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Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection

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Summary

Background: *Clostridium difficile* infection (CDI) is the commonest nosocomial cause of diarrhoea. Faecal microbiota transplantation (FMT) is an approved treatment for recurrent or refractory CDI but there is uncertainty about its use.

Aim: To evaluate the efficacy of FMT in treating recurrent and refractory CDI and investigate outcomes from modes of delivery and preparation.

Methods: A systematic review and meta-analysis was performed. MEDLINE, EMBASE, CINAHL, Cochrane Library, trial registers and conference proceedings were searched. Studies on FMT in recurrent and refractory CDI were included. The primary outcome was clinical resolution with subgroup analyses of modes of delivery and preparation. Random effects meta-analyses were used to combine data.

Results: Thirty seven studies were included; seven randomised controlled trials and 30 case series. FMT was more effective than vancomycin (RR: 0.23 95%CI 0.07-0.80) in resolving recurrent and refractory CDI. Clinical resolution across all studies was 92% (95%CI 89%-94%). A significant difference was observed between lower GI and upper GI delivery of FMT 95% (95%CI 92%-97%) vs 88% (95%CI 82%-94%) respectively (P=.02). There was no difference between fresh and frozen FMT 92% (95%CI 89%-95%) vs 93% (95%CI 87%-97%) respectively (P=.84). Administering consecutive courses of FMT following failure of first FMT resulted in an incremental effect. Donor screening was consistent but variability existed in recipient preparation and volume of FMT. Serious adverse events were uncommon.

Conclusion: Faecal microbiota transplantation is an effective treatment for recurrent and refractory *Clostridium difficile* infection, independent of preparation and route of delivery.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan. The Handling Editor for this article was Professor Peter Gibson, and it was accepted for publication after full peer-review.

1 | BACKGROUND

Clostridium difficile infection (CDI) is the most important cause of nosocomial diarrhoea usually related to antibiotic use. It is associated with significant morbidity, mortality and cost worldwide.[1] UK National Institute for Health and Care Excellence (NICE) guidelines published in March 2014 recommend the use of faecal microbiota transplantation (FMT) for patients with recurrent CDI that have failed to respond to antibiotics and other treatments.[2] However, a recent survey across England revealed that only just over 25% of hospital trusts perform FMT for this indication.[3] This poor uptake has been attributed by physicians in part to paucity of randomised controlled trial (RCT) data, the lack of a standard treatment protocol, and uncertainty about long-term safety of FMT.[3]

Clostridium difficile infection occurs mainly in the elderly and those with significant chronic illnesses.[1] The long-term cure rate from standard first line antibiotics (metronidazole or vancomycin) is low with CDI re-occurring after apparent resolution in about 35% of patients.[4] Recurrent CDI is defined as complete recovery without symptoms followed by at least one further episode of diarrhoea confirmed to be secondary to CDI. Recurrent attacks of CDI expose patients to risk of complications such as toxic dilatation of the colon and septicaemia, which are associated with high mortality. Commonly, tapering doses of vancomycin are used for recurrent and refractory CDI although the effectiveness of this therapy is uncertain with sustained cure rates reportedly ranging widely between 49% and 100%.[5] While fidoxamicin has been shown to be more effective than vancomycin in the resolution of CDI as a first-line agent, this agent has not been tested in recurrent CDI.[6,7]

Faecal microbiota transplantation for the treatment of CDI was attempted first in the modern era by Eiseman et al.[8] in a small number of patients. Over the past decade or so, FMT has been studied by several centres worldwide for management of recurrent and refractory CDI. However, uncontrolled studies make up the bulk of the supporting evidence. Previous systematic reviews and meta-analyses either have methodological limitations as they have a restrictive selection criteria, do not have a comprehensive search strategy or do not consider the effect of different modalities of preparation or delivery of FMT. Moreover, they do not include the most recent evidence, which to date includes more than five RCTs.[9-12] In this systematic review and meta-analysis, we therefore aim to address these issues to bring the evidence on FMT in recurrent and refractory CDI up to date.[13,14]

2 | METHODS

2.1 | Objectives

To systematically evaluate the effectiveness of FMT as treatment for recurrent and refractory CDI.

The review and meta-analysis were undertaken in line with guidance from the Cochrane Handbook of Systematic Reviews of Interventions, and reported in line with preferred reporting items for systematic reviews and meta-analysis.[13,14]

2.2 | Search strategy

The databases MEDLINE, EMBASE, CINAHL and Cochrane Library were searched from commencement of databases to October 2016 for relevant articles. Free text and index terms for faecal microbial transplantation and Clostridium difficile were combined and no study design or language of publication filters were used. The MEDLINE and EMBASE strategy are shown in Appendix S1. Details of ongoing trials and studies yet to be fully published were sought from trials registers (controlled-trials.com, clinicaltrials.gov), and microbiology, infection, and gastroenterology conferences proceedings (Digestive Diseases Week, British Society of Gastroenterology Conference, United European Gastroenterology Week) from September 2014 to October 2016. Reference lists of existing systematic reviews and articles included in this review were checked for additional studies.

Search results were entered into a bibliography manager and duplicate entries removed.

2.3 | Study selection

Titles and abstracts of each article were screened for relevance. Copies of relevant articles were obtained and assessed for inclusion in the review using the criteria below. Screening and selection were undertaken independently by two reviewers and any disagreements resolved through discussion. The reason for not-selecting studies for review was recorded.

2.3.1 | Type of studies

Randomised controlled trials, non-randomised trials and case series with 10 or greater participants were included. Studies published in abstract only format (for example, from conference supplements) were only included if they were RCTs.

2.3.2 | Type of participants

Studies recruiting patients of all ages with refractory or recurrent CDI were included. Patients include those with ongoing diarrhoea without resolution of symptoms despite standard antimicrobial therapy. Recurrent and refractory CDI was taken as defined by the authors.

2.3.3 | Comparator

For comparative study designs, there was no restriction on the type of comparator.

Primary outcome

Studies reporting clinical resolution of CDI based on improvement of symptoms or negative *C. difficile* stool culture or toxin were included.

2.4 | Data extraction

Data were extracted using a predesigned collection form on characteristics of study design, participants, type of CDI (recurrent and/or refractory) and outcomes. In addition, data were extracted on donor screening, procedural aspects (FMT preparation, pre-medications and number of infusions) to establish variation in practice. Data on adverse events were also collected.

There was no missing data or unclear information that necessitated contacting study authors for clarification. For papers not published in English, partial translations were undertaken (in one case). Data extraction and risk of bias assessment were undertaken by two reviewers independently. If there were any discrepancies, a third reviewer was consulted (in one case).

2.5 | Risk of bias

Randomised controlled trials were assessed with the Cochrane Collaboration's risk of bias tool.[13] For non-randomised trials, the same tool was to be used without application of criteria related to randomisation. Case series were assessed using the Centre for Reviews and Dissemination guidance.[15]

2.6 | Data assessment and analysis

The effect of FMT on clinical resolution of recurrent and refractory CDI was evaluated by analysing studies with direct comparison against a non-FMT arm. The overall effect of FMT was analysed using data from all studies (including the FMT arm data from RCTs).

The author's definition of outcome of CDI resolution was used at the time point specified by the author following the delivery of FMT. To study the effect of multiple infusions, the data were analysed to compare rate of clinical resolution if only a single infusion was administered and if more than one infusion was delivered.

