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Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: An updated systematic review and meta-analysis

Simon Mark Dahl Baunwall[a,1,*], Mads Ming Lee[a,1], Marcel Kjærsgaard Eriksen[a], Benjamin H. Mullish[b], Julian R. Marchesi[b,c], Jens Frederik Dahlerup[a], Christian Lodberg Hvas[a]

[a] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 35, DK-8200 Aarhus N, Denmark
[b] Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom
[c] School of Biosciences, Cardiff University, Cardiff, United Kingdom

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ABSTRACT

Background: Faecal microbiota transplantation (FMT) is effective for recurrent *Clostridioides difficile* infection (CDI), but inconsistent effect rates and uncertain evidence levels have warranted caution. To clarify, we aimed to establish the evidence of FMT for recurrent CDI, updated across different delivery methods, treatment regimens, and in comparison with standard antibiotics.

Methods: In this updated systematic review and meta-analysis, we searched PubMed, Scopus, Embase, Web of Science, Clinical Key, and Svemed+ for FMT literature published in English until November 11, 2019. We included observational and clinical trials with or without antibiotic comparators and excluded studies with below 8 weeks follow-up and fewer than 15 patients. The primary outcome was clinical outcome by week 8. We comprehensively extracted patient and procedural data. In a random-effects meta-analysis, we estimated the clinical effect for repeat or single FMT, different delivery methods, and versus antibiotics. We rated the evidence according to the Cochrane and GRADE methods. The PROSPERO preregistration number is CRD42020158112.

Findings: Of 1816 studies assessed, 45 studies were included. The overall clinical effect week 8 following repeat FMT (24 studies, 1855 patients) was 91% (95% CI: 89–94%, I^2=53%) and 84% (80–88%, I^2=86%) following single FMT (43 studies, 2937 patients). Delivery by lower gastrointestinal endoscopy was superior to all other delivery methods, and repeat FMT significantly increased the treatment effect week 8 (P<0·001). Compared with vancomycin, the number needed to treat (NNT) for repeat FMT was 1·5 (1·3–1·9, P<0·001) and 2.9 (1·5–37·1, P=0·03) for single FMT. Repeat FMT had high quality of evidence.

Interpretation: High-quality evidence supports FMT is effective for recurrent CDI, but its effect varies with the delivery method and the number of administrations. The superior NNT for FMT compared with antibiotics suggests that patients may benefit from advancing FMT to all instances of recurrent CDI.

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1. Introduction

Faecal microbiota transplantation (FMT) is an effective treatment for recurrent *Clostridioides difficile* infection (CDI) [1–3]. CDI is a leading cause of antibiotic-associated diarrhoea [4], and 22–32% experience prolonged or recurrent infections unresponsive to standard antibiotics [5,6]. Recurrent CDI is associated with a high mortality [7], and preventing the infection poses a substantial therapeutic challenge with limited treatment options. During the last decade, FMT has emerged as a viable treatment for recurrent CDI. With effect rates of up to 94% in clinical trials [1–3], FMT is now recommended by scientific societies and National Health agencies for patients with 2 or more recurrences of CDI [8–10].

Previous systematic reviews [11–17] have confirmed the high clinical effect of FMT for recurrent CDI and indicated that the treatment effect may depend on the method of delivery and treatment regimens [15,16]. Still, no clear clinical evidence exists for the cumulative effect of FMT following single or repeated treatment regimens,

Abbreviations: CDI, Clostridioides difficile infection; CDAD, CD associated diarrhoea; CI, Confidence interval; FMT, Faecal microbiota transplantation; GI, Gastrointestinal; NA, Not available; NOS, Newcastle-Ottawa quality assessment Scale; Number needed to treat, NNT; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; Randomised clinical trial, RCT; RR, Relative risk; RoB2, Cochrane Risk of Bias 2

* Corresponding author.
E-mail address: simjor@rm.dk (S.M.D. Baunwall).

[1] Share equal contributions.

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Research in context

Evidence before this study

Faecal microbiota transplantation (FMT) is recommended for patients with two or more recurrent *Clostridioides difficile* infections (CDI), but uncertain evidence levels limit the advancing of FMT. Prior to the present study, we searched PubMed, Scopus, Embase, Web of Science, Clinical Key, and Svemed+ for literature published until Jun 26, 2019 on the clinical use of FMT for recurrent CDI, using the search terms *Clostridiodes/Clostridium difficile*, faecal/fecal microbiota transplantation/ transplant, installation, and bacteriotherapy. Several previous systematic reviews confirmed an overall 92−93% clinical cure rate for recurrent CDI following FMT, but they did not compare FMT with the current standard of care and had limited power to evaluate the magnitude of effect for delivery methods and treatment regimens combined.

Added value of this study

This updated systematic review and meta-analysis establishes a high quality of evidence for repeat FMT administered for recurrent CDI with an overall 91% effect rate at week 8 and a number needed to treat (NNT) of 1.5 compared with standard antibiotics. The study provides effect estimates specific for each delivery method and treatment regimen, confirming that the effect of FMT varies accordingly. This will help clinicians inform their patients of anticipated treatment effects and more effectively plan treatment courses for recurrent CDI.

Implications of all the available evidence

A large body of high-quality evidence now underpins the conclusion that FMT is effective for managing recurrent CDI. The low NNT for FMT suggests that FMT should be translated from an experimental treatment reserved for the few to a standard of care offered to all patients with recurrent CDI.

and the quality of evidence for FMT compared with standard antibiotics has been rated as moderate in previous systematic reviews and guidelines due to inconsistencies [10,13]. These inconsistencies have resulted in caution and questioned the position of FMT in the CDI treatment algorithm until the evidence for FMT has been evaluated in more detail [18]. Now, further to these earlier systematic reviews, more evidence has accumulated, and new methods of delivery have emerged; as such, an update of the evidence with the latest data is pivotal to guide clinical decisions and improve the future recommendations for FMT in managing patients with recurrent CDI.

The aims of this systematic review and meta-analysis were to establish the evidence for using FMT in recurrent CDI, to provide updated effect estimates specific to different delivery methods and treatment regimens, and to compare the effect of FMT with that of standard antibiotics.

2. Methods

In this systematic review and meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary File 1) and the instructions described in the Cochrane Handbook [19,20]. The review protocol was preregistered and is accessible at http://www.crd.york.ac.uk/PROSPERO (CRD42020158112).

Overall, the review addressed three principal questions:

1 What is the overall effect of FMT in treating recurrent CDI?
2 Does the effect of FMT vary according to delivery method or treatment regimen?
3 What is the effect of FMT compared with standard antibiotics in patients with recurrent CDI?

2.1. Data sources and searches

We searched the medical databases PubMed, Scopus, Embase, Web of Science, Clinical Key, and Svemed+ for all available literature published until November 11, 2019. The search string was constructed to include the different terminologies used to describe the procedure (Supplementary Table 1).

