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Comparative efficacy of treatments for Clostridium difficile infection: a systematic review and network meta-analysis

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Summary

Background

Multiple new treatments have been recently investigated for Clostridium difficile infection (CDI). We aimed to compare and rank treatments for non-recurrent CDI in adults.

Methods

We performed a random effects network meta-analysis within a frequentist setting to obtain direct and indirect comparisons from trials. We searched MEDLINE, EMBASE, Web of Science, CENTRAL and clinicaltrials.gov for published and unpublished trials up to 30th June, 2017. We included randomised controlled trials of treatments for non-multiply recurrent CDI in adults, using the Cochrane risk of bias tool to appraise trial methodology. The primary outcome was sustained symptomatic cure, defined as the number of patients with resolution of diarrhoea minus the number with recurrence or death.

Findings

24 trials, involving 5361 patients and 13 different treatments were included in the final analysis. The overall quality of evidence was rated as moderate-low. For sustained symptomatic cure fidaxomicin (odds ratio [OR] 0·67, 95% confidence interval [CI] 0·55 to 0·82) and teicoplanin (0·37, 0·14 to 0·94) were significantly better than vancomycin. Teicoplanin, ridinilazole, fidaxomicin, surotomycin and vancomycin were better than metronidazole (0·27, 0·10 to 0·70; 0·41, 0·19 to 0·88; 0·49, 0·35 to 0·68; 0·66, 0·45 to 0·97; 0·73, 0·56 to 0·95). Bacitracin was inferior to teicoplanin and fidaxomicin, tolevamer was inferior to all agents apart from LFF571 and bacitracin. Global heterogeneity of the entire network was low, Cochrane Q = 15·70, p = 0·47.

Interpretation

Fidaxomicin demonstrates the best chance of sustained symptomatic cure in non-multiply recurrent CDI with the strongest evidence base. It is better than vancomycin for all patients except those with severe CDI and could be considered as first line therapy. Metronidazole should not be recommended for treatment of CDI.

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Introduction

Reclassification of Clostridium difficile as Clostridioides difficile has been recently proposed,[1] but a preference for the established name prevails. Clostridium difficile infection (CDI) is increasing and is the most common healthcare associated infection in USA, and is rising in the developing world.[2,3] In the USA there were 29, 000 deaths in 2011,[4] and in 2014 it posed a financial burden of 5·4 billion US dollars.[5,6] For more than three decades metronidazole and vancomycin have been the principal treatment options for CDI. However, sub-optimal rates of sustained cure and the increasing prevalence and associated morbidity and mortality from CDI warranted the development and evaluation of new therapeutic agents.

After demonstrating a higher sustained clinical cure rate than vancomycin, fidaxomicin was approved for CDI treatment in 2011.[7] However, the long-term response was not achieved in a significant proportion of patients and research to develop multiple agents to achieve a lasting cure are ongoing. There have been many treatments evaluated in clinical trials for treating CDI, such as tolevamer, an orally taken toxin-binding polymer, as well as multiple directly acting antimicrobials: bacitracin, fusidic acid, surotomycin, ridinidazole, teicoplanin, LFF571, nitazoxanide, cadazolid and rifaximin.

Several pairwise comparison meta-analyses have investigated the efficacy of CDI treatments.[8-12] However, they mostly focused on a subset of treatments investigated for this indication. In addition, there have been several novel and non-published trials which, to our knowledge, to date have not been included or synthesized in a systematic review. Furthermore, most of the agents do not have direct trial comparisons, making it impossible to generate a hierarchy of treatments through pairwise meta-analyses. We therefore performed a network meta-analysis (NMA) aiming to compare and rank treatments for non-multiply recurrent CDI in adults.

Methods

Search strategy

We searched MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov since database inception up to 30th June 2017 for full papers, conference abstracts and proceedings describing therapeutic randomised controlled trials (RCTs) against CDI (Appendix, page 5). We searched the reference lists of systematic reviews of Clostridium difficile treatments published between 1st Jan 2012 and 30th June 2017. To maximise the yield, both MeSH and free text terms were used and no language restrictions were applied. Non-English articles were translated. We searched pharmaceutical company databases, contacted pharmaceutical companies and study authors directly, where trials were registered, but not published.

Two authors (TB, NB) independently reviewed and assessed the eligibility of titles, abstracts and studies deemed relevant for full text review. Any disagreements were resolved through discussion with the third author (VS). A systematic review and NMA was performed according to the guidelines and recommendations from the preferred reporting items for systematic reviews and network meta‐analyses (PRISMA) checklist.[13] For the study protocol, see appendix, page 2.

Inclusion and exclusion criteria

Two authors (TB, NB) reviewed in full all RCTs investigating the therapeutic effects of at least two different treatments for CDI. Studies investigating pharmacological agents, probiotics, immunotherapy and faecal microbiota transfer (FMT) treatments were included if they met the following criteria.

Inclusion criteria:

- Randomised controlled trial.
- Adult patients (≥18 years old).
- Both primary symptomatic cure and recurrence of diarrhoea reported.
- Confirmed CDI, defined as active diarrhoea AND positive Clostridium difficile nucleic acid amplification test OR positive Clostridium difficile cytotoxin assay result OR stool culture growing Clostridium difficile OR pseudomembranes seen on colonoscopy.
- Only multiply recurrent or multiply relapsing Clostridium difficile patients were included. This patient group comprises a minority of patients with CDI and has very different prognosis from the overall patient cohort with CDI.

Exclusion criteria:

- Data not available for intention to treat analysis.
- Prophylactic rather than therapeutic effect of the agent investigated.
- Multiple active agents against CDI used simultaneously.

Outcome measures

Our primary outcome was sustained symptomatic cure, which was calculated as number of patients achieving a primary cure (resolution of diarrhoea per individual trial criteria) at the end of treatment minus the number of patients with recurrence (recurrence of diarrhoea or requirement for additional treatment) or death during the follow-up period. Secondary outcomes were primary cure and recurrence rate.

Data extraction and methodological quality assessment

Two authors (TB and NB) independently reviewed papers included in the final analyses and extracted relevant data (for list of data extracted see appendix, page 3).

The Cochrane risk of bias tool[14] was used to assess the risk of bias (Appendix, page 14) and Revman v5·0[15] to generate the risk of bias tables. We performed intention-to-treat analyses where drop-outs were assumed to be treatment failures. Any discrepancies with data extraction or risk of bias assessment were resolved through consensus decision with a third author (VS).

Statistical analysis

Multiple pairwise meta-analyses for antibiotics against Clostridium difficile have been recently reported by Nelson et al.[8] and were not repeated here. Network meta-analyses allow the comparison of evidence from clinical studies where direct, head-to-head, data is not available, and enables the ranking of treatments in order of efficacy.[16] We performed a random-effects NMA using a frequentist setting.[17] We used the 'Netmeta' package for R for numerical data analysis.[18] A random-effects model was used to obtain the relative treatment effects. Given its widespread use, vancomycin was chosen as a reference treatment. Forest plots were generated to illustrate the treatment effects compared to vancomycin. League tables were used to display the relative efficacy of all available pairwise comparisons of available treatments.[18]

The P-score was used to rank treatments, which can have a value between 0 and 1, with a higher P-scores indicating a greater chance of being the best treatment.[19] A scatter plot was used to spatially visualise the partial order of treatments with regards to primary cure and recurrence rates. NetmetaXL 1·6 ·1[20] was used to generate network graphs, which will be used to illustrate the evidence base. Treatment estimates are presented as odds ratios (ORs) with 95% confidence intervals.

Sensitivity and subgroup analyses

We performed three pre-specified sensitivity analyses. Firstly, non-blinded studies were excluded, as resolution of diarrhoea is semi-objective outcome that can be adversely affected by absence of blinding. In another sensitivity analysis we excluded trials published before 2000. CDI incidence has markedly increased since 2000, coinciding with the emergence of the hypervirulent BI/NAP1/027 strain.[21] We also excluded studies with <50 participants in each study arm to test for small-study effects. In one post-hoc sensitivity analysis, we excluded RCTs performed before 1990.

We further performed subgroup analyses and individual NMAs for patients with severe CDI, non-severe CDI, first CDI, non-first CDI, patients aged <65 years and ≥65 years. We used stratified patients into different severity categories as defined by each trial. These assessment criteria are summarized in the appendix, page 14. For subgroup analyses of fidaxomicin trials, we used review data[12], as primary publications did not provide the recurrence rate. Insufficient data were available to perform inpatient/outpatient subgroup analyses.

Assessment of heterogeneity and inconsistency

A generalised Cochran's Q statistic was used to assess the homogeneity of multivariate meta-analysis.[22] To identify single design and between design contributions to global heterogeneity in the random effects model, the global Cohran's Q score was further decomposed into within design heterogeneity[22] and between designs heterogeneity scores.[23] The between designs Q score was calculated based on a full design-by-treatment interaction random effects model,[23] defined via a generalised methods of moments estimate of the between-studies variance tau^2.[24] A network heat plot was used to visualise and identify the nodes of single-design inconsistency.[22] We checked the consistency between direct and indirect evidence using 'node-splitting'.[25] A p-value of < 0.10 was considered as significant

in inconsistency assessment. Comparison-adjusted funnel plots were generated using STATA (version 14·0) to assess publication and small study bias.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search identified 29, 976 references, of which, 19 publications, representing 20 RCTs, were deemed eligible and were included in the final NMA (Figure 1; Appendix, page 12). Two additional unpublished RCTs[26, 27] were retrieved from the pharmaceutical company database, one of which was published 9 months after the search[26]. Further two unpublished RCTs were provided by pharmaceutical company and authors through direct communication. One trial was in Japanese, the rest were in English. In total 24 RCTs, with 5, 361 unique patients were included in the NMA. Included studies were published between 1983 and 2017 and investigated 13 pharmacological interventions against CDI (Table 1). Follow up-time was between 21 and 30 days for all studies except Louie et al[43] who reported outcomes at 56 days and Guery et al[26] at 90 days. Guery et al[26] also reported results at 30 follow-up, which were used in our analysis to make them more comparable to other studies. None of the FMT, probiotic or immunotherapy trials met the inclusion criteria. All included trials had an active control.

The network was reasonably balanced and interconnected: 5 treatments had more than 400 patients, there were 11 loops. The mean study sample was 223 participants (range 12 – 629) (table 1). Vancomycin was the most frequent intervention, investigated in 21 RCTs

(N=2107), followed by metronidazole (7 RCTs, N=563) and fidaxomicin (6 RCTs, N=881). The mean participant age was 63 years and 53% were female (table 1). The duration of treatment ranged between 4 and 25 days, while the median duration of follow-up was 28 days (range 21-90). 71% trials were sponsored by industry, 8% jointly by government and industry, for 21% of trials funding information was not provided. Most RCTs were carried out in USA, Canada, Australia or Europe. NCT02179658 2016 RCT was carried in Japan, while Boix et al.,[40] also recruited patients from 2 centres in the Middle East. 42% of trials were multinational.

The overall quality of studies was moderate-low (figure 3; appendix, page 14, for supporting judgements). Random sequence generation procedures were adequate and clearly described in only 42% of RCTs, and 7/24 RCTs were non-blinded.

The network for efficacy assessment of sustained symptomatic cure can be seen in figure 2. Network graphs for primary cure and recurrence were identical. All agents had at least one direct comparison with vancomycin. The summary of the pairwise comparisons is shown in the league table (table 2). Teicoplanin (OR 0·37, 95% CI 0·14 to 0·94) and fidaxomicin (OR 0·67, 95% CI 0·55 to 0·82) were significantly better than vancomycin in attaining a sustained symptomatic cure. Vancomycin was superior to metronidazole (OR 0·73, 95% CI 0·56 to 0·95). Teicoplanin, ridinidazole, fidaxomicin and surotomycin were also more efficacious than metronidazole (table 2). Tolevamer was significantly inferior to all agents, apart from LFF571 and bacitracin. In our GRADE assessment, only fidaxomicin had high confidence in its treatment effect (appendix, page 41). Confidence in teicoplanin and ridinidazole treatment effects were rated as very low and moderate, respectively. Vancomycin ranked 7th and metronidazole 11th among 13 assessed agents.

Secondary outcomes: Primary cure and recurrence

No treatment was significantly superior to vancomycin in achieving a primary symptomatic cure (Appendix, page 22). Tolevamer was inferior to all treatments and metronidazole was inferior to vancomycin.

Fidaxomicin had significantly fewer recurrences than vancomycin and metronidazole (Appendix, page 24). Amongst 13 treatments, vancomycin and metronidazole ranked 9th and 11th, respectively.

Consistency of the NMA

Heterogeneity for the entire NMA for sustained symptomatic cure, was not significant (Cochrane Q = 15·70, p = 0·47; tau^2 = 0). Between designs heterogeneity for sustained symptomatic cure was low (Cochrane Q 3·19, p = 0·87) and non-significant for all 11 loops (Appendix, page 21). Within designs heterogeneity (Cochrane Q = 12·61, p = 0·18) was higher due to significant pairwise vancomycin - metronidazole comparison heterogeneity (Cochrane Q = 3·94, p = 0·047). This heterogeneity originated from a markedly higher sustained symptomatic cure rate in metronidazole arm demonstrated in the non-blinded Teasley 1983 trial [41] than in other trials investigating metronidazole and vancomycin. In this trial 1:1 randomisation resulted in markedly lower number of participants in the metronidazole arm (45 vs 56).

A heatplot identified only few faint nodes of direct - indirect evidence inconsistency (Appendix, page 20). This highlighted metronidazole - fusidic acid and fusidic acid - teicoplanin interactions that are influenced by results derived from a four-arm, non-blinded Wenisch et al. RCT.[29] Wenisch et al. results demonstrated a high sustained cure for teicoplanin and significantly higher recurrence rate for patients treated with fusidic acid than subsequent moderate-high quality Wullt et al. 2004 RCT[30] comparing fusidic acid and metronidazole.

Direct versus indirect comparisons of treatment estimates did not reveal any significant differences (Appendix, page 27). A comparison-adjusted funnel plot did not demonstrate any small trial or publication bias (Appendix, page 30). For primary cure global heterogeneity was low (Cochrane Q = 13·52, p = 0·63; tau^2 = 0) (Appendix, page 23). For recurrence, global heterogeneity was significant (Cochrane Q = 24·02, p = 0·09; tau^2 = 0·089), mainly due to significant between design heterogeneity, which was present in 9 out of 11 loops (Appendix, page 25). In isolation, recurrence NMA results should be interpreted with caution.

Sensitivity analysis

Exclusion of non-blinded trials eliminated all teicoplanin and LFF571 RCTs from the NMA (Appendix, page 31). With similar P-scores, ridinilazole and fidaxomicin remained the top ranking treatments. Estimates of other effect sizes did not change significantly and global heterogeneity was low (Cochrane Q = 7·97, p = 0·44, tau^2 = 0). Ridinilazole and fidaxomicin ranked the highest again, when small studies (<50 patients in each arm) and RCTs published before 2000 were excluded. Due to low total participant numbers in ridinilazole treatment arm (N=64), confidence intervals of its treatment effect estimates were very wide. All sensitivity analyses resulted only in minimal changes in treatment effect estimates from the ones seen in the overall NMA (Appendix, pages 31-34).

Subgroup analyses

A limited number of trials had available data for subgroup evaluation and there was no subgroup data for bacitracin, teicoplanin, rifaximin, LFF571 and cadazolid. In subgroup analyses fidaxomicin was superior to vancomycin in non-severe CDI, primary and non-primary CDI and in patients aged both <65 and ≥65 (Table 3). Ridinilazole was significantly better that vancomycin in attaining a sustained symptomatic cure in non-severe CDI and <65

age group. Ridinilazole ranked as the best treatment for severe, non-severe CDI, first CDI and patients <65 year old. Fidaxomicin ranked as the best treatment in non-first CDI and patients aged ≥65. Metronidazole was inferior to fidaxomicin in all subgroups. For full subgroup analyses and rankograms see appendix, pages 35-40.

Discussion

This study provides the most up-to-date and comprehensive synthesis of evidence for pharmacological treatment of Clostridium difficile infection. In addition to published trials, our NMA also included results from 3 unpublished trials that were not included in previous pairwise meta-analyses. In the final selection stage we excluded three recent high quality RCTs[49, 50] investigating the influence of monoclonal antibodies against Clostridium difficile toxins along with antibiotic therapy for achieving a primary cure and preventing the recurrence of CDI. In these trials participants were randomized only into monoclonal antibody or placebo arm, but vancomycin, metronidazole or fidaxomicin therapy was administered according to clinical assessment rather than being assigned randomly. These groups are therefore not comparable to the studies included in our network.

Based on P-score, in our NMA, teicoplanin ranked as the best treatment, ridinilazole and fidaxomicin, ranked second and third, respectively. However, the treatment effect estimates for teicoplanin (GRADE: very low; Appendix, page 41) were only based on two small RCTs, comprising 55 individuals, with high risk of bias, and were performed in 1992 and 1996. The 95% CI of the effect of teicoplanin is wide, reflecting the relatively small number of subjects contributing to the network analysis so the results should be interpreted with caution. The original RCTs[29, 45] used intravenous teicoplanin solution orally. Since 2013, oral teicoplanin liquid form has been licensed to be used for CDI in Europe, however, not in

USA.[51] Oral teicoplanin and vancomycin have been investigated in an earlier cohort study by de Lalla in 1989.[52] Both antibiotics showed excellent clinical response rates (100%), but the relapse rate was 13% vs 0% in vancomycin vs teicoplanin recipients, respectively. Ridinilazole (GRADE: moderate), a CDI specific antibiotic, has only been studied in two RCTs and 64 patients.[32, 48] A phase 3 trial is expected to commence in 2018. Ridinilazole did not demonstrate a high primary cure rate, but had the lowest chance of recurrence among all agents. Having been investigated in 6 RCTs[11, 26, 27, 33, 46, 48] and nearly 900 patients, fidaxomicin (GRADE: high) has the strongest evidence base to support its use. It is significantly better than vancomycin, metronidazole, bacitracin and tolevamer in achieving a sustained cure. On the basis of our results, tolevamer and bacitracin cannot be recommended for treatment of CDI.

Surotomycin and LFF571, two newly developed agents, did not demonstrate any superiority over vancomycin. At the time of writing, only phase 2 trial[36] results for cadazolid were fully available. However, a press release[53] indicates that cadazolid did not meet its primary endpoint in comparison with vancomycin in one of two large international phase 3 trials with more than 1200 patients combined (NCT01987895, NCT01983683).

Since 2014, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines have recommended metronidazole as the first line treatment for initial non-severe CDI.[54] In recent guidelines,[55] vancomycin or fidaxomicin have been recommended as first line treatment for CDI; metronidazole is only recommended for an initial episode of non-severe CDI in settings where access to vancomycin or fidaxomicin is limited.[56] In our NMA, metronidazole ranked only 11th among 13 treatments in achieving a sustained symptomatic cure, was significantly inferior to five other agents and was inferior to fidaxomicin in all subgroup analyses performed. Previous reports suggested high faecal metronidazole concentrations with intravenous administration and proposed its usage when

oral administration is not possible.[57, 58] Results of this NMA do not support use of metronidazole as first-line CDI therapy in oral form and intravenous form is equally unlikely to be effective. For non-initial CDI, ESCMID guidelines recommend vancomycin or fidaxomicin.[54] In our NMA, fidaxomicin had a significantly higher sustained cure rate than vancomycin in this patient group and might be considered as a better first-line agent. Furthermore, a very recent Guery et al. RCT[26] compared an extended duration dosage of fidaxomicin with conventional vancomycin, and demonstrated a high sustained symptomatic cure rate, owing to very low, and significantly reduced CDI recurrence rate compared with vancomycin (7/131 vs 30/136). The recurrence in a subgroup of patients with NAP1/BI/027 strain was not different between fidaxomicin and vancomycin arms in phase 3 trial.[33] However, this trial was not powered to determine the effectiveness of fidaxomicin against certain C difficile strains. The use of fidaxomicin as a first line CDI agent is partially supported by the overall body of economic evaluations, in which it was more cost-effective than either vancomycin or metronidazole.[59]

The overall consistency of NMA for sustained symptomatic cure was good with none of the loops showing significant heterogeneity. Nevertheless, there are several limitations to this study. We included all randomised controlled trials, even those without sufficient blinding. Teicoplanin, which ranked as the best treatment in overall NMA, was lost from NMA in sensitivity analysis, when non-blinded trials were excluded. Secondly, the majority of trials were sponsored by industry. Exclusion of these trials would have left almost no trials to compare and this sensitivity analysis could not be performed. Thirdly, no unified CDI severity assessment systems was used among RCTs. This makes non-severe versus severe CDI subgroup assessment less reliable. Finally, in our NMA we included all treatments that were investigated as monotherapy against CDI, even though some of them are no longer in clinical development for CDI treatment or their use is limited by licensing barriers:

353 teicoplanin is not licensed for CDI treatment in USA, Merck has discontinued the
354 development of surotomycin after its international phase 3 trial, while ridinilazole is still to
355 undergo a phase 3 trial. However, inclusion of data from these trials allows us to obtain more
356 accurate treatment effect estimates for the remaining members of the NMA. Given its
357 promise in small low quality RCTs, oral teicoplanin should be investigated in a large well
358 designed RCT to establish its sustained symptomatic cure effect more accurately.

