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Review Article

Beyond faecal microbiota transplantation, the non-negligible role of faecal virome or bacteriophage transplantation

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Abstract Intestinal microbiota, which contains bacteria, archaea, fungi, protists, and viruses including bacteriophages, is symbiotic and evolves together with humans. The balanced intestinal microbiota plays indispensable roles in maintaining and regulating host metabolism and health. Dysbiosis has been associated with not only intestinal diseases but other diseases such as neurology disorders and cancers. Faecal microbiota transplantation (FMT) or faecal virome or bacteriophage transplantation (FVT or FBT), transfers faecal bacteria or viruses, with a focus on bacteriophage, from one healthy individual to another individual (normally unhealthy condition), and aims to restore the balanced gut microbiota and assist in subduing diseases. In this review, we summarized the applications of FMT and FVT in clinical settings, discussed the advantages and challenges of FMT and FVT currently and proposed several considerations prospectively. We further provided our understanding of why FMT and FVT have their limitations and raised the possible future development strategy of FMT and FVT.

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Introduction

Gut microbiota, which consists of all the living microorganisms that inhabit the gastrointestinal tract, plays an essential role in maintaining human health.[1–3] Dysbiosis, defined as an imbalanced microbiota, has been associated with many diseases, including the gastrointestinal tract diseases such as *Clostridium difficile* infection (CDI), the metabolism disorder diseases such as obesity and cirrhosis, and neurological disorders neurological through the gut–brain axis such as stroke.[4]

Faecal microbiota transplantation (FMT) transfers the donor's intestinal microbiota to the recipient's intestine, thereby assisting in regulating the health of the recipient via transferred microbiota. FMT had obtained great success in treating intestinal infections, especially the ones related to pathogens with antibiotic resistance.[5] However, there were few cases of FMT in clinical use clearly clarifying functional microorganisms or compounds that contribute to the intestinal microbiota recovery and disease cure processes, and therefore more efforts are needed to identify the underlined mechanism.[6] The gut microbiota is a total collection of microorganisms found in the human intestine, including bacteria, archaea, fungi, protists, and viruses. Notably, gut viromes were changed in the successfully cured cases after FMT compared to the initial virome.[7] Recently, the enterovirus, such as bacteriophages, had shown promising results in protecting mice from dextran sulfate sodium-induced colitis, as the virus elimination in the intestine will lead to the exacerbation

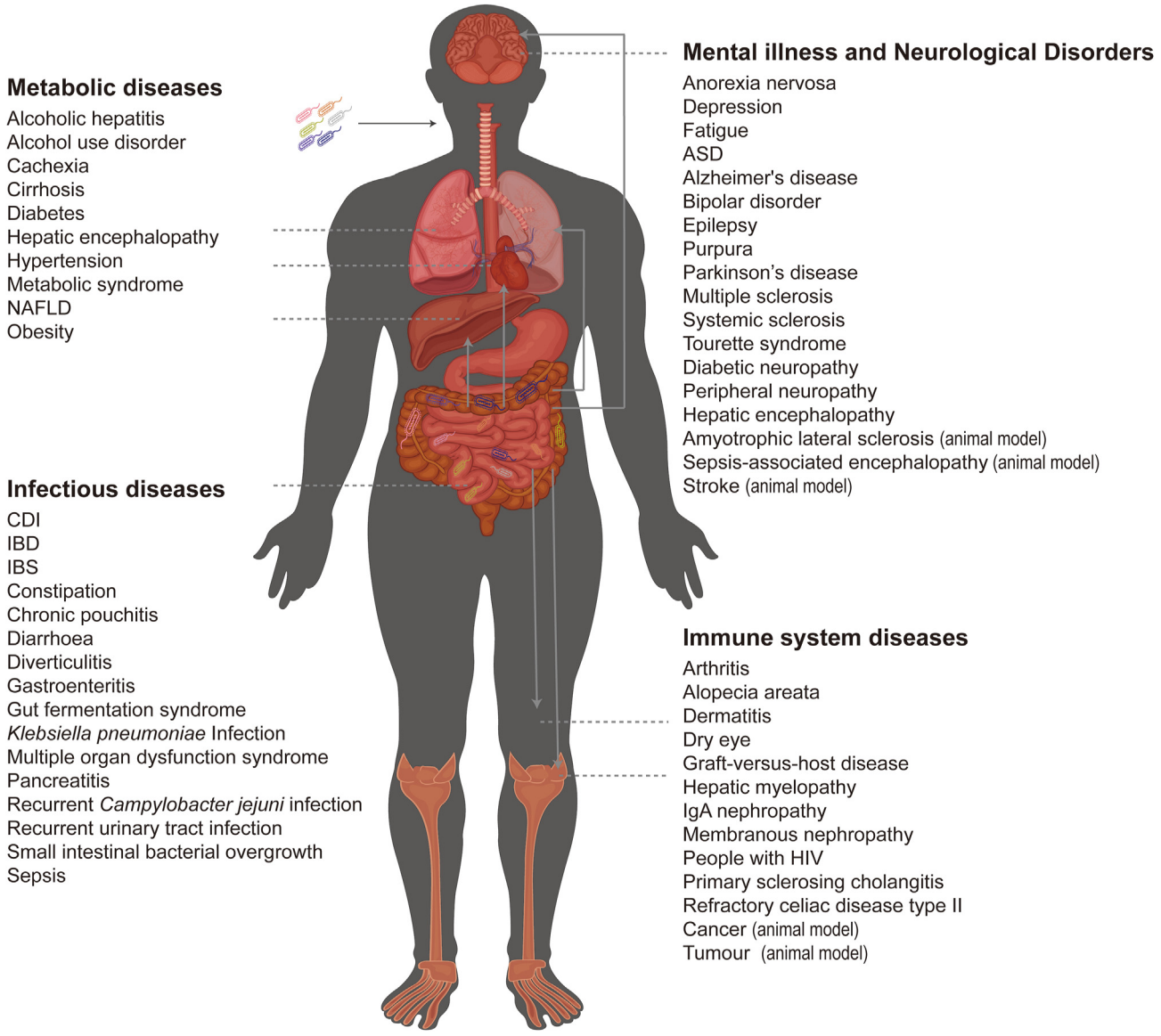

Figure 1. FMT for different kinds of disease. Unfortunately, due to various elements (i.e., mixed qualities, study designs, patient sizes, outcome measures, etc.) needing to be concerned, the included studies are not enough for evaluating the effect rank of FMT on different diseases. However, as shown in supplementary files, besides CDI, IBD and IBS, chronic pouchitis, Intestinal aGvHD, hepatic-associated disorders, obesity, metabolic syndrome, depression symptoms, and multiple sclerosis are the potential future priorities for FMT research.

of enteritis.[8] Moreover, researchers also proposed faecal virome transplantation (FVT) with a focus on transferring bacteriophages as a less invasive and more comprehensive treatment than FMT.[9] Hence, we reviewed and compared the clinical application of FMT and FVT, and discussed their current concerns and possible future development trends.

FMT

Clinical trials and standard of FMT

Since the first reported clinical use of FMT, there has been an increasing interest in its usage and diseases, including infectious diseases (such as CDI and inflammatory bowel disease (IBD)), metabolic diseases (such as obesity/diabetes, cardiovascular disease, and hepatitis), mental illnesses (such as depression), neurological disorders (such as autism, Parkinson's disease, and Alzheimer's disease), and immune system diseases (such as allergies) have been reported to be cured or ameliorated by using it (Fig. 1). With the maturity of FMT technology and the improvement of trial effects, as of 20 August, 2022, a total of 415 clinical trials were enrolled. Of these, there were 178 ongoing and planned clinical trials of FMT in the treatment of diseases on the clinicaltrials.gov website, and 111 clinical trials have been completed. (20 August, 2022, Intervention/treatment search 'FMT OR (fecal microbial transplantation) OR fecal OR faecal OR microbiota OR stool').

With the development of FMT therapy, a standard processed protocol for FMT, which contains the collection, preparation, and cryopreservation of faecal samples, was systemically constructed.[10] In addition, to minimize the risk of infection or other disease transmissions, a protocol for donor screening including thorough history checking, serological tests, and faecal tests for parasitic, virologic, and bacterial pathogens has been discussed and established (Fig. 2).[11]

FMT application in different diseases

FMT application in infectious diseases

C. difficile infections (CDI) and IBD. The CDI cases had grown up by 42.7% between 2001 and 2012, together with the increasing incidence of multiplying recurrent *C. difficile* infection (rCDI) by 188.8% in the United States.[12] We hypothesized that such a disproportionate increase is probably due to antibiotic overuse. Barkin and colleagues' research found that 134 out of 282 *C. difficile*-positive stool samples were found to have resistance to imidazole, 17 to vancomycin, and 9 to imidazole and vancomycin.[13] And, the meta-analysis by Slimings et al. that included 39 studies showed that the most important risk factor of healthcare facility-associated CDI was antibiotic use.[14] In addition, early antibiotic exposure was reported to increase the risk of FMT failure.[15] The standard protocol of FMT has been widely used in the clinical cure of CDI, especially the rCDI.[10] A meta-analysis focused on the effect of FMT on CDI treatment demonstrated the FMT treatment reached a 78.1%—94.8% cure rate which was defined as the successful resolution of CDI symptoms.[16] Moreover, another group reported that the ameliorative effects could be found in around 83.1% of patients with rCDI after FMT treatment during the 3 months' follow-up time (range 2-7.7 months).[17] But in a previous meta-analysis that included 5 studies (involving 3683