2.2. Study selection

Inclusion criteria were: published randomised clinical trials (RCT) and observational cohort studies with more than 15 patients. We included English language studies using FMT to treat recurrent CDI, with or without an antibiotic comparator, in an adult population (18+ years) with no prior FMT treatments and a follow-up period of at least 8 weeks. We defined FMT as the transfer of processed faeces from healthy, allogenic donors. We excluded autologous FMT and microbial treatments sourced from cultured microbial consortiums. As a cut-off value to restrict the study population to recurrent CDI only, studies were excluded if they included ≥10% adolescents or ≥10% patients with refractory, index CDI. Studies that failed to report clinical outcomes or had selective reporting were excluded. For studies reporting outcomes from the same population at different time points, we included the most recent if the superseding study was of equal quality. Subsidiary studies conducting additional sub-analyses were omitted in favour of the original study with more details.

All references were imported and managed in Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia.). Two independent reviewers (SMDB and MM) screened and fully read potential articles for eligibility, and one reviewer (CH) arbitrated discrepancies. Two reviewers (BHM and JRM) challenged the robustness of the final search strategy by checking for potential missing studies and inconsistencies.

2.3. Outcome assessment

The primary outcome was effect with sustained resolution week 8 following single or repeated courses of FMT, or antibiotics. We evaluated effect according to the guideline definitions for resolution of *C. difficile*-associated diarrhoea (CDAD) as either i) clinical resolution of diarrhoea, or ii) persistent diarrhoea with a negative CD test [8,10]. For FMT, the outcomes were grouped overall and according to delivery method.

We evaluated the FMT treatment effect according to treatment regimens in two categories for a) single FMT and b) repeat FMT. For single FMT, we defined treatment effect as the number of patients with effect following one FMT. We considered FMT performed in a pre-planned series as the same single FMT reflecting an increase in dose. For repeat FMT, we defined treatment effect as the total, cumulative number of patients with effect following one or more FMT, i.e., including both initial non-responders to the first FMT who later achieved treatment effect from a subsequent FMT as well as the patients only requiring one FMT to achieve treatment effect. Consequently, repeat FMT reflects the total FMT treatment effect if FMT is repeatedly performed as needed until resolution of symptoms. Follow-up time was from the last FMT.

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For delivery methods, we predefined four overall categories based on the method of application and retention times in: i) lower gastrointestinal (GI) endoscopy (colonoscopy, enteroscopy, sigmoideoscopy), ii) upper GI administration (nasojejunal/gastric tube, gastroscopy, gastrostomy tube), iii) capsules, and iv) enema (rectal installation and rectal catheter).

2.4. Data extraction

Two reviewers (SMDB and MM) independently extracted the data to an Excel spreadsheet with predefined record forms. One reviewer (MKE) validated all data in the final dataset. In case of unexplainable study discrepancies, the authors were contacted. To provide the most conservative estimates, data were extracted according to a strict intention to treat principle: For studies reporting outcomes only on patients with complete follow-up, drop-outs were registered as failures, and for studies summarising an overall treatment effect for both FMT and antibiotics, patients who did not achieve effect from the FMT but from a subsequent antibiotics course were also counted as failures. Studies that did not adhere to the CDAD definition for effect was as conservative measures based on the reporting of clinical effect. Death during failure up counted as failures.

For studies with >8 weeks follow-up, we extrapolated long-term, follow-up outcomes for sustained responses to week 8 outcomes, if the week 8 outcome was not reported separately. To account for reporting bias in studies with >8 weeks follow-up, we counted all CDI relapses in the >8-week period as treatment failures. We extracted week 1 data for single FMT when reported.

For delivery method specific estimates, we extracted data both separately and combined overall for each study if a study used more than one FMT delivery method. Patients who received repeat FMT with a change in delivery method were categorised according to their first delivery method.

To account for methodological, procedural, and patient-related aspects potentially influencing the clinical effect, we comprehensively extracted data for these parameters. From each study, donor type, processing method, and dose was extracted. Because a previous systematic reviews indicated a clinical effect of administrating 50 g of crude faeces or more [15,17], we included this as a binary variable for each study. Patient-related parameters included age, sex, previous number of CDI recurrences, comorbidity, and refractory CDI. Refractory CDI, defined as sustained symptoms despite sufficient standard antibiotics treatment, was assessed according to the reporting in each study.

2.5. Risk of bias assessment and quality of evidence

Two reviewers (SMDB and MM) evaluated the study quality for each study. Cohort studies were evaluated with the Newcastle-Ottawa quality assessment Scale (NOS) [21] and randomised clinical trials with the Cochrane Risk of Bias 2 (RoB2) tool [22]. NOS scores range from 0 (lowest) to 9 (highest) and require reviewers to incorporate predefined quality determinants for comparability. For FMT, we defined reporting processing method and dose as critical for comparability. The RoB2 tool categorises bias risk in three categories: low, moderate, and high. To yield comparable estimates, we considered a NOS score of 8−9 as low, 5−7 as moderate, and ≤4 as high risk of bias.

The GRADE methodology [23] was used to determine the quality of evidence for each of the three study questions and derive summary of findings tables.

2.6. Data analysis

For all statistical analyses, we used R version 3.6.1 with the "meta", "metafor", and "dmetar" extension packages [24,25]. We applied a random effects model with a DerSimonian−Laird tau^2 estimator and Z-based statistics for all meta-analyses, and when applicable, results were summarised in forest plots. *P*-values <0·05 were considered statistically significant, and all data were presented with 95% confidence intervals (CI).

The proportional FMT effect data were pooled as weighted averages overall and across the four categories for delivery method and according to single or repeat FMT. Only studies reporting stratified effect rates according to delivery method were included in the grouped analysis for delivery method, and only studies performing repeat FMT with a report of the pairwise effect rates were included in the cumulative effect analysis for single versus repeat FMT.

We transformed all effect data with the Freeman−Tukey Double Arcsine transformation to stabilise the variance and correct for the skewness introduced by high effect studies whose weight of the upper intervals is otherwise not accounted for. For all estimates, we calculated the prediction intervals indicating the expected FMT effect in future studies. The subgroup analyses of delivery methods were evaluated with Wald-type statistics and referenced with lower GI delivery. Repeat and single FMT was compared using a one-proportion *Z* statistics assuming a no difference null-hypothesis between the transformed repeat minus single FMT effect estimates. For the GRADE summary table, we used the absolute difference in weighted between single and repeat FMT. To detect if extreme study outliers influenced the estimates too heavily, we performed outlier and leave-one-out analyses for each analysis. We prespecified extreme outliers as studies whose confidence intervals did not overlap with the pooled estimate's confidence interval.

Only randomised clinical trials with an antibiotic comparator were included in the analysis of FMT versus antibiotics. Antibiotics was compared with both single and repeat FMT. The effects of FMT compared with antibiotics were expressed as risk difference and relative risk with a derived number need to treat (NNT) with confidence intervals. We calculated the NNT from the inverse absolute risk difference (risk antibiotics minus risk FMT).

