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Systematic review with meta-analysis: encapsulated faecal microbiota transplantation – evidence for clinical efficacy

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Abstract

Background: Faecal microbiota transplantation (FMT) is an effective treatment of recurrent *Clostridioides difficile* infection (rCDI) and is being applied experimentally in other diseases. Encapsulated administration may be equivalent in efficacy to delivery through other routes.

Methods: A systematic review was undertaken of studies using encapsulated FMT up to 26 October 2020. Data on indication, clinical outcomes, safety, treatment protocol and capsule preparation were collected and reported. Pooled rates of clinical efficacy in rCDI were calculated using random-effects meta-analysis. The impact of single variables on clinical efficacy was evaluated using univariate meta-regression.

Results: A total of 35 studies reporting the treatment of 960 patients with encapsulated FMT for eight different indications met the inclusion criteria. Most studies ($n = 18$, 51%) and patients ($n = 755$, 79%) were from studies on rCDI. Cure rates after single and multiple courses of treatments with encapsulated FMT in rCDI were 85% (95% CI: 82%-88%) and 93% (95% CI: 88%-96%) respectively. The treatment outcome was not significantly affected by dose, number of delivered capsules, anaerobic/aerobic processing, single/multi-donor treatment, lyophilisation, or any other single factor in the production or delivery of encapsulated FMT. Promising but non-comparable results from the treatment of ulcerative colitis and multidrug-resistant organisms were reported.

Conclusions: Encapsulated FMT is an effective and safe treatment of rCDI, with cure rates comparable to FMT delivered through other routes. The treatment is effective despite variations in donor screening, preparation and treatment protocol. For other indications, the role of FMT capsules is still not sufficiently examined, although some studies show promising results.

Plain Language Summary

Transfer of faecal material through capsules in the treatment of various diseases. Evidence for clinical efficacy

The bacteria and other microorganisms of the gut is different in patient with various diseases in comparison with healthy subjects.
Therefore, ways to change the microorganisms of the gut in a beneficial direction has been the subject of various research projects within recent years.

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Faecal microbiota transplantation often referred as FMT is a method of transferring microorganisms from healthy donors to patients with various diseases and is seen as one way to change the microbial community of the gut in a beneficial direction.
Faecal microbiota transplantation can be performed in different ways such as through endoscopy, enemas or capsules. The transfer through capsules is preferred by the patients and has advantages since it can be administered long-term and can be delivered to the patients in their home. In this paper, we evaluated all accessible research reporting treatment with encapsulated faecal microbiota transplantation in the treatment of various diseases. We report the following major findings:

-Treatment with capsules is safe when guidelines for screening donors and testing faecal material is followed.
-The treatment is highly effective in the treatment of recurrent *C. difficile* infection, a disease with high mortality often caused by repeated antibiotic treatments. The treatment was effective in 596 of 723 patients following one course of capsule treatment.
-Faecal microbiota transplantation delivered through capsules is as effective as treatment delivered through other routes in the treatment of *C. difficile* infection.
-The treatment is effective in the treatment of *C. difficile* infection across studies and countries, despite great differences in the ways the capsules were prepared and delivered.
-Increasing the amount of faecal material used in the production did not affect the efficacy of the treatment.
-There are promising results in the treatment of other diseases such as liver disease, inflammatory bowel disease and the treatment of multi-drug resistant bacteria.

Keywords: capsules, *Clostridioides difficile*, encapsulated, faecal microbiota transplantation, lyophilisation, meta-analysis, microbiome, systematic review, ulcerative colitis

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Introduction

Faecal microbiota transplantation (FMT) is the transfer of donor faeces from one individual to another with the aim of modifying the recipient's microbiota.[1,2] It is the most effective treatment for recurrent *Clostridioides* (formerly *Clostridium*) *difficile* infection (rCDI) and refractory CDI, with cure rates up to and above 90% after multiple treatments.[3,4] The clinical effect of antibiotic treatment followed by FMT exceeds the effect of antibiotic treatment alone,[5–9] and FMT is now a recommended treatment for rCDI.[10,11] FMT may be administered by either the upper or lower gastrointestinal tract through endoscopy, tube insertion, rectal enemas, or oral capsules. Administration through capsules has demonstrated high efficacy comparable to delivery through colonoscopy,[12] which in previous meta-analyses has been reported as superior to the other routes of administration.[8,13]

FMT has been administered to patients with gastrointestinal diseases other than rCDI, such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS), where an altered gut microbiota may be involved in disease pathogenesis.[14,15] Furthermore, FMT treatment has also been proposed in recent years for an increasing number of non-gastrointestinal diseases, such as psychiatric disorders, altered glucose metabolism and antibiotic-resistant infections.[16–18]

Encapsulated FMT makes the treatment more accessible than delivery through other routes, by resolving many of the logistical challenges related to FMT. Patients prefer capsules, and capsule-based FMT enables patients who cannot tolerate endoscopic procedures to receive the treatment, even in their own homes.[19–21] For conditions where multiple administrations may be needed,

capsules allow for continuous administration for longer periods on a daily basis.

Treatment by encapsulated FMT has not yet been standardised. This concerns both the preparation, storage and delivered dose of the treatment.[22] A recently published meta-analysis of encapsulated FMT in the treatment of rCDI reported no difference in clinical cure rates whether frozen or lyophilized faecal material was used.[23] Whether other aspects in the preparation and treatment regimen of rCDI, such as delivered dose, bowel cleansing prior to treatment or aerobic/anaerobic processing of faecal material is of importance in relation to both clinical efficacy and safety remains unknown.

The aim of this systematic review was to evaluate the current literature of treatment with FMT capsules and provide an overview of indications, treatment regimens and the outcomes of capsule-based FMT. A further objective was to assess whether procedure-related aspects, such as preparation, dose and storage of capsules, affected the clinical outcome.

Materials and methods

Search strategy

This systematic review and meta-analysis was performed in accordance with the PRISMA 2009 guidelines (Supplementary Table 1).[24] A literature search was performed using Medline (from 1948), EMBASE (from 1947) and the Cochrane Library (for all years) up to 26 October 2020. The search strategy combined the MESH terms and keywords: ("faecal microbiota transplantation" (MESH) OR "fecal" OR "faecal" OR "bacterial" OR "stool" OR "feces" OR "intestinal" OR "microflora" AND "microbiota transfer" OR "transplantation" OR "transplant" OR "infusion" AND "capsules" (MESH) OR "capsul*" OR "encapsul*" OR "microcapsule" OR "gelatin" OR "lyophile*"). Bibliographies of review articles and meta-analyses were searched to identify additional studies.[9,25–27] The detailed search strategy is outlined in Supplementary Table 2.