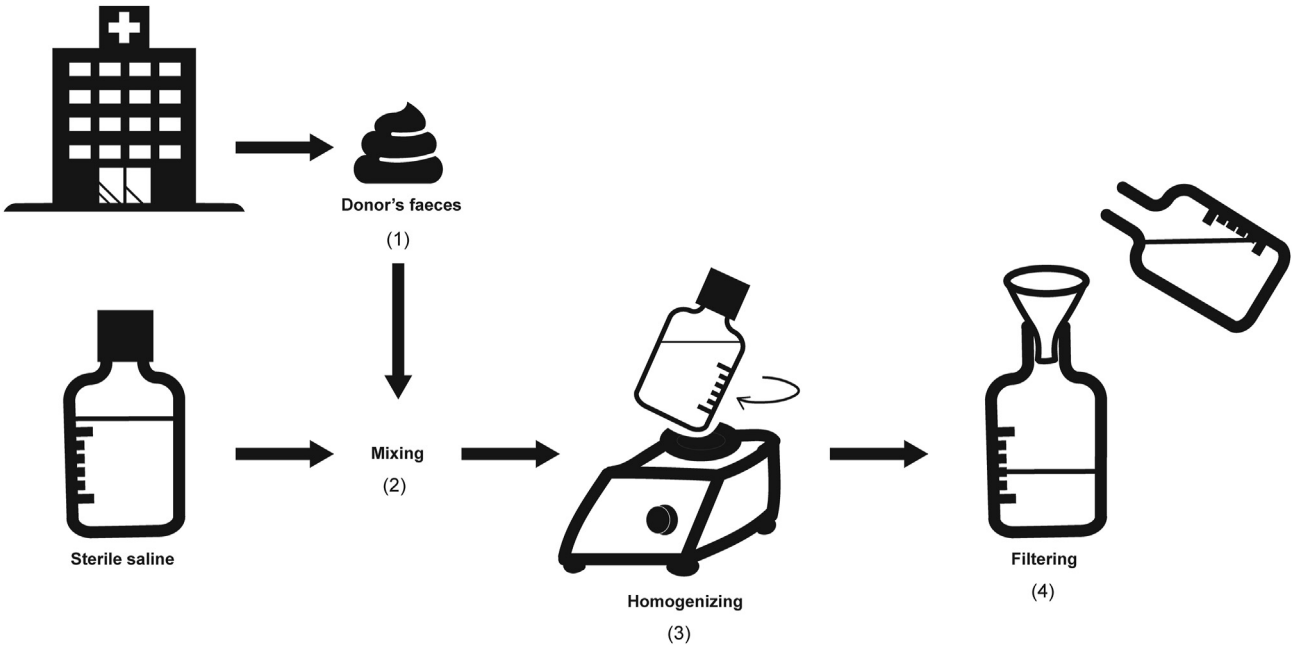

Figure 2. The process of faecal microbiota transplantation (FMT) sample preparation. (1) Collecting donors' faeces in the hospital (2) Mixing donors' faeces with sterile saline (3) Homogenizing the mix (4) The suspension of faeces gained after filtering and centrifugation.

participants), the mortality rate for certain conventional CDI treatments (diverting loop ileostomy and total abdominal colectomy) was 30.3%.[18] A meta-analysis also showed that FMT treatment has higher efficacy than vancomycin only or fidaxomicin only.[19] Faecal dilution has great potential to prevent mice from CDI.[20] Several reports on IBD patients with FMT treatment also found the remission rates of ulcerative colitis (UC) and Crohn's disease (CD). Patients were 39.6% and 47.5%, respectively, with a mean follow-up of 6.1 and 7.8 months for each.[21] On the other hand, in other IBD treatments (infliximab and vedolizumab), the clinical remission rates (dependent on Crohn's Disease Activity Index scores) are 39%-54% with a follow-up of 50-54 weeks.[22]

Other infectious diseases. FMT had been used in treating many other gut infectious diseases, including diarrhoea, chronic pouchitis, slow transit constipation, and pseudomembranous enteritis. We listed all the found reports in detail in Table S1. Unfortunately, most of the studies had a limited number of patients without a control group or to perform statistical analysis that makes clinical sense. In most of the studies, such as sepsis, chronic pouchitis and slow transit constipation, FMT showed positive results in ameliorating or curing diseases. For infectious diseases, *Klebsiella pneumoniae* infection and recurrent *Campylobacter jejuni* infection, although the size of cases was small, their result also revealed the possibility that FMT rebalances the gut microbiota.

In summary, these results indicate the efficiency and huge potential of FMT for treating related gut infectious diseases. However, FMT does not always work on all infectious diseases. Both recently published meta-analyses of FMT on irritable bowel syndrome (IBS) and acute pancreatitis treatment in Table S1 reflected that FMT is not significantly superior to the placebo groups. Furthermore, we found that the frequency of FMT and the dose of the FMT may also affect the outcomes of FMT therapy, which might explain the failed cases presented in Table S1.[23]

FMT application in metabolic diseases

With the fundamental reports that associated gut microbiota with metabolic diseases, there has been growing attention to testing FMT on metabolic diseases such as obesity, diabetes, and hepatic metabolic diseases (Table S2). In Table S2, the failure rates of FMT cases were not high, as they ranged from 14.3% to 40%, in the main types of metabolic diseases (obesity and diabetes (3/8), liver disease (1/7), and metabolic syndrome (2/5)). Notably, when referring to the potential mechanism, according to the listed studies that were involved in the treatment of hepatic diseases and indicated in Table S2, the restoration of the imbalance in the intestine could modulate the number of liver T cells and reduce liver steatosis to ameliorate liver diseases.[24,25] More than half of successful cases used more than once FMT to treat diseases, and it seems better to use more than 50 g of faeces at a time during administration. Non-failed cases recorded a high dose and frequency of use at the same time. Therefore, more systemic research with more patients should be carried out to clarify the influence of dose and frequency on trial efficiency.

FMT application in mental illness and neurological disorders

Unambiguous evidence showed the link between gut microbiota and the brain via the gut—brain axis.[26] Several studies also demonstrated that FMT induced a systemic change of plasma metabolites (such as short-chain fatty acids (SCFAs) and necrosis factor-α (TNF-α)), modulated the expression of proteins in brains (such as Iba1, α-synuclein, amyloid protein), and improved the scores of cognitive, behaviour and mood of both mental illness and neurological disorders.[27—29] As shown in Table S3, the major neurological disorders including autism spectrum disorder (ASD), Parkinson's disease (PD), Alzheimer's disease (AD) and dementia could be found to have significant remissions of 3/3 cases, 4/4, 2/2 and 2/2 respectively, after FMT. As the typical mental illness, of 9 depression cases involving 139 patients, 8 cases demonstrated that FMT brought positive results. And for other mental illnesses and neurological disorders, FMT also showed great ability in alleviating symptoms (e.g., bipolar disorder, fatigue, anorexia nervosa, multiple sclerosis, and neuropathy). Moreover, the effects of FMT on other neurological diseases, such as amyotrophic lateral sclerosis,[30] multiple sclerosises,[31] epilepsy,[32] strokes,[33] and sepsis-associated encephalopathy[34] have been respectively investigated in animals but not verified in clinical studies yet. Overall, the potential utilization of FMT for mental illness and neurological disorders treatment offered us a promising way to assist current treatments of these diseases.

FMT application in other diseases

Considering the close interaction between gut microbiota and the immune system, quite a few attempts had been made to adjust the immune response or inflammation with the FMT (Table S4). Intestinal acute graft-versus-host disease (aGvHD) is the most well-studied disease with a low failure rate (3/16). One of these cases confirmed that FMT had more significant effects ($P = 0.003$) in prolonging the progression-free survival period which was defined as no disease symptom, no death and no new infection with CMV and EBV in this period than the control group.[35] For skin diseases such as psoriatic arthritis, atopic dermatitis and alopecia areata, although the size of treatment and the number of trials are small, an exciting prospect that uses FMT to treat them is reflected. In the case of people with HIV, FMT could even stop antiretroviral therapy for several days.[36] It also showed the possibility for FMT to treat refractory celiac disease type II, primary sclerosing cholangitis, dry eye, hepatic myelopathy, IgA nephropathy, and membranous nephropathy in clinical trials (Table S4). In addition, with the help of prednisone, FMT also can alleviate systemic lupus erythematosus in mice.[37]

Further, gut microbiota had been found to play essential roles in enhancing the therapeutic effect of cancer immune therapy and reducing related side effects.[38] Many studies verified the interaction between microbiota and cancer, including cancer-associated intestinal microbiota, intratumoral microbiomes and strategies that microbiomes influence various cancer treatments.[39,40] Clinical trials evaluating gut microbiota-caused cancer immunotherapy efficiency changes have been widely set.[40] Interestingly, in the three cases of FMT treatment of CDI and non-infectious

diarrhoea, the patients' alopecia symptoms were also significantly relieved.[41,42] Recent studies have also shown that obesity accelerates hair follicle atrophy and induces hair loss.[43] FMT has shown great potential to reverse or mitigate the disbalance of gut microbiota and the dysfunction of organs induced by chemotherapy and allogeneic hematopoietic stem cell transplantation.[44,45] Unfortunately, due to various elements (i.e., mixed qualities, study designs, patient sizes, outcome measures, etc.) needing to be concerned, the included studies are not enough for evaluating the effect rank of FMT on different diseases. However, as shown in supplementary files, besides CDI, IBD and IBS, chronic pouchitis, Intestinal aGvHD, hepatic-associated disorders, obesity, metabolic syndrome, depression symptoms, and multiple sclerosis are the potential future priorities for FMT research.

