sample to start with this means that there is a fair proportion of missing data.	PN - The level of withdrawal due to ongoing follow-up in the RCT is unbalanced but for the primary outcome after initial treatment it is balanced between the groups.	PN - Though not formally assessed only 1 participant from each of 2 arms of the trial was missing/excluded.
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI - No rationale is provided for the missing data of the individual lost to follow up in the comparator arm.	NI - In the ongoing follow-up for the RCT it is unclear why the level of discontinuation in group C is much higher than in in group A or B. Only cursory explanation is given in Figure 1.	Not applicable
Risk-of-bias judgement for missing outcome data	Some concerns - Due to the nature of the missing data it is not possible to exclude bias due to the	Some concerns - The RCT includes outcome data for nearly all participants after initial treatment but there	Low - Missing data was not likely to have biased the results of this RCT.

	health status of the individual's data excluded from the analysis.	appears to be an unbalanced attrition from Group C in ongoing follow-up.	
Domain 4. Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	NI - The primary outcome was clinical response to treatment (stool assessment, frequency etc.) but it is unclear how this data was collected and by whom.	N - The primary outcome was (absence of diarrhoea after treatment) is appropriate.	Y - The primary outcome was cure without relapse at 10 weeks (diarrhoea with a positive CDI culture). This is a common outcome in similar trials.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	NI - No details of how clinical outcomes were ascertained is reported in the study.	PN - Some participants were declared as treatment failures and offered open-label treatment after only 1 blinded study treatment. However, these were still blinded to initial treatment allocation and all were regarded as protocol deviations and as failures for efficacy analysis.	PN - The follow-up appears to have been the same for all 3 arms.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PY - The only individuals reported to blinded to outcome were laboratory technicians (for microbiological outcomes). However, the rest of the trial was an open design (clinical outcomes).	N - All participants, investigators and site personnel who performed follow-up procedures were blinded to the assignment and study drug administration.	Not applicable
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY - One of the four criteria assessed for the clinical outcomes was abdominal pain which requires	Not applicable	Not applicable

	individual judgement. The results for each outcome are not reported separately.		
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY - Whilst it is unclear who assessed the clinical outcomes in the trial (self-report or clinician assessed) it is likely that given the open nature of the trial and the subjective nature of some of the clinical outcomes that it is likely that this outcome was influenced by knowledge of the intervention.	Not applicable	Not applicable
Risk-of-bias judgement for measurement of the outcome	High - Little detail on how clinical outcome data was collected and by whom, the subjective nature of some of the outcomes and the open nature of the trial means it is likely that some bias is present in the results.	Low - The study is at low risk of bias due to measurement of the outcome.	Low - This RCT was at low risk of bias due to measurement of the outcome.
Domain 5. Bias in selection of the reported result			
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Y - As far as can be ascertained the data analysis was prespecified before outcome data was available.	Y - The RCT was analysed appropriately in accordance with the trial protocol and analysis plan.	PY - The trial was analysed in accordance with the analytic plan; however, trial recruitment was ended due to interim safety analysis meaning the study did not recruit adequately to intended sample size.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome	N/PN - While the main clinical outcome (treatment	N/PN - The primary outcome was recurrence of	N/PN - The outcome was prespecified.

measurements (e.g. scales, definitions, time points) within the outcome domain?	success) is made of 4 criteria it was pre-specified that this was the case. Individual data for each criteria are not presented.	diarrhoea due to CDI is a common outcome in trials of CDI treatment.	
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN - There is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that all reported results for the outcome domain correspond to all intended analyses.	N/PN - The primary outcome is a simple dichotomous yes or no during follow-up period to the presence of diarrhoea.	N/PN - The data was analysed in accordance with the prespecified analysis plan.
Risk-of-bias judgement for selection of the reported result	Low - There is little to suggest the possibility of bias in this domain. However, it is noted that length of stay data was collected (and presented for each participant but not analysed.	Low - The RCT is at low risk of bias due to selection of the reported result.	Low - The RCT is at low risk of bias due to selection of the reported results.
Overall bias and Directness			
Risk of bias judgement	High - The intended nature of the trial is unclear as the methods section suggests this may be a per protocol analysis from a planned non inferiority study (mentions planned inferiority margin) but the reporting of the study is an open per protocol pilot RCT. The study is underpowered, and it is	Some concerns - The lack of description of allocation concealment and inadequate characteristics provided to check adequate randomisation in trial raise concern. As does the appearance of unbalanced trial withdrawal during ongoing follow-up. Otherwise there are few concerns about this trial.	Low - Despite failing to recruit sufficient participants due to the study recruitment ending early due to some safety concerns, there are few other concerns regarding this trials risk of bias.

	unclear if the resulting non-significant differences are due to small sample size or no significant effects. The study has many confounding elements (such as systemic antibiotics being used in both groups, but it is unclear at what time point these were implemented).		
Overall Directness	Directly applicable	Directly applicable	Directly applicable

Table 23: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Cammarota et al 2015	Hota et al 2017	Hvas et al 2019
Domain 1: Bias arising from the randomisation process			
1.1. Was the allocation sequence random	Y - Blocked randomisation of subjects was performed by an external person not involved in the study. Online random number generator software was used to provide random permuted blocks of 6 and an equal allocation ration.	NI - The RCT does not provide information on allocation sequence.	Y - This study is outlined as a randomized, active-comparator, open-label clinical trial.
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y - The sequence was concealed until the interventions were assigned.	NI - The RCT does not provide any details on allocation sequence concealment.	N - The study does not outline a blinding protocol. Given the focus on recurrence CDI based on referred participants it's unclear if blinding was possible or practical.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N - There were no significant differences in the	PY - 12 characteristics were assessed; however,	N - The study undertook an assessment of differences

	characteristics of the 2 groups. 15 measures assessed.	comparison was not between treatment comparators but between randomised and non-randomised patients. At least one outcome raises some concern (immunosuppression) between the treatment comparators as being potentially significantly different.	which indicated no statistically significant differences between trial arms at baseline.
Risk of bias judgement for the randomisation process	Low - Adequate allocation sequence generation and concealment. No significant baseline differences in the 2 groups.	Some concerns - A lack of information about allocation sequence and possible issues around difference in the groups means that risk of bias in the randomisation process cannot be ruled out.	High - There is a lack of blinding of both participants and staff involved in the study. The study is open label trial. Both are potential sources of study bias.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)			
2.1. Were participants aware of their assigned intervention during the trial?	Y - Yes this was an open label RCT.	Y - This is an open label RCT.	Y - This study is an open label trial that lacked blinding. Although both elements may not have been possible due to the focus on recurrent CDI these elements introduce potential bias into the study.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y - Yes this was an open label RCT.	Y - This is an open label RCT.	Y - This study is an open label trial that lacked blinding. Although both elements may not have been possible due to the focus on recurrent CDI

			these elements introduce potential bias into the study.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	N/PN - The authors report that no patient refused the proposed treatment. A small number of patients were treated with an alternative treatment after serious deterioration.	Y/PY - The RCT reports that 1 participant withdrew from the study (vancomycin arm) to seek FMT at another hospital.	Y/PY - The study outlines that due to clinical relapse before or at 8 weeks after allocated treatment 11 patients allocated to fidaxomicin and 11 patients initially allocated to vancomycin received FMT.
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable	PN - 2 participants in the vancomycin group were excluded from analysis (1 to seek intervention elsewhere and 1 due to repeated protocol violations [not detailed]) but none in the FMT arm.	PN - The study does not present a statistical analysis for deviations from treatment but outlines that 2/24 allocated to FMT, 11/24 allocated to fidaxomicin and 11/16 allocated to vancomycin received additional FMT due to clinical relapse before or at 8 weeks.
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable	PY - The 2 exclusions from the vancomycin arm account for 14% of those randomised to vancomycin.	PY - The study outlines the need for rescue FMT across antibiotic only arms. Identifying the efficacy of FMT with antibiotics compared to antibiotics only will be impaired by the introduction of FMT to these arms and no evidence is outlined of additional analysis to account for this.

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y - Both an ITT and per protocol analysis were conducted.	PN - The RCT primary analysis was 'per protocol' only a secondary analysis (data not presented) was ITT.	PN - The study outlines that pre-randomisation n=56 participants failed screening and were excluded from the study. However, these participants were analysed separately.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	PY - Even allowing for the 1 participant who withdrew to seek treatment elsewhere, the 1 participant who was excluded for treatment protocol violation accounted for 7% of the vancomycin only arm population.	PN - The study does not evidence the undertaking of ITT/mITT analysis however all randomised participants in trail arms are accounted for as are those that failed initial screening (n=56); Sample size across both arms met the predefined power calculations for primary outcome (n=22).
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low - Despite the open label nature of the trial there did not appear to be any unexplained deviations from the experimental context. An appropriate analysis was performed.	High - It is likely that bias arose from deviations from the intended interventions.	High - The study is open label, and not double-blind. There were deviations from intended interventions that is not accounted for in the analysis.
2.1. Were participants aware of their assigned intervention during the trial?	Y - This was an open label trial; no sham interventions were used.	Y - The RCT was open label.	Y - The study is an open label non-blinded study.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y - This was an open label RCT.	Y - The RCT was open label.	Y - The study is an open label non-blinded study.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	NI - No information is given regarding co-interventions.	NI - No information is given regarding co-interventions including any bowel	PN - The study does not present a statistical analysis for deviations from treatment but outlines that

		preparation or dietary requirements.	2/24 allocated to FMT, 11/24 allocated to fidaxomicin and 11/16 allocated to vancomycin received additional FMT due to clinical relapse before or at 8 weeks.
2.4. Could failures in implementing the intervention have affected the outcome?	PN - The FMT was more successful than oral vancomycin, it is possible that choosing an oral route may have led to less absorption than IV administration but probably not in that very little nausea was reported as adverse event.	N - There is no evidence to suggest that there were failures in implementing the intervention.	PN - The study outlines that overall that allocated interventions were implemented successfully for most participants.
2.5. Did study participants adhere to the assigned intervention regimen?	Y - No patient refused assignment during the trial and the main intervention was only given once in most cases. For the comparator group no alternative treatment was offered or reported.	N - There were documented instances in the vancomycin only arm of non-adherence to assigned intervention.	PY - The study outlines that all randomised participants (n=64) received the allocated treatment.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y - An ITT analysis was performed.	N - The analysis was 'per protocol' excluding trial participants who did not receive their allocated intervention.	PN - The study outlines does not refer to the use of analysis to estimate the effect of adhering to allocated intervention.
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns - As this was an open label RCT with both participants and carers aware of the treatment allocation in the	High - The RCT is at risk of bias due to deviations from intended interventions due to being open label, a lack of information about co-	High - The study was open-label and non-blinded. There were deviations from the allocated intervention protocols that were not

	study there are some concerns about risk-of-bias from deviations from intended interventions. No information was reported for co-interventions although participants in the intervention arm undergoing a second FMT dose were required to have additional meal and bowel preparation requirements.	interventions and using 'per protocol' analysis.	accounted for in the analysis
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y - Apart from those participants who died all participant data is accounted for in the trial report.	PN - The 2 exclusions from the vancomycin only arm account for 14% of the data from that arm.	Y - The study accounts for all randomised participants and data is presented for all.
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable	Y - The authors conducted a futility analysis using both per protocol and ITT data.	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	PN - The authors provide adequate rationale for the missingness of the data.	Not applicable
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable	Y - Both exclusions from the analysis were in the vancomycin only arm.	Not applicable
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	PN - The authors provide adequate rationale for the exclusions.	Not applicable
Risk-of-bias judgement for missing outcome data	Low	Low - There is little evidence that the results are biased by missing outcome data, but it cannot be completely excluded.	Low - The study presents data for and accounts for all randomised participants.

Domain 4. Bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	PY - The definition of recurrence was acceptable; the definition of recurrence did not require a positive stool toxin within 10 weeks from the end of therapy in the event of diarrhoea recurring.)	PN - The primary outcome was appropriate to the study question (recurrence of symptomatic, laboratory confirmed CDI, although the study follow-up period was quite long compared to other similar studies (120 days).	PN - The study outlines its primary outcomes as clinical resolution and a negative C. Diff test which were assessed in a hospital setting with the protocol for C. Diff testing outlined. The specific protocols for assessment of clinical resolution was not specified but it was led by a hospital physician.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PY - Due to the lack of requirement for a positive toxin test for recurrence it is possible that different standards were used to assess outcome.	PN - Although the study used some self-reporting of symptoms by participants in the follow-up period the clinical visits for assessment were fixed in the study.	PN - The study outlines the C. Diff test protocol which represents an objective measure. The assessment of clinical resolution is combined with a negative CD test result so despite the lack of specified criteria to confirm what constitutes clinical resolution this is couple with the objective assessment of C. Diff.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Not applicable	Y - The study was open label.	Y - The study is open label and non-blinded.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable	PN - Nearly all the pertinent outcomes were objectively assessed.	PN - The study outlines that the primary outcome is both clinical resolution and a negative C. Diff result. The protocol for clinical resolution is not outlined but this is combined with an objective measure making

			knowledge of treatment allocation of limited influence to assessment of outcome.
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Not applicable	Not applicable
Risk-of-bias judgement for measurement of the outcome	Low - It is possible that some differences were due to how the outcome of recurrence was measured but the primary outcome of cure would be unaffected.	Low - The RCT is at low risk of bias due to measurement of the outcomes, the outcomes were appropriate and assessed consistently between the arms. Although as an open label trial there might be influences associated with knowledge of the intervention but nearly all the outcomes had objective assessment criteria.	Low - The study outlines appropriate methods for outcome measurement which include C. Diff test couple with assessment of clinical resolution.
Domain 5. Bias in selection of the reported result			
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	PY - The trial authors assert that the analysis was conducted as planned. There is no mention of outcome assessors being blinded in this open label trial.	PN - The trial data was analysed in accordance with the pre-specified analyses plan, however, at the interim assessment stage a post-hoc Bayesian futility analysis was added and although this was appropriate it does not appear to have been considered a priori.	PY - The study outlines a pre-specified combined primary outcomes and secondary outcomes. Study was not blinded, and the analysis is not specified on the trials register but all primary and secondary outcomes are reported in line with the proposed analysis.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome	N/PN - Resolution of diarrhoea at a specific time	N/PN - The outcomes used in the RCT are typical of	N/PN - The study outlines that all primary and

measurements (e.g. scales, definitions, time points) within the outcome domain?	point is a common outcome in RCTs related to C. Diff infection.	similar studies and are assessed in a similar fashion.	secondary outcomes proposed are reported on. No evidence in the study of multiple scales utilized for outlined outcomes.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN - It is unlikely that the result selected is drawn from multiple analyses based on the low level of data and the prior specified analysis plan.	N/PN - The RCT was stopped based on the findings of the interim data. The results are published in keeping with the analysis plan.	N/PN - The study outlines that all primary and secondary outcomes proposed are reported on. No evidence in the study of multiple analysis of the data.
Risk-of-bias judgement for selection of the reported result	Low - This RCT is at low risk of bias from selection of the reported result, analyses were conducted in line with a pre-specified analysis plan using common outcomes for this type of RCT/intervention.	Low - The RCT is at a low risk of bias from selection of the reported results.	Low - The study outlines pre-specified primary and secondary outcomes that do not appear to be assessed in multiple ways. As the study is not blinded it is difficult to ascertain if the measures proposed were specified prior to the initiation of the study but no evidence to suggest otherwise.
Overall bias and Directness			
Risk of bias judgement	Low - Overall this study is judged to be at low risk of bias despite being an open label trial. It did not appear to deviate from its intended interventions and there was no apparent missing data. There was little bias arising from measurement of the	High - The RCT is at moderate to high risk of bias due to poor reporting of allocation sequencing and deviation from intended interventions.	High - The study is open label and unblinded; There were deviations from the treatments all of which introduce bias into the study.

	outcomes or selection bias of the reported results.		
Overall Directness	Directly applicable	Directly applicable	Directly applicable

G.1.7 Prebiotics in adults

Table 24: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Lewis et al 2005a
Domain 1: Bias arising from the randomisation process	
1.1. Was the allocation sequence random	Y – The study adopts a double-blind, randomised, placebo-controlled design, with computer-generated randomisation and treatment allocation administered via sealed envelopes
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y - The study adopts a double-blind, randomised, placebo-controlled design, with computer-generated randomisation and treatment allocation administered via sealed envelopes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN – The study does not outline a statistical comparison of trial arms but does outline IQ range
Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	N – The study adopts a double-blind randomised study design indicating that participants were unaware of assigned intervention
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N - The study adopts a double-blind randomised study design indicating that carers and people delivering the interventions were unaware of assigned intervention
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	Not applicable
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y – The study undertook an intention to treat analysis to account for the effect of assignment to intervention
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	N – The study adopts a double-blind randomised study design indicating that participants were unaware of assigned intervention
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N – The study adopts a double-blind randomised study design indicating that carers and people delivering the interventions were unaware of assigned intervention
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
2.4. Could failures in implementing the intervention have affected the outcome?	PY – The authors outline that Metronidazole was used as first-line treatment in 123 patients, vancomycin was used in 6, and no treatment was given in 13 patients. It is unclear what percentage of these participants were present in each study arm
2.5. Did study participants adhere to the assigned intervention regimen?	PY
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NI – The authors outline that an intention to treat analysis was undertaken but nothing that accounts for the different antibiotic regimens (n=129) or lack of antibiotics (n=13) – the analysis appears to ignore this difference.
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns – The study analysis does not account for those in the sample who received no antibiotic treatment in the analysis

Domain 3. Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y – The study accounts for all participants and those who commenced the study have data for the primary outcome
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N – The study undertook stool cultures for the presence of clostridium difficile at 30 and 60 days and participants were asked to report any abdominal symptoms such as bloating. Those undertaking the assessments were blinded.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N – The study methodology did not present any evidence to indicate that the measurement or ascertainment of outcome could have differed between intervention groups.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N – The study was of a double-blind design. Those responsible for data collection and analysis were blinded to which group patients were allocated.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Y – The study analysis reflects the finalised pre-specified plan.

5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN – The study presents no evidence to suggest that numerical results have been selectively reported based on the favourability of outcome. All outcomes have been reported.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN – The study presents no evidence to suggest that numerical results being assessed have been selected on the basis of the results from multiple analyses of the data. All outcomes have been reported.
Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	
Risk of bias judgement	Some concerns – The study lacks clarity regarding how the analysis accounted for participants not receiving any antibiotic treatment (n=13) and raises some concerns.
Overall Directness	Directly applicable

G.1.8 Probiotics in young people and children

Table 25: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	**Basu et al 2007**
Domain 1: Bias arising from the randomisation process	
1.1. Was the allocation sequence random	Y – The study adopts a double-blind, randomized, placebo-controlled design with clear reference to random allocation sequence which was computer generated.
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y - The study adopts a double-blind, randomized, placebo-controlled design with clear reference to blinding protocol

	and concealment of allocation until enrolment and intervention assignment.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN – The study does not present any evidence of undertaking a statistical test for differences but the study does state that there were no differences between groups.
Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	N - The study adopts a double-blind, randomized, placebo-controlled design and participants were not aware of their assignment to treatment which was allocated by concealed packs with nursing staff, mothers or doctors and residents also blinded.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N - The study adopts a double-blind, randomized, placebo-controlled design and participants, nursing staff, mothers, doctors or residents unaware of assignment to treatment which was allocated by concealed packs.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	Not applicable
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information – The study makes no reference to intention to treat analysis or other analysis to estimate the effect of intervention assignment.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PN – The study outlines that 253 participants were randomised, of which 18 were excluded and 235 completed and included in the study analysis (approx. 7% dropout); Rationale for exclusion include

	development of excluded conditions (septicaemia and renal failure), withdrawal of consent and discharged on request.
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns - The study does not provide information regarding estimating the effect of intervention assignment
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	N - The study adopts a double-blind, randomized, placebo-controlled design and participants were not aware of their assignment to treatment which was allocated by concealed packs with nursing staff, mothers or doctors and residents also blinded.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N - The study adopts a double-blind, randomized, placebo-controlled design and participants were not aware of their assignment to treatment which was allocated by concealed packs with nursing staff, mothers or doctors and residents also blinded.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
2.4. Could failures in implementing the intervention have affected the outcome?	PN – The study interventions were successfully implemented in approximately 93% (n=18) of those randomised with reasons for non-completion outlined.
2.5. Did study participants adhere to the assigned intervention regimen?	Y – The study outlines that approximately 93% (n=18) of the sample completed and provided data of those randomised with reasons for non-completion outlined.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	

3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y – The study outlines that approximately 93% (n=18) of those randomised provided data.
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	PY – The study measured the primary study outcome via stools tested for bacteria. It is assumed that vomiting was then linked to *C. diff* conformation via stool testing. The study also undertook self-report measures for incidences of diarrhoea and vomiting where mothers were provided with a piece of white paper and pen and were asked to make a stroke and a circle on a white paper for each purge and each vomit.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N – There is no evidence within in the study to suggest that measurement or ascertainment of outcomes may have differed between intervention groups as primary outcome was assessed via stool testing.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N – The study adopts a double-blind, randomized, placebo-controlled design and participants, nursing staff, mothers, doctors and residents were not aware of participant assignment to treatment which was allocated by concealed packs.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	PY – The study provides very little detail in the narrative but the analysis is in line with what is outlined which includes a chi^2, duration of diarrhoea and vomiting in both culture confirmed cases and more generally.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN – The study does not provide any evidence to suggest that the results assessed have been selected based on results achieved. Multiple outcome measurements were not undertaken for the primary outcome.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN – The study does not provide any evidence to suggest that the results assessed have been selected based on results achieved. Multiple outcome measurements were not undertaken for the primary outcome.
Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	
Risk of bias judgement	Some concerns
Overall Directness	Directly applicable

G.2 Prevention

G.2.1 Antibiotic prescribing strategy in adults, young people and children

No evidence identified

G.2.2 Antibiotic efficacy in adults

Table 26: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Mullane et al 2019	Johnson et al 2019	Major et al 2019	Garey et al 2011
Domain 1: Bias arising from the randomisation process				
1.1. Was the allocation sequence random	Y – Randomised double-blind, placebo controlled design	Y – Randomised double – blind placebo controlled design	Y- multisite, two arm, parallel group, blinded, randomised, placebo controlled trial - randomisation via computer generated pseudorandom code, using random permuted blocks of randomly varying size	Y - study outlined as double-blind placebo-controlled, single-centre pilot study
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY – It is unclear from the methods section what the exact randomisation and concealment procedure were, but it's reasonable to assume that given where the trial had taken place and who was involved that this was adequately done	PY - It is unclear from the methods section what the exact randomisation and concealment procedure were, but it's reasonable to assume that given where the trial had taken place and who was involved that this was adequately done	Y - multisite, two arm, parallel group, blinded, randomised, placebo controlled trial - randomisation via computer generated pseudorandom code, using random permuted blocks of randomly varying size	Y - study outlined as double-blind placebo-controlled, single-centre pilot study

1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN – No statistical calculation for difference between arms except for reasons for transplant (B-cell lymphoma 12 (4%) vs. 4 (1.3%)	PY - Authors outline that the OVP arm of the trial were exposed to more high-risk CDI antibiotics during the prior and index hospitalisation; and the duration (days) of treatment (ABX) was higher in the OVP arm	PN - No statistical analysis of difference undertaken - but appear similar	PY - Patients that received rifaximin were more likely to be Black or Hispanic compared with patients given placebo (P=0.04) – It is s unclear if this had an impact on treatment efficacy.
Risk of bias judgement for the randomisation process	Low - There is a lack of detail in the methods section and a lack of analysis regarding the differences in trial arms but given the size of the trial and those involved these are considered to be fine	Some concerns - Randomisation appears appropriate there is a lack of detail in the method. There were differences between arms in exposure to high-risk CDI antibiotics during the prior and index hospitalisation; and the duration (days) of treatment (both in the vancomycin prophylaxis arm)	Low - There is a lack of detail in the methods section and a lack of analysis regarding the differences in trial arms but these are considered to be fine	Some concerns – There was a difference between arms with Black or Hispanic represented significantly more than in the placebo arm but it is unclear if this impacts the primary outcomes but indicates possible issues with randomisation
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)				
2.1. Were participants aware of their assigned intervention during the trial?	PN – Study is outlined as a randomised double-blind trial - methods are brief regarding the specifics of the trial procedure	N – Authors outlined blinding of participants but a lack of detail regarding the specific method	N - Participants, were blind to the allocated treatment as active and placebo tablets were packaged in matching deidentified treatment packs and dispensed by the hospital pharmacy.	PN - Randomization was performed by the investigational drug pharmacist at the hospital who was not involved in the conduct of the study. Study medication and matching placebo were dispensed with a specific study number to ensure blinding of investigators

				and patients. All patients were inpatients at the time of randomization.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN – Study is outlined as a randomised double-blind trial - methods are brief regarding the specifics of the trial procedure	N – Authors outlined blinding of those involved in the delivery of the interventions but there was a lack of detail regarding the specific method	N - Clinicians, research nurses and the study team were blind to the allocated treatment as active and placebo tablets were packaged in matching deidentified treatment packs and dispensed by the hospital pharmacy.	PN - Randomization was performed by the investigational drug pharmacist at the hospital who was not involved in the conduct of the study. Study medication and matching placebo were dispensed with a specific study number to ensure blinding of investigators and patients. All patients were inpatients at the time of randomization.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	Not applicable	Not applicable	Not applicable	Not applicable
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable	Not applicable	Not applicable	Not applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable	Not applicable	Not applicable	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y – Modified intention to treat was undertaken	N – No evidence of ITT analysis or other analysis to account for the effect of intervention assignment	PY - No evidence of intention-to-treat (ITT) analyses or modified intention to treat (mITT) analyses or other; Sub-group and sensitivity analysis undertaken to account for missing data	Y - Intention to treat principles were utilised and included all randomised participants who received at least one dose of study medicine)

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	N – all participants were accounted for in the study	Not applicable	Not applicable
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low – Double-blind trial with mITT undertaken. Despite brief methods no issues identified	Some concerns - There was no evidence of ITT or other analysis to estimate the effect of assignment to the intervention but this was not considered to substantial impact findings based on participant randomisation.	Low – The lack of ITT or mITT raises some concerns but additional sensitivity analysis seeks to account for missing participants	Low – No issues identified with randomisation and ITT principles utilised and
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)				
2.1. Were participants aware of their assigned intervention during the trial?	PN – Double-blind trial but details of blinding protocol not outlined	N – Authors outline the blinding of participants to intervention assignment	N - Participants, were blind to the allocated treatment as active and placebo tablets were packaged in matching deidentified treatment packs and dispensed by the hospital pharmacy.	N - study outlined as double-blind placebo-controlled, single-centre pilot study
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN – Double-blind trial but details of blinding protocol not outlined	N – Authors outline the blinding of investigators to participant intervention assignment	N - Clinicians, research nurses and the study team were blind to the allocated treatment as active and placebo tablets were packaged in matching deidentified treatment packs and dispensed by the hospital pharmacy	N - study outlined as double-blind placebo-controlled, single-centre pilot study

2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable.	Not applicable	Not applicable.	Not applicable.
2.4. Could failures in implementing the intervention have affected the outcome?	PY – 35.5% and 35.8% of participants withdrew from the trail which may have impacted the overarching findings - this is outlined by study authors.	N – all participants enrolled in the study were accounted for within the intervention initially allocated to with no record of deviation from the study protocol post randomisation	PN - Figure one is not clear - target sample not reached due to funding issues but of those randomised 18% control arm and 11% intervention arm did not provide follow-up data due to death or withdrawal. Some inconsistency between narrative, supplementary analysis and study tables	PN - Total of 11/79 did not receive their allocated intervention and 5/68 discontinued intervention
2.5. Did study participants adhere to the assigned intervention regimen?	N – 75% of the those who engaged in the interventions also had additional antibiotic treatment some of which was non-CDI associated Diarrhoea effective/ There is a lack of detail regarding which arm of the study these individuals were located in or what the impact on outcomes were.	Y – 100/100 participants account for in each of the arms randomised to (n=50/arm)	PY - Nothing to indicate that adherence was not maintained. Follow-up data was unavailable for 17% and 11 % of control and intervention arms due to death and withdrawal	Y - 63/68 adhered to allocated treatment with 5 discontinuing.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	PY – A pre-specified sensitivity analysis was undertaken restricted to confirmed CDI associated Diarrhoea only to evaluate the incidence of	Not applicable	Not applicable	Not applicable

	CDI associated Diarrhoea independent of missing data.			
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns – Due to deviations from treatments outlined in protocol	Low – all participants accounted for in the arms randomised to with blinding of participants and investigators outlined	Some concerns - the lack of consistency between study flow of participants, tables of findings and supplementary analysis for certain adverse event outcomes and study withdrawals raises concerns	Low – All dropouts accounted for and were not considered to impact primary outcomes
Domain 3. Bias due to missing outcome data:				
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y – Nearly all - 600/611 in a mITT	Y – all participants 100/100 accounted for	PY - Follow-up data was unavailable for 17% and 11 % of control and intervention arms due to death and withdrawal – but there are some discrepancies regarding total deaths and how these match with participant flow, results tables and supplementary analysis	Y - All participants with data for primary and secondary outcomes were randomised - with all dropouts accounted for
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable	Not applicable	Not applicable	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable	Not applicable	Not applicable	Not applicable
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable	Not applicable	Not applicable	Not applicable

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable	Not applicable	Not applicable	Not applicable
Risk-of-bias judgement for missing outcome data	Low – The study accounts for all data from all participants	Low - The study accounts for all data from all participants	Some concerns – For the primary outcome Major et al (2019) outlines numbers of participants from whom data has been collected. What is less clear at both allocation and follow-up is additional figures for withdrawals	Low – All study participants and data were accounted for.
Domain 4. Bias in measurement of the outcome				
4.1 Was the method of measuring the outcome inappropriate?	N – The incidence of CDAD from the first dose of study drug through 30 days after the last dose of study drug. Confirmed CDAD was defined as diarrhoea (>3 unformed bowel movements in 24 hours) and a positive test for the presence of C. difficile (either by toxin immunoassay or NAAT). The additional sensitivity analysis measured prophylaxis failure: confirmed CDAD, (2) use of antibiotics potentially effective against CDAD (e.g. metronidazole) for any reason, including suspected CDAD or non-	N – The primary outcome of incidence of HCFO-CDI was defined as symptoms of loose stools or diarrhoea (in the absences of laxatives or other non-CDI causes) in a 24-hour period in patients with concurrent positive stool test for C. difficile (polymerase chain reaction [PCR], Xpert C. difficile/Epi; Cephied) >72 hours into hospitalization; Secondary outcome of CO-HCFA-CDI was determined by patient phone calls, which took place 28–32 days after discharge from the	N - CDI recurrence within 12 weeks; recurrence was defined as three or more loose stools for two or more days in conjunction with a positive stool toxin assay determined by research nurses (direct questioning, together with the laboratory results); Secondary outcomes were: (1) recurrence of CDI within 6 months; (2) rehospitalisation for CDI within 6 months; (3) length of in-hospital stay following start of trial medication	N - Primary output was recurrent diarrhoea including recurrence defined as a return of diarrhoea with and without positive toxin test

	CDAD indications (because CDAD-effective antibiotics would confound the CDAD assessment), and (3) missing CDAD assessments (clinical evaluation and/or toxin or NAAT assay) due to death or AE, or for any other reason (e.g. loss to follow-up, missed study visits	hospital, and medical record reviews up to 3 months post-discharge		
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N – Confirmed by confirmation of CDAD undertaken by objective measure: positive toxin immunoassay or NAAT	N – confirmed by incidence of symptoms of loose stools/diarrhoea with an objective measure of positive stool test for CDI.	N - CDI recurrence within 12 weeks; recurrence was defined as three or more loose stools for two or more days in conjunction with a positive stool toxin assay determined by research nurses (direct questioning, together with the laboratory results); Secondary outcomes were: (1) recurrence of CDI within 6 months; (2) rehospitalisation for CDI within 6 months; (3) length of in-hospital stay following start of trial medication	N - Object measure (conformation of toxin positive diarrhoea) and self-report (incidence of diarrhoea)
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the	PN – Outlined as a double-blind design - a	N – Outlined as a double-blind study, authors outlined blinding of	N - Clinicians, research nurses and the study team were blind to the	PN - Double blind study - investigators blinded from treatment allocation.

intervention received by study participants?	lack of details regarding blinding process	outcome assessors although details of precise method for this is lacking.	allocated treatment as active and placebo tablets were packaged in matching deidentified treatment packs and dispensed by the hospital pharmacy	However, investigators were in regular contact with patients and patients were already in the hospitals
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable	Not applicable	Not applicable	Not applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Not applicable	Not applicable	Not applicable
Risk-of-bias judgement for measurement of the outcome	Low	Low	Low	Low
Domain 5. Bias in selection of the reported result				
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Y – The pre-specified outcomes were all reported; the deviation from interventions allocated are outlined and accounted for	Y – pre-specified outcomes and processes that appeared to be finalised prior to randomisation and data collection	PY - Analytic plan outlined. Double blinding occurred prior to intervention commencement and data collection	PY - Method appears to be implemented as outlined with data collected after the study had been completed (3 months after treatment discontinuation))
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN – All outcomes pre-specified are reported with additional sensitivity analysis to account for drop out	N/PN - Data for all outcomes outlined in pre-defined methodology are presented	N/PN - Primary and secondary outcomes outlined with method of data collection and analysis outlined for each outcome	N/PN - Data for all outcomes outlined in pre-defined methodology are presented
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN – All of the pre-specified outcomes are reported.	N/PN – All of the pre-specified outcomes are reported	N/PN - All outcomes outlined have corresponding data in line with the method of its collection.	N/PN - Primary end point was recurrent diarrhoea measured via positive toxin test or self-report

Risk-of-bias judgement for selection of the reported result	Low	Low	Low	Low
Overall bias and Directness				
Risk of bias judgement	Some concerns – Some concerns regarding the risk of bias due to deviations from the intended interventions (effect of adhering to intervention) and although not formally assessed some concerns regarding potential bias due to missing outcomes	Some concerns - Randomisation appears appropriate there is a lack of detail in the method. Some issues with the randomisation process given the differences between arms in those who received intervention (prophylactic vancomycin) being exposed to more high-risk CDI antibiotics during the prior and index hospitalisation; and the duration (days) of treatment (ABX) was higher in the OVP arm	Some concerns - The study presents a flow of participants through the study there are a number of figures within this flow and in supplementary analysis that do not appear to tally or are unexplained for both the primary outcome and for secondary outcomes adverse events such as death.	Some concerns – The study outlined a significant difference between trial arms for some demographic factors indicating possible issues with randomisation coupled with the low number of participants indicate the need for caution in interpretation of the findings.
Overall Directness	Directly applicable	Directly applicable	Directly applicable	Directly applicable

G.2.3 Antibiotic efficacy in young people and children

No evidence identified

G.2.4 Antibiotic dose in adults

No evidence identified

G.2.5 Antibiotic course length in adults, young people and children

No evidence identified

G.2.6 Antibiotic route of administration in adults, young people and children

No evidence identified

G.2.7 Monoclonal antibodies in adults

Table 27: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Wilcox et al 2017
Domain 1: Bias arising from the randomisation process	
1.1. Was the allocation sequence random	NI - The only information given is that the study was randomised.
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI - The only information given is that the study was randomised.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN - Key baseline characteristics were balanced among the study groups.
Risk of bias judgement for the randomisation process	Some concerns - due to a lack of detailed information about the allocation sequence.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	PN - The study is reported to be double blind and a placebo arm was included.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN - The study is reported to be double blind and a placebo arm was included.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	N/A
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	N/A
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	N/A
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y - A modified intention to treat analysis was used.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	N/A
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low - The study is at low risk of bias from deviation from the intended intervention.

2.1. Were participants aware of their assigned intervention during the trial?	PN - The study is reported to be double blind and a placebo arm was included.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN - The study is reported to be double blind and a placebo arm was included.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	N/A
2.4. Could failures in implementing the intervention have affected the outcome?	PN - Only 2 participants did not receive their assigned intervention, too small a number to have affected the outcome.
2.5. Did study participants adhere to the assigned intervention regimen?	Y - The intervention was a single adjunctive infusion of monoclonal antibodies or placebo.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y - A modified intention to treat analysis was used.
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	L - The RCT is at low risk of bias due to deviation from the intended intervention.
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	N - The study does not provide detail for those participants who were randomised but not treated (n=2,665 randomised but only 2,580 treated) no rationale or explanation is given for the loss of 75 participants and the reasons for them not being treated.
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN - As an overall percentage of the data the 2.8% missing after randomisation but before treatment is unlikely to bias the outcome, other missing data was dealt with by assigning them as treatment failure.
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN - The number of participants missing after randomisation but before treatment is similar across the 4 arms.
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	N/A
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/A
Risk-of-bias judgement for missing outcome data	Low - The RCT is at low risk of bias due to missing outcome data.
Domain 4. Bias in measurement of the outcome	

4.1 Was the method of measuring the outcome inappropriate?	N - The outcomes assessed is plausibly sensitive to the intervention effect, and recurrence of symptoms is widely used in similar trials.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN - The passive follow-up of those with recurrent diarrhoea symptoms (self-report of diarrhoea followed by a repeat toxin test) may predispose to diagnostic detection bias, although the double-blind nature of the trial may mitigate this.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PN - It is unclear whether the first trials data had been unlocked prior to the start of the second trial, if so, this could predispose to diagnostic detection bias.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI - The study does not report whether data for each trial was unlocked separately or at the same time, it is possible that diagnostic detection bias may have occurred in the MODIFY II trial if data from MODIFY I was unlocked and made known prior to the second trial.
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN - There is a possibility that the MODIFY II trial may suffer from diagnostic detection bias. But it is uncertain at what point trial data was unlocked.
Risk-of-bias judgement for measurement of the outcome	Some concerns - Inadequate reporting of the data unlocking process for each trial means that diagnostic detection bias cannot be excluded.
Domain 5. Bias in selection of the reported result	
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	PY - The pooling of the data sets from MODIFY I and MODIFY II was pre-planned, however, it is unclear whether separate analyses were performed for each data set before the pre-planned analyses and before trial data from both trials had been accrued and unlocked.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN - The outcomes were pre-specified and reported in line with the statistical analyses plan.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN - The outcomes were pre-specified and reported in line with the statistical analyses plan.
Risk-of-bias judgement for selection of the reported result	Low - The trials were at low risk of bias from selection of the reported results.

Overall bias and Directness	
Risk of bias judgement	Some concerns - The trial has some reporting issues for allocation sequence and allocation concealment as well as the potential for diagnostic detection bias (particularly in the MODIFY II trial) but otherwise the trial appears to be at low risk of bias.
Overall Directness	Directly applicable.

G.2.8 Prebiotics in adults

Table 28: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Lewis et al 2005b
Domain 1: Bias arising from the randomisation process	
1.1. Was the allocation sequence random	PY - The authors state that the randomisation codes were generated by computer. No further details reported.
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY - The authors state that concealment was by sealed envelope. No further details reported.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN - The baseline characteristics between the placebo and intervention groups are similar, they were not formally statistically assessed.
Risk of bias judgement for the randomisation process	Low - The study is at low risk of bias from the randomisation process.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	PN - The trial is described as double-blind but no further details of the methods of blinding are described.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN - The trial is described as double-blind but no further details of the methods of blinding are described.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	N/A
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	N/A
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	N/A

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y - An intention-to-treat analysis was used.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	N/A
Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low - The study is at low risk of bias from deviations from the intended intervention.
2.1. Were participants aware of their assigned intervention during the trial?	PN - The trial is described as double-blind but no further details of the methods of blinding are described.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN - The trial is described as double-blind but no further details of the methods of blinding are described.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	N/A
2.4. Could failures in implementing the intervention have affected the outcome?	PN - The authors describe that in hospital 87% of doses of the trial powder were taken and compliance after discharge was 91%.
2.5. Did study participants adhere to the assigned intervention regimen?	PN - The authors describe that in hospital 87% of doses of the trial powder were taken and compliance after discharge was 91%.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low - The study is at low risk of bias from deviations from the intended interventions.
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes - There is no apparent loss to follow-up or missing data.

3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N/A
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/A
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	N/A
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/A
Risk-of-bias judgement for missing outcome data	Low - The study is at low risk of bias from missing outcome data.
Domain 4. Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	PN - The authors chose to use a stool scoring system that has not been reported as validated, however, the 4 categories map adequately to other stool scores such as the Bristol stool score. Other outcomes are adequate and appropriate.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN - The outcomes (particularly after hospital discharge) were self-reported, and passive in nature. Diagnostic detection bias cannot be excluded although the double-blind methodology mitigates this.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PN - Outcome assessment is described as blind to the intervention received.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/A
Risk-of-bias judgement for measurement of the outcome	Low - The study is at low risk of bias from measurement of outcome.

Domain 5. Bias in selection of the reported result	
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	PY - The authors specify that they undertook appropriate analyses based on frequency distribution (normality) assessment.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y/PY - The main outcome and aim of the trial was to reduce diarrhoea, which while reported in the tables is poorly reported in the results text and is not formally analysed as an outcome.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Y/PY - The main outcome and aim of the trial was to reduce diarrhoea, which while reported in the tables is poorly reported in the results text and is not formally analysed as an outcome.
Risk-of-bias judgement for selection of the reported result	High - The study is at higher risk of bias for selection of the reported result.
Overall bias and Directness	
Risk of bias judgement	Some concerns - The study is mostly at lower risk of bias, although further reporting of methods of blinding and allocation concealment would have increased confidence, however the study favours reporting subgroups and associations rather than key trial outcomes.
Overall Directness	Directly applicable.

G.2.9 Probiotics in children, young people and adults

Table 29: Overall risk of bias/quality assessment – systematic review (ROBIS systematic review checklist)

Study reference	**Goldenberg et al 2017**
DOMAIN 1: IDENTIFYING CONCERNS WITH THE REVIEW PROCESS: *Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:*	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y - Only randomized controlled trials (RCT) reporting incidence outcomes for CDAD (diarrhoea and detection of C. difficile toxin in stool) or detection of C. difficile (detection of C. difficile or toxin in stool) were considered for inclusion.
1.2 Were the eligibility criteria appropriate for the review question?	Y - The primary objectives were to assess the efficacy and safety of probiotics for the prevention of C. difficile-associated diarrhoea in adults and children.
1.3 Were eligibility criteria unambiguous?	Y - Randomized controlled trials (RCT) reporting incidence outcomes for CDAD (diarrhoea and detection of C. difficile toxin in stool) or detection of C. difficile (detection of C. difficile or toxin in stool) were considered for inclusion.
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y - No date limits were set, sample size as an exclusion criteria is not discussed, study quality was formally assessed using the Cochrane ROB tool.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PN - Grey literature was searched and no exclusion on the basis of language was mentioned.
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES - Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y - PubMed (1966 to 2017), EMBASE (1966 to 2017), CENTRAL (inception to 2017), and the Cochrane IBD Group Specialized Register were searched along with other sources, conference proceedings and databases.

2.2 Were methods additional to database searching used to identify relevant reports?	Y - conference proceedings as well as the British Society of Gastroenterology Annual General Meeting abstracts (years: 2006 to 2016) and The American Gastroenterological Association's Digestive Disease Week (years: 2009 to 2016). Authors of pertinent presentations were contacted for further information.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y - A full search strategy is presented in the SR.
2.4 Were restrictions based on date, publication format, or language appropriate?	Y - No date, publication format or language restrictions were applied.
2.5 Were efforts made to minimise error in selection of studies?	Y - Two authors independently screened titles and abstracts for potential full text eligibility. If reviewers deemed any title or abstract as potentially eligible, the articles were retrieved for full-text eligibility assessment. Two authors independently assessed the eligibility of each full-text article.
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL - Describe methods of study identification and selection (e.g. number of reviewers involved):	
3.1 Were efforts made to minimise error in data collection?	Y - Teams of two authors independently extracted data on patients, methods, interventions, and outcomes, using a pre-constructed, standardized data extraction form.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PY - The systematic review is large (39 RCTs) so space is limited in the study report to fully detail all study characteristics, but sufficient detail is available to make interpretation possible.
3.3 Were all relevant study results collected for use in the synthesis?	Y - Completed cases were included in the primary analysis, and subsequent sensitivity analyses were undertaken.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y - The Cochrane ROB tool was used.
3.5 Were efforts made to minimise error in risk of bias assessment?	Y - Two authors independently assessed the risk of bias in the individual RCTs as described in the Cochrane Handbook for Systematic Reviews of Interventions.

DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:		
4.1 Did the synthesis include all studies that it should?	PY - For the primary outcome of CDAD the synthesis included all relevant studies. For AAD the authors acknowledged that funnel plot analyses suggested publication bias, however, our review protocol excludes AAD as an outcome in prevention studies.	
4.2 Were all pre-defined analyses reported or departures explained?	Y - The authors largely kept to their protocol plan and any differences are explained in a section on differences between protocol and review section.	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY - Although the authors include many studies in their primary analyses, with often different populations and settings, the overall low level of heterogeneity suggests that this is acceptable.	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y - Heterogeneity in the analyses was generally low and an appropriate effects model was used when heterogeneity was significant.	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y - Funnel plot analysis was conducted.	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y - Sensitivity analysis based on ROB was conducted.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Low	Considerable effort has been made to clearly specify the review question and objectives, and to pre-specify and justify appropriate and detailed eligibility criteria that have been adhered to during the review.
2. Concerns regarding methods used to identify and/or select studies	Low	A substantial effort has been made to identify as many relevant studies as possible through a variety of search methods using a sensitive and

		appropriate search strategy and steps were taken to minimise bias and errors when selecting studies for inclusion.
3. Concerns regarding methods used to collect data and appraise studies	Low	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.
4. Concerns regarding the synthesis and findings	Low	The systematic review is at low risk of bias from the synthesis of findings.
RISK OF BIAS IN THE REVIEW: Describe whether conclusions were supported by the evidence:		
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Yes – overall there were very few concerns about the conduct of the review.	
B. Was the relevance of identified studies to the review's research question appropriately considered?	Yes - The review utilised Cochrane methods and process, undertook adequate searching and appraisal processes. The studies identified were of low quality but applicable to the review research question.	
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes - the authors adequately discuss the limitations of the findings.	
Risk of bias in the review RISK: Rationale for risk:	Low – 10 of the RCTs included in the systematic review were assessed using the Cochrane risk-of-bias tool to be at low risk of bias, the remaining studies were at high or unclear risk of bias. A sensitivity analysis of the main results using risk-of-bias was conducted.	

G.2.10 Probiotics in young people and children

Table 30: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	**Kolodziej and Szajewska 2019**

Domain 1: Bias arising from the randomisation process	
1.1. Was the allocation sequence random	Y - A computer-generated randomization list prepared by a person unrelated to the trial was used to allocate participants with a block of eight.
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y - All the investigators, caregivers, outcome assessors, and the person responsible for the statistical analysis remained blinded to the intervention until the completion of the study and the analysis of the data.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN - Although differences were not formally assessed there were no apparent differences between groups.
Risk of bias judgement for the randomisation process	Low - The RCT is at low risk of bias from the randomisation process.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	N - The RCT was double-blind.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N - The RCT was double-blind.
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context??	N/PN - In line with other similar studies compliance was assessed and was found to be >75% of all doses in all participants.
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	N/A
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	N/A
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y - An intention-to-treat analysis was used.
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	N/A

Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low - The RCT is at low risk of bias from deviation from the intended intervention.
2.1. Were participants aware of their assigned intervention during the trial?	N - The RCT was double-blind.
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N - The RCT was double-blind.
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	N/A
2.4. Could failures in implementing the intervention have affected the outcome?	PN - The authors report that compliance exceeded 75% in this RCT.
2.5. Did study participants adhere to the assigned intervention regimen?	PY - The authors report that compliance exceeded 75% in this RCT.
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N/A
Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low - The RCT is at low risk of bias from deviations from the intended interventions.
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y - There were only 3 participants lost to follow-up (1.2%).
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NI - The study reports the methods used to correct for missing data, but no detail of how much missing data occurred.
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI - The study reports the methods used to correct for missing data, but no detail of how much missing data occurred.