359 The findings of this NMA suggest that of the currently approved treatments,
360 fidaxomicin has the strongest evidence for being the most effective treatment in providing a
361 long-term cure against CDI. Apart from financial affordability, there is little ground for using
362 metronidazole as first-line treatment against CDI. Early data for ridinilazole suggest this can
363 potentially become a new efficacious treatment against CDI, but results of its phase 3 trials
364 are still awaited.

365 **Contributors**

366 TB wrote the study protocol, performed searches, study selection, data extraction, statistical
367 analyses and wrote the initial draft of the manuscript and performed revisions, NB wrote the
368 study protocol, performed study selection, data extraction, contributed to statistical analysis,
369 wrote the final manuscript and performed revision, MW contributed to data analysis and
370 interpretation and writing the final manuscript and performing manuscript revisions, VS
371 developed the study, was the arbiter for the study searches and data extraction, contributed to
372 the statistical analysis, writing the final manuscript and performing revisions.

373 **Declaration of interests**

374 TB, NB, VS declare no competing interests. MW reports grants and personal fees
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Tables and figures

Figure 1. Study selection

Table 1. Summary of the included trials.

BAC – bacitracin, BD – twice a day, CAD - cadazolid, FID- fidaxomicin, FUA – fusidic acid, IND – industry, GOV – government, MET – metronidazole, NIT – nitazoxanide, OC – oral capsule, OL- oral liquid, QDS – four time a day, RFX – rifaximin, RID – ridinidazole, SUR – surotomycin, TDS – three times a day, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin

*Although authors present follow-up results up to 90 days, we use 30 day follow-up results for our analysis to maximize the transitivity bet ween network meta-analysis studies

Figure 2. Network of eligible comparisons for efficacy of treatments of C. Diff.

Line width is proportional to the number of trials comparing every pair of treatments. The size of the circle is pr oportional to the number of patients assigned. BAC – bacitracin, CAD- cadazolid, FID- fidaxomicin, FUA – fusi dic acid, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, SUR – surotomycin, TEIC – teicoplani n, TOL – tolevamer, VAN – vancomycin.

Figure 3. Summary of risk of bias assessment.

Johnson et al. 2014 reported two trials – 301 and 302. Both were of identical design. For supporting judgements see appendix, page 14.

Table 2. League table of pairwise comparisons in network meta-analysis for attaining a sustained symptomatic cure.

Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence

intervals. Significant pairwise comparisons are highlighted. BAC – bacitracin, CAD - cadazolid, FID - fidaxomicin, FUE – Fusidic acid, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, SUR – surotomycin, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin.

Table 3. Summary of subgroup analyses for sustained symptomatic cure compared to vancomyc in.

Effect sizes provided in odds ratios. Significant interactions are highlighed. FID – Fidaxomicin, FUA – Fusidic acid, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, SUR – surotomycin, TOL – tolevamer

Research in context

Evidence before this study

We performed a systematic literature search on Pubmed, EMBASE and Web of Science for systematic reviews and meta-analyses of treatments for Clostridioides difficile infection (CDI). We performed search for period between 1st Jan 2010 and 1st June 2017 using MeSH terms „Clostridium difficile“ and „Meta-analysis“ as well as key words „CDI“, „CDAD“ and „systematic review“, „meta analysis“ (All fields), restricting the search to meta-analyses and systematic reviews. Only meta-analyses of randomized controlled trials for CDI treatment were included. 418 records were identified, of which 4 met the inclusion criteria. 1 meta-analysis focused on head-to-head comparison of fidaxomicin, metronidazole and vancomycin, 1 on fidaxomicin and vancomicin only and 2 meta-analyses on all antibiotics trialled for CDI. We found no network meta-analyses.

The most comprehensive Cochrane meta-analysis by Nelson and colleagues published in 2017 performed pairwise comparisons for different antibiotics, only where direct evidence was available. There have been no analyses of indirect evidence for treatments of primary CDI, to rank the treatments in order of efficacy.

Added value of this study

This is the first network meta-analysis of pharmacological treatments for Clostridium difficile infection. It comprises of 13 different treatments and allows comparison and ranking of efficacy for treatments that did not have direct head-to-head comparison. We included four trials that have not been published and were not included in previous, pairwise meta-analyses. Our study emphasizes that fidaxomicin is the treatment with the strongest evidence for achieving a sustained symptomatic cure in CDI, while metronidazole is poorer than many other agents at achieving a sustained symptomatic cure. We also demonstrate that teicoplanin

and ridinidazole could potentially be effective treatments for CDI, however, their routine implementation should await results from larger trials.

Implications of all the available evidence

Our findings indicate that fidaxomicin and vancomycin can be recommended as a first line treatments for Clostridium difficile infection. Metronidazole cannot be recommended for treatment of CDI. In Europe, if fidaxomicin or vancomycin are unavailable, treatment with oral teicoplanin might be attempted.

Figure 1

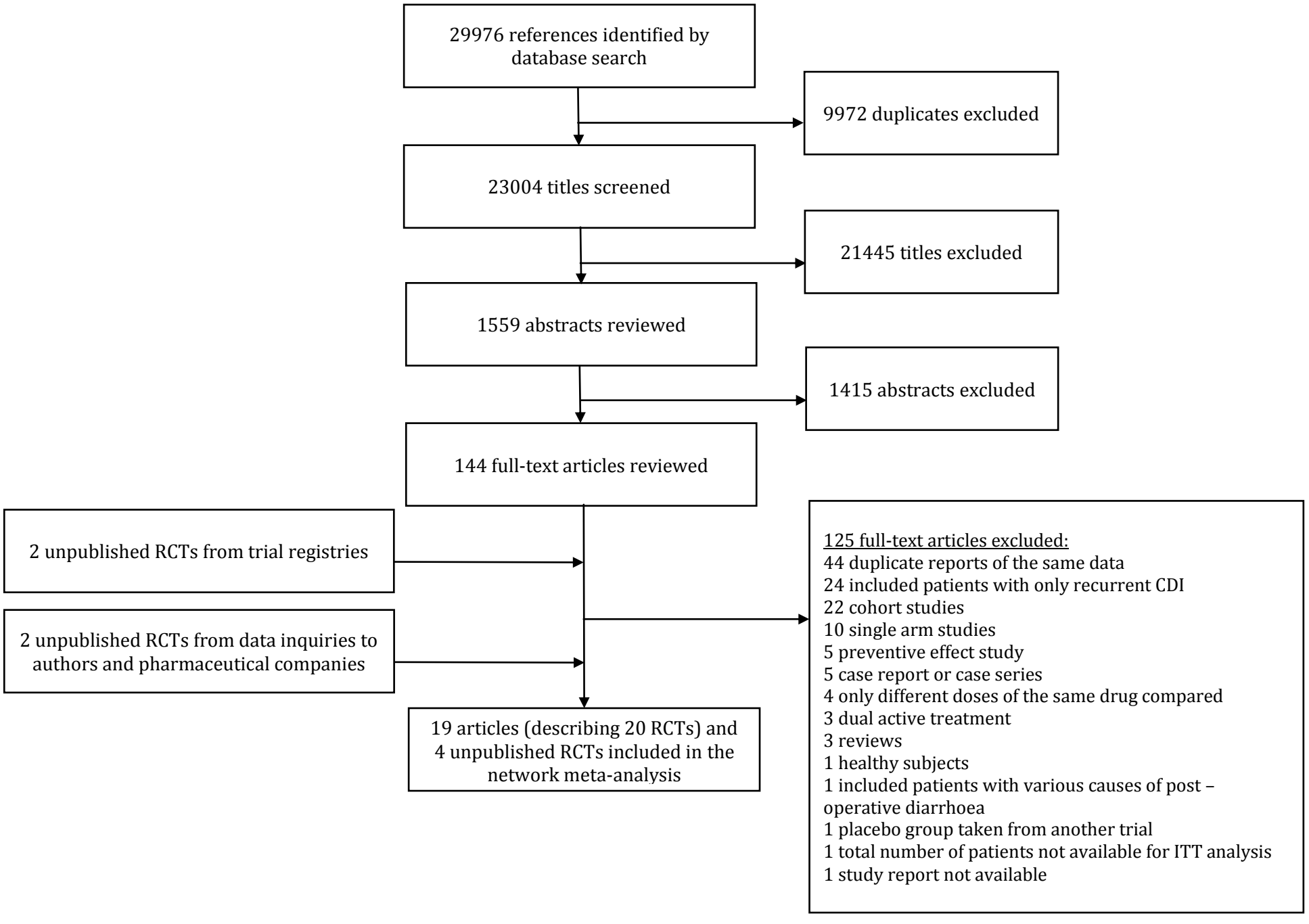

29976 references identified by database search
9972 duplicates excluded
23004 titles screened
21445 titles excluded
1559 abstracts reviewed
1415 abstracts excluded
144 full-text articles reviewed
2 unpublished RCTs from trial registries
2 unpublished RCTs from data inquiries to authors and pharmaceutical companies
19 articles (describing 20 RCTs) and 4 unpublished RCTs included in the network meta-analysis
125 full-text articles excluded:
44 duplicate reports of the same data
24 included patients with only recurrent CDI
22 cohort studies
10 single arm studies
5 preventive effect study
5 case report or case series
4 only different doses of the same drug compared
3 dual active treatment
3 reviews
1 healthy subjects
1 included patients with various causes of post – operative diarrhoea
1 placebo group taken from another trial
1 total number of patients not available for ITT analysis
1 study report not available

Figure 2

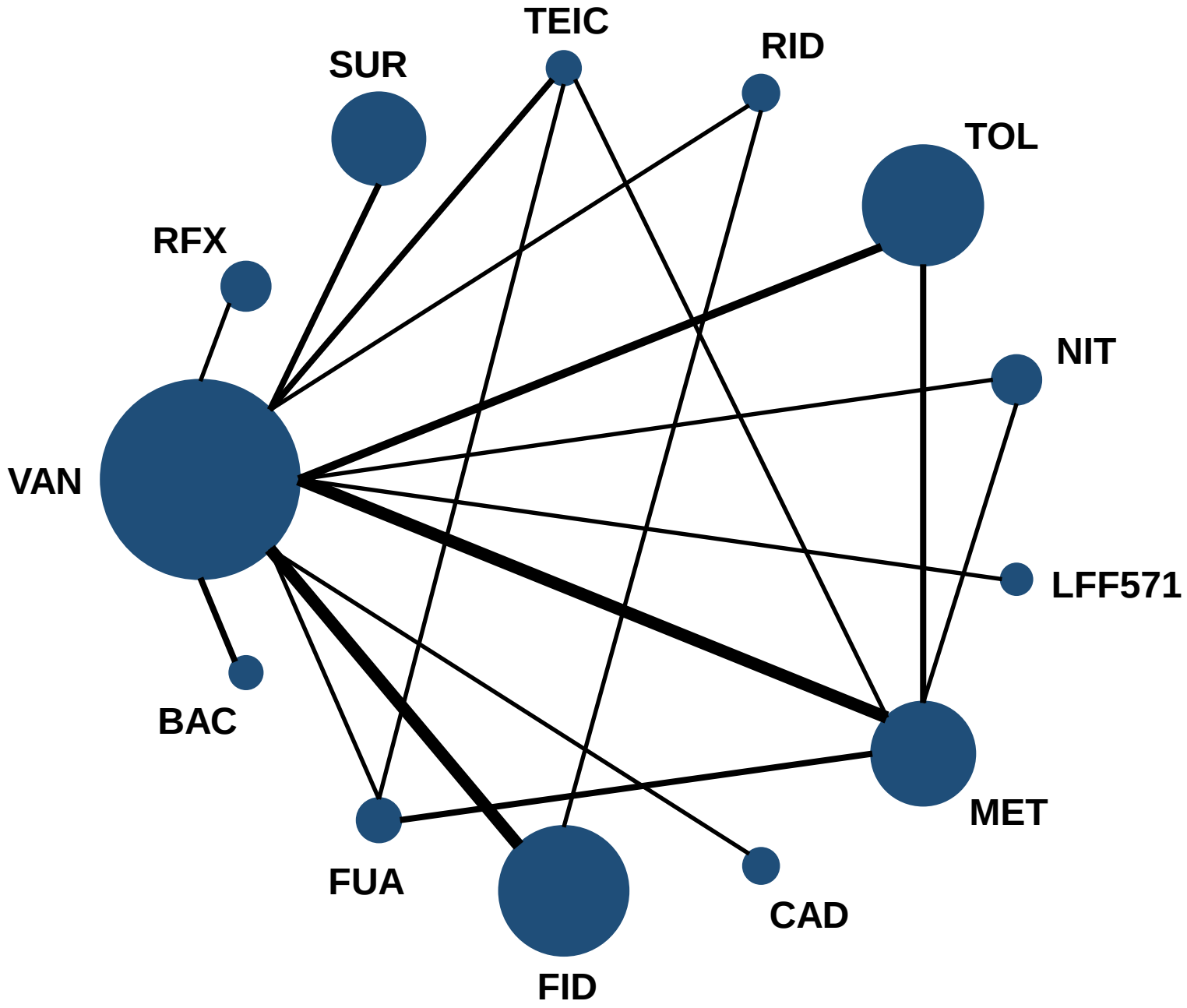


Figure 3

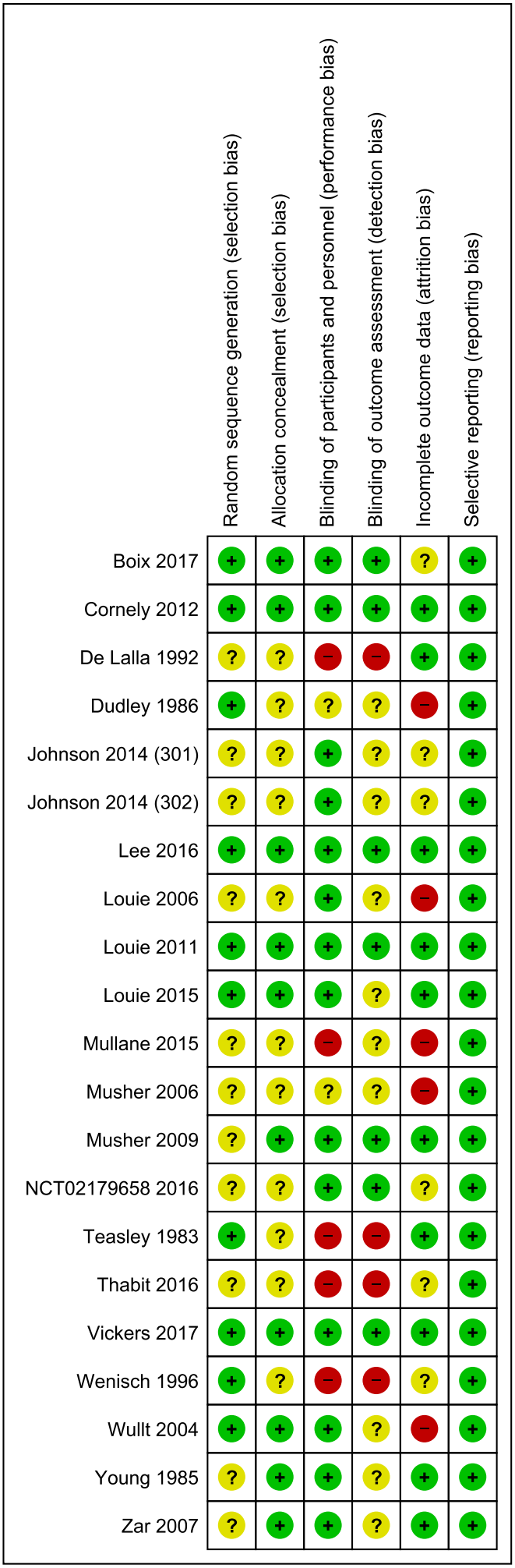

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Boix 2017
Cornely 2012
De Lalla 1992
Dudley 1986
Johnson 2014 (301)
Johnson 2014 (302)
Lee 2016
Louie 2006
Louie 2011
Louie 2015
Mullane 2015
Musher 2006
Musher 2009
NCT02179658 2016
Teasley 1983
Thabit 2016
Vickers 2017
Wenisch 1996
Wullt 2004
Young 1985
Zar 2007

Table 1 - 24th Apr

Study	Treatment, dose, form, frequency, duration (days), sample size	Follow-up (days)	Female	Mean age (years)	Severe CDI	Location	Sponsorship
Zar 2007 [28]	VAN 125mg OL QDS 10d, N=82 MET 250mg OC QDS 10d, N=90	N/A	41%	58	48%	USA	N/A
Wenisch 1996 [29]	VAN 500mg OC TDS 10d, N=31 MET 500mg OC TDS 10d, N=31 TEIC 400mg OL BD 10d, N=28 FUA 500mg OC TDS 10d, N=29	30	48%	42	N/A	Austria	N/A
Wullt 2004 [30]	MET 400mg OC TDS 7d, N=64 FUA 250mg OC TDS 7d, N=67	30	65%	58	N/A	Sweden	GOV + IND
Young 1985 [31]	VAN 125mg OC QDS 7d, N=21 BAC 20000 UNITS OC QDS 4d N=21	28	N/A	62	N/A	Australia	N/A
Vickers 2017 [32]	VAN 125mg OC QDS 10d, N=50 RID 200mg OC BD 10d, N=50	30	66%	57	16%	USA	IND
Louie 2011 [33]	VAN 125mg OC QDS 10d, N=327 FID 200mg OC BD 10d, N=302	28	56%	62	39%	USA, Canada	IND
Cornely 2012 [34]	VAN 125mg OC QDS 10d, N=265 FID 200mg OC BD 10d, N=270	28	61%	63	24%	USA, Canada, Europe	IND
Mullane 2015 [35]	VAN 125mg OC QDS 10d, N=26 LFF571 200mg OC QDS 10d, N=46	30	65%	58	20%	USA, Canada	IND
Louie 2015 [36]	VAN 125mg OC QDS 10d, N=22 CAD 250, 500, 1000mg OL BD 10d, N=62	30	39%	51	9%	Canada, Germany, United Kingdom, USA	IND
Musher 2006 [37]	MET 250mg OC QDS 10d, N=44 NIT 500mg OC BD 7d or 10d, N=98	21	24%	68	N/A	USA	IND
Musher 2009 [38]	VAN 125mg OC QDS 10d, N=27 NIT 500mg OC BD 10d, N=23	21	34%	63	41%	USA	IND
Dudley 1986 [39]	VAN 500mg OL QDS 10d, N=31 BAC 25000 UNITS OL QDS 10d, N=31	N/A	60%	69	N/A	USA	N/A
Boix 2017 [40]	VAN 125mg OC QDS 10d, N=298 SUR 250mg OC BD 10d, N=308	30	40%	61	34%	USA, Canada, Europe, Middle-East	IND
Teasley 1983 [41]	VAN 500mg OC QDS 10d, N=56 MET 250mg OC QDS 10d, N=45	21	N/A	65	N/A	USA	GOV + IND
Lee 2016 [42]	VAN 125mg OC QDS 10d, N=70 SUR 125, 250mg OCs BD 10d, N=139	28	63%	N/A	6%	USA, Canada	IND
Louie 2006 [43]	VAN 125mg OC QDS 10d, N=96 TOL 3g, 6g OCs TDS 14d, N=190	56	55%	67	1%	USA, Canada, UK	IND
Johnson 2014 (301) [44]	VAN 125mg OC QDS 10d, N=140 MET 375mg OC QDS 10d, N=149 TOL 3g OL TDS 14d, N=285	28	53%	62	34%	USA, Canada, Europe, Canada	IND
Johnson 2014 (302) [44]	VAN 125mg OC QDS 10d, N=126 MET 375mg OC QDS 10d, N=140 TOL 3g OL TDS 14d, N=278	28	54%	68	24%	USA, Canada, Europe, Canada	IND

De Lalla 1992 [45]	VAN 500mg OL QDS 10d, N=24 TEIC 100mg OL BD 10d, N=27	30	69%	N/A	N/A	Italy	N/A
Thabit 2016 [46]	VAN 125mg OC QDS 10d, N=5 FID 200mg OC BD 10d, N=7	28	50%	70	N/A	USA	IND
NCT02179658 2016 (unpublished) [27]	VAN 125mg OL QDS 10d, N=109 FID 200mg OC BD 10d, N=106	28	52%	75	22%	Japan	IND
Guery 2017 [26]	VAN 125mg OC QDS 10d, N=181 FID 200mg OC BD 5d, then OD every 2 days for 20d, N=183	90*	58%	75	27%	Europe, Turkey	IND
Pardi 2012 (unpublished) [47]	VAN 125mg OC QDS 10d, N=119 RFX 400mg OC TDS 10d, N=119	28	61%	60	N/A	USA	IND
Mitra 2017 (unpublished) [48]	RID 200mg OC BD 10d, N=14 FID 200mg OC BD 10d, N=13	30	N/A	N/A	7%	UK	IND

