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Review

Faecal microbiota transplantation for the decolonization of antibiotic-resistant bacteria in the gut: a systematic review and meta-analysis

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SUMMARY

Antibiotic resistance is a growing global problem associated with increased morbidity and mortality, and presents a significant financial and economic burden on healthcare. Faecal microbiota transplantation (FMT) has been proven effective for curing recurrent *Clostridium difficile* infections, however no systematic review to date has addressed its effectiveness for decolonization of antibiotic-resistant bacteria from the gut. The aim of this study was to establish whether faecal microbiota transplantation decolonizes antibiotic-resistant bacteria from the gut of colonized adults. A systematic review was performed by undertaking a comprehensive search on MEDLINE, Embase, CENTRAL, PubMed and CINAHL databases for evidence up until May 2018. Randomized and non-randomized studies evaluating the effects of FMT on gut colonization of antibiotic-resistant bacteria in adults were eligible. Studies were assessed using the Joanna Briggs Institution critical appraisal checklists. Quality of reporting was assessed using PROCESS and CARE checklists. Data was synthesized narratively, along with a meta-analysis of proportions for the primary outcome.

Five studies with a total number of 52 participants were included. Evidence of low quality showed that decolonization was achieved in half of the cases one month after FMT with higher response noted in *Pseudomonas aeruginosa*, and lower response in *Klebsiella pneumoniae* with New Delhi metallo-beta-lactamase 1 (NDM-1) and extended-spectrum β-lactamase (ESBL) mechanisms of resistance. In successful cases, 70% of decolonization cases occurred within the first week after FMT. Few temporary adverse events were identified.

Despite the limitations of the included studies, evidence from this review indicates a potential benefit of FMT as a decolonization intervention, which can only be confirmed by future well-designed RCTs.

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Introduction

Since their inception, antibiotics have been regarded as the panacea for treating bacterial infections in humans and animals [1,2]. However, antibiotic resistance has reduced the

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clinical effectiveness of available antibiotics tremendously as its spread outpaces the development of new treatment options [2].

The emergence of antibiotic resistance is mainly attributed to the misuse and overuse of antibiotics in agricultural and clinical settings over the years [2,3], creating a vicious cycle, where the increased use of antibiotics acts as a catalyst for antibiotic resistance and vice versa [4]. Globalization manifested by human trade and travel is also a driver of the worldwide spread of antibiotic resistance [5], along with poor practices of infection prevention and control in healthcare settings [6].

In 2014, around 700 000 deaths around the world were attributable to antimicrobial resistance each year. This number is estimated to reach 10 million deaths each year by the year 2050 if the problem of antimicrobial resistance is not tackled [7]. Additionally, the continued rise in antimicrobial resistance causes and will continue to cause a considerable financial and economic burden with an estimated global cost of £66 trillion by 2050 as a result of lengthier hospital stays and costlier intensive care. [8].

Of great concern is antibiotic resistance acquisition in Gram-negative bacteria, which are responsible for most antibiotic-resistant infections and deaths caused by antibiotic-resistant bacteria in humans [9] due to the limited existing treatment options and their development of resistance to last-line antibiotics, such as carbapenems [10].

Gut microbiota play an important role in preventing infections by exogenous pathogens through a mechanism called 'colonization resistance' by activating the body's immune responses that in turn target the pathogens, or through direct competition for nutrients and production of inhibitory substances [3,11,12]. Some of the commensal bacteria across the *Firmicutes*, *Bacteroidetes* and *Actinobacteria* phyla that confer this mechanism of colonization resistance have been identified [3].

However, exposure to antibiotics, especially broad-spectrum, alters the composition of the gut microbiota creating favourable conditions for the upregulation and rapid spread of antibiotic-resistance genes via horizontal-gene transfer and allows antibiotic-resistant and opportunistic bacteria to predominate and cause infections [3,13,14].

Based on the beneficial role of the gut microbiota, faecal microbiota transplantation (FMT), has gained international interest recently [11,15]. It includes the infusion of faecal material obtained from the faeces of a healthy donor into the dysbiotic gut of a recipient with the aim of restoring its healthy ecological state [16,17].

FMT has particularly gained popularity in the treatment of recurrent *Clostridium difficile* infections due to its ease of use, feasibility and efficacy [18,19], especially after an RCT showed its superiority over standard treatment [20]. Intestinal microbiota composition similar to the donors' is seen in recipients after FMT, with reconstitution of intestinal bacterial populations across phyla that persists for a long time [21,22].

In a murine model of gut colonization with vancomycin-resistant enterococci (VRE), Ubeda *et al.* [23] showed that faecal transplantation eradicated VRE colonization, which prompted further studies in humans for the potential of FMT in decolonizing various antibiotic-resistant bacteria from the gut. Some of these studies are identified and listed in a number of reviews [24—26].

Following a scoping search on the Cochrane Database of Systematic Reviews and PROSPERO in February 2018, no systematic review to date was identified examining the preliminary effectiveness of this procedure in decolonizing antibiotic-resistant bacteria from the gut. Hence, the aim of this systematic review is to answer the following research question: does FMT decolonize antibiotic-resistant bacteria from the gut of colonized adults?

Objectives

The primary objective was to assess the decolonization success rate at the 1-month time point after FMT in adults colonized by antibiotic-resistant bacteria in their gut. Success rate was defined as loss of detectable carriage by microbiological testing. Secondary objectives were: (1) to identify the antibiotic-resistant bacteria that FMT is most successful in decolonizing; (2) to identify the time frame for achievement of decolonization in participants; (3) to identify the adverse effects associated with the FMT procedure.

Methods

The Cochrane methodology [27], which guides systematic reviews of the effects of interventions, was followed in conducting this systematic review. Although this methodology mainly guides systematic reviews of randomized trials, it is also applicable for systematic reviews including non-randomized studies following the same format and methods [28].

An *a priori* protocol was not developed due to time constraints, and ethical approval was not necessary due to the exclusive use of secondary data [29].

Study selection criteria

Types of studies

Studies evaluating the effects of FMT on antibiotic-resistant bacteria gut colonization were eligible. Randomized and non-randomized observational studies, such as before-and-after studies, cohort studies, case series and case reports were considered. Literature reviews around this topic and expert opinion were excluded.

No time restriction was outlined, because studies were anticipated to be recent. Only studies reported in the English language were considered.