Potential underlined mechanism of FMT

With the increasing clinical use of FMT, the underlined mechanisms of FMT have also been evaluated. Transferred gut microbiota could restore recipients' intestinal microbiota, and improve the intestinal barrier function by affecting the signal expression pathways, cytokines, and tight junction proteins.[46] Furthermore, the augmentation of intestinal barrier function and enhancement of cellular mitochondrial and ribosomal activities in the intestine can further help the restoration of aberrant host metabolisms, the production of functional chemical compounds in sera, or the suppressed activation of inflammasomes, the consequence of which is ameliorating diseases symptoms of other organs.[47—49] FMT has also demonstrated the potential interaction with immune cell infiltrates, gene expression profiles in the tumour microenvironment,[39,40,50] the expression of innate immune activation markers and the activation of immune cells.[51,52]

Current challenges and opportunities of FMT

The biological safety of FMT has always been a concern and raised more attention in recent years. In March 2020, the US Food and Drug Administration (FDA) issued a safety alert regarding the use of FMT for CDI patients. In total, six CDI patients had different degrees of *Escherichia coli* infection, and four out of these six patients needed to be hospitalized for treatment.[53] Zellmer et al. proposed that *Shiga toxin-producing E. coli* may be transmitted to patients from healthy donors.[54] These pathogenic bacteria are probably induced by unthorough donor selections and biological examinations, or nonstandard processing procedures. In addition, new infections such as COVID-19 and currently unknown infections will also emerge to threaten the safety of the FMT.

In addition, to follow strictly the donor screening and FMT preparation procedures as mentioned earlier, several kinds of other FMT material preparation processes have been built, including the washed microbiota transplantation,[55] priority pathogens-absent FMT (RBX2660),[56] purified Firmicutes bacterial spores (SER-109),[57] anaerobically cultivated human intestinal microbiota, which was continuously cultured from the healthy donor without pathogens,[58] as well as the recent developed methods to design a complex community of bacteria that represents the most common taxa based on the human microbiome.[59,60] All these methods and conducts may be served as replacements for the FMT to obtain a more under-controlled and pathogens-free microbiota transplant in the future. Furthermore, considering the interaction between the donor bacteria and the resident bacteria of recipients, the faecal microbiota bank, which provides large possibilities to match the donors and recipients, has been encouraged.[61] For producing safer FMT products, both FDA and the Australian Therapeutic Goods Administration have announced guidances.[62—64] Some products also have been approved under these strict standards.[65,66] RBX2660, one of the approved products, has been conducted in many clinical trials and gained considerable results. Eight of these studies have been published on PubMed with 874 participants included and every trial has recorded a positive improvement.[67—69] Three extra completed trials and two undergoing trials can be found on clinicaltrials.gov up to 9 February 2023 (Intervention/treatment search "RBX2660", choose the status of recruiting, enrolling by invitation, active, and completed). Notably, scientists recently applied phage-delivered CRISPR-Cas9 to remove genes or kill targeted bacteria by inducing double-strand DNA breaks, thus modulating the microbiome *in vivo*.[70] This provides a great opportunity to avoid the transfer of antibiotic resistance pathogens by FMT.

Gut virome and FVT

Gut virome

Gut virome refers to all the intestinal viruses and their genomes, including 0.1% archaeal viruses, 2.1% eukaryotic viruses (including plant and mammalian viruses) and 97.7% bacteriophages.[71,72] The human intestine contains about 10^{15} bacteriophages, which are more than 100 times the number of bacterial cells or human cells.[2,73] Bacteriophages have two replication cycles: the lysogenic cycle (Fig. 3-(1)), that bacteriophages integrate their genetic content into the host bacterial genome and replicate together with the host, without producing a large number of virus particles; and the lytic cycle (Fig. 3-(2)), that bacteriophages deliver DNA into the host bacteria, replicate in large quantities, and then lysis the host bacteria to release progeny virus particles. The life cycle of virulent phages (also known as lytic phages), such as phage T4, is the solely lytic cycle, whereas temperate phages can utilize both the lytic cycle and the lysogenic cycle. In addition, certain pseudolysogenic bacteriophages (Fig. 3-(3)) do not integrate their genetic material into the bacterial genome but coexist with the host for a long time when the host is starving. With the supplement of nutrients, the pseudolysogenic bacteriophages either establish true lysogenicity or are activated to produce and release viral particles.[74] Further, although there is no standard way for FMT, FVT filtrate was generally obtained by filtering and centrifuging FMT filtrate. The details about how to gain the FVT filtrate of every research were shown in Table S5.

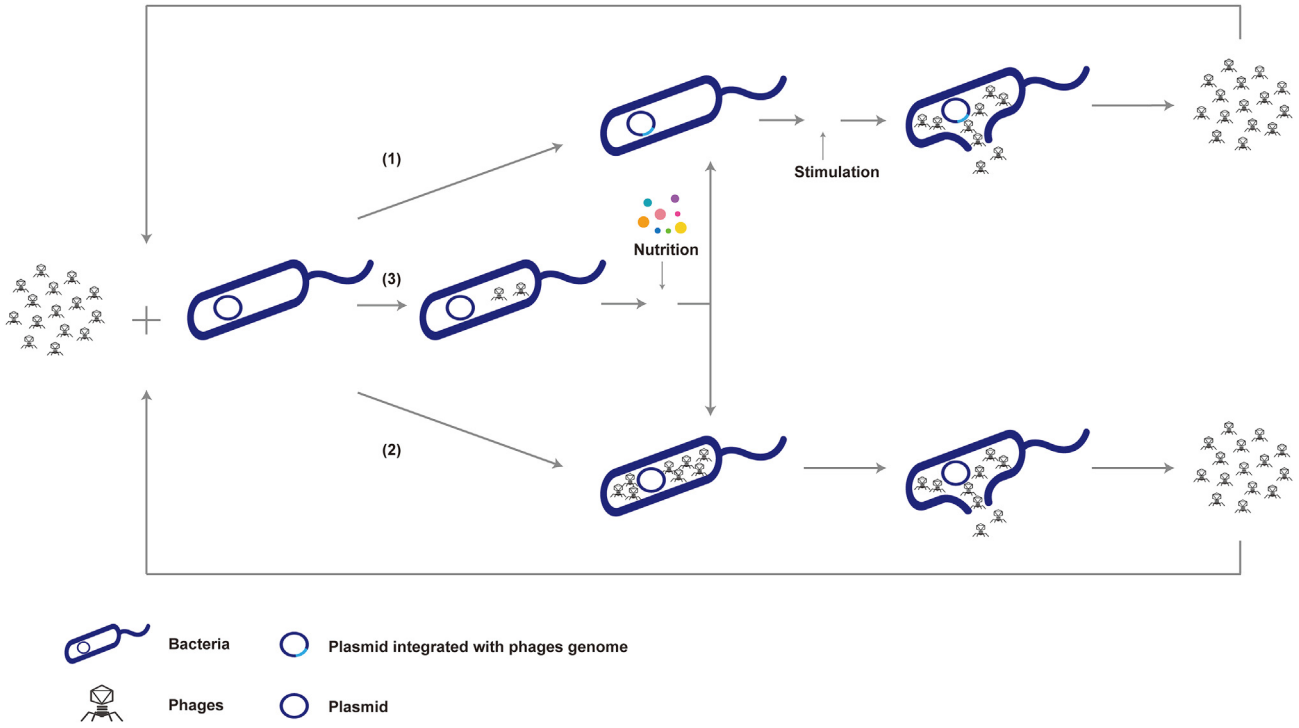

Figure 3. Replication strategies of phages. (1) The lysogenic cycle. The phages in the lysogenic cycle (also known as temperate phages) insert their genome into the genome of the host bacteria and replicate together with the host, without producing a large number of virus particles. (2) The lytic cycle. The phages in the lytic cycle deliver DNA into the host bacteria, replicate in large quantities, and then lysis the host bacteria to release progeny virus particles. (3) The cycle of pseudolysogenic bacteriophages. Pseudolysogenic bacteriophages do not integrate their genetic material into the bacterial genome but coexist with the host for a long time until there is enough nutrient supplement for the host's amplification.

Gut virome in diseases

Infections of eukaryotic viruses in the intestine, such as norovirus, rotavirus, circovirus, and herpes virus, also have been determined to be directly related to diarrhoea.[75] Moreover, Epstein—Barr virus infection, rotavirus infection, and adenovirus infection are associated with the exacerbation of IBD inflammation,[76] the induction of type 1 diabetes,[77] and the onset of celiac disease[78] respectively. Gut virome, especially gut bacteriophages, has been linked to different diseases.[79—82] Results from recent studies suggest that bacteriophages, like bacteria, are stable over time.[3,83]

Compared with healthy people, IBD patients' enteric virome has specific richness and relative abundance in *Caudovirales* taxa.[84] In the intestines of CDI patients, the eukaryotic viruses *Anelloviridae* usually increased, while the abundance of *Microviridae* and *crAssphage* which are bacteriophages of *Bacteriodetes* decreased among CDI patients.[85] Furthermore, the richness of *Caudovirales* in there was positively associated with the abundance of *Proteobacteria* and *Actinobacteria*.[7] While after FMT, such positive association numbers, which were evaluated by the changes of identified viral diversity and bacterial diversity and richness, had reduced.[7] Furthermore, scientists proposed that the richness of the original eukaryotic virome in the intestine may affect the therapeutic effect of FMT on UC patients.[86]

FVT application in mice model

Considering the importance of gut virome in diseases and the growing evidence that donors' virome can be transplanted to recipients during FMT, studies about FVT have been initiated, with most current studies performed in mouse models (Table S5).