Table 2

0·9386												
TEIC	0·8280											
0·65 [0·20; 2·12]	**RID**	0·7922										
0·55 [0·21; 1·44]	0·84 [0·41; 1·74]	**FID**	0·6951									
0·53 [0·13; 2·15]	0·82 [0·23; 2·86]	0·97 [0·34; 2·78]	**CAD**	0·5820								
0·41 [0·15; 1·10]	0·63 [0·29; 1·35]	0·75 [0·53; 1·06]	0·77 [0·26; 2·24]	**SUR**	0·5405							
0·39 [0·13; 1·21]	0·60 [0·23; 1·58]	0·72 [0·37; 1·41]	0·74 [0·22; 2·49]	0·96 [0·48; 1·94]	**NIT**	0·4850						
0·37 [0·14; 0·94]	0·57 [0·28; 1·15]	**0·67 [0·55; 0·82]**	0·69 [0·25; 1·94]	0·90 [0·68; 1·19]	0·93 [0·49; 1·78]	**VAN**	0·4296					
0·34 [0·11; 1·01]	0·52 [0·21; 1·28]	0·62 [0·34; 1·12]	0·64 [0·20; 2·06]	0·83 [0·44; 1·55]	0·86 [0·37; 2·02]	0·92 [0·53; 1·61]	**RFX**	0·3794				
0·31 [0·11; 0·89]	0·48 [0·19; 1·23]	0·57 [0·30; 1·09]	0·59 [0·18; 1·95]	0·77 [0·39; 1·50]	0·80 [0·35; 1·84]	0·85 [0·47; 1·57]	0·93 [0·41; 2·11]	**FUA**	0·3635			
0·29 [0·08; 1·15]	0·45 [0·13; 1·52]	0·54 [0·20; 1·46]	0·55 [0·13; 2·29]	0·72 [0·26; 1·99]	0·75 [0·23; 2·42]	0·80 [0·30; 2·13]	0·87 [0·28; 2·68]	0·94 [0·30; 2·97]	**LFF571**	0·2411		
0·27 [0·10; 0·70]	**0·41 [0·19; 0·88]**	**0·49 [0·35; 0·68]**	0·51 [0·17; 1·46]	**0·66 [0·45; 0·97]**	0·68 [0·37; 1·27]	**0·73 [0·56; 0·95]**	0·79 [0·43; 1·47]	0·86 [0·48; 1·52]	0·92 [0·33; 2·53]	**MET**	0·2006	
0·22 [0·06; 0·77]	0·34 [0·11; 1·00]	**0·40 [0·17; 0·94]**	0·42 [0·11; 1·55]	0·54 [0·23; 1·28]	0·56 [0·20; 1·59]	0·60 [0·26; 1·36]	0·65 [0·24; 1·76]	0·70 [0·25; 1·95]	0·75 [0·21; 2·70]	0·82 [0·35; 1·94]	**BAC**	0·0245
0·15 [0·06; 0·39]	**0·23 [0·11; 0·48]**	**0·27 [0·20; 0·37]**	**0·28 [0·10; 0·80]**	**0·36 [0·25; 0·53]**	**0·38 [0·20; 0·73]**	**0·40 [0·32; 0·51]**	**0·44 [0·24; 0·80]**	**0·47 [0·25; 0·87]**	0·50 [0·18; 1·39]	**0·55 [0·42; 0·72]**	0·67 [0·28; 1·58]	**TOL**

Table 3

	RID	FID	NIT	MET	SUR	TOL	FUA
Severe CDI	0·37 [0·05; 3·06]	0·57 [0·30; 1·11]	0·64 [0·09; 4·37]	1·47 [0·78; 2·78]	4·33 [0·14; 137·06]	**2·67 [1·30; 5·49]**	N/A
Non-Severe CDI	**0·36 [0·14; 0·93]**	**0·47 [0·33; 0·66]**	0·80 [0·15; 4·26]	**1·57 [1·06; 2·32]**	0·59 [0·31; 1·12]	**2·86 [2·00; 4·08]**	N/A
Initial CDI	0·43 [0·18; 1·05]	**0·52 [0·38; 0·70]**	0·71 [0·18; 2·76]	1·34 [0·90; 1·99]	0·56 [0·28; 1·11]	**3·10 [2·18; 4·40]**	0·84 [0·37; 1·90]
Non-initial CDI	0·37 [0·04; 3·61]	**0·45 [0·24; 0·84]**	1·50 [0·06; 40·63]	1·80 [0·86; 3·75]	0·76 [0·18; 3·23]	1·74 [0·90; 3·37]	N/A
≥65 year old	0·79 [0·22; 2·77]	**0·54 [0·38; 0·77]**	N/A	1·61 [1·00; 2·58]	1·01 [0·39; 2·60]	**2·90 [1·91; 4·41]**	N/A
<65 year old	**0·26 [0·08; 0·80]**	**0·47 [0·31; 0·71]**	N/A	1·30 [0·78; 2·18]	0·45 [0·20; 1·02]	**2·52 [1·60; 3·96]**	N/A

Comparative efficacy of treatments for Clostridium difficile infection: a network meta-analysis

Tumas Beinortas, Nicholas Burr, Mark Wilcox, Venkatamaran Subramanian

Supplementary appendix to the manuscript

Appendix 1. Study protocol

Comparative efficacy of treatments for Clostridium difficile infection: a network meta-analysis

Study protocol

Background

Clostridium difficile infection (CDI) has become the commonest iatrogenic infection in the developed world.[1] Multiple treatments have been investigated and trialled in this patient group. Previous meta-analyses compared only interventions that had direct head-to-head comparisons in randomised controlled trials. Such approach does not allow the comparison of efficacy of treatments that have not been compared directly in randomised controlled trials and therefore does not permit generation of treatment hierarchies. In addition, agents like tolevamer, a polymer, have been omitted from previous meta-analyses. To compare the efficacy of all pharmacological treatments against CDI and to create treatment efficacy hierarchies we will conduct a network meta-analysis (NMA). NMA allows the efficacy comparison of interventions that do and do not have direct head-to-head comparison and allows generation of treatment hierarchies. Like conventional meta-analyses, NMAs also have tools to assess the heterogeneity and inaccuracy of efficacy estimates.

Objectives

The main objective of this project is to obtain all possible evidence for treatment of CDI and to summarize the efficacy hierarchy of treatments investigated so far.

Study inclusion criteria

Types of studies

Randomised controlled trials, comparing at least two treatments for primary or recurrent CDI. Non-controlled, retrospective studies and studies, having fewer than 10 participants in total, will be excluded. Studies, comparing different dosing or delivery regimes of the same treatment modality without comparison with different treatment class, will be excluded. No language restrictions will be applied. Trials available only in abstract form or not reporting full patient numbers for intention-to-treat analysis will be excluded.

Types of participants

We included 18 year old and older patients with evidence of active Clostridium difficile associated diarrhoea.

Inclusion criteria:

18 year old and older patients
Confirmed Clostridium difficile infection:

1. Active diarrhoea AND
2. Positive C difficile nucleic acid amplification test OR
3. Positive C difficile cytotoxin assay result OR
4. Stool culture growing C difficile OR
5. Pseudomembranes seen on colonoscopy

Exclusion criteria:

No diarrhoea
Multiple active treatments used simultaneously
Multiply recurrent or multiply refractory CDI

Types of interventions

Studies investigating preventive therapies or multiple therapies in conjunction, will be excluded. Oral, intravenous pharmacological agents (antibiotics, resins, polymers, antibodies) or their enemas, probiotics, faecal microbiota transplant trials will be includedif they meet the criteria mentioned above.

Any interventions meeting the above criteria will be included in the analysis regardless of their licensing state.

Types of outcome measures

Primary outcome

Sustained symptomatic cure, defined as resolution of diarrhea at the end of treatment period, no recurrence of diarrhoea and no requirement of further treatment and no death during the follow-up period

Secondary outcomes

Primary cure, defined as resolution of diarrhoea at the end of treatment period.
Recurrence, defined as recurrence of diarhoea within the follow-up period after attainment of the primary cure.

Searching strategies

Electronic searches

MEDLINE, EMBASE, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL) will be searched since database inception using both plain and MeSH terms. No publication type and language restrictions will be applied.

Searching other sources

We will screen the reference lists of systematic reviews and/or meta-analyses published on CDI. We will search clinicaltrials.gov for all relevant trials and contact authors of important unpublished trials. We will also search the pharmaceutical company clinical trial databases for unpublished trials.

Data collection and analysis

Study selection

Two authors will independently screen all titles and abstracts for full paper review. Any disagreements for full paper review will be resolved by consensus decision. In case, where multiple articles describe the same trial, only the most comprehensive description will be included.

Data extraction

Data from selected papers will be extracted by two authors independently in a predesigned table. Any disagreements will be resolved through discussion with the third author. The following data will be extracted:

- First author name and year of publication
- Trial registration number
- Funding source
- Investigated agents
- Duration of follow-up
- Geographical location
- Definition of CDI severity
- Definition of primary cure
- Adjunctive therapy
- Ethnicity of study participants
- Patient characteristics in each study group (age, gender, duration of diarrhoea, % with previous CDI, % with severe CDI, % inpatient)
- Total number of patients randomised in each arm
- Outcome data: number of patients attaining a primary cure, number of patients experiencing a recurrence after primary cure. We will only use intention to treat results.

Assessment of risk of bias

Two authors will independently perform a critical appraisal of selected full studies. Cochrane risk of bias criteria will be used to evaluate the methodological quality of studies.[2] The following domains will be assessed: random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete outcome data (attrition bias), selective reporting (whether the most important outcomes have been reported).

Data analysis

Intention to treat analysis will be used to summarise the individual study results. Any treatment discontinuation will be considered as failure. Random effects model will be utilised for pairwise comparison of two agents.

Frequentist setting will be used to perform a network meta-analysis.

Dichotomous outcomes will be expressed as odds ratio with 95% confidence interval. Cochrane Q statistic will be used to report the degree of statistical heterogeneity. Clinical heterogeneity will be assessed by analysing the patient groups and treatment regimes.

Heterogeneity in network meta-analyses will be summarised by:

- Cochrane Q statistic
- Comparing direct and indirect evidence
- Inconsistency plot

Studies providing significant inconsistency will be removed in sensitivity analysis.

R statistical software package 'netmeta' will be employed for statistical analyses.[3]

Sensitivity analyses

We plan the follow sensitivity analyses:

- Only blinded RCTs
- Only trials published after 2000
- Only trials with 50 or more patients in each investigation group
- Only non-industry funded trials

Subgroup analyses

We plan the following subgroup analyses:

- ≥65 versus <65 year old
- Inpatient versus outpatient onset of CDI
- Severe versus non-severe CDI
- Initial versus non-initial CDI episode

References

1. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility-associated Clostridium difficile Infection and of healthcare-associated infection due to methicillin-resistant Staphylococcus aureus in community hospitals. Infection control and hospital epidemiology 2011; **32**(4): 387-90.
2. Higgins J. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. http://training.cochrane.org/handbook
3. Rücker G, Schwarzer G, Krahn U, König J. netmeta: Network Meta-Analysis using Frequentist Methods. R package version 0.8-0. 2015. http://cran.at.r-project.org/web/packages/netmeta/

Appendix 2. Search strategy

Ovid MEDLINE search

1. "clostridium difficile"[MeSH Terms]
2. "clostridium difficile"[All Fields]
3. “difficile” [All terms]
4. “C. difficile” [All Fields]
5. “c difficile” [All Fields]
6. “Enterocolitis, pseudomembranous” [MeSH Terms]
7. “pseudomembranous” [All Fields]
8. “antibiotic diarrhoea” [All Fields]
9. “antibiotic colitis” [All fields]
10. “CDI OR CDAD” [All Fields]
11. “Clostridium difficile infections” [All Fields]
12. “Clostridium difficile associated diarrhoea” [All Fields]
13. 1 OR 2 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13

14. "anti-bacterial agents"[MeSH Terms]
15. "anti-bacterial agents"[All Fields]
16. "anti-bacterial"[All Fields]
17. "antibiotic*"[All Fields]
18. “(Vancomycin or Metronidazole or Fusidic acid or Nitazoxanide or Teicoplanin or Rifampicin or Rifaximin or Bacitracin or Fidaxomicin or Amoxicillin or Azithromycin or Cephalosporin* or Cephalexin or Ciprofloxacin or Clarithromycin or Clindamycin or Doxycycline or Erythromycin or Flouroquinolone* or Levofloxacin or Macrolide* or Nitrofurantoin or Penicillin or Tetracycline or Trimethoprim or antibiotic* or Surotomycin or anti-bacterial* or anti bacterial* or antibacterial* or bacteriocid* or bactericid* or antimicrobial* or anti-microbial*)
19. 14 OR 15 OR 16 OR 17 OR 18

20. "styrenesulfonic acid polymer" [All Fields]
21. “cholestyramine resin” [MeSH Terms]
22. “Colestipol’ [MeSH Terms]
23. “(Tolevamer OR colestipol OR cholestyramine)” [All fields]
24. 20 OR 21 OR 22 OR 23

25. “Fecal microbiota transplantation” [MeSH Terms]
26. “Fecal microbiota transplantation” [All fields]
27. “Fecal microbiota transplant” [All fields]
28. “FMT” [All fields]
29. “fecal transplant” [All fields]
30. “faecal transplant” [All fields]
31. “(microbial OR microbiota) AND transplant*” [All fields]
32. 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31

33. “Probiotics” [MeSH Terms]
34. “Probiotic*” [All fields]
35. “Immunotherapy” [MeSH Terms]
36. “(immunoglobulin OR antibody OR antibodies OR immunotherapy)” [All fields]
37. 33 OR 34 OR 35 OR 36

38. 20 OR 25 OR 32 OR 37

39. 13 OR 38

EMBASE (Ovid) search

af=all fields
1. clostridium difficile.af.
2. Difficile.af.
3. c difficile.af.
4. pseudomembranous enterocolitis.af.
5. Pseudomembranous.af.

6. antibiotic diarrhoea.af.
7. antibiotic colitis.af.
8. (CDI or CDAD).af.
9. Clostridium difficile infections.af.
10. Clostridium difficile associated diarrhoea.af.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
12. antiinfective agent.af.
13. anti-bacterial agents.af.
14. Anti-bacterial.af.
15. Antibiotic*.af.
16. (Vancomycin or Metronidazole or Fusidic acid or Nitazoxanide or Teicoplanin or Rifampicin or Rifaximin or Bacitracin or Fidaxomicin or Amoxicillin or Azithromycin or Cephalosporin* or Cephalexin or Ciprofloxacin or Clarithromycin or Clindamycin or Doxycycline or Erythromycin or Flouroquinolone* or Levofloxacin or Macrolide* or Nitrofurantoin or Penicillin or Tetracycline or Trimethoprim or antibiotic* or Surotomycin or anti-bacterial* or anti bacterial* or antibacterial* or bacteriocid* or bactericid* or antimicrobial* or anti-microbial*).af.
17. 13 or 14 or 15 or 16 or 17
18. styrenesulfonic acid polymer.af.
19. cholestyramine resin.af.
20. Colestipol.af.
21. (Tolevamer or colestipol or cholestyramine).af.
22. 19 or 20 or 21 or 22
23. Fecal microbiota transplantation.af.
24. Fecal microbiota transplant.af.
25. FMT.af.
26. fecal transplant.af.
27. faecal transplant.af.
28. ((microbial or microbiota) and transplant*).af.
29. 24 or 25 or 26 or 27 or 28 or 29
30. Probiotics.af.
31. Probiotic.af.
32. Immunotherapy.af.
33. (immunoglobulin or antibody or antibodies or immunotherapy).af.
34. 31 or 32 or 33 or 34
35. 18 or 23 or 30 or 35
36. 11 AND 35

Web of Science search

1. ts=clostridium difficile
2. ts=Difficile
3. ts=c difficile
4. ts=pseudomembranous enterocolitis
5. ts=Pseudomembranous
6. ts=antibiotic diarrhoea
7. ts=antibiotic colitis
8. ts=(CDI or CDAD)
9. ts=Clostridium difficile infections
10. ts=Clostridium difficile associated diarrhoea
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
12. ts=Anti-infective agent*
13. ts=anti-bacterial agent*
14. ts=Anti-bacterial
15. ts=Antibiotic*
16. ts=(Vancomycin or Metronidazole or Fusidic acid or Nitazoxanide or Teicoplanin or Rifampicin or Rifaximin or Bacitracin or Fidaxomicin or Amoxicillin or Azithromycin or Cephalosporin* or Cephalexin or Ciprofloxacin or Clarithromycin or Clindamycin or Doxycycline or Erythromycin or Flouroquinolone* or Levofloxacin or Macrolide* or Nitrofurantoin or Penicillin or Tetracycline or Trimethoprim or antibiotic* or Surotomycin or anti-bacterial* or anti bacterial* or antibacterial* or bacteriocid* or bactericid* or antimicrobial* or anti-microbial*)
17. 13 or 14 or 15 or 16 or 17
18. ts=styrenesulfonic acid polymer
19. ts=cholestyramine resin
20. ts=Colestipol
21. ts=(Tolevamer or colestipol or cholestyramine)
22. 19 or 20 or 21 or 22
23. ts=Fecal microbiota transplantation

24. ts=Fecal microbiota transplant
25. ts=FMT
26. ts=fecal transplant
27. ts=faecal transplant
28. ts=((microbial or microbiota) and transplant*)
29. 24 or 25 or 26 or 27 or 28 or 29
30. ts=Probiotics
31. ts=Probiotic
32. ts=Immunotherapy
33. ts=(immunoglobulin or antibody or antibodies or immunotherapy)
34. 31 or 32 or 33 or 34
35. 18 or 23 or 30 or 35
36. 11 AND 35

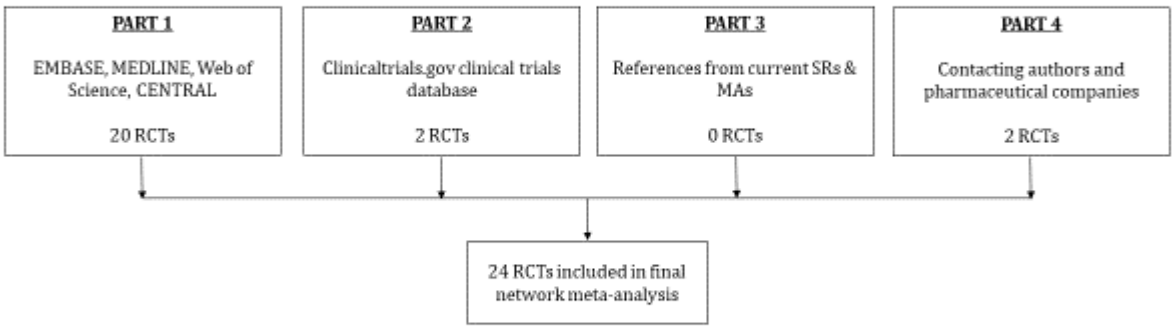
37. ts=randomized controlled trial
38. ts=Trial
39. ts=Longitudinal Stud*
40. ts=Prospective Stud*
41. ts=Random
42. ts=Cohort Stud*
43. ts=Prospective
44. ts=Rct
45. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 12 and 36 and 45