Types of participants

The population considered was adults (>18 years old) colonized by antibiotic-resistant bacteria in the gut. Drug-resistant organisms that are not bacteria, such as viruses and fungi, were excluded, as were patients colonized with antibiotic-resistant bacteria in the body outside the gut. The paediatric population was also excluded, because the gut microbiota composition is different from that of the adult population as it continues to mature with age [30]. The dynamically developing paediatric gut microbiome differs from the relatively stable adult microbiome [31,32] and hence the outcome and composition of the microbiota following FMT would be incomparable to those of adults. As such, for the purpose of this review, only adults were considered. Other exclusions included patients receiving antibiotic therapy concomitantly within the duration of the FMT procedure, because

the composition of the transplanted FMT could be affected [33]. However, patients whose antibiotic therapy was discontinued at least 24 h before the procedure were considered.

Upon further consideration, patients who had recurrent or refractory *C. difficile* infections in addition to antibiotic-resistant bacteria at time of FMT were excluded. *C. difficile* is not significantly resistant to antibiotics, hence the suppressive mechanisms of the gut microbiota on *C. difficile* infections might be different than on antibiotic-resistant bacteria decolonization, which this review aims to elucidate [25,34,35].

Types of interventions

Studies were included in which FMT was evaluated for effectiveness as a single intervention trial arm or compared to standard treatment of antibiotics, placebo or no treatment. FMT offered through various modalities, such as via the upper or lower gastrointestinal route, or orally via microbiota-based capsules were all considered. Both fresh and frozen FMT were included, as well as, FMT procured from both related and unrelated donors.

Types of outcome measures

The primary outcome of interest is decolonization rate of antibiotic-resistant bacteria in the gut assessed at least 1 month (30 days) after FMT from rectal swab or stool samples. Decolonization rate was defined as number of participants decolonized from antibiotic-resistant bacteria to total number of participants at a certain time point.

Ideally, decolonization would be evidenced by three separate negative rectal swabs, with at least one confirmed by PCR [36]. However, for the purpose of this review, the decolonization success definitions delineated by the individual studies were accepted.

Secondary outcomes include time frame for achievement of decolonization and adverse effects of FMT.

A summary of the inclusion and exclusion criteria is presented in Supplementary Table S1.

Search strategy

A systematic literature search for eligible studies up until May 2018 was undertaken on MEDLINE (1946 to May week 3 2018), Embase (1974 to May week 3 2018), CENTRAL (1898 to May week 4 2018), PubMed (1950 to May week 4 2018), and CINAHL (1961 to May week 4) databases.

The PICO framework was used to construct a facet analysis based on the population, intervention, and outcome elements of the research question (Supplementary Table S2). This allowed the generation of an exhaustive search strategy for database searching. The search terms within each facet were combined with the Boolean operator 'OR', and the results from each facet search were combined with the Boolean operator 'AND'. The resulting hits were limited to studies on humans and English language, but no date restriction was applied. The full electronic search strategy for the MEDLINE database is presented in Supplementary Table S3.

To identify further studies that might not have been captured through an electronic search, reference lists of relevant and included papers were screened and citation tracking was performed on search engines when possible. OpenGrey was searched for the identification of grey literature, which is literature that is not formally published.

Data collection and analysis

Study selection

After search completion, duplicates were removed using the bibliographic software Endnote X8. The remaining records were screened for eligibility by reviewing their titles and abstracts, and those meeting the inclusion criteria *prima facie* were considered. Full-text papers of the remaining articles were retrieved to assess them for eligibility against the inclusion and exclusion criteria. Eligible studies were included in the systematic review, while studies that did not fulfil the criteria were excluded and reasons stated (Supplementary Table S4).

Data extraction

Data extraction from the included studies was performed by the reviewer from the full-text articles, as well as the online appendices of two studies [37,38] using a data extraction form, which was adapted from an existing data extraction form [39] (Supplementary Table S5). The data extracted include: name of lead author, year of publication, country, setting, study aim, study design, number of participants and their characteristics, and information on the FMT procedures. The primary outcome of decolonization rate at 1 month was extracted along with the individual studies' definition of decolonization success. In addition, time frame to decolonization, and data on adverse events were also extracted to meet the objectives of this review.

For missing data or clarification, three study authors were contacted via email correspondence [40—42]. However, response was received from one study author [40] (Supplementary Table S6).

Quality assessment

For the assessment of risk of bias in non-randomized studies of interventions, the Cochrane Collaboration suggests the use of the ROBINS-I tool, which is specifically designed for observational studies, such as cohort, case—control, and cross-sectional studies [43]. However, because the identified studies in this systematic review were case series and case reports, this tool was deemed unsuitable.

In such cases, the Cochrane Collaboration advises that reviewers choose a tool suitable for their review. Therefore, the quality of included studies was assessed using the Joanna Briggs Institution (JBI) standardized critical appraisal checklists for case series and case reports [44].

The checklists were firstly used to assess the methodological quality of the studies, as having poor, moderate or good quality against preset criteria developed by the reviewer, as recommended by JBI [45] (Supplementary Table S7). The questions in the checklists that addressed selection, performance, detection and reporting biases were considered for weighing of the methodological quality. This allowed the exclusion of studies with low methodological quality before commencing the data extraction process. An answer of 'no' to three or more of the questions deemed the study to be of poor quality and was regarded as a threshold for exclusion from the systematic review.

The results of the critical appraisal of the included studies were interpreted in terms of risk of bias domains that non-

randomized studies are subject to, such as selection bias, performance bias, detection bias, reporting bias, confounding bias, attrition bias, publication bias and other biases [46].

Due to their descriptive nature, quality of reporting of the studies was assessed using an adapted version of the PROCESS guidelines for case series and CARE guidelines for case reports [47,48]. Quality of evidence was assessed following the GRADE recommendations [49] and completed on the GRADEpro online software.

Measures of treatment effect

The treatment effect of decolonization at the 1-month time point was extracted and presented in the form of proportions. Due to the lack of a comparator group in case series and case reports, it was not possible to calculate measures of relative effect, such as odds ratio or risk ratio [50].

Antibiotic-resistant bacteria decolonized at the 1-month time point with respect to pathogen type and mechanism of resistance were also extracted and presented in the form of proportions and percentages, as were the time frames for achievement of decolonization in successful cases at the end of each study per pathogen type and mechanism of resistance. Adverse events were presented narratively due to the lack of individual participant outcome data.

Data synthesis

A narrative synthesis rather than a statistical one was undertaken for all pre-specified primary and secondary outcomes to summarize and explain the findings of the review [29].

Meta-analysis was conducted only for the primary outcome, that is decolonization success at the 1-month time point. The outcomes were dichotomous data, where outcome can be expressed as one of two possible responses; in this case, decolonization success or failure.