FVT association with over-weight and dietary effects

By using the virome collected from the mice faeces before antibiotics treatment, Draper et al. verified that the FVT could restore the antibiotics-disturbed structure of the intestinal microbiota.[87] Several other studies[88—91] also obtained a similar result that gut virome could reshape recipients' intestinal microbiome. Bahr et al.[88] found that the transfer of gut virome reshaped by feeding risperidone could earn the same effect on weight gain as the dietary addition of risperidone. The study by Shute et al. demonstrated that the *Hymenolepis diminuta* infection-induced experimental colitis amelioration could be transferred by FVT.[89] Moreover, after Lin et al. conducted FVT in both normal diet mice and high-fat (HF) diet mice, they found similar results to the FMT group.[90] Rasmussen et al. transferred sterile-filtered faecal bacterial suspension from low-fat (LF) diet mice to HF mice, and the bacterial Shannon diversity index and the blood glucose tolerance of them were similar to those of the LF diet mice, but significantly differ from those of HF mice.[91] In addition, FVT significantly

reduces the weight gain of HF mice compared with the HF-only group.[91] In addition, both FMT and FVT have shown that the amelioration of green tea polyphenol-induced experimental colitis could be transferred.[92]

FVT application in intestinal diseases

Several studies have been performed on FVT in regulating intestinal diseases (Table S5). Sinha et al. emphasized the role FVT played in both causing disease and treating disease.[93] FVT from UC patients' faeces in mice increased colitis severity in mice compared to FVT from healthy individuals or the control groups with phosphate-buffered saline treatment only, and FVT from healthy patients' faeces had distinct effects on restoring the gut microbiota of UC mice.[93] Nevertheless, a recent study carried out by Brunse et al. used the necrotizing enterocolitis (NEC) model of premature piglets and found that oro-gastric bacteria-free faecal filtrate transfer (FFT) could significantly eliminate NEC incidence, which paved the way for the potential FVT application in treating the acute and life-threatening gastrointestinal diseases of premature infants.[94]

Notably, when comparing FMT with FVT, FMT, which could directly provide more SCFAs-producing bacteria, showed a better result in alleviating the colonic barrier damage compared with FVT.[92] In the study of Brunse et al., FMT had a better effect than FFT in restoring the mucosal-associated microbiota in the NEC models as well. In addition, FMT administration showed that the families of eukaryotic viruses increased, and the gene expression related to immune activation and host defence in the intestinal mucosa also increased, compared with CON, whereas the FFT group did not.[94] On the other hand, FFT had less disturbance to the intestinal microbiota than FMT, with significantly effective protection on the intestinal permeability compared with FMT.[94] Sinha et al. also demonstrated that FVT function in germ-free (GF) mice requested transfer of intestinal microbiota in advance, which reflected that FVT might works by modulating intestinal microbiota.[93]

FVT application in clinical trials

We found 12 FMT clinical trials for the treatment of various diseases that also have detected the change of enteroviruses, including both eukaryotic viruses and phages. As shown in Table S6, with follow-up of 7 weeks—12 months, except for the one case that has not compared the responders' virome with the donors', 8 of 9 cases focused on the CDI and IBD had demonstrated viral features associated with the efficient and significant viral transfer in responders' samples (similar virome with the donor) after FMT. Similar results could be found in intestinal aGvHD, metabolic syndrome (MetS) and ASD trials.[95—97] Broecker et al. found that the phage community recovered earlier than the bacteria community in responders after FMT.[98] What's more, studies by Zuo et al. (CDI),[7] Manrique et al. (MetS),[95] and Kang et al. (ASD)[96] showed that responders' virome structure was more similar to donors' compared with non-responders or samples collected before FMT. During transplantation, both temperate phages and lytic phages would be transferred by FMT, particularly in terms of *Caudovirales*, Siphoviridae, *Microviridae* and *crAssphage*.[85,99]

Only two FVT clinical trials on humans had been found so far, both for human rCDI treatment.[100,101] The first one is conducted by Ott et al., which performed FVT with 5 participants who had failed in antibiotic therapy before and followed up for up to 33 months. Positive results were recorded in all patients, and no CDI-associated symptom occurred until the end of the study.[101] Unfortunately, in these 5 patients of this study, there was only one patient who could provide eligible samples for virome profiles. But bacteriophage composition in these samples showed that the phageome was similar to the donor phageome after 6 weeks of transplantation, and some kinds of phages that were not detected in patients' samples before FFT could exist in recipients' gut for at least 6 weeks after FFT.[101] The second study is carried out by Kao et al. with 9 participants, 4 in the FFT and 5 in the FMT group, with the treatments followed up for 8 weeks. They found that the effect of FMT is similar to that of sterile FFT, for the cure rates of the lyophilized sterile FFT group and the lyophilized FMT group were 75% (3/4) and 80% (4/5) after first administration respectively.[100] In this trial, there was no mortality or administration-related infections. In conclusion of FVT and its comparison with FMT, we believe that although FMT might provide a more direct effect to restore the gut microbiota balance, the excessive addition of the extra microbiota could potentially cause the overloading of the intestinal environment, while the addition of FVT will be an alternative way to achieve a similar outcome.

Potential underlined mechanism of FVT

Eukaryotic viruses

Although most current knowledge on the mechanism of eukaryotic viruses is based on pathogenic viruses, eukaryotic viruses have also been found to bring favourable impacts on the health of the body besides the detrimental influence. Chen et al. found that the coxsackie-adenovirus receptor, which plays an important role in coxsackievirus infection, protected tight junctions and had an anti-inflammatory effect during the pathogenesis of IBD.[102] Infection of reovirus, norovirus and rotavirus had been linked to delaying the onset of diabetes in nonobese diabetic (NOD) mice, which were the experimental model of type 1 diabetes.[103—105] The number of T cells in the lamina propria and mesenteric lymph nodes, the production of mucosal and serum antibodies, and the villi width in murine norovirus-infected GF mice were more similar to those of conventional mice than those of healthy GF mice.[106] In this study, Kernbauer et al. also found that murine norovirus could up-regulate type I interferon (*IFN*) gene expression, thereby restoring the damage of intestinal structure and lymphocyte function in mice caused by antibiotic treatment (Fig. 4-(7)).[106]

The potential effect of eukaryotic viruses after FVT may not be limited to the intestine tract only. Eukaryotic viruses such as the hantavirus and rotavirus were able to enter the blood circulation to reach various organs (Fig. 4-(2)).[107,108] This suggests that other eukaryotic viruses could also pass through the intestine and interact with lymphocytes. When the intestine is severely damaged, the inactivated rotavirus had been recognized by the intracellular receptors Toll-like receptor 3 (TLR3) and TLR7 of plasmacytoid dendritic cells

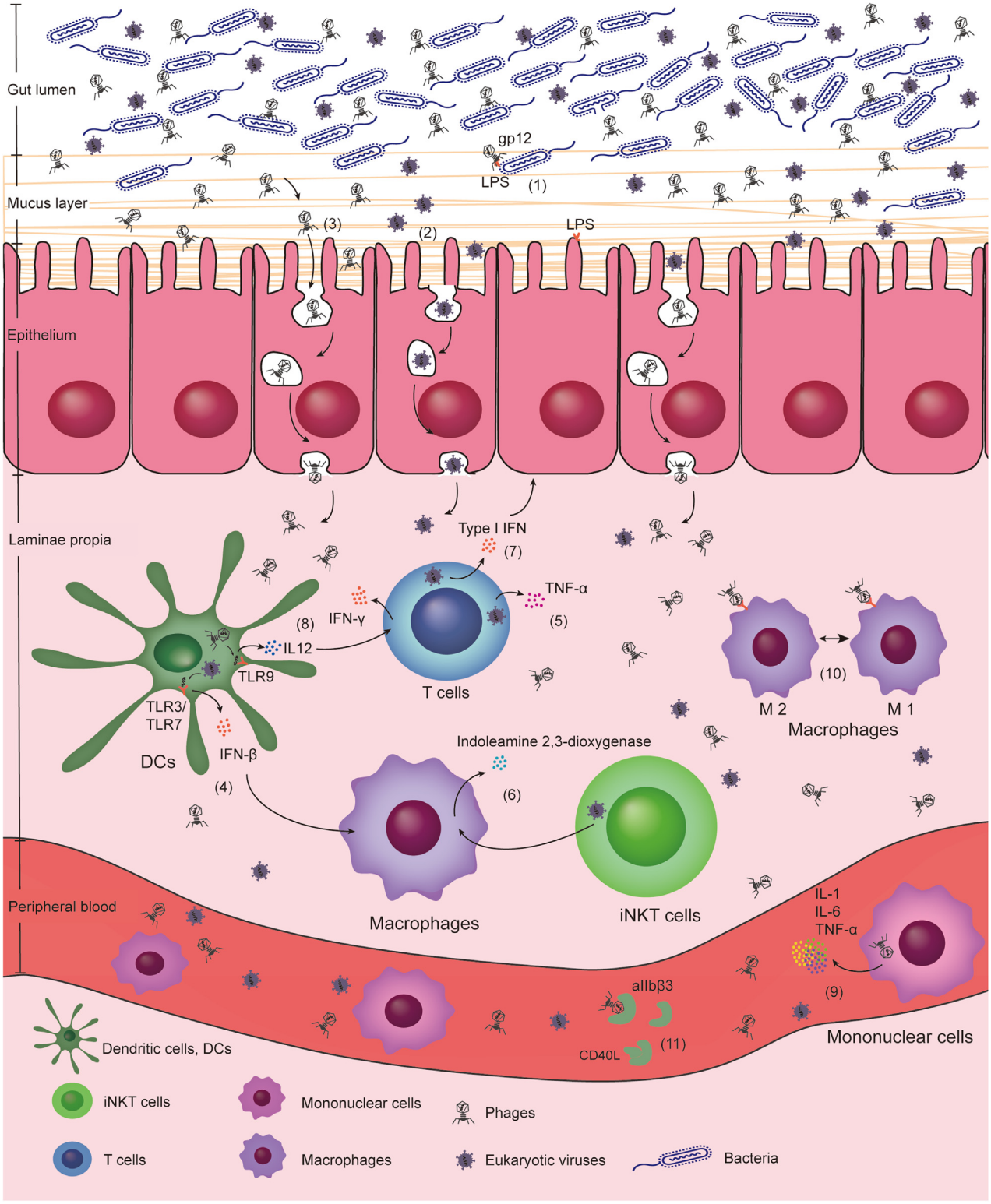

Figure 4. Possible mechanism of faecal virome transplantation (FVT) treatment of disease. (1) The gp12 protein of T4 bacteriophage can form a trimer with bacterial lipopolysaccharide (LPS) to reduce the damage of LPS to the intestinal tract. (2) Eukaryotic viruses and (3) Phages can pass through the intestine and play a role when there is no damage to the intestine. (4) Eukaryotic virus can be recognized by the intracellular receptors, Toll-like receptor 3 (TLR3) and TLR7 of plasmacytoid dendritic cells (pDCs), up-regulating the expression of interferon-β (*IFN-β*), and significantly reducing the number of infiltrated neutrophils and macrophages. (5) Eukaryotic virus infections will stimulate the increasing expression of necrosis factor-α (*TNF-α*) produced by regulatory T (Treg) cells. (6) The activation of invariant natural killer T cells (iNKT cells) caused by eukaryotic virus infection can infiltrate inhibitory macrophages, which can express indoleamine 2,3-dioxygenase into pancreatic islets. (7) Murine norovirus could