CENTRAL search

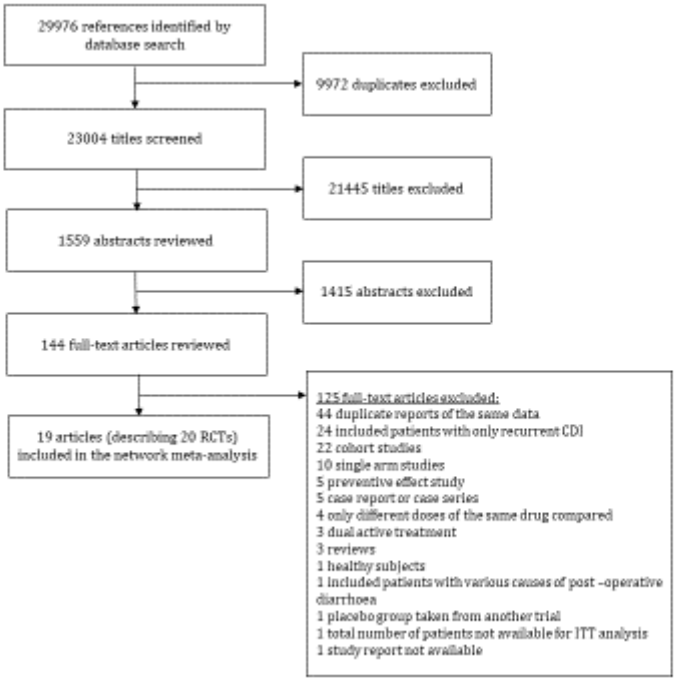
ID	Search
#1	"Clostridium difficile" (Word variations have been searched)
#2	difficile
#3	pseudomembranous
#4	pseudomembranous enterocolitis
#5	antibiotic diarrhoea
#6	antibiotic colitis
#7	CDI or CDAD
#8	Clostridium difficile infection
#9	Clostridium difficile associated diarrhoea
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	Antibiotics
#12	antibiotic
#13	antiinfective agent
#14	anti-bacterial
#15	(Vancomycin or Metronidazole or Fusidic acid or Nitazoxanide or Teicoplanin or Rifampicin or Rifaximin or Bacitracin or Fidaxomicin or Amoxicillin or Azithromycin or Cephalosporin* or Cephalexin or Ciprofloxacin or Clarithromycin or Clindamycin or Doxycycline or Erythromycin or Flouroquinolone* or Levofloxacin or Macrolide* or Nitrofurantoin or Penicillin or Tetracycline or Trimethoprim or antibiotic* or Surotomycin or anti-bacterial* or anti bacterial* or antibacterial* or bacteriocid* or bactericid* or antimicrobial* or anti-microbial*)
#16	#11 or #12 or #13 or #14 or #15
#17	"styrenesulfonic acid polymer"
#18	"cholestyramine"
#19	Colestipol
#20	Tolevamer or colestipol or cholestyramine
#21	#17 or #18 or #19 or #20
#22	"Fecal Microbiota Transplantation"
#23	Fecal microbiota transplant
#24	FMT
#25	fecal transplant
#26	(microbial or microbiota) and transplant
#27	#22 or #23 or #24 or #25 or #26
#28	Probiotic
#29	Probiotics
#30	Immunotherapy
#31	(immunoglobulin or antibody or antibodies or immunotherapy)
#32	#28 or #29 or #30 or #31
#33	#16 or #21 or #27 or #32

#34	#10 and #33

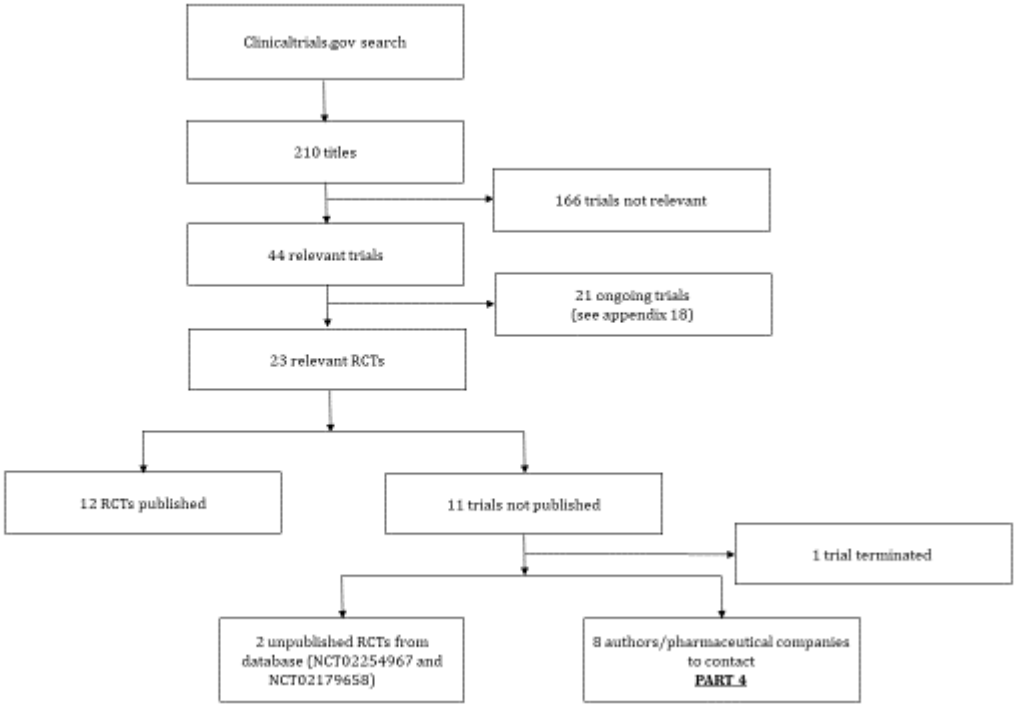
Appendix 3. Search flow diagrams



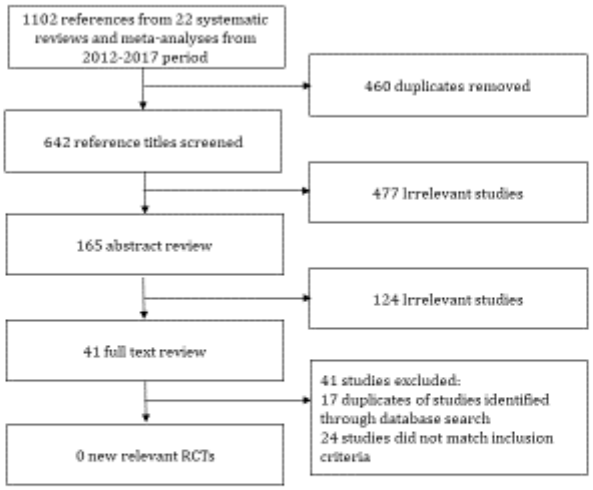
PART 1



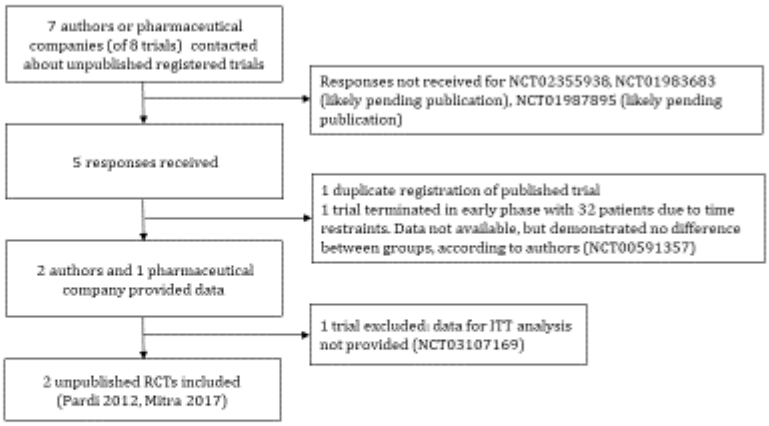
PART 2


Clinicaltrials.gov search
210 titles
166 trials not relevant
44 relevant trials
21 ongoing trials
(see appendix 18)
23 relevant RCTs
12 RCTs published
11 trials not published
1 trial terminated
2 unpublished RCTs from database (NCT02254967 and NCT02179658)
8 authors/pharmaceutical companies to contact
PART 4

PART 3


1102 references from 22 systematic reviews and meta-analyses from 2012-2017 period
460 duplicates removed
642 reference titles screened
477 Irrelevant studies
165 abstract review
124 Irrelevant studies
41 full text review
41 studies excluded:
17 duplicates of studies identified through database search
24 studies did not match inclusion criteria
0 new relevant RCTs

PART 4


7 authors or pharmaceutical companies (of 8 trials) contacted about unpublished registered trials
Responses not received for NCT02355938, NCT01983683 (likely pending publication), NCT01987895 (likely pending publication)
5 responses received
1 duplicate registration of published trial
1 trial terminated in early phase with 32 patients due to time restraints. Data not available, but demonstrated no difference between groups, according to authors (NCT00591357)
2 authors and 1 pharmaceutical company provided data
1 trial excluded: data for ITT analysis not provided (NCT03107169)
2 unpublished RCTs included (Pardi 2012, Mitra 2017)

Appendix 4. Individual trial definitions of cure and CDI severity, participant ethnicity, prevalence of previous CDI and inpatients at onset

Publication	Definition of cure	Definition of severity	Ethnicity	% with previous CDI episode	% Inpatient at onset
Zar 2007	Resolution of diarrhoea at day 6 and negative C difficile toxin in stool at days 6 and 10	Patients with ≥2 points were considered to have severe CDAD. One point each was given for age >60 years, temperature >38·3 C, albumin level <2·5 mg/dL, or peripheral WBC count 115,000 cells/mm3 within 48h of enrolment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit.	N/A	N/A	N/A
Wenisch 1996	Lack of symptoms (no loose stools, gastrointestinal symptoms, or fever) and normalization of serum levels of C-reactive protein and leukocyte counts.	Temperature, C-reactive protein, stool frequency and leukocyte count provided, but no severity criteria applied and patients were not categorized into separate severity categories.	N/A	N/A	N/A
Wullt 2004	Cessation of diarrhoea within 5–8 days of initiating treatment	N/A	N/A	0%	48%
Young 1985	Resolution of diarrhoea was taken as the first day of <3 stools, provided that stool frequency did not again increase above twice a day.	Stool frequency, duration of diarrhoea, fever, abdominal pain, and haemoglobin or albumin levels measured, but no severity criteria applied and patients were not categorized.	N/A	N/A	N/A
Vickers 2017	Less than or equal to three unformed bowel movements in a 24-h period or less than 200 mLunformed stool in rectal collection devices at test of cure	Modified European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria (non-severe vs severe). Severity categories were mild (<6 unformed bowel movements per day or white blood cell [WBC] count ≤12 000 μL), moderate (6–9 unformed bowel movements per day or WBC 12 001–15 000 μL), and severe (≥10 unformed bowel movements per day or WBC counts >15 000 μL).	White 92%, African American 4%, Native American 2 %, Multiple 2%	13%	23%
Louie 2011	Resolution of diarrhoea (i.e., three or fewer unformed stools for 2 consecutive days), with maintenance of resolution for the duration of therapy and no further requirement (in the investigator's opinion) for therapy for C difficile infection as of the second day after the end of the course of therapy.	Severity categories are defined as: Mild CDAD = 4-5 Unformed BM/day OR WBC ≤ 12,000/mm³; Moderate CDAD = 6-9 Unformed BM/day OR WBC 12,001-15,000 mm³; Severe CDAD = ≥ 10 Unformed BM/day OR WBC ≥ 15,001/mm³	N/A	17%	59%
Cornerly 2012	Three or fewer unformed bowel movements per day for 2 days consecutively for the duration of treatment and no further need for treatment (decided by the investigator) as of the second day after the last dose of study drug.	To be classified as severe, had to meet one or more of European Society of Clinical Microbiology and Infectious Diseases criteria: >15 000 white blood cells per μL, serum creatinine concentration >1·5 mg/dL, or body temperature >38·5°C	N/A	15%	68%
Mullane 2015	Resolution or improvement of the C difficile infection such that additional therapy was not needed. Patients considered to be clinically cured had to have had two consecutive days with an absence of severe abdominal pain or fever, as well as <3 non-liquid stools per day.	Severe: ≥ 10 unformed bowel movements per day or a white blood cell count of >15·0 10^9 /liter	93% Caucasian, 5·6% Black, 1·3% Asian	24%	N/A
Louie 2015	The primary endpoint was clinical cure (defined as resolution of diarrhoea with no further CDI therapy required) as assessed by the investigator at a test-of-cure visit. Resolution of diarrhoea was defined as 2 semi-formed or formed stools (types 1 to 4 on the Bristol Stool Chart) and no liquid or unformed stools for 2 consecutive 24h periods.	Severe CDAD was defined as any one of the following: white blood cell count of 15,000/mm3, creatinine of 1·5 mg, or core body temperature of 38·5°C.	91% Caucasian	20%	18%
Musher 2006	Complete clinical response at the end of 7 days of treatment, defined as return of normal stool pattern and absence of fever, abdominal pain, or leukocytosis, unless some other explanation was apparent.	Stool frequency, abdominal pain, presence of fever and white cell count provided, but no classification criteria used to classify patients into severe and non-severe CDI.	77·5% White, 16·9% Black, 5·6% Hispanic	N/A	100%
Musher 2009	End-of-treatment response was defined as complete resolution of all symptoms and signs attributable to CDI during the 3 days after completion of therapy.	Severe CDI was defined using a modification of the severity score recently described by Zar et al. 2007 (see above). One point each was assigned for age 60 years, 17 stools/day, temperature >38·3 C, albumin level <2·5 gm/dL, or WBC count ≥115,000 cells/mm3; a score of ≥2 points was regarded as severe disease.	69·4% White, 30·6% Black	N/A	86%

Dudley 1986	Diarrhoea was considered resolved on the day of therapy on which less than four loose stools were passed during a 24-hour period for at least two consecutive days.	N/A	N/A	N/A	N/A
Boix 2017	Resolution of diarrhoea (ie, ≤2 loose stools per 24 hours for 2 consecutive days) and no need for additional CDI treatment after the trial treatment period.	ESCMID Comprehensive Criteria, ESCMID Abbreviated Criteria, IDSA Criteria, UBM and WBC Criteria, Horn's Index	89% White, 6·5% Black or African, 4·7% Hispanic/Latino	18%	63%
Teasley 1983	Patients were judged to be cured if their diarrhoea resolved within 6 treatment days, they tolerated the complete treatment course, and they did not have a relapse of symptoms in the 21-day follow-up period	N/A	N/A	N/A	100%
Lee 2016	Cure was defined as either resolution of diarrhoea (i.e. <4 unformed bowel movements in a 24 h period for ≥2 consecutive days) sustained through 2 days after last dose of study drug, and no additional antibiotics needed to treat the same CDI episode; or clinically significant improvement, such as ≥50% reduction in UBMs, normal white blood cell count, normal body temperature and no additional antibiotics needed to treat the same CDI episode. Patients requiring a collection device were considered to have resolution of diarrhoea when the volume of stool (in 24 h) decreased by 75% versus baseline or the patient was no longer passing liquid stool.	Severe CDI was defined as the presence of pseudomembranous colitis documented by endoscopy; or being in the ICU at the time of randomisation; or diarrhoea with ≥2 of the following criteria: white blood cell count >15000/mm3; albumin <2·5 g/dL; aged >60 years; oral temperature >101·8F or 38.3C	89% White, 9% African American	17%	N/A
Louie 2006	The first day of 2 consecutive days when the patient had hard or formed stools (any number) or 2 stools of loose or watery consistency	Severe defined as >12 stools in the 24h period preceding screening.	91% White 7% Black, 1% Hispanic	6%	N/A
Johnson 2014 (301)	Resolution of diarrhoea and absence of severe abdominal discomfort for more than 2 consecutive days including day 10. Resolution of diarrhoea was defined as attainment of bowel movements with a hard or formed consistency on average of 2 or fewer BM/day with a loose or watery consistency on average.	CDI disease severity was categorized as mild (3-5 BM/day; white blood cell counts [WBC] ≤15,000/mm3; mild or absent abdominal pain due to CDI), moderate (6-9 BM/day; WBC 15,001 to 20,000/mm3; mild, moderate, or absent abdominal pain due to CDI); or severe (≥10 BM/day; WBC ≥20,001/mm3; severe abdominal pain due to CDI).	N/A	29%	56%
Johnson 2014 (302)	Identical to Johnson 2014 (301)	Identical to Johnson 2014 (301)	N/A	17%	91%
De Lalla 1992	The patients were considered clinically cured if they became asymptomatic (i.e., their symptoms and signs were eliminated).	N/A	N/A	N/A	100%
Thabit 2016	Normalization of stool consistency and reduction of stool frequency to less than three unformed stools per day by day 10 of therapy.	N/A	N/A	N/A	50%
NCT02179658 2016 (unpublished)	'Clinical cure'. 3rd Phase 3 trial for fidaxomicin versus vancomycin carried out by Astellas pharmaceuticals. It is reasonable to assume that the criteria for cure would be the same as in Louie 2011 and Cornely 2012 trials.	Not described. Might be reasonable to assume that the criteria the same as in Louie 2011 and Cornely 2012 trials for the same reasons.	Japanese (% not given)	14%	N/A
Guery 2017	'Clinical cure'. It is a Phase 3b/4 postmarketing trial and 4th RCT for fidaxomicin versus vancomycin carried out by Astellas pharmaceuticals. It is reasonable to assume that the criteria for cure would be the same as in Louie 2011 and Cornely 2012 trials.	Not described. Might be reasonable to assume that the criteria the same as in Louie 2011 and Cornely 2012 trials for the same reasons.	100% White	N/A	N/A
Pardi 2012 (unpublished)	< 3 unformed stools/day for 2 consecutive days at test-of-cure visit 14 days after initiation of treatment	N/A	88% White, 12% Non-white	N/A	N/A
Mitra 2017 (unpublished)	Not described. But Phase 2 trial (Vickers et al.) published earlier in the year by the same team. Criteria, likely, the same.	Modified ESCMID comprehensive criteria	N/A	N/A	N/A

Appendix 5. Support for judgements in risk of bias assessments

Author, Year	Cochrane RoB criteria	Judgement (1 - low, 2 - unclear, 3 - high)	Supporting comment
Zar 2007	**Randomisation**	2	A pharmacist picked up a card in the sealed envelope, but no mention of how random sequence was generated
	Allocation Concealment	1	Drug cards drawn from sealed envelopes.
	Blinding of participants and personnel	1	Similar looking tablets used for metronidazole and similar liquid for vancomycin
	Blinding of outcome assessment	2	No mention
	Incomplete outcome data	1	22/172 (12·8%) patients dropped out before completion of treatment. Although reasons for the dropout explained, only per protocol analysis performed. Patients, who died during treatment, were excluded from analysis, but balance between groups maintained and death causes similar.
	Selective reporting	1	All main outcomes reported
Wenisch 1996	**Randomisation**	1	Table of random numbers used
	Allocation Concealment	2	No mention of allocation concealment used
	Blinding of participants and personnel	3	Not blinded
	Blinding of outcome assessment	3	Not blinded
	Incomplete outcome data	2	126 randomised, but 3 died and 4 excluded - not mentioned which group these patients were randomised to and per protocol analysis performed. Unclear if these could have affected the outcomes.
	Selective reporting	1	All main outcomes reported
Wullt 2004	**Randomisation**	1	Statistician generated a set of random numbers
	Allocation Concealment	1	Medications provided in coded blister packs
	Blinding of participants and personnel	1	Quote "The placebo capsules and tablets did not differ in form or colour from the active counterparts"
	Blinding of outcome assessment	2	Investigator team was unaware of treatment arms through the identical looking treatment packs, but not clear whether blinded to outcome
	Incomplete outcome data	3	Total of 131 randomised, 20 lost from fusidic acid and 14 from metronidazole arms. High percentage and imbalanced attrition
	Selective reporting	1	All main outcomes reported
Young 1985	**Randomisation**	2	Sequence generated in random fashion, unclear how
	Allocation Concealment	1	Packages coded by independent physician
	Blinding of participants and personnel	1	Identical looking red capsules
	Blinding of outcome assessment	2	Not mentioned whether assessors were blinded as well
	Incomplete outcome data	1	No dropouts
	Selective reporting	1	All main outcomes reported
Vickers 2017	**Randomisation**	1	External stratified computer randomisation
	Allocation Concealment	1	Quote "Randomisation and study group assignment was done by an interactive voice and web response system (IVRS/IWRS)"
	Blinding of participants and personnel	1	Quote "Blinding was achieved by over-encapsulation of both study drugs (ridinidazole and vancomycin) and a placebo within identical size zero, Swedish orange, hard gelatine immediate-release capsules"