Accommodating for the types of studies in this systematic review that lacked a comparator group, a meta-analysis of proportions under the random-effects model [51] was suitable for case series [52,53] using StatsDirect v3 statistical software. Raw data of number of events (decolonization) and total number of participants in each study were entered into StatsDirect, which allowed the automatic generation of proportions. Case reports were excluded from the meta-analysis, because data from individual cases does not allow the estimation of an effect size and for which, therefore, only narrative synthesis is appropriate [53].

Clinical and methodological heterogeneity across the included studies were assessed descriptively, while statistical heterogeneity in the conducted meta-analysis for the primary outcome was assessed under the random-effects model [51] by calculating the I^2, Cochran's Q test and the associated *P*-value. A *P*-value of $\leq$0.1 was considered statistically significant for the presence of heterogeneity rather than the conventional *P*-value of 0.05, because Cochran's Q test has low power in meta-analysis when few studies are included, or studies are of small sample size [50]. The I^2 statistics allowed the quantification of inconsistency, which depicts the percentage of variability across studies that is due to heterogeneity rather than random error or chance [50]. The I^2 value was interpreted as follows: I^2 $<$50%: low heterogeneity; I^2 50–75%: moderate heterogeneity; I^2 $\geq$75%: high heterogeneity [50].

Results

The search strategy yielded 343 studies, none of which were obtained from grey literature. After removal of duplicates, the titles and abstracts of 175 studies were screened for eligibility. Twenty-eight full-text articles were assessed against the preset inclusion and exclusion criteria, resulting in seven eligible studies. However, after critical appraisal, two case reports were deemed of poor methodological quality and, according to the set criteria, were excluded from the review. This is described in further detail in the section 'Assessment of quality' below. Hence, only five studies were included in this review [37,38,40,54,55]. The process of the selection of studies is summarized in a PRISMA flow diagram [56] (Figure 1).

All five studies were conducted in hospital settings in European countries (Poland, France, The Netherlands), published in peer-reviewed medical journals and recent, ranging from 2014 to 2018. Of the five studies included in this review, three were case series [37,38,40], exploring the effects of FMT on decolonization of antibiotic-resistant bacteria from the gut using before-and-after design. One of the case series compared decolonization rate between two intervention groups (carbapenem-resistant *Enterobacteriaceae* (CRE) vs. VRE) receiving FMT without a control group [40]. While two were case studies [54,55] that reported cases where FMT was administered in an attempt to decolonize the patients.

All participants in included studies, total of 54, were adult patients with ages ranging from 21 to 80 years of age, and sample sizes ranged from 1 to 20 participants. In addition, recruited participants were colonized by various antibiotic-resistant bacteria in the gut, particularly CRE and VRE. Some participants across studies were colonized by only one antibiotic-resistant bacteria, while others were colonized with more than one. However, one study included a patient that had recurrent *C. difficile* infection at time of FMT and a patient who did not meet time point of 1-month follow up, hence these two participants were excluded from this review [37].

All studies, particularly case series, used somewhat similar eligibility criteria for participant recruitment, such as confirmation of colonization status prior to FMT, not severely immunocompromised, and not requiring concomitant antibiotic treatment. However, one described inclusion criteria in less detail [38].

The clinical diagnoses and comorbidities of the participants across studies included patients with blood disorders, renal failure, renal transplant, cardiovascular disease, diabetes mellitus types I and II, recurrent urinary tract infections [37,38,40,54,55].

The FMTs in all the included studies were procured from unrelated donors. All studies used fresh FMT, except for one that used frozen FMT [40]. All studies diluted the faecal samples with varying amounts of saline solution. The study that used frozen FMT, additionally used glycerol 10% solution for preservation [40]. All studies administered the FMT via the same route, intraduodenally through a nasoduodenal tube. Some of the studies [38,54,55] reported following the same protocol for FMT administration as the FECAL trial [20]. All studies administered FMT as a single procedure, except for one that administered FMT divided into two doses on two consecutive days [37]. All participants underwent FMT once, except for some patients in two studies, where they underwent repeat-FMT twice or three times at different time points during follow-up [37,38].