3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	NI - The study reports the methods used to correct for missing data, but no detail of how much missing data occurred.
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI - The study reports the methods used to correct for missing data, but no detail of how much missing data occurred.
Risk-of-bias judgement for missing outcome data	Some concerns - It is unclear how much missing data was abstracted rather than reported.
Domain 4. Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N - The outcomes used were similar to other studies of the same interventions.
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN - Outcome assessment was in hospital and assessed by the nursing team actively.
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N - The study was double-blind, and data secured until after the end of the trial.
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/A
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/A
Risk-of-bias judgement for measurement of the outcome	Low - The RCT is at low risk of bias from measurement of outcome.
Domain 5. Bias in selection of the reported result	
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Y - All the investigators, caregivers, outcome assessors, and the person responsible for the statistical analysis

	remained blinded to the intervention until the completion of the study and the analysis of the data.
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N/PN - The outcomes were reported were in line with the analytic plan and similar to other RCTs of the same intervention.
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	N/PN - The outcomes were reported were in line with the analytic plan and similar to other RCTs of the same intervention.
Risk-of-bias judgement for selection of the reported result	Low - The RCT is at low risk of bias from selection of the reported result.
Overall bias and Directness	
Risk of bias judgement	Some concerns - Overall the RCT is at low risk of bias, although there are concerns about the size and imputation of missing data.
Overall Directness	Directly applicable.

Table 31: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	**Goldenberg et al 2017**
DOMAIN 1: IDENTIFYING CONCERNS WITH THE REVIEW PROCESS: *Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:*	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y – Appendix 1 (separate document outlines full strategy) in document outlines clear eligibility criteria and PICO outlined.
1.2 Were the eligibility criteria appropriate for the review question?	Y – Research protocol restricted by RCT and was aligned with Cochrane methods and process.
1.3 Were eligibility criteria unambiguous?	N – The study clearly outlined and focused on C.Diff associated diarrhoea in adults focused on assessing antibiotic treatment for CDI; clearly outlined inclusion criteria, population and intervention of interest.

1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	N – Study criteria restricted by RCT and was aligned with Cochrane methods and process. This is clearly outlined. Not all studies featured in the subsequent analysis. No restrictions by date, study sample size, study quality or outcome measures
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	NI – No information was provided regarding restrictions in eligibility criteria based on sources of information
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES - Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y – An appropriate range of databases were searched including MEDLINE, EMBASE, CENTRAL and the Cochrane IBD Group Specialized Trials Register which were searched from inception to 26 January 2017. Also searched clinicaltrials.gov and clinicaltrialsregister.eu for ongoing trials. Restriction to RCT and SR meant unpublished reports not considered
2.2 Were methods additional to database searching used to identify relevant reports?	Y – Clinical trial registers including clinicaltrials.gov and clinicaltrialsregister.eu were searched for ongoing trials
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y – Nelson et al (2017) updates previous systematic review. A full and comprehensive search strategy was available as appendix. Search terms were appropriate and searches run up to 2017
2.4 Were restrictions based on date, publication format, or language appropriate?	Y - The systematic review does not include any data restrictions, and restrictions by participants, intervention, outcome measures align with the review question and pre-established outcomes
2.5 Were efforts made to minimise error in selection of studies?	Y - The review had strategies in place to minimise errors in study selection including at least two authors examining all the citations and abstracts derived from the electronic search strategy who independently selected trials to be included
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL - Describe methods of study identification and selection (e.g. number of reviewers involved):	
3.1 Were efforts made to minimise error in data collection?	Y - Data extraction was performed independently by at least two authors. Results were compared between reviewers and all studies were presented for group discussion. Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PN – Not all studies feature in meta-analysis and those that did not the characteristics of included studies section did not provide enough detail with which to understand how the results were generated for example antibiotic

	versus placebo – This did not detract from the comparison of the efficacy of antibiotics treatment for *C. difficile*-associated diarrhoea (CDAD), or CDI.
3.3 Were all relevant study results collected for use in the synthesis?	N – The review categorises some studies as contributing to 'main findings' (antibiotics vs antibiotics); Antibiotics vs placebo, Rifaximin versus Vancomycin (small study n=20); Fusidic acid versus vancomycin; Nitazoxanide versus vancomycin; Metronidazole versus Nitazoxanide; Metronidazole versus Metronidazole and Rifampin; Metronidazole versus Teicoplanin; Metronidazole versus Teicoplanin; Metronidazole versus Fusidic Acid; Teicoplanin versus Fusidic Acid; dose; dose timing; Rifaximin to diminish relapse risk; Cadazolid versus Vancomycin; LFF517 versus vancomycin; Surotomycin versus vancomycin do not feature in meta-analysis but are narratively outlined
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).
3.5 Were efforts made to minimise error in risk of bias assessment?	Y - Two review authors independently assessed the included studies using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011).
DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	PY – The rationale for not including studies was outlined and centred around poor quality, small study size and singular RCTs; All synthesis undertaken addresses the primary research question.
4.2 Were all pre-defined analyses reported or departures explained?	Y – This systematic review sought to investigate the efficacy and safety of antibiotic therapy for CDI, to identify the most effective antibiotic treatment for CDAD in adults and to determine the need for stopping the causative antibiotic during therapy; This is a Cochrane review and follows its methods and process
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y – The synthesis included all RCT, dichotomous outcomes and utilised a random-effects meta-analysis to account for differences across studies for example in antibiotic treatments
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	N – Heterogeneity was defined as significant if I^2 >60% or Chi^2 <0.10 - two meta-analysis had I^2 >40% but not >60% and two had Chi^2 <0.10 which none of the synthesis reached indicating high heterogeneity. The quality of the included RCT's was categorised as low.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y – Funnel plot was planned but does not appear to be undertaken; The study highlights issues with bias in included RCTs and being of very low to low quality. However, the method and process are clear and findings are limited but based on robust process

4.6 Were biases in primary studies minimal or addressed in the synthesis?	PN – The authors flag the very low to low quality and bias of the evidence. Authors state that they changed outcome assessment to reduce the risk of bias but it's not clear how – also it's not clear when this change occurred.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Low	The review method and process are clear and outlined. There was no information for assessment criteria 1.5 but all other aspects indicate low concern for risk of bias from study eligibility.
2. Concerns regarding methods used to identify and/or select studies	Low	The review clearly outlines its identification and selection of studies process and the methods and process underpinning this are clearly outlined and robust.
3. Concerns regarding methods used to collect data and appraise studies	Low	The review does not include all studies within the meta-analysis undertaken. Despite the absence of some studies in these synthesis the methods and process for the collection and appraisal of RCTs was consistent and clear. Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.
4. Concerns regarding the synthesis and findings	High	The study outlines the synthesis of some studies narratively and only provides limited data regarding these making fuller assessment of these findings within this study difficult. There was significant heterogeneity in the meta-analysis undertaken (assessed with Chi^2 or I^2). There was an absence of narrative explaining issues regarding bias in studies and the very low to low quality of studies was addressed.
RISK OF BIAS IN THE REVIEW: Describe whether conclusions were supported by the evidence:		

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PY – There were no issues raised across domains 1-4, apart from 4.6. However, the authors outline the limitations of the findings in discussion and conclusions section which addressed concerns raised.
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y – The review utilised Cochrane methods and process, undertook adequate searching and appraisal processes. The studies identified were of low quality but applicable to the review research question
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y - The authors flag the limitations of the findings outlining the high heterogeneity in the meta-analysis, very low to low quality evidence and identified bias in studies
Risk of bias in the review RISK: Rationale for risk:	Low/Moderate There were issues raised regarding the synthesis undertaken and the lack of narrative to explain how the low to very low quality of studies were addressed or accounted for within the review. However, the method and process underpinning the review are clear and robust and the issues with the identified studies are outlined

Appendix H: **Modified GRADE for network meta-analyses**

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is well established. However, the use of GRADE to assess the quality of evidence across a network meta-analysis is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when applying modified GRADE to a published network meta-analysis.

Risk of bias

The risk of bias assessment for each direct comparison reported by the published study was used to assess how the risk of bias from the direct comparisons would affect the indirect comparisons.

For direct comparisons with a large proportion of studies in a network, some decision rules were applied with respect to downgrading.

- If 50% or more studies in the network were inadequate or unclear for a particular parameter of quality, the outcome was downgraded by 1 level.

Inconsistency

The published study assessed and reported inconsistency for the heterogeneity of individual pairwise comparisons in the network and also for between direct and indirect comparisons, where both were available (that is, where there were ‘loops’ in the network).

Assessment of heterogeneity within the included NMA was completed using the following decision rules:

- If there was considerable heterogeneity for 1 link or more in a network, the outcome was downgraded 1 level.
- If there were more than 1 link in the network with considerable, substantial or moderate heterogeneity, consider downgrading 2 levels.

Indirectness

As with pairwise meta-analyses, studies included in the published NMA were assessed for how well they fit the PICO (population, intervention, comparator, outcome) specified in the review protocol.

Imprecision

This was assessed for a number of variables:

- Sufficient head-to-head trials in the network.
- Sufficient number of studies to form the network (if there is a high proportion of ‘links’ formed with only 1 trial, the outcome was downgraded).
- Imprecision in each of the pairwise effect estimates (size of confidence intervals and sample size of the included RCTs, including for each drug compared to

vancomycin and also size of confidence intervals for the overall rankings within the network)[a].

- For networks, imprecision was considered around both the direct and indirect effect estimates.

References

Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated March 2013; available from http://www.nicedsu.org.uk.

Dias, S., Welton, N.J., Sutton, A.J., Caldwell, D.M., Lu, G. & Ades, A.E. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence

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Dworkin RH, Turk DC, Farrar JT, et al (2005) Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113:9–19.

Elbourne DR, Altman DG, Higgins JPT et al. (2002) Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology 31: 140–49.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

a The outcome was downgraded 1 level if the 95%CI crossed the MID of OR1. A confidence interval was considered 'wide' if it was 4 or greater; an outcome was downgraded for imprecision if 50% or more interventions had wide confidence intervals for the OR when they were compared to vancomycin

Appendix I: **GRADE profiles**

I.1 Treatment

I.1.1 Antibiotics in adults

I.1.1.1 Antibiotics versus placebo

Table 32: GRADE profiles - Vancomycin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute		
Treatment: Vancomycin vs placebo (follow-up 5 days; assessed with: Symptomatic cure)												
1[1]	Randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	serious[4]	Numbers of participants were not outlined in Nelson et al (2017)		RR 9.0 (1.24 to 65.16)	-	⊕OOO VERY LOW	CRITICAL
Treatment: Vancomycin vs placebo (follow-up 5 days; assessed with: Bacteriological cure)												
1[1]	Randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	serious[4]	Numbers of participants were not outlined in Nelson et al (2017)		RR 10.0 (1.40 to 71.62)	-	⊕OOO VERY LOW	CRITICAL

[1] Nelson et al (2017)
[2]Downgraded 2 levels - Nelson et al 2017 assessed the RCT as at high risk of bias due to small sample size and high attrition
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, also very wide confidence intervals
[4] Downgraded 1 level – unclear population (age, gender and other characteristics)

I.1.1.2 Antibiotic versus antibiotic

Table 33: GRADE profiles – NMA for outcome of sustained symptomatic cure: vancomycin versus other antibiotics

Quality assessment						No of patients	Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision				
Vancomycin versus other antibiotics (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
24[1]	Randomised trials	no serious bias[2]	no serious[3]	no serious indirectness	serious[4]	5361	See section 3.1.2	⊕⊕⊕O MODERATE	CRITICAL
Vancomycin versus other antibiotics in people <65 years (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
6[1]	Randomised trials	no serious bias[5]	serious[6]	no serious indirectness	serious[4]	Not reported	See section 3.1.2	⊕⊕OO LOW	CRITICAL
Vancomycin versus other antibiotics in people ≥65 years (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
6[1]	Randomised trials	no serious bias[7]	no serious[8]	no serious indirectness	serious[4]	Not reported	See section 3.1.2	⊕⊕⊕O MODERATE	CRITICAL
Non-initial Clostridioides difficile infection (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
7[1]	Randomised trials	no serious bias[9]	no serious[8]	no serious indirectness	serious[4]	Not reported	See section 3.1.2	⊕⊕⊕O MODERATE	CRITICAL
Initial Clostridioides difficile infection (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
8[1]	Randomised trials	no serious bias[10]	no serious[8]	no serious indirectness	serious[4]	Not reported	See section 3.1.2	⊕⊕⊕O MODERATE	CRITICAL
Severe Clostridioides difficile infection (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
8[1]	Randomised trials	no serious bias[11]	serious[6]	no serious indirectness	very serious[4,12]	Not reported	See section 3.1.2	⊕OOO VERY LOW	CRITICAL
Non-severe Clostridioides difficile infection (follow-up [range] 21 to 90 days; assessed with: sustained symptomatic cure)									
8[1]	Randomised trials	no serious bias[13]	serious[6]	no serious indirectness	very serious[4,12]	Not reported	See section 3.1.2	⊕OOO VERY LOW	CRITICAL

[1] Beinortas et al (2018)
[2] Network meta-analysis was assessed as high quality using the NICE modified PRISMA checklist for network meta-analysis
[3] Heterogeneity for the whole NMA was not significant (Cochran's Q, 15.70; p=0.47; τ^2, 0); Comparisons of direct versus indirect treatment estimates did not identify any significant differences; a comparison-adjusted funnel plot did not demonstrate any small trial or publication bias.
[4] Downgrade 1 level – over 50% of the 95%CI of the pairwise comparisons for sustained symptomatic cure from the NMA cross the pre-defined MID (OR=1); The network diagram (see figure 1) indicates that comparisons between vancomycin-fidaxomicin, vancomycin-tolevamer, vancomycin-metronidazole were the largest comparisons
[5] Network meta-analysis sub-group analysis (<65 years of age) comprised of 7 direct and 8 indirect comparisons. The studies (n=6) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 4 out of 6 studies demonstrating a low risk of bias for all assessment criteria and 2 out of 6 studies demonstrating unclear risk of bias for 4 out of 6 risk of bias criteria.
[6] Downgrade 1 level - one pairwise link within the NMA (vancomycin–metronidazole) demonstrated significant heterogeneity (Cochran's Q 3.94; p=0.047)

[7] Network meta-analysis sub-group analysis (≥65 years of age) comprised of 7 direct and 8 indirect comparisons. The studies (n=6) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 4 out of 6 studies demonstrating a low risk of bias for all assessment criteria and 2 out of 6 studies demonstrating unclear risk of bias for 4 out of 6 risk of bias criteria.
[8] Low or moderate heterogeneity across pairwise comparisons as assessed by Beinortas et al (2018) via GRADE and Cochran's Q (p-values < 0.10 represented significant heterogeneity in the assessment of inconsistency)
[9] Network meta-analysis sub-group analysis (Non-initial CDI) comprised of 9 direct and 12 indirect comparisons. The studies (n=7) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 4 out of 7 studies demonstrating a low risk of bias for all assessment criteria; 1 out of 7 studies demonstrating unclear risk of bias for 1 out of 6 risk of bias criteria; 2 out of 7 studies demonstrating unclear risk of bias for 4 out of 6 risk of bias criteria.
[10] Network meta-analysis sub-group analysis (initial CDI) comprised of 10 direct and 18 indirect comparisons. The studies (n=8) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 1 out of 8 studies demonstrating a low risk of bias for 4 out of 6 risk of bias criteria; 5 out of 8 studies demonstrating low risk of bias for all risk of bias criteria; 2 out of 8 studies demonstrating unclear risk of bias for 4 out of 6 risk of bias criteria.
[11] Network meta-analysis sub-group analysis (severe CDI) comprised of 9 direct and 12 indirect comparisons. The studies (n=8) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 1 out of 8 studies demonstrating a low risk of bias for 5 out of 6 risk of bias criteria; 1 out of 8 studies demonstrating a low risk of bias for 4 out of 6 risk of bias criteria; 4 out of 8 studies demonstrating low risk of bias for all risk of bias criteria; 2 out of 8 studies demonstrating unclear risk of bias for 4 out of 6 risk of bias criteria.
[12] Downgraded 1 level – no standard definition of the criteria used to define severe or non-severe
[13] Network meta-analysis sub-group analysis (non-severe CDI) comprised of 10 direct and 18 indirect comparisons. The studies (n=13) comprising the direct comparisons were assessed by Beinortas et al (2018) using the Cochrane risk of bias tool (1.0) as being at low to moderate risk of bias with a total of 1 out of 13 studies demonstrating a low risk of bias for 5 out of 6 risk of bias criteria; 3 out of 13 studies demonstrating a low risk of bias for 4 out of 6 risk of bias criteria; 1 out of 13 studies demonstrating low risk of bias for 3 out of 6 risk of bias criteria; 4 out of 13 studies demonstrating low risk of bias for all risk of bias criteria; 3 out of 13 studies demonstrating unclear or high risk of bias for 4 out of 6 risk of bias criteria; 1 out of 13 studies demonstrating unclear or high risk of bias for 5 out of 6 risk of bias criteria.

I.1.1.3 Antibiotics compared with other antibiotics (with or without other intervention) for recurrence of Clostridioides difficile infection

Table 34: GRADE profile – Antibiotics compared with other antibiotics (with or without other intervention) for recurrence of Clostridioides difficile infection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Other intervention	Relative (95% CI)	Absolute		
Clinical resolution and a negative CD toxin test (follow-up 1 weeks; assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	2/16 (12.5%)	9/24 (37.5%)	RR 0.33 (0.08 to 1.35)[4]	251 fewer per 1000 (from 345 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL
Resolution of diarrhoea (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious	not applicable	no serious indirectness	very serious[5]	none	5/16 (31.3%)	13/24 (54.2%)	RR 0.58 (0.26 to 1.3)[4]	228 fewer per 1000 (from 401 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL

Clinical resolution and a negative CD toxin test (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	3/16 (18.8%)	8/24 (33.3%)	RR 0.56 (0.18 to 1.81)[4]	147 fewer per 1000 (from 273 fewer to 270 more)	⊕OOO VERY LOW	CRITICAL
Resolution of diarrhoea (follow-up 10 weeks[6]; assessed with vancomycin 500 mg four times daily for 14 days versus vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
1[7]	randomised trials	no serious risk of bias[8]	not applicable	no serious indirectness	very serious[9]	none	4/13 (30.8%)	3/13 (23.1%)	RR 1.33 (0.37 to 4.82)[4]	76 more per 1000 (from 145 fewer to 882 more)	⊕⊕OO LOW	CRITICAL
Relapse after 5 weeks (follow-up 5 weeks; assessed vancomycin 500 mg four times daily for 14 days versus vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
1[7]	randomised trials	no serious risk of bias[8]	not applicable	no serious indirectness	very serious[10]	none	8/13 (61.5%)	7/13 (53.8%)	RR 1.14 (0.59 to 2.22)[4]	75 more per 1000 (from 221 fewer to 657 more)	⊕⊕OO LOW	CRITICAL
Off protocol FMT after assigned treatment failure (follow-up 8 weeks[11]; assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[12]	none	10/11 (90.9%)	9/11 (81.8%)	RR 1.11 (0.79 to 1.55)[4]	90 more per 1000 (from 172 fewer to 450 more)	⊕⊕OO LOW	CRITICAL
Overall adverse events (assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[13]	none	8/16 (50%)	9/24 (37.5%)	RR 1.33 (0.65 to 2.72)[4]	124 more per 1000 (from 131 fewer to 645 more)	⊕OOO VERY LOW	CRITICAL
GI adverse events (assessed with vancomycin 125 mg four times daily for 10 days versus fidaxomicin 200 mg twice daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[14]	none	2/16 (12.5%)	6/24 (25%)	RR 0.50 (0.11 to 2.17)[4]	125 fewer per 1000 (from 222 fewer to 293 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, confidence interval; CD, *Clostridioides difficile* ; RR, relative risk; PCR, Polymerase chain reaction; FMT, faecal microbiota transplant; GI, gastrointestinal.												

[1] Hvas et al 2019
[2] Downgraded 1 level: This RCT was found to be at high risk of bias (open label RCT).
[3] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with vancomycin, and no meaningful difference or appreciable benefit with fidaxomicin
[4] NICE analysis.
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with vancomycin, and no meaningful difference or appreciable benefit with fidaxomicin
[6] 10 weeks after initiation of therapy
[7] van Nood et al 2013
[8] The RCT by van Nood et al 2013 was at low risk of bias
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, and no meaningful difference or appreciable harm with vancomycin plus bowel lavage
[10] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, and no meaningful difference or appreciable harm with vancomycin and bowel lavage
[11] 8 weeks after FMT plus vancomycin rescue therapy
[12] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with

vancomycin
[13] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, and no meaningful difference or appreciable harm with fidaxomicin
[14] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, and no meaningful difference or appreciable harm with fidaxomicin

I.1.1.4 Antibiotic dose

Table 35: GRADE profiles - high dose versus low dose vancomycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose vancomycin	Low dose vancomycin	Relative (95% CI)	Absolute		
Low vs high dose vancomycin (follow-up 5-15 days)												
1[1]	Randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	Numbers of participants were not outlined in Nelson et al (2017)		RR 0.95 (0.65 to 1.38)	Not estimable	⊕OOO VERY LOW	CRITICAL

[1] Nelson et al (2017)
[2] Downgraded 1 level - Single RCT within the Nelson et al (2017) systematic review was assessed as lacking allocation concealment and outcome assessor blinding; incomplete outcome data and selective outcome reporting
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR) or relative risk increase (RRI), the effect estimate is consistent with appreciable benefit and appreciable harm

Table 36: GRADE profile - High dose versus low dose Fidaxomicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose fidoxamicin	Low dose fidoxamixin	Relative (95% CI)	Absolute		
Low vs high dose fidaxomicin (follow-up 10 days)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	Numbers of participants were not outlined in Nelson et al (2017)		RR 1.26 (1.03 to 1.54)	Not estimable	⊕OOO VERY LOW	CRITICAL

[1] Nelson et al (2017)
[2] Downgraded 1 level - Single RCT within the Nelson et al (2017) systematic review was assessed as lacking allocation concealment and outcome assessor blinding; incomplete outcome data and selective outcome reporting

[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with high dose fidaxomicin

I.1.1.5 Antibiotic frequency

Table 37: GRADE profile – Teicoplanin 100 mg twice a day versus 50 mg four times a day

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Teicoplanin BD	Teicoplanin QDS	Relative (95% CI)	Absolute		
symptomatic cure												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	Numbers of participants were not outlined in Nelson et al (2017)		RR 0.57 (0.27 to 1.20)	-	⊕OOO VERY LOW	CRITICAL

[1]Nelson et al (2017)
[2]Downgraded 1 level - Nelson et al 2017 assessed the RCT as at high risk of bias uncertainty regarding randomisation, allocation concealment, blinding, other bias, incomplete outcome data and a high rate of drop out (47%)
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with teicoplanin bds

I.1.2 Faecal microbiota transplant (FMT) in adults

I.1.2.1 FMT versus oral antibiotic for *C. difficile* at first presentation in adults

Table 38: GRADE profile – FMT versus oral antibiotic for *C. difficile* at first presentation in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Faecal microbiota transplant	Oral antibiotic	Relative (95% CI)	Absolute		
Resolution of *Clostridioides difficile* after first FMT dose (follow-up 72 hours; assessed with: At least 2 criteria met within 72 hours[1])												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[4]	none	4/7 (57.1%)[5]	8/9 (88.9%)[6]	RR 0.64 (0.33 to 1.27)	320 fewer per 1000 (from 596 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL

Resolution of *Clostridioides difficile* after 2nd FMT dose (follow-up 72 hours; assessed with: At least 2 criteria met within 72 hours[1])												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[4]	none	5/7 (71.4%)[5]	8/9 (88.9%)[6]	RR 0.80 (0.48 to 1.35)	178 fewer per 1000 (from 462 fewer to 311 more)	⊕OOO VERY LOW	CRITICAL
Treatment failure (assessed with: ≥3 of the resolution criteria not met within 72 hours[1])												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[7]	none	2/7 (28.6%)[5]	1/9 (11.1%)[6]	RR 2.57 (0.29 to 22.93)	174 more per 1000 (from 79 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Mortality (all cause) (follow-up 30 days)												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[4]	none	2/7 (28.6%)[5]	4/9 (44.4%)[6]	RR 0.64 (0.16 to 2.56)	160 fewer per 1000 (from 373 fewer to 693 more)	⊕OOO VERY LOW	CRITICAL
Mortality (CDI attributable) (follow-up 30 days)												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[7]	none	1/7 (14.3%)	1/9 (11.1%)	RR 1.29 (0.1 to 17.14)	32 more per 1000 (from 100 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (follow-up 36 days; measured with median length of stay after Clostridioides difficile infection[8]; Better indicated by lower values)												
1[2]	randomised trials	very serious[3]	not applicable	no serious indirectness	very serious[9]	none	Median 7 days (range 4 to 19 days)[5]	Median 9 days (range 6 to 36 days)[6]	-	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; FMT, Faecal Microbiota Transplant; CDI, *Clostridioides difficile* Infection.

[1] Resolution criteria were a reduction in Bristol stool scale of at least 2 points. A reduction of at least 50% in the number of bowel movements during the first 72 hours after the FMT-FURM (second treatment). Absence of fever (not ≥38°C). Resolution of abdominal pain.

[2] Camacho-Ortiz et al 2017

[3] Downgraded 2 levels - unclear if superiority or per protocol analysis of a planned inferiority trial as mentions an inferiority margin in the methods section. RCT did not achieve planned sample size. Open label RCT. FMT arm was further divided by route of FMT administration (nasojejunal tube (n=7), superior endoscopy (n=1) and colonoscopy (n=1)) which were clinician assigned (not randomised). Unclear how the main outcomes (Bristol stool score, reduction in the number of bowel movements) were assessed (clinician or self-report). RCT did not recruit to target (n=19 at randomisation), however, 2 patients in the FMT arm were further excluded (1 died and 1 had antibiotics by mistake) and one patient in the vancomycin arm was removed at the clinicians request (no further details reported). Confounded by use of other antibiotics in both arms for other pathogens and the use of FMT-FURM in all cases in both arms in the event treatment failure (at day 3). Although it is unclear if the 1 treatment failure (due to resistance to vancomycin in the comparator arm) was treated with FMT-FURM as the patient died at day 4.

[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with FMT, and no meaningful difference or appreciable harm with vancomycin.

[5] Intervention was faecal donor-unrelated mix (FMT-FURM) transplantation. Donors were healthy adults (>18 years). Donor samples were pooled, mixed, suspended in 0.9% saline solution and filtered and stored (with added glycerol as a cryoprotectant) in 45 mL aliquots at -80C. Thawed within 60 minutes of administration by immersion in 30C water.

[6] Comparator was oral vancomycin 250 mg every 6 hours for 10 to 14 days.

[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with FMT, and no meaningful difference or appreciable benefit with vancomycin.

[8] No further details given

[9] Downgraded 2 levels: Only length of stay data provided by the study, summarised here as median with range.

I.1.2.2 FMT-based drug (RBX2660) compared with placebo for prevention of recurrent CDI

Table 39: GRADE profile – FMT-based drug (RBX2660) compared with placebo for prevention of recurrent CDI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Faecal microbiota-based drug (RBX2660)	Comparator	Relative (95% CI)	Absolute		
Recurrence of CDI (follow-up 8 weeks[1]; assessed with 2 doses of RBX2660 vs. placebo enema)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	25/41 (61%)[5]	20/44 (45.5%)[6]	RR 1.34 (0.89 to 2.01)[7]	155 more per 1000 (from 50 fewer to 459 more)	⊕⊕OO LOW	CRITICAL[8]
Recurrence of CDI (follow-up 8 weeks[1]; assessed with 1 dose of RBX2660 vs. placebo enema)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	28/42 (66.7%)[9]	20/44 (45.5%)[6]	RR 1.47 (1 to 2.16)[7]	214 more per 1000 (from 0 more to 527 more)	⊕⊕OO LOW	CRITICAL[8]
Recurrence of CDI (follow-up 8 weeks[1]; assessed with 2 doses of RBX2660 vs. 1 dose of RBX2660 enema)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[10]	none	25/41 (61%)[5]	28/42 (66.7%)[11]	RR 0.91 (0.66 to 1.27)[7]	60 fewer per 1000 (from 227 fewer to 180 more)	⊕⊕OO LOW	CRITICAL[8]
Recurrence of CDI (follow-up 8 weeks[1]; assessed with at least 1 dose of RBX2660 vs. placebo)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	53/83 (63.9%)[12]	20/44 (45.5%)[6]	RR 1.40 (0.98 to 2.02)[7]	182 more per 1000 (from 9 fewer to 464 more)	⊕⊕OO LOW	CRITICAL[8]
Adverse events (follow-up 0.1 to 15.9 months; assessed with all adverse events 2 doses of RBX2660 vs. 2 doses of placebo enema or 1 dose of RBX2660 and 1 dose placebo)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[20]	none	169/25[5]	105/26[6] or 105/31[9]	not estimable	-	⊕OOO VERY LOW	CRITICAL
Adverse outcomes (follow-up 0.1 to 15.9 months; assessed with GI adverse events 2 doses of RBX2660 vs. 2 doses of placebo enema or 1 dose of RBX2660 and 1 dose placebo)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[20]	none	78/21[5]	56/16[6] or 49/20[9]	not estimable	-	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 0.1 to 15.9 months 2 doses of RBX2660 vs. 2 doses of placebo enema or 1 dose of RBX2660 and 1 dose placebo)												
1[2]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[20]	none	19/13[5]	8/6[6] or 18/7[9]	not estimable	-	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 0.1 to 15.9 months; related to study drug[21] 2 doses of RBX2660 vs. 2 doses of placebo enema or 1 dose of RBX2660 and 1 dose placebo)												

1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[22]	none	3/41 (7.3%)[5]	0/87 (0%)[6, 9]	RR 14.67 (0.78 to 277.52)[7]	-	⊕OOO VERY LOW	CRITICAL
Mortality (assessed with the number of deaths in follow-up period 2 doses of RBX2660 vs. 2 doses of placebo enema)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[22]	none	3/41 (7.3%)[5]	0/44 (0%)[6]	RR 7.50 (0.4 to 140.91)[7]	-	⊕OOO VERY LOW	CRITICAL
Mortality (assessed with the number of deaths in follow-up period 1 dose of RBX2660 and 1 dose placebo vs. 2 doses of placebo enema)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[22]	none	3/43 (7%)[9]	0/44 (0%)[6]	RR 7.16 (0.38 to 134.6)[7]	-	⊕OOO VERY LOW	CRITICAL
Mortality (assessed with the number of deaths in follow-up period 2 doses of RBX2660 vs. 1 dose of RBX2660 and 1 dose placebo)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[22]	none	3/41 (7.3%)[5]	3/43 (7%)[9]	RR 1.05 (0.22 to 4.9)[7]	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, confidence interval; CDI, *Clostridioides difficile* infection; RR, relative risk; GI, gastrointestinal.												

[1] 8 weeks after second dose of assigned study treatment.
[2] Dubberke et al 2018
[3] Downgraded 1 level - there were concerns over the lack of allocation concealment and the low number of participant characteristics used to assess adequate randomisation. Also some unbalanced attrition between groups in the ongoing follow-up period.
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with 2 doses of FMT (RBX2660), and no meaningful difference or appreciable harm with 2 doses of placebo enema.
[5] Intervention was 2 doses of FMT (RBX2660) based enema drug.
[6] Comparator was 2 doses of placebo enema.
[7] NICE analysis.
[8] Successful prevention of recurrence was defined as the absence of diarrhoea and no retreatment for CDI any time after the first dose until 8 weeks after the second dose of assigned study treatment.
[9] Intervention was 1 dose of FMT (RBX2660) and 1 dose of placebo enema.
[10] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 2 doses of RBX2660, and no meaningful difference or appreciable benefit with 1 dose of RBX2660 and 1 dose of placebo enema.
[11] Comparator was 1 dose of FMT (RBX2660) and 1 dose of placebo enema.
[12] Intervention was either 2 doses of FMT (RBX2660) or 1 dose plus 1 dose of placebo.
[13] After 8 weeks the trial became an open label follow-up
[14] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with 1 dose of FMT, and no meaningful difference or appreciable harm with 2 doses of FMT.
[15] Intervention was 1 dose of FMT (RBX2660) enema.
[16] Comparator was 2 doses of FMT (RBX2660) enema.
[17] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 2 doses of RBX2660, and no meaningful difference or appreciable benefit with 2 doses of placebo enema.
[18] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 1 dose of RBX2660 and 1 dose of placebo, and no meaningful difference or appreciable benefit with 2 doses of placebo enema.
[19] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 2

doses of RBX2660, and no meaningful difference or appreciable benefit with 1 dose of RBX2660 and 1 dose of placebo enema.
[20] Downgraded 2 levels - not estimable
[21] Three of the SAEs were adjudged possibly related to the blinded study drug; 1 participant developed recurrent acute myeloid leukaemia, another reported abdominal cramping and pain, and a third experienced constipation that required hospitalisation.
[22] Downgraded 2 levels - at a minimal important difference of 0% relative risk increase (RRI), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures.

I.1.2.3 Vancomycin plus faecal microbiota transplant (FMT) versus antibiotics (with or without other intervention) for recurrent Clostridioides difficile infection (rCDI)

Table 40: GRADE profile – Vancomycin plus faecal microbiota transplant (FMT) versus antibiotics (with or without other intervention) for recurrent Clostridioides difficile infection (rCDI)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Faecal microbiota transplant (FMT)	Antibiotics	Relative (95% CI)	Absolute		
Clinical resolution and a negative CD toxin test (follow-up 1 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus vancomycin 125 mg four times daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	13/24 (54.2%)	2/16 (12.5%)	RR 4.33 (1.13 to 16.68)[4]	416 more per 1000 (from 16 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical resolution and a negative CD toxin test (follow-up 1 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus fidaxomicin 200 mg twice a day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	13/24 (54.2%)	9/24 (37.5%)	RR 1.44 (0.77 to 2.72)[4]	165 more per 1000 (from 86 fewer to 645 more)	⊕OOO VERY LOW	CRITICAL
Resolution of diarrhoea (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus vancomycin 125 mg four times daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	22/24 (91.7%)	5/16 (31.3%)	RR 2.93 (1.4 to 6.13)[4]	603 more per 1000 (from 125 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of diarrhoea (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus fidaxomicin 200 mg twice a day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[6]	none	22/24 (91.7%)	13/24 (54.2%)	RR 1.69 (1.15 to 2.49)[4]	374 more per 1000 (from 81 more to 807 more)	⊕⊕OO LOW	CRITICAL
Clinical resolution and a negative CD toxin test (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus vancomycin 125 mg four times daily for 10 days)												

1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[7]	none	17/24 (70.8%)	3/16 (18.8%)	RR 3.78 (1.32 to 10.82)[4]	521 more per 1000 (from 60 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical resolution and a negative CD toxin test (follow-up 8 weeks; assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus fidaxomicin 200 mg twice a day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[8]	none	17/24 (70.8%)	8/24 (33.3%)	RR 2.13 (1.14 to 3.96)[4]	377 more per 1000 (from 47 more to 987 more)	⊕⊕OO LOW	CRITICAL
Resolution of diarrhoea (follow-up 10 weeks[9]; assessed with vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 500 mg four times daily for 14 days)												
1[10]	randomised trials	no serious risk of bias[11]	not applicable	no serious indirectness	serious[12]	none	15/16 (93.8%)	4/13 (30.8%)	RR 3.05 (1.34 to 6.95)[4]	631 more per 1000 (from 105 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of diarrhoea (follow-up 10 weeks[12]; assessed with vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
1[10]	randomised trials	no serious risk of bias[11]	not applicable	no serious indirectness	serious[13]	none	15/16 (93.8%)	3/13 (23.1%)	RR 4.06 (1.49 to 11.05)[4]	706 more per 1000 (from 113 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of diarrhoea (follow-up 10 weeks[14]; assessed with vancomycin 125 mg four times daily for 3 days then FMT versus vancomycin 125 mg four times daily for 10 days (then pulsed regimen 125 mg to 500 mg/day every 2 to 3 days for at least 3 weeks)[15])												
1[16]	randomised trials	no serious risk of bias[17]	not applicable	no serious indirectness	serious[18]	none	18/20 (90%)	5/19 (26.3%)	RR 3.42 (1.59 to 7.36)[4]	637 more per 1000 (from 155 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Relapse after 5 weeks (follow-up 5 weeks; assessed with vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 500 mg four times daily for 14 days)												
1[10]	randomised trials	no serious risk of bias[11]	not applicable	no serious indirectness	no serious imprecision	none	1/16 (6.3%)	8/13 (61.5%)	RR 0.10 (0.01 to 0.71)[4]	554 fewer per 1000 (from 178 fewer to 609 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Relapse after 5 weeks (follow-up 5 weeks; assessed with vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
1[10]	randomised trials	no serious risk of bias[11]	not applicable	no serious indirectness	serious[19]	none	1/16 (6.3%)[16]	7/13 (53.8%)[19]	RR 0.12 (0.02 to 0.83)[4]	474 fewer per 1000 (from 92 fewer to 528 fewer)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality (follow-up 0 - 120 days; assessed with FMT arm of the RCTs versus vancomycin (without other intervention) arm of the RCTs (no deaths occurred in the other comparator arms of any trial)												
4[23]	randomised trials	serious[24]	no serious inconsistency	no serious indirectness	serious[25]	none	2/72 (2.8%)	7/64 (10.9%)	RR 0.31 (0.08 to 1.17)[4]	75 fewer per 1000 (from 101 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
CDI related mortality (assessed with vancomycin 125 mg four times daily for 3 days then FMT versus vancomycin 125 mg four times daily for 10 days (then pulsed regimen 125 mg to 500 mg/day every 2 to 3 days for at least 3 weeks))												

1[16]	randomised trials	no serious risk of bias[17]	not applicable	no serious indirectness	very serious[26]	none	2/20 (10%)	2/19 (10.5%)	RR 0.95 (0.15 to 6.08)[4]	5 fewer per 1000 (from 89 fewer to 535 more)	⊕⊕OO LOW	CRITICAL
Adverse events (assessed with vancomycin 125 mg four times daily for 3 days then FMT and vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 125 mg four times daily for 10 days (then pulsed regimen 125 mg to 500 mg/day every 2 to 3 days for at least 3 weeks) and vancomycin 500 mg four times daily for 14 days or vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
2[27]	randomised trials	no serious risk of bias[11,17]	no serious inconsistency	no serious indirectness	very serious[28]	none	34/36 (94.4%)	0/44 (0%)	RR 41.62 (5.97 to 289.87)[4]	-	⊕⊕OO LOW	CRITICAL
Adverse events (assessed with vancomycin 125 mg four times daily for 3 days then FMT and vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 125 mg four times daily for 10 days (then pulsed regimen 125 mg to 500 mg/day every 2 to 3 days for at least 3 weeks) and vancomycin 500 mg four times daily for 14 days or vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
2[27]	randomised trials	no serious risk of bias[11,17]	no serious inconsistency	no serious indirectness	serious[29]	none	17/36 (47.2%)	0/44 (0%)	RR 20.77 (2.8 to 153.91)[4]	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (assessed with vancomycin 500 mg four times daily for 4 or 5 days then bowel lavage then FMT versus vancomycin 500 mg four times daily for 14 days and vancomycin 500 mg four times daily for 14 days with bowel lavage on day 4 or 5)												
1[10]	randomised trials	no serious risk of bias[11]	not applicable	no serious indirectness	very serious[30]	none	3/16 (18.8%)	0/25 (0%)	RR 10.71 (0.59 to 194.46)[4]	-	⊕⊕OO LOW	CRITICAL
Adverse events (assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus vancomycin 125 mg four times daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[31]	none	12/24 (50%)	8/16 (50%)	RR 1.00 (0.53 to 1.88)[4]	0 fewer per 1000 (from 235 fewer to 440 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus fidaxomicin 200 mg twice a day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[32]	none	12/24 (50%)	9/24 (37.5%)	RR 1.33 (0.69 to 2.56)[4]	124 more per 1000 (from 116 fewer to 585 more)	⊕OOO VERY LOW	CRITICAL
GI Adverse events (assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus vancomycin 125 mg four times daily for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[33]	none	6/24 (25%)	2/16 (12.5%)	RR 2.00 (0.46 to 8.7)[4]	125 more per 1000 (from 67 fewer to 962 more)	⊕OOO VERY LOW	CRITICAL
GI Adverse events (assessed with vancomycin 125 mg four times daily for 4 to 10 days then FMT versus fidaxomicin 200 mg twice a day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[33]	none	6/24 (25%)	6/24 (25%)	RR 1.00 (0.38 to 2.66)[4]	0 fewer per 1000 (from 155 fewer to 415 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (mean number of days of diarrhoea experienced during follow-up; assessed with vancomycin 125 mg four times daily for 14 days then FMT versus vancomycin 125 mg four times daily for 14 days, followed by a taper over 4 weeks; better indicated by lower values)												
1[34]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	16	12	-	MD 0.90 lower (1.35 to 0.45 lower)[6]	⊕⊕⊕O MODERATE	CRITICAL

Serious adverse events (assessed with data from 2 RCTs)									
2[35]	randomised trials	serious[2]	not applicable	no serious indirectness	not assessable	none	1 RCT[1] reported a serious adverse event in 1 participant possibly related to FMT (sepsis like symptoms participant not admitted and symptoms spontaneously resolved within 24 hours without treatment). 1 RCT[46] reported 3 serious AE, none related to study interventions (UTI with fever; anasarca and end stage liver disease; perforated bowel secondary to diverticulitis 35 days after FMT).	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% confidence interval; CD, *Clostridioides difficile*; PCR, polymerase chain reaction; RR, relative risk; FMT, Faecal microbiota transplant; RCT, randomised controlled trial; CDI, *Clostridioides difficile* infection; GI, gastrointestinal.									