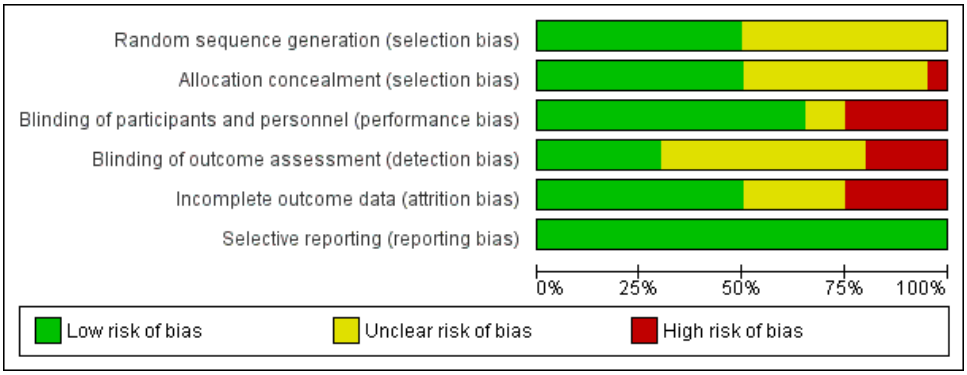
	Blinding of outcome assessment	1	Investigators and assessors blind until database lock
	Incomplete outcome data	1	Dropouts present but equal between groups
	Selective reporting	1	All main outcomes reported as provided in the registration protocol
Louie 2011	**Randomisation**	1	Computerised randomisation with stratification regarding primary/recurrent status
	Allocation Concealment	1	Interactive voice response system used to allocate the treatment package code
	Blinding of participants and personnel	1	Overencapsulated original capsules looked the same
	Blinding of outcome assessment	1	Randomisation schedule not revealed to investigators or assessors
	Incomplete outcome data	1	13% patients lost from both groups - balanced with balanced underlying reasons
	Selective reporting	1	All main outcomes reported as provided in the registration protocol
Cornely 2012	**Randomisation**	1	Computer generated randomisation schedule
	Allocation Concealment	1	Interactive voice response system used to allocate the treatment package code
	Blinding of participants and personnel	1	Overencapsulated original capsules looked the same
	Blinding of outcome assessment	1	Everyone blinded until database lock, then only statisticians non-blinded
	Incomplete outcome data	1	<10% dropout. Slightly more people discontinued treatment early in fidaxomicin group due to early cure compared to vancomycin.
	Selective reporting	1	All main outcomes reported as provided in the registration protocol
Mullane 2015	**Randomisation**	2	Not mentioned how random sequence was generated. Only described that randomisation cards drawn at every centre. At baseline groups differed in age and previous therapy
	Allocation Concealment	2	Site specific randomisation cards, but no further details
	Blinding of participants and personnel	3	No blinding mentioned
	Blinding of outcome assessment	2	Evaluator blind, but not explained how
	Incomplete outcome data	3	14/46 in LFF571 group and 2/26 in vancomycin group withdrew from the study
	Selective reporting	1	All main outcomes reported
Louie 2015	**Randomisation**	1	Computer generated, as interactive voice system used for allocation
	Allocation Concealment	1	Interactive voice response system
	Blinding of participants and personnel	1	Cadazolid and vancomycin had indistinguishable placebo
	Blinding of outcome assessment	2	Double-blind, but no mention of assessor blinding
	Incomplete outcome data	1	4/62 in Cadazolid and 1/22 in Vancomycin did not finish study - similar numbers
	Selective reporting	1	All main outcomes reported
Musher 2006	**Randomisation**	2	Randomised trial, but method for randomisation sequence not mentioned
	Allocation Concealment	2	No mention
	Blinding of participants and personnel	2	Double-blind, but no mention of blinding method
	Blinding of outcome assessment	2	Method not described
	Incomplete outcome data	3	10/44 in Metronidazole and 22/98 in nitazoxanide group did not complete treatment. This is >20%

	Selective reporting	1	All main outcomes reported
Musher 2009	**Randomisation**	2	Randomised, but random sequence generation method not described
	Allocation Concealment	1	Quote "each site sequentially assigned each patient a number from its allotment of blinded study medication. The randomisation code was sealed and maintained in the files of the study sponsor"
	Blinding of participants and personnel	1	Dummy placebo pill identical to nitazoxanide or vancomycin
	Blinding of outcome assessment	1	Investigators blind to study allocation by medication code until database lock
	Incomplete outcome data	1	4 patients lost from both arms - balanced. 8/50 dropouts in total
	Selective reporting	1	All main outcomes reported
Dudley 1986	**Randomisation**	1	Random number table
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	2	Vancomycin and bacitracin aliquots prepared by pharmacist, but no mention whether they looked the same.
	Blinding of outcome assessment	2	Coded treatment bottles in pharmacy, but not clear whether assessor was blind.
	Incomplete outcome data	3	Per protocol analysis only. Out of 62 enrolled, only 30 evaluated. High dropout due to non-confirmed C difficile infection at randomisation
	Selective reporting	1	All main outcomes reported
Boix 2017	**Randomisation**	1	Centralised stratified computer-randomisation
	Allocation Concealment	1	Interactive voice system for allocation withy codes held centrally
	Blinding of participants and personnel	1	Alternative dummy tablets of active comparator
	Blinding of outcome assessment	1	Investigators blind until study database lock. Adequate allocation concealment and patient /personnel blinding
	Incomplete outcome data	2	54/298 (18%) in vancomycin group and 68/308 (22%) in suratomycin group dropped out
	Selective reporting	1	All main outcomes reported
Teasley 1983	**Randomisation**	1	Random number table
	Allocation Concealment	3	Not described and no blinding mentioned
	Blinding of participants and personnel	3	No blinding
	Blinding of outcome assessment	3	No blinding
	Incomplete outcome data	1	7 dropouts. Equally distributed and explained
	Selective reporting	1	All main outcomes reported
Lee 2016	**Randomisation**	1	Centralised stratified computer-randomisation
	Allocation Concealment	1	Interactive voice system used
	Blinding of participants and personnel	1	Single dummy
	Blinding of outcome assessment	1	Each patient coded, blinding maintained until the study end
	Incomplete outcome data	1	8/139 in suratomycin group and 63/70 in vancomycin group dropped out
	Selective reporting	1	All main outcomes reported
Louie 2006	**Randomisation**	2	Sequence generation not described

	Allocation Concealment	2	Not described
	Blinding of participants and personnel	1	Study named as "double-blind". Matching placebo used
	Blinding of outcome assessment	2	Double-blind, but not clear if assessor blinded
	Incomplete outcome data	3	High attrition: 43/185 in tolevamer, 14/94 in vancomycin groups. Not balanced
	Selective reporting	1	All main outcomes reported
Johnson 2014 (301&302 – identical design)	**Randomisation**	2	Quote "Randomization was conducted using a centralized, blocked scheme". No mention of how sequence was generated
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	1	Double-dummy
	Blinding of outcome assessment	2	Blinding maintained until database lock.
	Incomplete outcome data	2	Did not complete follow-up: 101/563 in tolevamer, 36/266 in Vancomycin, 49/289 in Metronidazole group.
	Selective reporting	1	All main outcomes reported
De Lalla 1992	**Randomisation**	2	Sequence generation not described
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	3	No blinding
	Blinding of outcome assessment	3	No blinding
	Incomplete outcome data	1	Drop-outs: 4/24 in vancomycin and 1/27 in teicoplanin group
	Selective reporting	1	All main outcomes reported
Thabit 2016	**Randomisation**	2	Randomisation sequence generation not described
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	3	Open label study
	Blinding of outcome assessment	3	Open label study
	Incomplete outcome data	2	Drop outs: 1/7 in fidaxomicin and 1/5 in vancomycin group
	Selective reporting	1	All main outcomes reported
NCT02179658 2016 (unpublished)	**Randomisation**	2	Randomised trial, but method for randomisation sequence not mentioned
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	1	Double-dummy with fidaxomicin and vancomicin placebos looking identical
	Blinding of outcome assessment	1	Evaluator kept blind of which medication patient has been assigned by double-dummy blinding.
	Incomplete outcome data	2	92/106 in FID and 80/109 in VAN group finished antibiotic course. Reasons for drop out - side effects. Dropouts explained, higher in vancomycin group but exceeds 20%
	Selective reporting	1	All main outcomes reported
Guery 2017	**Randomisation**	2	Randomised trial, but method for randomisation sequence not mentioned
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	3	Open label study

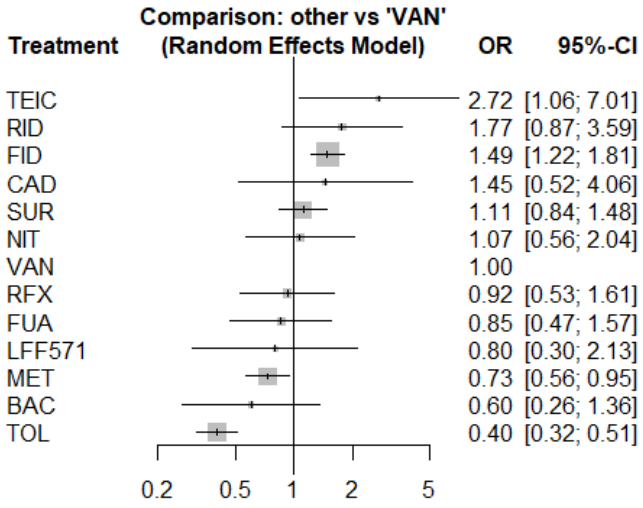
	Blinding of outcome assessment	3	Open label study
	Incomplete outcome data	2	51/183 in fidoxamicin and 56/181 in vancomycin arms discontinued study. Balanced, but high percentage of discontinuation, though study follow-up of 90 days is long.
	Selective reporting	1	All main outcomes reported
Pardi 2012 (unpublished)	**Randomisation**	1	Random permuted blocks used to generate a randomisation sequence
	Allocation Concealment	1	The numbered list of treatment sequence assignments will be provided by a central call-in phone number
	Blinding of participants and personnel	1	Identical appearing placebo tablets to vancomycin and rifaximin
	Blinding of outcome assessment	2	Patients coded with an assignment number, but blinding of outcome assessors not clear
	Incomplete outcome data	3	High attrition: 41/119 in rifaximin and 27/119 in vancomycin group discontinued trial. Attrition markedly higher in rifaximin group. Reasons: treatment failure and adverse events
	Selective reporting	1	All main outcomes reported
Mitra 2017	**Randomisation**	2	Randomised trial, but method for randomisation sequence not mentioned
	Allocation Concealment	2	Not described
	Blinding of participants and personnel	3	Open label study
	Blinding of outcome assessment	3	Open label study
	Incomplete outcome data	1	No dropouts
	Selective reporting	1	All main outcomes reported

Appendix 6. Cumulative risk of bias table

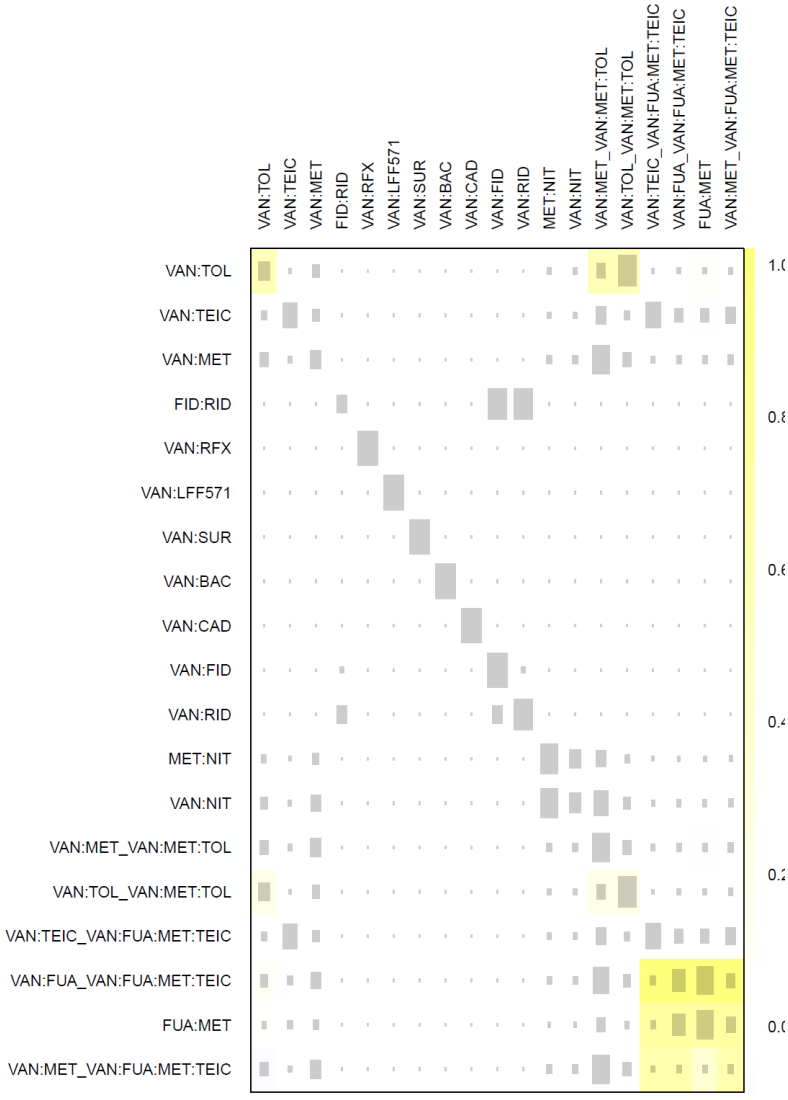


Appendix 7. Sustained symptomatic cure. Vancomycin as reference

a) Forest plot



b) Heatmap to identify points of single design heterogeneity



c) Heterogeneity and decomposition of Cochrane Q score in within and between designs components

Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Q statistics to assess homogeneity / consistency

	Q	df	p-value
Total	15.80	16	0.4673
Within designs	12.61	9	0.1813
Between designs	3.19	7	0.8669

Design-specific decomposition of within-designs Q statistic

Design	Q	df	p-value
VAN:BAC	0·48	1	0·4898
VAN:FID	2·66	4	0·6168
VAN:MET	3·94	1	0·0470
VAN:SUR	2·23	1	0·1358
VAN:MET:TOL	3·30	2	0·1918

Between-designs Q statistic after detaching of single designs

Detached design	Q	df	p-value
FID:RID	3·19	6	0·7847
FUA:MET	1·11	6	0·9810
MET:NIT	3·17	6	0·7868
VAN:FID	3·19	6	0·7847
VAN:MET	3·19	6	0·7846
VAN:NIT	3·17	6	0·7868
VAN:RID	3·19	6	0·7847
VAN:TEIC	3·18	6	0·7861
VAN:TOL	2·46	6	0·8732
VAN:FUA:MET:TEIC	0·77	4	0·9429
VAN:MET:TOL	2·44	5	0·7857

Q statistic to assess consistency under the assumption of
a full design-by-treatment interaction random effects model

	Q	df	p-value	tau.within	tau2.within
Between designs	2·74	7	0·9084	0·1616	0·0261

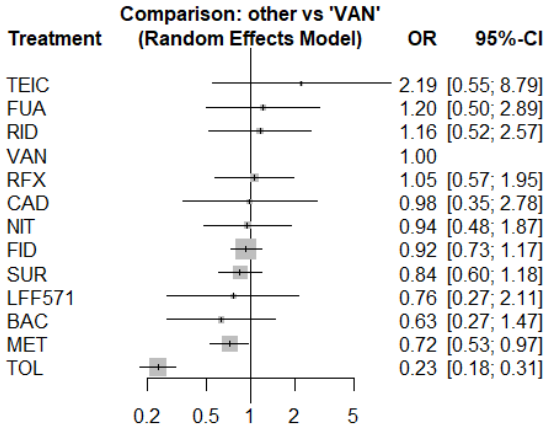
Appendix 8. Primary cure rate. Vancomycin as reference

a) League table

0·8732												
TEIC	0·6895											
0·55 [0·11; 2·64]	**FUA**	0·6712										
0·53 [0·11; 2·61]	0·96 [0·29; 3·14]	**RID**	0·6229									
0·46 [0·11; 1·83]	0·83 [0·35; 2·00]	0·87 [0·39; 1·93]	**VAN**	0·6228								
0·48 [0·10; 2·19]	0·87 [0·30; 2·55]	0·91 [0·33; 2·50]	1·05 [0·57; 1·95]	**RFX**	0·5554							
0·45 [0·08; 2·54]	0·81 [0·21; 3·18]	0·85 [0·23; 3·16]	0·98 [0·35; 2·78]	0·93 [0·28; 3·14]	**CAD**	0·5400						
0·43 [0·09; 2·00]	0·78 [0·27; 2·26]	0·82 [0·29; 2·34]	0·94 [0·48; 1·87]	0·90 [0·36; 2·26]	0·96 [0·28; 3·35]	**NIT**	0·5217					
0·42 [0·10; 1·72]	0·77 [0·31; 1·90]	0·80 [0·35; 1·82]	0·92 [0·73; 1·17]	0·88 [0·45; 1·71]	0·94 [0·32; 2·75]	0·98 [0·48; 2·02]	**FID**	0·4311				
0·38 [0·09; 1·60]	0·70 [0·27; 1·79]	0·73 [0·31; 1·74]	0·84 [0·60; 1·18]	0·80 [0·40; 1·63]	0·86 [0·29; 2·58]	0·89 [0·42; 1·91]	0·91 [0·60; 1·38]	**SUR**	0·4055			
0·35 [0·06; 1·94]	0·63 [0·16; 2·43]	0·66 [0·18; 2·41]	0·76 [0·27; 2·11]	0·72 [0·22; 2·39]	0·77 [0·18; 3·34]	0·80 [0·23; 2·75]	0·82 [0·29; 2·35]	0·90 [0·31; 2·65]	**LFF571**	0·2839		
0·29 [0·06; 1·46]	0·52 [0·15; 1·77]	0·55 [0·17; 1·75]	0·63 [0·27; 1·47]	0·60 [0·21; 1·72]	0·64 [0·17; 2·47]	0·67 [0·22; 1·98]	0·68 [0·28; 1·65]	0·75 [0·30; 1·87]	0·83 [0·22; 3·15]	**BAC**	0·2797	
0·33 [0·08; 1·33]	0·60 [0·26; 1·38]	0·62 [0·26; 1·46]	**0·72 [0·53; 0·97]**	0·68 [0·34; 1·36]	0·73 [0·25; 2·16]	0·76 [0·40; 1·45]	0·78 [0·53; 1·14]	0·85 [0·54; 1·34]	0·95 [0·32; 2·75]	1·14 [0·46; 2·80]	**MET**	0·0030
0·11 [0·03; 0·44]	**0·20 [0·08; 0·47]**	**0·20 [0·09; 0·47]**	**0·23 [0·18; 0·31]**	**0·22 [0·11; 0·44]**	**0·24 [0·08; 0·70]**	**0·25 [0·12; 0·50]**	**0·25 [0·18; 0·36]**	**0·28 [0·18; 0·43]**	**0·31 [0·11; 0·90]**	**0·37 [0·15; 0·91]**	**0·33 [0·25; 0·43]**	**TOL**

League table of pairwise comparisons in network meta-analysis for attaining a primary symptomatic cure. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. BAC – bacitracin, CAD - cadazolid, FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifaximin, RID – ridinidazole, SUR – suratomycin, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin.

b) Forest plot



c) Heterogeneity and decomposition of Cochrane Q score in within and between designs components

Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Q statistics to assess homogeneity / consistency

	Q	df	p-value
Total	13·52	16	0·6343
Within designs	6·60	9	0·6789
Between designs	6·92	7	0·4369

Design-specific decomposition of within-designs Q statistic

Design	Q	df	p-value
VAN:BAC	0·06	1	0·8072
VAN:FID	3·67	4	0·4524
VAN:MET	1·47	1	0·2249
VAN:SUR	0·56	1	0·4561
VAN:MET:TOL	0·84	2	0·6572

Between-designs Q statistic after detaching of single designs

Detached design	Q	df	p-value
FID:RID	5·27	6	0·5091
FUA:MET	6·69	6	0·3500
MET:NIT	6·92	6	0·3288
VAN:FID	5·27	6	0·5091
VAN:MET	6·90	6	0·3306
VAN:NIT	6·92	6	0·3288
VAN:RID	5·27	6	0·5091
VAN:TEIC	6·87	6	0·3328
VAN:TOL	2·25	6	0·8949
VAN:FUA:MET:TEIC	6·49	4	0·1652
VAN:MET:TOL	2·10	5	0·8345

Q statistic to assess consistency under the assumption of
a full design-by-treatment interaction random effects model