Heterogeneity, arising from other than statistical probability, was quantified with I^2 statistics and significance tested with a chi-squared method (*P*-values >0.05 was considered as significant heterogeneity). According to the Cochrane Handbook [20], we considered I^2-values between 0−40% as minimal, 30−60% as moderate, 50−90% as substantial, and 75−100% as considerable heterogeneity. Significant heterogeneity was examined using multimodal inference to construct, unbiased meta-regressions explaining influential study moderators while accounting for different moderator combinations.

Publication bias was evaluated by visual inspections of funnel plots and tested for asymmetry with Egger's test when 5 studies or more were included. Duval and Tweedie's trim-and-fill procedure [26] was applied to determine direction of potential publication bias.

2.7. Role of the funding source

The study was funded by the Innovation Fund Denmark (j.no. 8056-00006B). The funding source was independent of the study and had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

The search strategy identified 1816 unique studies, of which 332 were read in full following the initial screening of titles and abstracts. Of these, we included 45 studies [1−3,27−68] that comprised 9 randomised clinical trials and 36 cohort studies. Fig. 1 displays the outcome of the full search strategy, and Supplementary File 2 provides exact reasons for dismissal for each excluded study read in full.

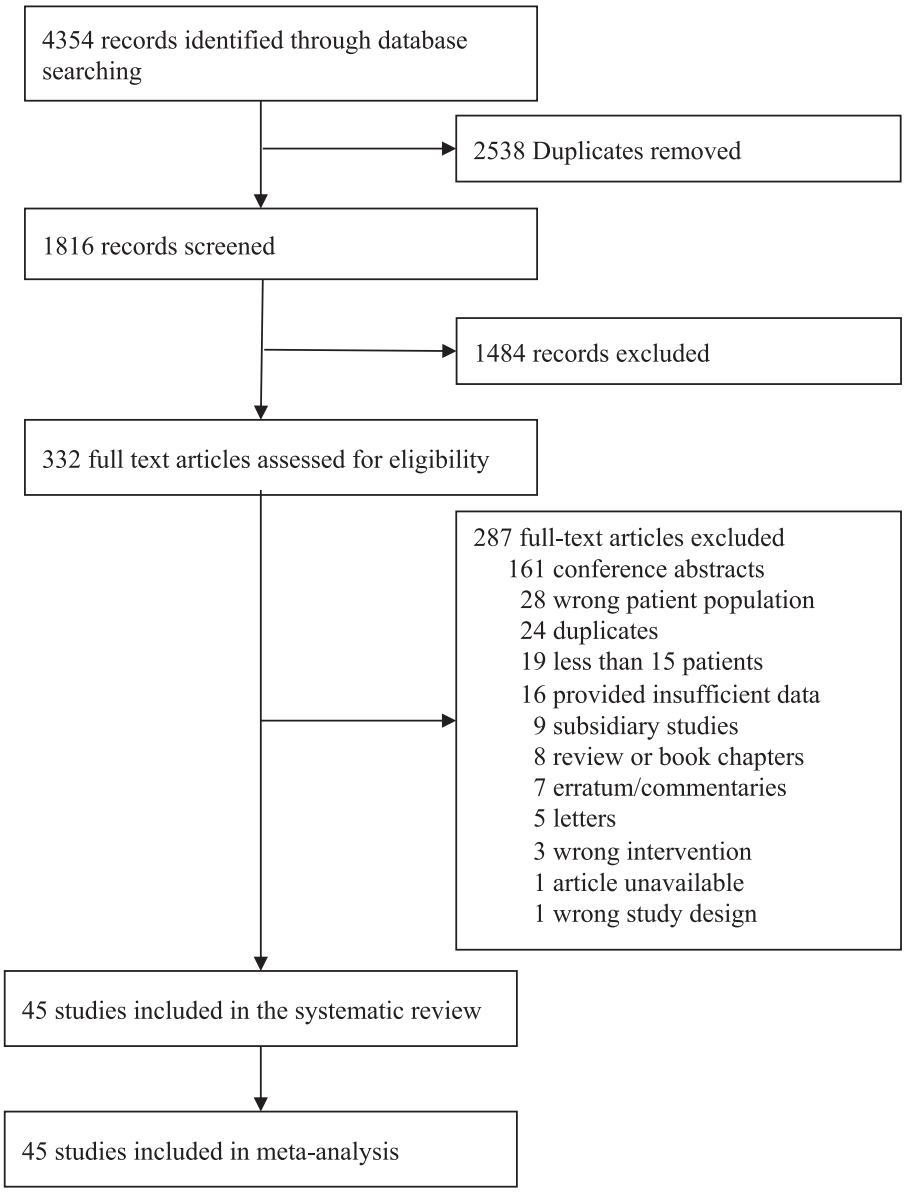

Fig. 1. PRISMA flowchart of included and excluded studies.

Table 1 presents the included studies and their characteristics. An overall summary of findings with GRADE quality of evidence are presented in Tables 2 and 3.

Across all studies, the mean patient age was 65·8 years with 66% being women experiencing on average 3·7 CDI episodes. Pre-treatment with antibiotics (metronidazole, vancomycin, or fidaxomicin) prior to FMT was described in all but four studies (9%) and lasted from four days up to long-term, tapered regimens. One study performed FMT without antibiotic pre-treatment on a subset of their cohort [61]. Risk of bias assessments for each study are provided in Supplementary Fig. 1 and Supplementary File 3. Supplementary Tables 2 and 3 describes processing methods, donor types, and patient characteristics in each of the included studies.

Clinical effect week 8 overall was 91% (89–94%, I^2=53%) for repeat FMT based on 24 studies with 1855 patients and 84% (95% CI 80–88%, I^2=86%) for single FMT based on 43 studies with 2937 patients. Two studies [44,67] for repeat FMT and seven studies [30,34,36,45,46,48,50] for single FMT were extreme study outliers. Omitting the studies, either separately or as a group, markedly reduced study heterogeneity (single FMT I^2=50%, repeat FMT I^2=24%) but did not affect the overall effect rates.

Clinical effect week 1 following single FMT was reported in nine studies with 384 patients. The pooled, overall effect week 1 was 94% (86–99%, I^2=76%) compared with 88% (80–94%, I^2=67%) week 8 (P=0·069). No studies were extreme outliers. Subgroup analyses were not possible because few studies provided week 1 outcome data.

Effect estimates specific to the delivery method were reported in 22 studies with 1513 patients for repeat FMT and 41 studies with 2754 patients for single FMT (Table 2). Delivery by lower GI endoscopy was superior to delivery by upper administration (repeat FMT P=0·001, single FMT P<0·001), capsules (repeat FMT P=0·051, single FMT P=0·001), and enema (repeat FMT P=0·009, single FMT P<0·001) (Table 2). We graded the quality of evidence for one delivery method (lower GI endoscopy) being superior to the other delivery methods as low for repeat FMT and as moderate for single FMT (Table 2). The low rating for repeat FMT was due to a low gain in absolute effect between the delivery methods. The prediction intervals for the estimated effect of FMT in future studies are presented in Table 4, and Supplementary Figs. 2 and 3 present the forest plots for the stratified, meta-analytic effect estimates.