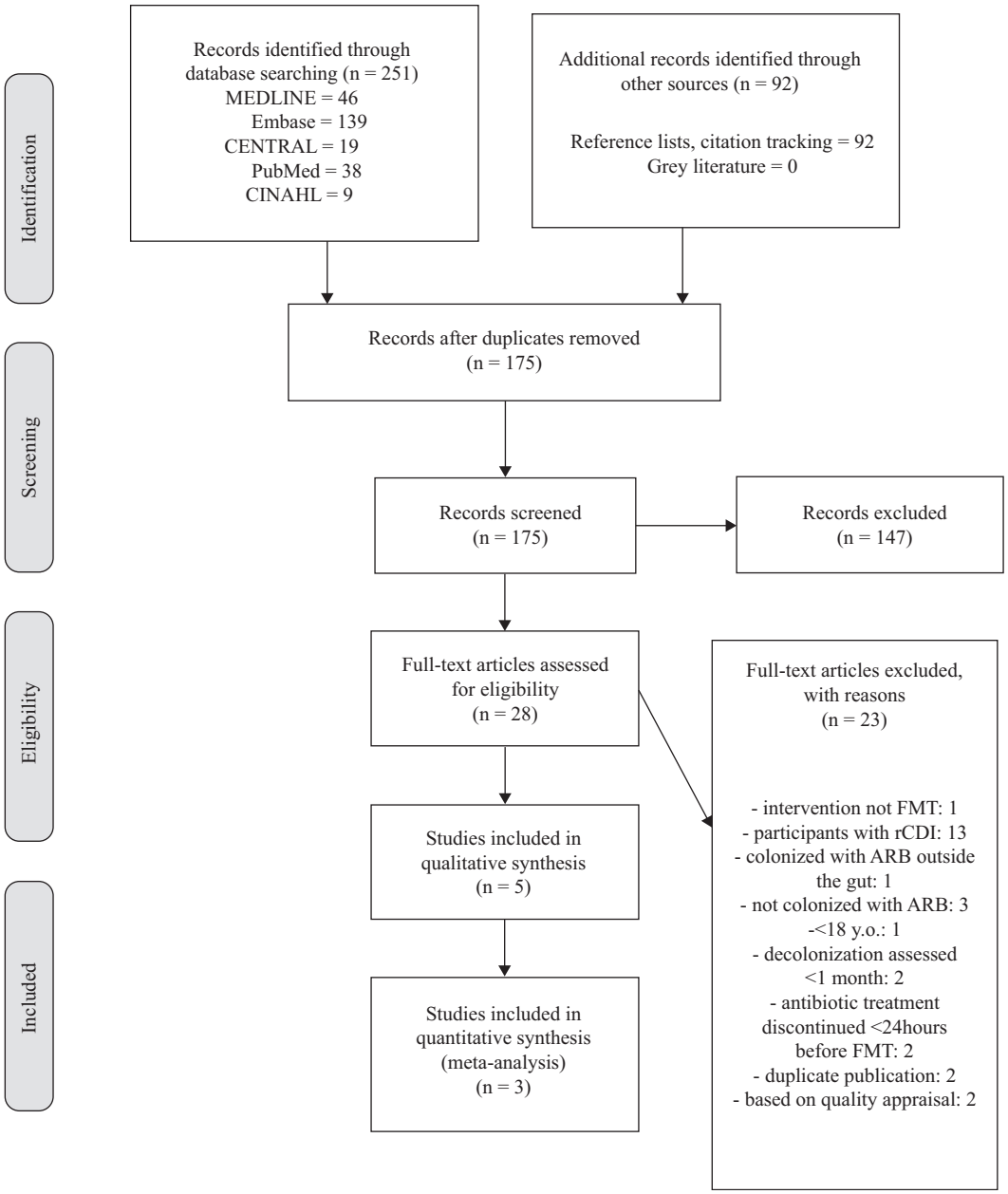

Figure 1. PRISMA flow diagram.

All included studies assessed decolonization rates after FMT infusion at different time points, ranging from 1 week to 6 months, using microbiological testing, culture and PCR. Additionally, some studies performed microbiota composition analyses via Next Generation Sequencing and amplification of the 16S rRNA gene or DNA microarrays [37,38,55] to compare microbiota abundance at species and phyla level before and after FMT. There was no significant difference in the diversity and composition of microbiota in responders and non-responders in two studies [37,38]. The characteristics of the included studies are summarized in Table I.

Assessment of quality

Based on the preset criteria, critical appraisal of the seven initially eligible studies using the JBI critical appraisal checklists resulted in the exclusion of two case reports from the review [41,42] due to poor methodological quality, as evidenced by five 'no' answers to the checklist questions, including the critical questions set by this review.

Five studies met the critical appraisal quality criteria and were included [37,38,40,54,55]. The completed checklists of all eligible studies can be found in Supplementary Data S8.

Summaries of the results obtained from the critical appraisal checklists for case series and case reports are presented in Supplementary Tables S9 and S10, respectively.

According to critical appraisal, the included studies are considered of moderate to high methodological quality. Some questions relating to the consecutiveness and completeness of inclusion of participants were unclear across the case series [37,38,40]. In addition, one study did not have clear eligibility

Table I
Characteristics of included studies

	Bilinski *et al.*, 2017 [37]	Dinh *et al.*, 2018 [40]	Singh *et al.*, 2018 [38]	Singh *et al.*, 2014 [54]	Stalenhoef *et al.*, 2017 [55]
Study type	Prospective, single-centre case series	Prospective, multi-centre comparative case series	Single-centre case series	Case report	Case report
Study aims	To test hypothesis: FMT can eradicate ARB in the human gut	To evaluate time to successful decolonization in CRE vs. VRE using FMT	To investigate decolonization of ESBL-producing Enterobacteriaceae using FMT	To attempt to decolonize patient from ESBL-producing *Escherichia coli* using FMT	To attempt to decolonize patient from ESBL-producing *E. coli* using FMT
Sample size/intervention	20	17	15	1	1
Participants meeting eligibility criteria for this review	18	17	15	1	1
Age, mean (SD) years	49.5 (18.67)	69.05 (12.77)	56.46 (14.59)	60	34
Sex (male, %)	70%	65%	33%	Male	Male
Study inclusion criteria	Age $\geq$ 18 years Colonization of the GI tract with ARB documented by at least two positive cultures of rectal swabs taken $<$2 weeks before FMT ANC on the day of FMT $\geq$5 $\times$ 10^8 neutrophils/L Written informed consent	Age $\geq$ 18 years Colonization of the GI tract with CRE or VRE confirmed by at least three consecutive positive cultures of rectal swabs at weekly intervals with last one taken 1 week before FMT Written informed consent	Colonization of the GI tract with ESBL-producing bacteria confirmed by positive rectal swabs upon retesting Life expectancy $>$ 6 months Written informed consent	N/A	N/A
Study exclusion criteria	- Planned use of strong myelosuppressive chemotherapy $<$2 days after FMT - Underwent HCT $<$ 1 month ago - Clinical signs of mucositis - Severe hepatic impairment - Requirement for intensive antimicrobial therapy	- Immunosuppression (HIV with CD4 $<$200 mm^3, immunosuppressive therapy including chemotherapy, corticosteroids $>$ 60mg/day $>$ 5days - Concomitant antibiotic use at the time of FMT - Previous CDI treated by FMT - Pregnancy or breastfeeding	- Severe immunodeficiency (CD4$<$ 200cells/μL) - Food allergies	N/A	N/A
Colonization status before FMT	*E. coli* ESBL+ *E. coli* OXA-48+ *K. pneumoniae* NDM-1+ *K. pneumoniae* ESBL+ Carbapenem-resistant *K. pneumoniae* VRE	*K. pneumoniae* NDM-1+ *K. pneumoniae* OXA-48+ *E. coli* OXA-48+ *E. faecium* VanA, VanB	*K. pneumoniae* ESBL+ *E. coli* ESBL+	*E. coli* ESBL+	*E. coli* ESBL+

(*continued on next page*)

Table I (*continued*)