Study selection

The eligibility criteria for study inclusion were defined prior to the search through registration of the research protocol at Prospero International Prospective Registry of Systematic Reviews (CRD42019134572). The inclusion criteria were human interventional studies using donor-derived FMT capsules of all study types, including randomised controlled trials (RCTs), non-randomised controlled studies, cohort studies and case studies (case series and case reports) to treat any acute or chronic disease where the authors hypothesised that the condition may be amenable to treatment with FMT capsules. In studies reporting data on the same patient population, the studies with the largest patient population were included, but in the event of missing data, the other studies were reviewed. Studies were only included if the participants were followed for at least 4 weeks after the start of treatment. Studies using FMT capsules as a standalone treatment were primarily evaluated, followed by studies using encapsulated FMT administered as a supplement to other methods of FMT delivery. Studies with adult participants (aged at least 18 years) were included, and data from participants aged below 18 years were excluded. The search was restricted to studies published in English.

All titles and abstracts from the search were screened for potential eligibility by two investigators (FC and SMDB) independently and in strict accordance with the inclusion and exclusion criteria. In the event of any dispute, the key decision was made by a third investigator (CLH).

Data extraction and outcome assessment

Data extraction was performed independently by two investigators (FC and SMDB). The following clinical information was extracted from each study: study first author, year of publication, location of study, study type, age and characteristics of study population, condition under consideration and severity, details of intervention and methodology (such as the amount of stool used in the production of capsules, dosage, frequency, duration and preparation of FMT material), primary and secondary outcome measures and results, number of patients responding to first and second/multiple treatments, duration of follow-up, registered adverse events and donor characteristics.

The main outcome in studies of rCDI was the number of patients with clinical resolution (cure), defined as resolution of diarrhoea, or diarrhoea with a negative stool test for *C. difficile*, at least 8

weeks after treatment.[28] This corresponds with the guidelines of the Infectious Disease Society of America (IDSA) where repeat testing of asymptomatic patients is not recommended.[11]

For multiple FMTs, treatment effect was defined 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.

Storage temperature of the capsules was defined as the lowest temperature reported by the authors. Anaerobic procedures were defined as any study reporting extended procedures to avoid oxygen in the capsule production. Data were extracted as an intention-to-treat analysis, with dropouts assumed to be treatment failures. In RCTs, only data from the FMT capsule arm were included in the quantitative meta-analysis. In the event of missing data or a need for clarification, the authors of the included studies were contacted to obtain further information.

Risk of bias

The Cochrane risk of bias tool was used to assess for bias in RCTs (Supplementary Table 3).[29] Risk of bias of the cohort and case studies was assessed using the US National Heart, Lung and Blood Institute quality assessment tools for cohort studies and case series (including case reports) with 8 weeks selected as the cut-off for appropriate follow-up (Supplementary Table 4 and 5).[30]

Data synthesis and statistical analysis

Meta-analysis was performed to summarise the clinical effect of treatment for the diseases where the treated patient groups, disease entity and outcome measures were comparable.

Pooled estimates and 95% confidence intervals of response rates of clinical resolution in studies of rCDI were estimated with a random effects model using the Freeman Tukey double arcsine transformation.[31] All study types were included in the meta-analysis. Sensitivity analyses were performed to test whether excluding studies with less than ten treated patients and excluding each single study changed the estimates. Heterogeneity was assessed using the I^2 statistic and with upper limits of 25%, 50% and 75% corresponding to low, moderate or high degrees of heterogeneity.[32]

Univariate meta-regression analyses with a mixed-effect-model using the Der-Simonian Laird estimator,[33] were performed testing the effect of the following variables on the primary cure rate following a single FMT treatment: study type, single/multi-donor capsules, lyophilisation, amount of glycerol used, bowel cleansing, storage temperature of capsules, days of treatment, number of capsules, delivered stool amount, and aerobic/anaerobic preparation of FMT material. Potential publication bias was assessed through a funnel plot and Eggers regression test.[34] All calculations were performed using R version 3.5.1 including the "metafor" and "meta" package.[35]

Results

The literature search identified 2,552 publications, of which 35 fulfilled the inclusion criteria (Figure 1). Ten were randomised controlled trials, while the remaining were 13 cohort studies, eight case series and four case reports (Supplementary Table 6). Studies investigating the effects of FMT capsules in rCDI accounted for 51% of the studies ($n = 18$) and 79% of the patients treated ($n = 755$) (Table 1). The mean duration of treatment was short in rCDI (1.7 days), but longer in chronic diseases such as ulcerative colitis (UC) (32.5 days) and IBS (6.2 days).

Patient characteristics in studies of encapsulated FMT treatment for recurrent C. difficile

A total of 755 patients from 18 studies were treated with encapsulated FMT for rCDI (Table 2). The mean number of recurrences prior to treatment was 3.7 (range: 1–10). The mean age of treated patients was 63.7 years (range: 18–94 years), and the majority (66%) of treated patients were female (Table 3). Treatment of patients on continuously immunosuppressive medication or with co-morbidities such as active cancer disease, organ transplant, cirrhosis was reported in several studies.[39,43,47,48,51,53]

Clinical outcomes in studies of encapsulated FMT treatment for recurrent C. difficile

The results from the RCTs comparing clinical efficacy of encapsulated FMT versus FMT