Analysis was carried out to study the effects on FMT efficacy of mode of FMT delivery (upper GI [foregut] vs lower GI [colonic]) and different preparations of donor stool (fresh vs frozen). These comparisons were performed first with RCTs (if any) and then on subgroups of case series for each assessment. As it was anticipated that studies on the whole would not clearly differentiate between patients with recurrent and refractory CDI, no separate analysis on these subgroups was undertaken. A descriptive analysis of adverse event data was performed.

2.7 | Statistical analysis

For the primary outcome, pooled estimates of relative risk from the RCTs, and response rates from case series, were estimated with a random effects model using the method of DerSimonian and Laird.[16,17] For the latter, the pooled estimate was calculated after the Freeman-Tukey Double Arcsine Transformation was applied to stabilise the variances facilitating synthesis of studies with 100% response rate.[18] Exact confidence intervals were calculated for the individual studies.

Heterogeneity was assessed using the I^2 statistic and calculation of 95% prediction intervals for the response proportion in a new study.[19,20] The latter were calculated using a logistic regression model with a random intercept. In interpreting I^2, we describe values from 0% to 30% as being likely minimal, values from 30% to 60% as likely moderate, and values from 60% to 100% as likely substantial heterogeneity. The possibility of small study effects was assessed by asymmetry of funnel plots if 10 or more studies contributed to a meta-analysis and the potential impact quantified using the Duval and Tweedie nonparametric "trim and fill" method.[21]

Confidence intervals for relative risks from individual RCTs were calculated assuming the sampling distributions of the log-relative risk are normally distributed. All analyses were performed in STATA version 14 (Texas, USA).

3 | RESULTS

3.1 | Study characteristics

The initial search identified 2097 publications. Of these, 1179 duplicates were excluded and an additional 615 were removed after screening titles and abstracts. Consequently, 303 papers were retrieved in full text. Of these 19 were systematic reviews from which no additional papers were identified. From the remaining 284 papers, 102 were overviews, summaries, opinion pieces and narrative reviews, 83 were case reports or case series with a sample size of less than 10 patients and 62 were case series published in abstract form. Therefore, 37 papers reporting studies met the selection criteria (Figure 1).

The 37 included studies are summarised in Table S1. Table S1 elaborates on the primary response rate data and assessment of study quality. Seven studies were RCTs (of which two were only published in abstract form) and 30 were case series. The different arms of the RCT data are summarised in Table S2. The included studies reported on a total of 1973 patients with 428 enrolled in RCTs (360 in the donor FMT arm and 68 in the non-donor FMT arm) and 1545 described in case series. Two RCTS were open label comparisons of vancomycin and FMT (van Nood et al. and Cammarota et al.).[22,23] Both were terminated early following interim analysis by the respective data and safety monitoring boards due to observed efficacy of FMT. One RCT compared autologous vs donor FMT (Kelly et al.), and the remaining RCTs compared different forms of FMT or modes of delivery: Fresh and frozen FMT (Lee et al.), capsule vs colonoscopic delivery (Kao et al.), low dose vs high dose FMT (Allegretti et al.), nasogastric vs colonoscopic delivery (Youngster et al.).[24–28,32]

Of the case series, 25 performed FMT solely using fresh stool, two studies solely used frozen stool, two studies performed FMT with both fresh and frozen and one did not report on FMT preparation. Eight studies delivered FMT via the upper GI route, 18 studies delivered FMT via the lower GI route and one study delivered FMT via both routes. The remaining studies used a combination of both routes but did not report on data separately. Almost all the 30

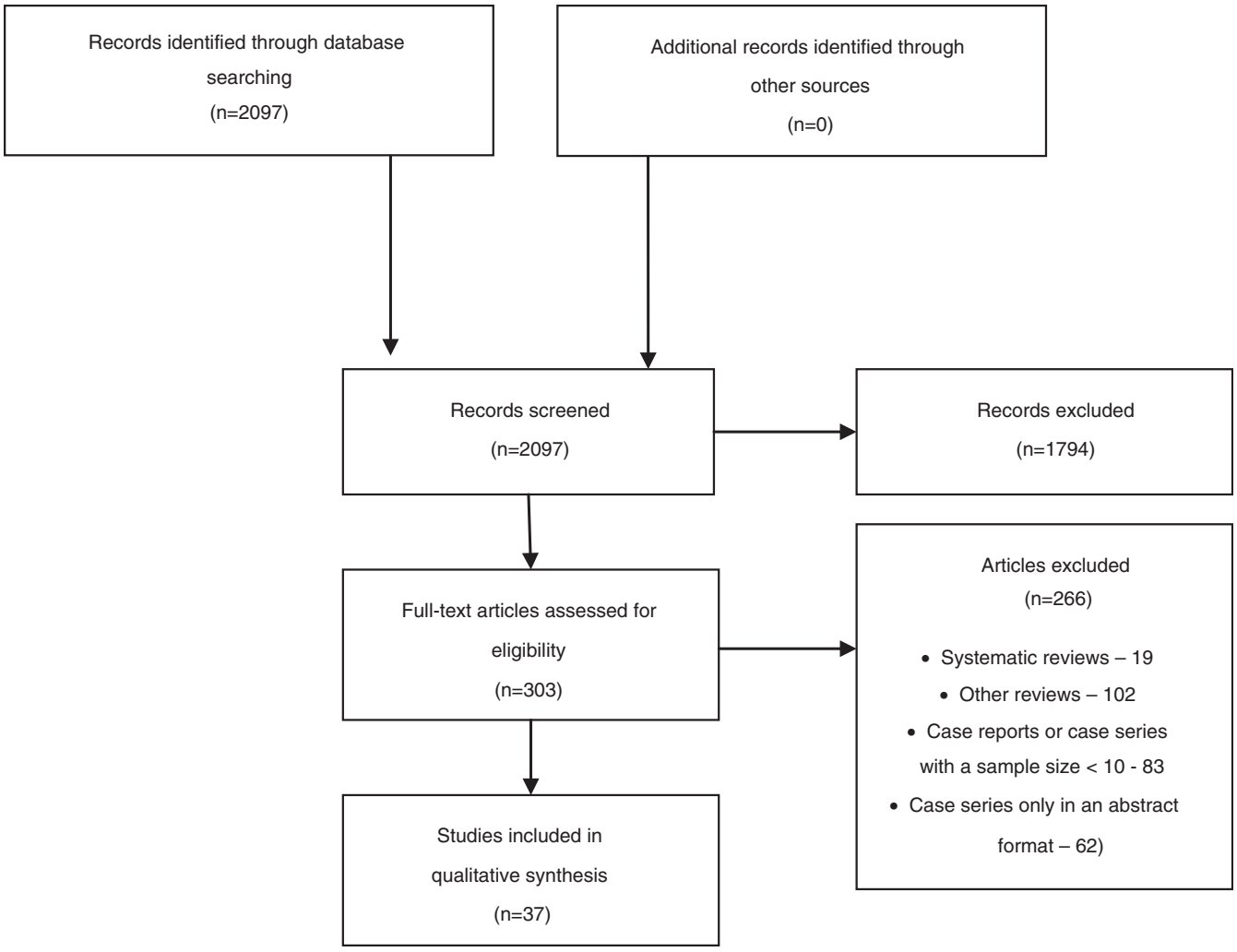

FIGURE 1 Flow chart of search

studies had similar cohorts with regard to age and gender and similar response rates were observed in older and younger groups and those with male or female predominance as shown in Table S1. There was a female preponderance in the studies with a male:female distribution of 2:3. No studies solely used toxin negativity to define clinical resolution. Prior endoscopic evaluation was undertaken in six studies.