	Q	df	p-value	tau.within	tau2.within
Between designs	6.92	7	0.4369	0	0

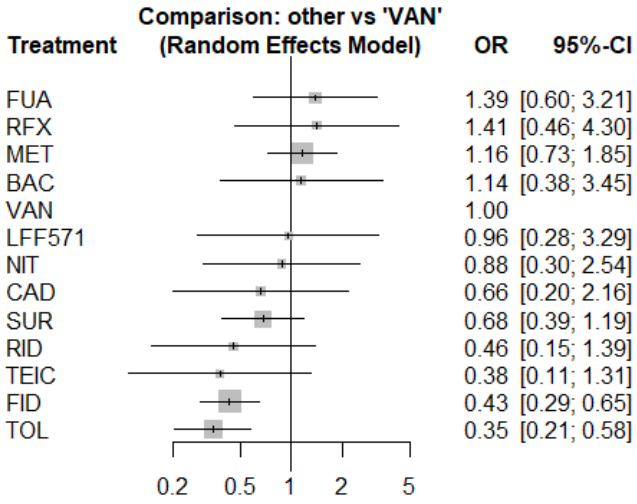
Appendix 9. Recurrence rate. Vancomycin as reference

a) League table

0·8835												
TOL	0·7965											
1·25 [0·65; 2·40]	**FID**	0·7964										
1·09 [0·29; 4·13]	0·88 [0·24; 3·25]	**TEIC**	0·7344									
1·32 [0·39; 4·50]	1·06 [0·34; 3·30]	1·20 [0·23; 6·40]	**RID**	0·5699								
1·97 [0·93; 4·21]	1·58 [0·80; 3·14]	1·81 [0·46; 7·05]	1·50 [0·43; 5·20]	**SUR**	0·5661							
1·91 [0·52; 6·97]	1·53 [0·44; 5·36]	1·75 [0·31; 9·75]	1·45 [0·29; 7·38]	0·97 [0·26; 3·58]	**CAD**	0·4330						
2·53 [0·82; 7·82]	2·03 [0·65; 6·34]	2·32 [0·47; 11·45]	1·92 [0·41; 8·98]	1·28 [0·39; 4·26]	1·33 [0·27; 6·52]	**NIT**	0·3928					
2·77 [0·73; 10·56]	2·22 [0·61; 8·13]	2·53 [0·44; 14·61]	2·10 [0·40; 11·09]	1·40 [0·36; 5·42]	1·45 [0·26; 8·02]	1·09 [0·21; 5·57]	**LFF571**	0·3497				
2·89 [1·72; 4·85]	**2·32 [1·55; 3·47]**	2·64 [0·76; 9·17]	2·19 [0·72; 6·68]	1·46 [0·84; 2·54]	1·51 [0·46; 4·95]	1·14 [0·39; 3·30]	1·04 [0·30; 3·59]	**VAN**	0·3068			
3·30 [0·97; 11·17]	2·65 [0·82; 8·58]	3·02 [0·57; 15·94]	2·51 [0·52; 12·03]	1·67 [0·49; 5·75]	1·73 [0·34; 8·73]	1·30 [0·28; 6·03]	1·19 [0·23; 6·25]	1·14 [0·38; 3·45]	**BAC**	0·2587		
3·36 [1·89; 5·97]	**2·69 [1·46; 4·98]**	3·07 [0·86; 10·93]	2·55 [0·76; 8·52]	1·70 [0·83; 3·50]	1·76 [0·49; 6·28]	1·32 [0·49; 3·56]	1·21 [0·32; 4·53]	1·16 [0·73; 1·85]	1·02 [0·31; 3·37]	**MET**	0·2175	
4·08 [1·20; 13·94]	3·27 [1·00; 10·70]	3·73 [0·70; 19·83]	3·10 [0·64; 14·98]	2·07 [0·60; 7·17]	2·14 [0·42; 10·87]	1·61 [0·35; 7·51]	1·48 [0·28; 7·78]	1·41 [0·46; 4·30]	1·24 [0·26; 5·94]	1·22 [0·36; 4·06]	**RFX**	0·1947
4·01 [1·59; 10·11]	**3·22 [1·27; 8·16]**	3·67 [0·93; 14·41]	3·05 [0·76; 12·28]	2·03 [0·74; 5·55]	2·10 [0·49; 8·97]	1·58 [0·45; 5·51]	1·45 [0·33; 6·45]	1·39 [0·60; 3·21]	1·22 [0·30; 4·87]	1·20 [0·55; 2·58]	0·98 [0·24; 3·96]	**FUA**

League table of pairwise comparisons in network meta-analysis for recurrence. Treatments order in the rank of their chance of being the best treatment. Higher numbers in grey boxes are P-Scores, which are used to rank the treatments, mean lower chance of getting recurrence. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. BAC – bacitracin, CAD - cadazolid, FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifaximin, RID – ridinidazole, SUR – suratomycin, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin.

b) Forest plot



c) Heterogeneity and decomposition of Cochrane Q score into within and between designs components

Quantifying heterogeneity / inconsistency:
tau^2 = 0·0885; I^2 = 33·4%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value	
Total		24·02	16	0·0891
Within designs	10·99	9	0·2761	
Between designs		13·02	7	0·0715

Design-specific decomposition of within-designs Q statistic

Design	Q	df	p-value	
VAN:BAC	0·63	1	0·4284	
VAN:FID	6·31	4	0·1768	
VAN:MET	2·11	1	0·1466	
VAN:SUR	0·66	1	0·4180	
VAN:MET:TOL		1·29	2	0·5249

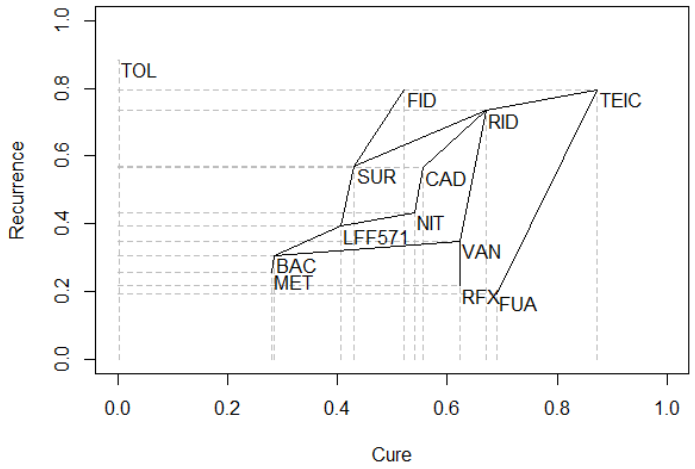
Between-designs Q statistic after detaching of single designs

Detached design		Q	df	p-value
FID:RID		10·93	6	0·0905
FUA:MET		11·79	6	0·0669
MET:NIT		12·87	6	0·0451
VAN:FID		10·93	6	0·0905
VAN:MET		12·97	6	0·0434
VAN:NIT		12·87	6	0·0451
VAN:RID		10·93	6	0·0905
VAN:TEIC		13·01	6	0·0428
VAN:TOL		3·68	6	0·7205
VAN:FUA:MET:TEIC		11·75	4	0·0193
VAN:MET:TOL		3·55	5	0·6165

Q statistic to assess consistency under the assumption of
a full design-by-treatment interaction random effects model

	Q	df	p-value	tau.within	tau2.within	
Between designs		10·99	7	0·1388	0·1709	0·0292

Appendix 10. Scatter plot



Scatter plot. Chance of being the best in primary cure versus having the lowest recurrence rate

X axis – P-score for being the best treatment in attaning a primary cure; Y axis – P-score for having the lowest chance of recurrence. BAC – bacitracin, CAD - cadazolid, FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifaximin, RID – ridinidazole, SUR – suratomycin, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin.

Appendix 11· Direct versus indirect evidence for sustained symptomatic cure

Random effects model

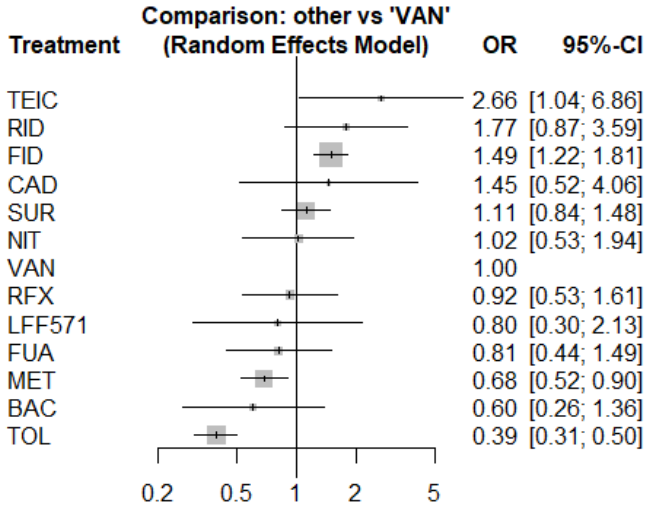
comparison	K	prop	nma	direct	indir·	RoR	z	p-value
BAC:CAD	0	0	2·41	·	2·41	·	·	·
BAC:FID	0	0	2·48	·	2·48	·	·	·
BAC:FUA	0	0	1·42	·	1·42	·	·	·
BAC:LFF571	0	0	1·33	·	1·33	·	·	·
BAC:MET	0	0	1·22	·	1·22	·	·	·
BAC:NIT	0	0	1·78	·	1·78	·	·	·
BAC:RFX	0	0	1·53	·	1·53	·	·	·
BAC:RID	0	0	2·94	·	2·94	·	·	·
BAC:SUR	0	0	1·85	·	1·85	·	·	·
BAC:TEIC	0	0	4·53	·	4·53	·	·	·
BAC:TOL	0	0	0·67	·	0·67	·	·	·
BAC:VAN	2	1	1·66	1·66	·	·	·	·
CAD:FID	0	0	1·03	·	1·03	·	·	·
CAD:FUA	0	0	0·59	·	0·59	·	·	·
CAD:LFF571	0	0	0·55	·	0·55	·	·	·
CAD:MET	0	0	0·51	·	0·51	·	·	·
CAD:NIT	0	0	0·74	·	0·74	·	·	·
CAD:RFX	0	0	0·64	·	0·64	·	·	·
CAD:RID	0	0	1·22	·	1·22	·	·	·
CAD:SUR	0	0	0·77	·	0·77	·	·	·
CAD:TEIC	0	0	1·88	·	1·88	·	·	·
CAD:TOL	0	0	0·28	·	0·28	·	·	·
CAD:VAN	1	1	0·69	0·69	·	·	·	·
FID:FUA	0	0	0·57	·	0·57	·	·	·
FID:LFF571	0	0	0·54	·	0·54	·	·	·
FID:MET	0	0	0·49	·	0·49	·	·	·
FID:NIT	0	0	0·72	·	0·72	·	·	·
FID:RFX	0	0	0·62	·	0·62	·	·	·
FID:RID	1	0·23	1·19	1·17	1·19	-0·98	0·03	0·9790
FID:SUR	0	0	0·75	·	0·75	·	·	·
FID:TEIC	0	0	1·83	·	1·83	·	·	·
FID:TOL	0	0	0·27	·	0·27	·	·	·
FID:VAN	5	0·99	0·67	0·67	0·66	1·02	0·03	0·9791
FUA:LFF571	0	0	0·94	·	0·94	·	·	·
FUA:MET	2	0·9	0·86	0·84	0·97	-0·87	0·15	0·8826
FUA:NIT	0	0	1·25	·	1·25	·	·	·
FUA:RFX	0	0	1·08	·	1·08	·	·	·
FUA:RID	0	0	2·07	·	2·07	·	·	·
FUA:SUR	0	0	1·3	·	1·3	·	·	·
FUA:TEIC	1	0·54	3·19	4·39	2·19	2·01	0·65	0·5161
FUA:TOL	0	0	0·47	·	0·47	·	·	·
FUA:VAN	1	0·28	1·17	1·8	0·99	1·83	0·88	0·3788
LFF571:MET	0	0	0·92	·	0·92	·	·	·
LFF571:NIT	0	0	1·34	·	1·34	·	·	·
LFF571:RFX	0	0	1·15	·	1·15	·	·	·
LFF571:RID	0	0	2·21	·	2·21	·	·	·
LFF571:SUR	0	0	1·39	·	1·39	·	·	·
LFF571:TEIC	0	0	3·41	·	3·41	·	·	·
LFF571:TOL	0	0	0·5	·	0·5	·	·	·
LFF571:VAN	1	1	1·25	1·25	·	·	·	·
MET:NIT	1	0·75	1·46	1·43	1·57	-0·91	0·13	0·8976
MET:RFX	0	0	1·26	·	1·26	·	·	·
MET:RID	0	0	2·42	·	2·42	·	·	·
MET:SUR	0	0	1·52	·	1·52	·	·	·
MET:TEIC	1	0·43	3·72	2·43	5·12	-0·47	0·75	0·4504
MET:TOL	2	0·83	0·55	0·54	0·62	-0·87	0·39	0·6973
MET:VAN	5	0·88	1·37	1·39	1·21	1·14	0·33	0·7448
NIT:RFX	0	0	0·86	·	0·86	·	·	·
NIT:RID	0	0	1·65	·	1·65	·	·	·
NIT:SUR	0	0	1·04	·	1·04	·	·	·
NIT:TEIC	0	0	2·55	·	2·55	·	·	·
NIT:TOL	0	0	0·38	·	0·38	·	·	·
NIT:VAN	1	0·29	0·93	0·88	0·96	-0·91	0·13	0·8976
RFX:RID	0	0	1·92	·	1·92	·	·	·
RFX:SUR	0	0	1·21	·	1·21	·	·	·
RFX:TEIC	0	0	2·95	·	2·95	·	·	·

RFX:TOL	0	0	0·44	·	0·44	·	·	·
RFX:VAN	1	1	1·08	1·08	·	·	·	·
RID:SUR	0	0	0·63	·	0·63	·	·	·
RID:TEIC	0	0	1·54	·	1·54	·	·	·
RID:TOL	0	0	0·23	·	0·23	·	·	·
RID:VAN	1	0·78	0·57	0·56	0·58	-0·98	0·03	0·9790
SUR:TEIC	0	0	2·44	·	2·44	·	·	·
SUR:TOL	0	0	0·36	·	0·36	·	·	·
SUR:VAN	2	1	0·9	0·9	·	·	·	·
TEIC:TOL	0	0	0·15	·	0·15	·	·	·
TEIC:VAN	2	0·9	0·37	0·38	0·3	1·27	0·15	0·8826
TOL:VAN	3	0·9	2·48	2·48	2·54	-0·97	0·06	0·9500

Legend:
comparison - Treatment comparison
k - Number of studies providing direct evidence
prop - Direct evidence proportion
nma - Estimated treatment effect (OR) in network meta-analysis
direct - Estimated treatment effect (OR) derived from direct evidence
indir. - Estimated treatment effect (OR) derived from indirect evidence
RoR - Ratio of Ratios (direct versus indirect)
z - z-value of test for disagreement (direct versus indirect)
p-value - p-value of test for disagreement (direct versus indirect)

Appendix 12. Sustained symptomatic cure NMA after removal of Teasley 1983 RCT

a) Forest plot



b) Heterogeneity assessment

Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	13·03	15	0·6001
Within designs	8·66	8	0·3716
Between designs	4·37	7	0·7368

Design-specific decomposition of within-designs Q statistic

Design	Q	df	p-value
VAN:BAC	0·48	1	0·4898
VAN:FID	2·66	4	0·6168
VAN:SUR	2·23	1	0·1358
VAN:MET:TOL	3·30	2	0·1918

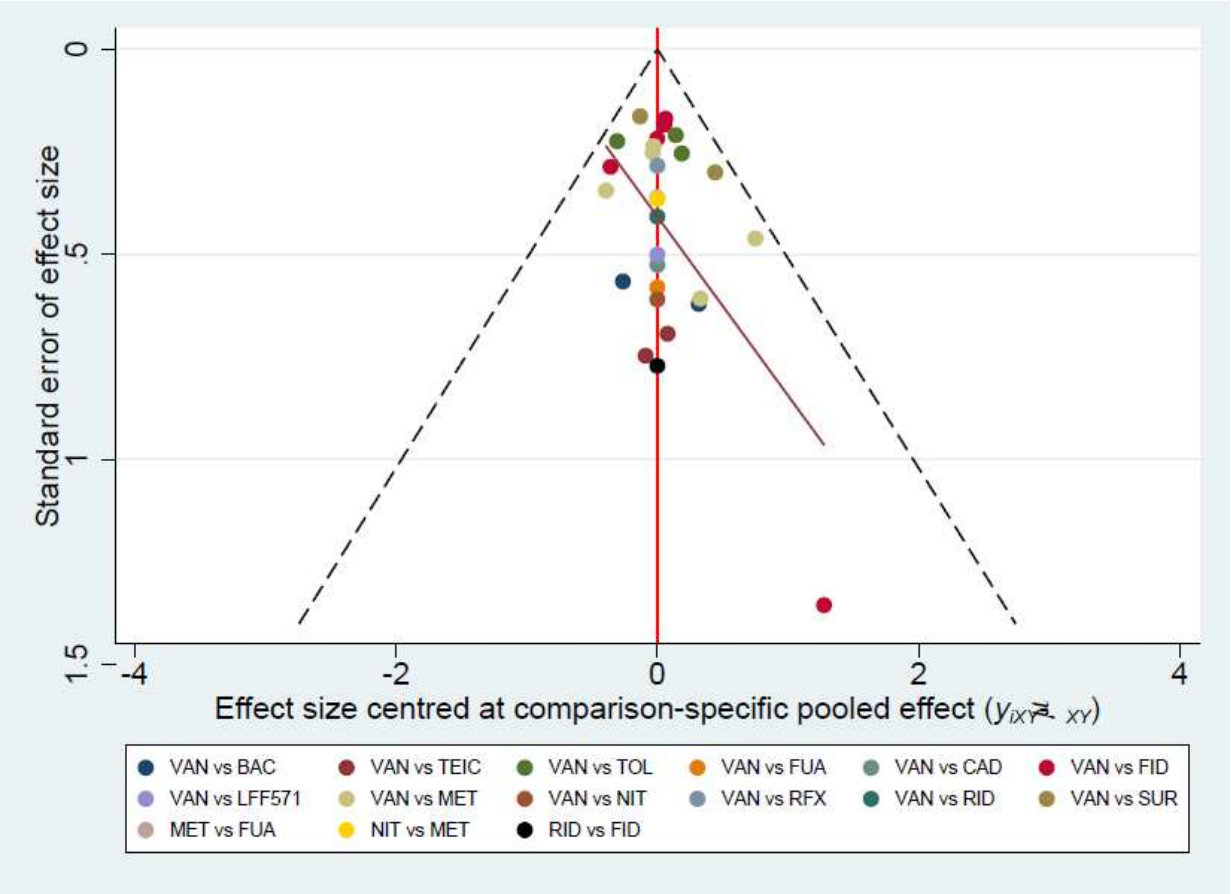
Between-designs Q statistic after detaching of single designs

Detached design	Q	df	p-value
FID:RID	4·37	6	0·6273
FUA:MET	2·46	6	0·8729
MET:NIT	4·32	6	0·6341
VAN:FID	4·37	6	0·6273
VAN:MET	3·19	6	0·7846
VAN:NIT	4·32	6	0·6341
VAN:RID	4·37	6	0·6273
VAN:TEIC	4·34	6	0·6304
VAN:TOL	3·38	6	0·7593
VAN:FUA:MET:TEIC	1·96	4	0·7423
VAN:MET:TOL	2·96	5	0·7056

Q statistic to assess consistency under the assumption of
a full design-by-treatment interaction random effects model

	Q	df	p-value	tau.within	tau2.within
Between designs	4·21	7	0·7556	0·0708	0·005

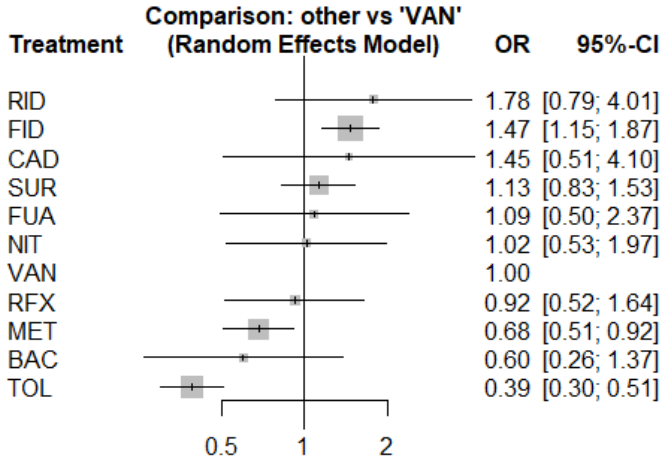
Appendix 13. Comparison-adjusted funnel plot for sustained symptomatic cure



Appendix 14. Sensitivity analysis for sustained symptomatic cure: non-blinded studies excluded