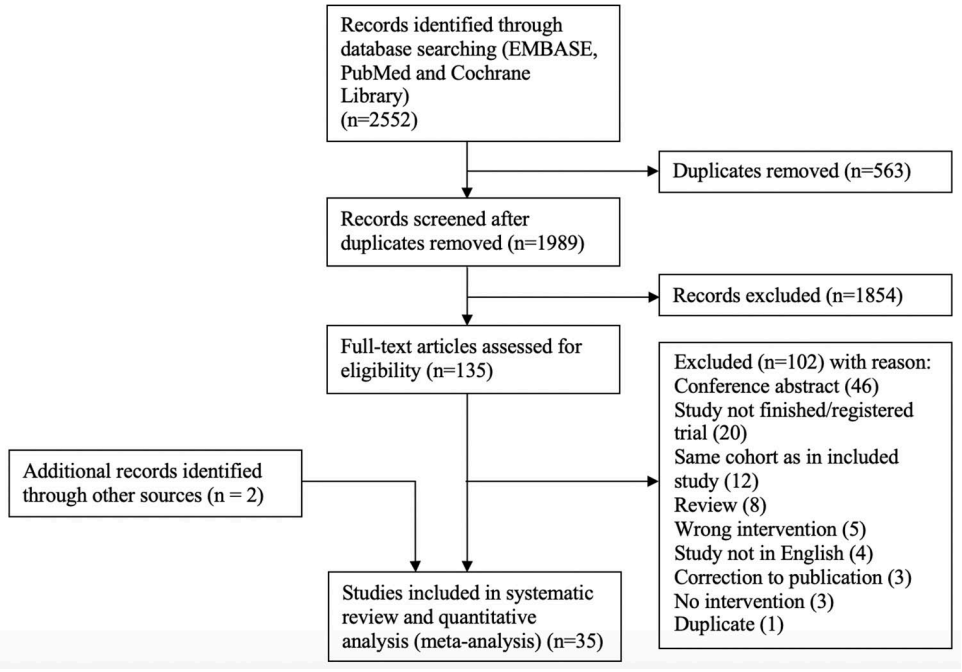

Figure 1. PRISMA flow diagram of assessment of studies identified in the systematic review and meta-analysis of capsule-based faecal microbiota transplantation (FMT).
n, number.

Table 1. Patients treated and studies performed with encapsulated FMT including all indications.

Indication	Patients treated, *n* (%)	Studies, *n* (%)	Mean duration of treatment[a] (range)
Total	960	35	
Recurrent *C. difficile*	755 (78.6%)	18 (51.4%)	1.7 (1–3)
Irritable bowel syndrome	74 (7.7%)	2 (5.7%)	6.2 (3–12)
Recurrent or multidrug-resistant infections	34 (3.5%)	4 (11.4%)	2 (2)
Ulcerative colitis	32 (3.3%)	3 (8.6%)	32.5 (6–60)
Post allogeneic haemopoietic cell transplantation/intestinal graft-versus-host disease	28 (2.9%)	4 (11.4%)	2.4 (2–7)
Obesity/insulin resistance	23 (2.4%)	2 (5.7%)	5.1 (3–7)
Hepatic encephalopathy	10 (1%)	1 (2.9%)	1
Chronic pouchitis	4 (0.4%)	1 (2.9%)	14

FMT, faecal microbiota transplantation; n, number.
[a]Days receiving FMT capsules.

Table 2. Summary of included studies treating recurrent *C. difficile* with FMT capsules.

Author and year	Study type	Mean number of recurrences (range)	Patients treated	Intervention: capsules x days	Follow-up, days	Clinical resolution[a], n, (%)
Allegretti and colleagues[36]	Cohort study	3.9	51	10-30 x 1–2	56	40 (78.4%)
Allegretti and colleagues[37]	Cohort study	3.4	47	15 x 2	56	40 (85.1%)
Chehri and colleagues[38]	Case series	4.6 (2–10)	9	25 x 3	180	8 (90 days) (88.9%)
Cheminet and colleagues[39]	Case series	3.1 (1–7)	15	15 x 2	128 (median)	13 (86.7%)
Garza-González and colleagues[40]	RCT	1.15 (1–3)	13	30 x 2	90 (mean)	12 (92.3%)
Greenberg and colleagues[41]	Retrospective Cohort study	3	37	15 x 2	183	34 (91.9%)
Hecker and colleagues[42]	Case series	4 (3–6)	20	20–40 capsules	204 (mean)	17 (85%)[b]
Hirsch and colleagues[43]	Retrospective Cohort study	4 (2–8)	19	6–22 capsules (mean of 10)	90	13 (90 days) (89.5%)
Jiang and colleagues[44]	RCT	3.9 (3–7)	31	27 capsules (total mean) in 1–2 days	90	26 (83.9%)
Jørgensen and colleagues[45]	Case series	1.5 (1–2)	2	30 x 1 (home treatment)	56	2 (100%)
Kao and colleagues[12]	RCT	4	57	40 x 1	84	51 (84 days) (89.5%)
Peri and colleagues[46]	Retrospective Cohort study	3.5 (2–5)	45	A total of 30–38 in 2 days	90	25/34 (90 days) (73.5 %)[c]
Pringle and colleagues[47]	Retrospective Cohort study	3.8[d]	272	15 x 2	56	225 (82.7%)
Reigadas and colleagues[48]	Case series	2.4 (1–6)	5	15 x 2	61	4 (80%)
Reigadas and colleagues[49]	Case series	2 (median) (1–3)	32	4–5 x 1	61	26 (81.3%)
Staley and colleagues[50]	Cohort study	$\geqslant 1$	95	2–27 capsules in 1–2 days	61	75 (78.9%)
Stollman and colleagues[51]	Case series	NR	4	15 x 2	77 (mean)	2 (50%)
Tian and colleagues[52]	Case report	NR	1	5 x 2	39	1 (39 days) (100%)

FMT, faecal microbiota transplantation; n, number; NR, not reported; RCT, randomised controlled trial.
[a]Clinical resolution 8 weeks after treatment unless otherwise described in parentheses.
[b]Time of clinical evaluation not reported.
[c]Only results from 33 patients were reported after 90 days, while 11 successfully treated patients were only followed for 30 days.
[d]Recurrences from 193 of the 272 treated patients from publication by Pringle and colleagues, reported in two publications by Youngster and colleagues.[53,54]

delivered through colonoscopy or enemas did not show any significant difference in cure rates.[12,44]

The overall, pooled response ratio of the sixteen studies reporting results at least eight weeks after delivery of a single treatment with FMT capsules was 85% (95% CI: 82–88), with low heterogeneity between studies ($I^2 = 0\%$) (Table 3 and Figure 2). When excluding studies with less than 10 treated patients the pooled response ratio of the twelve studies was 84% (95% CI 81;87).

The pooled response rate after repeated treatments (two or three) with FMT capsules increased to 93% (95% CI 88;96) (Supplementary Figure 1).