3.1.1 | Donor screening protocol

Donors were a mixture of spouses, intimates, relatives and healthy volunteers. Most studies used a screening procedure to exclude individuals with known exposure to transmissible viruses, sexually transmitted disease, those involved in high-risk sexual behaviours and those with a history of drug abuse. Those with known gastrointestinal co-morbidity were excluded as were those who had recently taken antibiotics. With regard to donor screening, there was considerable standardisation in screening for blood-borne viruses with screening for common transmissible agents such as hepatitis A, B, C, HIV 1&2, *Helicobacter pylori* and Treponema in blood. This also applied to stool pathogens including *C. difficile* toxin, common pathogens including *Cryptosporidium* and *Giardia* and the majority of studies also reported microscopic examination for ova, cysts and parasites in stool samples.

3.1.2 | Procedural aspects

FMT preparation

In eight studies, the solvent was water, saline in 20 and glycerol was used as a cytoprotectant in the three studies using frozen stool preparations. The remaining studies did not describe the diluent used to make up the transplant material. Where stated, time from collection to administration varied from 1 hour to 8 weeks (frozen stool) whilst the median time was 6 hours for studies using fresh stool samples. Quantity and volume of FMT material was very variable. In the studies using the upper route of delivery, the volume of material varied from 25 to 500 mL and the mass of faecal material also varied widely from 6 g up to about 140 g (median 40 g). In the studies reporting on the lower GI route of delivery, the volume of FMT was reported in 19 and this ranged from 100 to 1000 mL with a mean

volume of about 450 mL. The fresh mass of faecal matter used was variably reported from 30 to 152 g (median of 86 g). Two RCTs used capsulated forms of stool, however, further details on the preparation of these capsules was not available as the data were only published in an abstract form.[26,32]

Pre-medication

Standard colonoscopy bowel preparation was used in all studies undertaking FMT via the lower GI route. Proton pump inhibitors were given in most studies using the upper route with the exception of the Van Nood RCT.[22] The use of anti-diarrhoeals to prolong retention of the faecal suspension in the colon was also reported in two studies. Antibiotics were generally stopped 1-2 days before FMT with the exception of the van Nood RCT, where antibiotics were continued until the day of the treatment.[22]

Number of infusions

Twenty-four studies allowed more than one infusion/treatment of FMT in the event of failure of response. Of the 13 studies that only performed a single infusion of FMT nine were done using the lower GI route, three used only the upper GI route and one used either route.[26,27,33-43] In the remaining studies, FMT was administered up to four times for recurrent or unresolved symptoms.

3.2 | Assessment of study quality

The seven RCTs were assessed to have a low risk of bias and demonstrated adequate randomisation with concealed automated allocation and performed an intention-to-treat analysis. For case series, although selection criteria were defined in most of these studies, all mentioned or implied consecutive recruitment of patients. Patients were followed up until achievement or failure of the primary outcome. Consequently, few studies reported long term outcomes and adverse events. Follow-up ranged from 10 weeks to 8 years.

3.3 | Efficacy of FMT

Most studies differed in their definition/criteria for resolution of CDI. Hence, the author's definition of outcome of CDI resolution at their specified time point following the delivery of FMT was used. Based on the variability in definitions used in the literature, it was not possible to clearly separate data on "recurrent" vs "refractory" CDI. There were no true placebo controlled trials investigating the efficacy of FMT.

3.3.1 | Response to FMT-RCTs

There were three RCTs that compared FMT to a non-FMT intervention. In the two RCTs comparing FMT to vancomycin, the pooled relative risk of treatment failure of FMT against vancomycin was 0.23 (95% CI 0.20-0.80) with moderate heterogeneity (I^2=41%) indicating the superiority of FMT.[22,23] The relative risk against vancomycin and bowel lavage in the RCT by Camorotta et al. was 0.08 (95% CI 0.01-0.05).[23] The overall response rate from the two RCTs comparing FMT to vancomycin was 90% in the FMT arm while the response rate was less than 30% in the antibiotic arms. The RCT by Kelly compared single infusion of donor vs autologous FMT.[27] In the intention-to-treat analysis, 20 of 22 patients (90.9%) in the donor FMT group achieved clinical cure at 8 weeks compared with 15 of 24 (62.5%) in the autologous FMT group (P=.042).

The RCT by Lee and colleagues (comparing fresh vs frozen FMT) reported an overall combined clinical resolution rate with FMT of 72% in the intention-to-treat analysis, and 84% in the per protocol analysis across both arms.[24] This was 52% for a single infusion but increased to 96% in patients who received more than two FMTs in the 13 week period. The RCT by Youngster (comparing nasogastric vs colonic FMT) reported a primary response rate (one infusion) of 70% across both arms and this increased to 90% with a second infusion in those that failed to respond to the first.[28] A further two RCTs published in abstract form comparing efficacy with capsule vs colonic delivery and low dose vs high dose capsulated FMT both showed a response rate of 95% across both FMT arms.[26,32] Kao et al. demonstrated a cure rate of 100% vs 92% in colonoscopy and capsule delivered FMT respectively.[26] In the Allegretti study presented at the Digestive Diseases Week in San Diego 2016, the authors reported on remission in 14 of 19 patients treated with either a low or high dose of capsules.[32] The abstract reports that the five non-responders at 8 weeks were all given a high dose of capsules with cure in 4.

3.3.2 | Response to FMT—all studies

The mean pooled overall response for FMT in recurrent and refractory CDI based on all the included 37 studies regardless of the number of infusions was 92% (95% CI 89%-94%) with likely moderate heterogeneity (I^2=59%) (Figure 2). From the 34 studies that presented efficacy data for a single FMT infusion, the mean pooled response rate was 84% (95% CI 79%-89%) with a likely high degree of heterogeneity (I^2=84%). For a single infusion a 95% prediction interval for the response proportion in a new study is 49%-96%. On analysis by funnel plot, studies were not symmetrically distributed about the pooled estimate possibly indicating an absence of some smaller and medium sized studies with findings that, although favourable, are not as favourable as other small studies. There are many possible reasons for this including chance, small study effects and publication bias. When this funnel plot asymmetry was adjusted for, the efficacy of one or more FMT infusions was only reduced by a small amount to 79% (95% CI 73%-84%) (Figure S1).

The case series had cure rates ranging from 68% to 100% with only one study having an overall response rate of under 75% and eight case series demonstrating a response rate of 100% (although there was incomplete follow-up in some of these studies).

Only one study addressed the efficacy of FMT for treatment of CDI in immunocompromised patients.[30] This study included a series