(pDCs), up-regulated the expression of interferon-β (IFN-β), and significantly reduced the number of infiltrated neutrophils and macrophages (Fig. 4-(4)).[8] The body's immune response against gut eukaryotic viruses infection, such as the expression of *TNF-α*, the release of β-cell antigens, the increase in the number and function of regulatory T (Treg) cells, etc. had also been suggested to prevent or even eliminate autoimmune diabetes (Fig. 4-(5)).[103,104] The activation of invariant natural killer T cells (iNKT cells) caused by coxsackie virus can infiltrate inhibitory macrophages which express indoleamine 2,3-dioxygenase that is very important for inhibiting the development of diabetes (Fig. 4-(6)).[109] Kernbauer et al. also proved that introducing the murine norovirus to GF mice restored the intestinal morphology which was destroyed by antibiotics-treatment, and increased the total number of CD4+ T cells without causing obvious inflammation or diseases. It also alleviated the weight loss and diarrhoea caused by antibiotic treatment.[106]

Bacteriophages

Bacteriophages may be the major role players in FVT. Bacteriophages interact with intestinal bacteria more directly than eukaryotic viruses, and the theories for the interaction include Kill-the-Winner, Piggyback-the-Winner, Piggyback-the-Loser and Red Queen hypothesis.[110–114] For instance, the change that *Firmicutes* bloom and then collapse, in wetted biological soil crusts, is the result of *Caudovirales* predation by Kill-the-Winner.[114] Piggyback-the-Winner could be found in the co-existence of crAss-like phage crAss001 and its bacterial host *Bacteroides intestinalis*, in which both of them stayed in high densities and the phage was in a lysogenic circle.[113] And Piggyback-the-Loser is regarded as the supplement for the viral-host dynamic of Piggyback-the-Winner and Kill-the-Winner.[110,112] In Piggyback-the-Loser theory, phages will enter the lysogenic circle when their host abundance is low.[110] The mutation trend of probiotics in the gut during colonization was fluctuant but not linear, which is consistent with the Red Queen hypothesis.[111]

In addition to the killing and modification effects on the gut microbes by the lytic and the lysogenic cycle as mentioned earlier, other interactions have also been studied. For example, the gp12 protein of T4 bacteriophage can form a trimer with bacterial lipopolysaccharide (LPS) to reduce the damage of LPS to the intestinal tract (Fig. 4-(1)).[115] Moreover, T4 phages can bind to glycoproteins on the mucosa by the immunoglobulin-like (Ig-like) domains displayed on its capsid to decrease the chance of bacteria contacting epithelial cells, thereby protecting the intestinal epithelial cells.[116]

Similar to eukaryotic viruses, the effect of bacteriophages is also not limited to the gut. As early as 1971, Parent and Wilson found that phages could be detected in the serum of normal people.[117] More recently, Nguyen et al. found that Myoviridae, Siphoviridae, *Podoviridae*, and other bacteriophages have a strong apical-to-basal transport directionality and it only takes 10 min for T4 phage to pass through Madin–Darby canine kidney cells.[118] Thus, they estimated that approximately 31 billion bacteriophage particles enter the lamina propria through the epithelial cell layer of the intestine every day (Fig. 4-(3)).[118]

After bacteriophages pass through the intestinal epithelial cells, they may be recognized by the intracellular receptor TLR9 of DCs cells and produce interleukin-12 (IL-12), which in turn stimulates T cells to produce IFN-γ (Fig. 4-(8)).[119] In addition, a study had also shown that bacteriophages stimulated peripheral blood mononuclear cells to produce IL-1, IL-lra (IL-1RN), IL-6, and TNF-α, and up-regulate the expression of C-X-C motif chemokine ligand-1 (*CXCL-1*), *CXCL-5*, and the overall immune response predominantly with anti-inflammatory function (Fig. 4-(9)).[120] Nevertheless, Eriksson et al. found that bacteriophages transformed M2 macrophages into M1 phenotypes through TLR thereafter, the nitric oxide (NO) produced by M1 macrophages further assisted the host to destroy tumours (Fig. 4-(10)).[121] Moreover, the NO, produced by M1 macrophages, could also help to distantly prevent the epithelial cells ferroptosis that induced by the *Pseudomonas aeruginosa* infection.[122] Bacteriophages also could reduce reactive oxygen species produced by phagocytes, which was potentially applied in inflammation control and sepsis treatment.[123]

There is also evidence of how bacteriophages interact with humoral immunity after entering the bloodstream.[124] There is a domain on T4 phage which is similar to the structure that CD40L used to bind with aIIbβ3; consequently, T4 phage can block the CD40L-induced stimulating effect on platelets through competitive binding with aIIbβ3 (Fig. 4-(11)).[125] In this way, T4 phage could modulate the regulation of inflammation, immune regulation and hemostasis, and even relate to the restoration of atherosclerosis, diabetes and IBD.[125] Notably, Frenkel et al. found that instilled filamentous bacteriophages could cross the blood-brain barrier to reach the central nervous system,[126] which hinted at the potential application of FVT in treating mental illness or neurological disorders.

Challenges and opportunities of FVT

In addition to the very limited knowledge and large unknown viruses in the gut, another major risk for both FVT and FMT is considered horizontal gene transfer. Horizontal gene transfer is also known as bacteriophage conversion, that bacteriophages carried bacteria functional genes and encoded them in the bacteriophage genome. It is a mutual benefit and symbiosis for bacteria and bacteriophages, but it can also be transferred, for example, virulence genes and

up-regulate type I interferon gene expression, thereby restoring the damage to the intestinal structure and lymphocyte function in mice caused by antibiotic treatment. (8) Phages can be recognized by the intracellular receptor TLR9 of DCs cells to induce DCs to produce interleukin-12 (IL-12), which in turn stimulates T cells to produce IFN-γ. (9) Phages can stimulate peripheral blood mononuclear cells to produce IL-1, IL-6, and TNF-α. (10) Phages can drive M2 macrophages to transform into M1 phenotypes through TLR. (11) Phages have a domain that CD40L uses to bind with aIIbβ3; consequently, it can block the combination between CD40L and the aIIbβ3.

resistance genes, and other bacteria without these genes initially. These have been proved *in vitro*, as the bacteriophages of *Enterococcus faecalis* (*E. faecalis*) could transfer virulence genes or antibiotic-resistance genes to the genome of probiotic strain *E. faecalis* Symbioflor 1.[127,128] Genes of the diphtheria toxin of *Corynebacterium diphtheriae*,[129] the Shiga toxin of *E. coli*,[130] and the cholera toxin of *Vibrio cholerae*[131] have also been found to be transferable by bacteriophages. The excessive use of antibiotics may increase the independent transfer caused by bacteriophage conversion.[132] All of these risks need to be concerned before performing FMT and FVT.

Bacteriophage therapy has been discovered since 1926 and becomes popular recently due to the sharply increased antibiotic-resistant cases.[133] Now phage therapy has been widely used in treating various diseases.[134] However, current treatment is mainly focused on a single type of bacteriophage, normally with a targeted host range. This provides us with the tool to modify the gut microbiota with specific requests, such as treating the *C. difficile* infection. The addition of bacteriophages, such as in FVT, may lead to microbial composition changes in the entire intestinal tract.[73]

In addition to transferring bacteria and viruses, introducing bacteriophage-encoded lytic enzymes, such as endolysins and depolymerases, have been tested. These enzymes degraded phage-bacterial binding receptors, destroyed the structure of bacterial membranes, and stimulated peripheral blood mononuclear cells to produce IL-1RN and further down-regulated the expression of *CXCL-1* and *CXCL-5*.[119,120,134,135] Furthermore, to counter the bacteriophage-driven selective pressure, bacteria may modify the surface receptor which comes with the cost of the reduction of bacterial adaptability and virulence, and becomes more susceptible to antibiotic treatment and immune defence.[136,137] All these effects may be indirectly beneficial for the diseases' treatment after FVT.

Considerations for FMT and FVT

Although FMT has achieved promising results and FVT shows great potential in disease treatment, several important considerations are still worth discussing here.