Table 3. Patient characteristics and cure rates in studies using FMT capsules to treat patients with recurrent *C. difficile*.

Total number of studies, n	18
Total patient population, n	755
Mean treatment duration, days (range) ($n = 724$)	1.7 (1–3)
Mean number of capsules[a], *n* (range) ($n = 724$)	27.2 (2–60)
Mean number of recurrences (range), ($n = 476$)	3.7 (1–10)
Male/female participants[b], n	211/414
Mean age of patients, years (range), ($n = 562$)	63.7 (18–94)
Primary cure rate (95% CI) after eight weeks (ITT) %, ($n = 723$, studies = 16)	85% (82;88)
Cure rate (95% CI) after multiple treatments (ITT) %, ($n = 743$, studies = 17)	93% (88;96)

CI, confidence interval; FMT, faecal microbiota transplantation; ITT, intention-to-treat; n, number.
[a]The number of capsules used in the first treatment.
[b]Not all studies reported sex of participants.

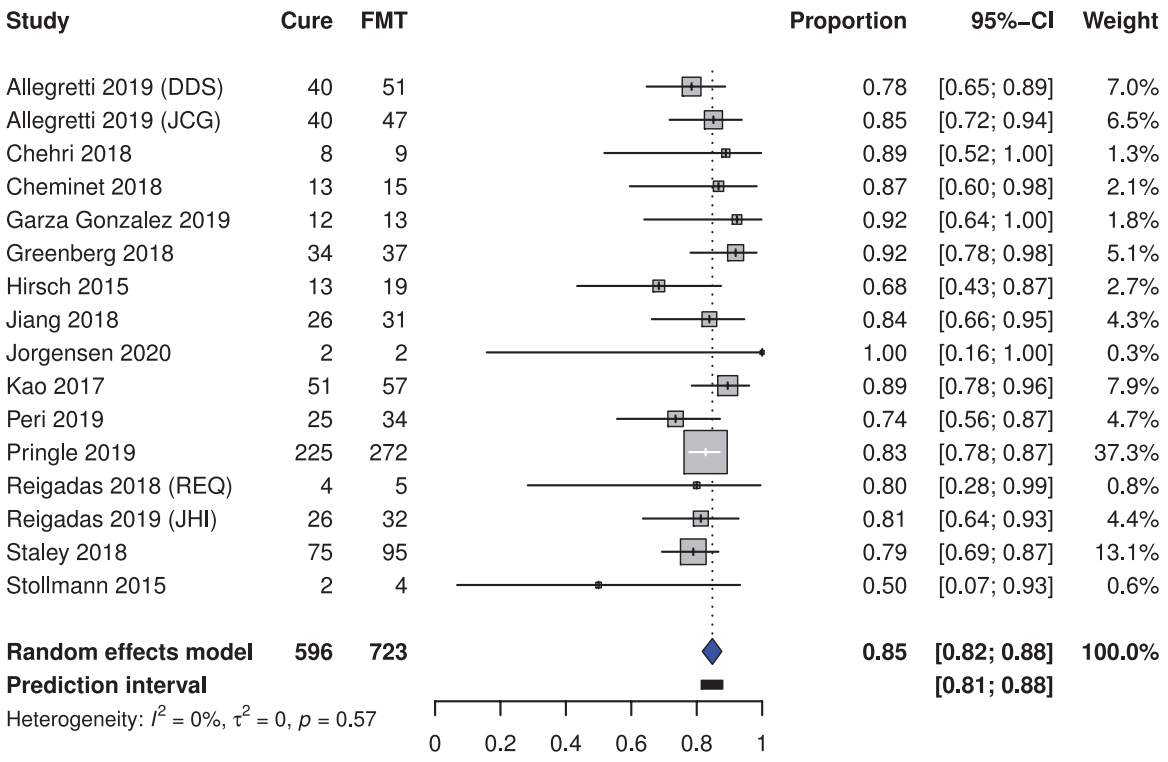

Figure 2. Forest plot of primary cure rates of studies of treatment with capsule FMT for recurrent *C. difficile* and random effects model of pooled clinical efficacy. Cure defined as clinical or microbiological resolution of CDI at least 8 weeks after a single course of treatment with encapsulated FMT.
CI, confidence interval; FMT, faecal microbiota transplantation.