For repeat and single FMT compared (Fig. 2), pairwise effect rates were reported in 23 studies with 1357 patients (Table 2). We found a high quality of evidence supporting that repeated use of FMT

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Table 1
Main characteristics of the 45 included studies (9 randomised clinical trials and 36 cohort studies).

Author	Country	Study type	FMT category	Patient No.	FMT Effect			Follow-up (weeks)[a]	Age (mean)	Female (%)	CDAD	No. CDI (mean)	Quality assessment	
					Week 1 Single	Week 8 Single	Week 8 Repeat						NOS	RoB2
Garborg et al., 2010 [27]	Norway	Cohort	Upper administration	40	..	29 (72%)	33 (82%)	11·4	75·0	53·0	+	NA	Low risk	..
Kelly, 2012 [28]	USA	Cohort	Lower GI endoscopy	26	..	24 (92%)	..	8·0	59·0	92·3	+	NA	Moderate risk	..
Brandt et al., 2012 [29]	USA	Cohort	Lower GI endoscopy	77	..	70 (91%)	72 (94%)	73·6	65·0	73·0	–	NA	High risk	..
Mattila et al., 2012 [30]	Finland	Cohort	Lower GI endoscopy	70	..	66 (94%)	66 (94%)	46·0	73·0	60·0	+	3·5	Low risk	..
Rubin et al., 2013 [31]	USA	Cohort	Upper administration	75	..	59 (79%)	..	8·6	63·0	65·3	–	NA	Moderate risk	..
van Nood et al., 2013 [1]	**Netherlands**	**RCT**	**Upper administration**	**16**	..	**13 (81%)**	**15 (94%)**	**10·0**	**73·0**	**50·0**	**+**	**3·0**	..	**Low risk**
Youngster et al., 2014 [32]	USA	Cohort	Capsule	20	14 (70%)	14 (70%)	18 (90%)	8·0	64·5	45·0	+	3·0	Low risk	..
Youngster et al., 2014 [33]	**USA**	**RCT**	**Overall**	**20**	**14 (70%)**	**14 (70%)**	**18 (90%)**	**8·0**	**54·5**	**55·0**	**+**	**4·5**	..	**Low risk**
	USA	**RCT**	**Lower GI endoscopy**	**10**	**8 (80%)**	**8 (80%)**	**10 (100%)**	**8·0**	**50·4**	**60·0**	**+**	**4·0**	..	**Low risk**
	USA	**RCT**	**Upper administration**	**10**	**6 (60%)**	**6 (60%)**	**8 (80%)**	**8·0**	**58·6**	**50·0**	**+**	**5·0**	..	**Low risk**
Dutta et al., 2014 [34]	USA	Cohort	Lower GI endoscopy	27	..	27 (100%)	..	89·3	64·5	81·5	–	5·0	Moderate risk	..
Khan et al., 2014 [35]	USA	Cohort	Lower GI endoscopy	20	..	18 (90%)	20 (100%)	12·0	66·3	65·0	+	5·0	Moderate risk	..
Lee et al., 2014 [36]	Canada	Cohort	Enema	94	..	45 (48%)	86 (91%)	26·0	71·8	56·4	–	2·1	Moderate risk	..
Cammarota et al., 2015 [2]	**Italy**	**RCT**	**Lower GI endoscopy**	**20**	..	**13 (65%)**	**18 (90%)**	**10·0**	**71·0**	**60·0**	**+**	**3·0**	..	**Low risk**
Costello et al., 2015 [37][b]	Australia	Cohort	Lower GI endoscopy	16	15 (94%)	14 (88%)	16 (100%)	13·0	69·0	NA	+	3·0	High risk	..
Hirsch et al., 2015 [38]	USA	Cohort	Capsule	19	..	13 (68%)	17 (89%)	13·0	61·0	68·4	+	4·0	Moderate risk	..
Satokari et al., 2015 [39][c]	Finland	Cohort	Lower GI endoscopy	38	..	36 (95%)	37 (97%)	12·0	57·8	65·8	+	4·0	Low risk	..
Youngster et al., 2016 [40]	USA	Cohort	Capsule	180	..	147 (82%)	164 (91%)	8·0	64·0	NA	+	NA	Moderate risk	..
Agrawal et al., 2016 [41]	USA, Canada, Australia	Cohort	Overall	146	..	128 (88%)	133 (91%)	53·3	78·6	68·5	+	NA	Low risk	..
Girotra et al., 2016 [42]	USA	Cohort	Lower GI endoscopy	29	..	27 (93%)	..	12·0	80·1	79·3	+	NA	Moderate risk	..
Kelly et al., 2016 [43][d]	USA	RCT	Lower GI endoscopy	22	..	20 (91%)	..	8·0	48·0	82·0	–	4·0	Moderate risk	..
Khoruts et al., 2016 [44]	USA	Cohort	Lower GI endoscopy	272	..	243 (89%)	262 (96%)	8·0	57·2	69·5	+	5·0	Low risk	..
Lee et al., 2016 [45]	Canada	RCT	Enema	219	..	113 (52%)	193 (88%)	13·0	72·7	66·7	+	2·6	..	Low risk
Orenstein et al., 2016 [46]	USA	Cohort	Enema	34	..	16 (47%)	27 (79%)	8·0	66·8	67·6	–	NA	Moderate risk	..
Waye et al., 2016 [47]	Canada	Cohort	Lower GI endoscopy	75	..	70 (93%)	..	13·0	65·6	52·0	+	4·0	Moderate risk	..
Anand et al., 2017 [48]	USA	Cohort	Lower GI endoscopy	28	28 (100%)	28 (100%)	..	299·3	62·6	78·5	+	NA	Moderate risk	..
Hefazi et al., 2017 [49]	USA	Cohort	Lower GI endoscopy	22	..	19 (86%)	..	8·6	66·0	57·0	+	4·0	Moderate risk	..
Hota et al., 2017 [50]	**Canada**	**RCT**	**Enema**	**16**	..	**7 (44%)**	..	**17·0**	**75·7**	**68·8**	**+**	**4·4**	..	**Low risk**
Jiang et al., 2017 [51]	**USA**	**RCT**	**Lower GI endoscopy**	**72**	..	**63 (88%)**	..	**8·0**	**67·0**	**72·2**	**+**	**NA**	..	**Low risk**
Kao et al., 2017 [52]	**Canada**	**RCT**	**Overall**	**116**	..	**101 (87%)**	**105 (91%)**	**12·0**	**58·0**	**68·1**	**+**	**4·0**	..	**Low risk**
	Canada	**RCT**	**Lower GI endoscopy**	**59**	..	**50 (85%)**	**52 (88%)**	**12·0**	**58·7**	**75·4**	**+**	**4·0**	..	**Low risk**
	Canada	**RCT**	**Capsule**	**57**	..	**51 (89%)**	**53 (93%)**	**12·0**	**57·4**	**61·0**	**+**	**4·0**	..	**Low risk**
Patron et al., 2017 [53]	USA	Cohort	Lower endoscopy	109	..	99 (91%)	..	12·0	63·5	64·2	+	4·0	Moderate risk	..
van Beurden et al., 2017 [54][e]	Netherlands	Cohort	Upper administration	43	..	32 (74%)	35 (81%)	8·0	73·0	59·0	+	4·0	Low risk	..
Staley et al., 2017 [55]	USA	Cohort	Capsule	39	..	35 (90%)	..	8·0	63·8	87·2	+	4·5	Low risk	..
Jiang et al., 2018 [56]	**USA**	**RCT**	**Overall**	**65**	..	**56 (86%)**	..	**13·0**	**65·0**	**70·8**	**+**	**4·0**	..	**High risk**
	USA	**RCT**	**Enema**	**34**	..	**30 (88%)**	..	**13·0**	**63·0**	**74·0**	**+**	**4·0**	..	**High risk**
	USA	**RCT**	**Capsule**	**31**	..	**26 (84%)**	..	**13·0**	**67·0**	**68·0**	**+**	**4·0**	..	**High risk**
Allegretti et al., 2018 [57]	USA	Cohort	Lower GI endoscopy	167	160 (96%)	139 (83%)	..	8·0	NA	NA	+	NA	High risk	..
Duarte-Chavez et al., 2018 [58]	USA	Cohort	Lower GI endoscopy	35	30 (86%)	28 (80%)	..	13·0	58·6	69·0	+	2·7	Moderate risk	..
Mihaela et al., 2018 [59]	Romania	Cohort	Lower GI endoscopy	30	28 (93%)	28 (93%)	..	52·0	57·8	46·7	+	2·0	Low risk	..
Niccum et al., 2018 [60]	USA	Cohort	Lower GI endoscopy	80	..	72 (90%)	..	13·0	66·4	73·8	+	3·8	Moderate risk	..
Peri et al., 2019 [61]	Germany	Cohort	Overall	196	..	153 (78%)	173 (88%)	12·9	75·0	61·3	+	3·0	High risk	..
	Germany	Cohort	Upper administration	93	..	68 (73%)	..	12·9	NA	NA	+	NA	High risk	..
	Germany	Cohort	Lower GI endoscopy	73	..	63 (86%)	..	12·9	NA	NA	+	NA	High risk	..
	Germany	Cohort	Capsule	33	..	25 (76%)	..	12·9	NA	NA	+	NA	High risk	..
	Germany	Cohort	Mixed	2	..	2 (100%)	..	12·9	NA	NA	+	NA	High risk	..
Shin et al., 2019 [62]	USA	Cohort	Lower GI endoscopy	44	44 (100%)	42 (95%)	..	12·0	67·0	79·0	+	3·0	Moderate risk	..
Lynch et al., 2019 [63]	USA	Cohort	Lower GI endoscopy	92	..	79 (86%)	..	12·0	64·8	66·3	+	NA	Moderate risk	..
Kim et al., 2019 [64]	USA	Cohort	Overall	35	..	30 (86%)	..	8·0	NA	85·7	–	NA	Moderate risk	..