Donor selection

As we described above, the FMT and FVT from mice that are fat or thin will affect the recipient mice, and the gut microbiota after FMT and FVT is significantly associated with donors.[90,91] The composition of the intestinal microbiota is also related to the individual's geographical location, ethnicity, diet habits, disease history, physiological state, etc. So how we define healthy and matched donors and how we can make sure to use different intestinal microbiota from different individuals and still achieve the same therapeutic effect need more effort and investment. Stallmach et al. and Cammarota et al. proposed that before using FMT to treat rCDI, donor selection should be performed from the donor's diseases, medical treatment (antibiotics use), travel history (whether donors have ever been to the countries with an increased risk of gastrointestinal infection), social factors (including blood transfusion, tattoos, etc.), and stool examination.[10] Notably, in the early stage of FMT in human clinical treatment, people will include kinship in the standard of donor selection.[138] However, Ramai et al. excluded the influence of kinship on FMT results. In the meta-analysis which included 26 studies with a total of 1309 individuals for rCDI, FMT from the mixture of related and unrelated donors showed a 94.5% overall cure rate compared to 95.7% with unrelated donors.[16]

Patient preparation

As shown in Tables S1—S4, most clinical trials have gained desirable results from FMT without antibiotic treatment 48 h prior to enrolment, which indicates that antibiotic treatment is not necessary as the pretreatment of FMT and FVT. This is consistent with a previous study.[139] In addition, the study by Spindelboeck et al. found that antibiotics hindered the reshaping of gut microbiota after FMT, and antibiotic administration was significantly associated with FMT failure.[140] After Allegretti et al. in their study adjusted for age, sex, and severity of CDI, the result still showed that antibiotic administration was substantially related to FMT failure.[15] Optionally, the study showed loperamide could be administered to the patient within 1 h before FMT or FVT; this assisted graft stayed in the intestine for 4-6 h and provided a longer time for bacteria to colonize and function.[141] In addition, special attention should be paid to patients with low immune function, as they may develop diarrhoea, colitis, bacteremia, pneumonia, and even death after FMT.[142] Although the mechanism of its specific adverse reactions is still unclear, it is enough to set off alarm bells to us. Moreover, it still needs to be considered whether it is better to use multiple low-dose and less invasive administration methods for patients with poor immunity, and if it is necessary to directly use surgery instead of FMT and FVT for patients with severe intestinal injury.

The way of administration

When FMT is used to treat CDI, Ramai et al. showed that the cure rate of FMT administrated with colonoscopy was equivalent to the capsule, better than an enema, nasoduodenal tube and nasogastric tube.[16] However, colonoscopy is more invasive and not all patients could tolerate the nasointestinal tube.[143] Although there is no consensus on choosing fresh or frozen faeces to intervene, several studies indicated no statistically significant differential therapeutic effects between fresh and frozen grafts in treating both CDI and IBD, which proved the possibility of stool banks.[16,144—147] Furthermore, Jiang et al. also indicated that after giving FMT capsule treatment and FMT rectal instillation treatment to 31 and 34 rCDI patients respectively, their adverse reaction rates and cure results were similar.[148] It is noteworthy that in this trial the amount of manure rectal infusion therapy only required half a dose of the faeces that were used in the capsule treatment. Thus, introducing gut microbiota in a capsule or rectal infusion therapy probably can increase the application and willingness to receive FMT or FVT in the future.

Safety

As mentioned in the FVT challenges, bacteriophage-mediated horizontal gene transfer of bacterial virulence factors and drug resistance need to be considered, and whether the donor microbiota will have a negative impact on the recipient microbiota also needs to be evaluated for each patient. Although we mentioned above that eukaryotic viruses may be beneficial for disease treatment, there are also adverse effects of FMT due to enteritis caused by a eukaryotic virus infection, like norovirus gastroenteritis,[149] or COVID-19,[150] so this is also a noteworthy aspect for FMT and FVT. Fortunately, FMT is generally considered safe so far. The meta-analysis by Marcella et al., which included 129 studies involving 4241 patients in the past 20 years, found that FMT-related severe adverse events are around 1.4%.[151] One study pointed out that FMT treatment might increase the incidence of myocardial infarction in CDI patients.[152] Therefore, long-term follow-up for the safety and influence of quality of life needs to be considered.

Efficiency

The long-term benefit of FMT on different diseases seems to vary. Among 77 patients treated with FMT for rCDI in the study performed by Brandt et al., the first FMT cure rate was 91% within 17 months on average, and the second FMT cure rate for relapsed patients was 98%.[153] Several trials also showed the effectiveness of FMT maintained for 3—15 years, with variations among different types of diseases including rCDI, IBS, alopecia areata, depression symptoms, and multiple sclerosis.[42,154—157] Yet, there is still a huge lack of data regarding the long-term efficacy of FMT and FVT, but with the increasing frequency of FMT and FVT, we believe more data for evaluating the sustainability of the treatment effects will be available in the next couple of years.

Stool banks

For facing regulatory challenges, establishing the stool bank is the inevitable trend in the whole FMT and FVT fields. OpenBiome in the United States has provided FMT services for over 1300 healthcare institutions in the United States, and manufactured and shipped more than 65,000 FMT treatments, since 2012.[158,159] Other countries have also established stool banks, including China, the United Kingdom, Italy, the Netherlands, Australia, Brazil, Singapore, Spain, and so on.[160—167] Although economic impacts and risks caused by COVID-19 affected the normal running of stool banks,[168—170] most of them are still operating normally and trying to produce new alternative drugs.[158,164—167] The stool banks in different countries represent the local gut microbiota which has minor variations due to geographic differences. But the standards on donor selection, supervision system, FVT procedure, etc. are still not unified in the world.[163]

Prospects of FMT and FVT

The ultimate goal of FMT or FVT treatment is to defeat various diseases by regulating the gut microbiota with the least harm to humans, and restoring the overall health of the body. More investigation and research are needed in evaluating and comparing FMT, FVT, and mixed microbiota products with phage therapy. The inspection and review process for these products needs to be more extensive, standardized and mature, and the preparation for treatment needs to be more complete and safer. Hopefully, in the near future, doctors could explore the characteristic gut microbiota of each patient, consider different diseases and immunity conditions, find the most suitable donor type, and design personalized treatments that are FMT, FVT, or other microbiota products.

Data availability statement

The authors declare that all the data supporting the findings of this study are available within the article and its supplementary information files, which were all obtained from the cited references.

Author contributions

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Shengru Wu and Xin Yang had primary responsibility for the final content.
All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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References

1. Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. *Curr Opin Gastroenterol* 2015;**31**:69—75.
2. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol* 2016;**14**:e1002533.
3. Jalanka-Tuovinen J, Salonen A, Nikkila J, Immonen O, Kekkonen R, Lahti L, et al. Intestinal microbiota in healthy adults: temporal analysis reveals individual and common core and relation to intestinal symptoms. *PLoS One* 2011;**6**:e23035.
4. Wozniak H, Beckmann TS, Frohlich L, Soccorsi T, Le Terrier C, de Watteville A, et al. The central and biodynamic role of gut microbiota in critically ill patients. *Crit Care* 2022;**26**:250.