De Lalla 1992, Mullane 2015, Teasley 1983, Thabit 2016, Wenisch 1996, Mitra 2017, Guery 2017 RCTs excluded

a) Forest plot. Vancomycin as reference



Quantifying heterogeneity / inconsistency:
tau^2 = 0·0052; I^2 = 7·5%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d·f.	p-value
Total	9·73	9	0·3726
Within designs	7·77	6	0·2556
Between designs	1·96	3	0·5800

b) League table·

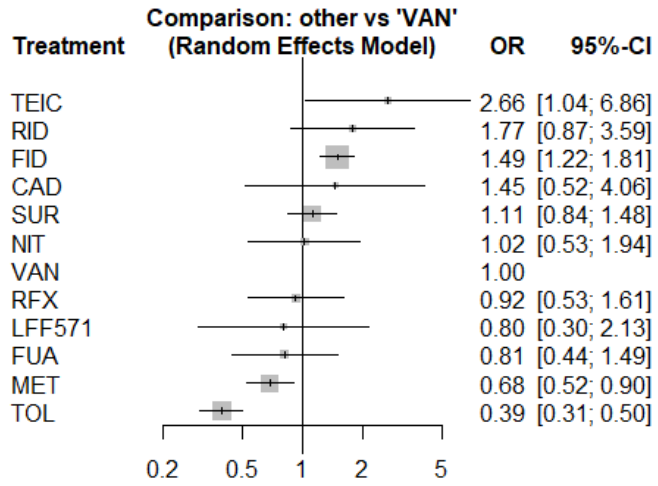
0·8566										
RID	0·8266									
0·83 [0·35; 1·93]	**FID**	0·7262								
0·81 [0·22; 3·05]	0·99 [0·34; 2·87]	**CAD**	0·6125							
0·63 [0·27; 1·51]	0·77 [0·52; 1·13]	0·78 [0·26; 2·30]	**SUR**	0·5729						
0·61 [0·20; 1·89]	0·74 [0·33; 1·68]	0·75 [0·20; 2·76]	0·96 [0·42; 2·23]	**FUA**	0·5259					
0·57 [0·20; 1·63]	0·69 [0·34; 1·40]	0·70 [0·20; 2·41]	0·90 [0·44; 1·87]	0·94 [0·36; 2·44]	**NIT**	0·4935				
0·56 [0·25; 1·27]	**0·68 [0·54; 0·87]**	0·69 [0·24; 1·95]	0·89 [0·65; 1·20]	0·92 [0·42; 2·01]	0·98 [0·51; 1·90]	**VAN**	0·4460			
0·52 [0·19; 1·40]	0·63 [0·34; 1·17]	0·64 [0·19; 2·09]	0·82 [0·43; 1·57]	0·85 [0·32; 2·24]	0·91 [0·38; 2·18]	0·92 [0·52; 1·64]	**RFX**	0·2121		
0·38 [0·16; 0·91]	**0·46 [0·32; 0·68]**	0·47 [0·16; 1·39]	**0·61 [0·40; 0·93]**	0·63 [0·30; 1·30]	0·67 [0·36; 1·26]	**0·68 [0·51; 0·92]**	0·74 [0·39; 1·41]	**MET**	0·2091	
0·34 [0·11; 1·08]	**0·41 [0·17; 0·97]**	0·42 [0·11; 1·57]	0·53 [0·22; 1·29]	0·55 [0·18; 1·73]	0·59 [0·21; 1·70]	0·60 [0·26; 1·37]	0·65 [0·24; 1·78]	0·88 [0·37; 2·12]	**BAC**	0·0186
0·22 [0·09; 0·52]	**0·27 [0·19; 0·38]**	**0·27 [0·09; 0·79]**	**0·35 [0·23; 0·52]**	**0·36 [0·17; 0·78]**	**0·38 [0·20; 0·75]**	**0·39 [0·30; 0·51]**	**0·42 [0·23; 0·80]**	**0·57 [0·43; 0·76]**	0·65 [0·27; 1·55]	**TOL**

League table of pairwise comparisons in network meta-analysis of sensitivity analysis including only blinded trials for sustained symptomatic cure. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. BAC – bacitracin, CAD - cadazolid, FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifaximin, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

Appendix 15. Sensitivity analysis for sustained symptomatic cure: trials published before 1990 excluded

Dudley 1986, Teasley 1983 and Young 1985 trials excluded

a) Forest plot



Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	12·55	14	0·5621
Within designs	8·19	7	0·3166
Between designs	4·37	7	0·7368

b) League table

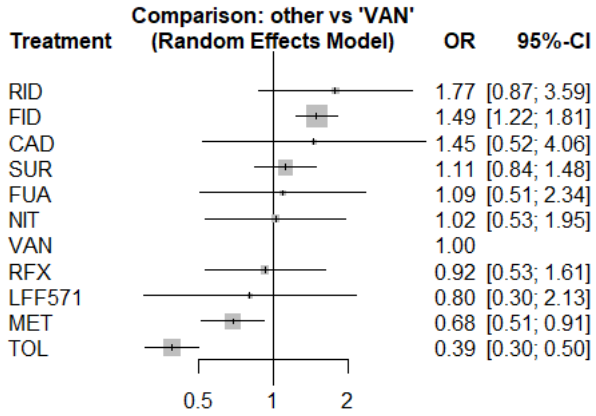
0·9309											
TEIC	0·8192										
0·66 [0·20; 2·16]	**RID**	0·7798									
0·56 [0·21; 1·47]	0·84 [0·41; 1·74]	**FID**	0·6833								
0·54 [0·13; 2·20]	0·82 [0·23; 2·86]	0·97 [0·34; 2·78]	**CAD**	0·5613							
0·42 [0·16; 1·12]	0·63 [0·29; 1·35]	0·75 [0·53; 1·06]	0·77 [0·26; 2·24]	**SUR**	0·4876						
0·38 [0·12; 1·18]	0·58 [0·22; 1·50]	0·68 [0·35; 1·34]	0·70 [0·21; 2·37]	0·91 [0·45; 1·85]	**NIT**	0·4598					
0·38 [0·15; 0·97]	0·57 [0·28; 1·15]	**0·67 [0·55; 0·82]**	0·69 [0·25; 1·94]	0·90 [0·68; 1·19]	0·98 [0·51; 1·88]	**VAN**	0·4099				
0·35 [0·12; 1·04]	0·52 [0·21; 1·28]	0·62 [0·34; 1·12]	0·64 [0·20; 2·06]	0·83 [0·44; 1·55]	0·91 [0·39; 2·13]	0·92 [0·53; 1·61]	**RFX**	0·3474			
0·30 [0·08; 1·17]	0·45 [0·13; 1·52]	0·54 [0·20; 1·46]	0·55 [0·13; 2·29]	0·72 [0·26; 1·99]	0·79 [0·24; 2·54]	0·80 [0·30; 2·13]	0·87 [0·28; 2·68]	**LFF571**	0·3251		
0·30 [0·11; 0·87]	0·46 [0·18; 1·17]	0·54 [0·29; 1·03]	0·56 [0·17; 1·85]	0·73 [0·37; 1·42]	0·79 [0·34; 1·84]	0·81 [0·44; 1·49]	0·88 [0·38; 2·00]	1·01 [0·32; 3·21]	**FUA**	0·1860	
0·26 [0·10; 0·67]	**0·39 [0·18; 0·83]**	**0·46 [0·33; 0·64]**	0·47 [0·16; 1·37]	**0·61 [0·41; 0·91]**	0·67 [0·36; 1·25]	**0·68 [0·52; 0·90]**	0·74 [0·40; 1·38]	0·86 [0·31; 2·37]	0·85 [0·48; 1·50]	**MET**	0·0097
0·15 [0·06; 0·39]	**0·22 [0·10; 0·47]**	**0·26 [0·19; 0·36]**	**0·27 [0·09; 0·78]**	**0·35 [0·24; 0·51]**	**0·38 [0·20; 0·74]**	**0·39 [0·31; 0·50]**	**0·42 [0·23; 0·78]**	0·49 [0·18; 1·35]	**0·48 [0·26; 0·90]**	**0·57 [0·44; 0·75]**	**TOL**

League table of pairwise comparisons in network meta-analysis of sensitivity analysis including only trials published after 1990. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. CAD- Cadazolid, FID- Fidaxomicin, FUA – Fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifaxamicin, RID – ridinidazole, SUR – suratomycin, TEIC – teicoplanin, TOL – tolevamer, VAN – vancomycin.

Appendix 16. Sensitivity analysis for sustained symptomatic cure: trials published before 2000 excluded

Dudley 1986, Teasley 1983 and Young 1985, De Lalla 1992 and Wenisch 1996 trials excluded

a) Forest plot



Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	10·15	11	0·5170
Within designs	8·19	7	0·3166
Between designs	1·96	4	0·7423

b) League table

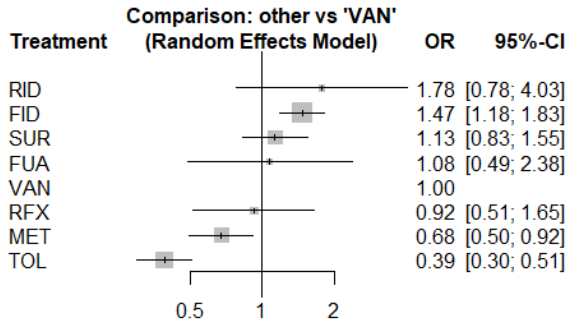
0·8632										
RID	0·8271									
0·84 [0·41; 1·74]	**FID**	0·7158								
0·82 [0·23; 2·86]	0·97 [0·34; 2·78]	**CAD**	0·5828							
0·63 [0·29; 1·35]	0·75 [0·53; 1·06]	0·77 [0·26; 2·24]	**SUR**	0·5566						
0·62 [0·22; 1·75]	0·73 [0·33; 1·61]	0·75 [0·21; 2·71]	0·98 [0·43; 2·21]	**FUA**	0·5060					
0·58 [0·22; 1·51]	0·68 [0·35; 1·35]	0·70 [0·21; 2·38]	0·91 [0·45; 1·86]	0·94 [0·36; 2·40]	**NIT**	0·4697				
0·57 [0·28; 1·15]	**0·67 [0·55; 0·82]**	0·69 [0·25; 1·94]	0·90 [0·68; 1·19]	0·92 [0·43; 1·97]	0·98 [0·51; 1·88]	**VAN**	0·4221			
0·52 [0·21; 1·28]	0·62 [0·34; 1·12]	0·64 [0·20; 2·06]	0·83 [0·44; 1·55]	0·85 [0·33; 2·18]	0·91 [0·38; 2·13]	0·92 [0·53; 1·61]	**RFX**	0·3600		
0·45 [0·13; 1·52]	0·54 [0·20; 1·46]	0·55 [0·13; 2·29]	0·72 [0·26; 1·99]	0·73 [0·21; 2·55]	0·79 [0·24; 2·55]	0·80 [0·30; 2·13]	0·87 [0·28; 2·68]	**LFF571**	0·1867	
0·39 [0·18; 0·83]	**0·46 [0·32; 0·65]**	0·47 [0·16; 1·38]	**0·61 [0·41; 0·92]**	0·63 [0·31; 1·28]	0·67 [0·36; 1·25]	**0·68 [0·51; 0·91]**	0·74 [0·40; 1·39]	0·86 [0·31; 2·38]	**MET**	0·0100
0·22 [0·10; 0·47]	**0·26 [0·19; 0·36]**	**0·27 [0·09; 0·78]**	**0·35 [0·24; 0·51]**	**0·36 [0·17; 0·77]**	**0·38 [0·20; 0·74]**	**0·39 [0·30; 0·50]**	**0·42 [0·23; 0·78]**	0·49 [0·18; 1·35]	**0·57 [0·44; 0·75]**	**TOL**

League table of pairwise comparisons in network meta-analysis of sensitivity analysis including only trials published after 2000. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. CAD - cadazolid, FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, NIT – nitazoxanide, RFX – rifampicin, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

Appendix 17. Sensitivity analysis for sustained symptomatic cure: trials with less than 50 patients in each arm were excluded

Remaining RCTs: Zar 2007, Wullt 2004, Vickers 2017, Louie 2011, Cornerly 2012, Boix 2017, Lee 2016, Louie 2006, Johnson 2014 (301) and Johnson 2014 (302), Pardi 2012, NCT02179658 2016, Guery 2017

a) Forest plot



Quantifying heterogeneity / inconsistency:
tau^2 = 0·0078; I^2 = 13·1%

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	9·20	8	0·3253
Within designs	7·29	6	0·2947
Between designs	1·91	2	0·3843

b) League table

0·8742							
RID	0·8484						
0·83 [0·35; 1·93]	**FID**	0·6131					
0·64 [0·26; 1·53]	0·77 [0·53; 1·13]	**SUR**	0·5654				
0·61 [0·19; 1·89]	0·73 [0·32; 1·67]	0·95 [0·41; 2·23]	**FUA**	0·4760			
0·56 [0·25; 1·28]	**0·68 [0·55; 0·85]**	0·88 [0·65; 1·21]	0·93 [0·42; 2·05]	**VAN**	0·4333		
0·52 [0·19; 1·42]	0·63 [0·34; 1·17]	0·81 [0·42; 1·58]	0·86 [0·32; 2·29]	0·92 [0·51; 1·65]	**RFX**	0·1882	
0·38 [0·16; 0·91]	**0·46 [0·32; 0·67]**	**0·60 [0·39; 0·93]**	0·63 [0·30; 1·31]	**0·68 [0·50; 0·92]**	0·73 [0·38; 1·42]	**MET**	0·0015
0·22 [0·09; 0·52]	**0·27 [0·19; 0·38]**	**0·34 [0·23; 0·52]**	**0·36 [0·16; 0·80]**	**0·39 [0·30; 0·51]**	**0·42 [0·22; 0·80]**	**0·58 [0·43; 0·77]**	**TOL**

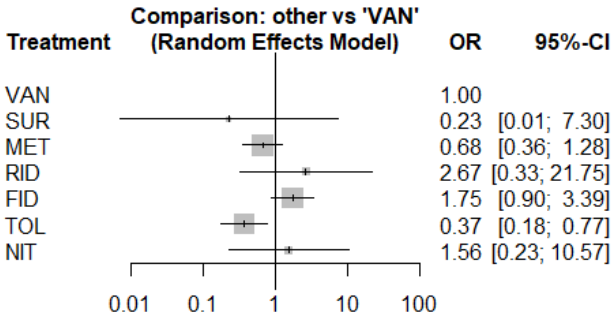
League table of pairwise comparisons in network meta-analysis of sensitivity analysis including only trials having 50 or more patients in each arm. Treatments order in the rank of their chance of being the best treatment. Numbers in grey boxes are P-Scores, which are used to rank the treatments. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, FUA – fusidic acid, MET – metronidazole, RFX – rifaximicin, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

Appendix 18. Subgroup analyses

a) Severe CDI

Data available from Zar 2007, Vickers 2017, Mucher 2009, Louie 2011, Cornely 2012, Lee 2016, Johnson 2014 (301) and Johnson 2014 (302) trials

i) Forest plot



ii) League table

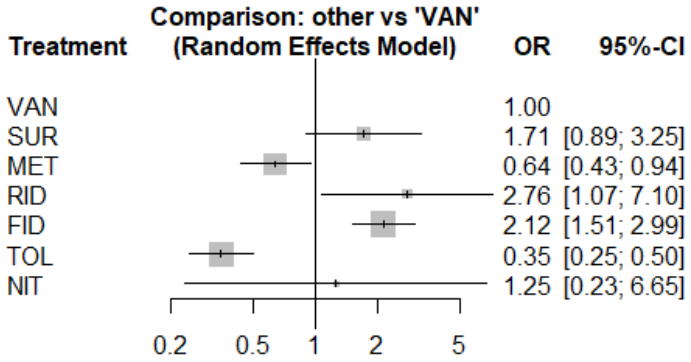
0.8070						
RID	0·7830					
0·66 [0·07; 5·92]	**FID**	0·6692				
0·58 [0·03; 10·00]	0·89 [0·12; 6·75]	**NIT**	0·5385			
0·37 [0·05; 3·06]	0·57 [0·30; 1·11]	0·64 [0·09; 4·37]	**VAN**	0·3570		
0·25 [0·03; 2·28]	**0·39 [0·16; 0·97]**	0·44 [0·06; 3·29]	0·68 [0·36; 1·28]	**MET**	0·2149	
0·09 [0·00; 4·93]	0·13 [0·00; 4·44]	0·15 [0·00; 7·71]	0·23 [0·01; 7·30]	0·34 [0·01; 11·39]	**SUR**	0·1305
0·14 [0·02; 1·29]	**0·21 [0·08; 0·57]**	0·24 [0·03; 1·86]	**0·37 [0·18; 0·77]**	0·55 [0·28; 1·10]	1·62 [0·05; 55·26]	**TOL**

League table of subgroup pairwise comparisons in network meta-analysis of severe Clostridium difficile infection treatment. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, sUR – Suratomycin, TOL – tolevamer, VAN – vancomycin.

b) Non-severe CDI

Data available from Zar 2007, Vickers 2017, Mucher 2009, Louie 2011, Cornely 2012, Lee 2016, Johnson 2014 (301) and Johnson 2014 (302) trials

i) Forest plot



ii) League table

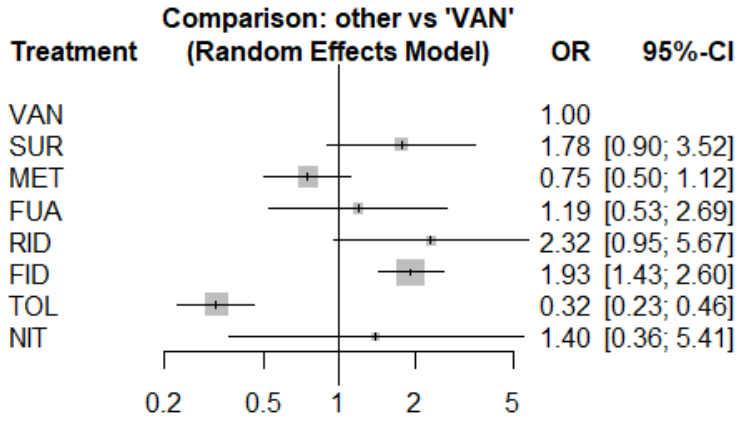
0·8771						
RID	0·7926					
0·77 [0·28; 2·10]	**FID**	0·6762				
0·62 [0·20; 1·94]	0·80 [0·39; 1·67]	**SUR**	0·5263			
0·45 [0·07; 3·09]	0·59 [0·11; 3·24]	0·73 [0·12; 4·40]	**NIT**	0·4092		
0·36 [0·14; 0·93]	**0·47 [0·33; 0·66]**	0·59 [0·31; 1·12]	0·80 [0·15; 4·26]	**VAN**	0·2066	
0·23 [0·08; 0·64]	**0·30 [0·18; 0·50]**	**0·37 [0·18; 0·79]**	0·51 [0·09; 2·84]	**0·64 [0·43; 0·94]**	**MET**	0·0121
0·13 [0·05; 0·35]	**0·16 [0·10; 0·27]**	**0·21 [0·10; 0·43]**	0·28 [0·05; 1·55]	**0·35 [0·25; 0·50]**	**0·55 [0·39; 0·78]**	**TOL**

League table of subgroup pairwise comparisons in network meta-analysis of non-severe Clostridium difficile infection treatment. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, sUR – Suratomycin, TOL – tolevamer, VAN – vancomycin.

c) Treatment of initial CDI

Data available from Wullt 2004, Vickers 2017, Mucher 2009, Louie 2011, Cornely 2012, Lee 2016, Johnson 2014 (301) and Johnson 2014 (302) trials

i) Forest plot



ii) League table

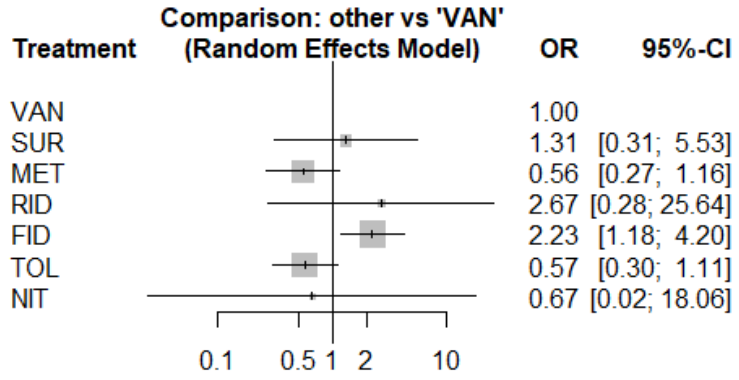
0·8389							
RID	0·7816						
0·83 [0·32; 2·13]	**FID**	0·7233					
0·77 [0·25; 2·36]	0·92 [0·44; 1·95]	**SUR**	0·5757				
0·60 [0·12; 3·05]	0·73 [0·18; 2·90]	0·79 [0·17; 3·58]	**NIT**	0·4989			
0·51 [0·15; 1·72]	0·62 [0·26; 1·47]	0·67 [0·23; 1·94]	0·85 [0·18; 4·13]	**FUA**	0·3791		
0·43 [0·18; 1·05]	**0·52 [0·38; 0·70]**	0·56 [0·28; 1·11]	0·71 [0·18; 2·76]	0·84 [0·37; 1·90]	**VAN**	0·1997	
0·32 [0·12; 0·86]	**0·39 [0·24; 0·64]**	**0·42 [0·19; 0·93]**	0·53 [0·13; 2·19]	0·63 [0·31; 1·28]	0·75 [0·50; 1·12]	**MET**	0·0029
0·14 [0·05; 0·36]	**0·17 [0·11; 0·27]**	**0·18 [0·08; 0·39]**	**0·23 [0·06; 0·93]**	**0·27 [0·12; 0·60]**	**0·32 [0·23; 0·46]**	**0·43 [0·31; 0·61]**	**TOL**

League table of subgroup pairwise comparisons in network meta-analysis of initial Clostridium difficile infection treatment. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID- Fidaxomicin, FUA – Fusidic acid, MET – Metronidazole, NIT – Nitazoxanide, RID – Ridinidazole, SUR – Suratomycin, TOL – Tolevamer, VAN – Vancomycin.