		Bilinski *et al.*, 2017 [37]	Dinh *et al.*, 2018 [40]	Singh *et al.*, 2018 [38]	Singh *et al.*, 2014 [54]	Stalenhoef *et al.*, 2017 [55]
		Carbapenem-resistant *P. aeruginosa* *P. aeruginosa* MBL+ *S. maltophilia* *A. ursingii* MBL+				
Colonization confirmation		2 positive rectal swabs < 2 weeks before FMT	3 consecutive positive rectal swabs, weekly intervals, last one in the week before FMT	Positive rectal swab in the week before FMT	Four positive rectal swabs, one prior to FMT	Positive rectal swab months before and positive stool culture a day before FMT
FMT	Donor	Unrelated	Unrelated	Unrelated	Unrelated	Unrelated
	Fresh/Frozen	Fresh	Frozen and preserved at -80°C	Fresh	Fresh	Fresh
	Dilution	100 g of faeces diluted with 200 mL of saline solution	70—100 g of faeces diluted with 250 mL saline/glycerol 10% solution	200—300g of faeces diluted with 500 mL saline solution	Faeces diluted with 500 mL saline solution	75 g of faeces diluted with saline solution
	Route	Intraduodenally via a nasoduodenal tube	Intraduodenally via a nasoduodenal tube	Intraduodenally via a nasoduodenal tube	Intraduodenally via a nasoduodenal tube	Intraduodenally via a nasoduodenal tube
	Mode	2-day FMT, 50 g/100 mL administered on two consecutive days	1-day FMT	1-day FMT	1-day FMT	1-day FMT
	Repeat-FMT	20%	Nil	47%	Nil	nil
Patient preparation	Antibiotics	Discontinued at least one day before FMT	No antibiotics before FMT	No antibiotics before or during FMT	No antibiotics before FMT	Discontinued 6 weeks before FMT
	PPI	PO or IV PPI administered the evening before FMT, BID on day of FMT	PO PPI during 2 days before FMT	? Unknown	? Unknown	? Unknown
	NPO	Kept NPO from afternoon before FMT and 2 h after (except fluids)	? Unknown	Overnight NPO	? Unknown	? Unknown
	Bowel cleansing	Single dose phosphate macrogol PO (Fortrans)	X-prep solution (sennosides)	Macrogol solution (Klean-prep) one day before FMT	4 L of macrogol solution (Klean-prep)	4 L of macrogol solution (Klean-prep)
Length of follow up		Intended: 6 months Mean (range): 187 days (9—482)	Intended: 3 months	Intended: 4 weeks, another 4 weeks for repeat FMTs	12 weeks	3 months
Assessment time points		1 week 1 month 6 months	1 week1 month 2 weeks2 months 3 weeks3 months	1 week 2 weeks 1 month	1 week1 month 2 weeks12 weeks	1 week2 months 2 weeks3 months 1 month
Source of funding		Statutory funding from the Medical University of Warsaw	Internal funding	Supported by grant	? Unknown	? Unknown

ANC, absolute neutrophil count; ARB, antibiotic, resistant bacteria; BID, twice a day; CD4, cluster of differentiation 4; CRE, carbapenem-resistant Enterobacteriaceae; CDI, *Clostridium difficile* infection; ESBL, extended-spectrum beta-lactamase; FMT, faecal microbiota transplantation; GI, gastrointestinal; HCT, haematopoietic cell transplant; HIV, human immunodeficiency virus; IV, intravenous; MBL, metallo-beta-lactamase; NDM, New Delhi metallo-beta-lactamase; NPO, nil per os (nothing by mouth); OXA, oxacillinase; PO, per os (by mouth); PPI, proton pump inhibitor; SD, standard deviation; VanA/VanB, vancomycin, resistance genes; VRE, vancomycin, resistant enterococci.

criteria [38], while another did not describe microbiological assessment methods in detail [54].

Risk of bias

Overall, based on the results of critical appraisal of the studies, risk of bias was assessed to be either unclear or high across most domains sufficient to affect the interpretation of results and confidence in relationship between intervention and effect [46]. This was mainly attributed to the study designs, which are inherently prone to bias [57]. Risk of bias across studies is summarized in Supplementary Table S11.

Blinding of data collectors and outcome assessors was not reported in any of the studies, which is a potential source of bias. However, measures were taken for the standard and reliable measurement of decolonization outcomes among all participants in all studies, using standard microbiological and molecular tests for detection of antibiotic-resistant bacteria, except for Singh *et al.* [54], who did not provide information on the microbiological assessment methods.

Because all studies were non-randomized, they were considered at high risk for confounding bias, due to dissimilar age, sex, clinical diagnosis at baseline, and use of antibiotics after FMT in some of the studies [37,40], which could have confounded the outcomes [29]. Although these characteristics were documented, most were not taken into account when discussing outcomes. Also, staff adherence to infection control and prevention practices is unreported, which could have contributed to recolonization and transmission of pathogens among patients.

Studies were also found to be at high risk of selective outcome reporting. Singh *et al.*'s [38] study protocol was registered retrospectively, which precludes comparing the intended methodology and the actual study conduction. As per their study protocol, Dinh *et al.* [40] intended to follow up patients up to 6 months, however outcomes up to only 3 months were reported in their published paper without addressing this discrepancy. Bilinski *et al.* [37] reported that complete decolonization was achieved in 15/20 of their study participants, including those who underwent repeat FMTs. However, when individual participant data were examined, decolonization was evident in 13/20 participants. The remaining two participants, who were considered to be decolonized by the study authors, were in fact recolonized by antibiotic-resistant bacteria 6 months and 26 weeks after FMT and underwent repeat-FMTs, after which decolonization was not achieved.

Assessment of quality of reporting

According to the PROCESS [47] and CARE checklists [48], overall quality of reporting was poor to moderate, with lack of reporting identified chiefly in the reporting of methods and results, which affected assessment of risk of bias.

The completed PROCESS checklists for case series, and CARE checklists for case reports can be found in Supplementary Data S12 (Table 1).

Effects of interventions

Decolonization rate at 1-month time point

In their case series, Bilinski *et al.* [37] showed decolonization of various antibiotic-resistant bacteria was achieved in 12/18 (67%) patients 1 month after undergoing FMT, 18 being the number of patients that met the review criteria. Combining the total number of patients in Dinh *et al.*'s [40] study rather than the two separate intervention groups of CRE and VRE, identified 9/17 (53%) patients were decolonized from antibiotic-resistant bacteria at 1 month. In Singh *et al.*'s [38] case series, 3/15 (20%) patients were decolonized at 1 month. Conversely, Singh *et al.*'s [54] case report showed success, while Stalenhoef *et al.* [55] showed failure in decolonization in their patient case at the 1-month time point. A summary of the decolonization outcome at the 1-month time point is presented in Table II showing that decolonization was achieved in 25/52 (48.1%) patient cases included in this review (Table III).

Additionally, a meta-analysis of proportions for this outcome on the three case series [37,38,40] shows that FMT was successful in decolonizing antibiotic-resistant bacteria from the gut of participants in 46% (24/50) of the cases (0.46 95% confidence interval (CI) 0.20–0.74), presented in a forest plot (Figure 2). The details of the meta-analysis are included in Supplementary Data S13.