5. Saha S, Tariq R, Tosh PK, Pardi DS, Khanna S. Faecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. *Clin Microbiol Infect* 2019;**25**:958—63.
6. Petrof EO, Khoruts A. From stool transplants to next-generation microbiota therapeutics. *Gastroenterology* 2014;**146**:1573—82.
7. Zuo T, Wong SH, Lam K, Lui R, Cheung K, Tang W, et al. Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. *Gut* 2018;**67**:634—43.
8. Yang JY, Kim MS, Kim E, Cheon JH, Lee YS, Kim Y, et al. Enteric viruses ameliorate gut inflammation via toll-like receptor 3 and toll-like receptor 7-mediated interferon-beta production. *Immunity* 2016;**44**:889—900.
9. Rasmussen TS, Koefoed AK, Jakobsen RR, Deng L, Castro-Mejia JL, Brunse A, et al. Bacteriophage-mediated manipulation of the gut microbiome - promises and presents limitations. *FEMS Microbiol Rev* 2020;**44**:507—21.
10. Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017;**66**:569—80.
11. Kim KO, Gluck M. Fecal microbiota transplantation: an update on clinical practice. *Clin Endosc* 2019;**52**:137—43.
12. Ma GK, Brensinger CM, Wu Q, Lewis JD. Increasing incidence of multiply recurrent Clostridium difficile infection in the United States: a cohort study. *Ann Intern Med* 2017;**167**:152—8.
13. Barkin JA, Sussman DA, Fifadara N, Barkin JS. Clostridium difficile infection and patient-specific antimicrobial resistance testing reveals a high metronidazole resistance rate. *Dig Dis Sci* 2017;**62**:1035—42.
14. Slimings C, Riley TV. Antibiotics and healthcare facility-associated Clostridioides difficile infection: systematic review and meta-analysis 2020 update. *J Antimicrob Chemother* 2021;**76**:1676—88.
15. Allegretti JR, Kao D, Sitko J, Fischer M, Kassam Z. Early antibiotic use after fecal microbiota transplantation increases risk of treatment failure. *Clin Infect Dis* 2018;**66**:134—5.
16. Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, et al. Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent clostridioides difficile infection: a systematic review and meta-analysis. *Dig Dis Sci* 2021;**66**:369—80.
17. Tariq R, Hayat M, Pardi D, Khanna S. Predictors of failure after fecal microbiota transplantation for recurrent Clostridioides difficile infection: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2021;**40**:1383—92.
18. Shellito AD, Russell MM. Diverting loop ileostomy for Clostridium difficile colitis: a systematic review and meta-analysis. *Am Surg* 2020;**86**:1269—76.
19. Rokkas T, Gisbert JP, Gasbarrini A, Hold GL, Tilg H, Malfertheiner P, et al. A network meta-analysis of randomized controlled trials exploring the role of fecal microbiota transplantation in recurrent Clostridium difficile infection. *United European Gastroenterol J* 2019;**7**:1051—63.
20. Lesniak NA, Tomkovich S, Henry A, Taylor A, Colovas J, Bishop L, et al. Diluted fecal community transplant restores clostridioides difficile colonization resistance to antibiotic-perturbed murine communities. *mBio* 2022:e0136422.
21. Lai CY, Sung J, Cheng F, Tang W, Wong SH, Chan PKS, et al. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. *Aliment Pharmacol Ther* 2019;**49**:354—63.
22. Peyrin-Biroulet L, Arkkila P, Armuzzi A, Danese S, Guardiola J, Jahnsen J, et al. Comparative efficacy and safety of infliximab and vedolizumab therapy in patients with inflammatory bowel disease: a systematic review and meta-analysis. *BMC Gastroenterol* 2022;**22**:291.
23. Cui J, Lin Z, Tian H, Yang B, Zhao D, Ye C, et al. Long-term follow-up results of fecal microbiota transplantation for irritable bowel syndrome: a single-center, retrospective study. *Front Med* 2021;**8**:710452.
24. Ferrere G, Wrzosek L, Cailleux F, Turpin W, Puchois V, Spatz M, et al. Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice. *J Hepatol* 2017;**66**:806—15.
25. Tilg H, Mathurin P. Altered intestinal microbiota as a major driving force in alcoholic steatohepatitis. *Gut* 2016;**65**:728—9.
26. Tarawneh R, Penhos E. *The gut microbiome and Alzheimer's disease: complex and bidirectional interactions*. Neurosci Biobehav Rev.; 2022, 104814.
27. Goo N, Bae HJ, Park K, Kim J, Jeong Y, Cai M, et al. The effect of fecal microbiota transplantation on autistic-like behaviors in Fmr1 KO mice. *Life Sci* 2020;**262**:118497.
28. Mazzawi T, Lied GA, Sangnes DA, El-Salhy M, Hov JR, Gilja OH, et al. The kinetics of gut microbial community composition in patients with irritable bowel syndrome following fecal microbiota transplantation. *PLoS One* 2018;**13**:e0194904.
29. Munoz-Pinto MF, Empadinhas N, Cardoso SM. The neuromicrobiology of Parkinson's disease: a unifying theory. *Ageing Res Rev* 2021:101396.
30. Blacher E, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, et al. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature* 2019;**572**:474—80.
31. Schepici G, Silvestro S, Bramanti P, Mazzon E. The gut microbiota in multiple sclerosis: an overview of clinical trials. *Cell Transplant* 2019;**28**:1507—27.
32. Citraro R, Lembo F, De Caro C, Tallarico M, Coretti L, Iannone LF, et al. First evidence of altered microbiota and intestinal damage and their link to absence epilepsy in a genetic animal model, the WAG/Rij rat. *Epilepsia* 2021;**62**:529—41.
33. Chen R, Xu Y, Wu P, Zhou H, Lasanajak Y, Fang Y, et al. Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. *Pharmacol Res* 2019;**148**:104403.
34. Li S, Lv J, Li J, Zhao Z, Guo H, Zhang Y, et al. Intestinal microbiota impact sepsis associated encephalopathy via the vagus nerve. *Neurosci Lett* 2018;**662**:98—104.
35. Qi X, Li X, Zhao Y, Wu X, Chen F, Ma X, et al. Treating steroid refractory intestinal acute graft-vs.-host disease with fecal microbiota transplantation: a pilot study. *Front Immunol* 2018;**9**:2195.
36. Utay NS, Monczor AN, Somasunderam A, Lupo S, Jiang ZD, Alexander AS, et al. Evaluation of six weekly oral fecal microbiota transplants in people with HIV. *Pathog Immun* 2020;**5**:364—81.
37. Wang M, Zhu Z, Lin X, Li H, Wen C, Bao J, et al. Gut microbiota mediated the therapeutic efficacies and the side effects of prednisone in the treatment of MRL/lpr mice. *Arthritis Res Ther* 2021;**23**:240.
38. Wu X, Zhang T, Chen X, Ji G, Zhang F. Microbiota transplantation: targeting cancer treatment. *Cancer Lett* 2019;**452**:144—51.
39. Cullin N, Azevedo Antunes C, Straussman R, Stein-Thoeringer CK, Elinav E. Microbiome and cancer. *Cancer Cell* 2021;**39**:1317—41.
40. Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, et al. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. *J Hematol Oncol* 2022;**15**:47.

41. Xie WR, Yang XY, Xia HH, Wu LH, He XX. Hair regrowth following fecal microbiota transplantation in an elderly patient with alopecia areata: a case report and review of the literature. *World J Clin Cases* 2019;**7**:3074—81.
42. Rebello D, Wang E, Yen E, Lio PA, Kelly CR. Hair growth in two alopecia patients after fecal microbiota transplant. *ACG Case Rep J* 2017;**4**:e107.
43. Morinaga H, Mohri Y, Grachtchouk M, Asakawa K, Matsumura H, Oshima M, et al. Obesity accelerates hair thinning by stem cell-centric converging mechanisms. *Nature* 2021;**595**:266—71.
44. An L, Wuri J, Zheng Z, Li W, Yan T. Microbiota modulate Doxorubicin induced cardiotoxicity. *Eur J Pharmaceut Sci* 2021;**166**:105977.
45. Merli P, Putignani L, Ruggeri A, Del Chierico F, Gargiullo L, Galaverna F, et al. Decolonization of multi-drug resistant bacteria by fecal microbiota transplantation in five pediatric patients before allogeneic hematopoietic stem cell transplantation: gut microbiota profiling, infectious and clinical outcomes. *Haematologica* 2020;**105**:2686—90.
46. Gai X, Wang H, Li Y, Zhao H, He C, Wang Z, et al. Fecal microbiota transplantation protects the intestinal mucosal barrier by reconstructing the gut microbiota in a murine model of sepsis. *Front Cell Infect Microbiol* 2021;**11**:736204.
47. Lai HC, Lin TL, Chen TW, Kuo YL, Chang CJ, Wu TR, et al. Gut microbiota modulates COPD pathogenesis: role of anti-inflammatory Parabacteroides goldsteinii lipopolysaccharide. *Gut* 2021;**71**:309—21.
48. Liu Y, Fan L, Cheng Z, Yu L, Cong S, Hu Y, et al. Fecal transplantation alleviates acute liver injury in mice through regulating Treg/Th17 cytokines balance. *Sci Rep* 2021;**11**:1611.
49. Rao J, Qiao Y, Xie R, Lin L, Jiang J, Wang C, et al. Fecal microbiota transplantation ameliorates stress-induced depression-like behaviors associated with the inhibition of glial and NLRP3 inflammasome in rat brain. *J Psychiatr Res* 2021;**137**:147—57.
50. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021;**371**:602—9.
51. Hensley-McBain T, Zevin AS, Manuzak J, Smith E, Gile J, Miller C, et al. Effects of fecal microbial transplantation on microbiome and immunity in simian immunodeficiency virus-infected macaques. *J Virol* 2016;**90**:4981—9.
52. Vujkovic-Cvijin I, Rutishauser RL, Pao M, Hunt PW, Lynch SV, McCune JM, et al. Limited engraftment of donor microbiome via one-time fecal microbial transplantation in treated HIV-infected individuals. *Gut Microb* 2017;**8**:440—50.
53. U.S. Food and Drug Administration. Safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse events likely due to transmission of pathogenic organisms. Available: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely [Accessed 25 January 2023].
54. Zellmer C, Sater MRA, Huntley MH, Osman M, Olesen SW, Ramakrishna B. Shiga toxin-producing Escherichia coli transmission via fecal microbiota transplant. *Clin Infect Dis* 2021;**72**:e876—80.
55. Zhang T, Lu G, Zhao Z, Liu Y, Shen Q, Li P, et al. Washed microbiota transplantation vs. manual fecal microbiota transplantation: clinical findings, animal studies and in vitro screening. *Protein Cell* 2020;**11**:251—66.
56. Khanna S, Assi M, Lee C, Yoho D, Louie T, Knapple W, et al. Efficacy and safety of RBX2660 in PUNCH CD3, a phase III, randomized, double-blind, placebo-controlled trial with a bayesian primary analysis for the prevention of recurrent clostridioides difficile infection. *Drugs* 2022;**82**:1527—38.
57. Feuerstadt P, Louie TJ, Lashner B, Wang EEL, Diao L, Bryant JA, et al. SER-109, an oral microbiome therapy for recurrent clostridioides difficile infection. *N Engl J Med* 2022;**386**:220—9.
58. Hu YOO, Hugerth LW, Bengtsson C, Alisjahbana A, Seifert M, Kamal A, et al. Bacteriophages synergize with the gut microbial community to combat Salmonella. *mSystems* 2018;**3**.
59. Cheng AG, Ho PY, Aranda-Diaz A, Jain S, Yu FB, Meng X, et al. Design, construction, and in vivo augmentation of a complex gut microbiome. *Cell* 2022;**185**:3617—3636 e19.
60. Dsouza M, Menon R, Crossette E, Bhattarai SK, Schneider J, Kim YG, et al. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe* 2022;**30**:583—598 e8.
61. Keller JJ, Ooijevaar RE, Hvas CL, Terveer EM, Lieberknecht SC, Hogenauer C, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. *United European Gastroenterol J* 2021;**9**:229—47.
62. Australian Therapeutic Goods Administration. Faecal microbiota transplant (FMT) products: interpretative and technical guidance on GMP requirements. Available: https://www.tga.gov.au/resources/resource/guidance/faecal-microbiota-transplant-fmt-products-interpretative-and-technical-guidance-gmp-requirements [Accessed 25 January 2023].
63. U.S. Food and Drug Administration. Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat Clostridium difficile infection not responsive to standard therapies. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota [Accessed 25 January 2023].
64. Haifer C, Kelly CR, Paramsothy S, Andresen D, Papanicolas LE, McKew GL, et al. Australian consensus statements for the regulation, production and use of faecal microbiota transplantation in clinical practice. *Gut* 2020;**69**:801—10.
65. Australian Therapeutic Goods Administration. Faecal microbiota transplant - BiomeBank (399066). Available: https://www.tga.gov.au/resources/artg/399066 [Accessed 25 January 2023].
66. U.S. Food and Drug Administration. FDA approves first fecal microbiota product. Available: https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product [Accessed 25 January 2023].
67. Javed QUA, Afzal M, Ilyas K, Sarfraz A, Sarfraz Z. Treatment efficacy of fecal microbiota-based live biotherapeutics (RBX2660) for the prevention of recurring Clostridioides difficile infection. *Eur J Intern Med* 2022. Online ahead of print.
68. Papazyan R, Ferdyan N, Srinivasan K, Gonzalez C, Shannon WD, Blount K, et al. Human fecal bile acid analysis after investigational microbiota-based live biotherapeutic delivery for recurrent clostridioides difficile infection. *Microorganisms* 2023;**11**.
69. Tillotson G, Archbald-Pannone L, Johnson S, Ng S, Ando M, Harvey A, et al. Microbiota-based live biotherapeutic RBX2660 for the reduction of recurrent clostridioides difficile infection in older adults with underlying comorbidities. *Open Forum Infect Dis* 2023;**10**:ofac703.
70. Lam KN, Spanogiannopoulos P, Soto-Perez P, Alexander M, Nalley MJ, Bisanz JE, et al. Phage-delivered CRISPR-Cas9 for strain-specific depletion and genomic deletions in the gut microbiome. *Cell Rep* 2021;**37**:109930.
71. Gregory AC, Zablocki O, Zayed AA, Howell A, Bolduc B, Sullivan MB. The gut virome database reveals age-dependent