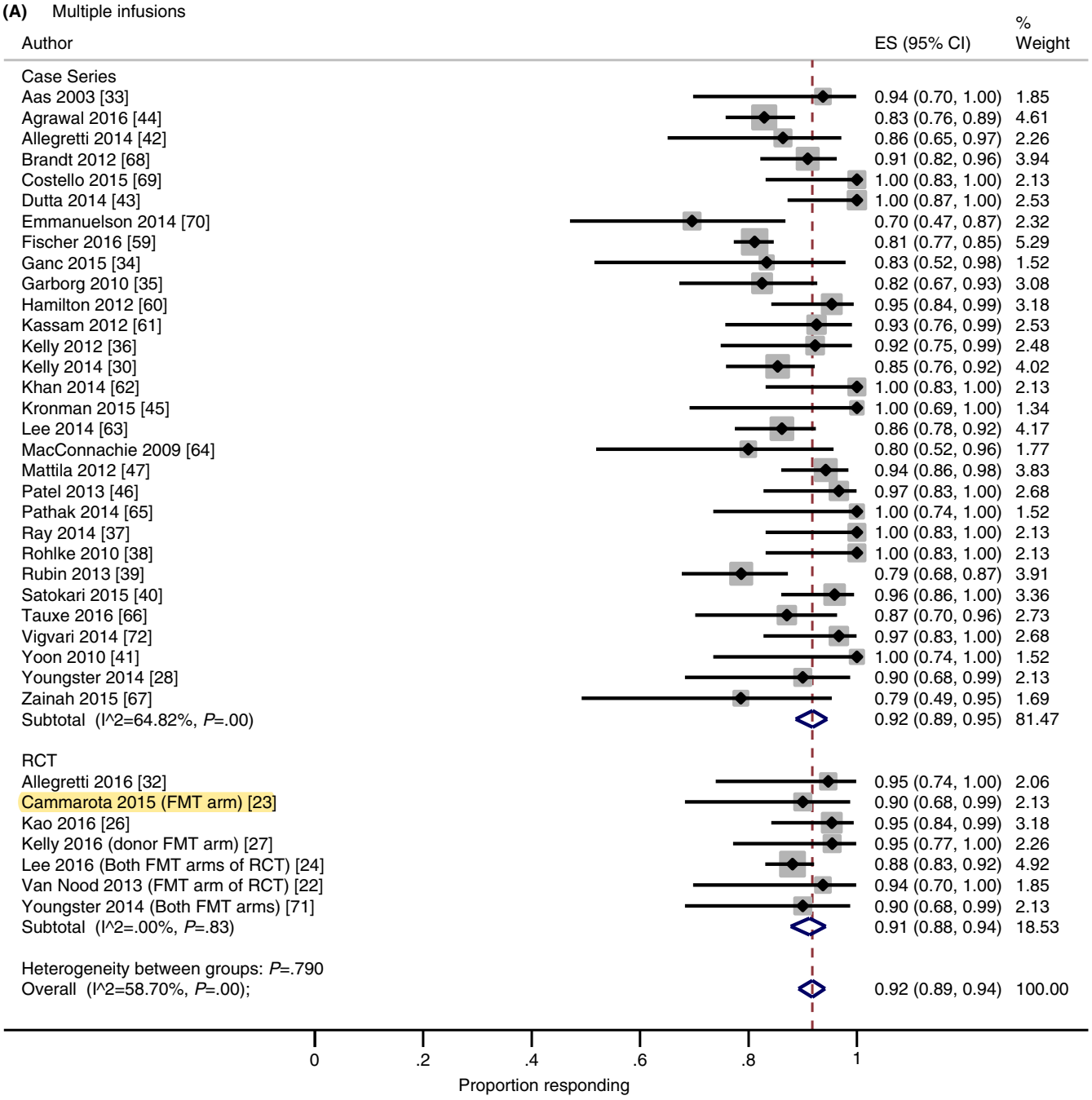

FIGURE 2 Forest plot of the proportion responding to treatment for all included studies. A, Multiple infusions. ES (95% CI) is the proportion responding with its 95% confidence interval. B, Single infusion. ES (95% CI) is the proportion responding with its 95% confidence interval

of patients with IBD, solid organ transplants on immunosuppression, HIV and cancers. The CDI cure rate observed after a single FMT was 78%, with an overall cure rate of 89% following a second transplant.

3.3.3 | Comparison between upper GI and lower GI routes of delivery

The RCT that compared nasogastric (upper GI) vs colonic delivery of FMT reported a cure rate of 60% at 8 weeks with a single infusion and an overall cure rate 80% after second infusion when delivered via NG.[28] The cure rate with colonic delivery was 80% with a single infusion at 8 weeks and an overall cure rate of 100% after a second infusion.

Of the remaining studies, 25 case series and seven RCTs had separate outcome data for modes of FMT delivery. Twenty-two delivered FMT by the lower GI route (colonoscopy or retention enema) and 11 delivered FMT by the upper gastrointestinal route (upper GI endoscopy, nasogastric tube or naso-jejunal tube). Results are displayed in Figure 3. The pooled response of CDI to

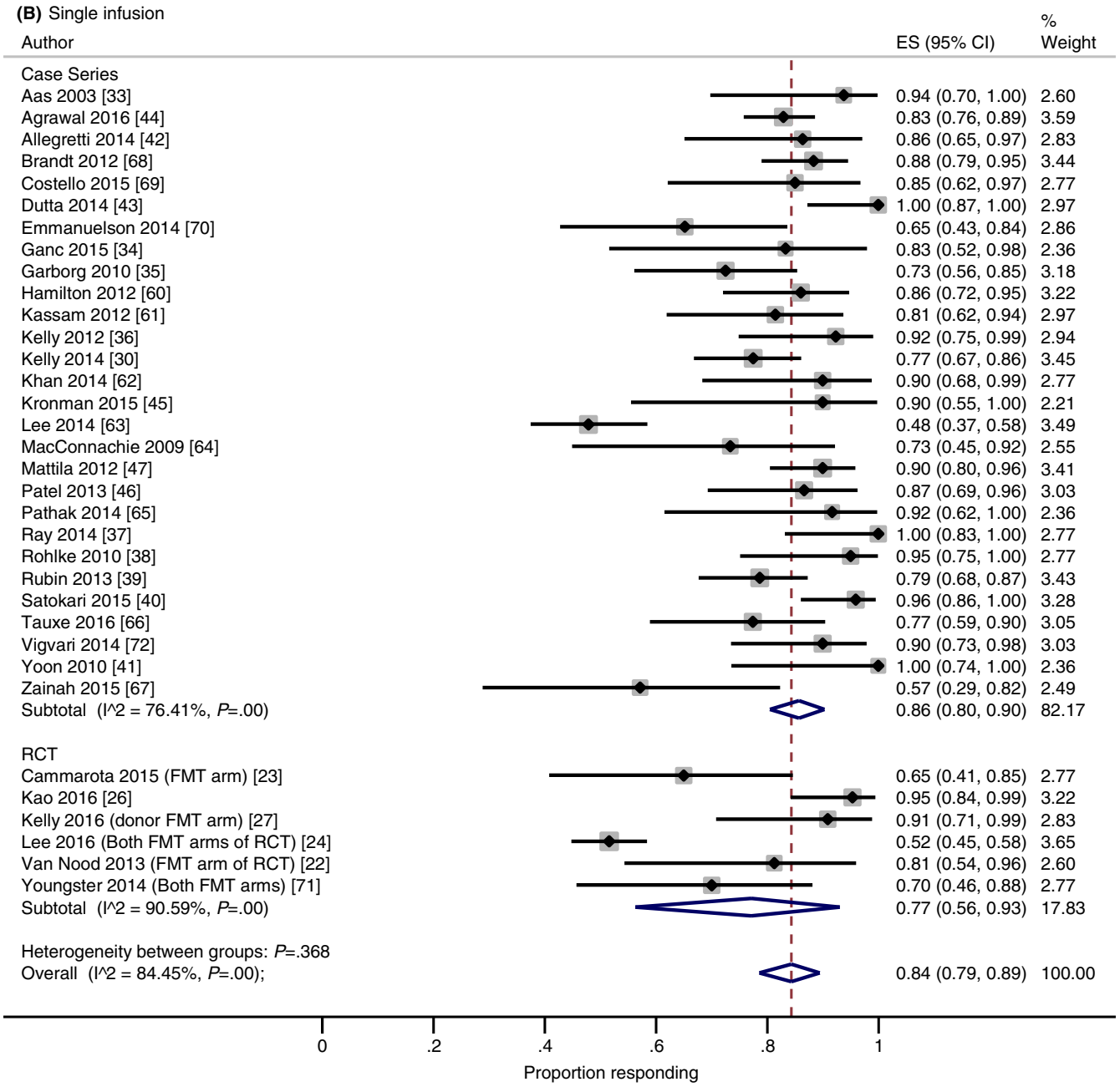

FIGURE 2 (Continued)

lower GI-delivered FMT was 95% (95% CI 92%-97%) with likely moderate heterogeneity between the studies (I^2=48%). When adjusted for funnel plot asymmetry overall response was 90%. This compared to the overall pooled response rate to upper GI FMT of 88% (95% CI 82%-94%) with moderate observed heterogeneity between the studies adjusting for funnel plot asymmetry revealing a response rate of 83%. There was evidence of a difference between the delivery methods with respect to response to FMT (*P*=.02). Analysis of cure rate with a single infusion did not show a significant difference with route of delivery with a response of CDI of 81% (95% CI 73%-88%) to lower GI-delivered FMT and of 87% (95% CI 79%-94%) for upper GI-delivered FMT (*P*=.20).