Antibiotic-resistant bacteria that FMT is most successful in decolonizing

Subgroup analysis was not appropriate to be conducted due to small sample sizes of the few included studies, which would lead to erroneous conclusions [58]. Hence, results are presented as percentages (Table III). The results vary; however, decolonization was achieved in more than 48% of each pathogen colonization case with the highest success in eradicating *P. aeruginosa* at 1 month (100% decolonization in four cases). Based on the mechanism of resistance of pathogens,

Table II
Decolonization success rate at the 1-month time point

Study	Definition of decolonization	n decolonized	Total N	Percentage
Bilinski *et al.*, 2017 [37]	At least two consecutive negative rectal swab cultures (±qPCR for CPE ARG)	12	18	67%
Dinh *et al.*, 2018 [40]	At least two consecutive negative rectal swabs (culture + PCR) with 24-h interval	9	17	53%
Singh *et al.*, 2018 [38]	Negative rectal swab cultures	3	15	20%
Singh *et al.*, 2014 [54]	Negative rectal swab cultures	1	1	100%
Stalenhoef *et al.*, 2017 [55]	Negative stool sample cultures	0	1	0%
Total		25	52	48.1%

ARG, antibiotic-resistance genes; CPE, carbapenem-producing Enterobacteriaceae; qPCR, quantitative polymerase chain reaction.

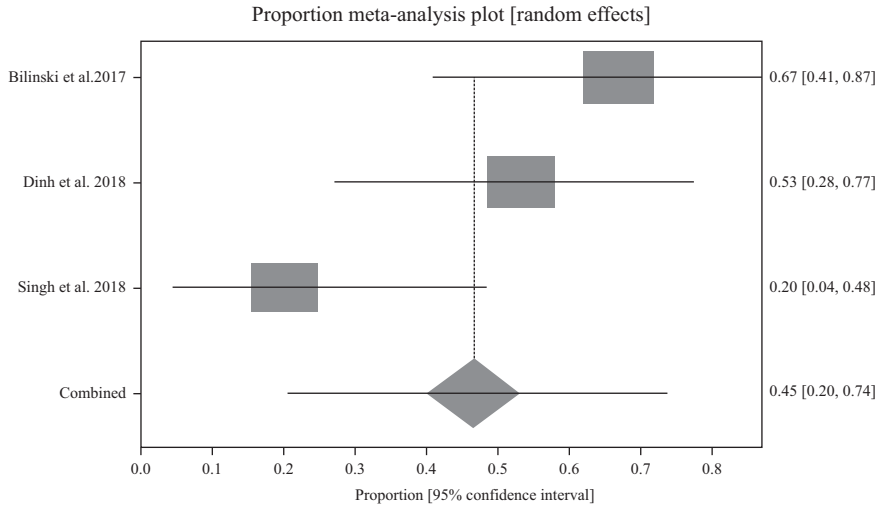

Figure 2. Forest plot, meta-analysis of proportions for decolonization success at 1 month.

K. pneumoniae with the NDM-1 and ESBL resistance genes appear to be the least responsive to FMT with a decolonization rate of 36.4% and 40%, respectively, at 1 month (Table IV).

Time frame for achievement of decolonization

Similarly, to evaluate the time frame for achievement of decolonization in successful cases, it was inappropriate to perform subgroup analysis due to the limited number of studies of small sample sizes [58]. Thus, results are presented in proportions. To note that decolonization could have been achieved any time before the specified follow up time points in the studies. Hence, these time points are arbitrary.

The results presented in Table IV signify that in 47 successful decolonization cases at the last follow up across studies, 70% were achieved within the first week following FMT (Table V).

Adverse Effects of FMT procedure

As reported by the studies, participants experienced mild temporary discomfort including vomiting, loose stools and diarrhoea, abdominal cramps and abdominal pain [37,38,40,54,55].

Bilinski *et al.* [37] provided more detail on the clinical outcome of their patients during the 6-month follow-up period showing that four patients (22%) experienced recolonization and a few patients experienced spontaneous decolonization.

Six patients across the studies died during the time period of conduction of the studies due to underlying disease.

Assessment of heterogeneity

Clinical heterogeneity

Great clinical variability was noted in the included studies. Firstly, participants were colonized in the gut by a variety of antibiotic-resistant bacteria with different characteristics: Gram-negative and Gram-positive; diverse mechanisms of resistance: ESBL, NDM-1, OXA-48, MBL, VanA, VanB; and clinical diagnoses. Age was somewhat similar across studies, however more male participants were noted in the studies except for Singh *et al.*, [38] who had more females.

Regarding the intervention of FMT, the method of preparation and administration was highly similar across studies. It was

Table III
Decolonization of particular pathogens and strains at the 1-month time point

Pathogen/mechanism of resistance			*n* dec.	Total	%	% Pathogen
Klebsiella pneumoniae	NDM-1$^+$		4	11	36.4%	48%
	ESBL$^+$		2	5	40%	
	OXA-48$^+$		3	6	50%	
	Other, carbapenem-resistant		3	3	100%	
Pseudomonas aeruginosa	MBL$^+$		2	2	100%	100%
	Other, carbapenem-resistant		2	2	100%	
Escherichia coli	ESBL$^+$		15	26	57.7%	58.6%
	OXA-48$^+$		2	3	66.7%	
VRE	*Enterococcus faecium*	VanA	5	8	62.5%	66.7%
		VanB	1	2	50%	
	Other		2	2	100%	
Stenotrophomonas maltophilia			1	1	100%	100%
Acinetobacter ursingii MBL$^+$			1	1	100%	100%

ESBL, extended spectrum beta-lactamase; dec., decolonized; MBL, metallo-beta-lactamase; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillinase; VanA/VanB, vancomycin-resistance genes; VRE-vancomycin-resistant enterococci.

Table IV
Time frame for achievement of decolonization in successful cases

ARB/mechanism of resistance			*n* dec.	1W	2W	3W	1M	5W	2M	3M
Klebsiella pneumoniae	NDM$^+$		4	4/4*						
	ESBL$^+$		1	1/1						
	OXA-48$^+$		3	2/3	1/3					
	Other, carbapenem-resistant		3	2/3			1/3			
Pseudomonas aeruginosa	MBL$^+$		2	2/2						
	Other, carbapenem-resistant		2	1/2	1/2					
Escherichia coli	ESBL$^+$		18	13/18	2/18			3/18		
	OXA-48$^+$		2	2/2						
VRE	*Enterococcus faecium*	VanA	7	2/7	1/7	1/7			1/7	2/7
		VanB	1							1/1
	Other		2	2/2						
Stenotrophomonas maltophilia			1	1/1						
Acinetobacter ursingii MBL$^+$			1	1/1						
Total			47	33	5	1	1	3	1	3

ARB, antibiotic-resistant bacteria; ESBL, extended spectrum beta-lactamase; dec., decolonized; M, month; MBL, metallo-beta-lactamase; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillinase; VanA/VanB, vancomycin-resistance genes; VRE, vancomycin-resistant enterococci; W, week.
* One patient decolonized after 4 days.

procured from unrelated donors, diluted with saline solution, and administered intraduodenally via a nasoduodenal tube. All FMTs were fresh, except for in Dinh *et al.* [40] where a frozen sample was used. All were administered in a single dose, except for Bilinski *et al.* [37] where it was administered on two consecutive days.