[1] Hvas et al 2019
[2] Downgraded 1 level - this RCT(s) was found to be at high risk of bias (open label RCT)
[3] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin and FMT, and very wide 95% CI RR 4.33 (1.13 to 16.68)
[4] NICE analysis.
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin and FMT, and no meaningful difference or appreciable harm with fidaxomicin
[6] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin and FMT
[7] Downgraded 1 level - very wide 95% confidence intervals RR 3.78 (95%CI 1.32 to 10.82)
[8] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin FMT
[9] 10 weeks after initiation of therapy
[10] van Nood et al 2013
[11] The RCT by van Nood et al 2013 was at low risk of bias
[12] Downgraded 1 level - very wide 95% confidence intervals RR 3.05 (95%CI 1.34 to 6.95)
[13] Downgraded 1 level - very wide 95% confidence intervals RR 4.06 (95%CI 1.49 to 11.05)
[14] 10 weeks after the end of treatments
[15] Also reported was resolution of diarrhoea in a subgroup with pseudomembranous colitis who received FMT 5/7 (71%) there was no comparator for this group
[16] Cammarota et al 2015
[17] The study by Cammarota et al 2015 was at low risk of bias
[18] Downgraded 1 level - very wide 95% confidence intervals RR 3.42 (95%CI 1.59 to 7.36)
[19] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin and bowel lavage
[20] 8 weeks after FMT plus vancomycin rescue therapy
[21] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with vancomycin plus FMT, and no meaningful difference or appreciable benefit with vancomycin
[22] van Nood et al 2013; Hota et al 2017
[23] Hvas et al 2019; Hota et al 2017; Cammarota et al 2015; van Nood et al 2013
[24] Downgraded 1 level - Included RCTs found to be at risk of bias
[25] Downgraded 1 level - at a minimal important difference of 0% relative risk reduction (RRR), the effect estimate is consistent with appreciable benefit
[26] Downgraded 2 levels - at a minimal important difference of 0% relative risk reduction (RRR), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures
[27] Cammarota et al 2015; van Nood et al 2013
[28] Downgraded 1 level - very wide 95% confidence intervals RR 41.62 (95%CI 5.97 to 289.87)

[29] Downgraded 1 level - very wide 95% confidence intervals RR 20.77 (95%CI 2.80 to 153.91)
[30] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin, bowel lavage and FMT, and no meaningful difference or appreciable harm with vancomycin or vancomycin with bowel lavage
[31] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with vancomycin and FMT, and no meaningful difference or appreciable benefit with vancomycin
[32] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with vancomycin and FMT, and no meaningful difference or appreciable benefit with vancomycin
[33] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin plus FMT, and no meaningful difference or appreciable harm with fidaxomicin
[34] Hota et al 2017
[35] Hvas et al 2019; Hota et al 2017

I.1.3 Prebiotics in adults

Table 41: GRADE profile - Metronidazole or vancomycin with oligofructose versus metronidazole or vancomycin with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prebiotics with antibiotics	Antibiotics only	Relative (95% CI)	Absolute		
Metronidazole or vancomycin with oligofructose vs metronidazole or vancomycin with placebo (Relapses of diarrhoea after initial CDAD)												
1[1]	Randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/72 (8.3%)	24/70 (34.3%)	RR 0.24 (0.11 to 0.56)	261 fewer per 1000 (from 151 fewer to 305 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Metronidazole or vancomycin with oligofructose vs metronidazole or vancomycin with placebo (follow-up 30 days; Positive for Clostridioides difficile)												
1[1]	Randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	20/72 (27.8%)	14/70 (20%)	RR 1.39 (0.76 to 2.53)	78 more per 1000 (from 48 fewer to 306 more)	⊕⊕OO LOW	CRITICAL
Metronidazole or vancomycin with oligofructose vs metronidazole or vancomycin with placebo (follow-up 60 days; Positive for Clostridioides difficile)												
1[1]	Randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	14/72 (19.4%)	7/70 (10%)	RR 2.17 (0.82 to 5.76)	117 more per 1000 (from 18 fewer to 476 more)	⊕⊕OO LOW	CRITICAL
Metronidazole or vancomycin with oligofructose vs metronidazole or vancomycin with placebo (mortality)												
1[1]	Randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/72 (12.5%)	10/70 (14.3%);	RR 0.88 (0.38 to 2.02).	17 fewer per 1000 (from 89 fewer to 146 more)	⊕⊕⊕O VERY LOW	CRITICAL

[1] Lewis et al 2005a
[2] Downgraded 1 level - based on assessment with the Cochrane risk of bias tool Lewis et al 2005a the risk of bias judgement demonstrated 'some concerns' based on the study being stopped early and under powering for outcomes intended

[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with metronidazole or vancomycin with oligofructose
[4]Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with metronidazole or vancomycin with oligofructose

I.1.4 Antibiotics in young people and children

I.1.4.1 Oral metronidazole versus oral rifaximin

Table 42: GRADE profile - Oral metronidazole versus oral rifaximin in children with inflammatory bowel disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral metronidazole	Oral rifaximin	Relative (95% CI)	Absolute		
Oral metronidazole vs oral rifaximin in children with inflammatory bowel disease (assessed with: Clostridioides difficile infection cure rates)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/17 (70.6%)	11/14 (78.6%)	RR 0.90 (0.60 to 1.36)	79 fewer per 1000 (from 314 fewer to 283 more)	⊕OOO VERY LOW	CRITICAL
Oral metronidazole vs oral rifaximin in children with inflammatory bowel disease (assessed with: Recurrent Clostridioides difficile infection cure rates)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/12 (16.7%)	0/11 (0%)	RR 4.62 (0.25 to 86.72)	Not estimable	⊕OOO VERY LOW	CRITICAL
Oral metronidazole vs oral rifaximin in children with inflammatory bowel disease (Crohn's disease) (assessed with: Recurrent Clostridioides difficile infection cure rates)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/6 (66.7%)	6/6 (100%)	RR 0.69 (0.38 to 1.25)	310 fewer per 1000 (from 620 fewer to 250 more)	⊕OOO VERY LOW	CRITICAL
Oral metronidazole vs oral rifaximin in children with inflammatory bowel disease (Ulcerative colitis) (assessed with: Recurrent Clostridioides difficile infection cure rates)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/11 (72.7%)	5/8 (62.5%)	RR 1.16 (0.61 to 2.22)	100 more per 1000 (from 244 fewer to 763 more)	⊕OOO VERY LOW	CRITICAL

[1] Gawronska et al 2017
[2] Downgraded 1 level - based on assessment with the Cochrane risk of bias tool Gawronska et al 2017 the risk of bias judgement demonstrated 'some concerns' based on the study being stopped early and under powering for outcomes intended
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR) or relative risk increase (RRI), the effect estimate is consistent with appreciable benefit and appreciable harm

I.1.4.2 Oral fidaxomicin versus oral vancomycin

Table 43: GRADE profile – Oral fidaxomicin versus oral vancomycin in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral fidaxomicin	Oral Vancomycin	Relative (95% CI)	Absolute		
Oral fidaxomicin versus oral vancomycin in children and young people: all participants (assessed with: confirmed clinical response with no further requirement for CDI therapy at 12 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	76/98 (77.6%)	31/44 (70.5%)	RR 1.10 (0.88 to 1.37)	70 more per 1000 (from 85 fewer to 261 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: < 2 years (assessed with: confirmed clinical response with no further requirement for CDI therapy at 12 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	13/20 (65%)	9/10 (90%)	RR 0.72 (0.49 to 1.06)	252 fewer per 1000 (from 459 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: ≥2 years (assessed with: confirmed clinical response with no further requirement for CDI therapy at 12 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63/78 (80.8%)	22/34 (64.7%)	RR 1.25 (0.95 to 1.64)	162 more per 1000 (from 32 fewer to 414 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: ≥2 years with positive toxin test (assessed with: confirmed clinical response with no further requirement for CDI therapy at 12 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23/32 (71.9%)	11/18 (61.1%)	RR 1.18 (0.77 to 1.80)	110 more per 1000 (from 141 fewer to 489 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people (assessed with: resolution of diarrhoea at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	74/98 (75.5%)	32/44 (72.7%)	RR 1.04 (0.84 to 1.28)	29 more per 1000 (from 116 fewer to 204 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: all participants (assessed with: Global cure at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	67/98 (68.4%)	22/44 (50%)	RR 1.37 (0.99 to 1.89)	185 more per 1000 (from 5 fewer to 445 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: >2 years (assessed with: Global cure at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	56/78 (71.8%)	15/34 (44.1%)	RR 1.63 (1.09 to 2.44)	232 more per 1000 (from 24 more to 552 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: <2 years (assessed with: Global cure at 30 days)												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/20 (55.0%)	7/10 (70.0%)	RR 0.79 (0.45 to 1.39)	46 fewer per 1000 (from 113 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: ≥2 years with positive toxin test (assessed with: Global cure at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	24/32 (75%)	7/18 (38.9%)	RR 1.93 (1.05 to 3.56)	362 more per 1000 (from 19 more to 996 more)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: all participants (assessed with: CDI recurrence at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	9/76 (11.8%)	9/31 (29%)	RR 0.41 (0.18 to 0.93)	171 fewer per 1000 (from 20 fewer to 238 fewer)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: <2 years (assessed with: CDI recurrence at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/13 (15.4%)	2/9 (22.2%)	RR 0.69 (0.12 to 4.05)	69 fewer per 1000 (from 196 fewer to 678 more)	⊕OOO VERY LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: >2 years (assessed with: CDI recurrence at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	7/63 (11.1%)	7/22 (31.8%)	RR 0.35 (0.14 to 0.88)	207 fewer per 1000 (from 38 fewer to 274 fewer)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people: ≥2 years with positive toxin test (assessed with: CDI recurrence at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	1/23 (4.3%)	4/11 (36.4%)	RR 0.12 (0.02 to 0.95)	320 fewer per 1000 (from 18 fewer to 356 fewer)	⊕⊕OO LOW	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people (assessed with: number of people with treatment-emergent adverse events at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/98 (73.5%)	33/44 (75%)	RR 0.98 (0.80 to 1.21)	15 fewer per 1000 (from 150 fewer to 158 more)	⊕⊕⊕O MODERATE	CRITICAL
Oral fidaxomicin versus oral vancomycin in children and young people (assessed with: number of people with serious treatment-emergent adverse events at 30 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	24/98 (24.5%)	12/44 (27.3%)	RR 0.86 (0.39 to 1.94)	38 fewer per 1000 (from 166 fewer to 256 more)	⊕OOO VERY LOW	CRITICAL
Drug related serious treatment-emergent adverse events (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/98 (7.1%)	5/44 (11.4%)	RR 0.63 (0.21 to 1.87)	42 fewer per 1000 (from 90 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Treatment-emergent adverse events leading to death (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/98 (3.1%)	0/44 (0%)	RR 3.18 (0.17 to 60.32)	-	⊕OOO VERY LOW	CRITICAL
Treatment-emergent adverse events leading withdrawal of treatment (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/98 (1%)	1/44 (2.3%)	RR 0.45 (0.03 to 7.02)	12 fewer per 1000 (from 22 fewer to 137 more)	⊕OOO VERY LOW	CRITICAL

[1] Wolf et al. 2019

[2] Downgraded 1 level: based on assessment with the Cochrane risk of bias tool Wolf et al 2019 the risk of bias judgement demonstrated 'some concerns' based on the study's allocation concealment not being fully blinded; some differences in relevant baseline factors such as infection and diarrhoea 3 months before screening; there was a 10%-20% deviation from study protocols between arms that were not balanced.
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with fidaxomicin
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with fidaxomicin and no meaningful difference or appreciable benefit with vancomycin
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with vancomycin
[6] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with fidaxomicin and no meaningful difference or appreciable benefit with fidaxomicin

I.1.5 Probiotics in young people and children

I.1.5.1 Oral rehydration solution with probiotic (Lactobacillus rhamnosus GG) versus Oral rehydration in young people and children

Table 44: GRADE profile – Oral rehydration solution with probiotic (Lactobacillus rhamnosus GG) versus Oral rehydration in young people and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral rehydration solution with probiotic (Lactobacillus rhamnosus GG)	Oral rehydration solution	Relative (95% CI)	Absolute		
Clostridioides difficile positive diarrhoea (follow-up 7 days; measured with: duration of diarrhoea - days ; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Mean duration of diarrhoea 3.2 days	Mean duration of diarrhoea 8.0	-	MD 4.80 lower (7.53 to 2.07 lower)	⊕⊕⊕O LOW	CRITICAL
Clostridioides difficile positive vomiting (follow-up 7 days; measured with: duration of vomiting - days Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	Mean duration of vomiting 2.0 days	Mean duration of vomiting 1.8 days	-	MD 0.2 lower (0.77 lower to 1.17 higher)	⊕⊕OO VERY LOW	CRITICAL

[1] Basu et al (2007)

[2] Downgraded 2 levels - based on assessment with the Cochrane risk of bias tool Basu et al 2017 the risk of bias judgement demonstrated 'some concerns' due to a lack of information regarding how the impact of intervention assignment was assessed for example via an intention to treat analysis; the study was very small (n=14)
[3] Downgraded 1 level - at a minimal important difference of 0.5 x standard deviation of treatment arm (0.5 x 1.0 = 0.5), data are consistent with no meaningful difference or appreciable harm with targeted treatment

I.1.6 Antibiotic route of administration for adults and children population

No systematic reviews or randomised controlled trials met the inclusion criteria

I.1.7 Antibiotic course length for adults and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

I.1.8 Antibiotic frequency for children

No systematic review or randomised controlled trials met the criteria for inclusion

I.2 Prevention

I.2.1 Antibiotics in adults

I.2.1.1 Prophylactic antibiotics plus antibiotic versus prophylactic antibiotics plus placebo

Table 45: GRADE profiles - Fluoroquinolone (regimen not outlined) plus oral fidaxomicin 200 mg once daily for ≤40 days versus prophylactic fluoroquinolone (regimen not outlined) and placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone (regimen not outlined) plus fidaxomicin 200 mg once daily </= 40 days	Fluoroquinolone (regimen not outlined) plus placebo	Relative (95% CI)	Absolute		
Prophylaxis failure 30 days after end of treatment (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests for CDI)												

1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	86/301 (28.6%)	92/299 (30.8%)	RR 0.93 (0.73 to 1.19)[4]	22 fewer per 1000 (from 83 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
Secondary time point: Confirmed CDI 60 days after end of treatment (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests for CDI)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	106/301 (35.2%)	107/299 (35.8%)	RR 0.98 (0.79 to 1.22)[4]	7 fewer per 1000 (from 75 fewer to 79 more)	⊕⊕⊕O MODERATE	CRITICAL
Secondary time point: Confirmed CDI 70 days after start of treatment (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests for CDI)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	88/301 (29.2%)	93/299 (31.1%)	RR 0.94 (0.74 to 1.20)[4]	19 fewer per 1000 (from 81 fewer to 62 more)	⊕⊕OO LOW	CRITICAL
Prophylaxis failure: Confirmed CDI at 30 days (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests for CDI)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	13/301 (4.3%)	32/299 (10.7%)	RR 0.40 (0.22 to 0.75)[4]	64 fewer per 1000 (from 27 fewer to 83 fewer)	⊕⊕OO LOW	CRITICAL
Sensitivity analysis: Confirmed diarrhoea associated with CDI 60 days after end of treatment (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	17/301 (5.6%)	32/299 (10.7%)	RR 0.53 (0.30 to 0.93)[4]	50 fewer per 1000 (from 7 fewer to 75 fewer)	⊕⊕OO LOW	CRITICAL
Sensitivity analysis: Confirmed diarrhoea associated with CDI 70 days after the start of treatment (assessed with: >3 unformed bowel movements in 24 hours and either a positive toxin immunoassay or nucleic acid amplification tests)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	14/301 (4.7%)	32/299 (10.7%)	RR 0.43 (0.24 to 0.80)[4]	61 fewer per 1000 (from 21 fewer to 81 fewer)	⊕⊕OO LOW	CRITICAL
Secondary analysis: treatment emergent adverse events (assessed with: Number of adverse events)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	297/300 (99%)	299/300 (99.7%)	RR 0.99 (0.98 to 1.01)[4]	10 fewer per 1000 (from 20 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Secondary analysis: moderate or severe adverse events (assessed with: Number of moderate and severe adverse events)												

1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	262/300 (87.3%)	262/300 (87.3%)	RR 1.00 (0.94 to 1.06)[4]	0 fewer per 1000 (from 52 fewer to 52 more)	⊕⊕⊕O MODERATE	CRITICAL
Secondary analysis: serious adverse events (assessed with: Number of serious events)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	98/300 (32.7%)	92/300 (30.7%)	RR 1.07 (0.84 to 1.35)[4]	21 more per 1000 (from 49 fewer to 107 more)	⊕⊕OO LOW	CRITICAL
Secondary analysis: adverse events leading to death (assessed with: Number of serious events)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[6]	none	13/300 (4.3%)	14/300 (4.7%)	RR 0.93 (0.44 to 1.94)[4]	3 fewer per 1000 (from 26 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Secondary analysis: adverse events Diarrhoea (assessed with: Number of participants with diarrhoea)												
1[1]	randomised trials	very serious[7]	not applicable	no serious indirectness	serious[3]	none	18/300 (6%)	31/300 (10.3%)	RR 0.58 (0.33 to 1.01)[4]	43 fewer per 1000 (from 69 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
Secondary analysis: adverse events Vomiting (assessed with: Number of participants with vomit)												
1[1]	randomised trials	very serious[7]	not applicable	no serious indirectness	very serious[6]	none	12/300 (4%)	15/300 (5%)	RR 0.80 (0.38 to 1.68)[4]	10 fewer per 1000 (from 31 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Time to onset of confirmed diarrhoea associated with CDI (assessed with: Hazard ratio >1 favours fidaxomicin group)												
1[1]	randomised trials	very serious[8]	not applicable	no serious indirectness	serious[9]	none	Sample size: 599		Hazard Ratio 1.95, 95% CI 1.08 to 3.50, p=0.027		⊕OOO VERY LOW	CRITICAL

[1] Mullane et al 2019
[2] Downgraded 1 level - Some concerns regarding the risk of bias due to deviations from the intended interventions (effect of adhering to intervention) and some concerns regarding potential bias due to missing outcomes
[3] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm of Fluoroquinolone (regimen not outlined) plus oral fidaxomicin 200 mg once daily for ≤40 days compared prophylactic fluoroquinolone (regimen not outlined) and placebo
[4] NICE analysis
[5]Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with fluroquinolone prophylaxis and oral fidaxomicin 200 mg once daily for ≤40 days compared with fluroquinolone prophylaxis with placebo.
[6] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with Fluoroquinolone (regimen not outlined) plus oral fidaxomicin 200 mg once daily for ≤40 days compared prophylactic fluoroquinolone (regimen not outlined) and placebo
[7] Downgraded 2 levels - Some concerns regarding the risk of bias due to deviations from the intended interventions (effect of adhering to intervention), some concerns regarding potential bias due to missing outcomes and differences in data reported in the main narrative and supplementary data tables
[8]Downgraded 2 levels - Some concerns regarding the risk of bias due to deviations from the intended interventions (effect of adhering to intervention), some concerns regarding potential bias due to a lack of details within the study narrative providing details of the analysis

[9] Downgraded 1 level: at a default minimal important difference of 25% the effect estimate (Hazard ratio) is consistent with no meaningful difference or appreciable benefit with fluroquinolone prophylaxis and oral fidaxomicin 200 mg once daily for ≤40 days compared with fluroquinolone prophylaxis with placebo.

Table 46: GRADE profiles - Vancomycin 125 mg once daily whilst taking and up to 5 days post-completion of systemic antibiotics (regimens not outlined) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vancomycin	Placebo	Relative (95% CI)	Absolute		
Healthcare facility-onset CDI (assessed with: Incidence of >/=3 symptoms of loose stools or diarrhoea in a 24-hr period with positive stool test for C.Diff >72-hr into hospitalisation)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/50 (0%)	6/50 (12%)	RR 0.08 (0 to 1.33)	110 fewer per 1000 (from 120 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Community-onset healthcare facility-associated CDI after hospital discharge (follow-up 3 months; assessed with: patient-reported symptoms with CDI diagnosis by a medical provider or charted diagnosis of CDI with symptoms)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	0/50 (0%)	2/50 (4%)	RR 0.20 (0.01 to 4.06)	32 fewer per 1000 (from 40 fewer to 122 more)	⊕OOO VERY LOW	CRITICAL

[1] Johnson et al (2019)
[2] Downgraded 1 level - Some concerns regarding the risk of bias due to the application of the randomisation process with the intervention group having a higher number of participants exposed to high-risk systemic antibiotics compared to the control group; Some concerns regarding the risk of bias due to deviations from the intended interventions
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral Vancomycin (125mg once daily for up to up to 5 days post-completion of systemic antibiotics) compared to placebo for healthcare facility-onset CDI
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral Vancomycin (125mg once daily for up to up to 5 days post-completion of systemic antibiotics) compared to placebo for community-onset healthcare facility-associated CDI

I.2.1.2 Antibiotics versus placebo for prevention of recurrence of Clostridioides difficile infection

Table 47: GRADE profiles - Oral rifaximin (400 mg three times a day for 14 days reduced to 200mg three times a day for a further 14 days) plus standard care versus placebo plus standard care.

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifaximin	Placebo	Relative (95% CI)	Absolute		
CDI recurrence within 12 weeks; assessed with: CDI recurrence												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	11/69 (15.9%)	18/61 (29.5%)	RR 0.54 (0.28 to 1.05)[4]	136 fewer per 1000 (from 212 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Secondary outcomes: CDI recurrence within 6 months; assessed with: number of participant CDI recurrence												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	14/66 (21.2%)	20/61 (32.8%)	RR 0.65 (0.36 to 1.16)[4]	115 fewer per 1000 (from 210 fewer to 52 more)	⊕⊕OO LOW	CRITICAL
Recurrences resulting in re-hospitalisation within 6 months; assessed with: number of participants re-hospitalised												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	9/66 (13.6%)	8/61 (13.1%)	RR 1.04 (0.43 to 2.52)[4]	5 more per 1000 (from 75 fewer to 199 more)	⊕OOO VERY LOW	CRITICAL
Recurrent diarrhoea due to CDI (follow-up 3 months; assessed with: Number of participants with diarrhoea associated with CDI)												
1[6]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[7]	none	7/33 (21.2%)	17/35 (48.6%)	RR 0.44 (0.21 to 0.92)[4]	272 fewer per 1000 (from 39 fewer to 384 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Recurrent CDI (follow-up 3 months; assessed with: Number of participants with CDI)												
1[6]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[7]	none	5/33 (15.2%)	11/35 (31.4%)	RR 0.48 (0.19 to 1.24)[4]	163 fewer per 1000 (from 255 fewer to 75 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrent diarrhoea non-CDI confirmed (follow-up 3 months; assessed with: Number of participants with diarrhoea associated with CDI)												
1[6]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[8]	none	2/33 (3%)	6/35 (17.1%)	RR 0.35 (0.08 to 1.68)[4]	111 fewer per 1000 (from 158 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
Time to recurrent diarrhoea confirmed CDI by toxin test and self-reported diarrhoea not CDI confirmed (assessed with: Hazard ratio >1 favours fidaxomicin group)												
1[1]	randomised trials	serious[9]	not applicable	no serious indirectness	serious[10]	none	sample size: n= 68		Hazard Ratio 2.72, 95% CI 1.1 to 6.6, P=0.010		⊕⊕OO LOW	CRITICAL
Time to recurrent diarrhoea associated with CDI confirmed by toxin test (assessed with: Hazard ratio >1 favours fidaxomicin group)												
1[1]	randomised trials	serious[5]	not applicable	no serious indirectness	serious[11]	none	sample size: n= 68		Hazard Ratio 2.4, 95% CI 0.82 to 7.1, P=0.11		⊕⊕OO LOW	CRITICAL
Time to recurrent self-reported diarrhoea not CDI confirmed (assessed with: Hazard ratio >1 favours fidaxomicin group)												

1[1]	randomised trials	serious[5]	not applicable	no serious indirectness	serious[11]	none	sample size: n= 68		Hazard Ratio 3.5, 95% CI 0.08 to 1.68, P=0.13		⊕⊕OO LOW	CRITICAL
Serious adverse events at up to 28 days; assessed with: number of participants experiencing a serious adverse event												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[11]	none	12/77 (15.6%)	17/74 (23%)	RR 0.68 (0.35 to 2.65)[4]	74 fewer per 1000 (from 149 fewer to 379 more)	⊕OOO VERY LOW	CRITICAL
Non-serious adverse events at up to 28 days; assessed with: number of participants experiencing a non-serious adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[11]	none	18/77 (23.4%)	22/74 (29.7%)	RR 0.79 (0.46 to 1.34)[4]	62 fewer per 1000 (from 161 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL

[1] Major et al 2019
[2] Downgraded 2 levels - some concerns regarding risk of bias due to a lack of explanation regarding number of participants who withdrew from the study and how they are accounted for in the total numbers who provided data for the primary outcome. There are some inconsistencies in the reporting of adverse events such as death within the supplementary analysis and in the main study narrative. There is a lack of information regarding what is standard care in the control arm.
[3] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with rifaximin 400 mg three times a day for 14 days reduced to 200mg three times a day for a further 14 days) plus standard care and placebo plus standard care for CDI recurrence
[4] NICE analysis
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with rifaximin 400 mg three times a day for 14 days reduced to 200mg three times a day for a further 14 days) plus standard care and placebo plus standard care for serious events
[6] Garey et al 2011
[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with rifaximin and placebo
[8] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with rifaximin compared and placebo
[9] Downgraded 1 level - some concerns regarding potential bias due to a lack of details within the study narrative providing details of the analysis
[10] Downgraded 1 level: at a default minimal important difference of 25% the effect estimate (Hazard ratio) is consistent with no meaningful difference or appreciable benefit with rifaximin compared and placebo.
[11] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with rifaximin 400 mg three times a day for 14 days reduced to 200mg three times a day for a further 14 days) plus standard care and placebo plus standard care for non-serious events

I.2.1.3 Antibiotic versus antibiotic

No systematic review or randomised controlled trials met the criteria for inclusion

I.2.1.4 Antibiotic dose

No systematic review or randomised controlled trials met the criteria for inclusion

I.2.1.5 Antibiotic frequency

No systematic review or randomised controlled trials met the criteria for inclusion

I.2.2 Faecal microbiota transplant (FMT) in adults

No systematic review or randomised controlled trials met the criteria for inclusion

I.2.3 Bezlotoxumab in adults

Table 48: GRADE profile – Bezlotoxumab versus placebo for *Clostridium difficile* infection in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bezlotoxumab	Placebo	Relative (95% CI)	Absolute		
Initial clinical cure (follow-up 2 days; assessed with: bezlotoxumab (10mg per kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[1])												
2[2]	randomised trials[3]	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	625/781 (80%)	621/773 (80.3%)	RR 1.00 (0.88 to 1.13)[6]	0 fewer per 1000 (from 96 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	129/781 (16.5%)	206/773 (26.6%)	RR 0.62 (0.51 to 0.76)[6]	126 fewer per 1000 (from 80 fewer to 159 fewer)	⊕⊕OO LOW	CRITICAL
Time to recurrence of CDI (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	serious[10]	none	14% (95% CI 11 to 17%)	26% (95% CI 22 to 29%)	12%	-	⊕OOO VERY LOW	CRITICAL
Time to recurrence of CDI (follow-up 8 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	serious[10]	none	20% (95% CI 16 to 23%)	32% (95% CI 28 to 36%)	12%	-	⊕OOO VERY LOW	CRITICAL
Time to recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	serious[10]	none	21% (95% CI 18 to 25%)	34% (95% CI 30 to 38%)	13%	-	⊕OOO VERY LOW	CRITICAL

Recurrence of diarrhoea (assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[11])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	213/781 (27.3%)	290/773 (37.5%)	RR 0.73 (0.63 to 0.84)[6]	101 fewer per 1000 (from 60 fewer to 139 fewer)	⊕⊕OO LOW	CRITICAL
Sustained cure (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[12])												
2[2]	randomised trials[3]	serious[4]	serious[13]	no serious indirectness	serious[14]	none	496/781 (63.5%)	415/773 (53.7%)	RR 1.18 (1.01 to 1.39)[6]	97 more per 1000 (from 5 more to 209 more)	⊕OOO VERY LOW	CRITICAL
Mortality at 4 weeks (all cause) (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	very serious[15]	none	32/786 (4.1%)	32/781 (4.1%)	RR 0.99 (0.61 to 1.61)[6]	0 fewer per 1000 (from 16 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Mortality at 12 weeks (all cause) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	very serious[16]	none	56/786 (7.1%)	59/781 (7.6%)	RR 0.94 (0.66 to 1.34)[6]	5 fewer per 1000 (from 26 fewer to 26 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of CDI in those with initial clinical cure (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[1,7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	129/625 (20.6%)	206/621 (33.2%)	RR 0.62 (0.52 to 0.76)[6]	126 fewer per 1000 (from 80 fewer to 159 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (aged 65 years or over) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/390 (15.4%)	127/405 (31.4%)	RR 0.49 (0.37 to 0.65)[6]	160 fewer per 1000 (from 110 fewer to 198 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup (no CDI in past 6 months) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	75/556 (13.5%)	114/545 (20.9%)	RR 0.65 (0.5 to 0.84)[6]	73 fewer per 1000 (from 33 fewer to 105 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (1 or more episodes of CDI in the past 6 months) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	54/216 (25%)	90/219 (41.1%)	RR 0.61 (0.46 to 0.8)[6]	160 fewer per 1000 (from 82 fewer to 222 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (2 or more episodes of CDI ever) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												

2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	29/100 (29%)	53/126 (42.1%)	RR 0.68 (0.47 to 0.98)[6]	135 fewer per 1000 (from 8 fewer to 223 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (immunocompromised) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7,17])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	26/178 (14.6%)	42/153 (27.5%)	RR 0.55 (0.35 to 0.84)[6]	124 fewer per 1000 (from 44 fewer to 178 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (severe CDI: Zar score equal to or more than 2) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	13/122 (10.7%)	28/125 (22.4%)	RR 0.47 (0.26 to 0.87)[6]	119 fewer per 1000 (from 29 fewer to 166 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup (strains 027, 078 or 244) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	22/102 (21.6%)	37/115 (32.2%)	RR 0.65 (0.41 to 1.04)[6]	113 fewer per 1000 (from 190 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Subgroup (strain 027) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	21/89 (23.6%)	34/100 (34%)	RR 0.68 (0.42 to 1.08)[6]	109 fewer per 1000 (from 197 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Subgroup (participants with 1 or more risk factor) recurrence of CDI (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	serious[18]	no serious indirectness	no serious imprecision	none	100/592 (16.9%)	174/583 (29.8%)	RR 0.57 (0.46 to 0.7)[6]	128 fewer per 1000 (from 90 fewer to 161 fewer)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (subgroup - inpatient) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	73/530 (13.8%)	120/520 (23.1%)	RR 0.60 (0.46 to 0.78)[6]	92 fewer per 1000 (from 51 fewer to 125 fewer)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (subgroup - outpatient) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	56/251 (22.3%)	86/253 (34%)	RR 0.66 (0.49 to 0.87)[6]	116 fewer per 1000 (from 44 fewer to 173 fewer)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (subgroup - metronidazole) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												

2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	56/379 (14.8%)	85/374 (22.7%)	RR 0.65 (0.48 to 0.88)[6]	80 fewer per 1000 (from 27 fewer to 118 fewer)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (subgroup - vancomycin) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	67/372 (18%)	114/373 (30.6%)	RR 0.59 (0.45 to 0.77)[6]	125 fewer per 1000 (from 70 fewer to 168 fewer)	⊕⊕OO LOW	CRITICAL
Recurrence of CDI (subgroup - fidaxomicin) (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[7])												
2[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	very serious[19]	none	6/30 (20%)	7/26 (26.9%)	RR 0.75 (0.29 to 1.94)[6]	67 fewer per 1000 (from 191 fewer to 253 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - infusion specific reactions (follow-up 1 days; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9,18]	no serious indirectness	serious[20]	none	81/786 (10.3%)	59/781 (7.6%)	RR 1.36 (0.99 to 1.88)[6]	27 more per 1000 (from 1 fewer to 66 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - treatment stopped due to adverse reactions - infusion specific reactions (follow-up 1 days; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	very serious[21]	none	1/786 (0.13%)	0/781 (0%)	RR 2.98 (0.12 to 73.06)[6]	-	⊕OOO VERY LOW	CRITICAL
Adverse events - 1 or more adverse events (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	no serious imprecision	none	485/786 (61.7%)	478/781 (61.2%)	RR 1.01 (0.93 to 1.09)[6]	6 more per 1000 (from 43 fewer to 55 more)	⊕⊕OO LOW	CRITICAL
Serious adverse events (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	no serious imprecision	none	156/786 (19.8%)	167/781 (21.4%)	RR 0.93 (0.76 to 1.13)[6]	15 fewer per 1000 (from 51 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Drug related adverse events (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic[22])												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	serious[14]	none	59/786 (7.5%)	46/781 (5.9%)	RR 1.27 (0.88 to 1.85)[6]	16 more per 1000 (from 7 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Serious drug related events (follow-up 4 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												

2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	very serious[23]	none	4/786 (0.51%)[24]	2/781 (0.26%)[25]	RR 1.99 (0.37 to 10.82)[6]	3 more per 1000 (from 2 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 12 weeks; assessed with: bezlotoxumab (10 mg per Kg) plus standard-of-care antibiotic vs. placebo infusion (0.9% saline) plus standard-of-care antibiotic)												
2[2]	randomised trials[3]	serious[4]	serious[9]	no serious indirectness	no serious imprecision	none	231/786 (29.4%)	255/781 (32.7%)	RR 0.90 (0.78 to 1.04)[6]	33 fewer per 1000 (from 72 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% confidence interval; mg, milligram; Kg, Kilogram; RR, relative risk; CDI, *Clostridium difficile* infection.												

[1] No diarrhoea for 2 consecutive days after completion of standard-of-care antibiotic administered for ≤16 days.
[2] Wilcox et al 2017 (2 RCTs not reported separately).
[3] MODIFY I and MODIFY II were randomized, double-blind, placebo-controlled trials.
[4] Downgraded 1 level - there were some concerns about the quality of the RCT (allocation sequence and diagnostic detection bias).
[5] Downgraded 1 level - heterogeneity >50%, NICE meta-analysis I^2=84% using a random effects model.
[6] NICE analysis.
[7] A new episode of *C. difficile* infection after initial clinical cure of the baseline episode.
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with bezlotoxumab.
[9] Downgraded 1 level - unable to assess risk of inconsistency as individual trial numbers were not reported separately for this outcome.
[10] Downgraded 1 level - unable to assess imprecision as adequate data not reported in the study report.
[11] A new diarrhoeal episode, regardless of whether it was associated with toxigenic *C. difficile.*
[12] Initial clinical cure without recurrent infection in 12 weeks.
[13] Downgraded 1 level - heterogeneity >50%, NICE meta-analysis I^2=72% using a random effects model.
[14] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with bezlotoxumab.
[15] Downgraded 2 levels - at a minimal important difference of 0% relative risk reduction (RRR), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures.
[16] Downgraded 2 levels - at a minimal important difference of 0% relative risk reduction (RRR), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures
[17] The determination of whether a participant was immunocompromised was made on the basis of medical history or use of immunosuppressive therapy.
[18] Downgraded 1 level - this was a post hoc analysis performed by the authors, unable to assess risk of inconsistency as individual trial numbers were not reported separately for this subgroup.
[19] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with bezlotoxumab, and no meaningful difference or appreciable harm with placebo.
[20] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with bezlotoxumab.
[21] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with bezlotoxumab, and no meaningful difference or appreciable benefit with placebo.
[22] Causality of drug related adverse events was assessed by the investigator, who was unaware of the study-group assignments.
[23] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with bezlotoxumab, and no meaningful difference or appreciable benefit with placebo.
[24] Severe adverse events in this group included moderate diarrhoea in 1 participant, ventricular tachycardia in 1 participant, haematuria in 1 participant and cerebral haemorrhage with sepsis in 1 participant.
[25] Severe adverse events in the placebo arm were squamous cell carcinoma in 1 participant and pulmonary embolism in 1 participant.

I.2.4 Prebiotics in adults

Table 49: GRADE profile – Oligofructose versus placebo for prevention of diarrhoea or CDI in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oligofructose	Placebo	Relative (95% CI)	Absolute		
Diarrhoea at follow-up (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day[1])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[5]	none	56/215 (26%)	60/220 (27.3%)	RR 0.96 (0.70 to 1.30)[6]	11 fewer per 1000 (from 82 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Significant diarrhoea at follow-up (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day[1,7])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[5]	none	36/215 (16.7%)	37/220 (16.8%)	RR 1.00 (0.66 to 1.51)[6]	0 fewer per 1000 (from 57 fewer to 86 more)	⊕OOO VERY LOW	CRITICAL
Non-significant diarrhoea at follow-up (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day[1,8])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[5]	none	20/215 (9.3%)	23/220 (10.5%)	RR 0.89 (0.50 to 1.57)[6]	12 fewer per 1000 (from 52 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
***Clostridium difficile* associated diarrhoea at follow-up (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day[1])**												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[5]	none	22/215 (10.2%)	27/220 (12.3%)	RR 0.83 (0.49 to 1.42)[6]	21 fewer per 1000 (from 63 fewer to 52 more)	⊕OOO VERY LOW	CRITICAL
Significant *Clostridium difficile* associated diarrhoea at follow-up (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day[1,7])												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[5]	none	19/215 (8.8%)	21/220 (9.5%)	RR 0.93 (0.51 to 1.67)[6]	7 fewer per 1000 (from 47 fewer to 64 more)	⊕OOO VERY LOW	CRITICAL
Mortality - all cause (follow-up not specified; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[9]	none	4/215 (1.9%)	2/220 (0.91%)	RR 2.05 (0.38 to 11.06)[6, 10]	10 more per 1000 (from 6 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Median length of hospital stays (IQR) in those with significant *Clostridium difficile* associated diarrhoea (follow-up to discharge; assessed with oligofructose 12 g/ day versus placebo (sucrose 12 g/ day)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[11]	none	n=1,746 17 days (IQR 13 to 22)	n=1,738 15 days	-	-	⊕OOO VERY LOW	CRITICAL

								(IQR 11 to 18)				

Abbreviations: 95% CI, 95% confidence interval; g, grams; RR, relative risk; IQR, Interquartile range.

[1] Intervention and placebo were started on the same day as antibiotics and continued for 1 week after end of antibiotic therapy, follow-up was 1 week later.
[2] Lewis et al 2005b.
[3] Downgraded 1 level - there were some concerns regarding incomplete reporting of blinding and allocation concealment and the selection of results for reporting.
[4] Downgraded 1 level - this outcome was any episode of diarrhoea regardless of *C. difficile* positivity.
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oligofructose, and no meaningful difference or appreciable harm with placebo.
[6] NICE analysis.
[7] Significant diarrhoea was defined as at least three loose stools in a 24-hour period.
[8] Non-significant diarrhoea was defined as as one or two loose stools within a 24-hour period.
[9] Downgraded 2 levels - at a minimal important difference of 0% relative risk increase (RRI), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures.
[10] Of those who died 3 had not experienced diarrhoea, 2 had significant diarrhoea associated with Clostridium difficile and 1 had non-significant diarrhoea not associated with Clostridium difficile.
[11] Not calculable.

I.2.5 Probiotics in adults

Table 50: GRADE profile – Probiotics versus alternative prophylaxis or no treatment for *Clostridium difficile* in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Probiotics**	**Alternative prophylaxis or no treatment**	**Relative (95% CI)**	**Absolute**		
Incidence of CDAD: complete cases (assessed with probiotic versus comparator/no treatment)												
24[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/4080 (1.37%)	121/3720 (3.25%)	RR 0.40 (0.3 to 0.54)[3]	23 fewer per 1000 (from 18 fewer to 26 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of CDAD: inpatients (assessed with probiotic versus comparator/no treatment)												
19[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/3399 (1.6%)	115/3089 (3.7%)	RR 0.40 (0.29 to 0.54)[3]	22 fewer per 1000 (from 17 fewer to 26 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of CDAD: outpatients (assessed with probiotic versus comparator/no treatment)												
2[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/237 (0%)	1/225 (0.44%)	RR 0.31 (0.01 to 7.47)[3]	3 fewer per 1000 (from 4 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Incidence of CDAD: mixed settings studies (assessed with probiotic versus comparator/no treatment)												

2[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/296 (0.67%)	4/304 (1.31%)	RR 0.57 (0.12 to 2.66)[3]	5 fewer per 1000 (from 11 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Incidence of C. difficile infection (stool sample) (assessed with probiotic versus comparator/no treatment)												
13[1]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	64/506 (12.6%)	58/455 (12.7%)	RR 0.85 (0.61 to 1.17)[3]	19 fewer per 1000 (from 50 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Incidence of C. difficile infection (stool sample) inpatients (assessed with probiotic versus comparator/no treatment)												
6[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	54/330 (16.4%)	46/287 (16%)	RR 0.86 (0.60 to 1.23)[3]	22 fewer per 1000 (from 64 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
Incidence of C. difficile infection (stool sample) outpatients (assessed with probiotic versus comparator/no treatment)												
4[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/56 (5.4%)	7/56 (12.5%)	RR 0.46 (0.14 to 1.53)[3]	67 fewer per 1000 (from 108 fewer to 66 more)	⊕OOO VERY LOW	CRITICAL
Incidence of C. difficile infection (stool sample) mixed settings studies (assessed with probiotic versus comparator/no treatment)												
1[1]	randomised trials	serious[5]	not applicable	no serious indirectness	very serious[6,9]	none	3/74 (4.1%)	3/76 (3.9%)	RR 1.03 (0.21 to 4.93)	1 more per 1000 (from 31 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (assessed with probiotic versus comparator/no treatment)												
28[1]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[8]	none	620/3890 (15.9%)	677/3527 (19.2%)	RR 0.90 (0.82 to 0.98)[3]	19 fewer per 1000 (from 4 fewer to 35 fewer)	⊕⊕OO LOW	CRITICAL
Length of hospital stay (measured with probiotics versus comparator/no treatment; better indicated by lower values)												
4[1]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1746	1738	-	MD 0.17 lower (1.03 lower to 0.68 higher)[3]	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CDAD, *Clostridium difficile* associated diarrhoea; 95% CI, 95% confidence interval; RR, relative risk; MD, mean difference.												

[1] Goldenberg et al 2017.
[2] Downgraded 1 level - 7 of the 26 studies were assessed by the Cochrane assessors as at low risk of bias, and 19 were assessed as at high or unclear risk of bias.
[3] NICE analysis, I^2<50%, fixed effect model used.
[4] Downgraded 1 level - 7 of the 19 studies were assessed by the Cochrane assessors as at low risk of bias, 12 were assessed as at high or unclear risk of bias.
[5] Downgraded 1 level - none of the studies assessed by the Cochrane assessors were at low risk of bias.
[6] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with probiotic, and no meaningful difference or appreciable harm with comparator no treatment.
[7] Downgraded 1 level - none of the 13 studies was assessed by the Cochrane assessors as at low risk of bias.
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with probiotic.
[9] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with probiotics, and no meaningful difference or appreciable benefit with comparator or no treatment.

[10] Downgraded 1 level - 6 of the 28 studies were assessed by the Cochrane assessors as at low risk of bias, 22 were at high or unclear risk of bias.
[11] Downgraded 1 level - 1 of the 4 studies was assessed by the Cochrane assessors as at risk of bias, 3 were assessed as high or unclear risk of bias.

I.2.6 Probiotics in children

Table 51: GRADE profile – Probiotics versus other prophylaxis or no treatment for *Clostridium difficile* in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Other prophylaxis or no treatment	Relative (95% CI)	Absolute		
Incidence of CDAD: complete cases (assessed with probiotic versus comparator/no treatment)												
7[1,2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/689 (2.0%)	44/699 (6.3%)	RR 0.33 (0.19 to 0.59)[4]	30 fewer per 1000 (from 14 fewer to 37 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of CDAD: inpatients (assessed with probiotics versus comparator/no treatment)												
4[1,2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/389 (1.8%)	26/394 (6.6%)	RR 0.29 (0.13 to 0.62)[4]	47 fewer per 1000 (from 25 fewer to 57 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of CDAD: mixed study settings (assessed with probiotics versus comparator/no treatment)												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	7/300 (2.3%)	18/305 (5.9%)	RR 0.40 (0.17 to 0.94)[4]	43 fewer per 1000 (from 6 fewer to 59 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of C. difficile infection (stool sample) inpatients only (assessed with probiotic versus comparator/no treatment)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	34/127 (26.8%)	41/126 (32.5%)	RR 0.82 (0.56 to 1.21)[4]	59 fewer per 1000 (from 143 fewer to 68 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (assessed with probiotic versus comparator/no treatment)												
5[1,2]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/562 (0.53%)	7/573 (1.2%)	RR 0.43 (0.11 to 1.63)[4]	7 fewer per 1000 (from 11 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CDAD, Clostridium difficile associated diarrhoea; 95% CI, 95% confidence interval; RR, relative risk.												

[1] Goldenberg et al 2017.
[2] Kolodziej et al 2019.
[3] Downgraded 1 level - 4 of the 6 RCTs were assessed as at low risk of bias, 2 RCTs were assessed as at high or unclear risk of bias.
[4] NICE analysis; I^2<50%, fixed effect model used.
[5] Downgraded 1 level - 2 of the 4 studies were assessed by the Cochrane or NICE reviewers as at low risk of bias, 2 were assessed as at high or unclear risk of bias.
[6] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with

probiotics.
[7] Downgraded 1 level - 3 of the 5 RCTs were assessed by the Cochrane or NICE assessors as at low risk of bias, 2 were assessed as at high or unclear risk of bias.
[8] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with probiotic, and no meaningful difference or appreciable harm with comparator or no treatment.

I.2.7 Antibiotic route of administration for adults and children population

No systematic reviews or randomised controlled trials met the inclusion criteria

I.2.8 Antibiotic course length for adults and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

I.2.9 Antibiotic frequency for children

No systematic review or randomised controlled trials met the criteria for inclusion

Appendix J: **Studies not-prioritised**

Study reference
Al Momani, Laith A, Abughanimeh, Omar, Boonpheng, Boonphiphop et al. (2018) Fidaxomicin vs Vancomycin for the Treatment of a First Episode of Clostridium Difficile Infection: A Meta-analysis and Systematic Review. Cureus 10(6): e2778
Allen S, Wareham K, Wang D, Bradley C, Sewell B, Hutchings H, Harris W, Dhar A, Brown H, Foden A, Gravenor M, Mack D, Phillips C (2013) A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and Clostridium difficile diarrhoea in older people admitted to hospital: a multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). Health Technology Assessment 17(57)
Avadhani, Amita and Miley, Helen (2011) Probiotics for prevention of antibiotic-associated diarrhea and Clostridium difficile-associated disease in hospitalized adults--a meta-analysis. Journal of the American Academy of Nurse Practitioners 23(6): 269-74
Butler, Mary, Olson, Andrew, Drekonja, Dimitri et al. (2016) No title provided.
Cai J., Zhao C., Du Y. et al. (2018) Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. United European Gastroenterology Journal 6(2): 169-180
Chapman, Brandon C, Moore, Hunter B, Overbey, Douglas M et al. (2016) Fecal microbiota transplant in patients with Clostridium difficile infection: A systematic review. The journal of trauma and acute care surgery 81(4): 756-64
Dendukuri, Nandini, Costa, Vania, McGregor, Maurice et al. (2005) Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne 173(2): 167-70
D'Souza A L, Rajkumar C, Cooke J, Bulpitt C J (2002) Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ 324: 1361-1364
Health Quality Ontario (2016) Fecal Microbiota Therapy for Clostridium difficile Infection: A Health Technology Assessment. Ontario health technology assessment series 16(17): 1-69
Housman, Seth T, Thabit, Abrar K, Kuti, Joseph L et al. (2016) Assessment of Clostridium difficile Burden in Patients Over Time With First Episode Infection Following Fidaxomicin or Vancomycin. Infection control and hospital epidemiology 37(2): 215-8
Hsu, J, Abad, C, Dinh, M et al. (2010) Prevention of endemic healthcare-associated Clostridium difficile infection: reviewing the evidence. The American journal of gastroenterology 105(11): 2327-2340
Igarashi, Yuki, Tashiro, Sho, Enoki, Yuki et al. (2018) Oral vancomycin versus metronidazole for the treatment of Clostridioides difficile infection: Meta-analysis of randomized controlled trials. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy 24(11): 907-914
Johnston, Bradley C, Lytvyn, Lyubov, Lo, Calvin Ka-Fung et al. (2018) Microbial Preparations (Probiotics) for the Prevention of Clostridium difficile Infection in Adults and Children: An Individual Patient Data Meta-analysis of 6,851 Participants. Infection control and hospital epidemiology 39(7): 771-781
Johnston, Bradley C, Ma, Stephanie S Y, Goldenberg, Joshua Z et al. (2012) Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Annals of internal medicine 157(12): 878-88
Khan, Muhammad Y, Dirweesh, Ahmed, Khurshid, Talal et al. (2018) Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent Clostridium difficile infection: a systematic review and meta-analysis. European journal of gastroenterology & hepatology 30(11): 1309-1317
Rokkas T.; Gisbert J.P.; Gasbarrini A.; Hold G.L.; Tilg H.; Malfertheiner P.; Megraud F.; O'Morain C. (2019). A network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in recurrent Clostridium difficile infection. United European Gastroenterology Journal; 2019

Study reference
Rajkumar, C; Wilks, M; Islam, J et al (2020) Do probiotics prevent antibiotic-associated diarrhoea? Results of a multicentre randomized placebo-controlled trial. The Journal of hospital infection; 2020; vol. 105 (no. 2); 280-288
Lau C.S. and Chamberlain R.S. (2016) Probiotics are effective at preventing Clostridium difficile-associated diarrhea: A systematic review and meta-analysis. International Journal of General Medicine 9: 27-37
Li, Rui, Lu, Laichun, Lin, Yu et al. (2015) Efficacy and Safety of Metronidazole Monotherapy versus Vancomycin Monotherapy or Combination Therapy in Patients with Clostridium difficile Infection: A Systematic Review and Meta-Analysis. PloS one 10(10): e0137252
McFarland L.V. (2015) Probiotics for the primary and secondary prevention of C. difficile infections: A meta-analysis and systematic review. Antibiotics 4(2): 160-178
McFarland, L V (2015) Deciphering meta-analytic results: a mini-review of probiotics for the prevention of paediatric antibiotic-associated diarrhoea and Clostridium difficile infections. Beneficial microbes 6(2): 189-94
McFarland, Lynne V (2006) Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. The American journal of gastroenterology 101(4): 812-22
Moayyedi, Paul, Yuan, Yuhong, Baharith, Harith et al. (2017) Faecal microbiota transplantation for Clostridium difficile-associated diarrhoea: a systematic review of randomised controlled trials. The Medical journal of Australia 207(4): 166-172
Ng, Qin Xiang, Loke, Wayren, Foo, Nadine Xinhui et al. (2019) A systematic review of the use of rifaximin for Clostridium difficile infections. Anaerobe 55: 35-39
O'Horo, J C, Jindai, K, Kunzer, B et al. (2014) Treatment of recurrent Clostridium difficile infection: a systematic review. Infection 42(1): 43-59
Pattani, Reena, Palda, Valerie A, Hwang, Stephen W et al. (2013) Probiotics for the prevention of antibiotic-associated diarrhea and Clostridium difficile infection among hospitalized patients: systematic review and meta-analysis. Open medicine: a peer-reviewed, independent, open-access journal 7(2): e56-67
Pillai Anjana, Nelson Richard L (2008) Probiotics for treatment of Clostridium difficile-associated colitis in adults. Cochrane Database of Systematic Reviews: Reviews issue1
Ritchie, Marina L and Romanuk, Tamara N (2012) A meta-analysis of probiotic efficacy for gastrointestinal diseases. PloS one 7(4): e34938
Salari, Pooneh; Nikfar, Shekoufeh; Abdollahi, Mohammad (2012) A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. Inflammation & allergy drug targets 11(1): 3-14
Scheike I, Connock M, Taylor R, Fry-Smith A, Ward D (2005) Probiotics for the prevention of antibiotics associated diarrhea: a systematic review. Birmingham: West Midlands Health Technology Assessment Collaboration: 118isb0704425807
Shen, Nicole T, Maw, Anna, Tmanova, Lyubov L et al. (2017) Timely Use of Probiotics in Hospitalized Adults Prevents Clostridium difficile Infection: A Systematic Review With Meta-Regression Analysis. Gastroenterology 152(8): 1889-1900e9
Sinclair A, Xie X, Dendukuri N (2011) The use of Lactobacillus probiotics in the prevention of antibiotic associated clostridium difficile diarrhea. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC)
Sinclair, Alison, Xie, Xuanqian, Saab, Lama et al. (2016) Lactobacillus probiotics in the prevention of diarrhea associated with Clostridium difficile: a systematic review and Bayesian hierarchical meta-analysis. CMAJ open 4(4): e706-e718
Song, Hyun Joo, Kim, Jin-Yong, Jung, Sung-Ae et al. (2010) Effect of probiotic Lactobacillus (Lacidofil cap) for the prevention of antibiotic-associated diarrhea: a prospective, randomized, double-blind, multicenter study. Journal of Korean medical science 25(12): 1784-91
Sridharan K. and Sivaramakrishnan G. (2019) Which Antimicrobial Agent is Likely to be the Best for Treating Clostridium difficile Infections? A Bayesian Network Meta-Analysis of Randomized Clinical Trials. Drug Research 69(4): 194-200