(*continued on next page*)

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Table 1 (*Continued*)

Author	Country	Study type	FMT category	Patient No.	FMT Effect			Follow-up (weeks)[a]	Age (mean)	Female (%)	CDAD	No. CDI (mean)	Quality assessment	
					Week 1 Single	Week 8 Single	Week 8 Repeat						NOS	RoB2
Allegretti et al., 2019 [65]	USA	Cohort	Overall	150	..	131 (87%)	..	8·0	61·5	68·7	+	3·3	Moderate risk	..
	USA	Cohort	Lower GI endoscopy	103	..	91 (88%)	..	8·0	NA	NA	+	3·3	Moderate risk	..
	USA	Cohort	Capsule	47	..	40 (85%)	..	8·0	NA	NA	+	3·3	Moderate risk	..
Hvas et al., 2019 [3]	**Denmark**	**RCT**	**Overall**	**24**	**24 (100%)**	**22 (92%)**	**23 (96%)**	**8·0**	**68·0**	**69·0**	**+**	**4·0**	..	**Low risk**
	Denmark	**RCT**	**Lower GI endoscopy**	**19**	**19 (100%)**	**17 (89%)**	**18 (95%)**	**8·0**	**NA**	**NA**	**+**	**4·0**	..	**Low risk**
	Denmark	**RCT**	**Upper administration**	**5**	**5 (100%)**	**5 (100%)**	**5 (100%)**	**8·0**	**NA**	**NA**	**+**	**4·0**	..	**Low risk**
Park et al., 2019 [66]	Canada	Cohort	Lower GI endoscopy	19	..	12 (63%)	19 (100%)	8·0	67·3	31·6	–	NA	Moderate risk	..
Allegretti et al., 2019 [67]	USA	Cohort	Capsule	51	..	..	40 (78%)	8·0	63·0	68·0	+	3·7	Moderate risk	..
Kim et al., 2019 [68]	USA	Cohort	Lower GI endoscopy	105	..	..	91 (87%)	8·0	66·0	62·9	+	3·3	Low risk	..
Antibiotics														
van Nood et al., 2013 [1]	Netherlands	RCT	Vancomycin, standard	26	..	7 (27%)	7 (27%)	10·0	67·5	38·5	+	2·5	..	Low risk
Cammarota et al., 2015 [2]	Italy	RCT	Vancomycin, pulsed tapered	19	..	5 (26%)	5 (26%)	10·0	75·0	58·0	+	3·0	..	Low risk
Hota et al., 2017 [50]	Canada	RCT	Vancomycin, tapered	14	..	9 (64%)	..	17·0	69·6	66·7	+	4·4	..	Low risk
Hvas et al., 2019 [3]	Denmark	RCT	Vancomycin, standard	16	11 (69%)	5 (31%)	5 (31%)	8·0	72·0	69·0	+	3·0	..	Low risk
Hvas et al., 2019 [3]	Denmark	RCT	Fidaxomicin, standard	24	19 (79%)	13 (54%)	13 (54%)	8·0	64·0	54·0	+	4·0	..	Low risk

Abbreviations: CDAD: Clostridioides associated diarrhoea, CDI: Clostridioides difficile infection, GI: Gastrointestinal, RCT: Randomised clinical trial, NA: Not available, NOS: Newcastle-Ottawa quality assessment Scale, ROB2: Cochrane Risk of Bias 2

[a] Average follow-up time to which the outcome is benchmarked.

[b] Describes FMT for 20 patients, but for 4 of the patients, demographic data is not reported. 3/4 achieves treatment effect, but is excluded due to lack of data. Data is based on the 16 patients.

[c] 11 of 49 patients overlap with Mattila 2012, data is based on new patient data from the 38 of 49 patients. Data is available from the publication.

[d] The extracted data is based on only the donor faeces arm of the RCT.

[e] Reports data based on 39 patients, but have performed FMT on 43 patients. According to ITT these are included here.

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[m5G;November 26, 2020;12:54]

Table 2
Summary of findings table for faecal microbiota transplantation (FMT) according to delivery method and treatment regimen.