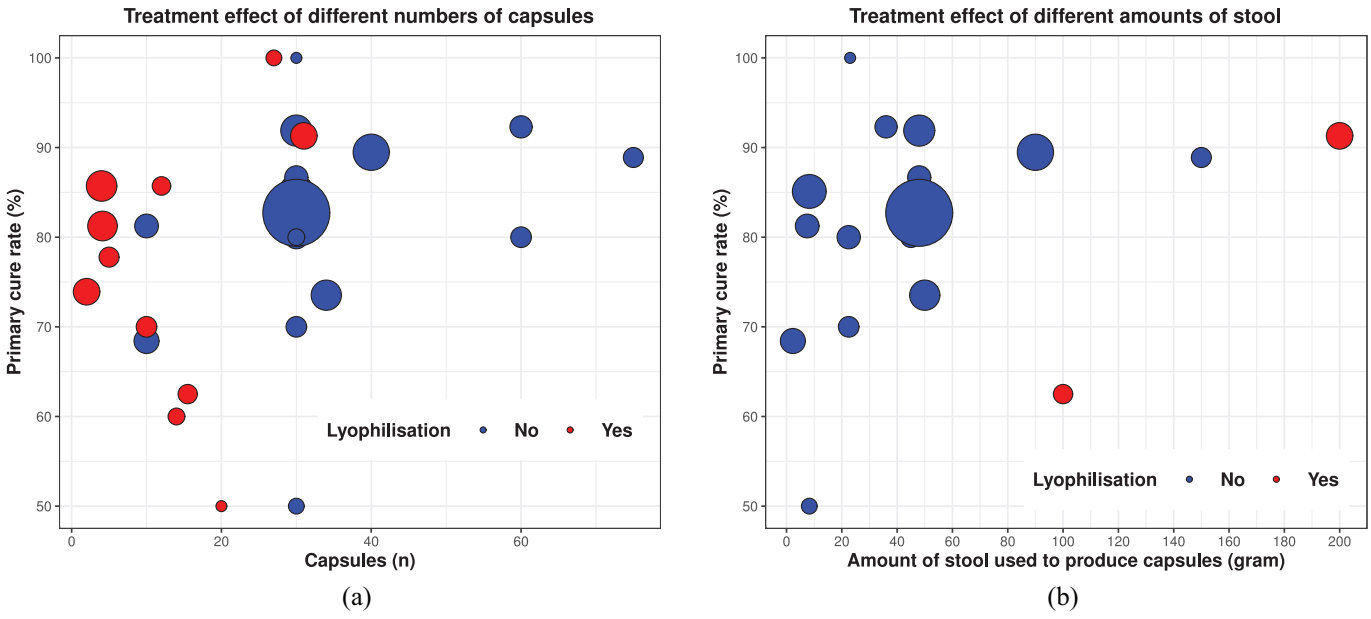

Figure 3. (a and b) Effects of number of delivered capsules and amount of stool used in production on primary cure rates in studies of capsule FMT for recurrent *C. difficile*. Size of bubbles is based on size (number of patients) of whole study or group of patients from study treated with a certain number of capsules delivered in one FMT treatment or the amount of stool used in the production of FMT capsules for one treatment.
FMT, faecal microbiota transplantation; n, number.

Production of FMT capsules and treatment in studies of recurrent C. difficile *studies*

FMT capsules were produced and delivered differently in the studies in relation to delivered dose, amount of stool used to produce the dose, bowel cleansing, and production and storage of capsules. The first oral administration of FMT capsules was supervised in a hospital setting or in the patients' home. In three of the studies reporting the use of lyophilised faecal material in the capsules, the use of further capsules administered at home later the same day or the following days was reported.[42,44,50] The use of capsules that could be stored in the patients' refrigerators for up to two days before use was reported.[50] Most studies reported the use of double encapsulated size 00 and 0 capsules (length of 23.6 mm) (Supplementary Table 7). No single factor was found to be significantly associated with an increased chance of clinical effect. Evaluating the number of capsules, the chance of clinical resolution increased by 0.2% (95% CI 0.0;0.4) with each extra capsule delivered ($p = 0.06$) (Figure 3(a)). The delivered amount of stool used to produce one FMT capsule treatment dose ranged from 2.3 to 200 g. The chance of clinical resolution increased by 0.06% (95% CI: -0.01;0.12) ($p = 0.09$) with every extra gram of stool used in the production (Figure 3(b)). None of the other discrepancies, such as days of treatment, capsule storage temperature, anaerobic preparation, amount of glycerol (data not shown), use of bowel cleansing before treatment or use of lyophilised faecal material, was significantly associated with changes in the primary cure rates (Table 4). Capsule storage time before use was only reported in a few studies, therefore the effect of this parameter on the cure rate was not calculated. More than half of the patients were treated with exactly 30 capsules. The lowest rate of clinical resolution was reported in the studies using fewer than 30 capsules for each treatment. Since no single element in the production significantly affected the likelihood of clinical resolution, multivariate regression was not performed.

Safety of FMT capsules in studies of encapsulated FMT treatment for recurrent C. difficile

Although six studies reported deaths of treated patients within the follow-up period, none of the deaths was considered related to the FMT treatment.[12,39,40,43,44,48] In the three RCTs, there were no

Table 4. Preparation of FMT capsules, pre-treatment, delivered material and study type in studies of recurrent *C. difficile*.

Characteristics of capsule preparation	Treated patients, *n*	Studies, *n*	Primary cure rate (95% CI)	*p* value for difference
Single-donor capsules	696	13	83.3% (80.2;86.4)	$p = 0.21$
Multi-donor capsules	22	2	91.1% (79.3;100)	
Lyophilisation	158	3	80.5% (74.3;86.7)	$p = 0.26$
No lyophilisation	565	13	84.6% (81.1;88.9)	
Storage temperature				
• (-80°C)	581	11	82.4% (78.9;85.9)	$p = 0.85$
• (-70°C)	70	1	90.1% (83.2;97.1)	
• (-20°C)	9	1	88.9% (68.4;100)	
• (4°C)	63	2	82.6% (73.3;91.9)	
Bowel cleansing	88	3	87.9% (81.2;94.7)	$p = 0.14$
No bowel cleansing	468	10	82.2% (78.7;85.6)	
Aerobic processing	551	11	84.4% (80.4;88.5)	$p = 0.47$
Anaerobic processing	104	2	80.3% (72.7;87.9)	
Duration of treatment:				
• One day	250	7[a]	82.3% (77.6;86.9)	$p = 0.31$
• Two days	464	11[a]	85.0% (81.7;88.3)	
• Three days	9	1	88.9% (68.4;100)	
Study type				
• RCT	101	3	88.7% (82.6;94.8)	$p = 0.12$
• Non RCT	633	13	80.5% (75.5;85.6)	
Total number of capsules				
• Below 30	170	5[b]	79.4% (73.4;85.3)	$p = 0.11$
• 30	407	8[b]	84.2% (80.7;87.7)	
• Above 30	146	6[b]	87.8% (82.6;93)	

C, Celsius; CI, confidence interval; FMT, faecal microbiota transplantation; n, number; RCT, randomised controlled trial.
Primary cure rates following single FMT treatment from studies using different approaches to treatment. P values are calculated based on univariate meta-regression analyses of the different approaches to capsule production, storage, delivery, pre-treatment, treatment protocol or study type impact on primary cure rates.
[a]Studies by Allegretti and colleagues (DDS), Jiang and colleagues and Staley and colleagues reported patients treated both one or two days.
[b]Studies by Allegretti and colleagues (DDS) and Jiang and colleagues included patients that were treated with different numbers of capsules which are included in the respective sub-groups.

significant differences in the number of total adverse events or specified adverse events between the patients treated with FMT capsules and the patients receiving FMT treatment by other routes or FMT capsules with added *Lactobacillus* (Supplementary Table 8).[12,40,44] In the non-RCT studies, 13 serious

adverse events were reported, when excluding recurrence of *C. difficile* infection as a serious adverse event (Supplementary Table 9). Of these, only three, which were all from the same study, were considered possibly related to the treatment.[54] One patient experienced fever, causing hospitalisation, and two patients were diagnosed with UC. The diagnosis was already suspected in advance in one of the patients. Minor self-limiting gastrointestinal adverse effects, such as bloating, flatulence, constipation, abdominal pain, nausea and vomiting, were reported in several studies.[12,36,37,40,41,43,44,53,54]

Risk of bias in studies of encapsulated FMT treatment of recurrent C. difficile

A sensitivity analysis excluding every single study showed no significant change when any of the studies were excluded (Supplementary Figure 2). Based on Egger's statistical test ($z = -1.22$, $p = 0.22$) and asymmetry of the funnel plot (Supplementary Figure 3), no indication of publication bias was found. In several of the included cohort studies or case series, the quality analysis performed indicated that a risk of bias cannot be excluded, based on the fact that the quality rating of the studies was only good in three of seven cohort studies and two of eight case series/reports (Supplementary Table 3, 4 and 5).