Study reference
Szajewska, H and Kolodziej, M (2015) Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. Alimentary pharmacology & therapeutics 42(7): 793-801
Tariq, Raseen, Pardi, Darrell S, Bartlett, Mark G et al. (2019) Low Cure Rates in Controlled Trials of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 68(8): 1351-1358
Tung, Jennifer M; Dolovich, Lisa R; Lee, Christine H (2009) Prevention of Clostridium difficile infection with Saccharomyces boulardii: a systematic review. Canadian journal of gastroenterology = Journal canadien de gastroenterologie 23(12): 817-21
Vernaya, Marina; McAdam, Jennifer; Hampton, Michelle DeCoux (2017) Effectiveness of probiotics in reducing the incidence of Clostridium difficile-associated diarrhea in elderly patients: a systematic review. JBI database of systematic reviews and implementation reports 15(1): 140-164
Wu, Zhi-Juan; DU, Xi; Zheng, Jian (2013) Role of Lactobacillus in the prevention of Clostridium difficile-associated diarrhea: a meta-analysis of randomized controlled trials. Chinese medical journal 126(21): 4154-61
Wullt, Marlene, Johansson Hagslatt, Marie-Louise, Odenholt, Inga et al. (2007) Lactobacillus plantarum 299v enhances the concentrations of fecal short-chain fatty acids in patients with recurrent clostridium difficile-associated diarrhea. Digestive diseases and sciences 52(9): 2082-6

Appendix K: **Excluded studies**

Study reference	Reason for exclusion
Abou Chakra CN, Pepin J, Valiquette L (2012) Prediction tools for unfavourable outcomes in Clostridium difficile infection: a systematic review. PLOS ONE 7(1): e30258	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Abughanimeh, Omar, Qasrawi, Ayman, Kaddourah, Osama et al. (2018) Clostridium difficile infection in oncology patients: epidemiology, pathophysiology, risk factors, diagnosis, and treatment. Hospital practice (1995) 46(5): 266-277	Exclude study design: study was not an RCT or a SR
Abujamel, T, Cadnum, JL, Jury, LA et al. (2013) Defining the Vulnerable Period for Re-Establishment of Clostridium difficile Colonization after Treatment of C. difficile Infection with Oral Vancomycin or Metronidazole. Plos one 8(10)	Exclude outcomes: study did not report outcomes that matched our protocol
Abu-Sbeih, Hamzah; Ali, Faisal S; Wang, Yinghong (2019) Clinical Review on the Utility of Fecal Microbiota Transplantation in Immunocompromised Patients. Current gastroenterology reports 21(4): 8	Exclude study design: study was not an RCT or a SR
Agrawal, M, Aroniadis, OC, Brandt, LJ et al. (2016) The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated clostridium difficile infection in 146 elderly individuals. Journal of clinical gastroenterology 50(5): 403-407	Exclude study type: study was not an RCT or a SR
Akiyama, S.; Yamada, A.; Komaki, Y et al (2020). Efficacy and Safety of Monoclonal Antibodies Against Clostridioides difficile Toxins for Prevention of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Journal of clinical gastroenterology	Exclude duplicate: SR Studies already identified and included or excluded
Alam, Seema and Mushtaq, Mudasir (2009) Antibiotic associated diarrhea in children. Indian pediatrics 46(6): 491-6	Exclude study design: study was not an RCT or a SR
Alhifany, Abdullah A; Almutairi, Abdulaali R et al (2019). Comparing the efficacy and safety of faecal microbiota transplantation with bezlotoxumab in reducing the risk of recurrent Clostridium difficile infections: a systematic review and Bayesian network meta-analysis of randomised controlled trials. *BMJ open*, 9, 11 e031145	Exclude duplicate: SR Studies already identified and included or excluded
Al-Jashaami L.S. and DuPont H.L. (2016) Management of clostridium difficile infection. Gastroenterology and Hepatology 12(10): 609-616	Exclude study design: study was not an RCT or a SR
All Wales Medicines Strategy Group (AWMSG) (2012) Fidaxomicin (DificlirÂ®) 200 mg film-coated tablets. Penarth: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG)	Exclude study design: study was not an RCT or a SR
Allegretti, J R, Fischer, M, Papa, E et al. (2016) Fecal microbiota transplantation delivered via oral capsules achieves microbial engraftment similar to traditional delivery modalities: safety, efficacy and engraftment results from a multi-center cluster randomized dose-finding study. Gastroenterology 1: 540	Exclude study type: study was not an RCT or a SR
Allen, S J, Wareham, K, Wang, D et al. (2013) A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and Clostridium difficile diarrhoea in older	Exclude duplicate: study was identified in another journal

Study reference	Reason for exclusion
people admitted to hospital: a multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE).. Health technology assessment (Winchester, England) 17(57): 1-140	
Allen, Stephen J, Wareham, Kathie, Wang, Duolao et al. (2013) Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 382(9900): 1249-57	Exclude duplicate: study was identified in another journal
Amrane, S.; Lagier, J.-C. (2020). Fecal microbiota transplantation for antibiotic resistant bacteria decolonization Human Microbiome Journal. 16, 100071	Exclude study design: study was not an RCT or a SR
Anderson, J L; Edney, R J; Whelan, K (2012) Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. Alimentary pharmacology & therapeutics 36(6): 503-16	Exclude study design: study was not an RCT or a SR
Anjewierden S., Han Z., Foster C.B. et al. (2019) Risk factors for Clostridium difficile infection in pediatric inpatients: A meta-analysis and systematic review. Infection control and hospital epidemiology 40(4): 420-426	Exclude study design: study was not an RCT or a SR
Anonymous (2011) Fidaxomicin (Dificid) for Clostridium difficile infection. The Medical letter on drugs and therapeutics 53(1373): 73-4	Exclude study type: study was not an RCT or a SR
Anonymous. (2017) Exam 1: Timely Use of Probiotics in Hospitalized Adults Prevents Clostridium difficile Infection: A Systematic Review With Meta-Regression Analysis. Gastroenterology 152(8): e13-e14	Exclude study design: study was not an RCT or a SR
Arbel, Leor T; Hsu, Edmund; McNally, Keegan (2017) Cost-Effectiveness of Fecal Microbiota Transplantation in the Treatment of Recurrent Clostridium Difficile Infection: A Literature Review. Cureus 9(8): e1599	Exclude study design: study was not an RCT or a SR
Aziz M., Desai M., Fatima R. et al. (2019) Surotomycin (a novel cyclic lipopeptide) vs Vancomycin for treatment of Clostridioides difficile infection: A systematic review and Meta-analysis. Current clinical pharmacology	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Bagdasarian, Natasha; Rao, Krishna; Malani, Preeti N (2015) Diagnosis and treatment of Clostridium difficile in adults: a systematic review. JAMA 313(4): 398-408	Exclude study design: study was not an RCT or a SR
Babar, S; El Kurdi, B; El Iskandarani, M et al (2020). Oral vancomycin prophylaxis for the prevention of Clostridium difficile infection: A systematic review and meta-analysis. Infection control and hospital epidemiology 01-Aug	Exclude duplicate: SR Studies already identified and included or excluded
Barker, Anna K, Duster, Megan, Valentine, Susan et al. (2017) A randomized controlled trial of probiotics for Clostridium difficile infection in adults (PICO). The Journal of antimicrobial chemotherapy 72(11): 3177-3180	Exclude study type: study was not an RCT or a SR
Barreto, Tyler W and Lin, Kenneth W (2018) Clostridium difficile Infection: Prevention and Treatment. American family physician 97(3): 196-199	Exclude study design: study was not an RCT or a SR
Basu A., Prabhu V.S., Dorr M.B. et al. (2018) Bezlotoxumab is associated with a reduction in cumulative inpatient-days: Analysis	Exclude duplicate: study was identified in another journal

Study reference	Reason for exclusion
of the hospitalization data from the MODIFY I and II clinical trials. Open Forum Infectious Diseases 5(11)	
Baxter, M and Colville, A (2016) Adverse events in faecal microbiota transplant: a review of the literature. The Journal of hospital infection 92(2): 117-27	Exclude outcomes: study did not report outcomes that matched our protocol
Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P, West Midlands Research Collaborative (2012) Systematic review and meta-analysis of outcomes following emergency surgery for Clostridium difficile colitis. British Journal of Surgery 99(11): 1501-1513	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Birch T., Golan Y., Rizzardini G. et al. (2018) Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for Clostridium difficile infection. Journal of Antimicrobial Chemotherapy 73(9): 2524-2528	Exclude duplicate: study identified and included in an identified SR
Bloomfield MG, Sherwin JC, Gkrania-Klotsas E (2012) Risk factors for mortality in Clostridium difficile infection in the general hospital population: a systematic review. Journal of Hospital Infection 82(1): 1-12	Exclude outcomes: study did not report outcomes that matched our protocol
Boghossian, TA, Rashid, FJ, Thompson, W et al. (2017) Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database of Systematic Reviews	Exclude outcomes: study did not report outcomes that matched our protocol
Boix V., Fedorak R.N., Mullane K.M. et al. (2017) Primary outcomes from a phase 3, randomized, double- blind, active-controlled trial of surotomycin in subjects with Clostridium difficile infection. Open Forum Infectious Diseases 4(1): ofw275	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Bouza, E.; Aguado, J.M.; Alcala, L et al (2020). Recommendations for the diagnosis and treatment of clostridioides difficile infection: An official clinical practice guideline of the spanish society of chemotherapy (SEQ), spanish society of internal medicine (SEMI) and the working group of postoperative infection of the spanish society of anesthesia and reanimation (SEDAR). Revista Espanola de Quimioterapia, 33, 2, 151-175.	Exclude study design: study was not an RCT or a SR
Bouza, E; Cornely, O A; Ramos-Martinez, A et al (2020). Analysis of C. difficile infection-related outcomes in European participants in the bezlotoxumab MODIFY I and II trials. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology	Exclude duplicate: Sub-group/post-hoc analysis – main analysis already included
Bozzo J. and Jorquera J.I. (2017) Use of human immunoglobulins as an anti-infective treatment: the experience so far and their possible re-emerging role. Expert Review of Anti-Infective Therapy 15(6): 585-604	Exclude study design: study was not an RCT or a SR
Braun L. (2011) Antibiotics and probiotics: The evidence. Australian Journal of Pharmacy 92(1099): 48-49	Exclude study type: study was not an RCT or a SR
Brodszky V, Gulacsi L, Ludwig E, Prinz G, Banai J, Remenyi P, Strbak B, Kertesz A, Kopcsone Nemeth I, Zsoldine Urban E, Baji P, Pentek M (2013) [Antimicrobial therapy of Clostridium difficile infection. Systematic literature review and meta-analysis]. Orvosi Hetilap 154(23): 890-899	Exclude Language: study was unavailable in English

Study reference	Reason for exclusion
Brown C.C., Manis M.M., Bohm N.M. et al. (2019) Oral Vancomycin for Secondary Prophylaxis of Clostridium difficile Infection. Annals of Pharmacotherapy 53(4): 396-401	Exclude outcomes: study did not report outcomes that matched our protocol
Burke, Kristin E and Lamont, John T (2013) Fecal transplantation for recurrent Clostridium difficile infection in older adults: a review. Journal of the American Geriatrics Society 61(8): 1394-8	Exclude study design: study was not an RCT or a SR
Burton, Hannah E; Mitchell, Stephen A; Watt, Maureen (2017) A Systematic Literature Review of Economic Evaluations of Antibiotic Treatments for Clostridium difficile Infection. PharmacoEconomics 35(11): 1123-1140	Exclude study design: study was not an RCT or a SR
Butler M, Bliss D, Drekonja D, Filice G, Rector T, MacDonald R, Wilt T (2011) Effectiveness of early diagnosis, prevention, and treatment of Clostridium difficile infection.	Exclude updated: a more recent update of this study was identified and considered at full paper
Butler M, Bliss D, Drekonja D, Filice G, Rector T, MacDonald R, Wilt T (2011) Effectiveness of early diagnosis, prevention, and treatment of clostridium difficile infection. Agency for Healthcare Research and Quality (AHRQ)	Exclude duplicate: study was identified in another journal
Butler M, Olson A, Drekonja D, Shaukat A, Schwehr N, Shippee N, Wilt TJ (2016) Early diagnosis, prevention, and treatment of Clostridium difficile: update. Agency for Healthcare Research and Quality (AHRQ)	Exclude duplicate: study was identified in another journal
Butler, Mary, Bliss, Donna, Drekonja, Dimitri et al. (2011) No title provided.	Exclude duplicate: study was identified in another journal
CADTH (2013) Fecal bacteriotherapy for patients with recurrent C. difficile: clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)	Exclude study design: study was not an RCT or a SR
CADTH (2013) Probiotics for antibiotic-associated diarrhea, clostridium difficile infection and irritable bowel syndrome: a review of clinical evidence and safety. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)	Exclude study design: study was not an RCT or a SR
CADTH (2014) Fecal bacteriotherapy for adult patients with recurrent clostridium difficile infection: update of clinical, cost-effectiveness, and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH)	Exclude study design: study was not an RCT or a SR
Cammarota, Giovanni; Ianiro, Gianluca; Gasbarrini, Antonio (2014) Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. Journal of clinical gastroenterology 48(8): 693-702	Exclude study design: study was not an RCT or a SR
Campbell, Christopher T; Poisson, Margaret Oates; Hand, Elizabeth Oates (2019) An Updated Review of Clostridium difficile Treatment in Pediatrics. The journal of pediatric pharmacology and therapeutics: JPPT: the official journal of PPAG 24(2): 90-98	Exclude study design: study was not an RCT or a SR
Can, Mehmet, Besirbellioglu, Bulent Ahmet, Avci, Ismail Yasar et al. (2006) Prophylactic Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea: a prospective study. Medical science monitor: international medical journal of experimental and clinical research 12(4): pi19-22	Exclude duplicate: study considered in an identified SR
Capurso, Lucio (2019) Thirty Years of Lactobacillus rhamnosus GG: A Review. Journal of clinical gastroenterology 53suppl1: 1-s41	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Carlson, T J; Blasingame, D; Gonzales-Luna, A J; et al (2020). Clostridioides difficile ribotype 106: A systematic review of the antimicrobial susceptibility, genetics, and clinical outcomes of this common worldwide strain. Anaerobe, 62, P1021-42	Exclude duplicate: SR Studies already identified and included or excluded
Carlson, T J; Gonzales-Luna, A J (2020). Utilizing antibiotics to prevent Clostridioides difficile infection: does exposure to a risk factor decrease risk? A systematic review. The Journal of antimicrobial chemotherapy	Exclude duplicate: SR Studies already identified and included or excluded
Chahine, Elias B; Cho, Jonathan C; Worley, Marylee V (2018) Bezlotoxumab for the Prevention of Clostridium difficile Recurrence. The Consultant pharmacist: the journal of the American Society of Consultant Pharmacists 33(2): 89-97	Exclude study design: study was not an RCT or a SR
Chahine, Elias B; Sucher, Allana J; Mantei, Karelee (2014) Fidaxomicin: a novel macrolide antibiotic for Clostridium difficile infection. The Consultant pharmacist: the journal of the American Society of Consultant Pharmacists 29(9): 614-24	Exclude study design: study was not an RCT or a SR
Chapin, Ryan W, Lee, Tiffany, McCoy, Christopher et al. (2017) Bezlotoxumab: Could This be the Answer for Clostridium difficile Recurrence? The Annals of pharmacotherapy 51(9): 804-810	Exclude study design: study was not an RCT or a SR
Chatterjee, S, Kar, P, Das, T et al. (2013) Randomised placebo-controlled double blind multicentric trial on efficacy and safety of Lactobacillus acidophilus LA-5 and Bifidobacterium BB-12 for prevention of antibiotic-associated diarrhoea. Journal of the Association of Physicians of India 61(10): 708-712	Exclude outcomes: study did not report outcomes that matched our protocol
Chen, Luke F and Anderson, Deverick J (2012) Efficacy and safety of fidaxomicin compared with oral vancomycin for the treatment of adults with Clostridium difficile-associated diarrhea: data from the OPT-80-003 and OPT-80-004 studies.. Future microbiology 7(6): 677-83	Exclude study type: study was not an RCT or a SR
Cho, J M; Pardi, D S; Khanna, S (2020). Update on Treatment of Clostridioides difficile Infection. Mayo Clinic proceedings, 95, 4, 758-769	Exclude duplicate: 10 non-RCT, 2 RCT already included, 1 RCT identified separately in updated search
Cimolai, N (2020). Does oral vancomycin use necessitate therapeutic drug monitoring? Infection, 48, 2, 173-182	Exclude study design: study was not an RCT or a SR
Cocanour, Christine S (2011) Best strategies in recurrent or persistent Clostridium difficile infection. Surgical infections 12(3): 235-9	Exclude study design: study was not an RCT or a SR
Cornely, Oliver A, Crook, Derrick W, Esposito, Roberto et al. (2012) Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. The Lancet. Infectious diseases 12(4): 281-9	Exclude duplicate: study considered in an identified SR
Cornely, Oliver A, Miller, Mark A, Fantin, Bruno et al. (2013) Resolution of Clostridium difficile-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 31(19): 2493-9	Exclude outcomes: study did not report outcomes that matched our protocol
Cornely, Oliver A, Miller, Mark A, Louie, Thomas J et al. (2012) Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 55suppl2: 154-61	Exclude duplicate: study considered in an included SR

Study reference	Reason for exclusion
Cornely, Oliver A, Nathwani, Dilip, Ivanescu, Cristina et al. (2014) Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in Clostridium difficile infections: a meta-analysis and indirect treatment comparison. The Journal of antimicrobial chemotherapy 69(11): 2892-900	Exclude updated: a more recent update of this article was identified
Cornely, O A; Mullane, K M; Birch, T; et al (2020). Exploratory Evaluation of Bezlotoxumab on Outcomes Associated With Clostridioides difficile Infection in MODIFY I/II Participants With Cancer. Open forum infectious diseases, 7, 2, aa038	Exclude duplicate: Sub-group/post-hoc analysis – main analysis already included
Cornely, O A; Vehreschild, M J G T; Adomakoh, N et al (2019). Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection: EXTEND study subgroup analyses. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 38 6 1187-1194	Exclude duplicate: Sub-group/post-hoc analysis – main analysis already included
Cornely, O A; Watt, M; McCrea, C; et al (2018). Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients aged >=60 years (EXTEND): analysis of cost-effectiveness. The Journal of antimicrobial chemotherapy, 73, 9, 2529-2539	Exclude economic study
Crook, Derrick W, Walker, A Sarah, Kean, Yin et al. (2012) Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 55suppl2: 93-103	Exclude updated: a more recent update of this article was identified
Cruz M.P. (2012) Fidaxomicin (Dificid), a novel oral macrocyclic antibacterial agent for the treatment of clostridium difficile-associated diarrhea in adults. P and T 37(5): 278-281	Exclude study type: study was not an RCT or a SR
Czepiel, Jacek, Drozdz, Miroslaw, Pituch, Hanna et al. (2019) Clostridium difficile infection: review. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 38(7): 1211-1221	Exclude study design: study was not an RCT or a SR
Czerucka, D; Piche, T; Rampal, P (2007) Review article: yeast as probiotics -- Saccharomyces boulardii.. Alimentary pharmacology & therapeutics 26(6): 767-78	Exclude study design: study was not an RCT or a SR
Daley, P, Louie, T, Lutz, J E et al. (2017) Surotomycin versus vancomycin in adults with Clostridium difficile infection: primary clinical outcomes from the second pivotal, randomized, double-blind, Phase 3 trial. The Journal of antimicrobial chemotherapy 72(12): 3462-3470	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Dailey, F.E.; Turse, E.P.; Rossow, B et al (2019). Probiotics for gastrointestinal and liver diseases: An updated review of the published literature. Endocrine, Metabolic and Immune Disorders - Drug Targets, 19, 5, 549-570	Exclude study type: Not a SR or RCT
D'Aoust, Julie; Battat, Robert; Bessissow, Talat (2017) Management of inflammatory bowel disease with Clostridium difficile infection. World journal of gastroenterology 23(27): 4986-5003	Exclude study design: study was not an RCT or a SR
de Castro Soares, GG, Marinho, CH, Pitol, R et al. (2017) Sporulated Bacillus as alternative treatment for diarrhea of hospitalized adult patients under enteral nutrition: a pilot randomized controlled study. Clinical nutrition ESPEN 22: 13-18	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium

Study reference	Reason for exclusion
	difficile infection was confirmed or suspected
de Vrese, M, Kristen, H, Rautenberg, P et al. (2011) Probiotic lactobacilli and bifidobacteria in a fermented milk product with added fruit preparation reduce antibiotic associated diarrhea and Helicobacter pylori activity. Journal of dairy research 78(4): 396-403	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
De Wolfe, T J, Eggers, S, Barker, A K et al. (2018) Oral probiotic combination of Lactobacillus and Bifidobacterium alters the gastrointestinal microbiota during antibiotic treatment for Clostridium difficile infection. PloS one 13(9): e0204253	Exclude outcomes: study did not report outcomes that matched our protocol
Dendukuri N, Costa V, McGregor M, Brophy J (2005) The use of probiotics in the prevention and treatment of clostridium difficile diarrhea. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC)	Exclude duplicate: Study was included in an identified SR
Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, Hernandez AV, Donskey CJ (2013) Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. Journal of Antimicrobial Chemotherapy 68(9): 1951-1961	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Di, Xiuzhen, Bai, Nan, Zhang, Xin et al. (2015) A meta-analysis of metronidazole and vancomycin for the treatment of Clostridium difficile infection, stratified by disease severity. The Brazilian journal of infectious diseases: an official publication of the Brazilian Society of Infectious Diseases 19(4): 339-49	Exclude study design: study was not an RCT or a SR
Dietrich, CG; Kottmann, T; Alavi, M (2014) Commercially available probiotic drinks containing Lactobacillus casei DN-114001 reduce antibiotic-associated diarrhea. World journal of gastroenterology 20(42): 15837-15844	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Dingle, Kate E, Didelot, Xavier, Quan, T Phuong et al. (2017) Effects of control interventions on Clostridium difficile infection in England: an observational study. The Lancet. Infectious diseases 17(4): 411-421	Exclude study design: study was not an RCT or a SR
Diorio C., Robinson P.D., Ammann R.A. et al. (2018) Guideline for the management of clostridium difficile infection in children and adolescents with cancer and pediatric hematopoietic stem-cell transplantation recipients. Journal of Clinical Oncology 36(31): 3162-3171	Exclude study design: study was not an RCT or a SR
Dodin, M and Katz, D E (2014) Faecal microbiota transplantation for Clostridium difficile infection. International journal of clinical practice 68(3): 363-8	Exclude study design: study was not an RCT or a SR
D'Ostroph, Amanda R and So, Tsz-Yin (2017) Treatment of pediatric Clostridium difficile infection: a review on treatment efficacy and economic value. Infection and drug resistance 10: 365-375	Exclude study design: study was not an RCT or a SR
Drekonja, Dimitri M, Butler, Mary, MacDonald, Roderick et al. (2011) Comparative effectiveness of Clostridium difficile treatments: a systematic review. Annals of internal medicine 155(12): 839-47	Exclude updated: a more recent version of this SR has been identified

Study reference	Reason for exclusion
Drekonja, Dimitri, Reich, Jon, Gezahegn, Selome et al. (2014) No title provided.	Exclude study design: study was not an RCT or a SR
Drekonja, Dimitri, Reich, Jon, Gezahegn, Selome et al. (2015) Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Annals of internal medicine 162(9): 630-8	Exclude study design: study was not an RCT or a SR
Dubberke, ER, Mullane, KM, Gerding, DN et al. (2016) Clearance of vancomycin-resistant Enterococcus concomitant with administration of a microbiota-based drug targeted at recurrent Clostridium difficile infection. Open forum infectious diseases 3(3nopagination)	Exclude outcomes: study did not report outcomes that matched our protocol
Dubberke, E R; Gerding, D N; Kelly, C P et al (2020). Efficacy of Bezlotoxumab in Participants Receiving Metronidazole, Vancomycin, or Fidaxomicin for Treatment of Clostridioides (Clostridium) difficile Infection. Open forum infectious diseases 7, 6 of aa157.	Exclude study design: study was not an RCT or a SR
Duman, DG, Bor, S, Ozütemiz, O et al. (2005) Efficacy and safety of Saccharomyces boulardii in prevention of antibiotic-associated diarrhoea due to Helicobacterpylori eradication. European journal of gastroenterology & hepatology 17(12): 1357-1361	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected.
Dupont, Herbert L (2013) Diagnosis and management of Clostridium difficile infection. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 11(10): 1216-e73	Exclude study design: study was not an RCT or a SR
Eddins C. and Gray M. (2008) Are probiotic or synbiotic preparations effective for the management of Clostridium difficile-associated or radiation-induced diarrhea? Journal of Wound, Ostomy and Continence Nursing 35(1): 50-58	Exclude study design: study was not an RCT or a SR
Edwards-Marshall M. (2011) Can probiotics prevent antibiotic-or clostridium difficile-associated diarrhea in long-term care residents? Annals of Long-Term Care 19(6): 28-32	Exclude study design: study was not an RCT or a SR
Egan, G.; Robinson, P.D.; Martinez, J.P.D.; Alexander, S. et al (2019). Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: A systematic review of randomized trials. Cancer Medicine 8, 10, 4536-4546.	Exclude outcomes: study did not report outcomes that matched our protocol
Ehrhardt, Stephan, Guo, Nan, Hinz, Rebecca et al. (2016) Saccharomyces boulardii to Prevent Antibiotic-Associated Diarrhea: A Randomized, Double-Masked, Placebo-Controlled Trial. Open forum infectious diseases 3(1): ofw011	Exclude duplicate: study was identified in an included SR
Eyre, David W, Babakhani, Farah, Griffiths, David et al. (2014) Whole-genome sequencing demonstrates that fidaxomicin is superior to vancomycin for preventing reinfection and relapse of infection with Clostridium difficile. The Journal of infectious diseases 209(9): 1446-51	Exclude study type: study was not an RCT or a SR
Eze, Paul, Balsells, Evelyn, Kyaw, Moe H et al. (2017) Risk factors for Clostridium difficile infections - an overview of the evidence base and challenges in data synthesis. Journal of global health 7(1): 010417	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol

Study reference	Reason for exclusion
Feher, Csaba; Soriano, Alex; Mensa, Josep (2017) A Review of Experimental and Off-Label Therapies for Clostridium difficile Infection. Infectious diseases and therapy 6(1): 1-35	Exclude study design: study was not an RCT or a SR
Ferrada P, Velopulos CG, Sultan S, Haut ER, Johnson E, Praba-Egge A, Enniss T, Dorion H, Martin ND, Bosarge P, Rushing A, Duane TM (2014) Timing and type of surgical treatment of Clostridium difficile-associated disease: a practice management guideline from the Eastern Association for the Surgery of Trauma. Journal of Trauma and Acute Care Surgery 76(6): 1484-1493	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Forrester, Joseph D, Cai, Lawrence Z, Mbanje, Chenesa et al. (2017) Clostridium difficile infection in low- and middle-human development index countries: a systematic review. Tropical medicine & international health: TM & IH 22(10): 1223-1232	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Francavilla, R, Lionetti, E, Castellaneta, S et al. (2012) Randomised clinical trial: lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea--a double-blind study. Alimentary pharmacology & therapeutics 36(4): 363-369	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Friedman-Korn, T, Livovsky, DM, Maharshak, N et al. (2018) Fecal Transplantation for Treatment of Clostridium Difficile Infection in Elderly and Debilitated Patients. Digestive diseases and sciences 63(1): 198-203	Exclude study type: study was not an RCT or a SR
Gallo, Antonella, Passaro, Giovanna, Gasbarrini, Antonio et al. (2016) Modulation of microbiota as treatment for intestinal inflammatory disorders: An uptodate. World journal of gastroenterology 22(32): 7186-202	Exclude study design: study was not an RCT or a SR
Gao, Xing Wang, Mubasher, Mohamed, Fang, Chong Yu et al. (2010) Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea prophylaxis in adult patients. The American journal of gastroenterology 105(7): 1636-41	Exclude duplicate: study was identified in an included SR
Garey, Kevin W, Salazar, Miguel, Shah, Dhara et al. (2008) Rifamycin antibiotics for treatment of Clostridium difficile-associated diarrhea. The Annals of pharmacotherapy 42(6): 827-35	Exclude study design: study was not an RCT or a SR
Garza-Gonzalez, E; Mendoza-Olazaran, S; Morfin-Otero, R; et al (2019). Intestinal Microbiome Changes in Fecal Microbiota Transplant (FMT) vs. FMT Enriched with Lactobacillus in the Treatment of Recurrent Clostridioides difficile Infection. Canadian journal of gastroenterology & hepatology, 4549298	Exclude outcomes: Comparison of FMT modes/types are excluded
Georgieva M., Pancheva R., Rasheva N. et al. (2015) Use of the probiotic Lactobacillus reuteri DSM 17938 in the prevention of antibioticassociated infections in hospitalized bulgarian children: A randomized, controlled trial. Journal of IMAB - Annual Proceeding (Scientific Papers) 21(4): 895-900	Exclude duplicate: study was identified in an included SR
Gerding D.N., Cornely O.A., Grill S. et al. (2019) Cadazolid for the treatment of Clostridium difficile infection: results of two double-blind, placebo-controlled, non-inferiority, randomised phase 3 trials. The Lancet Infectious Diseases 19(3): 265-274	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-

Study reference	Reason for exclusion
	pharmacological interventions outlined in our protocol
Gerding D.N., Kelly C.P., Rahav G. et al. (2018) Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection in Patients at Increased Risk for Recurrence. Clinical Infectious Diseases 67(5): 649-656	Exclude duplicate: study was identified via another journal
Gerding, D N, Kelly, C P, Rahav, G et al. (2018) Bezlotoxumab for prevention of recurrent C. difficile infection in patients at increased risk for recurrence. Clinical infectious diseases 10: 10	Exclude duplicate: study was identified via another journal
Gerding, Dale N, Kelly, Ciaran P, Rahav, Galia et al. (2018) Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection in Patients at Increased Risk for Recurrence. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 67(5): 649-656	Exclude duplicate: study was identified via another journal
Golan, Y; DuPont, H L; Aldomiro, F; et al (2020). Renal Impairment, C. difficile Recurrence, and the Differential Effect of Bezlotoxumab: A Post Hoc Analysis of Pooled Data From 2 Randomized Clinical Trials. Open forum infectious diseases 7, 7 of aa248	Exclude duplicate: Sub-group/post-hoc analysis – main analysis already included
Goldenberg J.Z., Lytvyn L., Steurich J. et al. (2015) Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews 2015(12): cd004827	Exclude updated: a more recent version of this SR was identified
Goldenberg J.Z., Yap C., Lytvyn L. et al. (2017) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews 2017(12): cd006095	Exclude duplicate: study already identified
Goldenberg Joshua Z, Ma Stephanie SY, Saxton Jane D, Martzen Mark R, Vandvik Per O, Thorlund Kristian, Guyatt Gordon H, Johnston Bradley C (2013) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews: Reviews issue5	Exclude updated
Goldenberg, Joshua Z, Ma, Stephanie S Y, Saxton, Jane D et al. (2013) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. The Cochrane database of systematic reviews: cd006095	Exclude updated
Goldenberg, JZ, Yap, C, Lytvyn, L et al. (2017) Probiotics for the prevention of Clostridium difficile associated diarrhea in adults and children. Cochrane Database of Systematic Reviews	Exclude duplicate: study is considered in an identified SR
Goldstein, Ellie J C, Citron, Diane M, Sears, Pamela et al. (2011) Comparative susceptibilities to fidaxomicin (OPT-80) of isolates collected at baseline, recurrence, and failure from patients in two phase III trials of fidaxomicin against Clostridium difficile infection.. Antimicrobial agents and chemotherapy 55(11): 5194-9	Exclude outcomes: study did not report outcomes that matched our protocol
Goldstein, EJC; Citron, DM; Gerding, DN et al (2019). Bezlotoxumab for the Prevention of Recurrent Clostridioides difficile Infection: 12-Month Observational Data From the Randomized Phase III Trial, MODIFY II. Clinical infectious diseases	Exclude duplicate: Sub-group/post-hoc analysis – primary study included
Goodhand, J R; Alazawi, W; Rampton, D S (2011) Systematic review: Clostridium difficile and inflammatory bowel disease. Alimentary pharmacology & therapeutics 33(4): 428-41	Exclude study design: study was not an RCT or a SR
Gosar J.G. (2002) Saccharomyces boulardii in the prevention of pseudomembranous colitis. Journal of Pharmacy Technology 18(1): 3-8	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Gough, Ethan; Shaikh, Henna; Manges, Amee R (2011) Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 53(10): 994-1002	Exclude study design: study was not an RCT or a SR
Guo B, Harstall C, Nguyen T, Ohinmaa A (2011) Fecal transplantation for the treatment of clostridium difficile-associated disease or ulcerative colitis. Edmonton: Institute of Health Economics (IHE)	Exclude study design: study was not an RCT or a SR
Guo, B, Harstall, C, Louie, T et al. (2012) Systematic review: faecal transplantation for the treatment of Clostridium difficile-associated disease. Alimentary pharmacology & therapeutics 35(8): 865-75	Exclude study design: study was not an RCT or a SR
Guo, Q, Goldenberg, JZ, Humphrey, C et al. (2019) Probiotics for the prevention of pediatric antibiotic associated diarrhea. Cochrane Database of Systematic Reviews	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
Guery, Benoit, Menichetti, Francesco, Anttila, Veli-Jukka et al. (2018) Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. The Lancet. Infectious diseases 18(3): 296-307	Exclude duplicate: study is considered in an identified SR
Guery, B; Georgopali, A; Karas, A; K, G et al (2020). Pharmacokinetic analysis of an extended-pulsed fidaxomicin regimen for the treatment of Clostridioides (Clostridium) difficile infection in patients aged 60 years and older in the EXTEND randomized controlled trial. The Journal of antimicrobial chemotherapy, 75, 4, 1014-1018	Exclude study type: Pharmacokinetic analysis
Gurram, Br; Sue, P K (2019). Fecal microbiota transplantation in children: current concepts. Current opinion in pediatrics, 315, pp623-629	Exclude study type: Not a SR or RCT
Haber, S L; Raney, C R K; Larson, T L; et al (2019). Fecal microbiota transplantation for recurrent Clostridioides difficile infection. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists 76, 13, pp935-942	Exclude study type: Not a SR or RCT
Hamed A. and Miller A.C. (2019) Coadministration of Probiotics With Prescribed Antibiotics for Preventing Clostridium difficile Diarrhea. Academic Emergency Medicine 26(4): 454-456	Exclude study type: study was not an RCT or a SR
Hashan, M R; Elhusseiny, K M; Huu-Hoai, L; et al (2020). Effect of nitazoxanide on diarrhea: A systematic review and network meta-analysis of randomized controlled trials. Acta tropica 210, 105603	Exclude duplicate: All included studies already considered in other included SR
HAYES, Inc. (2016) Fecal microbiota transplant for refractory or recurrent Clostridium difficile infection in adults. Lansdale, PA: HAYES, Inc	Exclude could not be obtained
Health Quality Ontario (2016) Fecal microbiota therapy for clostridium difficile infection: a health technology assessment. Toronto: Health Quality Ontario	Exclude duplicate: study is considered in an identified SR
Health Quality Ontario (2016) Fecal microbiota therapy for clostridium difficile infection: OHTAC recommendation. Toronto: Health Quality Ontario	Exclude duplicate: study is considered in an identified SR

Study reference	Reason for exclusion
Henker, J, Laass, MW, Blokhin, BM et al. (2008) Probiotic Escherichia coli Nissle 1917 versus placebo for treating diarrhea of greater than 4 days duration in infants and toddlers. Pediatric infectious disease journal 27(6): 494-499	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected or Adults and children receiving antibiotic therapy for any reason.
Hickson, Mary, D'Souza, Aloysius L, Muthu, Nirmala et al. (2007) Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ (Clinical research ed.) 335(7610): 80	Exclude duplicate: study is considered in an identified SR
Hong, A.S.; Yu, W.Y.; Hong, J.M. et al (2020). Proton pump inhibitor in upper gastrointestinal fecal microbiota transplant: A systematic review and analysis. Journal of Gastroenterology and Hepatology (Australia) 35, 6, 932-940	Exclude duplicate: All included studies already considered in an identified/included SR
Hui W., Li T., Liu W. et al. (2019) Fecal microbiota transplantation for treatment of recurrent C. Difficile infection: An updated randomized controlled trial meta-analysis. PLoS ONE 14(1): e0210016	Exclude outcomes: study did not report outcomes that matched our protocol
Hull, Mark W and Beck, Paul L (2004) Clostridium difficile-associated colitis. Canadian family physician Medecin de famille canadien 50: 1536-5	Exclude study design: study was not an RCT or a SR
Hundal Rajveer, Kassam Zain, Johnstone Jennie, Lee Christine, Marshall John K (2011) Fecal transplantation for recurrent or refractory Clostridium difficile diarrhea. Cochrane Database of Systematic Reviews: Reviews issue9	Exclude study design: study was not an RCT or a SR
Ianiro G., Bibbo S., Scaldaferri F. et al. (2014) Fecal microbiota transplantation in inflammatory bowel disease: Beyond the excitement. Medicine (United States) 93(19): e97	Exclude study design: study was not an RCT or a SR
Ianiro G., Maida M., Burisch J. et al. (2018) Efficacy of different faecal microbiota transplantation protocols for Clostridium difficile infection: A systematic review and meta-analysis. United European Gastroenterology Journal 6(8): 1232-1244	Exclude study design: study was not an RCT or a SR
Ianiro G., Masucci L., Quaranta G. et al. (2018) Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection-single versus multiple infusions. Alimentary Pharmacology and Therapeutics 48(2): 152-159	Exclude outcomes: study did not report outcomes that matched our protocol
Imase, Kyoto, Takahashi, Motomichi, Tanaka, Akifumi et al. (2008) Efficacy of Clostridium butyricum preparation concomitantly with Helicobacter pylori eradication therapy in relation to changes in the intestinal microbiota. Microbiology and immunology 52(3): 156-61	Exclude outcomes: study did not report outcomes that matched our protocol
Iqbal, Umair; Anwar, Hafsa; Karim, Muhammad A (2018) Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent Clostridium difficile infection: a systematic review. European journal of gastroenterology & hepatology 30(7): 730-734	Exclude study design: study was not an RCT or a SR
Isakow, Warren; Morrow, Lee E; Kollef, Marin H (2007) Probiotics for preventing and treating nosocomial infections: review of current evidence and recommendations. Chest 132(1): 286-94	Exclude study design: study was not an RCT or a SR
Islek, Ali, Sayar, Ersin, Yilmaz, Aygen et al. (2014) The role of Bifidobacterium lactis B94 plus inulin in the treatment of acute	Exclude population: study did not consider adults and

Study reference	Reason for exclusion
infectious diarrhea in children. The Turkish journal of gastroenterology: the official journal of Turkish Society of Gastroenterology 25(6): 628-33	children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected or Adults and children receiving antibiotic therapy for any reason.
Jaber, M Raffat, Olafsson, Snorri, Fung, Wesley L et al. (2008) Clinical review of the management of fulminant clostridium difficile infection. The American journal of gastroenterology 103(12): 3195-3204	Exclude study design: study was not an RCT or a SR
Jiang, Z D, Ajami, N J, Petrosino, J F et al. (2017) Randomised clinical trial: faecal microbiota transplantation for recurrent Clostridum difficile infection - fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy.. Alimentary pharmacology & therapeutics 45(7): 899-908	Exclude outcomes: study did not report outcomes that matched our protocol
Jiang, Zhi-Dong, Jenq, Robert R, Ajami, Nadim J et al. (2018) Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: A randomized clinical trial.. PloS one 13(11): e0205064	Exclude outcomes: study did not report outcomes that matched our protocol
Jodlowski, Tomasz Z, Oehler, Richard, Kam, Linda W et al. (2006) Emerging therapies in the treatment of Clostridium difficile-associated disease. The Annals of pharmacotherapy 40(12): 2164-9	Exclude study design: study was not an RCT or a SR
John M. Eisenberg Center for Clinical Decisions and Communications Science (2007) Clostridium difficile Infections: Diagnosis, Treatment, and Prevention.	Exclude study design: study was not an RCT or a SR
Johnson, Stuart, Maziade, Pierre-Jean, McFarland, Lynne V et al. (2012) Is primary prevention of Clostridium difficile infection possible with specific probiotics? International journal of infectious diseases: IJID : official publication of the International Society for Infectious Diseases 16(11): e786-92	Exclude duplicate: study is considered in an identified SR
Johnson, Stuart, Louie, Thomas J, Gerding, Dale N et al. (2014) Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 59(3): 345-54	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Juul, FE, Garborg, K, Bretthauer, M et al. (2018) Fecal Microbiota Transplantation for Primary Clostridium difficile Infection. New England journal of medicine 378(26): 2535-2536	Exclude study type: study was not an RCT or a SR
Kao D.H., Roach B., Silva M. et al. (2018) A prospective, non-inferiority, multi-center, randomized trial comparing colonoscopy vs oral capsule delivered fecal microbiota transplantation (Fmt) for recurrent clostridium difficile infection (Rcdi). Journal of the Canadian Association of Gastroenterology 1(supplement1): 27-29	Exclude study type: study was not an RCT or a SR
Kao, D, Roach, B, Hotte, N et al. (2016) A prospective, dual center, randomized trial comparing colonoscopy versus capsule delivered fecal microbiota transplantation (FMT) in the management of recurrent clostridium difficile infection (RCDI). Canadian journal of gastroenterology and hepatology. Conference	Exclude study type: study was not an RCT or a SR

Study reference	Reason for exclusion
Kao, Dina, Roach, Brandi, Silva, Marisela et al. (2017) Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 318(20): 1985-1993	Exclude outcomes: study did not report outcomes that matched our protocol
Kassam, Zain, Lee, Christine H, Yuan, Yuhong et al. (2013) Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. The American journal of gastroenterology 108(4): 500-8	Exclude study design: study was not an RCT or a SR
Kazanowski, M, Smolarek, S, Kinnarney, F et al. (2014) Clostridium difficile: epidemiology, diagnostic and therapeutic possibilities-a systematic review. Techniques in coloproctology 18(3): 223-32	Exclude study design: study was not an RCT or a SR
Kechagias, K S; Chorepsima, S; Triarides, N A; et al (2020). Tigecycline for the treatment of patients with Clostridium difficile infection: an update of the clinical evidence. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology, 48, 2, pp152-159	Exclude study design: not an SR or RCT
Kee, Vicki R (2012) Clostridium difficile infection in older adults: a review and update on its management. The American journal of geriatric pharmacotherapy 10(1): 14-24	Exclude study design: study was not an RCT or a SR
Keller P.M. and Weber M.H. (2014) Rational therapy of Clostridium difficile infections. Viszeralmedizin: Gastrointestinal Medicine and Surgery 30(5): 304-309	Exclude study design: study was not an RCT or a SR
Kelly, Colleen R, Khoruts, Alexander, Staley, Christopher et al. (2016) Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Annals of internal medicine 165(9): 609-616	Exclude outcomes: study did not report outcomes that matched our protocol
Khanafer, N, Daneman, N, Greene, T et al. (2018) Susceptibilities of clinical Clostridium difficile isolates to antimicrobials: a systematic review and meta-analysis of studies since 1970. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 24(2): 110-117	Exclude outcomes: study did not report outcomes that matched our protocol
Khanna, S, Pardi, DS, Kelly, CR et al. (2016) A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent Clostridium difficile Infection. Journal of infectious diseases 214(2): 173-181	Exclude study type: study was not an RCT or a SR
Khorasani, S; Dossa, F; McKechnie, T et al (2020). Association Between Preoperative Oral Antibiotics and the Incidence of Postoperative Clostridium difficile Infection in Adults Undergoing Elective Colorectal Resection: A Systematic Review and Meta-analysis. Diseases of the colon and rectum 63, 4, 545-561.	Exclude duplicate: Studies in SR have been considered in identified and included SR
Killeen, S, Martin, S T, Hyland, J et al. (2014) Clostridium difficile enteritis: a new role for an old foe. The surgeon: journal of the Royal Colleges of Surgeons of Edinburgh and Ireland 12(5): 256-62	Exclude study design: study was not an RCT or a SR
Klingler, P J, Metzger, P P, Seelig, M H et al. (2000) Clostridium difficile infection: risk factors, medical and surgical management. Digestive diseases (Basel, Switzerland) 18(3): 147-60	Exclude study design: study was not an RCT or a SR
Koretz, R L (2018). Probiotics in Gastroenterology: How Pro Is the Evidence in Adults? The American journal of gastroenterology 113, 8, pp1125-1136	Exclude duplicate: Most studies included - 4 RCT that are not have been checked and are excludes

Study reference	Reason for exclusion
Kotowska, M; Albrecht, P; Szajewska, H (2005) Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. Alimentary pharmacology & therapeutics 21(5): 583-90	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Laffan, Alison M, McKenzie, Robin, Forti, Jennifer et al. (2011) Lactoferrin for the prevention of post-antibiotic diarrhoea. Journal of health, population, and nutrition 29(6): 547-51	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
Lagrotteria, Danny, Holmes, Serena, Smieja, Marek et al. (2006) Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of Clostridium difficile-associated diarrhea. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 43(5): 547-52	Exclude duplicate: study is considered in an identified SR
Lai C.Y., Sung J., Cheng F. et al. (2019) Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. Alimentary Pharmacology and Therapeutics 49(4): 354-363	Exclude study design: study was not an RCT or a SR
Lam, Simon W, Neuner, Elizabeth A, Fraser, Thomas G et al. (2018) Cost-effectiveness of three different strategies for the treatment of first recurrent Clostridium difficile infection diagnosed in a community setting. Infection control and hospital epidemiology 39(8): 924-930	Exclude study design: study was not an RCT or a SR
Lancaster, Jason W and Matthews, S James (2012) Fidaxomicin: the newest addition to the armamentarium against Clostridium difficile infections. Clinical therapeutics 34(1): 1-13	Exclude study design: study was not an RCT or a SR
Landy J., Al-Hassi H.O., McLaughlin S.D. et al. (2011) Review article: Faecal transplantation therapy for gastrointestinal disease. Alimentary Pharmacology and Therapeutics 34(4): 409-415	Exclude study design: study was not an RCT or a SR
Larson, Kelly C; Belliveau, Paul P; Spooner, Linda M (2011) Tigecycline for the treatment of severe Clostridium difficile infection. The Annals of pharmacotherapy 45(78): 1005-10	Exclude study design: study was not an RCT or a SR
Lau, V I; Rochwerg, B; Xie, F; et al (2020). Probiotics in hospitalized adult patients: a systematic review of economic evaluations. Canadian journal of anaesthesia = Journal canadien d'anesthesie, 67, 2, pp247-261	Exclude duplicate: study is considered in an identified SR
Laupland K.B. and Fisman D.N. (2011) A new paradigm for clinical trials in antibiotherapy? Canadian Journal of Infectious Diseases and Medical Microbiology 22(2): 39-42	Exclude study type: study was not an RCT or a SR
Lawrence, SJ; Korzenik, JR; Mundy, LM (2005) Probiotics for recurrent Clostridium difficile disease. Journal of medical microbiology 54(pt9): 905-906	Exclude study type: study was not an RCT or a SR
Le P., Nghiem V.T., Mullen P.D. et al. (2018) Cost-Effectiveness of Competing Treatment Strategies for Clostridium difficile Infection: A Systematic Review. Infection Control and Hospital Epidemiology 39(4): 412-424	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Lee C., Louie T.J., Weiss K. et al. (2016) Fidaxomicin versus Vancomycin in the Treatment of Clostridium difficile Infection: Canadian Outcomes. Canadian Journal of Infectious Diseases and Medical Microbiology 2016: 8048757	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Lee Y., Lim W.I., Bloom C.I. et al. (2017) Bezlotoxumab (Zinplava) for clostridium difficile infection: The first monoclonal antibody approved to prevent the recurrence of a bacterial infection. P and T 42(12): 735-738	Exclude study type: study was not an RCT or a SR
Lee, Christine H, Patino, Hernando, Stevens, Chris et al. (2016) Surotomycin versus vancomycin for Clostridium difficile infection: Phase 2, randomized, controlled, double-blind, non-inferiority, multicentre trial. The Journal of antimicrobial chemotherapy 71(10): 2964-71	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Lee, Christine H, Steiner, Theodore, Petrof, Elaine O et al. (2016) Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 315(2): 142-9	Exclude outcomes: study did not report outcomes that matched our protocol
Leong C. and Zelenitsky S. (2013) Treatment strategies for recurrent Clostridium difficile infection. Canadian Journal of Hospital Pharmacy 66(6): 361-368	Exclude study design: study was not an RCT or a SR
Li, Y-T, Cai, H-F, Wang, Z-H et al. (2016) Systematic review with meta-analysis: long-term outcomes of faecal microbiota transplantation for Clostridium difficile infection. Alimentary pharmacology & therapeutics 43(4): 445-57	Exclude study design: study was not an RCT or a SR
Lonnermark, Elisabet, Friman, Vanda, Lappas, Georg et al. (2010) Intake of Lactobacillus plantarum reduces certain gastrointestinal symptoms during treatment with antibiotics. Journal of clinical gastroenterology 44(2): 106-12	Exclude duplicate study is considered in an identified SR
Louh, Irene K, Greendyke, William G, Hermann, Emilia A et al. (2017) Clostridium Difficile Infection in Acute Care Hospitals: Systematic Review and Best Practices for Prevention. Infection control and hospital epidemiology 38(4): 476-482	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Louie T., Miller M., Donskey C. et al. (2009) Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with Clostridium difficile infection. Antimicrobial Agents and Chemotherapy 53(1): 223-228	Exclude duplicate study is considered in an identified SR
Louie, Thomas J, Cannon, Kris, Byrne, Brendan et al. (2012) Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 55suppl2: 132-42	Exclude outcomes: study did not report outcomes that matched our protocol
Louie, Thomas J, Emery, Judy, Krulicki, Walter et al. (2009) OPT-80 eliminates Clostridium difficile and is sparing of bacteroides species during treatment of C. difficile infection. Antimicrobial agents and chemotherapy 53(1): 261-3	Exclude outcomes: study did not report outcomes that matched our protocol