Effect of FMT for recurrent *Clostridioides difficile* infection grouped by application method and no. of administrations

Patient or population: Patients with recurrent *Clostridioides difficile* infection Setting: Hospital, outpatient care, home Intervention: Faecal microbiota transplantation (FMT) Comparison: Delivery method and treatment regimen

Comparison: Delivery method (Superiority of one delivery method)

Outcomes	Anticipated absolute effect (95% CI)		Absolute difference (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	FMT	FMT, Lower GI endoscopy				
CDAD week 8, Single FMT:						The quality of the evidence measures the level certainty that one method (Lower GI endoscopy) is superior to other delivery methods.
Overall	84% (80–87%)	–	Not estimable	2743 (41)	⊕⊕⊕○ MODERATE[b,c,d]	
Lower GI endoscopy	90% (87–92%)	–	Not estimable	1654 (28)		
Upper administration	75% (70–80%)	90%	15 less per 100 (8 to 22 fewer)	277 (6)[a]		
Capsule	83% (78–87%)	90%	7 less per 100 (2 to 12 fewer)	426 (8)[a]		
Enema	57% (42–70%)	90%	33 less per 100 (15 to 52 fewer)	397 (5)[a]		
(Observational studies)						
CDAD week 8, Repeat FMT:					⊕⊕⊕□□	The low quality of evidence suggests delivery method following repeat FMT to be largely equal.
Overall	92% (89–94%)	–	Not estimable	1513 (22)	LOW[b,c]	
Lower GI endoscopy	95% (92–98%)	–	Not estimable	725 (12)		
Upper administration	86% (78–92%)	95%	9 less per 100 (1 to 21 fewer)	114 (5)[a]		
Capsule	89% (84–94%)	95%	6 less per 100 (0 to 15 fewer)	327 (5)[a]		
Enema	88% (83–93%)	95%	7 less per 100 (2 to 14 fewer)	347 (3)[a]		
(Observational studies)						

Comparison: Single versus repeat administrations

Outcomes	Anticipated effect (95% CI)		Absolute difference (95% CI)[e]	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	FMT, Single	FMT, Repeat				
CDAD week 8, repeat administrations:					⊕⊕⊕⊕ HIGH [c,d]	The quality of the evidence measures the level of certainty for the superiority of repeat FMT.
Overall	79% (71–86%)	93% (90–95%)	14 more per 100 (13 to 16 more)	1357 (23)		
Lower GI endoscopy	88% (83–92%)	96% (94–98%)	6 more per 100 (7 to 11 more)	620 (11)		
Upper administration	76% (67–84%)	86% (78–92%)	10 more per 100 (6 to 17 more)	114 (5)		
Capsule	81% (72–89%)	92% (88–95%)	11 more per 100 (8 to 15 more)	276 (4)		
Enema	50% (45–55%)	88% (83–93%)	38 more per 100 (33 to 43 more)	347 (3)		
(Observational studies)						

Abbreviations: CDAD: Clostridioides difficile-associated diarrhoea CI: Confidence intervals, GI: Gastrointestinal
For observational studies the quality of evidence is rated as low per standard.
[a] Does not include the number of participants in the lower endoscopy group.
[b] Rated 1 down for risk of bias due to the general lack of comparator a group in each study.
[c] Rated 1 up for a large magnitude of effect.
[d] Rated 1 up for a dose-response gradient based on a higher effect following repeat administrations.
[e] The absolute difference is based on the difference in the weighted average and a generalised *Z*-statistic for the anticipated difference.

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Table 3
Summary of findings table for faecal microbiota transplantation (FMT) compared with vancomycin.

FMT compared to vancomycin for patients with recurrent *Clostridioides difficile* infection						
Patient or population: Patients with recurrent *Clostridioides difficile* infection Setting: Hospital, outpatient care, homeIntervention: Faecal microbiota transplantation (FMT) Comparison: Vancomycin (standard and tapered regimens)						
Outcomes	Anticipated absolute effect (95% CI)[a]		Difference (95% CI)	Relative effect (95% CI)	No. of Participants (Studies)	Quality of the evidence (GRADE)
	Vancomycin	FMT				
CDAD week 8, Single FMT: *(Randomised clinical trials)*	35% (25–46%)	72% (61–82%)	35 more per 100 (3 to 67)	RR 1.95 (0.93 to 4.0)	151 (4)	⊕⊕⊕○ MODERATE[c]
CDAD week 8, Repeat FMT: *(Randomised clinical trials)*	27% (18–40%)[b]	93% (84–97%)	65 more per 100 (52 to 78)	RR 3.33 (2.2 to 5.0)	117 (3)	⊕⊕⊕⊕ HIGH[d,e]

Abbreviations: CDAD: Clostridioides difficile-associated diarrhoea CI: Confidence intervals, RR: Relative Risk.
For randomised clinical trials the quality of evidence is rated as high per standard.
[a] Anticipated absolute effect is calculated as the crude proportions with corresponding confidence intervals.
[b] Lower effect in the repeat FMT vancomycin comparator may be due to the exclusion of the group receiving a tapered vancomycin regime in Hota 2017 [50].
[c] Rated 1 down for imprecision (relative effect CI contains 0) and NOT rated down for inconsistency that may be explained by the use of single FMT enema.
[d] Rated 1 up for a large magnitude of effect.
[e] Rated 1 up for a dose-response gradient based on a higher effect following repeat administrations.

Table 4
Estimated effect of fecal microbiota transplantation (FMT) in future studies stratified according to delivery method.

Intervention	Patients no.	Estimated effect range[a]
Single FMT, Overall	2754	54–100%
Single FMT, Lower GI endoscopy	1654	81–96%
Single FMT, Upper administration	277	70–80%
Single FMT, Capsule	426	75–90%
Single FMT, Enema	397	26–84%
Repeat FMT, Overall	1513	81–99%
Repeat FMT, Lower GI endoscopy	725	88–100%
Repeat FMT, Upper administration	114	78–92%
Repeat FMT, Capsule	327	80–96%
Repeat FMT, Enema	347	80–95%

[a] Equivalent to the prediction interval.

significantly increased the overall treatment effect week 8 regardless of delivery method (Fig. 2). The highest absolute increase in treatment effect was observed for enema FMT that increased from 50% (45–55%, I^2=0%) following single FMT to 88% (83–93%, I^2 = 37%) for repeat FMT (P<0·001) (Table 2).

FMT was compared with antibiotics in four RCTs [1-3,50] with 151 patients (Tables 1 and 3). Repeat FMT was performed in three studies with 117 patients; and for repeat FMT compared with standard or tapered vancomycin, repeat FMT had a 65% (52–78%, I^2=0%, Fig. 3) gain in absolute treatment effect equivalent to an NNT of 1·5 (1·3–1·9, P<0·001). High quality of evidence supported repeat FMT. For single FMT versus standard or tapered vancomycin, single FMT had a 35% (3–67%, I^2=81%, Fig. 3) gain in absolute treatment effect equivalent to an NNT of 2·9 (1·5–37·1, P=0·03). Moderate quality of evidence supported single FMT. One study with single enema FMT [50] accounted for all study heterogeneity.