Indications and patient characteristics in studies of encapsulated FMT treatment for conditions other than CDI

Seventeen studies reported the use of encapsulated FMT for 205 patients. The conditions treated ranged from chronic disorders, such as IBS, to life-threatening diseases, such as recurrent infections in immunocompromised patients, graft-versus-host disease, and liver cirrhosis with recurrent hepatic encephalopathy (HE) (Table 5).[56,58,66,70]

Clinical outcomes in studies of encapsulated FMT treatment of conditions other than CDI

Irritable bowel syndrome. Two placebo-controlled RCTs using encapsulated FMT reported no beneficial effects of FMT compared with the placebo, as evaluated by the IBS-severity scoring system (IBS-SSS).[55,56] Halkjaer and colleagues[56] treated 52 patients with IBS (all types) with either FMT or a placebo for twelve days. Both groups improved significantly with decreases in IBS-SSS after three months, with the placebo group experiencing significantly greater improvements in symptoms assessed through IBS-SSS. In a crossover trial, Aroniadis and colleagues[55] treated 48 patients with diarrhoea-predominant IBS with three days of either FMT or a placebo, with patients changing treatment group after 12 weeks. IBS-SSS did not differ between FMT recipients or placebo recipients after 12 weeks following adjustment for baseline scores.

Recurrent or multidrug-resistant bacterial infections. Four studies investigated the effects of FMT capsules to treat or eradicate multidrug-resistant bacteria or recurrent infections.[57–60] In a multicentre RCT, Huttner and colleagues[59] treated carriers of multidrug-resistant *Enterobacteriaceae* with 2 days of FMT capsules preceded by 5 days of antibiotics. Seven of the sixteen FMT-treated patients were decolonised from extended spectrum beta-lactamase *Enterobacteriaceae* (ESBL-E) or carbapenemase-producing *Enterobacteriaceae* (CPE) as opposed to 3 of 13 in the placebo group that did not receive any treatment. In a cohort study by Bar-Yoseph and colleagues,[57] two days of FMT capsules successfully decolonised nine of fifteen carriers of CPE. Torres Soto and colleagues reported how two patients with recurrent relatively resistant *Salmonella infantis* cleared their symptoms and had no microbiological sign of infection after two days of FMT treatment.[60] In one case study, Biehl and colleagues[58] treated a patient with recurrent, predominantly ESBL-producing *E. coli* urinary tract infections (UTIs) with two days of FMT capsules, and found no clinical sign of UTI throughout the nine-month follow-up period.

Ulcerative colitis. Three uncontrolled studies investigated the effects in a total of 32 patients with UC.[61–63] All found beneficial effects of encapsulated FMT. Adler and colleagues[61] found that 6 weeks of 10 FMT capsules per week was well-tolerated and kept patients in clinical remission after a single course of FMT by colonoscopy. In the study by Cold and colleagues, 25 FMT capsules per day for 50 days significantly improved symptoms evaluated by the Simple Colitis Clinical Activity Index (SCCAI) and decreased faecal calprotectin after both 4 and 8 weeks in the seven treated patients.[62,72] Here, the improvements were no longer statistically significant after 12 weeks. Steube and colleagues reported improved symptoms through the Mayo score after 12 weeks of 2 x 5 daily capsules.[63,73]

Table 5. Summary of included studies treating conditions other than recurrent *C. difficile* with FMT capsules.

Indication	Author and year	Study type	Patients treated	Intervention: capsules x days	Follow-up, days	Primary outcomes[a]
Irritable bowel syndrome	Aroniadis and colleagues[55]	RCT (crossover trial)	48	25 x 3	84	No clinical improvement compared with placebo after 12 weeks
	Halkjaer and colleagues[56]	RCT	26	25 x 12	183	Placebo treatment superior after three months
Recurrent or multidrug-resistant infections	Bar-Yoseph and colleagues[57]	Cohort study	15	15 x 2	183	9/15 eradicated CPE after 1 month
	Biehl and colleagues[58]	Case report	1	At least 30 capsules delivered in two days	274	No recurrence of UTI after 9 months
	Huttner and colleagues[59]	RCT	16	15 x 2	150–210	7/16 FMT and 3/13 placebo-treated patients cleared ESBL-E/CPE after 35–48 days
	Torres Soto and colleagues[60]	Case series	2	15 x 2	91 (mean)	Both patients without infection after 1 or 2 cycles of FMT
Ulcerative colitis	Adler and colleagues[61]	Cohort study	15	10 capsules weekly for 6 weeks. Preceded by FMT through colonoscopy	42	No SAEs. Maintained remission at end of follow-up
	Cold and colleagues[62]	Cohort study	7	25 x 50	183	Clinical remission in 5/7 patients after both 4 and 8 weeks
	Steube and colleagues[63]	Cohort study	10	2x5 capsules per day for 5 consecutive days for 12 weeks	84	Symptoms improved in 7/8 patients after 12 weeks
Post allogeneic haemopoietic cell transplantation/gut graft-vs-host disease (gGVHD)	DeFilipp and colleagues[64]	Cohort study	13	15 x 2 capsules a median of 27 days after HCT	456 (median)	13 out of 14 eligible patients received treatment. One SAE (transient abdominal pain)
	Goloshchapov and colleagues[65]	Cohort study	13	A total of 30 capsules in 2–3 days	765 (median)	Complete response in 5/13 and partial response in 13/13 patients after 120 days
	Kaito and colleagues[66]	Case report	1	15 capsules per day on days 125, 130, 133, 144, 173, 181, and 189 after transplantation	90	Improved gGVHD from stage 3 to 1 after full treatment
	Mao and colleagues[67]	Case report	1	30 capsules on day 1 and 3. Second cycle of 30 capsules on day 13	72	Sustained improvement two months after second cycle of FMT
Obesity/insulin resistance	Allegretti and colleagues[68]	RCT	11	30 capsules at baseline and 12 capsules after 4 and 8 weeks	84	No SAEs. No clinical improvement after 12 weeks
	Yu and colleagues[69]	RCT	12	2 days of 15 capsules followed by 15 capsules once a week for 5 next weeks	84	No clinical improvement in insulin sensitivity after 6 weeks
Hepatic encephalopathy	Bajaj and colleagues[70]	RCT	10	15 x 1	152	Fewer SAEs in FMT arm (1) than in placebo arm (11). Improved brain function after 30 days
Chronic pouchitis	Herfarth and colleagues[71]	RCT	4	Endoscopically delivered FMT followed by 14 days of 6 daily FMT capsules	112	No SAEs. All patients experienced relapse during or shortly after FMT