Patient preparation varied across studies, however some information was not clearly reported to allow assessment of heterogeneity, such as use of proton-pump inhibitor and patient fasting. Bowel cleansing was performed using macrogol solution in all studies, except for Dinh *et al.* [40] which used sennosides.

Outcome measurement was highly similar across the studies using microbiological testing and PCR; however, the time points of outcome assessment varied.

Methodological heterogeneity

Non-randomized studies are subject to more heterogeneity due to methodological diversity and bias [28]. However, case series and case reports are similar, because they are descriptive studies [59], even though case series have more participants and follow a protocol [53].

Nevertheless, in this review, the included case series and case reports had somewhat similar degrees of bias [50].

Statistical heterogeneity

Statistical heterogeneity was assessed for the meta-analysis of the primary outcome (Figure 2).

Under the random-effects model [51], the I^2 statistics for inconsistency was 73.1% (95% CI 0–89.9), Cochran's Q= 7.43 (degrees of freedom (df)=2), *P*-value= 0.0244. This indicates statistical significance for the presence of heterogeneity and that 73.1% of the variability in effect estimates was due to heterogeneity rather than random error signifying moderate heterogeneity (I^2 50–75%) [50].

After assessment of the quality of the included studies and exploration of heterogeneity, confidence in the results is very low.

Quality was downgraded for high risk of bias across most domains of bias across all studies. Similarly, quality was downgraded for inconsistency, due to high clinical and statistical heterogeneity. The small number of included studies with small sample sizes warranted downgrading the quality due to imprecision. High suspicion of publication bias due to the evident selective outcome reporting in the included studies further downgraded the quality of evidence. The primary outcome of decolonization at 1 month is presented in a GRADE evidence table (Table V).

Discussion

Decolonization of antibiotic-resistant bacteria from the gut

This systematic review of case series and case reports resulted in low-quality evidence showing that FMT decolonized antibiotic-resistant bacteria from the gut of colonized adults in half of the cases and is relatively low-risk.

These study designs have been the basis of systematic reviews and meta-analyses that have evaluated the preliminary efficacy, and effectiveness of FMT in treating recurrent and refractory *C. difficile* infection [19,60–62], even though systematic reviews that additionally included RCTs yielded evidence with higher certainty [19].

In a prospective, randomized control pilot study, Bulow *et al.* [63] demonstrated that there was no difference between autologous FMT, where the previously stored faecal material of the participants was used, and a placebo saline enema in restoring gut microbiota species composition and abundance to pre-antibiotic exposure state.

In contrast, literature suggests that spontaneous decolonization without intervention takes a long time and occurs less often. Data from a study analysing patients in long-term facilities showed that spontaneous decolonization occurred in only 9% of the patients and the median duration of colonization with multi-drug-resistant Gram-negative bacteria was 144 days [64], while another study [65] showed that in intensive care unit (ICU) patients, the median time to spontaneous clearance was 4.8 months. Meanwhile, Hayden *et al.* [66] showed that a

Table V
GRADE evidence table for decolonization success at 1 month

Certainty assessment							No. of patients		Certainty
No. of studies/study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		FMT	Standard treatment	
Five observational studies	Very serious[a]	Very serious[b]	Not serious	Very serious[c]	Publication bias strongly suspected[d]		25/52 (48.1%)	—	⊕◯◯◯ VERY LOW

FMT, faecal microbiota transplantation.
[a] Evidence from all studies was assessed to be at high risk of bias.
[b] Heterogeneity was assessed to be high: both clinical and statistical (I^2=73.1%, P=0.0244).
[c] Small number of studies with small sample sizes.
[d] Publication bias is highly suspected, because positive outcomes are more likely to be published and the studies had high risk of selective outcome reporting.

combination of contact isolation, infection prevention and control protocols, and staff training was associated with a decrease in the prevalence of carbapenemase-producing *K. pneumoniae* in long-term acute-care hospitals, however only 17% were decolonized within 4 weeks [67].

A retrospective observational study [68] showed that targeted oral antibiotics decolonized antibiotic-resistant bacteria in 42% of cases 2 weeks after end of treatment, while a randomized, double-blind, placebo-controlled trial showed targeted oral antibiotics caused a temporary reduction in *Enterobacteriaceae* ESBL$^+$ carriage, but were not successful in decolonization after 4 weeks [69]. This was not the case in Saidel-Odes *et al.*'s [70] randomized, double-blind, placebo-controlled trial, in which selective digestive decontamination for decolonization of carbapenem-resistant *K. pneumoniae* showed sustained effect with 58.8% decolonization rate at 6 weeks.

Nonetheless, use of antibiotics in antibiotic resistance cases is controversial, because, as stated in the introduction, antibiotic use is a catalyst for antibiotic resistance, especially due to its implications on the gut microbial composition [4]. In an ICU, where selective digestive tract decontamination was applied, rapid emergence of colistin resistance among *K. pneumoniae* ESBL$^+$ was observed [71]. Similarly, in another study, this regimen was associated with doubling the abundance of antibiotic-resistance genes in the microbiota [72].

Thus, on a preliminary account, compared to other treatments, decolonization of gut antibiotic-resistant bacteria using FMT is safer and more effective.

Detection of antibiotic-resistant bacteria

All of the studies used standard microbiological culture-dependent methods, as well as PCR for detection of resistance genes. However, a caveat of culture-dependent methods is that they are often time-consuming, while PCR methods, due to their high sensitivity, can give rise to false-positive results and overestimation of target sequences [73—75]. This gives rise to uncertainty in decolonization results, where PCR could be detecting residual bacterial DNA from eradicated bacteria [76]. FMT has also been associated with reducing antibiotic-resistance genes from the gut resistome below the level of detection by microbiological testing [77,78].

Hence, definitions of success of decolonization should be clarified in future research.

Mechanism of action of FMT

It has been acknowledged that colonization resistance mediated by the gut microbiota is the underlying mechanism against colonization by pathogens [79]. In a murine model, Ubeda *et al.* [23] identified a correlation between VRE decolonization and reconstitution of microbiota with bacteria from *Barnesiella* species.

However, a case series [80] showed that transfer of sterile-filtered donor stool that did not contain bacteria was sufficient in resolving recurrent *C. difficile* infections in five patients. This signifies that other components, such as bacterial proteins, bacterial metabolites, and bacteriophages might mediate the effects seen in FMT rather than the intact faecal microbiota. Additionally, a metagenomic analysis [81] showed

that donor and recipient microbial strains of the same species coexisted for 3 months after FMT.