3.3.4 | Comparison of freshly prepared vs frozen FMT

In the RCT by Lee, patients received either FMT prepared no more than 5 hours earlier (n=111) or FMT frozen for up to 30 days (n=108).[24] The clinical resolution of diarrhoea using intention-to-treat analysis showed no evidence of a difference in outcome between preparations, with a relative risk of failure to respond of 1.19 (95%CI 0.77-1.84) with a 70% response in the fresh FMT group and 75% in the frozen FMT group. This increased to 85.6% and 90.7% respectively when patients were given multiple infusions FMT due to lack of response.

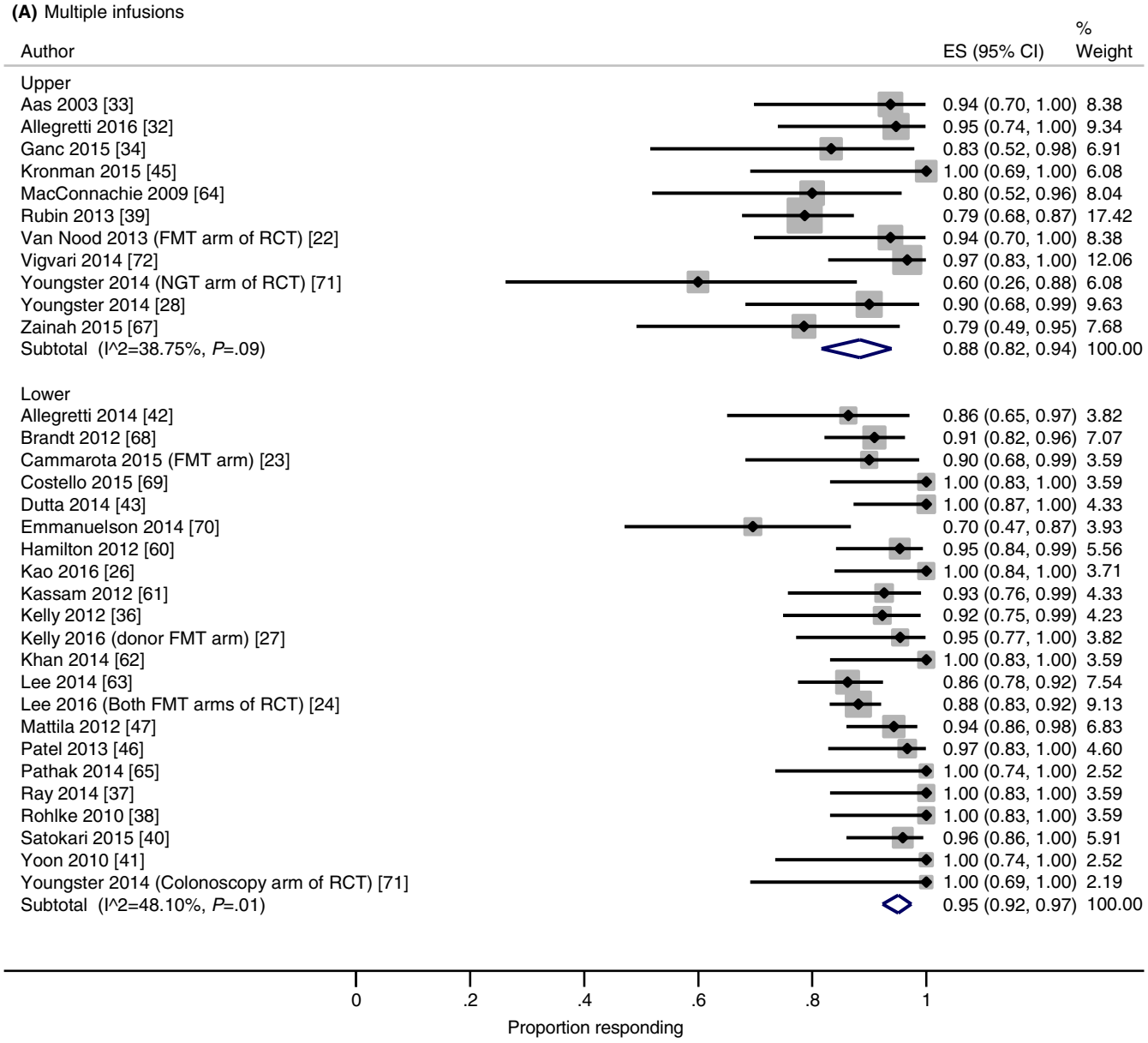

FIGURE 3 Forest plot of the proportion responding to treatment by upper GI ad lower GI routes of delivery. A, Multiple infusions. ES (95% CI) is the proportion responding with its 95% confidence interval. B, Single infusion. ES (95% CI) is the proportion responding with its 95% confidence interval

Of the other studies, 30 case studies used fresh stool and four studies (two case series, two RCTs) used frozen stool to prepare FMT and a response rate was calculable for each group. For the fresh FMT studies, the overall response rate was 92% (95% CI 89%-95%) with moderate heterogeneity between the studies (I^2=54%). When adjusted for funnel plot asymmetry, the overall response rate was 87%. The overall response in frozen FMT studies was 93% (95% CI 87%-97%) with minimal observed heterogeneity between the studies (I^2=19%). There were insufficient studies to assess funnel plot asymmetry. There was no evidence of a difference in response between the two groups (*P*=.84) (Figure 4). Analysis of a single infusion revealed a response rate of 85% (95% CI 79%-90%) for fresh FMT and a lower response rate of 68% (95% CI 47%-86%) for frozen FMT, but there was only very weak statistical evidence of a difference (*P*=.10).