CPE, carbapenemase-producing *Enterobacteriaceae*; ESBL-E, extended spectrum beta lactamase *Enterobacteriaceae*; FMT, faecal microbiota transplantation; gGVHD, gut graft-vs-host disease; HCT, haematopoietic cell transplantation; RCT, randomised controlled trial; SAE, serious adverse event; UTI, urinary tract infection.
[a]Primary outcome as described by authors. In the event of primary outcome of safety or feasibility, the primary clinical outcome as reported by the authors is also reported.

Post haemopoietic cell transplantation. In four studies, the safety and effects of encapsulated FMT on graft-versus-host disease in patients post allogeneic haemopoietic cell transplantation were examined in a total of 28 patients.[64–67] In a case study, Kaito and colleagues tested FMT as a third-line treatment in a patient with acute gut graft-versus-host disease (gGVHD) and concluded that improvement of diarrhoea from stage 3 (>1500 ml/day) to stage 1 (<500 ml/day) after two cycles of FMT was possibly caused by the treatment.[66] In an open-label pilot study by DeFilipp and colleagues[64] primarily investigating safety, FMT was considered safe and increased faecal diversity in the 13 treated patients. Goloshchapov and colleagues reported the successful treatment of steroid refractory acute or chronic GVHD with a complete response in five (38%) and partial response in 13 (100%) of the 13 treated patients 120 days after two to three days of FMT treatment.[65] In a case study, Mao and colleagues[67] reported the successful treatment of a 31-year-old male with steroid-refractory intestinal GVHD after two cycles of treatment with FMT.

Obesity/insulin resistance. The effect of encapsulated FMT derived from lean donors has been investigated in two double-blinded RCTs in the treatment of obese patients without diabetes and in the treatment of obese patients with mild to moderate insulin resistance.[68,69] Both studies reported that the treatment was safe, but did not result in beneficial metabolic changes when compared with the placebo group.

In 22 obese patients (body mass index (BMI) $\geqslant 35$ kg/m^2) without a diagnosis of diabetes Allegretti and colleagues[68] tested the effects of a dose of 30 FMT capsules at baseline followed by 12 capsules at week four and eight compared to placebo. No significant change in BMI or area under the curve of the hormone Glucagon-like peptide-1, which has glucose lowering properties,[74] was observed in either group. Yu and colleagues reported the effects of 2 days of 15 capsules followed by 15 capsules once a week for the five next weeks compared to placebo in 24 adults with obesity and mild-moderate insulin resistance (homeostatic model assessment of insulin-resistance (HOMA-IR) between 2.0 and 8.0).[69] Following treatment there was no significant difference in insulin sensitivity in the FMT group compared to the placebo group.

Liver cirrhosis – hepatic encephalopathy. In a placebo-controlled RCT with safety as a primary outcome, Bajaj and colleagues[70] treated 20 patients with cirrhosis and recurrent HE with 1 day of 15 FMT or placebo capsules. FMT was safe and the patients experienced significantly fewer episodes of HE in the FMT group than in the placebo group (one versus seven) throughout the 5-month follow-up.

Chronic pouchitis. In a placebo-controlled RCT, Herfarth and colleagues[71] treated six patients with chronic pouchitis with FMT or a placebo delivered through sigmoidoscopy followed by 14 days of FMT or placebo capsules. The study was halted early because of lower than expected clinical efficacy and low donor engraftment rate.

Production of FMT capsules and treatment in conditions other than CDI

The treatment was prepared and delivered in very different ways in relation to donor selection, multi-donor/single-donor treatment, the use of anaerobic processing, bowel cleansing prior to treatment, dose (from a total of 15 to a total of 1250 capsules) and length of treatment (one day to 12 weeks). The first oral administration of FMT capsules was supervised in a hospital setting in all studies. In two studies reporting the use of long-term treatment with daily administration of capsules for 12 and 50 days the patient or a deputy picked up new FMT capsules every fourth day that could be stored in the patients' freezers until use.[56,62] Most studies reported the use of double encapsulated size 00 and 0 capsules (length of 23.6 mm) (Supplementary Table 10).

Safety of FMT capsules in studies of encapsulated FMT treatment for conditions other than CDI

Deaths following treatment were reported in two of the studies and were considered not to be related to the FMT treatment.[64,70] Data from the included RCTs showed diverging results. Halkjaer and colleagues[56] reported more adverse events, in particular diarrhoea, in the FMT than in the placebo group. In the other RCTs, the presentation of adverse events was equally distributed in the FMT and placebo groups without any significant differences (Supplementary Table 11). Minor transient gastrointestinal adverse effects, such as diarrhoea, constipation, bloating and

flatulence, were described in the non-RCT studies (Supplementary Table 12).[61,63,65]

Discussion

This systematic review investigated current indications and the results of studies using encapsulated FMT as the treatment. The essential finding from studies with encapsulated FMT used for rCDI was that the treatment is highly effective, with efficacy comparable to FMT delivered through other routes. The treatment is effective, irrespective of the different laboratory preparations and administration of capsules in the various studies. There are promising results in the treatment of other diseases, such as UC and HE, and treatment of multidrug-resistant and recurrent bacterial infections with encapsulated FMT. However, further RCTs and clearly defined reproducible endpoints across studies are still missing. Thus, in the treatment of conditions other than rCDI, encapsulated FMT should still only be used in research settings.