One study [3] compared FMT with fidaxomicin and found a 92% week 8 effect rate among 24 patients treated with FMT compared with 42% in 24 patients treated with fidaxomicin.

Publication bias was examined for repeat and single FMT overall and according to delivery method. For single FMT, the visual inspection of funnel plots (Supplementary Fig. 4) indicated negative publication bias that approached statistical significance (Eggert P=0·057). Stratifying according to the delivery method (Supplementary Fig. 5) abrogated this asymmetry, indicating that the asymmetry was introduced by a few, low-effect enema studies relative to the many high-

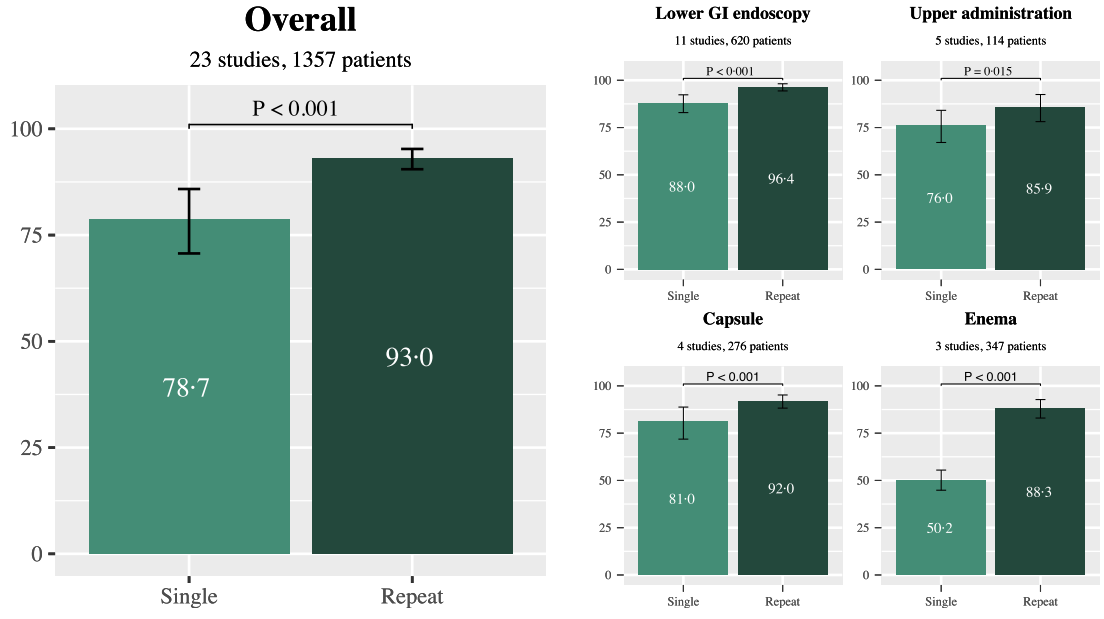

Fig. 2. The cumulative effect of faecal microbiota transplantation (FMT) week 8 on recurrent *Clostridioides difficile* infection (CDI) following single and repeated administrations grouped by delivery method. The vertical bars indicate the 95% confidence limits. Abbreviations: GI: Gastrointestinal.

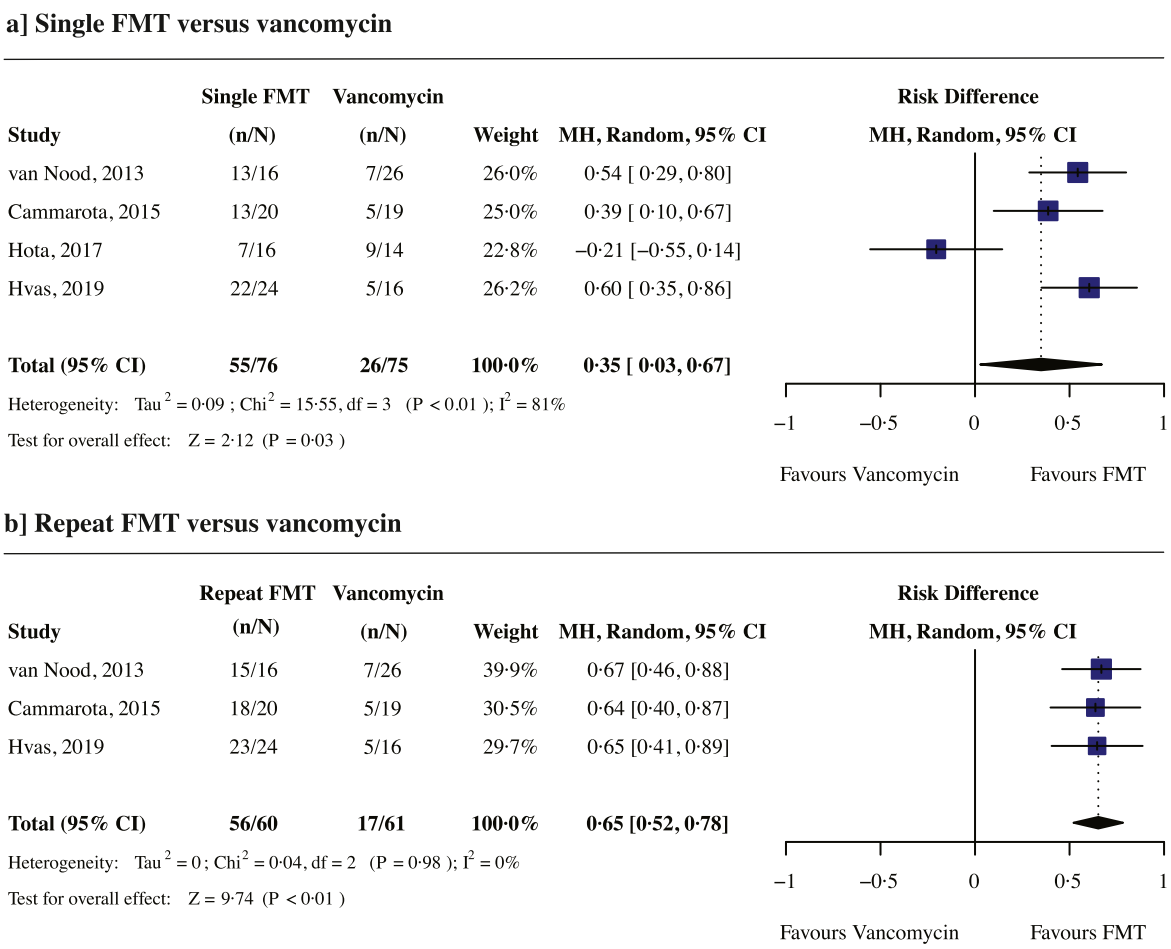

Fig. 3. Forest plots of the week 8 effects for A) single and B) repeat faecal microbiota transplantation (FMT) versus vancomycin (standard and tapered regimens) on recurrent CDI in randomised clinical trials.

effect, lower GI endoscopy studies and not publication bias. For repeated FMT (Supplementary Fig. 4), we found no indications of publication bias (Eggert *P*=0·773).