Study reference	Reason for exclusion
Louie, Thomas J, Miller, Mark A, Crook, Derrick W et al. (2013) Effect of age on treatment outcomes in Clostridium difficile infection. Journal of the American Geriatrics Society 61(2): 222-30	Exclude study type: study was not an RCT or a SR
Louie, Thomas J, Miller, Mark A, Mullane, Kathleen M et al. (2011) Fidaxomicin versus vancomycin for Clostridium difficile infection. The New England journal of medicine 364(5): 422-31	Exclude duplicate study is considered in an identified SR
Louie, Thomas J, Peppe, Jennifer, Watt, C Kevin et al. (2006) Tolevamer, a novel nonantibiotic polymer, compared with vancomycin in the treatment of mild to moderately severe Clostridium difficile-associated diarrhea. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 43(4): 411-20	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Louie, Thomas, Nord, Carl Erik, Talbot, George H et al. (2015) Multicenter, Double-Blind, Randomized, Phase 2 Study Evaluating the Novel Antibiotic Cadazolid in Patients with Clostridium difficile Infection. Antimicrobial agents and chemotherapy 59(10): 6266-73	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Lowy, Israel, Molrine, Deborah C, Leav, Brett A et al. (2010) Treatment with monoclonal antibodies against Clostridium difficile toxins. The New England journal of medicine 362(3): 197-205	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Lubbert, Christoph; John, Endres; von Muller, Lutz (2014) Clostridium difficile infection: guideline-based diagnosis and treatment. Deutsches Arzteblatt international 111(43): 723-31	Exclude study design: study was not an RCT or a SR
Ma, Y; Yang, J Y; Peng, X et al (2020). Which probiotic has the best effect on preventing Clostridium difficile-associated diarrhea? A systematic review and network meta-analysis. Journal of digestive diseases 21, 2, pp 69-80	Exclude duplicate: all studies already included in identified SR
Madoff, S E; Urquiaga, M; Alonso, C D; et al (2020). Prevention of recurrent Clostridioides difficile infection: A systematic review of randomized controlled trials. Anaerobe 61, 102098	Exclude duplicate: all studies already included in identified SR
Major, Giles, Bradshaw, Lucy, Boota, Nafisa et al. (2019) Follow-on RifAximin for the Prevention of recurrence following standard treatment of Infection with Clostridium Difficile (RAPID): a randomised placebo controlled trial. Gut 68(7): 1224-1231	Exclude duplicate: study is considered in an identified SR
Malnick, Stephen D H and Zimhony, Oren (2002) Treatment of Clostridium difficile-associated diarrhea. The Annals of pharmacotherapy 36(11): 1767-75	Exclude study design: study was not an RCT or a SR
Manthey, C F; Eckmann, L; Fuhrmann, V (2017) Therapy for Clostridium difficile infection - any news beyond Metronidazole and Vancomycin? Expert review of clinical pharmacology 10(11): 1239-1250	Exclude study design: study was not an RCT or a SR
Marshall, Leisa L; Peasah, Samuel; Stevens, Gregg A (2017) Clostridium difficile Infection in Older Adults: Systematic Review of Efforts to Reduce Occurrence and Improve Outcomes. The Consultant pharmacist: the journal of the American Society of Consultant Pharmacists 32(1): 24-41	Exclude study design: study was not an RCT or a SR
Mattila, Eero, Anttila, Veli-Jukka, Broas, Markku et al. (2008) A randomized, double-blind study comparing Clostridium difficile immune whey and metronidazole for recurrent Clostridium difficile-	Exclude intervention: study was not an interventional study that

Study reference	Reason for exclusion
associated diarrhoea: efficacy and safety data of a prematurely interrupted trial. Scandinavian journal of infectious diseases 40(9): 702-8	assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
McCoy, Ryan M, Klick, Andrew, Hill, Steven et al. (2016) Luminal Toxin-Binding Agents for Clostridium difficile Infection. Journal of pharmacy practice 29(4): 361-7	Exclude intervention: study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
McFarland, L V, Ship, N, Auclair, J et al. (2018) Primary prevention of Clostridium difficile infections with a specific probiotic combining Lactobacillus acidophilus, L. casei, and L. rhamnosus strains: assessing the evidence. The Journal of hospital infection 99(4): 443-452	Exclude study type: study was not an RCT or a SR
McFarland, Lynne V (2011) Emerging therapies for Clostridium difficile infections. Expert opinion on emerging drugs 16(3): 425-39	Exclude study design: study was not an RCT or a SR
McFarland, Lynne V; Elmer, Gary W; Surawicz, Christina M (2002) Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. The American journal of gastroenterology 97(7): 1769-75	Exclude study type: study was not an RCT or a SR
McFarland, Lynne Vernice, Ozen, Metehan, Dinleyici, Ener Cagri et al. (2016) Comparison of pediatric and adult antibiotic-associated diarrhea and Clostridium difficile infections. World journal of gastroenterology 22(11): 3078-104	Exclude study design: study was not an RCT or a SR
McFarland, L V, Ship, N, Auclair, J et al. (2018) Primary prevention of Clostridium difficile infections with a specific probiotic combining Lactobacillus acidophilus, L. casei, and L. rhamnosus strains: assessing the evidence. The Journal of hospital infection 99(4): 443-452	Exclude duplicate: study is considered in an identified SR
Meda, Manjula, Virgincar, Nilangi, Gentry, Victoria et al. (2019) Clostridium difficile infection in pregnant and postpartum women in 2 hospitals and a review of literature. American journal of infection control 47(1): e7-e14	Exclude study design: study was not an RCT or a SR
Mikamo, Hiroshige, Aoyama, Norihiro, Sawata, Miyuki et al. (2018) The effect of bezlotoxumab for prevention of recurrent Clostridium difficile infection (CDI) in Japanese patients. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy 24(2): 123-129	Exclude duplicate: study is considered in an identified SR
Mikamo, Hiroshige, Tateda, Kazuhiro, Yanagihara, Katsunori et al. (2018) Efficacy and safety of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in a randomized, double-blind, comparative Phase III study in Japan. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy 24(9): 744-752	Exclude duplicate: study is considered in an identified SR
Mizui, T, Teramachi, H, Tachi, T et al. (2013) Risk factors for Clostridium difficile-associated diarrhea and the effectiveness of prophylactic probiotic therapy. Die pharmazie 68(8): 706-710	Exclude study type: study was not an RCT or a SR
Moloo J. (2013) Probiotics to prevent Clostridium difficile - Associated diarrhoea. Medicine Today 14(1): 62-63	Exclude study design: study was not an RCT or a SR
Morrow, Lee E; Kollef, Marin H; Casale, Thomas B (2010) Probiotic prophylaxis of ventilator-associated pneumonia: a	Exclude population: study did not consider adults and children (aged 72 hours and

Study reference	Reason for exclusion
blinded, randomized, controlled trial. American journal of respiratory and critical care medicine 182(8): 1058-64	older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
Muhammad, A.; Madhav, D.; Rawish, F.; Viveksandeep, T.C.; Albert, E.; Mollie, J.; Prateek, S. (2019). Surotomycin (A novel cyclic lipopeptide) vs. vancomycin for the treatment of clostridioides difficile infection: A systematic review and meta-analysis. Current Clinical Pharmacology 14, 3, pp 166-174	Exclude duplicate: study was not an RCT or a SR
Muhammad, A; Simcha, W; Rawish, Fatima; S, et al (2020). Cadazolid vs Vancomycin for the Treatment of Clostridioides difficile Infection: Systematic Review with Meta-analysis. Current clinical pharmacology 15, 1, 04-Oct.	Exclude duplicate: study was not an RCT or a SR
Mullane, Kathleen M, Cornely, Oliver A, Crook, Derrick W et al. (2013) Renal impairment and clinical outcomes of Clostridium difficile infection in two randomized trials. American journal of nephrology 38(1): 1-11	Exclude study type: study was not an RCT or a SR
Mullane, KM, Adachi, J, Dubberke, E et al. (2016) Outcomes of deflect-1: a multicenter, blinded, randomized clinical trial of fidaxomicin (FDX) vs. placebo (PLC) for prophylaxis of Clostridium difficile-associated diarrhea (CDAD) in subjects undergoing hematopoietic stem cell transplantation (HSCT). Biology of blood and marrow transplantation 22(3suppl1): 171	Exclude study type: study was not an RCT or a SR
Mullane, KM, Miller, MA, Weiss, K et al. (2011) Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clinical infectious diseases 53(5): 440-447	Exclude outcomes: study did not report outcomes that matched our protocol
Mullane, Kathleen, Lee, Christine, Bressler, Adam et al. (2015) Multicenter, randomized clinical trial to compare the safety and efficacy of LFF571 and vancomycin for Clostridium difficile infections. Antimicrobial agents and chemotherapy 59(3): 1435-40	Exclude duplicate: study is considered in an identified SR
Mullane, K M; Winston, D J; Nooka, A; et al (2019). A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of Clostridium difficile-associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 68, 2, pp196-203	Exclude duplicate: study is considered in an identified SR
Murphy M.M.; Patatanian E.; Gales M.A. (2018) Extended duration vancomycin in recurrent Clostridium difficile infection: a systematic review. Therapeutic Advances in Infectious Disease 5(6): 111-119	Exclude study design: study was not an RCT or a SR
Musgrave, Caitlin R, Bookstaver, P Brandon, Sutton, S Scott et al. (2011) Use of alternative or adjuvant pharmacologic treatment strategies in the prevention and treatment of Clostridium difficile infection. International journal of infectious diseases: IJID : official publication of the International Society for Infectious Diseases 15(7): e438-48	Exclude study design: study was not an RCT or a SR
Musher, Daniel M, Logan, Nancy, Bressler, Adam M et al. (2009) Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 48(4): e41-6	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol

Study reference	Reason for exclusion
Musher, Daniel M, Logan, Nancy, Hamill, Richard J et al. (2006) Nitazoxanide for the treatment of Clostridium difficile colitis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 43(4): 421-7	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Nelson Richard L, Kelsey Philippa, Leeman Hayley, Meardon Naomi, Patel Haymesh, Paul Kim, Rees Richard, Taylor Ben, Wood Elizabeth, Malakun Rexanna (2011) Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database of Systematic Reviews: Reviews issue 9	Exclude updated: a more recent version of this SR has been identified
Nerandzic, Michelle M, Mullane, Kathleen, Miller, Mark A et al. (2012) Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 55suppl2: 121-6	Exclude outcomes: study did not report outcomes that matched our protocol
Ng, S C C, Wong, S H, Lui, R N et al. (2017) Vancomycin followed by fecal microbiota transplantation versus vancomycin for initial clostridium difficile infection: an open-label randomised controlled trial. United european gastroenterology journal 5 (5 Supplement 1): a314	Exclude study type: study was not an RCT or a SR
NIHR HSRIC (2016) Bezlotoxumab for treatment and prevention of recurrence of Clostridium difficile infection. Birmingham: NIHR Horizon Scanning Research&Intelligence Centre	Exclude study design: study was not an RCT or a SR
Noren, T, Wullt, M, Akerlund, Thomas et al. (2006) Frequent emergence of resistance in Clostridium difficile during treatment of C. difficile-associated diarrhea with fusidic acid. Antimicrobial agents and chemotherapy 50(9): 3028-32	Exclude outcomes: study did not report outcomes that matched our protocol
Nowels D. (2008) Treating C. difficile-associated diarrhea. Journal of Pain and Palliative Care Pharmacotherapy 22(2): 146-148	Exclude study type: study was not an RCT or a SR
Ofori, E, Ramai, D, Dhawan, M et al. (2018) Community-acquired Clostridium difficile: epidemiology, ribotype, risk factors, hospital and intensive care unit outcomes, and current and emerging therapies. The Journal of hospital infection 99(4): 436-442	Exclude outcomes: study did not report outcomes that matched our protocol
Ofosu, Andrew (2016) Clostridium difficile infection: a review of current and emerging therapies. Annals of gastroenterology 29(2): 147-54	Exclude study design: study was not an RCT or a SR
O'Horo, John and Safdar, Nasia (2009) The role of immunoglobulin for the treatment of Clostridium difficile infection: a systematic review. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 13(6): 663-7	Exclude study design: study was not an RCT or a SR
Okumura, H; Fukushima, A; Taieb, V; Shoji, S; English, M (2020). Fidaxomicin compared with vancomycin and metronidazole for the treatment of Clostridioides (Clostridium) difficile infection: A network meta-analysis. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy, 26, 1, pp43-50	Exclude duplicate: studies in SR are considered in an identified SR
Ooijevaar, R E, van Beurden, Y H, Terveer, E M et al. (2018) Update of treatment algorithms for Clostridium difficile infection. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 24(5): 452-462	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Otete, Eroboghene H, Ahankari, Anand S, Jones, Helen et al. (2013) Parameters for the mathematical modelling of Clostridium difficile acquisition and transmission: a systematic review. PloS one 8(12): e84224	Exclude study design: study was not an RCT or a SR
Ouwehand, Arthur C, DongLian, Cai, Weijian, Xu et al. (2014) Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. Vaccine 32(4): 458-63	Exclude duplicate: study is considered in an identified SR
Pant C., Deshpande A., Larson A. et al. (2013) Diarrhea in solid-organ transplant recipients: A review of the evidence. Current Medical Research and Opinion 29(10): 1315-1328	Exclude study design: study was not an RCT or a SR
Pant, Chaitanya, Deshpande, Abhishek, Altaf, Muhammad A et al. (2013) Clostridium difficile infection in children: a comprehensive review. Current medical research and opinion 29(8): 967-84	Exclude study design: study was not an RCT or a SR
Patro-Golab B.; Shamir R.; Szajewska H. (2015) Yogurt for treating antibiotic-associated diarrhea: Systematic review and meta-analysis. Nutrition 31(6): 796-800	Exclude outcomes: study did not report outcomes that matched our protocol
Phatharacharukul, Parkpoom, Thongprayoon, Charat, Cheungpasitporn, Wisit et al. (2015) The Risks of Incident and Recurrent Clostridium difficile-Associated Diarrhea in Chronic Kidney Disease and End-Stage Kidney Disease Patients: A Systematic Review and Meta-Analysis. Digestive diseases and sciences 60(10): 2913-22	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Pillai, A and Nelson, R (2008) Probiotics for treatment of Clostridium difficile-associated colitis in adults. The Cochrane database of systematic reviews: cd004611	Exclude updated: a more recent version of this SR has been identified
Pimentel, M, Schoenfeld, P S, Heimanson, Z et al. (2018) Rifaximin repeat treatment for diarrhea-predominant irritable bowel syndrome (IBS-D) and impact on clostridium difficile infection development. Journal of general internal medicine 33 (2 Supplement 1): 337	Exclude study type: study was not an RCT or a SR
Plummer, Sue, Weaver, Mark A, Harris, Janine C et al. (2004) Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of C. difficile diarrhoea. International microbiology: the official journal of the Spanish Society for Microbiology 7(1): 59-62	Exclude duplicate: study is considered in an identified SR
Postigo, R and Kim, J H (2012) Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: a review and pooled analysis. Infection 40(6): 643-8	Exclude study design: study was not an RCT or a SR
Pozzoni, Pietro, Riva, Alessia, Bellatorre, Alessandro Giacco et al. (2012) Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. The American journal of gastroenterology 107(6): 922-31	Exclude duplicate: study is considered in an identified SR
Prabhu, Vimalanand S, Cornely, Oliver A, Golan, Yoav et al. (2017) Thirty-Day Readmissions in Hospitalized Patients Who Received Bezlotoxumab With Antibacterial Drug Treatment for Clostridium difficile Infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 65(7): 1218-1221	Exclude duplicate: a post hoc analysis of the Wilcox study with a focus on costs
Qazi, Taha, Amaratunga, Thelina, Barnes, Edward L et al. (2017) The risk of inflammatory bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis. Gut microbes 8(6): 574-588	Exclude outcomes: study does not consider outcomes in line with the research protocol

Study reference	Reason for exclusion
Quraishi, M N, Widlak, M, Bhala, N et al. (2017) Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Alimentary pharmacology & therapeutics 46(5): 479-493	Exclude outcomes: study does not consider outcomes in line with the research protocol
Rac H., Gould A.P., Eiland L.S. et al. (2019) Common Bacterial and Viral Infections: Review of Management in the Pregnant Patient. Annals of Pharmacotherapy 53(6): 639-651	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
Ramai D.; Noorani A.; Ofosu A.; Ofori E.; Reddy M.; Gasperino J. (2019). Practice measures for controlling and preventing hospital associated Clostridium difficile infections. Hospital practice (1995); 2019	Exclude study design: narrative overview antimicrobial stewardship intervention
Ramai, D; Zakhia, K; Fields, P J et al (2020). Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Digestive diseases and sciences	Exclude outcomes: comparison of FMT modes
Rivkin, Anastasia and Gim, Suzanna (2011) Rifaximin: new therapeutic indication and future directions. Clinical therapeutics 33(7): 812-27	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected or Adults and children receiving antibiotic therapy for any reason.
Rossen, Noortje G, MacDonald, John K, de Vries, Elisabeth M et al. (2015) Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World journal of gastroenterology 21(17): 5359-71	Exclude study design: study was not an RCT or a SR
Rubio-Terres, C; Aguado, J M; Almirante, B; et al (2019). Extended-pulsed fidaxomicin versus vancomycin in patients 60 years and older with Clostridium difficile infection: cost-effectiveness analysis in Spain. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 38, 6, pp1105-1111	Exclude outcomes: cost-effectiveness
Ruszczynski, M; Radzikowski, A; Szajewska, H (2008) Clinical trial: effectiveness of Lactobacillus rhamnosus (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. Alimentary pharmacology & therapeutics 28(1): 154-61	Exclude duplicate: study is considered in an identified SR
Safdar, N, Barigala, R, Said, A et al. (2008) Feasibility and tolerability of probiotics for prevention of antibiotic-associated diarrhoea in hospitalized US military veterans. Journal of clinical pharmacy and therapeutics 33(6): 663-8	Exclude duplicate: study is considered in an identified SR
Saha, S; Tariq, R; Tosh, P K; Pardi, D S; Khanna, S (2019) Faecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 25, 8, pp958-963	Exclude duplicate: study is considered in an identified SR

Study reference	Reason for exclusion
Salavert M., Cobo J., Pascual A. et al. (2018) Cost-Effectiveness Analysis of Bezlotoxumab Added to Standard of Care Versus Standard of Care Alone for the Prevention of Recurrent Clostridium difficile Infection in High-Risk Patients in Spain. Advances in Therapy 35(11): 1920-1934	Exclude study type: study was not an RCT or a SR
Sarna K.V. and Gross A.E. (2019) Vancomycin Versus Metronidazole for Non-severe Clostridioides difficile Infection: Are the Data Adequate to Change Practice? Annals of Pharmacotherapy 53(8): 845-852	Exclude study design: study was not an RCT or a SR
Schmidt-Hieber M., Bierwirth J., Buchheidt D. et al. (2018) Diagnosis and management of gastrointestinal complications in adult cancer patients: 2017 updated evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Annals of Hematology 97(1): 31-49	Exclude study design: study was not an RCT or a SR
Siciliano, V; Nista, E Celestino; R et al (2020). Clinical Management of Infectious Diarrhea. Reviews on recent clinical trials	Exclude study type: not a SR or RCT
Sclar, David Alexander, Robison, Linda M, Oganov, Ambartsum M et al. (2012) Fidaxomicin for Clostridium difficile-associated diarrhoea: epidemiological method for estimation of warranted price. Clinical drug investigation 32(8): e17-24	Exclude outcomes: study did not report outcomes that matched our protocol
Sebastian Domingo, Juan Jose (2017) Review of the role of probiotics in gastrointestinal diseases in adults. Gastroenterologia y hepatologia 40(6): 417-429	Exclude study design: study was not an RCT or a SR
Segarra-Newnham, Marisel (2007) Probiotics for Clostridium difficile-associated diarrhea: focus on Lactobacillus rhamnosus GG and Saccharomyces boulardii. The Annals of pharmacotherapy 41(7): 1212-21	Exclude study design: study was not an RCT or a SR
Selinger, C P, Bell, A, Cairns, A et al. (2013) Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized, placebo-controlled clinical trial. The Journal of hospital infection 84(2): 159-65	Exclude duplicate study is considered in an identified SR
Seufferlein, T; Kleger, A; Nitschmann, S (2014) Recurrent Clostridium difficile infection. Treatment with duodenal infusion of donor feces. Der internist 55(4): 455-459	Exclude Language: study not available in English
Sha, S, Liang, J, Chen, M et al. (2014) Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. Alimentary pharmacology & therapeutics 39(10): 1003-32	Exclude study design: study was not an RCT or a SR
Shan, L-S, Hou, P, Wang, Z-J et al. (2013) Prevention and treatment of diarrhoea with Saccharomyces boulardii in children with acute lower respiratory tract infections. Beneficial microbes 4(4): 329-34	Exclude duplicate study is considered in an identified SR
Shen, Nicole T, Leff, Jared A, Schneider, Yecheskel et al. (2017) Cost-Effectiveness Analysis of Probiotic Use to Prevent Clostridium difficile Infection in Hospitalized Adults Receiving Antibiotics. Open forum infectious diseases 4(3): ofx148	Exclude study design: study was not an RCT or a SR
Shogbesan, Oluwaseun, Poudel, Dilli Ram, Victor, Samjeris et al. (2018) A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplant for Clostridium difficile Infection in Immunocompromised Patients. Canadian journal of gastroenterology & hepatology 2018: 1394379	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Skinner, A M; Scardina, T; Kociolek, L K (2020). Fidaxomicin for the treatment of Clostridioides difficile in children. Future microbiology	Exclude study design: study was not an RCT or a SR
Smith J.D., Roach B., Hassanzadeh Keshteli A. et al. (2018) Donor Body Mass Index (BMI) does not impact recipient BMI following fecal microbiota transplantation for recurrent clostridium difficile infection. Journal of the Canadian Association of Gastroenterology 1(supplement1): 476-478	Exclude outcomes: study did not report outcomes that matched our protocol
Sofi, Aijaz Ahmed, Silverman, Ann Lynn, Khuder, Sadik et al. (2013) Relationship of symptom duration and fecal bacteriotherapy in Clostridium difficile infection-pooled data analysis and a systematic review. Scandinavian journal of gastroenterology 48(3): 266-73	Exclude study design: study was not an RCT or a SR
Stalder, T; Kapel, N; Diaz, S et al (2020). A systematic review of economic evaluation in fecal microbiota transplantation. Infection control and hospital epidemiology, 01-Sep	Exclude outcomes: cost-effectiveness/economic
Stein, Benjamin E; Greenough, William B 3rd; Mears, Simon C (2012) Management and prevention of recurrent clostridium difficile infection in patients after total joint arthroplasty: a review. Geriatric orthopaedic surgery & rehabilitation 3(4): 157-63	Exclude study design: study was not an RCT or a SR
Stein, GY, Nanim, R, Karniel, E et al. (2007) Probiotics as prophylactic agents against antibiotic-associated diarrhea in hospitalized patients. Harefuah 146(7): 520-2, 575	Exclude Language: study not available in English
Stier H. and Bischoff S.C. (2016) Influence of saccharomyces boulardii CNCM I-745 on the gut-associated immune system. Clinical and Experimental Gastroenterology 9: 269-279	Exclude study design: study was not an RCT or a SR
Sullivan, Karyn M and Spooner, Linda M (2010) Fidaxomicin: a macrocyclic antibiotic for the management of Clostridium difficile infection. The Annals of pharmacotherapy 44(2): 352-9	Exclude study design: study was not an RCT or a SR
Surawicz, C M, McFarland, L V, Greenberg, R N et al. (2000) The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 31(4): 1012-7	Exclude study type: study was not an RCT or a SR
Surowiec, Dorothy, Kuyumjian, Arpi G, Wynd, Michael A et al. (2006) Past, present, and future therapies for Clostridium difficile-associated disease. The Annals of pharmacotherapy 40(12): 2155-63	Exclude study design: study was not an RCT or a SR
Szajewska H, Ruszczynski M, Radzikowski A (2006) Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. Journal of Pediatrics 149(3): 367-372	Exclude updated: A more recent version of this study was identified
Szajewska H.; Konarska Z.; Kolodziej M. (2016) Probiotic Bacterial and Fungal Strains: Claims with Evidence. Digestive Diseases 34(3): 251-259	Exclude study design: study was not an RCT or a SR
Szajewska, Hania, Canani, Roberto Berni, Guarino, Alfredo et al. (2016) Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. Journal of pediatric gastroenterology and nutrition 62(3): 495-506	Exclude outcomes: study did not report outcomes that matched our protocol
Tan, X; Johnson, S (2019). Fecal microbiota transplantation (FMT) for C. difficile infection, just say 'No'. Anaerobe, 60, pp1020-92	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Tang, Guihua; Yin, Wen; Liu, Wenen (2017) Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: A meta-analysis? Diagnostic microbiology and infectious disease 88(4): 322-329	Exclude study design: study was not an RCT or a SR
Tchouaket N, Eric; B, Idrissa; S, et al (2020). Economic analysis of healthcare-associated infection prevention and control interventions in medical and surgical units: Systematic review using a discounting approach. The Journal of hospital infection.	Exclude outcomes: economic
Teng, Chengwen, Reveles, Kelly R, Obodozie-Ofoegbu, Obiageri O et al. (2019) Clostridium difficile Infection Risk with Important Antibiotic Classes: An Analysis of the FDA Adverse Event Reporting System. International journal of medical sciences 16(5): 630-635	Exclude study design: study was not an RCT or a SR
Thabit, Abrar K, Alam, M Jahangir, Khaleduzzaman, Mohammed et al. (2016) A pilot study to assess bacterial and toxin reduction in patients with Clostridium difficile infection given fidaxomicin or vancomycin. Annals of clinical microbiology and antimicrobials 15: 22	Exclude outcomes: study did not report outcomes that matched our protocol
The Regional Health Technology Assessment Centre (HTA-centrum) (2009) [Probiotics in the prevention of clostridium difficile-associated colitis and antibiotic associated diarrhea in adult in-patients]. Gothenburg: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland	Exclude Language: study not available in English
Thomas, M R, Litin, S C, Osmon, D R et al. (2001) Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. Mayo Clinic proceedings 76(9): 883-9	Exclude duplicate: study is considered in an identified SR
Tobar-Marcillo, Marco, Guerrero-Duran, Maria, Avecillas-Segovia, Ariana et al. (2018) Metronidazole in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection in high-risk hospitalised patients. Gastroenterologia y hepatologia 41(6): 362-368	Exclude Language: study not available in English
Tran, Mai-Chi N; Kullar, Ravina; Goldstein, Ellie J C (2019) Investigational drug therapies currently in early-stage clinical development for the treatment of clostridioides (clostridium) difficile infection. Expert opinion on investigational drugs 28(4): 323-335	Exclude study design: study was not an RCT or a SR
Trubiano J.A., Cheng A.C., Korman T.M. et al. (2016) Australasian Society of Infectious Diseases updated guidelines for the management of Clostridium difficile infection in adults and children in Australia and New Zealand. Internal Medicine Journal 46(4): 479-493	Exclude study design: study was not an RCT or a SR
Tschudin-Sutter, S, Kuijper, E J, Durovic, A et al. (2018) Guidance document for prevention of Clostridium difficile infection in acute healthcare settings. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 24(10): 1051-1054	Exclude study design: study was not an RCT or a SR
Turner, R Brigg, Smith, Carmen B, Martello, Jay L et al. (2014) Role of doxycycline in Clostridium difficile infection acquisition. The Annals of pharmacotherapy 48(6): 772-6	Exclude study design: study was not an RCT or a SR
Van Beurden Y.H., Nieuwdorp M., Van De Berg P.J.E.J. et al. (2017) Current challenges in the treatment of severe Clostridium difficile infection: Early treatment potential of fecal microbiota	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
transplantation. Therapeutic Advances in Gastroenterology 10(4): 373-381	
Vardakas, Konstantinos Z, Polyzos, Konstantinos A, Patouni, Konstantina et al. (2012) Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. International journal of antimicrobial agents 40(1): 1-8	Exclude study design: study was not an RCT or a SR
Vehreschild M.J.G.T., Vehreschild J.J., Hubel K. et al. (2013) Diagnosis and management of gastrointestinal complications in adult cancer patients: Evidence-based guidelines of the infectious diseases working party (AGIHO) of the german society of hematology and oncology (DGHO). Annals of Oncology 24(5): 1189-1202	Exclude study design: study was not an RCT or a SR
Venuto, Charles, Butler, Mary, Ashley, Elizabeth Dodds et al. (2010) Alternative therapies for Clostridium difficile infections. Pharmacotherapy 30(12): 1266-78	Exclude study design: study was not an RCT or a SR
Vickers, Richard J, Tillotson, Glenn S, Nathan, Richard et al. (2017) Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study.. The Lancet. Infectious diseases 17(7): 735-744	Exclude study type: study was not an RCT or a SR
Videlock, E J and Cremonini, F (2012) Meta-analysis: probiotics in antibiotic-associated diarrhoea. Alimentary pharmacology & therapeutics 35(12): 1355-69	Exclude outcomes: study did not report outcomes that matched our protocol
Vincent, Yasmeen, Manji, Arif, Gregory-Miller, Kathleen et al. (2015) A Review of Management of Clostridium difficile Infection: Primary and Recurrence. Antibiotics (Basel, Switzerland) 4(4): 411-23	Exclude study design: study was not an RCT or a SR
Viswanathan, V K; Mallozzi, M J; Vedantam, Gayatri (2010) Clostridium difficile infection: An overview of the disease and its pathogenesis, epidemiology and interventions. Gut microbes 1(4): 234-242	Exclude study design: study was not an RCT or a SR
Wang, Ming-fei, Ding, Zhao, Zhao, Jian et al. (2013) Current role of surgery for the treatment of fulminant Clostridium difficile colitis. Chinese medical journal 126(5): 949-56	Exclude study design: study was not an RCT or a SR
Ward C.O. (2003) Diagnosis, Treatment, and Prevention of Clostridium difficile Colitis. Consultant Pharmacist 18(12): 1050-1054	Exclude study design: study was not an RCT or a SR
Watt, Maureen, Dinh, Aurelien, Le Monnier, Alban et al. (2017) Cost-effectiveness analysis on the use of fidaxomicin and vancomycin to treat Clostridium difficile infection in France. Journal of medical economics 20(7): 678-686	Exclude study type: study was not an RCT or a SR
Watt, Maureen, McCrea, Charles, Johal, Sukhvinder et al. (2016) A cost-effectiveness and budget impact analysis of first-line fidaxomicin for patients with Clostridium difficile infection (CDI) in Germany. Infection 44(5): 599-606	Exclude study type: study was not an RCT or a SR
Weiss K., Louie T., Miller M.A. et al. (2015) Effects of proton pump inhibitors and histamine-2 receptor antagonists on response to fidaxomicin or vancomycin in patients with Clostridium difficile-Associated diarrhea. BMJ Open Gastroenterology 2(1): e000028	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol

Study reference	Reason for exclusion
Whelan K. and Myers C.E. (2010) Safety of probiotics in patients receiving nutritional support: A systematic review of case reports, randomized controlled trials, and nonrandomized trials. American Journal of Clinical Nutrition 91(3): 687-703	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected
Whitman, Craig B and Czosnowski, Quinn A (2012) Fidaxomicin for the treatment of Clostridium difficile infections. The Annals of pharmacotherapy 46(2): 219-28	Exclude study design: study was not an RCT or a SR
Williams, O Martin and Spencer, Robert C (2009) The management of Clostridium difficile infection. British medical bulletin 91: 87-110	Exclude study design: study was not an RCT or a SR
Wong, Samford, Jamous, Ali, O'Driscoll, Jean et al. (2014) A Lactobacillus casei Shirota probiotic drink reduces antibiotic-associated diarrhoea in patients with spinal cord injuries: a randomised controlled trial. The British journal of nutrition 111(4): 672-8	Exclude duplicate: study is considered in an identified SR
Wullt, Marlene and Odenholt, Inga (2004) A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of Clostridium difficile-associated diarrhoea. The Journal of antimicrobial chemotherapy 54(1): 211-6	Exclude duplicate study is considered in an identified SR
Wullt, Marlene; Hagslatt, Marie-Louise Johansson; Odenholt, Inga (2003) Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. Scandinavian journal of infectious diseases 35(67): 365-7	Exclude outcomes: study did not report outcomes that matched our protocol
Xie X, McGregor M, Dendukuri N (2009) The use of probiotics in the prevention and treatment of clostridium difficile diarrhea: an update. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC)	Exclude study design: study was not an RCT or a SR
Xie, Chunhong, Li, Jiajing, Wang, Kejia et al. (2015) Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: a systematic review. Travel medicine and infectious disease 13(2): 128-34	Exclude study design: study was not an RCT or a SR
Yakob, Laith, Riley, Thomas V, Paterson, David L et al. (2014) Assessing control bundles for Clostridium difficile: a review and mathematical model. Emerging microbes & infections 3(6): e43	Exclude intervention study was not an interventional study that assessed antimicrobial, non-antimicrobial or non-pharmacological interventions outlined in our protocol
Yazar, AS; Güven, Ş; Dinleyici, EÇ (2016) Effects of zinc or synbiotic on the duration of diarrhea in children with acute infectious diarrhea. Turkish journal of gastroenterology 27(6): 537-540	Exclude population: study did not consider adults and children (aged 72 hours and older) with acute infectious diarrhoea where Clostridium difficile infection was confirmed or suspected or Adults and children receiving antibiotic therapy for any reason.
Yoon, Y K; Suh, J W; Kang, E; Kim, J Y (2019). Efficacy and safety of fecal microbiota transplantation for decolonization of intestinal multidrug-resistant microorganism carriage: beyond	Exclude study design: study was not an RCT or a SR

Study reference	Reason for exclusion
Clostridioides difficile infection. Annals of medicine, 51, 78, pp379-389	
Young V.B. (2016) Therapeutic manipulation of the microbiota: past, present, and considerations for the future. Clinical Microbiology and Infection 22(11): 905-909	Exclude study design: study was not an RCT or a SR
Youngster, Ilan, Sauk, Jenny, Pindar, Christina et al. (2014) Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 58(11): 1515-22	Exclude outcomes: study did not report outcomes that matched our protocol
Yuan T. and Li Z. (2018) Fecal microbiota transplantation as a treatment for gastrointestinal diseases: A systemic review and meta-analysis. Gazzetta Medica Italiana Archivio per le Scienze Mediche 177(12): 26-41	Exclude study design: study was not an RCT or a SR
Zar, Fred A, Bakkanagari, Srinivasa R, Moorthi, K M L S T et al. (2007) A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 45(3): 302-7	Exclude duplicate: study is considered in an identified SR
Zahid, Umar, Sagar, Fnu, Al Mohajer, Mayar et al. (2018) Management of Recurrent Clostridium difficile Infection During Intensive Chemotherapy and Stem Cell Transplantation for Leukemia: Case with Literature Review. Cureus 10(4): e2413	Exclude study design: study was not an RCT or a SR
Zhanel G.G.; Walkty A.J.; Karlowsky J.A. (2015) Fidaxomicin: A novel agent for the treatment of Clostridium difficile infection. Canadian Journal of Infectious Diseases and Medical Microbiology 26(6): 305-312	Exclude study design: study was not an RCT or a SR
Zhang, DM, Xu, BB, Yu, L et al. (2017) A prospective control study of Saccharomyces boulardii in prevention of antibiotic-associated diarrhea in the older inpatients. Zhonghua nei ke za zhi [Chinese journal of internal medicine] 56(6): 398-401	Exclude Language: study not available in English
Zhou, Z, Ling, N, Huang, C-W et al. (2004) Rifaximin in treatment of acute bacterial diarrhea: a randomized, single-blind and multicenter clinical trial. Chinese journal of antibiotics 29(5): 307-310	Exclude Language: study not available in English
Zuo, Tao, Wong, Sunny H, Lam, Kelvin et al. (2018) Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 67(4): 634-643	Exclude outcomes: study did not report outcomes that matched our protocol

Appendix L: **Updated NMA**

When considering the Beinortas NMA, the committee identified that, whilst all fidaxomicin dosing regimens where combined in one node in that analysis, it was reasonable to assume there may be a difference in effectiveness between a standard fidaxomicin dosing regimen (twice daily for 10 days) from an extended dosing regimen (twice daily for 5 days, then once daily every 2 days for 20 days). An updated version of the NMA was therefore run, separating out the fidaxomicin data into 2 separate nodes for these different dosing regimens.

This analysis was run as a replica of the analysis in Beinortas 2018. This has the advantage that it means we can be confident that any differences in the results obtained are solely as a result of the changes to the way the data are categorised in the analysis, rather than any changes to the method of analysis. Specifically, this means we conducted a random-effects frequentist NMA using the netmeta package in R, with vancomycin as the reference treatment. As in Beinortas 2018, homogeneity was assessed using a generalised Cochran's Q statistic, and inconsistency checked using a network heat plot and node-splitting.

Subgroup analyses were conducted based on severity of infection, and whether the infection is an initial infection or a recurrence. Due to a lack of data, it is not possible to simultaneously consider the impact of severity and initial/recurrence in a single analysis, and therefore these were considered separately. Consequently, 10 NMAs were conducted in total:

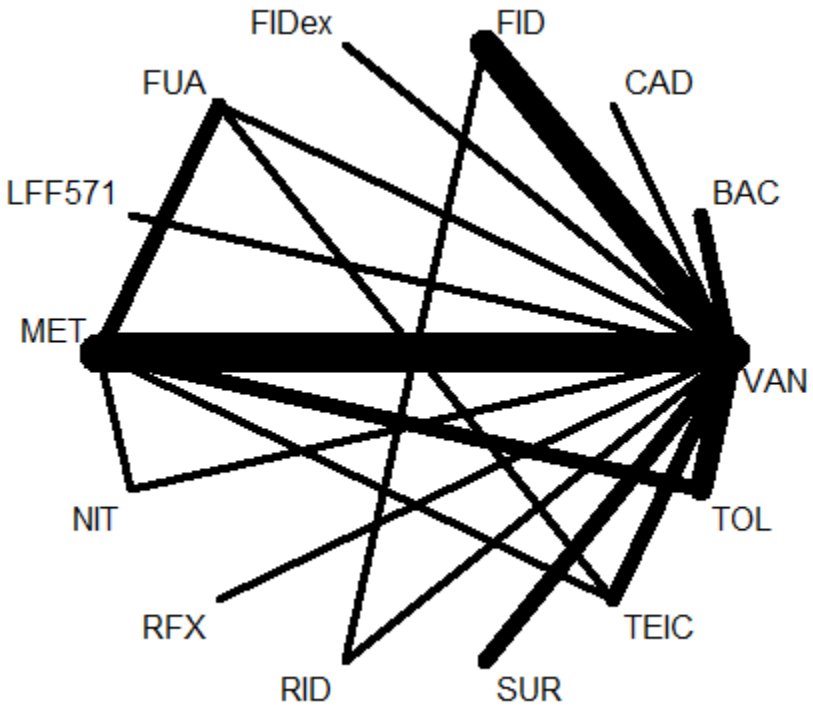
- Full population (initial cure rates and recurrence rates)
- People with a severe infection (initial cure rates and recurrence rates)
- People with a mild to moderate infection (initial cure rates and recurrence rates)
- People with an initial infection (initial cure rates and recurrence rates)
- People with a recurrence following a cured initial infection (initial cure rates and recurrence rates)

Analyses were conducted on initial cure rates and recurrence, rather than initial cure rates and sustained cure rates, as that removes the possibility of recurrence rates being higher than initial cure rates, without the need to include additional constraints to prevent this in the economic model itself. The committee were only interested in results for metronidazole, vancomycin, teicoplanin and fidaxomicin (standard and extended treatment) as these were considered the relevant options in a UK treatment context. However, all the treatments included in the Beinortas NMA were still included in this analysis, so that these extra studies can both supply additional indirect data where relevant and contribute to estimates of heterogeneity. However, full results tables are only presented for the comparators of interest.

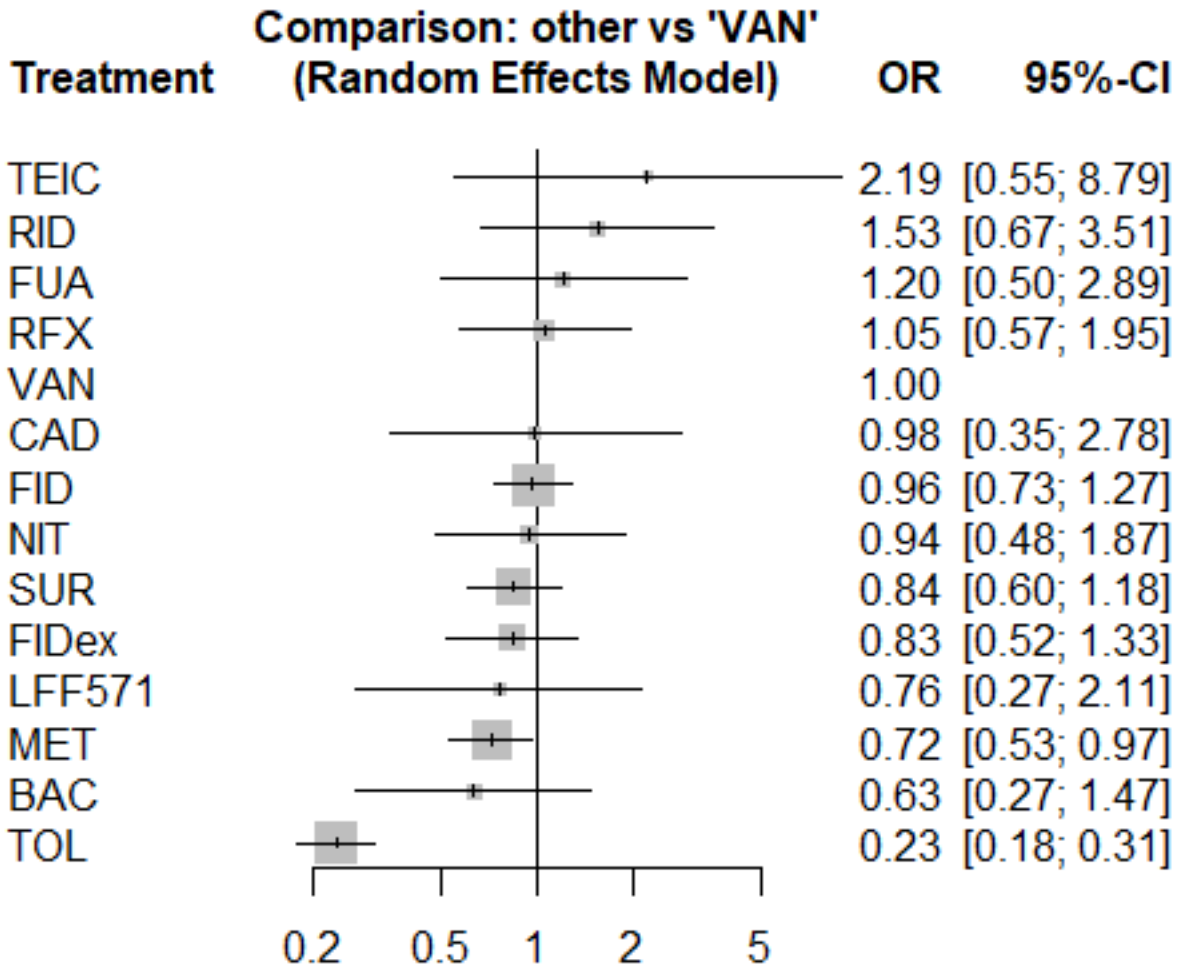
L.1 Full population

L.1.1 Initial cure

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



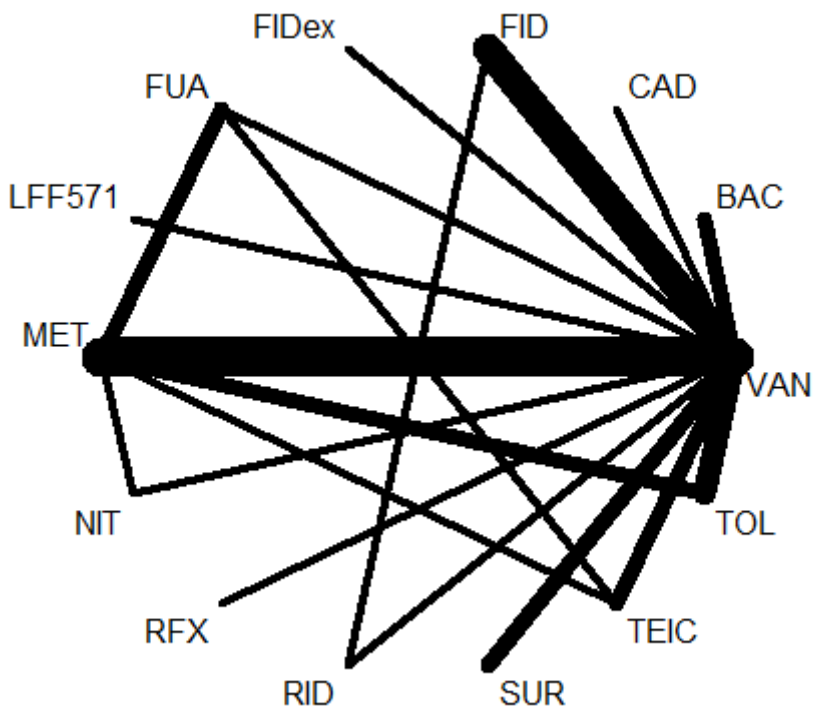
Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted.