3.3.5 | Adverse events

The RCT by Van Nood et al. reported no significant adverse events (SAEs) in 16 patients treated with FMT, however, there were two urinary tract infections and one patient suffered from choledocholithiasis.[22] No SAEs related to FMT were reported in other RCTs. Transient mild diarrhoea and cramping was very common in the FMT arm of three RCTs by Lee, Cammarota, Van Nood, and about 25% of the recruits in the RCT by Lee reported long term constipation and flatulence following FMT. Similarly, 19% of patients in the

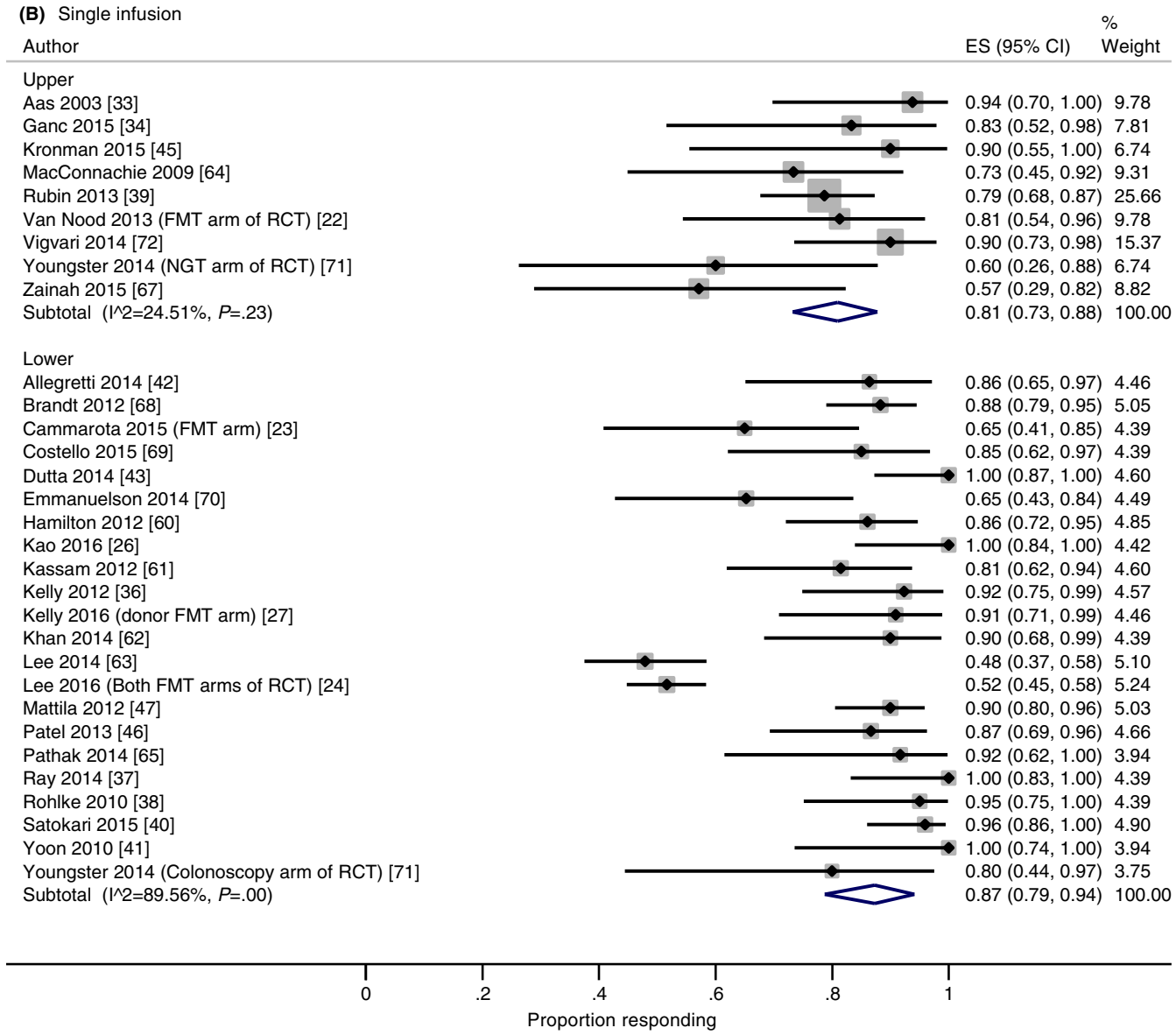

FIGURE 3 (Continued)

FMT arm reported constipation in follow-up period in the van Nood RCT. Mild abdominal pain and bloating was reported in 20% of patients treated by a frozen inoculum of FMT.[28] In the RCT by Kelly et al. comparing FMT with autologous vs heterologous (donor) stool administered by colonoscopy, chills were observed more frequently in autologous group.[27] Rates of other minor AEs did not differ significantly between groups.

In the case series, most side effects were minor and often transient: bloating, belching, abdominal cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever, urinary tract infections, self-limiting diarrhoea, and irregular bowel movement being seen. However, recurrent and refractory CDI negative diarrhoea or worsening diarrhoea following FMT was also reported although the duration of this adverse event was not reported.[37,44] The data from these case series did not allow an assessment of any differences in adverse events by route of treatment or use of fresh or frozen transplant.

There were no reported cases of aspiration following FMT delivery via the upper GI route. In one case, the patient vomited immediately after FMT application via nasogastric tube.[45] There was only one reported case of mucosal tear and micro perforation following colonoscopic delivery of FMT.[30,46] Hospitalisation with self-limited FMT related abdominal pain, was reported in one patient.[30]

There were 50 deaths reported in the studies reviewed, however, these were almost all due to critical illness of elderly patients with multiple comorbidities or unrelated illness and were not directly attributed to the FMT. However, there was a death as a result of aspiration at the time of sedation for the colonoscopy to administer the FMT.[30] Two patients with recurrent diarrhoea and initial response to the FMT died subsequently from complications of ileus and colonic perforation. Four deaths in patients infected with the ribotype 027 strain who did not respond to FMT and died within 3 months were also reported.[47]