We explored the substantial among study heterogeneity in a meta-regression including studies reporting effect rates stratified by delivery method. For repeat FMT, adjusting for the delivery method reduced the study heterogeneity to minimal (I^2=32%). For single FMT, adjusting for the delivery method and long follow-up times reduced the study heterogeneity to minimal to moderate (I^2=40%). Neither of the other extracted study parameters, e.g. study type, donor type, processing methods, nor patient characteristics, including refractory CDI, listed in Supplementary Tables 2 and 3 influenced study heterogeneity.

We did a sensitivity analysis to test the robustness of the findings and the methodological assumptions. In a series of separate subgroup analyses, neither high risk of bias, follow-up times above 8 weeks, nor faecal doses above 50 g significantly changed the estimated effect rates for repeat or single FMT.

4. Discussion

This updated systematic review and meta-analysis demonstrates a high quality of evidence for the repeated use of FMT in recurrent CDI and supports that FMT is superior to vancomycin with a number needed to treat of 1.5 for repeated administrations. The clinical effect 8 weeks after FMT preceded by antibiotics was 91% following repeat FMT and 84% following a single FMT. Delivery by lower GI endoscopy was superior to all other delivery methods, and the most definite difference appeared in comparison with delivery by enema.

Previous systematic reviews [11–16] demonstrated similar high effect rates for FMT but did not include both observational and controlled studies. By including both, this review is the first to establish the quality of evidence for several important clinical determinants needed to consolidate FMT as an evidence-based treatment. By updating to the current literature, the sample size almost doubled, powering this review to evaluate aspects with hitherto less clear evidence.

The clinical effect of FMT varied according to the delivery method and the number of administrations. In contrast to previous reviews [14–16], the current review demonstrates that lower GI endoscopy is superior to all other delivery modalities and not only enema or upper administration. This underpins lower GI endoscopy as the gold standard despite the absolute gain of effect relative to the other delivery methods following repeat FMT is minimal. When choosing delivery method, the ease of use is an essential factor, and both capsule and enema FMT have practical benefits that make FMT easily applicable. Because enema application requires repeat administrations for a comparable effect, capsule FMT may eventually prove the better first choice. In this context, delivery by lower GI endoscopy may be reserved for patients who fail their initial FMT.

The increase in cumulative FMT effect following repeated administrations highlights the importance of distinguishing single from repeat FMT, particularly when evaluating treatment effect. High quality of evidence applies to repeat FMT only, and studies that solely

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used single FMT are expected to have a lower effect rate. This effect rate may further decline with the use of certain delivery methods, e. g. enema. Thus, Hota et al. [50] demonstrated that a single administration of enema FMT was inferior to tapered vancomycin. In future studies, both treatment regimen and application methods should be optimised to achieve optimal effect.

The study heterogeneity was substantial and may be due to procedural study differences. In our analysis of study heterogeneity, the delivery method was the decisive determinant, but we could not reproduce the previous finding [15,17] that the use of 50 g crude faeces or more was associated with increased treatment success. Nor did we find that other procedural or methodological factors such as donor type, fresh, frozen, or lyophilised FMT accounted for study differences. These factors may still influence the treatment effect, and the considerable procedural difference between the studies calls for studies that evaluate the independent effects of these factors.

The definition of treatment effect differed between the studies. While most studies reported clinical outcomes according to the CDAD definition and had a similar long-term follow-up, the short-term evaluation of the FMT effect varied. In some studies [45], the treatment effect was evaluated on day 4 while other [44,58] waited until week 1 after FMT despite ongoing CDAD symptoms. The differences illustrate the difficulties in keeping a balance between over-treatment and preventing disease progression. The close-to-significant effect of FMT at week 1 compared with week 8 indicates that most patients have an initial treatment response and that most CDI recurrences happen after week 1. Awaiting week 1 for the treatment effect to settle may thus be suitable if the patients are monitored and the CDI course is not progressive. To harmonise, future clinical guidelines should make recommendations for the short-term monitoring and evaluation of patients following FMT.

In all studies, antibiotics treatment of varying duration preceded FMT, and FMT should be regarded interchangeably as *FMT preceded by antibiotics*. The different durations of antibiotics pre-treatment challenges whether FMT is used prophylactically to prevent further recurrences or actively to treat an acute CDI. Some patients receive long-term tapered antibiotics before FMT and have no symptoms at the time of FMT. In these instances, FMT may be regarded as prophylactic. The distinction may be clinically relevant, but our ability to evaluate if FMT was applied prophylactically or for the active disease was limited because no studies made clear distinctions. In the four RCTs [1−3,50] with an active antibiotic comparator, FMT was used as an active treatment for the acute CDI and achieved similar effect rates to the observational studies that used FMT following prolonged vancomycin courses.

Despite the vast evidence for the effect of FMT on clinical CDAD resolution, the evidence levels for FMT to reduce mortality or colectomy rate could not be determined because FMT was offered as a rescue treatment in most studies. A few observational studies [69,70] indicate that FMT reduces the three-month mortality rate, but providing conclusive evidence may prove difficult because it may be considered unethical to withhold patients FMT as a rescue treatment [69]. Acknowledging this limitation may be necessary when evaluating FMT in future clinical guidelines.

Important limitations apply to this systematic review. We did not include patients with refractory, index CDI and therefore excluded high-quality studies reporting combined outcomes; accordingly, the presented data are only applicable to recurrent CDI. Data to describe the incremental effect of each repeated administration could not be extracted. Still, the high effect of repeat FMT suggests that if FMT is continued until resolution of symptoms occurs, almost all patients with recurrent CDI eventually achieve treatment effect. Our extrapolation of effect rates reported beyond week 8 may have underestimated the true effect, and it limits the ability to evaluate the effect of FMT strictly at week 8 according to recommendations for follow-up [10]. Only few of the included studies performed FMT on patients with the hypervirulent ribotype 027. Instead to control for the clinical impact, we used refractory CDI infection as measure for severity of the infection and found no influence on the clinical effect, but the clinical effect rates reported in this systematic review may be anticipated to differ for patients with the hypervirulent ribotypes.

Future research may determine how FMT performs without antibiotic pre-treatment and how it measures in patients with their initial CDI. Investigations of treatment kinetics, time to effect, required dosing, and mechanisms of action may guide the clinical use of FMT. Application of encapsulated donor faeces holds practical benefits but requires more processing steps that need evaluation in clinical studies.

In conclusion, high-quality evidence documents FMT as an effective treatment for recurrent CDI. The effect varies with the delivery method and the number of administrations, with repeat FMT by lower GI endoscopy being most effective. The low NNT for FMT versus antibiotics suggests that advancing the treatment recommendations for FMT to all instances of recurrent CDI may effectively manage the infection and provide the most effective patient care.

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Declaration of Interests

BHM receives consultancy fees from Finch Therapeutics Group. All other authors declare no conflicts of interest.

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Data sharing

The study protocol available from http://www.crd.york.ac.uk/PROSPERO (CRD42020158112), and the full data set and statistical code is available from Simon Mark Dahl Baunwall.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100642.

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