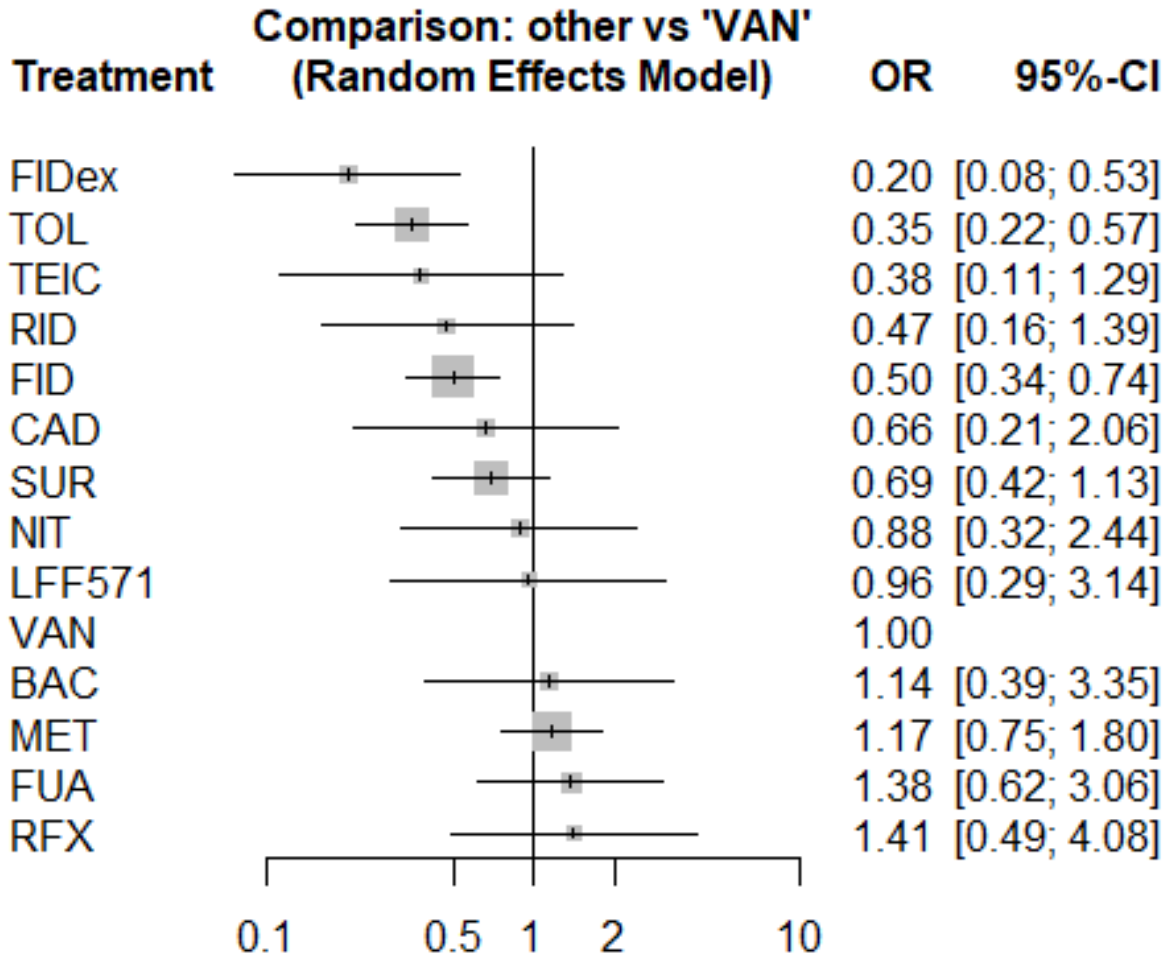
0.8655				
Teicoplanin	0.6081			
0.4560 (0.1138, 1.8274)	**Vancomycin**	0.5580		
0.4400 (0.1068, 1.8127)	0.9649 (0.7305, 1.2745)	**Fidaxomicin (standard)**	0.4214	
0.3801 (0.0879, 1.6436)	0.8336 (0.5233, 1.3279)	0.8639 (0.5022, 1.4860)	**Fidaxomicin (extended)**	0.2724
0.3267 (0.0803, 1.9423)	0.7165 (0.5309, 0.9669)	0.7425 (0.4933, 1.1178)	0.8595 (0.4940, 1.4954)	**Metronidazole**

L.1.2 Recurrence

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



Relevant pairwise comparisons from NMA

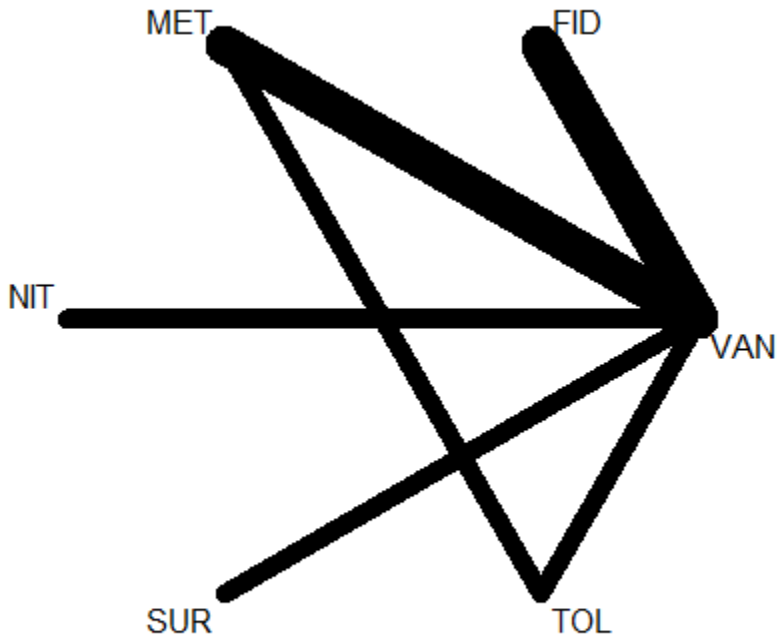
Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted.

0.9483				
Fidaxomicin (extended)	0.7640			
1.8871 (0.3945, 9.0270)	**Teicoplanin**	0.6969		
2.4883 (0.8685, 7.1285)	1.3186 (0.3641, 4.7755)	**Fidaxomicin**	0.3235	
4.9953 (1.8841, 13.2440)	2.6471 (0.7781, 9.0057)	2.0075 (1.3506, 2.9839)	**Vancomycin**	0.2339
5.8237 (2.0019, 16.9419)	3.0861 (0.8869, 10.7380)	2.3405 (1.2989, 4.2171)	1.1658 (0.7543, 1.8019)	**Metronidazole**

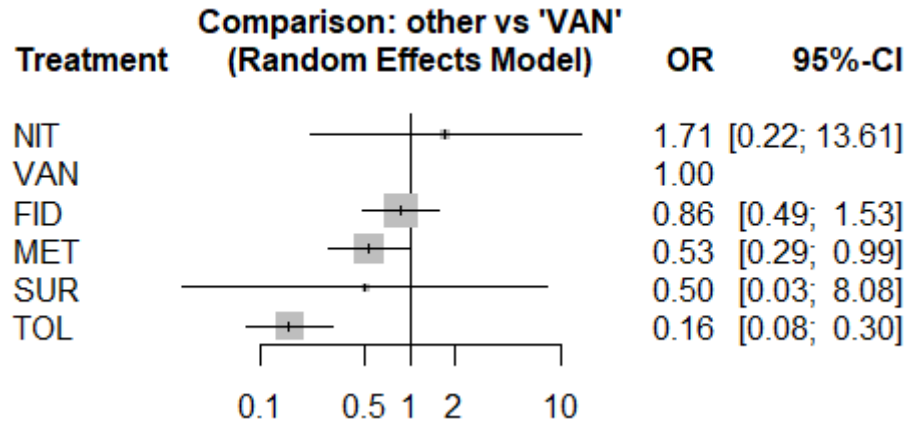
L.2 People with a severe infection

L.2.1 Initial cure

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



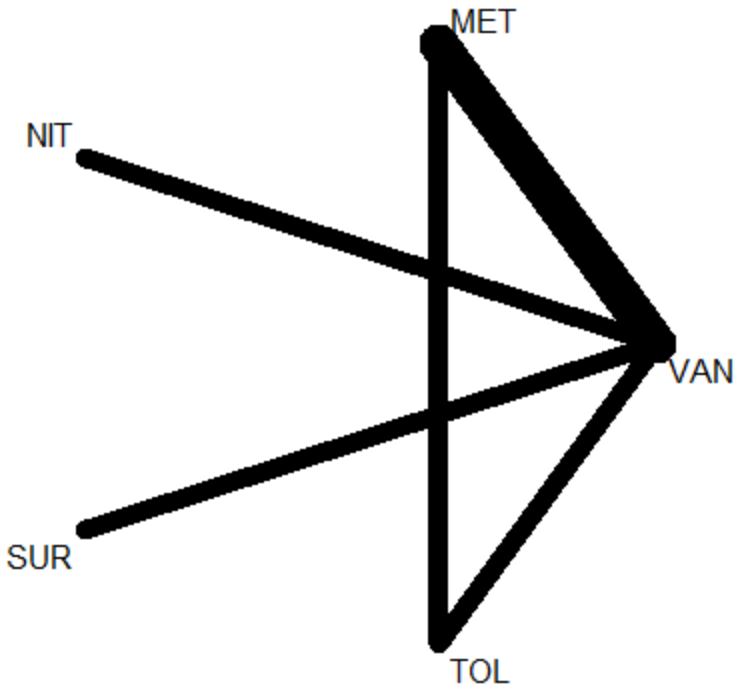
Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or an extended fidaxomicin regimen in the severe population.

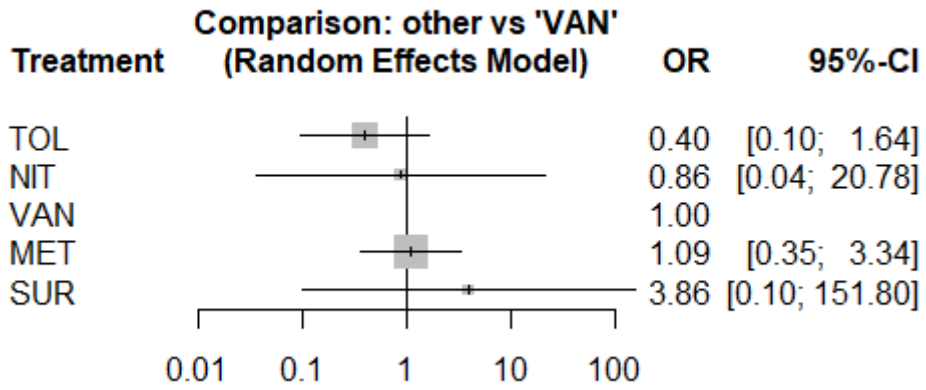
0.7327		
Vancomycin	0.6181	
0.8634 (0.4885, 1.5259)	**Fidaxomicin**	0.3623
0.5311 (0.2863 0.9853)	0.6152 (0.2655, 1.4254)	**Metronidazole**

L.2.2 Recurrence

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



Relevant pairwise comparisons from NMA

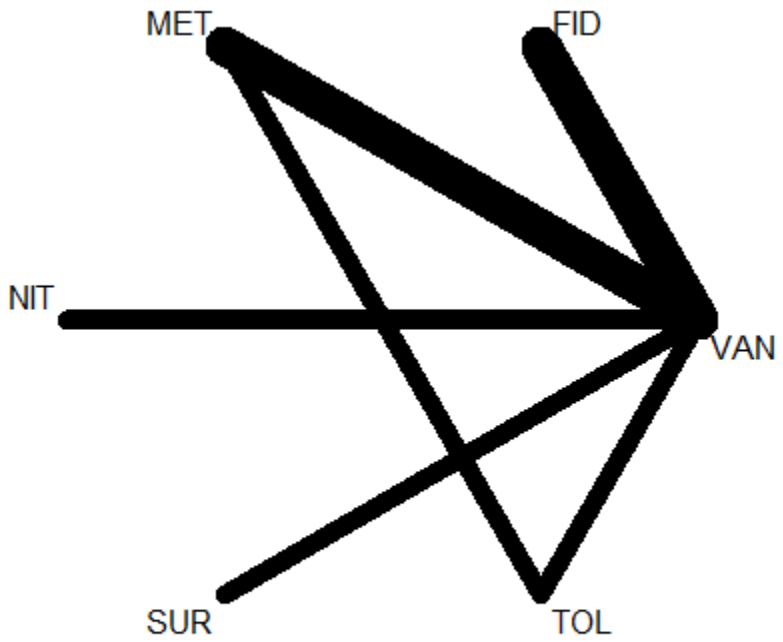
Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or fidaxomicin in the severe population.

0.4717	
Vancomycin	0.4267
1.0894 (0.3549, 3.3448)	**Metronidazole**

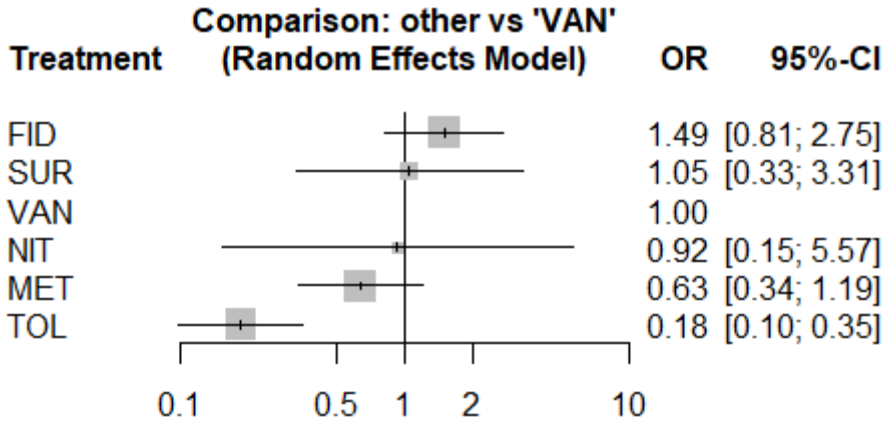
L.3 People with a mild to moderate infection

L.3.1 Initial cure

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



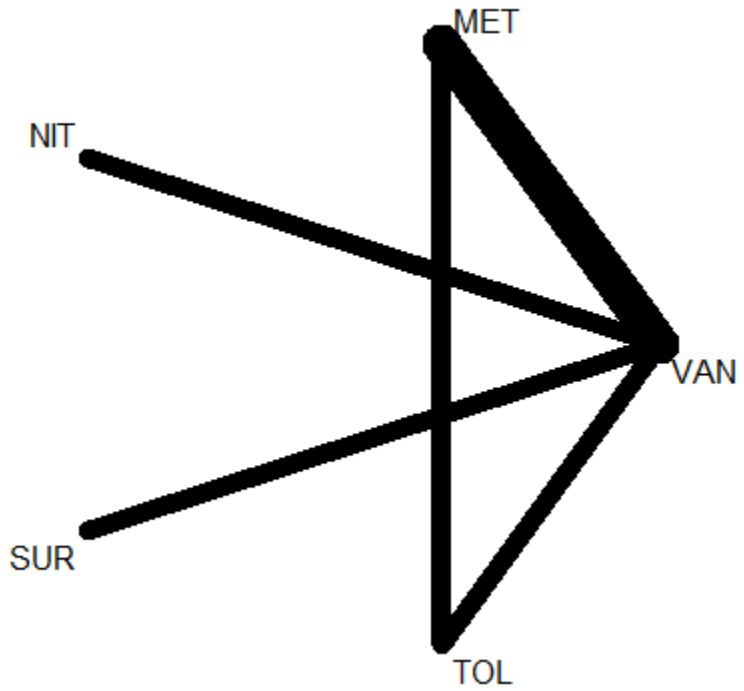
Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or an extended fidaxomicin regimen in the mild to moderate population.

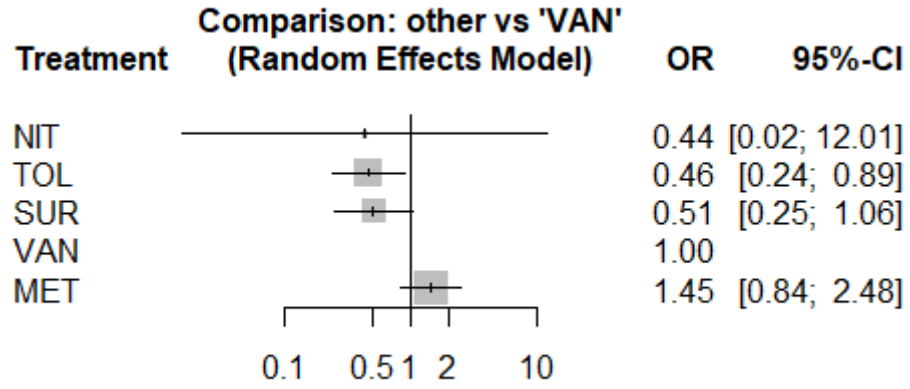
0.8520		
Fidaxomicin	0.6060	
0.6726 (0.3640, 1.2414)	**Vancomycin**	0.3361
0.4255 (0.1769, 1.0236)	0.6330 (0.3378, 1.1860)	**Metronidazole**

L.3.2 Recurrence

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



Relevant pairwise comparisons from NMA

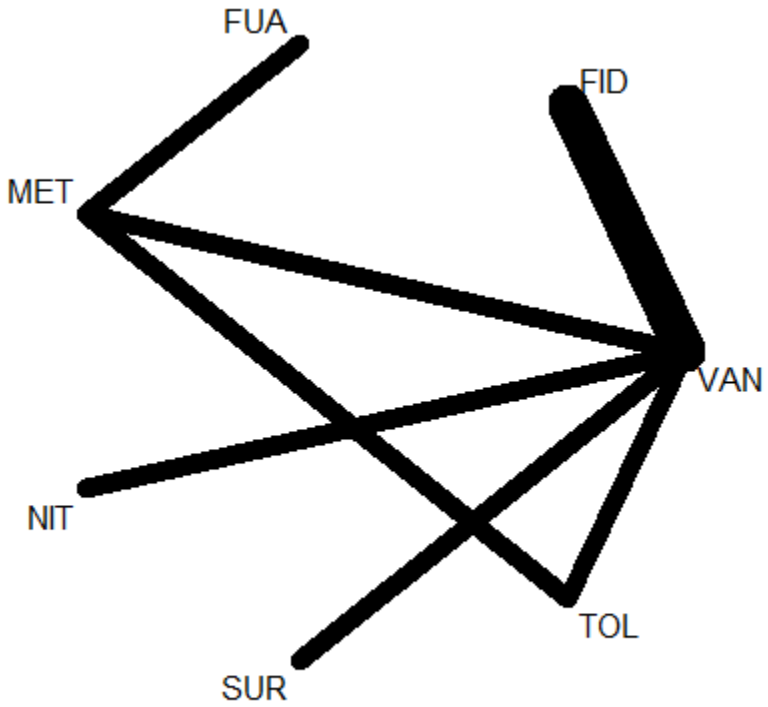
Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or fidaxomicin in the mild to moderate population.

0.3172	
Vancomycin	0.0865
1.4458 (0.8427, 2.4805)	**Metronidazole**

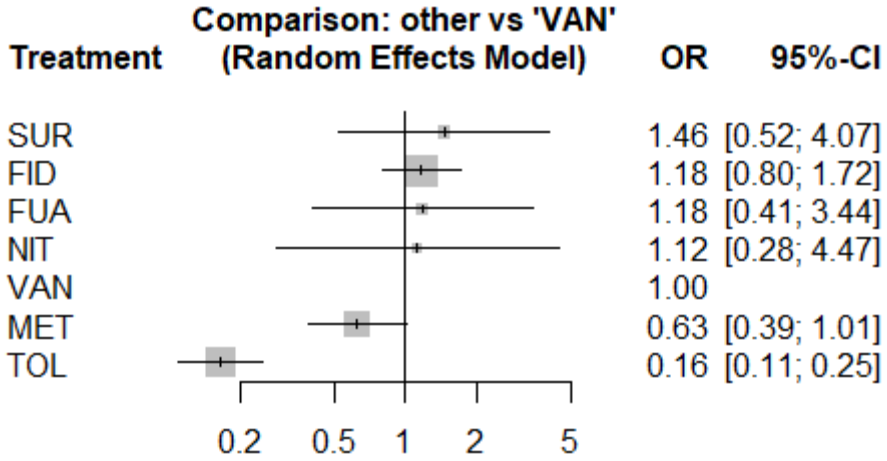
L.4 People with an initial infection

L.4.1 Initial cure

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



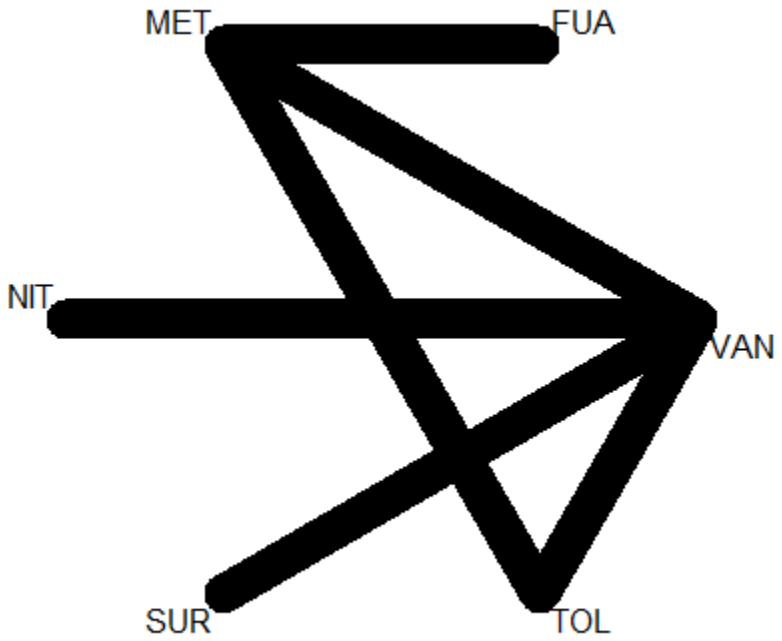
Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or an extended fidaxomicin regimen in the initial infection population.

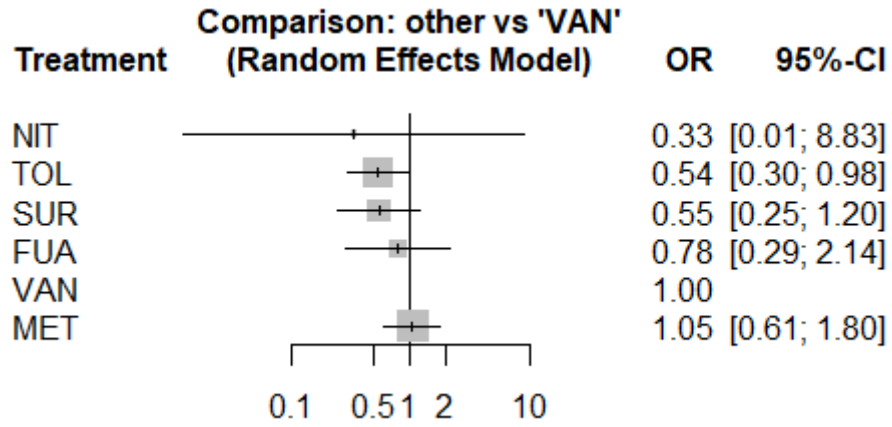
0.6908		
Fidaxomicin	0.5374	
0.8511 (0.5818, 1.2449)	**Vancomycin**	0.2395
0.5344 (0.2903, 0.9836)	0.6279 (0.3897, 1.0117)	**Metronidazole**

L.4.2 Recurrence

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



Relevant pairwise comparisons from NMA

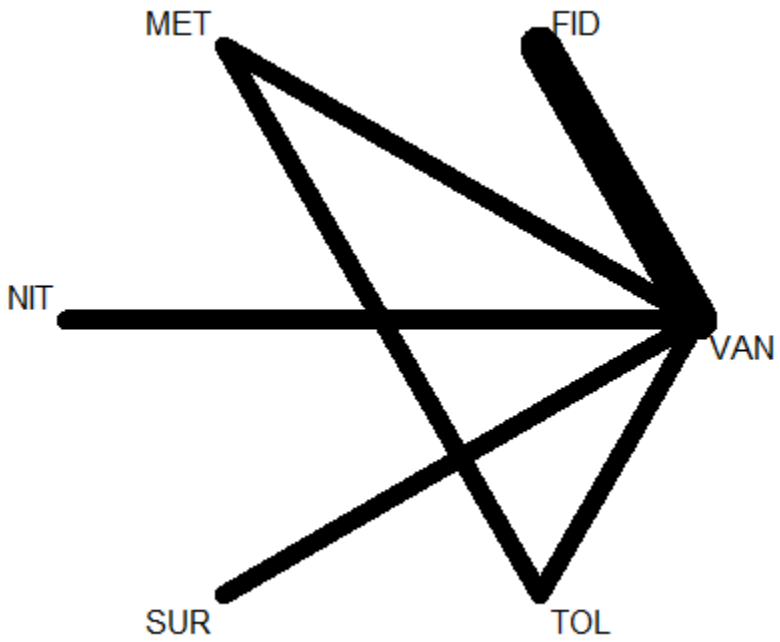
Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or fidaxomicin in the initial infection population.

0.2454	
Vancomycin	0.2082
1.0474 (0.6103, 1.7978)	**Metronidazole**

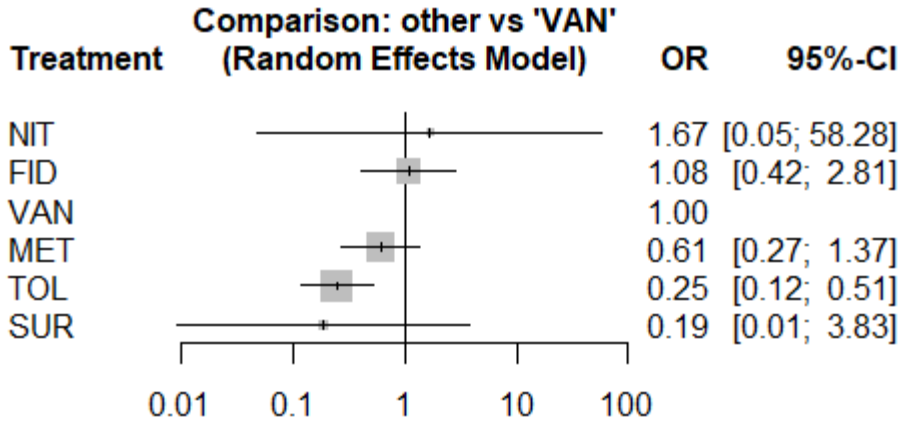
L.5 People with a recurrent infection

L.5.1 Initial cure

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



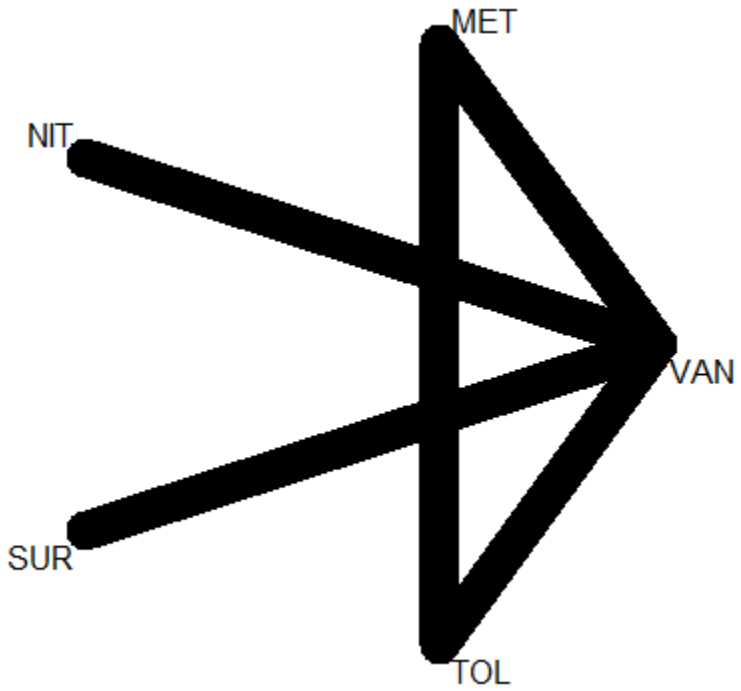
Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or an extended fidaxomicin regimen in the recurrent infection population.

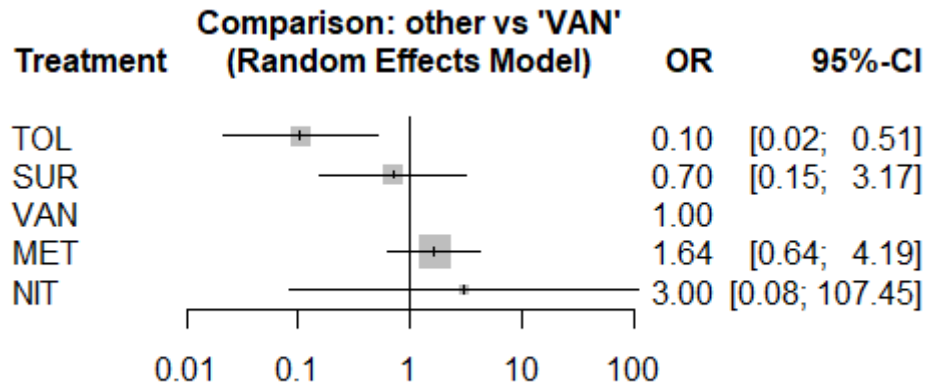
0.7280		
Fidaxomicin	0.7149	
0.9264 (0.3562, 2.4096)	**Vancomycin**	0.4714
0.5607 (0.1596, 1.9696)	0.6053 (0.2678, 1.3679)	**Metronidazole**

L.5.2 Recurrence

Network diagram



Pairwise comparisons from NMA (versus vancomycin)



Relevant pairwise comparisons from NMA

Treatments are ordered in the rank of their chance of being the best treatment. Numbers in grey boxes are P scores, which are used to rank the treatments (ranking takes into account all treatments in the network, not just the ones of interest). Treatment estimates are provided as odds ratios with 95% CIs. Significant pairwise comparisons are highlighted. No evidence was available for teicoplanin or fidaxomicin in the recurrent infection population.

0.4751	
Vancomycin	0.2373
1.6414 (0.6425, 4.1933)	**Metronidazole**

Appendix M: **Economic model**

M.1 Introduction

M.1.1 Background

Clostridioides difficile (*C. difficile*) is a bacterium that can infect the bowel. The infection can cause symptoms ranging from mild diarrhoea and abdominal pain, to the possibility of fulminant colitis and eventually death. There were 11,986 cases of *C. difficile* infection (CDI) reported in the 2018-19 financial year in the UK [1]. In the same period, there were 1,625 all-cause fatalities in patients who had a CDI diagnosis. This demonstrates the high level of mortality associated with CDI (a case-fatality rate of 13.6%). Alongside poor clinical outcomes, CDI also represents a substantial economic burden on healthcare. One reason for this is the high level of recurrence associated with CDI, either as a relapse within around 12 weeks of an initial cure, or as a reinfection after that. There is a high cost of hospitalisation for CDI (in the UK this is estimated to be £7,713 per patient [2]) and a possibility of numerous recurrences. These factors, along with the risk of progression into fulminant colitis which necessitates either a colectomy or additional medical treatment, mean that treatment per patient can become very expensive.

CDI can be treated with numerous interventions including a variety of antibiotics, and a faecal microbiota transplant (FMT). Antibiotics licensed for treatment of CDI in the UK include vancomycin, fidaxomicin, metronidazole and teicoplanin. Bezlotoxumab, a human monoclonal antitoxin antibody, can be given alongside an antibiotic to reduce the risk of recurrence.

M.1.2 Objectives

As part of an update to the National Institute for Health and Care Excellence (NICE) CDI antimicrobial prescribing guideline, NICE commissioned York Health Economics Consortium (YHEC), as part of its role as the Economic and Methodological Unit, to develop a cost-effectiveness model for the treatment of CDI. This model set out to find the most cost-effective sequence of antibiotic treatment options for:

- A population with the characteristics of the ‘average’ CDI patient (base-case population)
- An ‘at increased risk’ population for which recurrence rates are increased by 25% and are all severe, and the starting age of the population is increased
- An ‘at decreased risk’ population for which recurrence rates are decreased by 25% and have a lower chance of being severe, and the starting age of the population is decreased

The changes in recurrence rate for the ‘at increased risk’ and ‘at decreased risk’ populations were arbitrarily selected to illustrate how the results would change as the risk changes rather than being based on clinical evidence.

A treatment sequence for CDI was defined as a first-line intervention, a different second-line intervention, a set third-line intervention and a set fourth-line intervention. Bezlotoxumab could be selected as an adjunctive therapy in combination with the first-line treatment. The first-line treatment was chosen from 4 pharmaceutical options and the second-line treatment was chosen from 5 pharmaceutical options. For the third-line treatment, a combination of FMT and vancomycin taper pulse (VTP) was used. The only intervention used as a fourth-line treatment was FMT.

This report outlines the modelling approach used to estimate the cost-effectiveness of each treatment sequence, and the corresponding results. The model was built with guidance from the NICE ‘Managing Common Infections’ committee (‘the Committee’), which provided advice on the model structure and inputs.

M.2 Methods

M.2.1 Decision problem

This model evaluates the cost-effectiveness of different treatment sequences for the treatment of CDI in the NHS healthcare system, focussing on the first- and second-line pharmaceutical options. The model allows for treatment after initial infection, and for treatment after up to 2 recurrences. Costs were applied from the perspective of the NHS, outcomes were quantified in terms of quality-adjusted life years (QALYs) and both costs and QALYs were discounted at 3.5% per annum in line with the NICE Reference Case [3]. While the main results are reported for a life-time time horizon, the model can also produce short-term (90-day) results. The model population were a hypothetical cohort of 1,000 patients who entered the model after diagnosis of a CDI. The results for the base-case population use standard, age specific, population norms for mortality and health. In the 'at increased risk', and 'at decreased risk' populations these norms were modified in opposing directions.

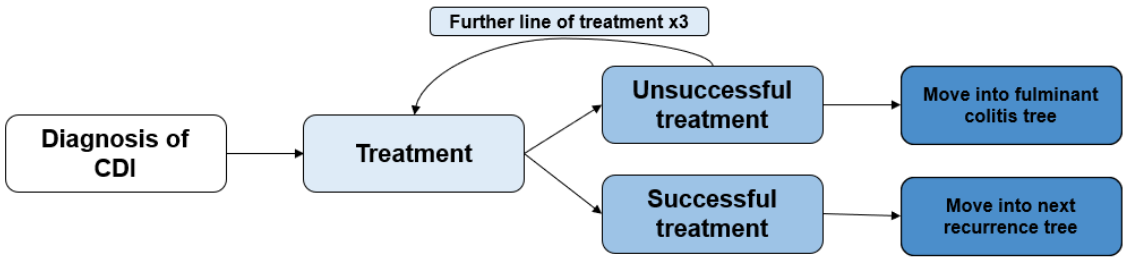
M.2.2 Model structure

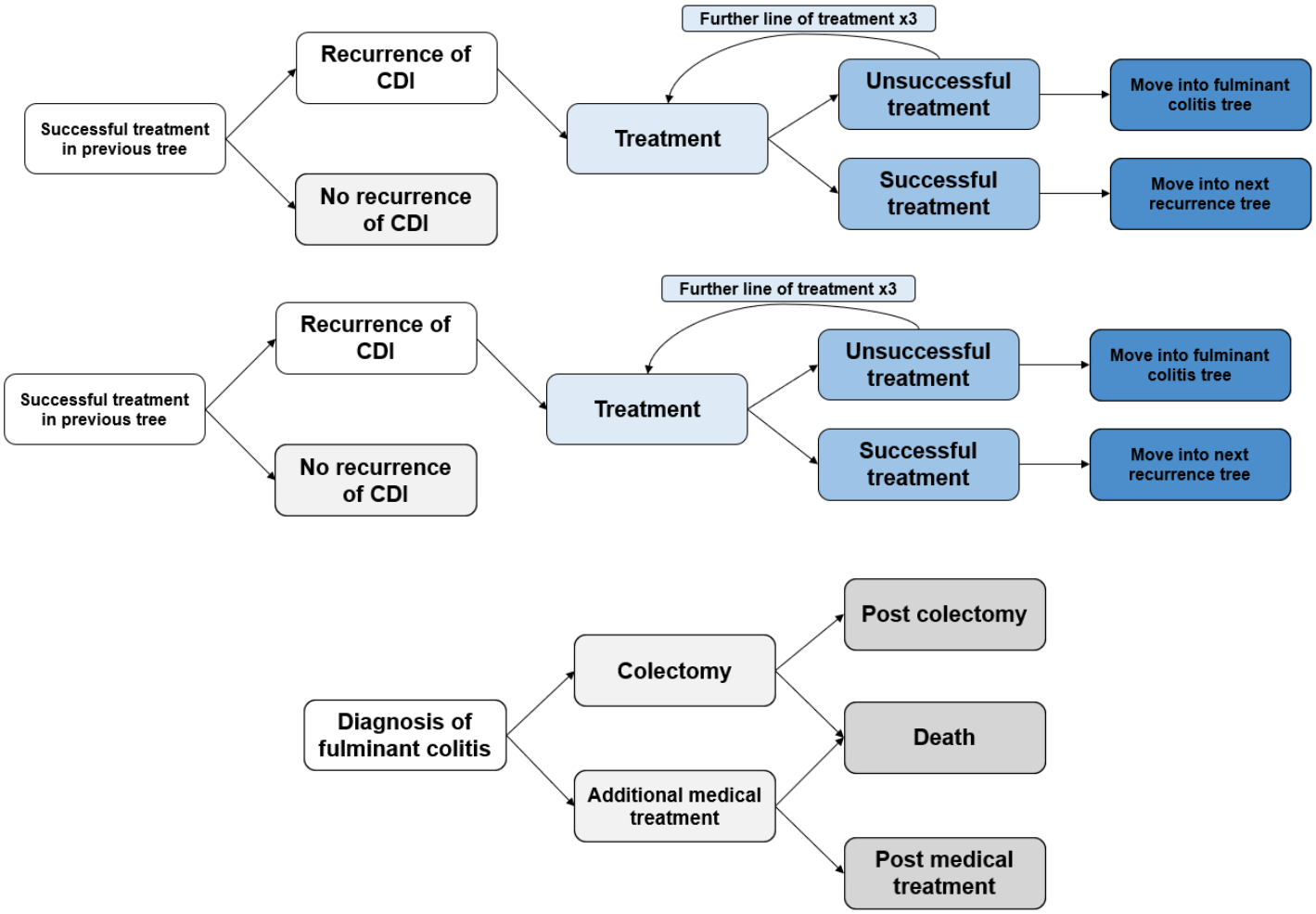
A *de novo* model was developed for this cost-effectiveness analysis. It was made up of 2 distinct parts to accurately capture the short- and long-term cost and benefits. Short-term outcomes were determined by a series of 4 linked decision trees. Long-term outcomes were determined by both the decision trees, and a Markov model.

M.2.2.1 Short-term decision tree

The short-term model used a time horizon of 90 days. This represented the time period in which a recurrence in CDI is considered a relapse. 90 days was the maximum time period used to measure recurrence in any of the randomised controlled trials (RCT) included in the network meta-analysis (NMA) that was used for the baseline characteristics and antibiotic efficacy [4]. The short-term model comprised 4 decision-tree components as shown in Figure 2.

Figure 2 Decision tree structure. In order: first tree (initial treatment), second tree and third tree (identical - recurrence round one and recurrence round two), fourth tree (fulminant colitis tree).





CDI – *Clostridioides difficile* infection

The first tree was for treatment of the initial infection. Patients could receive up to 4 lines of treatment in this initial infection period. If an intervention was unsuccessful, then the patients would be at risk of fulminant colitis and would either move onto the next line of the treatment sequence or move into the fulminant colitis tree. Acute mortality from CDI was limited to the first decision tree in the model. The 30-day all-cause acute mortality rate was split into 3 scenarios; death could occur straight after diagnosis, after an unsuccessful first-line treatment or after an unsuccessful second-line treatment.

Patients treated successfully in the initial treatment tree then moved to the second and third trees, at which point CDI either recurred or did not recur. Those for who CDI did not recur moved to the 'successful treatment' endpoint. For those with CDI recurrence, the tree was then identical in structure to the first tree with the possibility for all four lines of treatment. Recurrence was limited to 2 rounds due to the low proportion of the patient cohort who would experience a recurrence in any further round. Around 10% of the cohort experienced a recurrence in the first round of recurrence (second tree) and around 1% of the cohort experienced a recurrence in the second round of recurrence (third tree). It was calculated that only 0.1% of the cohort would experience a recurrence in the third round if it were included.

The fourth tree was populated by the cohort of patients who had developed fulminant colitis in each of the other trees. Each patient in the tree was treated with either a colectomy or additional medical treatment specific to fulminant colitis. The proportion of patients receiving each treatment was fixed. If treatment was unsuccessful the patient died.

The possible interventions for each line of treatment are shown in Table 52.

Table 52 Possible interventions in each line of treatment

First-line treatments	Second-line treatments	Third-line treatments	Fourth-line treatments
Vancomycin	Vancomycin	Faecal microbiota transplant	FMT
Metronidazole	Metronidazole	Vancomycin taper pulse	
Teicoplanin	Teicoplanin		
Fidaxomicin (standard regimen)	Fidaxomicin (standard regimen)		
	Fidaxomicin (extended regimen)		

FMT – faecal microbiota transplant

The antibiotic interventions are the same across the first-line and second-line treatments with the exception of fidaxomicin (extended regimen) which is an unlicensed dosing variation of fidaxomicin. The committee advised that it would not be given as a first-line intervention. Only one drug from each line can be selected per sequence. The second-line treatment cannot be the same drug as the first-line treatment (including for fidaxomicin where the extended regimen cannot be selected after the standard regimen). Because the focus of the model was the sequencing of antibiotics, the third-line and fourth-line treatments were fixed across all sequences. The split between the use of vancomycin taper pulse (VTP) and faecal microbiota transplantation (FMT) as third-line treatments was modifiable by the user, and all patients reaching the fourth-line treatment received FMT. To ensure that each patient progressed correctly through the trees and eventually the Markov model, the efficacy of the fourth-line treatment was assumed to be 100%.

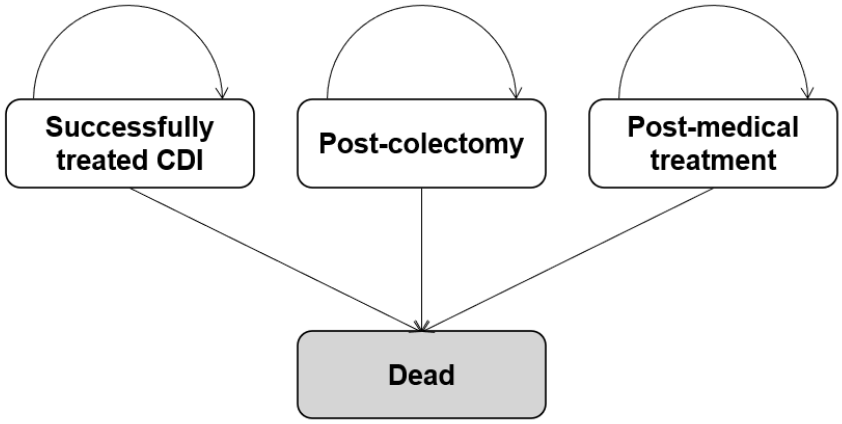
The costs and health utility decrements associated with each health state were tracked as the cohort progressed through the series of decision trees. Each terminal node of the overall decision tree corresponded with a starting health state in the Markov model.

M.2.2.2 Long-term cohort Markov model

The cohort Markov model used a life-time time horizon with one-year cycles. The Markov model included four health states:

- Successfully treated CDI
- Survived fulminant colitis after a colectomy (post-colectomy)
- Survived fulminant colitis after additional medical treatment (post-medical treatment)
- Dead

Figure 3 Cohort Markov model structure



Patients could not transition between the 3 'alive' health states. Patients could only progress from their original health state to 'dead'. The transition probability for each state was simply the background mortality rate associated with the age of the patient. While the model did have the ability to increase the relative risk of mortality in each health state, there was no quantitative evidence of differential mortality. Each health state had an associated cost and health-related quality of life. These were tracked as the model progressed and were summed at the end of the model to find the total costs and QALYs for the entire cohort.

M.2.3 Model Inputs

M.2.3.1 Model set up

The model follows a hypothetical cohort diagnosed with CDI. The cohort enters the model at a starting age of 63 years. This age was determined by the baseline characteristics of the RCT studies included in the NMA conducted by Beinortas et al. (2018) that estimated the relative efficacy between pharmaceutical interventions in treating CDI [4]. For the 'at increased risk' population, this age was increased to the average age of patients in the severe subgroup from the NMA. For the 'at decreased risk' population, the age was decreased by the same magnitude as it was increased for the increased risk population. The Committee advised that a proportion of patients would move straight to the second-line treatment in recurrence. In the absence of quantitative data, the Committee advised that making this proportion 50% would be a reasonable assumption. These inputs are shown in Table 53.

Table 53 Model set-up inputs

Category	Parameter	Value	Source
Patient starting age	Base-case pop.	63	Beinortas et al. (2018)
	'At increased risk'	71	
	'At decreased risk'	55	Assumption
Discount rate	Costs	3.5%	NICE Reference Case
	QALYs	3.5%	
% patients straight to 2nd-line in recurrence	Base case	50%	Clinical advice

% split of FMT versus VTP in 3rd line	Base case	50%	

FMT – faecal microbiota transplant; QALY – quality adjusted life-year; VTP - vancomycin taper pulse.

M.2.3.2 Treatment effectiveness and clinical data

Odds ratios for the initial cure rate ('resolution of diarrhoea, per individual trial criteria') (Table 54) and the recurrence rate ('recurrence of diarrhoea or death within the follow-up period of each trial') (Table 55) were adapted from the NMA conducted by Beinortas et al. (2018) [4]. These odds ratios compared the efficacy of each antibiotic with the efficacy of vancomycin. Alongside the base case data, the NMA provided subgroup data for 'severe', 'non-severe', 'initial infection' and 'recurrent infection' groups. This data included the initial cure rates and recurrence rates for vancomycin and metronidazole, and the sustained symptomatic cure rate for fidaxomicin. This sustained symptomatic cure rate could not be separated into the initial cure rate and recurrence rate, so fidaxomicin could not be included in the subgroup analysis. In addition, the baseline initial cure efficacy for vancomycin was higher for all subgroups (including severe) than the base case. This meant that the subgroup data lacked face validity, and the results associated with the subgroup data were only briefly reported.

Table 54 Odds ratios for initial cure rate efficacy (Beinortas et al. 2018)

1st and 2nd line interventions	Base case	Severe	Non severe	Initial	Recurrent
Metronidazole	0.72	0.53	0.63	0.63	0.61
Vancomycin	1.00	1.00	1.00	1.00	1.00
Teicoplanin	2.19				
Fidaxomicin standard regimen	0.96				
Fidaxomicin extended regimen	0.83				

Table 55 Odds ratios for recurrence rate efficacy (Beinortas et al. 2018)

1st and 2nd line interventions	Base case	Severe	Non severe	Initial	Recurrent
Metronidazole	1.17	1.09	1.45	1.05	1.64
Vancomycin	1.00	1.00	1.00	1.00	1.00
Teicoplanin	0.38				
Fidaxomicin standard regimen	0.50				
Fidaxomicin extended regimen	0.20				

The absolute efficacy of vancomycin was also adapted from Beinortas et al. (2018) and is shown in Table 56. Data for the absolute initial cure rate and absolute recurrence rate of vancomycin was pooled from each RCT featured in the NMA. Specifically, events (i.e. patients cured or recurrences) and sample sizes in the vancomycin arm of each trial were each weighted by sample size and summed. The total events were then divided through by the total sample size to find the absolute rate. For the cohort in the 'at increased risk' population, the recurrence rate was increased by 25% and for the cohort in the 'at decreased risk' population this was decreased by 25%.

Table 56 Absolute efficacy rates for vancomycin (Beinortas et al. 2018)

Vancomycin efficacy	Base case	Severe	Non severe	Initial	Recurrent

Absolute initial cure rate	79.6%	80.8%	86.4%	84.6%	85.3%
Absolute recurrence rate	18.8%	26.1%	18.4%	21.2%	30.2%

The relative odds ratios data and the absolute vancomycin data were combined to find the absolute initial cure rates and absolute recurrence rates of each of the antibiotics. The odds ratios were transformed into relative risk values that were then applied to the absolute vancomycin rates. The relative risk for recurrence with bezlotoxumab was also taken from the Beinortas et al. NMA. This relative risk was applied to the final absolute recurrence rate of the chosen first-line treatment. Based on the findings from the clinical review, it was assumed that bezlotoxumab had no impact on the initial cure rate.