This could be an explanation for the non-significant difference in diversity and composition of microbiota in responders and non-responders in Bilinski *et al.* [37] and Singh *et al.*'s [38] studies.

Pathogens most responsive to FMT

This systematic review showed that at 1 month, *P. aeruginosa* was the most successful pathogen in being decolonized by FMT, while *K. pneumoniae* with NDM-1 and ESBL mechanisms of resistance was least responsive to FMT.

In a mouse model, Mahieu *et al.* [82] showed that FMT was more effective in decreasing faecal carriage of VRE (*Enterococcus faecium*) compared to CPE (*Escherichia coli* NDM-1$^+$), however it was unsuccessful in complete decolonization. This systematic review did not comprise of cases of *E. coli* NDM-1$^+$, however the NDM-1 mechanism of resistance seems to be associated with lower response rate to FMT.

It is also speculated that FMT has a different effect on antibiotic-resistant bacteria compared to *C. difficile* infections. A case study [83] of a patient colonized by both *C. difficile* and VRE, reported success in curing refractory *C. difficile* infection but failure in eradicating VRE.

Another question arises regarding partial versus complete decolonization. In Bilinski *et al.*'s [37] study, where most patients were colonized by more than one type of antibiotic-resistant bacteria, partial decolonization was achieved in some participants — some antibiotic-resistant bacteria were decolonized but not others.

Hence, it can be reasoned that antibiotic-resistant bacteria differ in their response to FMT and mechanism of resistance plays an important role in the response.

Time frame to decolonization achievement

This systematic review shows that in 47 successful decolonization cases at the last follow-up across studies, 70% were achieved within the first week following FMT.

This is similar to the results in a murine model of VRE colonization [23], which showed that decolonization of vancomycin-resistant *E. faecium* was achieved within 15 days after FMT and the density of this pathogen was reduced within 7 days of FMT. While, a murine model of CRE colonization [84] showed that within 2 weeks, FMT decreased *E. coli* NDM$^+$ carriage.

In contrast, in a systematic review and meta-analysis of decolonization strategies, such as selective bowel decontamination and/or antibiotic therapy versus placebo or no treatment for ESBL/CRE carriage, colonization persisted up to 1 year in a significant proportion of cases [36].

Likewise, surveillance studies of duration of colonization, showed that median duration of colonization with VRE was 306 days after selective bowel decontamination [85], mean time to CRE decolonization without intervention was 387 days [86], and the median time of colonization with carbapenemase-producing *K. pneumoniae* with combined interventions of contact isolation, infection prevention and control, and staff training was 205 days [67].

Hence, based on comparisons to evidence from literature, it can be inferred that in comparison to other methods, FMT requires less time to achieve decolonization.

Adverse effects

Only mild temporary adverse effects were experienced by participants of this review, ranging from vomiting and diarrhoea to abdominal cramps and pain. However, in Bilinski *et al.* [37] where follow-up time period was longer — 6 months compared to up to 3 months in the other studies, recolonization and colonization with new bacterial strains was noted in a few patients (22%). Longer follow-up periods in the other studies, could have given clearer evidence on this adverse event.

In contrast, in an observational study for targeted antibiotic decolonization, 54% of the successful decolonization cases were recolonized within 3 months [68]. Additionally, Jouhten *et al.* [77] showed the possibility of transfer of resistance genes from donors to FMT recipients, where VanB resistance gene not present before was observed in recipients as well as donors. This is congruent with the results by Leung *et al.* [87], which showed that acquisition of resistance genes is likely with FMT.

FMT seems to be safe in terms of short-term side-effects, however not enough evidence exists for its long-term effects in terms of recolonization, colonization with new bacterial strains and transfer of resistance genes.

Strengths and limitations of the studies and this review

The strength of this systematic review is evidenced by rigorous and comprehensive searching of the literature for identification of relevant studies. However, it had several limitations. Even though the intention is to be as rigorous and transparent as possible, only one author conducted this systematic review, which the reviewer acknowledges as a potential source of bias [27]. In addition, search was limited to English-language publications, which could have introduced language bias, because positive findings are more likely to be published in English-language journals [88]. There is also a possibility that some unpublished trials and grey literature were missed.

Excluding participants who also had recurrent or refractory *C. difficile* infections in addition to antibiotic-resistant bacteria could have excluded important evidence about the effect of FMT, because patients often have co-colonization of these bacteria in their gut due to the same state of gut dysbiosis, which leads to their emergence [11]. In contrast, exclusion of the paediatric population did not necessarily impact the review outcome, as only one was found to date as listed in Supplementary Table S4 [89].

Moreover, the limited number of studies included in this review, as well as their small sample sizes reduces the probability of detecting a true effect [90]. The study design of the included studies was also considered a limitation, because single-arm trials without comparators make the interpretation of the results more difficult without any frame of reference [91]. The small sample sizes and limited number of studies precluded performing subgroup analyses, which may have provided greater confidence in the findings of this review.

Finally, all studies were conducted in European countries, which limits generalizability and any conclusions of wider applicability to other countries.

Conclusions

Antibiotic resistance is a growing global problem, which along with the limited available treatment options, presents a substantial challenge and a major threat to human health [7]. Based on a small number of studies of small sample sizes and poor methodological quality, this systematic review can cautiously serve as a preliminary effectiveness review of the decolonization success of FMT, which is relatively low-cost, low-risk and cleared half of the cases.

Nevertheless, several gaps were identified. Although FMT seems to be able to decolonize antibiotic-resistant bacteria from the gut, RCTs are needed to evaluate the superiority of this intervention over no-treatment, selective bowel decontamination, and infection prevention and control strategies. In addition, long-term observational studies are needed for establishing the time frame needed for decolonization and determining the long-term effects of this treatment in terms of recolonization, colonization with new bacterial strains, and transfer of infectious agents from donor stools. Further research is also needed on dosage, preparation and administration techniques of FMT, as well as the effectiveness of autologous and repeat-FMT.

Moreover, due to the complexity and novelty of use of the gut microbiota as a biological treatment, future studies should elucidate the mechanisms or components of the gut microbiota that underlie the success of FMT, and its indication based on pathogen response rate. Furthermore, of utmost importance is the clarification and standardization of what defines decolonization success in future research.

Despite the limitations mentioned above, evidence from this review does indicate a potential benefit of FMT as a decolonization intervention, which can only be confirmed by future well-designed RCTs, based on which implications on clinical practice can be drawn.

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Conflict of interest
The author has no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.03.010.

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