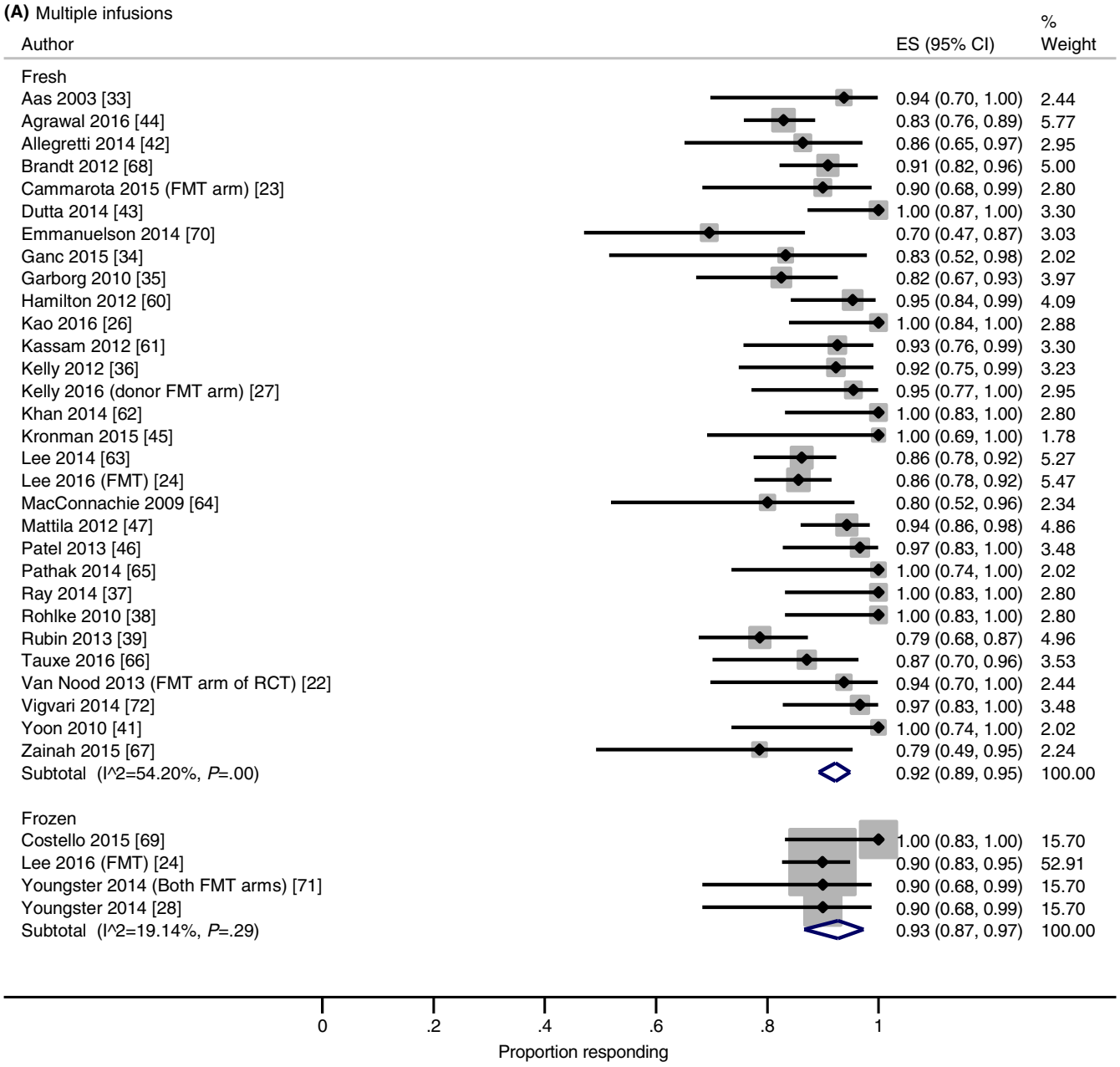

FIGURE 4 Forest plot of the proportion responding to treatment by freshly prepared vs frozen FMT. A, Multiple infusions. ES (95% CI) is the proportion responding with its 95% confidence interval. B, Single infusion. ES (95% CI) is the proportion responding with its 95% confidence interval

Of note, a case series of FMT in 80 immunocompromised patients with 3 month follow-up did not report any serious adverse events.[30] However, four patients with inflammatory bowel disease in this cohort experienced a flare up of their condition after FMT. Similarly a case series of 146 elderly patients that were followed up for 1 year did not report any serious adverse events.[48]

4 | DISCUSSION

This systematic review and meta-analysis has demonstrated that FMT is a highly effective treatment for resolution of recurrent and refractory CDI. Even the most conservative analysis gives an estimate of 49% response rate for FMT in this setting based on the lower prediction interval for a single infusion. Previous systematic reviews and meta-analyses have reported the marked efficacy of FMT for treatment of CDI in the range of 88%-92%, similar to our findings.[9,10] These, however, pre-dated or failed to include the five recent RCTs and included far fewer case series.[23,24] There is good agreement between the efficacy demonstrated in observed response rates in the seven RCTs (only three of which have a non-FMT comparator arm) performed to date and the reports from case series. The limited data on mortality and SAEs suggests that FMT is safe and generally well tolerated, even in sick immunocompromised elderly patients.[30]

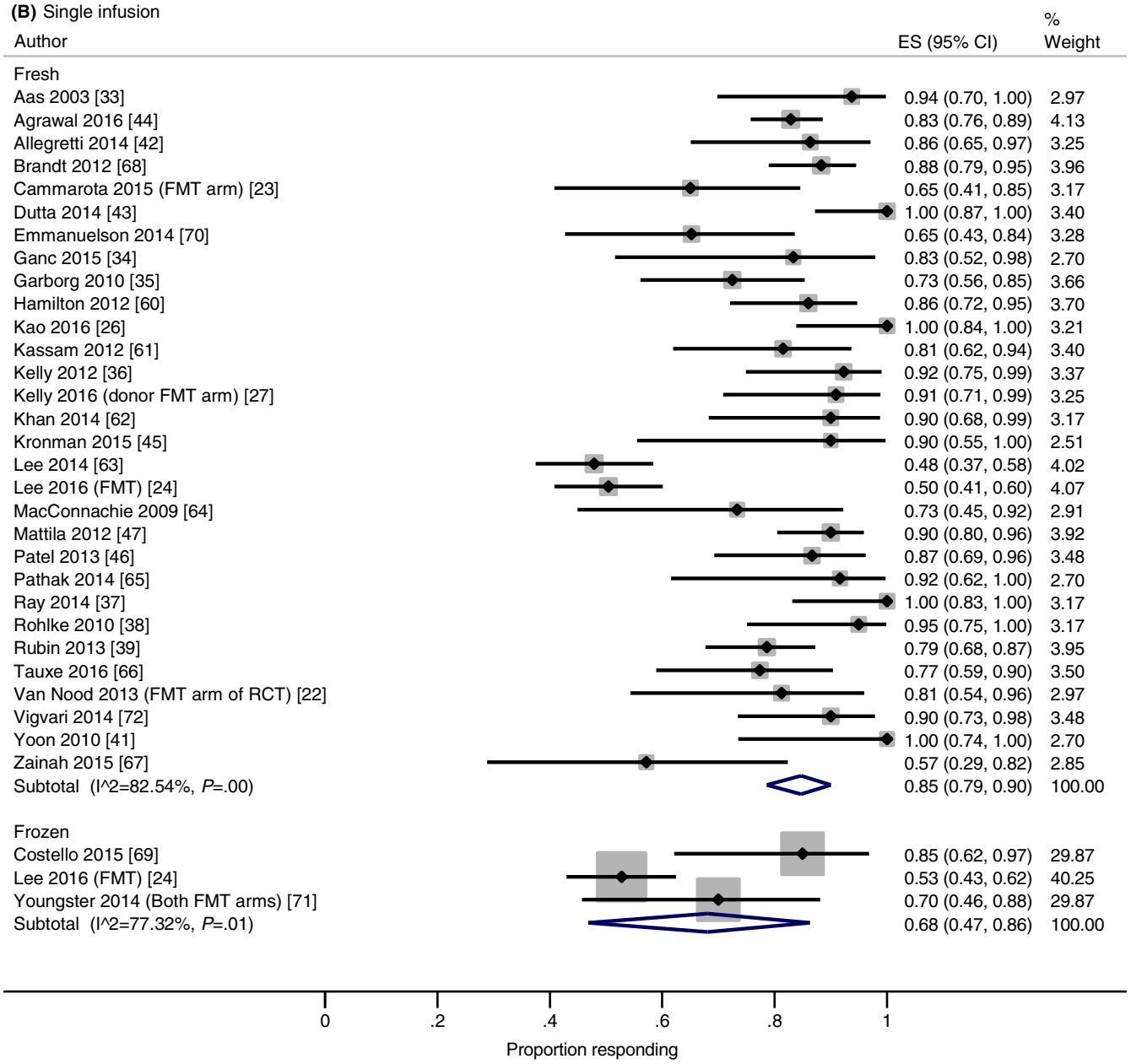

FIGURE 4 (continued)

No previous meta-analysis has compared fresh and frozen FMT in treatment of recurrent CDI, and the present study shows no difference in efficacy between these modes of stool preparation. The review also demonstrates that repeated infusions of FMT in nonresponders resulted in a higher cure rate albeit with some limited data for this analysis. Previous reviews have suggested that the efficacy for lower GI route is greater than upper GI route (Kassam et al.; 91% vs 80% respectively [*P*=.046]).[10] We have however shown that this difference was no longer significant when efficacy with only a single infusion was analysed.