The absolute initial cure rates and absolute recurrence rates associated with FMT and VTP as third-line treatments were taken from published models. The usage split between these 2 treatments was assumed to be 50% in the base case, based on the clinical advice from the Committee. This assumption was varied in sensitivity analysis. For the fourth-line treatment, FMT was set to a 100% absolute initial cure rate with the same recurrence rate that was used in the third line. This simplifying assumption was used to ensure the entire cohort was in a defined post-treatment health-state upon entering the Markov model. This simplifying assumption only affected a small proportion (~1%) of the hypothetical cohort and did not have a material effect on the results of the model. The above rates are shown in Table 57.

Table 57 Additional efficacy rates

Category	Parameter	Value	Source
Absolute 3rd line intervention efficacy	Faecal microbial transplant	76.1%	Tariq et al. (2019)
	Vancomycin taper pulse	69.0%	Konjeti et al. (2014)
Absolute 4th line intervention efficacy	Faecal microbial transplant	100%	Assumption
Recurrence relative risk	Bezlotoxumab	0.620	Beinortas et al. (2018)
Absolute 3rd line intervention recurrence rate	Faecal microbial transplant	9.1%	Konjeti et al. (2014)
	Vancomycin taper pulse	27.4%	Konjeti et al. (2014)
Absolute 4th line intervention recurrence rate	Faecal microbial transplant	9.1%	Konjeti et al. (2014)

The proportion of recurrences that required hospital admission (and, as such, were subject to the resource use of hospitalisation) was determined using 3 separate parameters:

- The percentage of severe recurrences that required hospital admission (Nathwani et al. 2014 [7])
- The percentage of non-severe recurrences that required hospital admission (Nathwani et al. 2014)
- The proportion of recurrences that were severe versus non-severe (Prabhu et al. 2018 [8])

An average of the former 2 parameters was weighted by severity with the third parameter to find the rate for the base-case population. In the ‘at increased risk’ population, all recurrences were severe, so 100% of recurrences required hospital admission. In the ‘at decreased risk’ population, no recurrences were severe so 67% of recurrences required hospital admission. The parameters are shown in Table 58.

Table 58 Inputs for the proportion of recurrences that required hospital admission

Category	Parameter	Value	Source
% of recurrences that are severe	-	9.9%	Prabhu et al. (2018)
% of recurrences hospitalised	Severe	100.0%	Nathwani et al. (2014)
	Non severe	67.0%	Nathwani et al. (2014)
Proportion of recurrences that required hospital admission	Base-case population	70.3%	Calculation
	'At increased risk' population	100.0%	Calculation
	'At decreased risk' population	67.0%	Calculation

The prevalence of fulminant colitis, which was applied after an unsuccessful treatment, was taken from a published model by Varier et al (2014) [9]. To prevent overestimating the prevalence rate in the decision trees, the rate was split depending on the number of possible unsuccessful treatments a patient could receive. All patients in the first tree (initial treatment) could receive up to 3 unsuccessful treatments (it was possible that the first-line, second-line and third-line treatments could all be unsuccessful). This meant that the prevalence rate was split into 3 (i.e. multiplied by 1/3) and was applied after each unsuccessful treatment. Patients who started with first-line treatment in the recurrence round one and recurrence round two trees also could receive up to three unsuccessful treatments and the same multiplier was applied. In contrast, patients who skipped first-line treatment in these could only receive up to 2 lines of unsuccessful treatment (the second-line treatment and third-line treatment could both be unsuccessful). This meant that the prevalence rate for this cohort of patients was only split into 2 (i.e. multiplied by 1/2) and was only applied after an unsuccessful second-line treatment and an unsuccessful third-line treatment.

The proportion of people receiving a colectomy versus additional medical treatment after a fulminant colitis diagnosis was determined by advice from the committee. The efficacy and mortality rate associated with each fulminant colitis treatment were taken from a published study by Sailhamer et al. (2009) [10]. The parameters for fulminant colitis are shown in Table 59.

Table 59 Fulminant colitis inputs

Category	Parameter	Value	Source
Fulminant colitis prevalence after unsuccessful treatment	Base case	16.0%	Varier et al (2014)
% split colectomy vs. additional medical treatment	Base case	10.0%	Clinical advice
Absolute fulminant colitis treatment efficacy	Colectomy	68.0%	Sailhamer et al (2009)
	Additional medical treatment	63.7%	

M.2.3.3 Costs, resource use, and health-related quality of life (HRQoL)

The cost per pack of the majority of antibiotics were taken from the NHS eMIT database [11], though the cost per pack of fidaxomicin came from the NHS Electronic Drug Tariff [12] since it had no eMIT cost (parameters shown in Table 60). The final cost of each drug was based on the number of necessary doses and pack size (shown in Table 61). For the cost of bezlotoxumab, the average weight of men and women in the general population was calculated (87.89kg for men and 74.43kg for women) and then the appropriate number of vials for that body weight was determined. This was determined to be one vial. This method led to a conservative estimate for the resource use of bezlotoxumab since a certain

proportion of the population who were above the average weight would need more than one vial while no one from the population could receive less than one vial. The cost per vial was taken from the BNF [13]. The regimen associated with each treatment was the licensed dosing information given by NICE, and is shown along with the final cost per course of each antibiotic in Table 61.

Table 60 Cost per pack for pharmaceuticals used in the model

Drug	Cost per pack	Source
Metronidazole (400mg)	£0.52	Drugs and pharmaceutical electronic market information tool (eMIT), 2020
Vancomycin (125mg)	£51.69	
Teicoplanin (200mg)	£3.45	
Vancomycin taper pulse (125mg)	£51.69	
Fidaxomicin standard regimen (200mg)	£1,350.00	NHS Electronic Drug Tariff, 2020
Fidaxomicin extended regimen (200mg)	£1,350.00	
Bezlotoxumab (1g vial)	£2,470.00	BNF, 2020

Table 61 Cost per course of treatment

Drug	Regimen	Packs necessary	Cost
Metronidazole (400mg)	400mg every 8 hours for 10 days	2	£1.04
Vancomycin (125mg)	125mg every 6 hours for 10 days	2	£103.38
Teicoplanin (200mg)	200mg twice daily for 10 days	20	£69.00
Vancomycin taper pulse (125mg)	125mg every 6 hours for 10 days, then 125mg once every 2 to 3 days for 3 weeks	2	£103.38
Fidaxomicin standard regimen (200mg)	200mg every 12 hours for 10 days	1	£1,350.00
Fidaxomicin extended regimen (200mg)	200mg every 12 hours for 5 days, then 200mg once every 2 days for 20 days	1	£1,350.00
Bezlotoxumab (1g vial)	One dose dependent on patient weight: 10mg per kg	1	£2,470

All of the unit cost figures that were not in 2019 prices were inflated using the Personal Social Services Research Unit (PSSRU) Inflation Index [14]. The cost, and future cost per year, of a colectomy were taken from a NICE costing statement on ulcerative colitis [15]. The recurrence hospitalisation cost was taken from a published study by Wilcox et al (2017) [2]. The cost of additional medical treatment was an average of 4 NHS non-elective tariff codes for inflammatory bowel disease [16]. The cost of FMT was an average between 2 methods from a study by Abdali et al. (2020) that had been micro-costed using the British National Formulary (BNF), the PSSRU, NHS Reference costs, expert opinion and British Society of Gastroenterology & Healthcare Infection Society guidelines [17]. These parameters are shown in Table 62.

Table 62 Procedural cost inputs

Category	Parameter	Value	Source

FMT costs	Colonoscopy method cost	£3,006.17	Abdali, Z et al. (2020)
	Nasogastric tube method cost	£740.16	
	% split	50%	Clinical advice
	Final cost per patient	£1,873	Calculated
Event costs	Recurrence hospitalisation cost	£7,713	Wilcox MH et al. (2017)
	Colectomy	£13,652	NICE Costing statement: Ulcerative colitis (2015)
	Medical treatment	£5,135	2018/19 NHS National Tariff[1]
Health state costs	Successfully treated CDI	£0	Clinical advice
	Post-colectomy	£2,428	NICE Costing statement: Ulcerative colitis (2015)
	Post-med treatment	£0	Clinical advice

[1] Average of 4 NHS non-elective spell tariff codes:
FZ37K Inflammatory Bowel Disease with Multiple Interventions, with CC Score 3+
FZ37L Inflammatory Bowel Disease with Multiple Interventions, with CC Score 0-2
FZ37M Inflammatory Bowel Disease with Single Intervention, with CC Score 4+
FZ37N Inflammatory Bowel Disease with Single Intervention, with CC Score 0-3

Baseline utility population norms by age were taken from a study by Love-Koh et al (2015) [18]. The event utility decrements were calculated using published utility values and the age-specific norms. The utility associated with CDI was taken from the Wilcox et al study (2017) and the decrement was applied for 15 days per line of treatment (the length of time each line of treatment generally takes). The utilities associated with a colectomy and the additional medical treatment were taken from the Konijeti et al (2014) [6] study, and the decrements were applied for 30 days. The post-colectomy health state decrement applied in the Markov model was also taken from this study and was applied every cycle. These utility parameters are shown in Table 63.

Table 63 Utility inputs

Category	Parameter	Value	Source
Event utility	CDI utility value	0.420 for 15 days	Wilcox et al. (2017)
	Colectomy utility value	0.610 for 30 days	Konjeti et al. (2014)
	Medical treatment	0.710 for 30 days	
Health state utility	Colectomy	0.002	
	Additional medical treatment	0.000	Clinical advice
Age-specific population norms	0-15	1.000	Love-Koh et al. (2015)
	16-24	0.928	
	23-34	0.915	
	35-44	0.877	
	45-54	0.844	
	55-64	0.799	

	65-74	0.795	
	75+	0.723	

M.2.4 Mortality

Acute mortality for the decision tree was taken from the PHE 30-day all-cause fatality rate for CDI [19]. Data for men and women was averaged to find a general rate by age.

No FMT-related mortality was included in the decision tree. Although some data on the mortality rate associated with FMT was found, the Committee decided it was not robust enough to be used.

The background mortality rates for the Markov model were taken from the ONS National Life Tables [20], with a weighted average used to find the general rate by age to account for differences in the number of men and women.

M.2.5 Outcomes

The following outcomes were generated in each treatment sequence of the model, and the difference between the sequences was calculated:

- Total costs per patient
- Total QALYs per patient

These were found by summing the 'per patient' costs and quality of life from the short-term model and lifetime model. These 'per patient' values were then used to perform incremental cost-effectiveness analysis between all possible sequences.

The incremental cost-effectiveness analysis ranks each sequence by the cost per patient. The lowest cost sequence is considered the 'reference' sequence. The costs per patient and the QALYs per patient are then compared for each 'comparator' sequence versus the 'reference' sequence. An incremental cost-effectiveness ratio (ICER) is found for each of these pairwise comparisons. This ICER is expressed as the incremental cost per QALY of being treated with the 'comparator' sequence when compared with the 'reference' sequence. This is the ratio of the difference in cost and the difference in QALYs between the 'comparator' sequence and 'reference' sequence:

$$\text{ICER} = \frac{\text{Cost}_{\text{comparator}} - \text{Cost}_{\text{reference}}}{\text{QALY}_{\text{comparator}} - \text{QALY}_{\text{reference}}}$$

For a 'comparator' sequence to be considered cost-effective versus the 'reference' sequence at the NICE threshold (assumed to be £20,000 to £30,00), the ICER has to be less than the threshold. A 'comparator' sequence is said to be dominant if it is both less costly and results in better health outcomes than the 'reference' sequence. A 'comparator' sequence can be said to be 'extended dominated' if it has a higher ICER than the next most effective sequence. In the context of this report, a 'comparator' sequence would be 'extended dominated' if it has a higher ICER when compared with the 'reference' sequence than another 'comparator' sequence.

M.2.6 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed for the most relevant pairwise sequence comparisons to determine the probability that the 'comparator' sequence was cost-effective versus the 'reference' sequence at a pre-determined threshold. The model uses a sample of 10,000 iterations since the net monetary benefit trace stabilised at 8,000 iterations

for test analyses. Each iteration used a different set of values for the inputs. The distributions of the odds ratios associated with each pharmaceutical were sampled independently rather than using covariances.

The ICER generated from each iteration was collected and the incremental cost and incremental QALYs were then plotted on a cost-effectiveness plane (incremental cost on the x axis and incremental QALYs on the y axis) to show the spread of results in the model. This can be used to determine the robustness of the results of the model. In addition, it can provide an estimate of the level of confidence in the direction of results in the model. The PSA reports the proportion of iterations where the ICER falls below the threshold, and therefore, in what proportion of iterations the 'comparator' sequence was estimated to be cost-effective versus the 'reference' sequence.

To generate the input values for each iteration, distributions were fitted to uncertain parameters within the model. The distribution fitted to each parameter is included in Table 64.

Table 64 PSA distributions

Parameter or parameter group	Distribution	Justification	Source
Odds ratios for efficacy	Lognormal		Decision Modelling for Health Economic Evaluation. Briggs, Claxton, and Schulpher (2006) [21]
Absolute efficacy rates	Beta	The parameter is bound by 0 and 1.	
Relative risk for bezlotoxumab	Lognormal		
Costs	Gamma	The parameter will always be a value greater than or equal to 0.	
Utility values	Beta	The parameter is bound by 0 and 1.	
Disutility values	Gamma	The parameter will always be a value greater than or equal to 0.	
Patient starting age	Gamma	The parameter will always be a value greater than or equal to 0.	
Clinical guidance on % splits of treatment etc.	Beta	The parameter is bound by 0 and 1.	
Prevalence of fulminant colitis	Beta	The parameter is bound by 0 and 1.	

M.2.7 Deterministic sensitivity analysis

Due to the large amount of pairwise comparisons in the model, the main form of deterministic sensitivity analyses (DSA) that were conducted was scenario analysis. This analysis established the level that certain model parameters would have to be for a treatment sequence to be cost-effective versus a comparator in a certain population (i.e. what level an input parameter would have to be to change which sequence was the most cost-effective). To represent the NICE threshold, results were reported at both a £20,000 threshold and £30,000 threshold.

M.3 Results

M.3.1 Deterministic results summary

The results in this section are presented over a life-time time horizon from the perspective of the NHS and Personal Social Services (PSS). The cost-effectiveness results are presented in a series of tables starting with a full set of results and then subsequent tables with different treatment options removed from the analysis to demonstrate a range of different pairwise

comparisons that could be considered. The Committee provided advice on the most sensible drug combinations to be included in the analysis.

Four of the 6 treatment sequences which included first-line teicoplanin were the least costly and also produced higher QALYs. However, the Committee were concerned about the extensive limitations of the 2 small studies that included teicoplanin in the NMA, both of which were at considerable risk of bias. Additionally, they included wide 95% confidence intervals which meant there was a high level of uncertainty in the estimates for efficacy. The Committee concluded that further research was needed on teicoplanin for treating CDI. This led to the presentation of results with teicoplanin excluded.

The Committee also advised that it was unlikely that metronidazole would be used as a second-line treatment in a clinical setting. This was because when CDI was not clinically cured using first-line vancomycin or fidaxomicin it is likely to represent infection that is harder to treat. The lower relative efficacy of metronidazole when compared with the other pharmaceuticals means that the harder to treat infection would be less likely to respond to metronidazole, meaning metronidazole would not be effective as a second-line agent. This led to the presentation of results with both second-line metronidazole and teicoplanin excluded.

Finally, the Committee highlighted that the fidaxomicin extended regimen was not a licensed dosage regimen for the UK and not commonly used in NHS hospitals. This led to the presentation of results with fidaxomicin (extended regimen), second-line metronidazole and teicoplanin excluded.

For ease of notation, strategies are written with the antibiotics abbreviated as 1st-2nd (i.e. teicoplanin as the first-line treatment and vancomycin as the second-line treatment will be written as TEIC-VAN).

- VAN – Vancomycin
- MET – Metronidazole
- TEIC - Teicoplanin
- FID – Fidaxomicin standard regimen
- FIDEX – Fidaxomicin extended regimen
- B – Bezlotoxumab

In tables, Fidaxomicin ER refers to the fidaxomicin extended regimen, and Fidaxomicin SR to the fidaxomicin standard regimen. Separate analyses are reported, using NICE thresholds of £20,000 and £30,000.

M.3.2 Base-Case Population

M.3.2.1 Full deterministic base case results

Table 65 shows the results and incremental analysis for all possible sequences in the base-case population (excluding bezlotoxumab). TEIC-VAN dominated (lower cost per patient and higher health benefit per patient) all other sequences except TEIC-FID. TEIC-FID had a greater health benefit, though this was small in magnitude and led to an ICER that exceeded £200,000 per QALY gained.

Table 65 Base case deterministic results

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Teicoplanin	Vancomycin	£713	10.7801			Reference

Teicoplanin	Metronidazole	£729	10.7769			Dominated
Teicoplanin	Fidaxomicin ER	£802	10.7800			Dominated
Teicoplanin	Fidaxomicin SR	£835	10.7806	£122	0.0005	£241,324
Vancomycin	Teicoplanin	£1,252	10.7533			Dominated
Metronidazole	Teicoplanin	£1,262	10.7361			Dominated
Vancomycin	Metronidazole	£1,518	10.7336			Dominated
Metronidazole	Vancomycin	£1,548	10.7202			Dominated
Vancomycin	Fidaxomicin ER	£1,660	10.7408			Dominated
Vancomycin	Fidaxomicin SR	£1,732	10.7420			Dominated
Metronidazole	Fidaxomicin ER	£1,763	10.7210			Dominated
Metronidazole	Fidaxomicin SR	£1,853	10.7222			Dominated
Fidaxomicin SR	Teicoplanin	£2,144	10.7566			Dominated
Fidaxomicin SR	Vancomycin	£2,371	10.7461			Dominated
Fidaxomicin SR	Metronidazole	£2,405	10.7403			Dominated

M.3.2.2 Base case deterministic results with teicoplanin excluded

Table 74 shows the base case results when teicoplanin was excluded. VAN-MET became the comparator and dominated every other strategy that also included metronidazole. VAN-FIDEX was considered plausibly cost-effective at the NICE threshold versus VAN-MET, making it the comparator in the following table (Table 66).

Table 66 Base case deterministic results with teicoplanin excluded

1st-line drug		2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin		Metronidazole	£1,518	10.7336			Reference
Metronidazole		Vancomycin	£1,548	10.7202			Dominated
Vancomycin		Fidaxomicin ER	£1,660	10.7408	£142	0.0072	£19,540
Vancomycin		Fidaxomicin SR	£1,732	10.7420	£214	0.0084	£25,572
Metronidazole		Fidaxomicin ER	£1,763	10.7210			Dominated
Metronidazole		Fidaxomicin SR	£1,853	10.7222			Dominated
Fidaxomicin SR		Vancomycin	£2,371	10.7461	£853	0.0125	£68,342
Fidaxomicin SR		Metronidazole	£2,405	10.7403			Ext. dom.

M.3.2.3 Base case deterministic results with teicoplanin and second-line metronidazole excluded

Table 67 shows that once second-line metronidazole was removed, VAN-FIDEX was the cost-effective option at the NICE threshold since when VAN-FID was directly compared with VAN-FIDEX, the ICER was above the NICE threshold.

Table 67 Base case deterministic results with teicoplanin and second-line metronidazole excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin ER	£1,660	10.7408			Reference
Vancomycin	Fidaxomicin SR	£1,732	10.7420	£72	0.0011	£64,390
Metronidazole	Fidaxomicin ER	£1,763	10.7210			Dominated
Metronidazole	Fidaxomicin SR	£1,853	10.7222			Dominated
Fidaxomicin SR	Vancomycin	£2,371	10.7461	£711	0.0052	£135,916

M.3.2.4 Base case deterministic results with teicoplanin, second-line metronidazole and fidaxomicin extended regimen excluded

Once fidaxomicin (extended regimen) was also excluded, and the dominated strategies were discounted, there were only two sequences to compare. Table 68 shows that while FID-VAN had greater health benefits, the ICER was above the NICE cost-effectiveness threshold. This means that based on the assumptions in our model and a NICE threshold of £20,000 to £30,000, VAN-FID was the optimum strategy since no other sequence was cost-effective versus it at the NICE threshold.

Table 68 Base case deterministic results with teicoplanin, second-line metronidazole and fidaxomicin extended regimen excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin SR	£1,732	10.7420			Reference
Metronidazole	Fidaxomicin SR	£1,853	10.7222			Dominated
Fidaxomicin SR	Vancomycin	£2,371	10.7461	£639	0.0041	£155,527

M.3.3 'At increased risk' population

M.3.3.1 Full 'at increased risk' population deterministic results

Table 69 shows the results for every sequence when used in an 'at increased risk' population. Similar to the base-case population results, TEIC-VAN dominated all but two of the other sequences. TEIC-FID and TEIC-FIDEX both had larger health benefits per patient, but the ICERs for these sequences were above the threshold.

Table 69 'At increased risk' population deterministic results

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Teicoplanin	Vancomycin	£1,125	7.8843			Reference
Teicoplanin	Fidaxomicin ER	£1,149	7.8845	£24	0.0002	£113,833
Teicoplanin	Metronidazole	£1,153	7.8809			Dominated
Teicoplanin	Fidaxomicin SR	£1,211	7.8850	£86	0.0007	£119,792

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Teicoplanin	£2,020	7.8578			Dominated
Metronidazole	Teicoplanin	£2,096	7.8410			Dominated
Vancomycin	Fidaxomicin ER	£2,429	7.8448			Dominated
Vancomycin	Metronidazole	£2,455	7.8362			Dominated
Metronidazole	Vancomycin	£2,556	7.8235			Dominated
Vancomycin	Fidaxomicin SR	£2,567	7.8457			Dominated
Fidaxomicin SR	Teicoplanin	£2,591	7.8624			Dominated
Metronidazole	Fidaxomicin ER	£2,593	7.8255			Dominated
Metronidazole	Fidaxomicin SR	£2,764	7.8263			Dominated
Fidaxomicin SR	Vancomycin	£2,939	7.8512			Dominated
Fidaxomicin SR	Metronidazole	£2,997	7.8452			Dominated

M.3.3.2 'At increased risk' population deterministic results with teicoplanin excluded

Table 70 shows that, when teicoplanin was excluded, VAN-FIDEX became the 'reference' sequence and dominated four of the other sequences (which all included metronidazole at some line). The ICERs for each of the other sequences versus VAN-FIDEX were all above the threshold.

Table 70 'At increased risk' population deterministic results with teicoplanin excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin ER	£2,429	7.8448			Reference
Vancomycin	Metronidazole	£2,455	7.8362			Dominated
Metronidazole	Vancomycin	£2,556	7.8235			Dominated
Vancomycin	Fidaxomicin SR	£2,567	7.8457	£138	0.0009	£160,853
Metronidazole	Fidaxomicin ER	£2,593	7.8255			Dominated
Metronidazole	Fidaxomicin SR	£2,764	7.8263			Dominated
Fidaxomicin SR	Vancomycin	£2,939	7.8512	£510	0.0063	£80,880
Fidaxomicin SR	Metronidazole	£2,997	7.8452	£568	0.0003	£1,834,869

M.3.3.3 'At increased risk' population deterministic results with teicoplanin and second-line metronidazole excluded

Table 71 shows there was no change in results from excluding second-line metronidazole and the other dominated strategies.

Table 71 'At increased risk' population deterministic results with second-line metronidazole and teicoplanin excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin ER	£2,429	7.8448			Reference
Metronidazole	Vancomycin	£2,556	7.8235			Dominated
Vancomycin	Fidaxomicin SR	£2,567	7.8457	£138	0.0009	£160,854
Metronidazole	Fidaxomicin ER	£2,593	7.8255			Dominated
Metronidazole	Fidaxomicin SR	£2,764	7.8263			Dominated
Fidaxomicin SR	Vancomycin	£2,939	7.8512	£510	0.0063	£80,881

M.3.3.4 'At increased risk' population deterministic results with teicoplanin, second-line metronidazole, and fidaxomicin extended regimen excluded

When fidaxomicin (extended regimen) was also excluded (Table 72), VAN-FID is again left as the optimum strategy to treat CDI at the NICE threshold since no other sequence is cost-effective versus it.

Table 72 'At increased risk' population deterministic results with teicoplanin, second-line metronidazole, and fidaxomicin extended regimen excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin SR	£2,567	7.8457			Reference
Metronidazole	Fidaxomicin SR	£2,764	7.8263			Dominated
Fidaxomicin SR	Vancomycin	£2,939	7.8512	£373	0.0055	£68,314

M.3.4 'At decreased risk' population

M.3.4.1 Full 'at decreased risk' deterministic population results

Table 73 shows the results for every sequence when used in an 'at decreased risk' population. Similar to the base case and 'at increased risk' population results, TEIC-VAN dominated all but one of the other sequences. Only TEIC-FID had greater health benefits per patient, though the ICER was higher than the NICE threshold.

Table 73 'At decreased risk' population deterministic results

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Teicoplanin	Vancomycin	£534	13.0830			Reference
Teicoplanin	Metronidazole	£544	13.0805			Dominated
Teicoplanin	Fidaxomicin ER	£641	13.0826			Dominated
Teicoplanin	Fidaxomicin SR	£661	13.0832	£127	0.0003	£497,468

Metronidazole	Teicoplanin	£906	13.0450			Dominated
Vancomycin	Teicoplanin	£924	13.0599			Dominated
Metronidazole	Vancomycin	£1,111	13.0330			Dominated
Vancomycin	Metronidazole	£1,111	13.0450			Dominated
Vancomycin	Fidaxomicin ER	£1,302	13.0499			Dominated
Vancomycin	Fidaxomicin SR	£1,346	13.0510			Dominated
Metronidazole	Fidaxomicin ER	£1,374	13.0327			Dominated
Metronidazole	Fidaxomicin SR	£1,430	13.0340			Dominated
Fidaxomicin SR	Teicoplanin	£1,923	13.0617			Dominated
Fidaxomicin SR	Vancomycin	£2,089	13.0534			Dominated
Fidaxomicin SR	Metronidazole	£2,111	13.0488			Dominated

M.3.4.2 'At decreased risk' population deterministic results with teicoplanin excluded

Table 74 shows that, when teicoplanin was excluded, MET-VAN became the comparator but unlike the base case and 'at increased risk' populations, did not dominate the other sequences. VAN-FIDEX and VAN-FID were both cost-effective versus MET-VAN at the NICE threshold, as was VAN-MET (though this was excluded in the next table).

Table 74 'At decreased risk' population deterministic results with teicoplanin excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Metronidazole	Vancomycin	£1,111	13.0330			Reference
Vancomycin	Metronidazole	£1,111	13.0450	£0	0.0120	£4
Vancomycin	Fidaxomicin ER	£1,302	13.0499	£191	0.0169	£11,275
Vancomycin	Fidaxomicin SR	£1,346	13.0510	£235	0.0181	£13,025
Metronidazole	Fidaxomicin ER	£1,374	13.0327			Dominated
Metronidazole	Fidaxomicin SR	£1,430	13.0340	£319	0.0011	£295,391
Fidaxomicin SR	Vancomycin	£2,089	13.0534	£978	0.0204	£47,877
Fidaxomicin SR	Metronidazole	£2,111	13.0488	£1,000	0.0159	£63,086

M.3.4.3 'At decreased risk' population deterministic results with teicoplanin and second-line metronidazole excluded

Table 75 shows the results when the reference was changed to VAN-FIDEX (as it was cost-effective at a £20,000 threshold versus MET-VAN). VAN-FID was not cost-effective versus VAN-FIDEX at the NICE threshold.

Table 75 'At decreased risk' population deterministic results with teicoplanin and second-line metronidazole excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin ER	£1,302	13.0499			Reference
Vancomycin	Fidaxomicin SR	£1,346	13.0510	£44	0.0011	£39,101
Metronidazole	Fidaxomicin ER	£1,374	13.0327			Dominated
Metronidazole	Fidaxomicin SR	£1,430	13.0340			Dominated
Fidaxomicin SR	Vancomycin	£2,089	13.0534	£787	0.0035	£225,118

M.3.4.4 'At decreased risk' population deterministic results with teicoplanin, second-line metronidazole, and fidaxomicin extended regimen excluded

Table 76 shows that, when fidaxomicin extended regimen was also excluded, VAN-FID was once again left as the optimum strategy to treat CDI at the NICE threshold since no other sequence was cost-effective versus it. The ICER for FID-VAN had a greater magnitude in this 'at decreased risk' population than the other two populations.

Table 76 'At decreased risk' population deterministic results with teicoplanin, second-line metronidazole, and fidaxomicin extended regimen excluded

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Vancomycin	Fidaxomicin SR	£1,346	13.0510			Reference
Metronidazole	Fidaxomicin SR	£1,430	13.0340			Dominated
Fidaxomicin SR	Vancomycin	£2,089	13.0534	£743	0.0024	£314,725

M.3.5 Bezlotoxumab

M.3.5.1 Selection of deterministic results that included bezlotoxumab alongside the first-line treatment

Table 77 shows a variety of comparisons between the most cost-effective non-bezlotoxumab sequences with their with-bezlotoxumab counterparts. No 'with-bezlotoxumab' sequence was cost-effective at the NICE threshold versus its counterpart, with all the ICERs exceeding £300,000 per QALY.

Table 77 Selected pairwise deterministic results of sequences with and without bezlotoxumab

1st-line drug	2nd-line drug	Cost per patient	QALYs per patient	Incr. cost	Incr. QALYs	ICER
Teicoplanin	Vancomycin	£713	10.7801			Reference
Teicoplanin (w/ Bez)	Vancomycin	£3,133	10.7825	£2,419	0.0024	£999,348

Teicoplanin	Fidaxomicin SR	£835	10.7806			Reference
Teicoplanin (w/ Bez)	Fidaxomicin SR	£3,224	10.7830	£2,389	0.0024	£1,010,150
Vancomycin	Fidaxomicin ER	£1,660	10.7408			Reference
Vancomycin (w/ Bez)	Fidaxomicin ER	£3,925	10.7482	£2,265	0.0074	£306,557
Vancomycin	Fidaxomicin SR	£1,732	10.7420			Reference
Vancomycin (w/ Bez)	Fidaxomicin SR	£4,011	10.7482	£2,279	0.0063	£363,837
Fidaxomicin SR	Vancomycin	£2,371	10.7461			Reference
Fidaxomicin SR (w/ Bez)	Vancomycin	£4,781	10.7494	£2,410	0.0034	£714,963

M.3.6 NMA subgroup analysis

The subgroup data (for severe, non-severe, initial infection and recurrent infection) from the Beinortas et al. NMA only contained odds ratios for metronidazole versus vancomycin. VAN-MET dominated MET-VAN in every scenario apart from 'initial infection NMA data' for the three population types, where the ICER was still less than £5,000 per QALY in each.

M.3.7 Sensitivity analysis

M.3.7.1 Probabilistic sensitivity analysis

A cost-effectiveness plane with the incremental costs and incremental QALYs plotted for each iteration is shown for each analysis.

In the base-case population (shown in Figure 4), when VAN-FID and FID-VAN were directly compared, FID-VAN had a 0.2% likelihood of being cost-effective versus VAN-FID at a £20,000 threshold, and a 1.8% likelihood at a £30,000 threshold. In the 'at increased risk' population (shown in Figure 5), these increased to a 11.6% likelihood at a £20,000 threshold and a 19.7% likelihood at a £30,000 threshold.

Figure 4: Cost-effectiveness plane for FID-VAN vs. VAN-FID in the base-case population

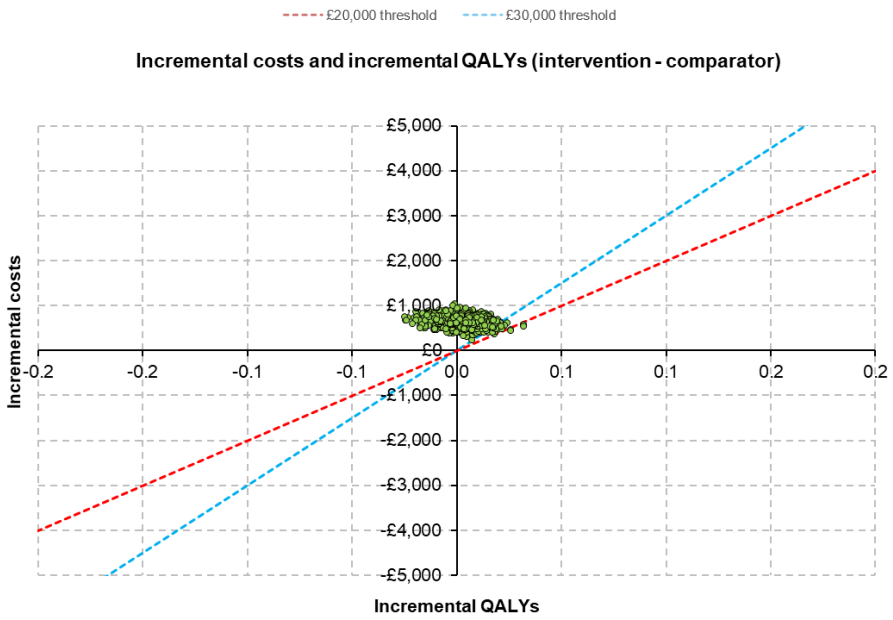
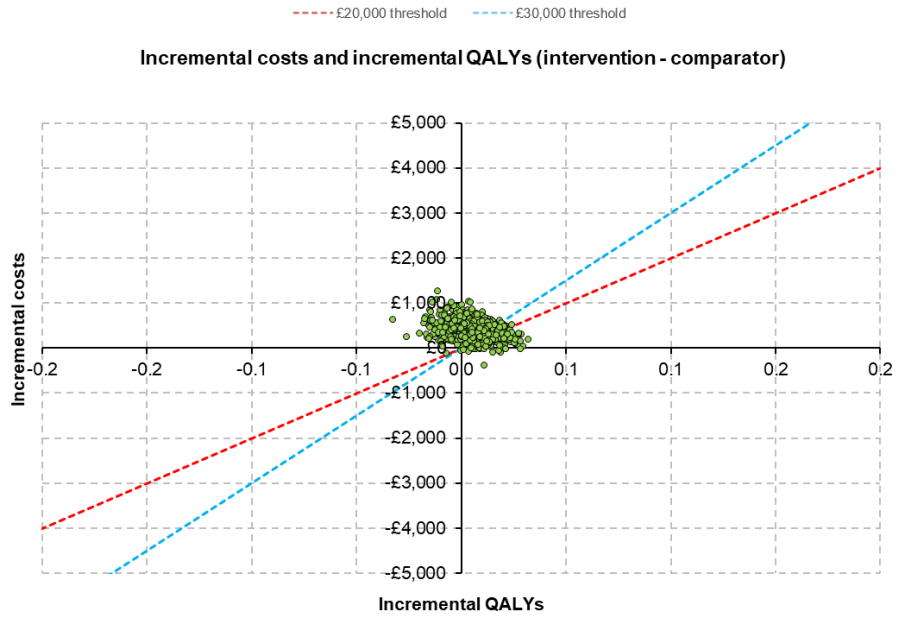


Figure 5: Cost-effectiveness plane for FID-VAN vs. VAN-FID in the 'at increased risk' population



VAN-FID and VAN-FIDEX were also directly compared because they had similar costs per patient and health benefits per patient. In the base-case population VAN-FID had an 32.0% likelihood of being cost-effective versus VAN-FIDEX at a £20,000 threshold, and an 35.6% likelihood at a £30,000 (shown in Figure 6). In the 'at increased risk' population VAN-FID had a 24.4% likelihood of being cost-effective versus VAN-FIDEX at a £20,000 threshold, and a 28.2% likelihood at £30,000 (shown in Figure 7).

Figure 6: Cost-effectiveness plane for VAN-FID vs. VAN-FIDEX in the base-case population

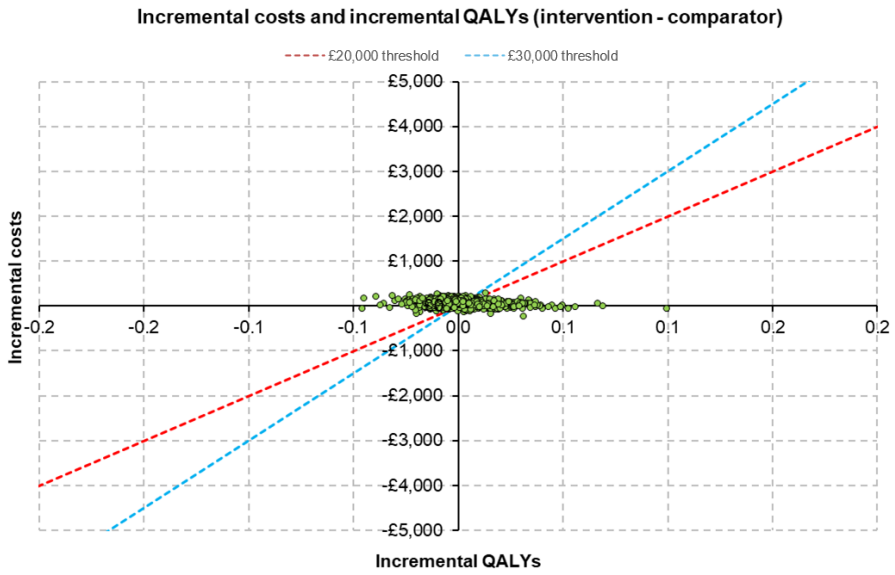
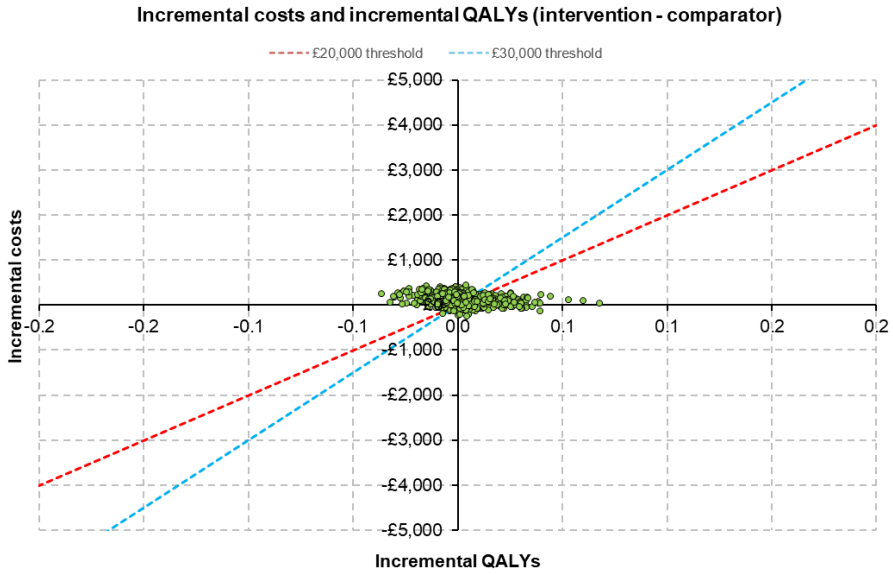
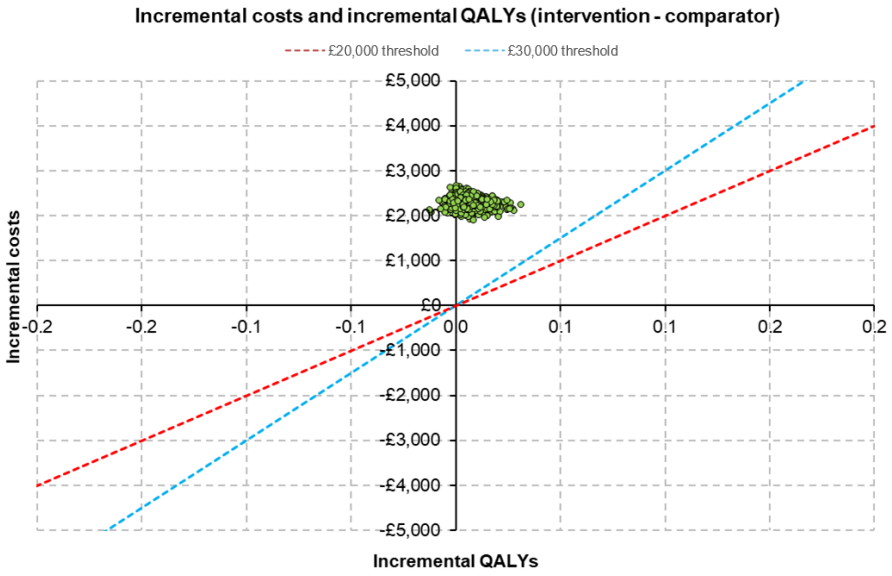


Figure 7: Cost-effectiveness plane for VAN-FID vs. VAN-FIDEX in the 'at increased risk' population



To explore the likelihood that a sequence including bezlotoxumab was cost-effective versus its counterpart sequence at the NICE threshold, VAN-B-FID was compared with VAN-FID. In the base-case population VAN-B-FID had a no likelihood of being cost-effective versus VAN-FID at a either a £20,000 threshold or a £30,000 threshold (shown in Figure 8).

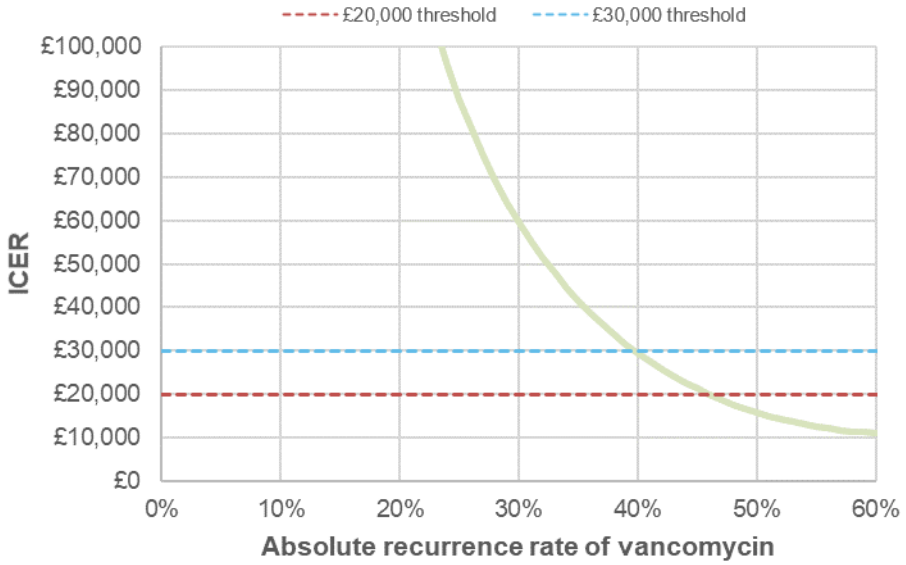
Figure 8: Cost-effectiveness plane for VAN-B-FID vs. VAN-FID in the base-case population



M.3.7.2 Scenario analysis for the absolute recurrence rate of vancomycin

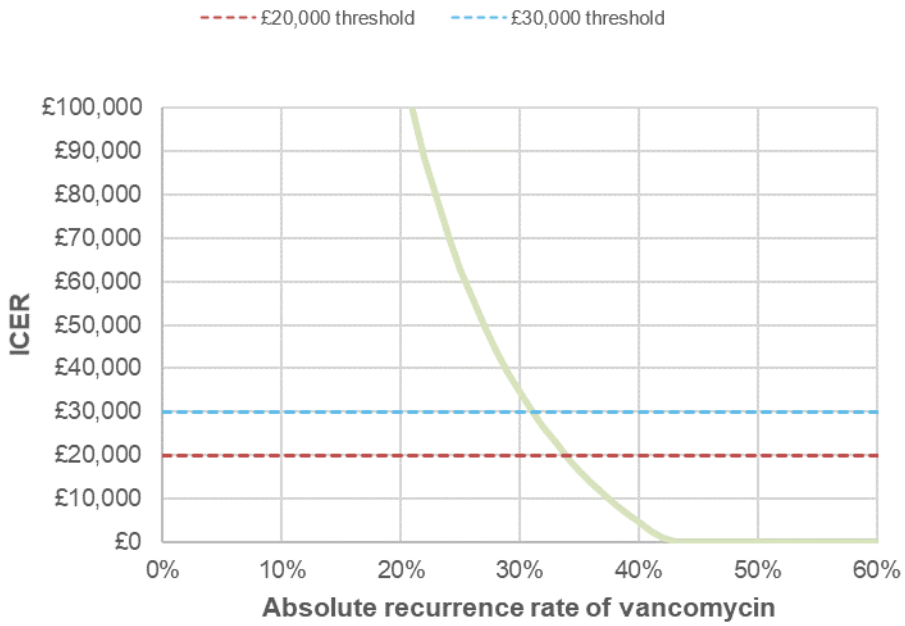
Threshold analysis around the baseline recurrence rate in the population (i.e. the absolute recurrence rate for vancomycin) was conducted for FID-VAN versus VAN-FID. The base case absolute recurrence rate for vancomycin was 18.76%. At a £20,000 threshold, the recurrence rate would have to be 46.96%, a 28.2% incremental increase, for FID-VAN to be cost-effective versus VAN-FID. At a £30,000 threshold, this rate would only have to be 39.71%, a 20.95% incremental increase, for FID-VAN to be cost-effective versus VAN-FID. Figure 9 shows the ICER for VAN-FID vs. FID-VAN as the absolute recurrence rate of vancomycin increases. The red line represents a £20,000 cost-effectiveness threshold while the blue line represents the £30,000 threshold.

Figure 9: ICER for FID-VAN vs. VAN-FID across absolute recurrence rate of vancomycin



The same analysis was conducted for the 'at increased risk' population. The base case absolute recurrence rate for vancomycin was 18.76%. At a £20,000 threshold, the recurrence rate would have to be 33.69%, a 14.93% incremental increase, for FID-VAN to be cost-effective versus VAN-FID. At a £30,000 threshold, the rate would only have to be 30.92%, a 12.16% incremental increase, for FID-VAN to be cost-effective versus VAN-FID. Figure 10 shows the ICER for VAN-FID vs. FID-VAN as the absolute recurrence rate of vancomycin increases. The red line represents a £20,000 cost-effectiveness threshold while the blue line represents the £30,000 threshold.

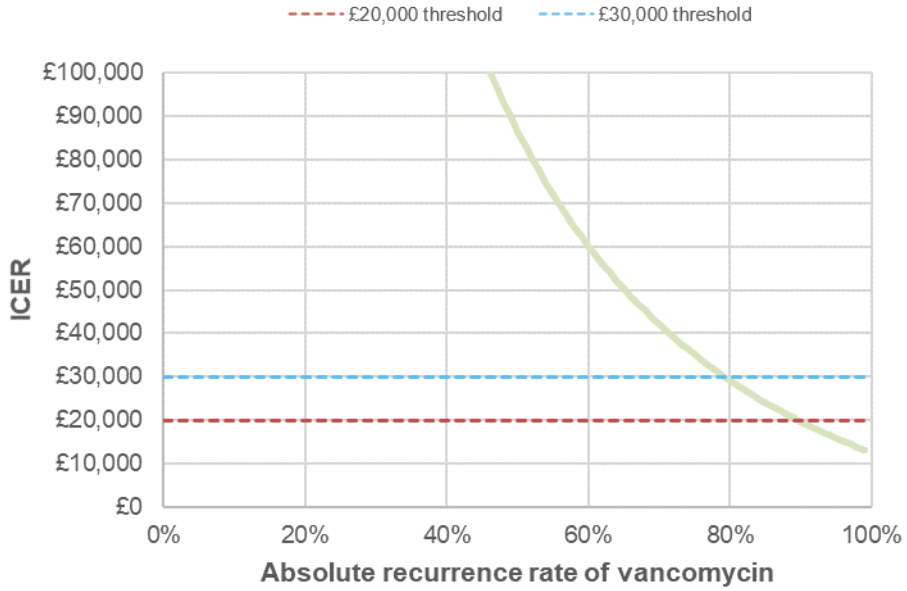
Figure 10: ICER for FID-VAN vs. VAN-FID across absolute recurrence rate of vancomycin in an 'at increased risk' population



The impact of the absolute recurrence rate of vancomycin was also explored for sequences that included bezlotoxumab. The base case absolute recurrence rate for vancomycin remained 18.76%. At a £20,000 threshold, the recurrence rate would have to be 89.60%, a 70.84% incremental increase, for VAN-B-FID to be cost-effective versus VAN-FID. At a £30,000 threshold, this rate would have to be 79.26%, a 60.50% incremental increase for VAN-B-FID to be cost-effective versus VAN-FID. Figure 11 shows the ICER for VAN-FID vs. VAN-B-FID as the absolute recurrence rate of vancomycin increases. The red line represents a £20,000 cost-effectiveness threshold while the blue line represents the £30,000 threshold.