In this updated meta-analysis of encapsulated FMT used for rCDI, the cure rates of 85% after one and 93% following repeat (two or three) treatments are similar to previous meta-analyses including results from studies investigating the effect of FMT delivered by other routes.[3,8,9] Pooled cure rates of 84% and 91% after a single versus multiple treatments were reported by Baunwall and colleagues in a meta-analysis of FMT delivered through all routes of administration for rCDI.[8] In another meta-analysis, including a total of 132 studies and 4609 patients treated for rCDI by Lai and colleagues, encapsulated FMT was reported to have comparable cure rates to treatment delivered through other routes of administration.[9] Furthermore, encapsulated FMT had comparable cure rates to FMT given through other routes, in the RCTs included in this review, further indicating that the treatment effects are comparable with other routes of administration.[12,44]

Important limitations apply to this meta-analysis of the treatment effect of encapsulated FMT in rCDI, and some of the findings should be handled with caution. In particular, only three of the studies included were RCTs. Nevertheless, several findings are reported that point to a low risk of bias. There was low heterogeneity between the results of the studies, a sensitivity analysis indicated a low risk of bias, and the results of testing for publication bias did not point to substantial bias.

The finding that FMT given through capsules is as effective as FMT given through other routes is of importance for future large-scale treatment of rCDI. Encapsulated FMT is safer because an endoscopic procedure can be avoided and furthermore the treatment can be delivered to patients as an outpatient treatment or delivered to them in their homes. The capsule size of 23.6 mm used in most studies can be a problem in patients with swallowing problems, but otherwise the treatment can be administered to most patients with rCDI including frail patients that cannot come to the hospital.[45] The cure rates in the five included studies using lyophilised faecal material were comparable to the other studies, which has also been previously reported.[23,42,44,49,50,52] The introduction of encapsulated FMT with lyophilised faeces will only reinforce the applicability of the treatment since it can be administered with fewer capsules to swallow and potentially storage in the patients' refrigerator or freezer in case of treatment regimens of more than one day.

The procedural differences investigated in the present review did not affect the cure rates of encapsulated FMT in rCDI. The clinical effect appeared robust despite a considerable difference between the studies in terms of delivered doses, preparation and storage and whether bowel cleansing was performed prior to treatment. A tendency was reported, nearly reaching statistically significance, of a greater chance of resolution with an increased number of capsules ($p = 0.06$) delivered and amount of stool ($p = 0.09$) used in production of treatment, hence a dose-response relationship cannot be ruled out.

The mechanism behind the effect of FMT delivered through capsules and other routes of administration in the treatment of rCDI is still not fully understood. The effect is purportedly caused by the beneficial transfer of bacteria, other microorganisms or metabolites.[75–77] Interestingly, successful FMT treatments have recently also been connected to the transfer from donor to recipient of bacteriophages, the viruses that infect bacteria.[75] Further corroborating this hypothesis, cell-free faecal filtrates, including bacteriophages, from donors were effective for rCDI.[76,78]

Whether an altered microbiome is the cause or a consequence of the disease in conditions other than single-pathogen diseases such as rCDI is still not fully understood.[79,80] There is also a lack of good definitions of microbiome alterations related to disease, often described as gut dysbiosis, and different dysbiosis indexes have been proposed.[81] In general, the treatment of other diseases requires more than the removal of one pathogenic microbial component, and possibly the complete transfer and establishment of a healthy microbiome. There are promising results from FMT treatment of diseases other than rCDI, in particular from RCTs for the treatment of UC by FMT delivered through other routes of administration than capsules[14,82,83] and from the treatment of multidrug-resistant bacterial infections.[18] Despite the promising results of several of the included studies using encapsulated FMT, the lack of RCTs and the low number of treated patients prevent a conclusion being drawn as to whether FMT delivered through capsules is an effective treatment of diseases other than rCDI, and further studies are warranted.

In contrast to capsule treatment of rCDI, differences in relation to preparation, dose and route of administration could be of great importance in the treatment of other diseases where it is presumably not simply a question of removing a single infecting organism, as in rCDI. The potentially harmful role of a dysbiotic microbiome in these diseases probably differs from disease to disease. Thus, a one-size-fits-all way of preparing and delivering FMT is probably not appropriate and the route of administration could also influence the effects of the treatment. In the treatment of IBS, a recent meta-analysis of FMT in IBS by Ianiro and colleagues reported a reduced relative risk of 0.63 (CI 95% 0.43-0.93) of IBS symptoms not improving following treatment delivered through colonoscopy.[15] No beneficial effect of FMT treatment when compared with the placebo was reported when all RCTs including studies using encapsulated FMT were analysed. Another important factor in the treatment of conditions other than rCDI could be rational donor selection. In the successful treatment of HE, Bajaj and colleagues screened a donor based on the knowledge of low values of *Lachnospiraceae* and *Ruminococcaceae* in the gut microbiome of patients with cirrhosis and recurrent hepatic encephalopathy.[84,85] Thus, it is important that future studies continue to assess whether certain FMT treatment protocols are more effective than others in the treatment of diseases other than rCDI.

FMT treatment is generally considered safe when donor-screening protocols are followed.[23,27,86–88] No cases of transferred diseases were reported in any of the studies included in this review and only a few serious adverse events, mostly considered not related to treatment, were reported. Encapsulated FMT did not introduce more adverse events than FMT through other routes, but it may possibly introduce more than placebo when administered long term, as reported by Halkjaer and colleagues.[56]

Conclusion

Encapsulated FMT is an effective and safe treatment for recurrent *C. difficile* infection, with cure rates comparable with FMT delivered through other routes. The treatment is effective, despite variations in donor screening, preparation and treatment protocol. Despite promising results in the treatment of ulcerative colitis, hepatic encephalopathy and multidrug-resistant organisms, further studies, in particular through randomised placebo-controlled trials, are warranted before the use of encapsulated FMT can be implemented as a treatment of other diseases.

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Study concept and design: F.C., S.M.D.B., and C.L.H.; acquisition of data: F.C. and S.M.D.B.; analysis and interpretation of data: F.C. and S.M.D.B.; drafting of the manuscript: F.C.; critical revision of the manuscript for important intellectual content: F.C., S.M.D.B., J.F.D., A.M.P., C.L.H., and L.H.H. All authors approved the final version of the manuscript.

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Data availability statement

All data included in the review were obtained from previously published data. The recorded data and R scripts will be available upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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