With regard to attempting to differentiate between the efficacy of FMT for recurrent or refractory CDI, we found that the distinction between recurrent and refractory disease in the case series is often vaguely reported and not robust enough to allow for meaningful sub-group analysis. Similarly, previous reviewers have reported that no studies have compared refractory CDI to standard therapy and from the small numbers of patients being treated for solely refractory CDI meaningful analysis is difficult.[11,12]

This systematic review and meta-analysis is a comprehensive ascertainment of the available evidence through a detailed search strategy, and includes the seven RCTs to date. Structured analyses were performed to address key issues with regard to storage and administration of FMT that may improve wider uptake of this treatment strategy. There are, however, limitations to our analysis. Characterisation of initial/primary response depended on the authors' definitions, hence varying between studies and being sometimes poorly defined. Although almost all studies defined initial response as resolution or improvement of diarrhoea, but the time to response

varied from 1 to 90 days and the overall response varied from 7 days to 3 months. Most studies failed to report *Clostiridum difficile* toxin for assessment of clearance in several studies lacked long-term data. A recent paper has highlighted the high incidence of IBS after an attack of CDI.[48] There was significant variability in dose of FMT and several studies defined their clinical resolution following use of more than one infusion of FMT. The use of concomitant medications and other biases may be greatly underestimated given the retrospective nature of most of the case series included in this review.

The data suggest that, irrespective of route of delivery or method of preparation repeated treatments has an incremental benefit. There are no clear strategies for this and guidelines are required, as well as additional RCTs to further determine the optimal dose and long-term outcomes and side effects of FMT are required. Finally, "corrected" estimates calculated using the Trim and Fill method should be treated with great caution and as indicative as the method does not take into account reasons for funnel plot asymmetry other than publication bias and limited numbers to detect differences in subgroup analyses.[13]

Included studies exhibited substantial heterogeneity in procedural aspects of FMT preparation and delivery. However donor screening appeared to be robust and studies consistently had strict exclusion criteria based on history of high-risk behaviours, recent antibiotic use and a comprehensive serological testing for blood borne viruses and stool cultures for pathogens. FMT was prepared using water or saline along with glycerol in most studies. However, the quantity and volume of stool and solvent used to prepare the transplant was very variable.

Patients who underwent FMT via the lower GI route received a larger amount/concentration of FMT compared to those who had it delivered via the upper GI route. The number of infusions prior to achieving clinical resolution as defined by the authors also varied significantly between studies although most studies only gave a single infusion. There is little uniformity of practice with regard to treatment protocol with respect to the triggering of subsequent treatments after the first.

This review is focussed on FMT and, as such, we have not included emerging data from investigations using faecal bacteriotherapy in which the microbiota is altered or in which specific bacteria are infused.[25,49,50]

Short-term adverse events were reported in almost all the studies, however, there was lack of consistency in long-term follow-up for adverse events in uncontrolled studies and this was often reported on an ad-hoc basis. Follow-up was also limited to 10-13 weeks in RCTs. Most adverse events were self-limiting gastrointestinal symptoms including abdominal cramps, constipation, diarrhoea and usually occurred within 24 hours of the procedure and resolved within a week of the FMT. Deaths reported following FMT were almost always due to inter-current illness unrelated to CDI, FMT and overt failure to respond to FMT. On the whole, the current evidence suggests a good short-term safety of FMT, however, data are limited and uncertainty remains concerning unrecognised long-term consequences. It should also be noted that in this review studies were selected based on whether they reported an outcome related to resolution of CDI and that case series with less than ten patients were not analysed. Thus, it could be argued that this review is not comprehensive of all studies that might report adverse events.

Despite uncertainty FMT for the treatment of CDI associated colitis has been adopted as the biological rationale for its use is compelling and the treatment is cheap. The second line antibiotic treatment for CDI associated colitis after standard antibiotics (metronidazole and vancomycin) is fidaxomicin and this is vastly more expensive than FMT.[1] Moreover, there is no current evidence for fidaxomicin in the treatment of recurrent CDI and as yet no direct comparison of the effectiveness of this antibiotic against FMT.

In the UK, NICE has approved FMT "for patients for with recurrent CDI that have failed to respond to antibiotics and other treatments".[2] However, despite this official stamp of approval, standards of governance with respect to the procedure itself remain undefined. This is perhaps particularly pertinent now that manipulation of the microbiome is being considered in younger cohorts of patients for indications other than CDI associated colitis.[51,52]

Most studies appear to comply with the donor screening criteria outlined by the American Gastroenterology Association.[53,54] However, there is no agreement as to what constitutes an acceptable donor with respect to, for example, relatedness to the patient, lifestyle, diet, co-morbidity, body mass index and there is no mandate with regard to follow-up of donors. Similarly no consensus exists about fundamental aspects concerning the actual process of delivering FMT. Some investigators use the upper GI route for the administration of FMT whereas others (the majority of published studies) use colonoscopy or retention enemas. There is little evidence of uniformity with respect to stopping other treatments prior to FMT or concomitant treatments to be used to facilitate FMT. However, despite a lack of consistent approach the clinical efficacy for FMT is universally positive and much greater than that seen with antibiotics. A recent International Consensus has highlighted current uncertainties concerning route of delivery, donor selection (household members/healthy volunteers), the place of routine pre-treatment with antibiotics and bowel preparation and, in the light of long term safety concerns, the desirability of establishing a patient registry.[55] The utility of frozen FMT has gained significant interest as it allows the ability to deliver treatment on demand and to a wider population. As a result, recent regulatory discussions concerning FMT provision in the European Union have led to the situation that FMT use in the context of clinical trials is to be controlled by regulatory authorities.[56]

Data are beginning to emerge regarding the association of microbiome alteration with response to FMT. In a recent study from the USA, the authors reported specific gut microbiota signatures associated with response to or recurrence after FMT.[57] This raises the possibility of predicting which patients may not respond to primary treatment with antibiotics and those then likely to need FMT. In another intriguing study from this group, it was reported that microbiota changes associated with bile salt metabolism following FMT may also indicate patients likely to progress to recurrent CDI and the need for FMT.[58]

In the future, it is likely that we will see further data emerging from investigators who prepare "designer" FMT or by culturing

specific organisms in vitro particularly as we better understand microbiota profiles which differentiate health from disease and the profile which is associated with successful FMT.[49,50]

In conclusion, FMT appears to be an effective and apparently safe treatment strategy for recurrent and refractory CDI. The efficacy is similar in both controlled and uncontrolled studies. The current data are relatively heterogeneous with regard to the methodology for transplantation and the outcome measure for resolution of CDI. While this could be explored with the current evidence base to refine estimates and potentially suggest effect modifiers, the effect of FMT on resolution of recurrent/refractory CDI is markedly evident and appears to be quantitatively in excess of that seen with other anti-microbial therapies such as vancomycin. Further studies should be of robust design and focus on determining the optimal procedures and long-term outcomes and side effects of FMT in order that FMT is available to help alleviate the burden of this significant iatrogenic hazard.

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AUTHORSHIP

Guarantor of the article: Tariq H Iqbal.

Author contributions: TI received a commission from APT in 2015 to undertake a systematic review and meta-analysis of the literature concerning the efficacy of FMT in treating CDI. TI conceived and designed the review. DM, MNQ, MP developed the review protocol. MNQ and TI performed eligibility screening, carried out the data extraction and methodological quality assessment. MNQ, TI, NS and MW provided advice and arbitration on the selection process, data extraction and methodological quality assessment. MNQ, NS, MW and TI analysed the data. DM and MP interpreted the data. MNQ, TI, NS and NB wrote the original draft, and all authors revised the draft critically for important intellectual content and approved the final version of the paper, including the authorship list.

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SUPPORTING INFORMATION

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