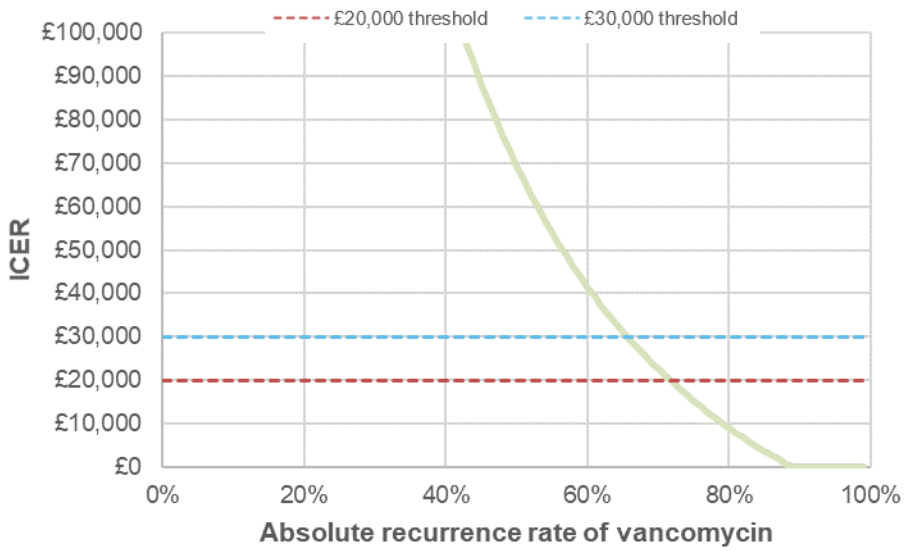
Figure 11: ICER for VAN-B-FID vs. VAN-FID across absolute recurrence rate of vancomycin

In the 'at increased risk' population, the recurrence rate would have to be 71.60%, a 52.84%



incremental increase, for VAN-B-FID to be cost-effective versus VAN-FID at a £20,000 threshold. At a £30,000 threshold, this rate would only have to be 79.26%, a 60.50% incremental increase for VAN-B-FID to be cost-effective versus VAN-FID. Figure 12 shows the ICER for VAN-FID versus VAN-B-FID as the absolute recurrence rate of vancomycin increases in the 'at increased risk' population. The red line represents a £20,000 cost-effectiveness threshold while the blue line represents the £30,000 threshold.

Figure 12: ICER for VAN-B-FID vs. VAN-FID across absolute recurrence rate of vancomycin in an 'at increased risk' population



M.3.7.3 Scenario analysis on the cost of fidaxomicin

The model assumes that the cost of fidaxomicin was the full NHS tariff price. It is possible that patient access schemes with Clinical Commissioning Groups (CCGs) may reduce the cost per pack of fidaxomicin. In the base-case population, for FID-VAN to be cost-effective at a £20,000 threshold versus VAN-FID, there would need to be a 52.3% pricing discount. At a £30,000 threshold, this would have to be a 48.4% discount, for FID-VAN to be cost-effective versus VAN-FI. In the 'at increased risk' population, for FID-VAN to be cost-effective at a £20,000 threshold versus VAN-FID, a 24.7% pricing discount was necessary. At a £30,000 threshold, this would have to be a 19.5% discount, for FID-VAN to be cost-effective versus VAN-FID.

The effect of changing the possible discount on the ICER of FID-VAN versus VAN-FID is shown in Figure 13 (base-case population) and Figure 14 ('at increased risk' population).

Figure 13: FID-VAN vs. VAN-FID ICER across price discount for fidaxomicin in the base-case population

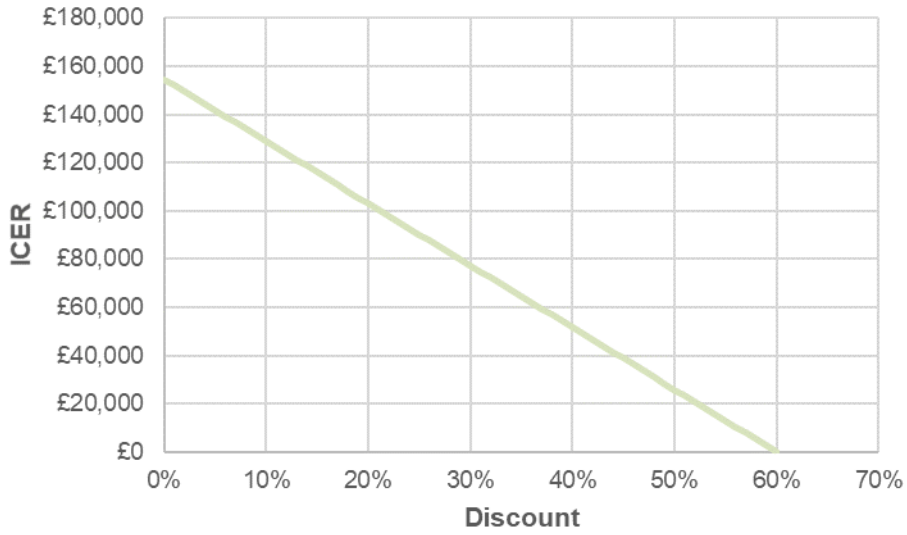
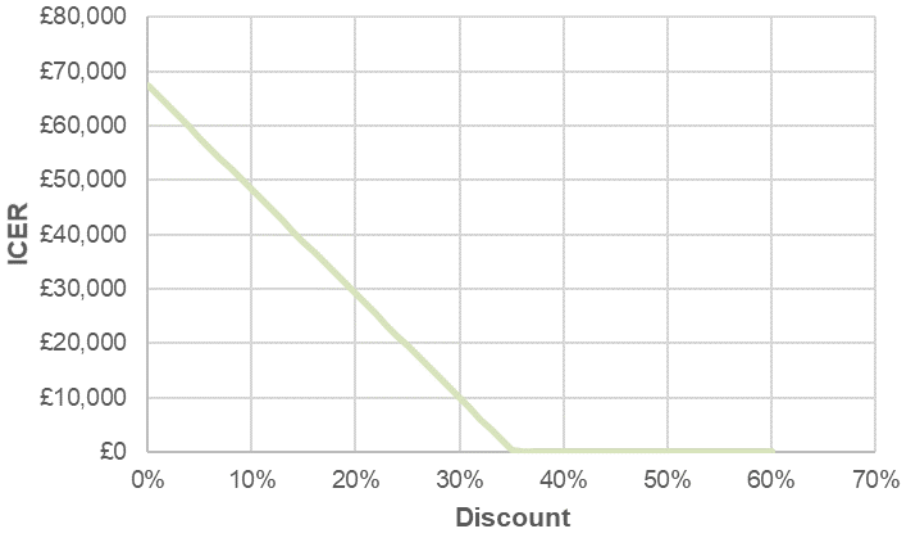


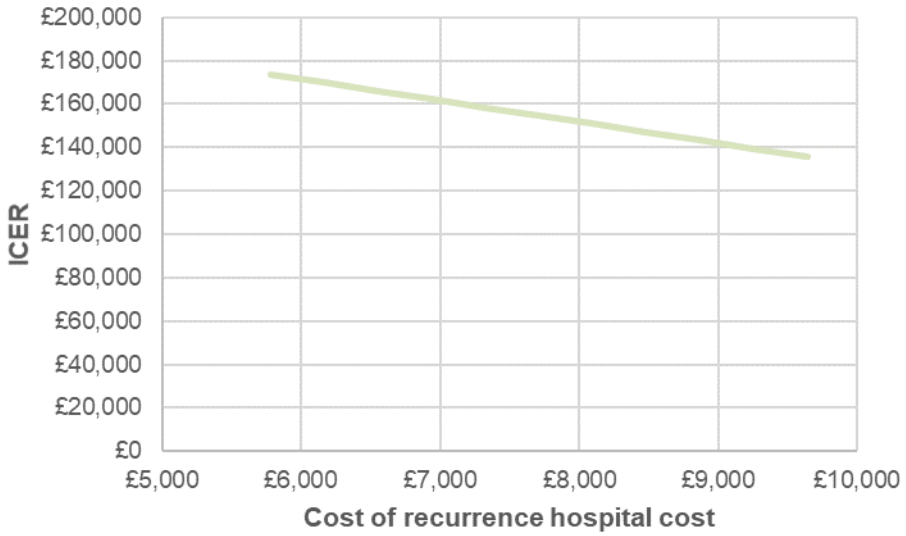
Figure 14: FID-VAN vs. VAN-FID ICER across price discount for fidaxomicin in 'at increased risk' population



M.3.7.4 Scenario analysis on the cost of a recurrence hospital admission

The cost associated with recurrence hospital admission was taken from a published study which collected UK hospital resource data for recurrent C Diff infections. An increase in the cost changed the ICER in favour of the drug/sequence with the lower level of recurrence. Figure 15 shows the ICER for FID-VAN versus VAN-FID when the cost varied from 75% of the cost to 125% of the cost. In the base case, fidaxomicin had a recurrence rate of 10.35% compared with vancomycin's rate of 18.76%, demonstrating that when a pharmaceutical with a lower recurrence rate is used in the first-line, the ICER reduces as the cost of recurrence increases.

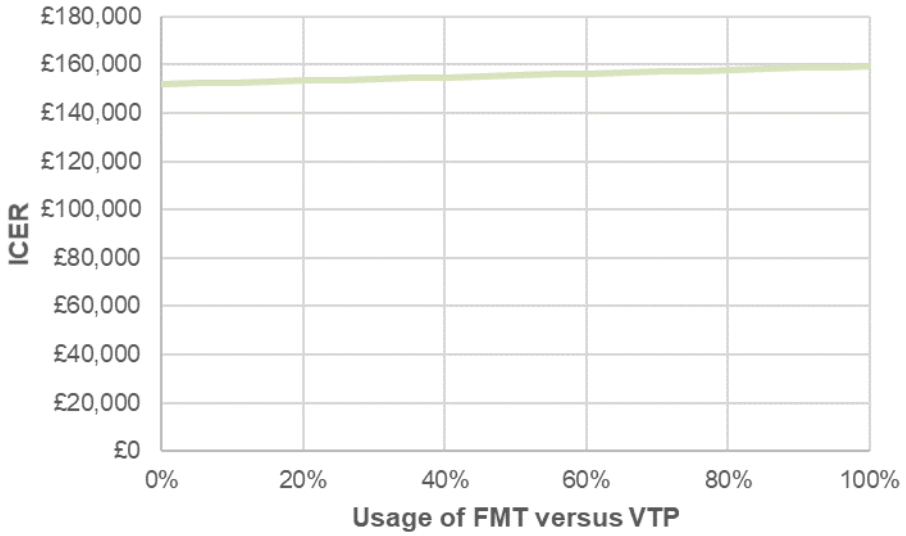
Figure 15: FID-VAN vs. VAN-FID ICER across the cost of recurrence hospital admission



M.3.7.5 Scenario analysis on the usage split of FMT and VTP as third-line treatments

The Committee provided clinical advice that the usage split of FMT and VTP as third-line treatments should be a 50%. The effect of changing this usage split on the ICER of FID-VAN versus VAN-FID was investigated (shown in Figure 16). Decreasing the use of FMT (increasing the use of VTP) caused the ICER to reduce, while increasing the use of FMT (decreasing the use of VTP) led to the ICER increasing. The range of ICERs for FID-VAN versus VAN-FID was £151,923 at 100% VTP usage to £159,364 at 100% FMT usage.

Figure 16: FID-VAN vs. VAN-FID ICER across the usage split of FMT and VTP as third-line treatments

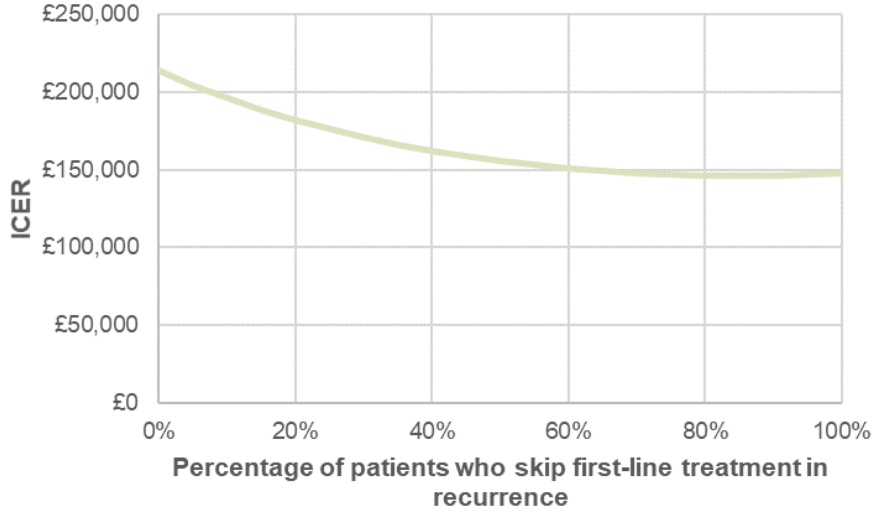


M.3.7.6 Scenario analysis on the proportion of patients who go straight to second-line treatment after recurrence

The Committee provided clinical advice that the proportion of patients who skip first-line treatment and go straight to second-line treatment in the two recurrence trees should be 50%. The effect of changing this usage split on the ICER of FID-VAN versus VAN-FID was investigated (shown in Figure 17). When no patients skip first-line treatment, the ICER was

£213,397, and when all patients skip straight to second-line treatment, the ICER was £147,891.

Figure 17: FID-VAN vs. VAN-FID ICER across the proportion of patients who go straight to second-line treatment after recurrence



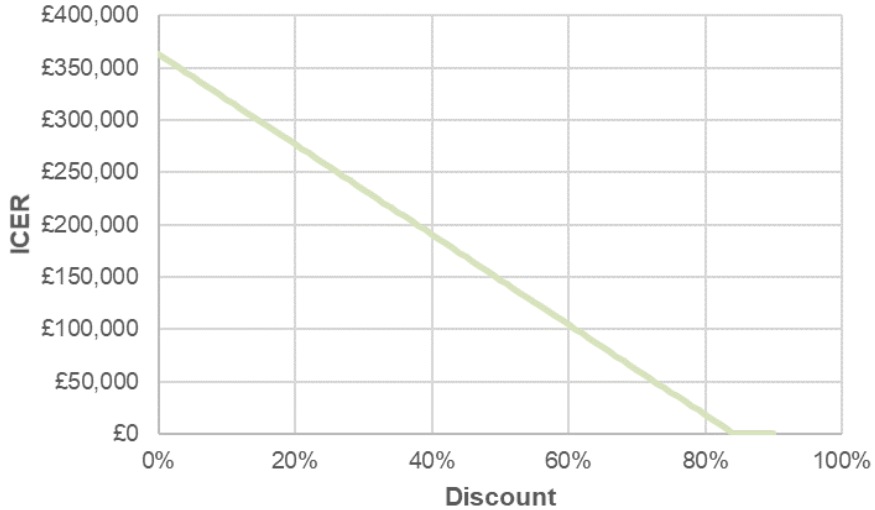
M.3.7.7 Scenario analysis on the price of bezlotoxumab

The model assumes that the cost of bezlotoxumab was the full BNF price. It is possible that patient access schemes with Clinical Commissioning Groups (CCGs) may reduce the cost per vial of bezlotoxumab. In the base-case population, for VAN-B-FID to be cost-effective at a £20,000 threshold versus VAN-FID, there would need to be a 79.6% pricing discount. At a £30,000 threshold, this would have to be a 77.2% discount. The effect of the discount on the ICER of VAN-B-FID versus VAN-FID is shown in Figure 18.

Figure 18: VAN-B-FID vs. VAN-FID across the price discount for bezlotoxumab

M.3.7.8 Scenario analysis on the mortality associated with FMT

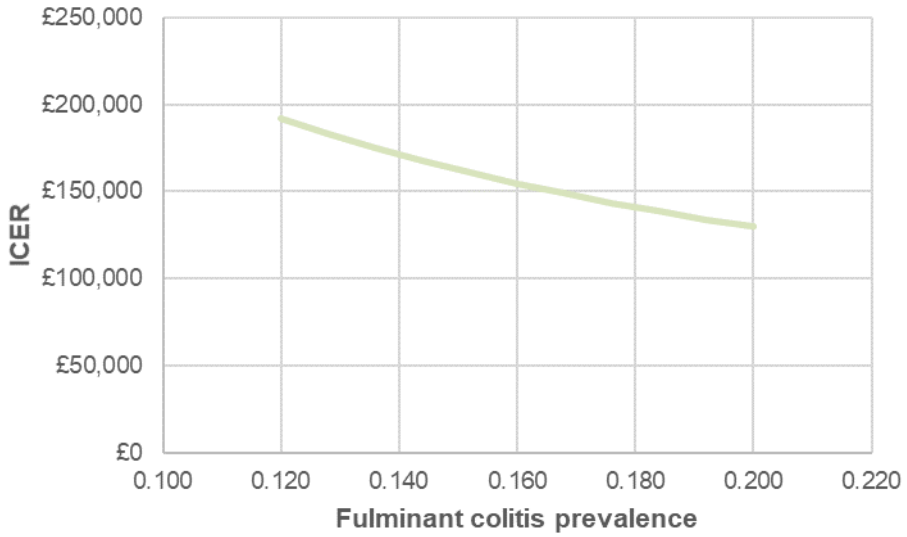
Mortality associated with FMT was not included in the main model. A model published Varier et al. (2018) [9] used a FMT mortality rate of 0.03%. When this mortality rate was included in the model, the ICER for FID-VAN versus VAN-FID reduced from £155,527 to £155,040.



M.3.7.9 Scenario analysis on the prevalence of fulminant colitis

The prevalence of fulminant colitis in the CDI population was taken from a published source (Varier et al. 2014). Figure 19 shows how changing the prevalence by 25% in each direction affected the ICER of FID-VAN versus VAN-FID. It demonstrated that as prevalence increased, the ICER reduced in favour of FID-VAN. Similar to the recurrence hospital cost, an increase in prevalence positively affects the first-line drug with the lower recurrence rate (in this case it was fidaxomicin).

Figure 19: FID-VAN vs. VAN-FID ICER across the prevalence of fulminant colitis



M.4 Discussion

M.4.1 Results discussion

The results for all 3 populations (base-case, 'at increased risk' and 'at decreased risk') indicated that teicoplanin as the first-line treatment and vancomycin as the second-line treatment was the cost-effective option to treat CDI in the NHS at the NICE threshold versus other pharmaceutical combinations. However, the paucity of data on teicoplanin created material uncertainty about the results of that analysis. We recommend that this analysis should be run again if new evidence about the clinical efficacy of teicoplanin becomes available.

The Committee advised that the teicoplanin studies used in the clinical efficacy NMA were poor quality with low participant numbers which created bias in the results. For this reason, all results that included teicoplanin as an intervention were excluded. In addition, the Committee advised that using a less efficacious treatment in the second-line would not make clinical sense, as it is likely the majority of patients who would have been cured by that treatment would already have been treated successfully from the first-line intervention. For that reason, second-line metronidazole (which had much lower initial cure efficacy than the other antibiotics) was also excluded from the results. Finally, the Committee decided that there was not sufficient evidence of the benefits from fidaxomicin (extended regimen) to justify recommending the off-label regimen over the licensed, standard regimen, so any strategies including fidaxomicin (extended regimen) were excluded.

The final pairwise comparison in all 3 populations was FID-VAN versus VAN-FID as the comparator. The ICER for FID-VAN exceeded the NICE threshold in each. In the base case, FID-VAN had only had a 0.2% likelihood of being cost-effective versus VAN-FID at a £20,000

threshold, and a 1.8% likelihood at a £30,000 threshold. Similarly, in the 'at increased risk' population, the likelihoods were 11.6% and 19.7% respectively.

Fidaxomicin (standard regimen) had a lower initial cure rate than vancomycin. However, it had a lower recurrence rate. The rate of absolute recurrence in the model was dependent on the population, and had uncertainty associated with it. In the base-case population, the recurrence rate was 18.8%. The threshold analysis around the parameter concluded that an absolute recurrence rate in the base-case population of 39.71% was necessary for FID-VAN to be cost-effective versus VAN-FID. This dropped to 33.69% in the 'at increased risk' population. These rates are plausible in higher risk populations, for instance people who have already had a recurrence or relapse, so fidaxomicin (standard regimen) may be appropriate as a first-line intervention in populations where the absolute recurrence rate is high.

M.4.2 Limitations

Two major assumptions on the clinical data used in the model were that the initial cure rate and recurrence rate of each antibiotic would remain constant for both lines of treatment and across each round of recurrence. While there were no clinical data to contradict this assumption, real-world efficacy may show that the cure rate changes with recurrence. For example, patients most likely to be cured would be successfully treated by the first-line treatment whereas patients less likely to be cured would require second-line treatment. This would mean that patients who reach the second-line treatment would be less likely to be cured and the efficacy rate of each drug when used as a second-line treatment would be reduced. It could be argued that each drug would have a similar drop in efficacy in the second-line, but the real-world advice given by the Committee on second-line metronidazole disputes this (a less efficacious drug would do comparatively worse with regards to other drugs if used as a second-line treatment). While the results did account for this issue by excluding second-line metronidazole, there was no analysis conducted on the effect on efficacy when other drugs are used as second-line treatments. This meant that it is possible that the model overestimated second-line efficacy at different rates for each intervention, causing bias. A similar argument to this can be made about using less efficacious drugs as first-line or second-line treatments in the two rounds of recurrence. Patients less likely to be cured may be more likely to experience a recurrence, so the efficacy of each antibiotic in the recurrence rounds may be reduced. The rate at which the efficacy reduced could be different, and the results did not account for this nor explore the possibility.

In terms of treatment options, this model was limited in scope to first- and second-line antibiotic treatment options with no option to explore which third-line treatment option would be more cost-effective versus the other. FMT is a relatively new and potentially efficacious treatment option which could have been explored as a second-line treatment option or compared against VTP as a third-line treatment strategy.

The Committee advised that the same antibiotic would not be used as both a first-line treatment and second-line treatment option in clinical practice therefore, this was not explored in the model.

The Committee also advised that fidaxomicin (extended regimen) is an off-label treatment and would therefore not be used as a first-line treatment. Although it was excluded from the final results, it did feature as a second-line treatment in some of the more promising strategies and could have been a feasible first-line treatment if it were a licensed dosing regimen.

When looking at the assumptions made for costs, bezlotoxumab and fidaxomicin are still currently on patent so the full BNF/tariff price was used. The main results and subsequent committee recommendations did not take the possibility of patient access schemes for CCGs into account. The scenario analysis demonstrated that if there was a 50% discount on fidaxomicin in place for the base-case population, FID-VAN would become cost-effective

versus VAN-FID at a £20,000 threshold. In the 'at increased risk' population this dropped to a 25% discount. The scenario analysis around the price of bezlotoxumab suggested that around an 80% discount was necessary for VAN-B-FID to be cost-effective versus VAN-FID at the £20,000 and £30,000 thresholds.

Another limitation was that certain costs were excluded from the model. Teicoplanin and fidaxomicin are both administered using an injection. If they are administered in secondary care, the cost for the injection is included in the reference cost. However, the reference cost for teicoplanin and fidaxomicin in the primary care setting does not capture the costs for administering the injection (e.g. health care professional time and equipment). These were therefore omitted from the model. If included, these costs would likely increase the cost per QALY associated with each sequence that included teicoplanin or fidaxomicin.

Finally, the model does not address pertinent current issues like the increasing rate of antimicrobial resistance (AMR). AMR may mean the efficacy of certain antibiotics in the model could be reduced. This would reduce the health benefits associated with each antibiotic, and this could be at different relative rates depending against which antibiotics the C. difficile bacteria develop resistance.

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Appendix N: **Expert testimony**

N.1 Committee Meeting 2: 12/11/2019

Section A: Developer to complete	
Name:	Mark Wilcox
Role:	Consultant / Head of Microbiology Research & Development / Infection Lead of Leeds NIHR Diagnostic Technologies Medical Technology and In Vitro Diagnostic Co-operative, Leeds Teaching Hospitals NHS Trust Professor of Medical Microbiology, Sir Edward Brotherton Chair of Bacteriology, Lead on C. difficile infection, Public Health England Medical Advisor to National Infection Prevention & Control Lead, NHS Improvement
Institution/Organisation (where applicable):	Leeds Teaching Hospitals NHS Trust University of Leeds Public Health England NHS Improvement
Guideline title:	Clostridium difficile infection: antimicrobial prescribing
Guideline Committee:	Managing common infections
Subject of expert testimony:	*Clostridium difficile* infection
Evidence gaps or uncertainties:	How is *C difficile* infection managed in clinical practice, including prevention of recurrence? Evidence identified not consistent with current guidelines.

Section B: Expert to complete	
Summary testimony:	Committee Meeting 2: 12/11/2019

The expert witness responded to specific questions posed by the committee chair or other committee members. The responses to those questions are summarised below and are the expert's opinion (unless otherwise stated).

Comments on the accuracy of background information?

- Colonisation with *C difficile* (CD) is uncommon. 1–2 % of adults, up to 10% in older/hospitalised people. More common in children under 2 years.
- Avoid using term CDAD. *Clostridium difficile* infection (CDI) is preferred.
- Bezlotoxumab – not entirely correct to say preventative treatment. Given in acute phase with the treating antibiotic. Major aim of treatment is to reduce recurrence.

How should CDI severity be defined?

- No consensus. Mild/moderate/severe categorisation is too much. Non-severe and severe is more helpful.
- Life threatening CDI is uncommon and obvious.
- Only universally agreed severity biomarker is blood white cell count (WCC).

What's the relationship between CDI and toxin in testing?

- Testing as per PHE guidance.
- Finding CD bug doesn't tell you much. Faecal toxin detection is much more specific for CDI. Detecting toxin gene is not sufficiently predictive of CDI. ~70% of CDI diagnoses in US are made using standalone PCR testing for toxin gene – this leads to considerable overdiagnosis of CDI and so need to consider this in US studies. Can find faecal toxin in some asymptomatic people.

What's different in the community?

- Pan European study – rate of missed CDI diagnosis 5x higher in primary care.
- Current testing guidance not widely followed. Younger people can develop CDI.
- In several studies, 1/3 people in community who are toxin positive have not had recent antibiotics.

- CDI in community seems to be different from hospital. Most studies are in hospital.

What are the consequences of CDI?

- PHE data based on HES is 99% complete for mandatory reported CDI.
- 30-day mortality is 15% – half of that is directly attributable to CDI. On a par with meningococcal meningitis.
- For people who survive, post CDI IBS is poorly measured. Relatively common not to return to normal bowel function.

What about frail elderly people?

- CDI often the straw that breaks the camel's back. If person has lots of comorbidities and is frail, CDI can lead to death.
- Older UK reports in particular have highlighted many examples of delayed diagnosis, delayed treatment, poor management and delayed follow up, all of which have contributed to death.

What about the lack of evidence on stopping PPIs?

- This has been recognised as a gap and calls for RCTs to be conducted.
- Some studies have found no association. No evidence on relapse/recurrence if PPIs are continued. If there is an effect, it is substantially less than with antibiotics.

Comments on the network meta-analysis?

- Ethics committee wouldn't approve a placebo-controlled study now.
- List of antibiotics can be simplified. Cadazolid, suroptomycin, tolevamer – all discontinued. Ridinilazole – 7 months into phase 3 trials, more than 24 months before reaches market.
- Bacitracin is never used. Never seen nitazoxanide used (only in a clinical trial).
- Teicoplanin data are limited and claim of increased efficacy is likely to be a spurious result (based on a few small trials). CDI is included in the (European) indications for teicoplanin, using the IV powder/solution for oral administration.
- Only UK options are fidaxomicin, vancomycin, metronidazole and bezlotoxumab.
- Very convincing that metronidazole is significantly inferior to vancomycin.

- NNTs for fidaxomicin versus vancomycin and bezlotoxumab versus no bezlotoxumab range from 2 to 7 to prevent a recurrence. Metronidazole is the exception, as it is inferior. Very little metronidazole gets to where needed (in the lumen of the colon).

- Main ranking of CDI treatment agents is according to rates of sustained cure. Drugs are generally similar in rates of initial clinical cure; the efficacy differences are according to whether they prevent recurrence. Initial clinical cure and prevention of recurrence = sustained clinical cure.

Is there a relationship between severity of disease and recurrence?

- Yes, some relationship. ZAR score used to assess severity – higher ZAR, more likely to have recurrence. WCC is most important aspect of ZAR. People with severe infection are more likely to die and need most effective treatment.

- Need to keep severity assessments simple.

- Certain types of CD are more likely to cause severe disease.

Why is fidaxomicin not recommended for severe CDI in US guidelines?

- No high-quality evidence that fidaxomicin is effective in severe CDI.

- Some patients in RCTs have severe CDI, but evidence dominated by non-severe patients. Implausible that it wouldn't also work the same in patients with severe CDI.

Are there any resistance issues in CDI?

- Not a major issue. Levels of antibiotic in gut lumen are very high (apart from metronidazole).

Will losing mild/mod/severe categorisation have any impact?

- No.

Who should be treated in hospital?

- In someone who is ill, their reserve is very small. You would worry about them and need to do a WCC. If some diarrhoea but clinically well, may not need referral. It's a balance that is all part of diarrhoea assessment pathway.

What's natural history of mild CDI in people that don't get treatment?

- Old data suggest 25% will symptomatically resolve without treatment. Can't identify who these are.

- Pragmatism is needed – person is well, mild diarrhoea, result back, they're better – probably wouldn't treat. This is not a reason to create 'mild' as a 'category' and could be unhelpful.
- It may occasionally be reasonable not to treat some elderly people, but this wouldn't be the norm.

What about CDI in children?

- Very difficult to make diagnosis, especially in infants because CD is a normal component of gut flora.
- Beyond 2 years of age, CDI is very uncommon. If you do see it, it would usually be in immunocompromised children

If no cost implications, what is your first-choice antibiotic?

- Fidaxomicin – halves recurrence rate (25% versus 13%).

Will there be a problem with resistance if we start to use it more?

- Based on current knowledge, no.
- Much higher level of drug given than what is needed to kill CD. Caveat – fidaxomicin has not been heavily used to date. Post marketing surveillance over 5 years found no evidence of emergence of resistance.

What's the incidence of nausea and vomiting with fidaxomicin?

- Not common, all antibiotics used are well tolerated as not absorbed.
- None reduce time to resolution of diarrhoea. Need time to get rid of toxins.
- People typically respond in 3–5 days. Unlikely to get past 6 days without improving, apart from metronidazole which takes a relatively long time.

Is more research needed on teicoplanin, or other interventions?

- Don't think it would give any advantage over vancomycin. Achieves same high levels compared with what's needed. More important areas to research.
- Fidaxomicin extend (Guery RCT) – administration is spaced out over 25 days (standard dosage is for 10 days). Total overall dose is the same. Rate of recurrence of 'extend' administration was lower than seen historically with standard fidaxomicin.

What's the role of motility agents?

- Not able to get rid of the toxin, may make things worse. Should not be used in acute CDI.

- May have a role in recurrent diarrhoea if person not sick and can be observed.
- Concern not just related to CDI – no evidence of benefit and potential for harm.

What's current practice in children?

- Based on adult practice. Sunshine study of fidaxomicin in children – expect it to be licensed in children.

What's the role of FMT?

- ESBL bacteraemia death has been reported following FMT, infected by donor who wasn't adequately screened.
- Experimental procedure. Not a regulated product. Deaths have occurred. No robust long term safety data.
- Costs – not just drug cost, also administration and set up costs.
- Can be efficacious, it's when to use it. It should not be used for the first episode, and only after other treatments have been tried.
- Bezlotoxumab patients awaiting FMT have not gone on to need FMT after being treated with bezlotoxumab.
- Overall efficacy in open label studies 82%, compared with 67% in non-open label studies (Tariq R et al., Clin Infect Dis 2019).
- BSG recommended at 2nd recurrence, IDSA at 3rd recurrence.
- Need to also consider fidaxomicin extend and vancomycin pulsed treatment. This is important.
- Whole programmes of children's FMT in US. CDI very rare here.
- FMT is a fee paying procedure in US.
- Gut microbiome related to other conditions e.g. cancer, hypertension, diabetes, obesity. We don't know what consequences are of transferring one person's microbiome to another person.

What's the rate of relapse/recurrence in CDI?

- Baseline risk of recurrence is 25%. Once you've had recurrence this increases to 45%, then the next recurrence risk is 60%.

Comments about prebiotics & probiotics?

- Probiotics – live organism (one bug).

- Prebiotic – a food, not a live bug. It affects other live bugs in GI microbiome. Poor research compared with probiotics.
- There are many problems with oligofructose study results – not been able to reproduce, poor accuracy with toxin detection kit, open study, not well reported. Would be wary about its use based on evidence.

Would you change antibiotics in CDI?

- If responding to antibiotics, better to stay on it rather than change. Multiple (i.e. new) antibiotics may increase the risk of CDI. Review, but not necessarily stop.

When would you use IV antibiotics?

- Rarely, if you can't use oral e.g. in intensive care. IV vancomycin and IV metronidazole can be used for dual therapy. This is a very specialised scenario.

N.2 Committee Meeting 3: 19/12/2019

Section A: Developer to complete	
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Institution/Organisation (where applicable):	Leeds Teaching Hospitals NHS Trust University of Leeds Public Health England NHS Improvement
Guideline title:	Clostridiodes difficile infection: antimicrobial prescribing

Guideline Committee:	Managing common infections
Subject of expert testimony:	*Clostridiodes difficile* infection
Evidence gaps or uncertainties:	How is *C difficile* infection managed in clinical practice, including prevention of recurrence? Evidence identified not consistent with current guidelines.

Section B: Expert to complete

Summary testimony:	Committee Meeting 3: 19/12/2019

The following questions are related to the health economic modelling

Can you explain extended or pulsed antibiotic interventions?

- FMT always includes short-course vancomycin as part of the intervention, as preconditioning. This is just with vancomycin, never seen fidaxomicin used in this way.
- Extended fidaxomicin is used less commonly. This is an extended duration (25 days) of fidaxomicin beyond 10 days. The course is extended to prevent germination of the spores that can still be found after end of treatment (10 days), and so, by increasing the duration of antibiotic presence in the colon, try to prevent recurrence. Poor evidence suggests this is better than conventional fidaxomicin. But in EXTEND study – comparator is standard vancomycin. Ideal study would be standard fidaxomicin, standard vancomycin, extended vancomycin and extended fidaxomicin. Recurrence rate with fidaxomicin extend was 7%, 13% with standard fidaxomicin and 25% with standard vancomycin. These data are not all from same study (indirect comparisons).
- Vancomycin taper then pulse is given over 4-6 weeks (no standard dosing). Given 4 x day in 1st week, 3 x day in 2nd week, and so on. In 5th and 6th weeks vancomycin is pulsed every 2 or 3 days. Still have residual spores – if you pulse antibiotic, germinating spores are killed (analogous to head coming out of shell and being chopped off).

What's the timepoint that you would call a recurrence?

- Conventionally 30 days after end of treatment (treatment for 10 days, then 30 days after this). Exception is bezlotoxumab – this would be 90 days because it has a long half-life of 19 days.

- You need to have achieved initial clinical cure, before you can then have recurrence.

- About 50-75% of 2nd episodes (i.e. 'recurrences') are 'relapses' (i.e. identical to primary strain). In 25-50% it's a different strain compared with the primary one (these are typically called 're-infections').

Is treatment for recurrence the same as primary infection?

- Current PHE guidance considers using same antibiotic again. But there is a change in thinking on this (i.e. in recent US guidelines), with a strong move to use a different antibiotic for recurrence.

What happens in first line treatment failure?

- Flowchart makes sense. RHS of flowchart is very uncommon. Majority (80-90%) do achieve initial cure.

- Colectomy is very uncommon now, about 0.5%. This is not coded well (for whether this relates to CDI).

How many lines of treatment is it worth going onto?

- 3 lines of treatment is reasonable for modelling. If in ITU with fulminant colitis, patients will die unless they get surgery.

- There will be no good evidence to support 3rd line treatment.

What are the first-line treatment strategies we are interested in?

- Commonly used antibiotics i.e. vancomycin, fidaxomicin (or, for completeness, metronidazole) needs to be in the model.

- Teicoplanin needs to go into model.

- Fidaxomicin extend is used for primary CDI – no licensed dosage but evidence is there. Fidaxomicin is different to fidaxomicin extend and needs to be considered separately. Total dose for both is the same overall – so costs the same.

- Vancomycin tapered/pulsed is a separate intervention to standard vancomycin – but this is not licensed/used for 1st line use.

- Rifaximin is considerably more expensive. No point including in model. Fusidic acid should also not be included in the model.

- Bezlotoxumab only licensed when given with standard care antibiotics (see first line above).

- No good evidence to show probiotics are effective for primary treatment. Probiotics tend to be used on their own for long periods as 'preventative' options.

What are the second-line treatment strategies we are interested in?

- Metronidazole wouldn't be an option 2nd line.
- FMT tends not to be used in primary CDI that failed first line treatment. Tends to be used if someone who had successful treatment first line then has recurrence – usually after multiple (2 or more) recurrences. In theory you could include in model as 2nd line treatment.
- FMT – bundle all methods together.
- Bezlotoxumab is given at any point during standard 10-day antibiotic course. Can't infer from the evidence which is the better antibiotic (fidaxomicin, vancomycin, or metronidazole) to go with it – this is because the choice of antibiotic in the bezlotoxumab phase 3 trials was at the discretion of each investigator and so was prone to bias. Bezlotoxumab and antibiotics are working on different pathways. If we think fidaxomicin is the best antibiotic, you might think fidaxomicin plus bezlotoxumab is the best option – but no evidence to support this.

What are the cost implications?

- MHRA has got involved with FMT. You need to set yourself up as a medicines production unit/service to carry this out. There are substantial set up costs, and costs to remain licensed to do this.

What are the quality of life implications?

- You are worried about FMT because of its unknown adverse events (especially long term, for example predisposing to cancer). There have been some rare cases of aspiration pneumonia and death. Recently cases of Gram-negative septicaemia because donors were not screened appropriately. You can't screen for what is unknown. Modelling can look at acute adverse events, but not long term effects, that would be impossible.
- Data from bezlotoxumab trial show adverse events are low. There is a caution around congestive heart failure patients. There was a numerical difference in deaths, which has been flagged by EMA and FDA.

What about people who are more difficult to treat?

- Old belief was that metronidazole was OK for mild to moderate CDI, but not severe. Now known to be inferior for all CDIs on an ITT basis. Very low concentrations get in lumen of colon and get lower as CDI progresses. Metronidazole gets there through an inflamed colitic wall. Therefore, it's plausible that it may work better for more severe colitis – but no evidence to support this.
- Failure to respond to antibiotic treatment is uncommon and could indicate that the diagnosis is incorrect. If you then fail second-line treatment, this would be really unusual, and you would need to reconsider diagnosis.

- There are no highly specific risk factors for recurrence.
- No good data national surveillance on the rate of CDI recurrence. Another episode within 30 days doesn't need to be reported. Real world data on recurrence rate is always lower than RCTs because you lose patients and there is a lack of follow up. RCTs don't overestimate recurrence, that's the best quality data available.
- Very difficult to recruit people to CDI trials; the more unwell they are the harder to get them in. Mortality rates are lower in trials. Alternatives to RCT treatment efficacy data are poor quality.
- Epidemiology hasn't shifted over last 6-7 years.
- You'd expect all of us to have anti-toxin antibodies, but some have significantly more than others.
- No evidence about impact of delayed diagnosis. For other conditions, the sooner you get treated, the better the outcomes.
- Tempting to say test anti-toxin antibodies, but there is no commercial assay. Emerging evidence for host snips/polymorphisms associated with treatment response to bezlotoxumab. Reality is that prognostic scores only have 70% predictive value for recurrence.

The following questions are related to the evidence

What's the usual dose of rifaximin?

- Couldn't quote an optimal dosage for rifaximin in CDI - it is rarely used. Don't think there are any dosing ranging studies. Dosing in CDI is not the same as in hepatic impairment.

Do you have any comments on the Mullane study?

- How did they define CDI – toxin positive or PCR positive? Predictive power of PCR very low. Study was reported in abstract form and didn't report accurately – claimed just toxin positive. Consider this when thinking about effectiveness.
- Stem cell/bone marrow transplant patients appear to have higher CDI rates, but as diarrhoea and carriage of toxigenic C. difficile is higher in these, diagnostic accuracy is an issue.

What's licensed for preventing CDI?

- Only agent licensed for prevention of CDI is bezlotoxumab. No antibiotics are licensed for prevention.

Do you have any comments on the MODIFY studies?

- Actoxumab – used on its own was discontinued because of futility. Not available as a commercial product.

- In the MODIFY studies, and for regulatory approval – you can give bezlotoxumab at any time during the 10 days of antibiotic treatment. Half the people in MODIFY were treated as an outpatient. Severity assessment was done on the day bezlotoxumab or placebo was infused – this should have been done on day 1. This is an acknowledged as a trial fault. Plausible that more subjects would have had severe CDI at baseline than was reported in the study.

- There is a study by Prabhu (2018), which is a post hoc sub-group analysis (all pre-defined). This study found that where there are 2 or more different risk factors for CDI, the NNT (to prevent recurrence) drops to ~2.5.

- There were 2 stratification variables in MODIFY – hospitalisation and standard of care. Decision on which standard of care (SoC) was down to treating physician.

- Issue with fidaxomicin (as SoC) is small numbers (n=56). You can't make robust inferences from the fidaxomicin data. A few NHS trusts don't use any metronidazole or vancomycin i.e. fidaxomicin for all CDIs.

- Adverse events – there is an unexplained numerical imbalance in number of deaths (not statistically significant) in patients receiving bezlotoxumab with underlying congestive cardiac failure. It's a caution, not a contraindication.

How is severity assessment done?

- ZAR score is not used at bedside to aid treatment decisions. It is most often used in studies. Not as easy as saying over 65 and previous CDI.

- Bristol stool chart is an assessment of the type of diarrhoea, not assessment of severity. Diarrhoea frequency and consistency is not useful as a severity criterion.

What's the role of prebiotics and probiotics?

- There are issues with the Cochrane review on probiotics. We don't know if any individually are effective. Individual studies have major flaws that are not addressed in the review.

- Gao study – the placebo group had a claimed CDI risk of 40%, which was halved in probiotic recipients. This baseline risk is implausible. 3% incidence rate of CDI across all those tested in NHS.

- Hickson study – used lactose-based placebo (meaning that placebo recipients could have been biased towards diarrhoea).

- Allen UK study – pivotal study – the largest ever RCT of a probiotic to prevent CDI – no treatment benefit.
- There are small uncontrolled studies on probiotics to prevent CDI / recurrence. Lots of issues with these studies, lots of different definitions, and different products.
- European treatment guidelines from 2014/15 reviewed all probiotic studies – no recommendation made given lack of robust evidence.

How is CDI managed in children?

- Incidence of CDI in children is very low. Would have concerns about how it was diagnosed. Need to ensure that toxin based diagnosis.
- Aware of SUNSHINE study of fidaxomicin in children. This was required for regulatory approval.
- Children treated as per adults, but with care that you have the right diagnosis.

What's the role of bezlotoxumab?

- Only RCT data are from MODIFY studies. There are some limited real world efficacy data.
- Bezlotoxumab has no benefit for initial cure (which is why SoC antibiotic is still required).
- You need antibiotics to stop replication, but monoclonal antibody attacks toxin that has been released by replication. If you dampen down disease process, environment left is less conducive to CD germination. If high toxin load (e.g. very unwell), bezlotoxumab may help theoretically, but this is unproven.

How important is toxin A?

- Controversy over which toxin is important. Anti-toxin A (actoxumab) is not effective. All data points to B being more important in humans.

N.3 Committee Meeting 4: 29/09/2020

Section A: Developer to complete	
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Institution/Organisation (where applicable):	Leeds Teaching Hospitals NHS Trust University of Leeds Public Health England NHS Improvement
Guideline title:	Clostridioides difficile infection: antimicrobial prescribing
Guideline Committee:	Managing common infections
Subject of expert testimony:	*Clostridioides difficile* infection
Evidence gaps or uncertainties:	How is *C difficile* infection managed in clinical practice, including prevention of recurrence? Evidence identified not consistent with current guidelines.

Section B: Expert to complete	
Summary testimony:	Committee Meeting 4: 29/09/2020

The expert witness responded to specific questions posed by the committee chair or other committee members. The responses to those questions are summarised below and are the expert's opinion (unless otherwise stated).

The model makes an assumption that effectiveness of a treatment used 2nd line is the same as if you use it 1st line. Is this assumption correct?

- There is no evidence to argue one way or another.

So, if you believe they are less effective 2nd line, you'd use more effective drug 2nd line?

- Yes. That makes sense. There are no data on response of the same treatment used 1st line compared with 2nd line.

Any comments on the base case that includes teicoplanin?

- Don't understand concentration on teicoplanin. No other guidelines have done that. Data are not robust enough. No UK experience of using to teicoplanin to treat C diff infection (CDI). Using it would be a learning curve for clinicians, and it means using an IV preparation orally.

- The vancomycin/fidaxomicin and vancomycin/fidaxomicin extend populations are not directly comparable; the studies were conducted in different populations. This applies for whichever comparison is looked at.

Any comments on the base case that excludes teicoplanin?

- Clinically, metronidazole 2nd line isn't plausible. This is because there are good data showing it is inferior to vancomycin (as a 1st line treatment). If you give metronidazole 2nd line it would be less clinically effective than what had been given 1st line. Recurrence is the primary reason for clinical failure, when on that pathway, the prognosis is increasingly worse with each new recurrence. It's not clinically acceptable to use an inferior treatment as a 2nd line option.

Why are you confident fidaxomicin is cost effective 2nd line compared with metronidazole 2nd line, as the QALY is in the £20,000 range

- They are not the same populations. If you fail on 1st line treatment – these patients are elderly, who will suffer most consequences of not having an effective treatment. Metronidazole has a 10% absolute chance of clinical success compared with vancomycin. In the fidaxomicin (extend?) studies, patients were significantly older. There are poor quality data, clinical observations, that patients on metronidazole take longer to respond than

with other treatments. This is miserable for patients and carers – it also increases the risk of transmission.

What are the adverse effects of vancomycin given orally?

- In clinical trials of CDI you hardly ever see ototoxicity or nephrotoxicity with oral vancomycin. It is absorbed in negligible quantities when given orally. Adverse effects listed in BNF are dominated by the IV formulation/route of administration.

Is fidaxomicin/fidaxomicin an option?

- No data. It would be expensive in terms of acquisition cost. You would be using the most effective agent twice. It doesn't look like a cost-effective option (from the model). If you ignore cost, there is some plausibility of a fidaxomicin/fidaxomicin strategy.

Comments on bezlotoxumab table?

- None of the comparators (to bezlotoxumab) in the bottom part of table are the ones that have been discussed. No one would consider bezlotoxumab for everybody. The NNT is 2 for someone with 2 risk factors for recurrence/poor outcome. Need to target its use for people who are most likely to benefit.

- Potential people who might benefit most are people with risk factors – that is, if you've had a previous episode of CDI in the last 6m. The other risk factor could be age or immunosupression. Guesstimating – this is a minority of people, up to 20% of all people with CDI. This population has a recurrence rate that is higher – about 50%.

For fidaxomicin to become cost effective, recurrence rate would need to be 1/3 (33%). Are we near that?

- Baseline risk of recurrence with vancomycin is approximately 20-25%, this approximately doubles to about 40% if you've already had a recurrence. It's about 60% if you've had 2 recurrences. Small studies have come up with those figures. But there is an incremental risk.