d) Non-initial CDI

Data available from Vickers 2017, Mucher 2009, Louie 2011, Cornely 2012, Lee 2016, Johnson 2014 (301) and Johnson 2014 (302) trials

i) Forest plot



ii) League table

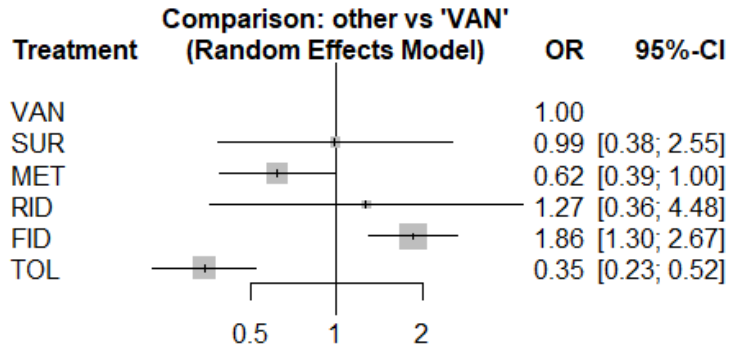
0·8226						
FID	0·7688					
1·20 [0·11; 12·54]	**RID**	0·5897				
0·59 [0·12; 2·83]	0·49 [0·03; 7·18]	**SUR**	0·5082			
0·45 [0·24; 0·84]	0·37 [0·04; 3·61]	0·76 [0·18; 3·23]	**VAN**	0·3879		
0·30 [0·01; 8·60]	0·25 [0·00; 13·66]	0·51 [0·01; 18·64]	0·67 [0·02; 18·06]	**NIT**	0·2186	
0·26 [0·10; 0·64]	0·22 [0·02; 2·27]	0·44 [0·09; 2·14]	0·57 [0·30; 1·11]	0·86 [0·03; 24·87]	**TOL**	0·2042
0·25 [0·09; 0·66]	0·21 [0·02; 2·25]	0·42 [0·08; 2·14]	0·56 [0·27; 1·16]	0·83 [0·03; 24·48]	0·97 [0·54; 1·75]	**MET**

League table of subgroup pairwise comparisons in network meta-analysis of non-initial Clostridium difficile infection treatment. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

e) ≥ 65 years old

Data available from Vickers 2017, Louie 2011, Cornely 2012, Lee 2016, Johnson 2014 (301) and Johnson 2014 (302) trials

i) Forest plot (Vancomycin as reference)



ii) League table

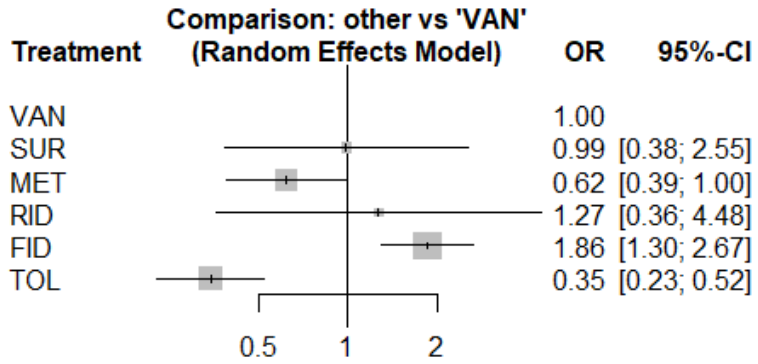
0·9205					
FID	0·6759				
0·68 [0·18; 2·54]	**RID**	0·5676			
0·54 [0·38; 0·77]	0·79 [0·22; 2·77]	**VAN**	0·5530		
0·53 [0·19; 1·47]	0·78 [0·16; 3·76]	0·99 [0·38; 2·55]	**SUR**	0·2727	
0·33 [0·18; 0·61]	0·49 [0·13; 1·87]	0·62 [0·39; 1·00]	0·63 [0·22; 1·80]	**MET**	0·0104
0·19 [0·11; 0·32]	0·27 [0·07; 1·02]	**0·35 [0·23; 0·52]**	**0·35 [0·12; 0·98]**	**0·56 [0·37; 0·83]**	**TOL**

League table of subgroup pairwise comparisons in network meta-analysis of Clostridium difficile infection treatment for patients aged ≥65. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, MET – metronidazole, NIT – nitazoxanide, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

f) < 65 years old

Data available from Vickers 2017, Louie 2011, Cornely 2012, Lee 2016, Johnson 201 (301) and Johnson (302) trials

i) Forest plot (Vancomycin as reference)



ii) League table

0·9216					
RID	0·7418				
0·57 [0·14; 2·32]	**SUR**	0·7244			
0·54 [0·16; 1·83]	0·96 [0·38; 2·39]	**FID**	0·376		
0·26 [0·08; 0·80]	0·45 [0·20; 1·02]	**0·47 [0·31; 0·71]**	**VAN**	0·2359	
0·20 [0·06; 0·69]	**0·35 [0·13; 0·91]**	**0·36 [0·19; 0·70]**	0·77 [0·46; 1·29]	**MET**	0·0003
0·10 [0·03; 0·35]	**0·18 [0·07; 0·46]**	**0·19 [0·10; 0·35]**	**0·40 [0·25; 0·63]**	**0·52 [0·34; 0·80]**	**TOL**

League table of subgroup pairwise comparisons in network meta-analysis of Clostridium difficile infection treatment for patients aged <65. Treatments order 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. Treatment estimates are provided as odds ratios with 95% confidence intervals. Significant pairwise comparisons are highlighted. FID - fidaxomicin, MET – metronidazole, RID – ridinidazole, SUR – suratomycin, TOL – tolevamer, VAN – vancomycin.

Appendix 19. Confidence in sustained symptomatic cure estimates by GRADE system (per Salanti et al. 2014)

Comparison	Study limitations	Imprecision OR [95% CI]	Heterogeneity and inconsistency	Indirectness	Publication bias	Confidence in odds ratio for sustained symptomatic cure
VAN vs RFX	100% of estimate from studies of moderate risk.	0·92 [0·53; 1·61]	Evidence from only one direct comparison study. No heterogeneity and inconsistency.	Only one trial. No subgroup analyses to assess transitivity.	Only one study. Unpublished, but provided by authors. RFX treatment effect inferior to VAN. Bias undetectable by conventional methods.	Very low (downgrade by 3 levels for study limitations, imprecision and indirectness)
VAN vs SUR	100% estimate from studies of low risk	0.90 [0·68; 1·19]	Moderate heterogeneity as assessed by Cochran's Q 2·22 and p-value = 0·13. Boix et al. 2017 trial included significantly higher proportion of patients with severe CDI compared to Lee et al. 2016 trial. Only direct evidence, no node-splitting inconsistency.	Subgroup analyses provide slightly different efficacy of SUR and VAN for different subgroups.	No publication bias detectable by conventional methods.	Low (downgrade by 2 levels for heterogeneity and imprecision)
VAN vs TEIC	100% of estimate from studies with high risk of bias.	0·37 [0·14; 0·94]	Very low heterogeneity as assessed by Cochran's Q 0·015 and p-value = 0·90. Both direct and indirect effect estimates very similar.	Not enough patient information to assess transitivity.	Only two old unregistered trials. No publication bias detected by conventional methods. One very small old trial excluded for not reporting recurrence and therefore making sustained symptomatic cure assessment impossible (Boero et al. 1990). There exists likelihood of other old unpublished trials.	Very low (downgrade by 2 levels for study limitations, by 1 level for indirectness and by 1 level for publication bias. Upgrade by 1 level for large effect size)
VAN vs RID	22% of estimate from studies with high risk of bias, 78% from studies with low risk of bias	0·57 [0·28; 1·15]	Evidence from two trials with different comparators. No heterogeneity. Nearly identical estimates from direct and indirect evidence.	Identical treatment in both trials. Similar effect sizes across different patient groups.	No publication bias detectable by conventional methods. One trial provided by pharmaceutical company. Other unpublished RCTs unlikely.	Moderate (downgrade by 1 level for imprecision)
VAN vs TOL	100% of estimate from studies with moderate risk of bias	0·40 [0·32; 0·51]	Moderate heterogeneity as assessed by Cochran's Q (2·22) and P-value (0·33). Both direct and indirect effect estimates very similar.	Two different TOL doses in Louie 2006 compared to Johnson et al. 2014 trials. Consistent and similar effect sizes across different patient groups.	No publication bias detectable by conventional methods.	Moderate (downgrade by 2 levels for study limitations and heterogeneity. Upgrade by 1 level for large effect size).
NIT vs VAN	71% of estimate from studies with high risk of bias, 29% of estimate from studies with low risk of bias	0·93 [0·49; 1·78]	No heterogeneity for one direct study. Both direct and indirect effect estimates very similar.	Similar treatments and patient groups. Similar treatment effect size in subgroup analyses.	No publication bias detectable by conventional methods.	Low (downgrade by 2 levels for study limitations and imprecision)

VAN vs LFF571	100% of estimate from trials with high risk of bias	0·80 [0·30; 2·13]	Evidence from only one direct comparison study. No heterogeneity and inconsistency.	Only one trial. No subgroup analyses to assess transitivity.	No publication bias detectable by conventional methods.	Very low (downgrade by 2 levels for study limitations, by 1 level for imprecision and by 1 level for indirectness)
VAN vs MET	19% of estimate from trials with high risk of bias, 81% from trials with moderate risk of bias.	0·73 [0·56; 0·95]	Moderate heterogeneity as assessed by Cochran's Q (4·12) and P-value (0·38). This is largely due to Teasley et al. 1983 study, which demonstrated a higher treatment effect for metronidazole than later better quality RCTs. Removal of Teasley trial resolved heterogeneity, but did not significantly affect the effect estimate. Direct and indirect effect estimates similar.	Similar treatment regime and patient groups across trials. Consistent treatment effect size across different subgroups.	No publication bias detectable by conventional methods, older unpublished trials possible, but unlikely to affect treatment effect estimate significantly, unless unpublished RCT is very large.	Moderate (downgrade by 1 level for study limitations)
CAD vs VAN	100% of estimate from trials with low risk of bias	0·69 [0·25; 1·94]	Evidence from only one direct comparison study. No heterogeneity and inconsistency.	Only one trial. No subgroup analyses to assess transitivity.	Two very large phase 3 trials have been finished but were not published at the time of the analysis. They are likely to change the treatment effect estimate.	Very low (downgrade by 3 levels for imprecision, indirectness and publication bias)
FID vs VAN	20% of estimate from trials with high risk, 13% with moderate risk, 67% from low risk of bias	0·67 [0·55; 0·82]	Mild heterogeneity as assessed by Cochran's Q (2·62) and P-value (0·62). Direct and indirect effect estimates very similar.	One trial assessed slightly prolonged FID dosing regime. Unlikely to affect the overall effect estimate. Consistent treatment effect size across different subgroups.	No publication bias detectable by conventional methods. Two registered, but unpublished trials uncovered. Further unpublished data unlikely.	High
VAN vs FUA	28% of estimate from trials with high risk, 72% from moderate risk of bias.	0·85 [0·47; 1·57]	Direct evidence from one trial. No heterogeneity. Significantly different estimates from direct and indirect evidence (RoR 1·83).	Different doses in two trials. Not enough information to assess transitivity.	No publication bias detectable by conventional methods.	Very low (downgrade by 4 levels for study limitations, imprecision, inconsistency and indirectness)
VAN vs BAC	60% of estimate from trials with high risk of bias, 40% from moderate risk of bias.	0·60 [0·26; 1·36]	Mild heterogeneity as assessed by Cochran's Q (0·48) and P-value (0·49). Evidence from two direct trials, no indirect estimate possible.	No subgroup analyses to assess transitivity.	No publication bias detectable by conventional methods. Old unregistered unpublished trials possible.	Very low (downgrade by 2 levels for study limitations, by 1 level for indirectness)
RID vs FID	23% of estimate from trials of high risk of bias. 77% from low risk of bias. Direct evidence is of high risk of bias.	0·84 [0·41; 1·74]	Direct evidence from only one trial. No heterogeneity. Direct and indirect effect estimates very similar.	Similar treatment effect size across subgroups. Treatments in both trials identical.	No publication bias detectable by conventional methods. Further unpublished data unlikely.	Moderate (downgrade by 1 level for imprecision)
FUA vs MET	31% of estimate from trials with high risk of bias, 69% from trials with moderate risk of bias.	0·86 [0·48; 1·52]	Moderate heterogeneity as assessed by Cochran's Q (1·60) and P-value (0·21). Similar direct and indirect estimates of treatment effect.	Different FUA and MET doses used in both trials, patient age different. Not enough data for FUA subgroup analyses.	No publication bias detectable by conventional methods.	Very low (downgrade by 3 levels for study limitations, imprecision and indirectness)
TEIC vs FUA	100% of estimate from trials with high risk of bias.	0·31 [0·11; 0·89]	Direct evidence from one trial. No heterogeneity. Significantly different estimates from direct and indirect evidence (RoR 2·01).	One direct trial. The rest of the estimate derived from indirect evidence. Insufficient data for assessment of transitivity.	No publication bias detectable by conventional methods. Old unregistered unpublished trials possible.	Very low (downgrade by 2 levels for study limitations, by 1 level for inconsistency and 1 level for indirectness.

						Upgrade by 1 level for large treatment effect)
NIT vs MET	75% of estimate from trials with high risk of bias. 25% from trials with low risk of bias.	0·68 [0·37; 1·27]	Direct evidence from one trial. No heterogeneity. Direct and indirect effect estimates similar.	Consistent treatment effects across different subgroups.	No publication bias detectable by conventional methods.	Low (downgrade by 2 levels for study limitations and imprecision)
MET vs TEIC	100% of estimate from trials with high risk of bias.	0·27 [0·10; 0·70]	Direct evidence from one trial. No heterogeneity. Significantly different estimates from direct and indirect evidence (RoR 0·47).	Insufficient data for assessment of transitivity.	No publication bias detectable by conventional methods. Old unregistered unpublished trials possible.	Very low (downgrade by 2 levels for study limitations, by 1 level for inconsistency and 1 level for indirectness. Upgrade by 1 level for large treatment effect)
MET vs TOL	100% of estimate from studies with moderate risk of bias.	0·55 [0·42; 0·72]	Moderate heterogeneity as assessed by Cochran's Q (1·75) and P-value (0·18). Direct and indirect effect estimates similar.	Consistent treatment effects across different subgroups.	No publication bias detectable by conventional methods.	Moderate (downgrade by 2 levels for study limitations and heterogeneity. Upgrade by 1 level for large treatment effect)
Ranking of treatments	18% overall estimates from trials with high risk of bias, 41% from moderate risk of bias, 41% from low risk of bias.	P-score based ranking does not allow quantification of ranking imprecision.	There was no global heterogeneity and inconsistency (Cochrane Q = 15·70, p = 0·47; I^2 0%; tau^2 = 0)	The overall patient cohort was relatively comparable between different interventions. Few trials provided enough data for sufficient transitivity analysis	No dominant publication bias detectable by comparison-adjusted funnel plots.	Low (downgrade by 2 levels for study limitations and indirectness)

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014; **9**(7): e99682.

Appendix 20. Results of individual studies

Study	t1	t2	t3	t4	n1	cure1	recu1	ssc1	n2	cure2	recu2	ssc2	n3	cure3	recu3	ssc3	n4	cure4	recu4	ssc4
Zar 2007	VAN	MET			82	69	5	64	90	66	9	57								
Wenish 1996	VAN	MET	TEIC	FUA	31	29	5	24	31	29	5	24	28	27	2	25	29	27	8	19
Wullt 2004	MET	FUA			64	51	15	36	67	59	14	45								
Young 1985	VAN	BAC			21	18	6	12	21	16	5	11								
Vickers 2017	RID	VAN			50	36	4	32	50	37	12	25								
Louie 2011	FID	VAN			302	253	39	214	327	265	67	198								
Cornerly 2012	FID	VAN			270	221	28	193	265	223	60	163								
Mullane 2015	LFF571	VAN			46	29	12	17	26	18	7	11								
Louie 2015	CAD	VAN			62	42	17	25	22	15	8	7								
Musher 2006	NIT	MET			98	68	17	51	44	28	9	19								
Musher 2009	NIT	VAN			23	17	1	16	27	20	2	18								
Dudley 1986	BAC	VAN			31	12	5	7	31	15	3	12								
Boix 2017	SUR	VAN			308	229	53	176	298	234	63	171								
Teasley 1983	MET	VAN			45	37	2	35	56	45	6	39								
Lee 2016	SUR	VAN			139	119	27	92	70	59	21	38								
Louie 2006	TOL	VAN			190	106	27	79	96	73	16	57								
Johnson 2014 (301)	TOL	VAN	MET		285	124	11	113	140	109	27	82	149	103	29	74				
Johnson 2014 (302)	TOL	VAN	MET		278	112	13	99	126	101	19	82	140	99	20	79				
De Lalla 1992	TEIC	VAN			27	25	2	23	24	20	4	16								
Thabit 2016	FID	VAN			7	6	2	4	5	3	2	1								
NCT02179658 2016	FID	VAN			106	87	17	70	109	95	24	71								
Guery 2017	FID	VAN			183	131	7	124	181	136	30	106								
Pardi 2012	RFX	VAN			119	94	11	83	119	93	8	85								
Mitra 2017	RID	FID			14	12	5	7	13	8	2	6								

t - treatment; n - number of participants randomized intro treatment group; cure - number of participants attaining a primary cure; recu - number of participants experiencing recurrence after attaining a primary cure, ssc - number of participants attaining a sustained symptomatic cure

Appendix 21. List of ongoing RCTs

Clinicaltrials.gov number	Study title	Expected finish date
NCT01959048	Efficacy and Safety of Fecal Microbiota Transplantation for Severe Clostridium Difficile Associated Colitis	December 2017
NCT02301000	IMT for Primary Clostridium Difficile Infection	February 2018
NCT02857582	Transplantation of Cultured Gut Microflora to Repeat Antibiotic-induced Diarrhea Due to Clostridium Difficile	December 2017
NCT02801656	Fecal Microbiota Transplantation for Primary Clostridium Difficile Diarrhea	null
NCT02686645	Fecal Microbiota Therapy for Recurrent Clostridium Difficile Infection	December 2021
NCT02326636	Fecal Microbiota Transplant for Recurrent Clostridium Difficile Infection	May 2018
NCT02981316	Treatment of Recurrent Clostridium Difficile Infection With RBX7455	November 2018
NCT03065374	Treatment for Clostridium-difficile Infection With IMM529	May 2018
NCT02299570	Microbiota Restoration Therapy for Recurrent Clostridium Difficile Infection	January 2018
NCT03183128	ECOSPOR III - SER-109 Versus Placebo in the Treatment of Adults With Recurrent Clostridium Difficile Infection	June 2019
NCT03183141	ECOSPOR IV: An Open-Label Extension of Study SERES 0012 Evaluating SER-109 in Subjects With Recurrent Clostridium Difficile Infection	August 2019
NCT02464306	Fidaxomicin Versus Standard of Care Therapy in Solid Organ Transplant Recipients With Clostridium Difficile Infection	June 2019
NCT03053505	A Novel Faecal Microbiota Transplantation System for Treatment of Primary and Recurrent Clostridium Difficile Infection	October 2018
NCT02255305	FMT Versus Antimicrobials for Initial Treatment of Recurrent CDI	December 2018
NCT02774382	Rectal Bacteriotherapy, Fecal Microbiota Transplantation or Oral Vancomycin Treatment of Recurrent Clostridium Difficile Infections	null
NCT02692651	A Comparison of Fidaxomicin and Vancomycin in Patients With CDI Receiving Antibiotics for Concurrent Infections	April 2020
NCT03030248	Treatment of Clostridium Difficile in Colonized Patients in the Hematology Oncology Population	May 31, 2019
NCT03110133	Efficacy, Safety, and Tolerability Study of Oral Full-Spectrum MicrobiotaTM (CP101) in Subjects With Recurrent C. Diff	May 2019
NCT02466698	Intestinal Lavage for the Treatment of Severe C. Difficile Infections	August 2017
NCT02667418	Optimal Treatment for Recurrent Clostridium Difficile	December 29, 2017
NCT02570477	FMT for Moderate to Severe CDI: A Randomised Study With Concurrent Stool Microbiota Assessment	December 2017

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PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	4-5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Appendix page 2.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix pages 5-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	5-6

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix page 3
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	7-8
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	7-8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • Handling of multi-arm trials; • Selection of variance structure; • Selection of prior distributions in Bayesian analyses; and • Assessment of model fit.	7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • Alternative formulations of the treatment network; and • Use of alternative prior distributions for Bayesian analyses (if applicable).	8

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10, 21, Appendix 9-11
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	24
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	22-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	25, appendix 12-19
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	Appendix 44
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	10-11, 26, appendix 22-25
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	11-12, appendix 22-25, 27-29
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix 22-25, 30
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	12-13, 27, appendix 31-42
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	13-15, Appendix 41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of	13-15

		the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	3

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.