patterns of virome diversity in the human gut. *Cell Host Microbe* 2020;**28**:724—740 e8.
72. Spencer L, Olawuni B, Singh P. Gut virome: role and distribution in health and gastrointestinal diseases. *Front Cell Infect Microbiol* 2022;**12**:836706.
73. Tetz GV, Ruggles KV, Zhou H, Heguy A, Tsirigos A, Tetz V. Bacteriophages as potential new mammalian pathogens. *Sci Rep* 2017;**7**:7043.
74. Ripp S, Miller RV. Dynamics of the pseudolysogenic response in slowly growing cells of Pseudomonas aeruginosa. *Microbiology (Read)* 1998;**144**(Pt 8):2225—32.
75. Fulci V, Stronati L, Cucchiara S, Laudadio I, Carissimi C. Emerging roles of gut virome in pediatric diseases. *Int J Mol Sci* 2021;**22**.
76. Andari S, Hussein H, Fadlallah S, Jurjus AR, Shirinian M, Hashash JG, et al. Epstein-barr virus DNA exacerbates colitis symptoms in a mouse model of inflammatory bowel disease. *Viruses* 2021;**13**.
77. Honeyman MC, Coulson BS, Stone NL, Gellert SA, Goldwater PN, Steele CE, et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* 2000;**49**:1319—24.
78. Kagnoff MF, Paterson YJ, Kumar PJ, Kasarda DD, Carbone FR, Unsworth DJ, et al. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease. *Gut* 1987;**28**:995—1001.
79. Jiang L, Lang S, Duan Y, Zhang X, Gao B, Chopyk J, et al. Intestinal virome in patients with alcoholic hepatitis. *Hepatology* 2020;**72**:2182—96.
80. Mangalea MR, Paez-Espino D, Kieft K, Chatterjee A, Chriswell ME, Seifert JA, et al. Individuals at risk for rheumatoid arthritis harbor differential intestinal bacteriophage communities with distinct metabolic potential. *Cell Host Microbe* 2021;**29**:726—739 e5.
81. Tetz G, Brown SM, Hao Y, Tetz V. Parkinson's disease and bacteriophages as its overlooked contributors. *Sci Rep* 2018;**8**:10812.
82. Yang K, Niu J, Zuo T, Sun Y, Xu Z, Tang W, et al. Alterations in the gut virome in obesity and type 2 diabetes mellitus. *Gastroenterology* 2021;**161**:1257—1269 e13.
83. Shkoporov AN, Clooney AG, Sutton TDS, Ryan FJ, Daly KM, Nolan JA, et al. The human gut virome is highly diverse, stable, and individual specific. *Cell Host Microbe* 2019;**26**:527—541 e5.
84. Norman JM, Handley SA, Baldridge MT, Droit L, Liu CY, Keller BC, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. *Cell* 2015;**160**:447—60.
85. Draper LA, Ryan FJ, Smith MK, Jalanka J, Mattila E, Arkkila PA, et al. Long-term colonisation with donor bacteriophages following successful faecal microbial transplantation. *Microbiome* 2018;**6**:220.
86. Conceicao-Neto N, Deboutte W, Dierckx T, Machiels K, Wang J, Yinda KC, et al. Low eukaryotic viral richness is associated with faecal microbiota transplantation success in patients with UC. *Gut* 2018;**67**:1558—9.
87. Draper LA, Ryan FJ, Dalmasso M, Casey PG, McCann A, Velayudhan V, et al. Autochthonous faecal viral transfer (FVT) impacts the murine microbiome after antibiotic perturbation. *BMC Biol* 2020;**18**:173.
88. Bahr SM, Weidemann BJ, Castro AN, Walsh JW, deLeon O, Burnett CM, et al. Risperidone-induced weight gain is mediated through shifts in the gut microbiome and suppression of energy expenditure. *EBioMedicine* 2015;**2**:1725—34.
89. Shute A, Callejas BE, Li S, Wang A, Jayme TS, Ohland C, et al. Cooperation between host immunity and the gut bacteria is essential for helminth-evoked suppression of colitis. *Microbiome* 2021;**9**:186.
90. Lin DM, Koskella B, Ritz NL, Lin D, Carroll-Portillo A, Lin HC. Transplanting fecal virus-like particles reduces high-fat diet-induced small intestinal bacterial overgrowth in mice. *Front Cell Infect Microbiol* 2019;**9**:348.
91. Rasmussen TS, Mentzel CMJ, Kot W, Castro-Mejia JL, Zuffa S, Swann JR, et al. Faecal virome transplantation decreases symptoms of type 2 diabetes and obesity in a murine model. *Gut* 2020;**69**:2122—30.
92. Wu Z, Huang S, Li T, Li N, Han D, Zhang B, et al. Gut microbiota from green tea polyphenol-dosed mice improves intestinal epithelial homeostasis and ameliorates experimental colitis. *Microbiome* 2021;**9**:184.
93. Sinha A, Li Y, Mirzaei MK, Shamash M, Samadfam R, King IL, et al. Transplantation of bacteriophages from ulcerative colitis patients shifts the gut bacteriome and exacerbates severity of DSS-colitis. *bioRxiv* 2021. https://doi.org/10.1101/2021.09.10.459444.
94. Brunse A, Deng L, Pan X, Hui Y, Castro-Mejia JL, Kot W, et al. Fecal filtrate transplantation protects against necrotizing enterocolitis. *ISME J* 2021;**16**:686—94.
95. Manrique P, Zhu Y, van der Oost J, Herrema H, Nieuwdorp M, de Vos WM, et al. Gut bacteriophage dynamics during fecal microbial transplantation in subjects with metabolic syndrome. *Gut Microb* 2021;**13**:1—15.
96. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome* 2017;**5**:10.
97. Zhang F, Zuo T, Yeoh YK, Cheng FWT, Liu Q, Tang W, et al. Longitudinal dynamics of gut bacteriome, mycobiome and virome after fecal microbiota transplantation in graft-versus-host disease. *Nat. Commun.* 2021;**12**:65.
98. Broecker F, Russo G, Klumpp J, Moelling K. Stable core virome despite variable microbiome after fecal transfer. *Gut Microb* 2017;**8**:214—20.
99. Chehoud C, Dryga A, Hwang Y, Nagy-Szakal D, Hollister EB, Luna RA, et al. Transfer of viral communities between human individuals during fecal microbiota transplantation. *mBio* 2016;**7**:e00322.
100. Kao DH, Roach B, Walter J, Lobenberg R, Wong K. Effect of lyophilized sterile fecal filtrate vs lyophilized donor stool on recurrent Clostridium difficile infection (rcdi): preliminary results from a randomized, double-blind pilot study. *Journal of the Canadian Association of Gastroenterology* 2019;**2**:101—2.
101. Ott SJ, Waetzig GH, Rehman A, Moltzau-Anderson J, Bharti R, Grasis JA, et al. Efficacy of sterile fecal filtrate transfer for treating patients with Clostridium difficile infection. *Gastroenterology* 2017;**152**:799—811 e7.
102. Chen X, Liu R, Liu X, Xu C, Wang X. Protective role of coxsackie-adenovirus receptor in the pathogenesis of inflammatory bowel diseases. *BioMed Res Int* 2018;**2018**:7207268.
103. Wetzel JD, Barton ES, Chappell JD, Baer GS, Mochow-Grundy M, Rodgers SE, et al. Reovirus delays diabetes onset but does not prevent insulitis in nonobese diabetic mice. *J Virol* 2006;**80**:3078—82.
104. Pearson JA, Tai N, Ekanayake-Alper DK, Peng J, Hu Y, Hager K, et al. Norovirus changes susceptibility to type 1 diabetes by altering intestinal microbiota and immune cell functions. *Front Immunol* 2019;**10**:2654.
105. Graham KL, O'Donnell JA, Tan Y, Sanders N, Carrington EM, Allison J, et al. Rotavirus infection of infant and young adult nonobese diabetic mice involves extraintestinal spread and delays diabetes onset. *J Virol* 2007;**81**:6446—58.
106. Kernbauer E, Ding Y, Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria. *Nature* 2014;**516**:94—8.

107. Witkowski PT, Perley CC, Brocato RL, Hooper JW, Jurgensen C, Schulzke JD, et al. Gastrointestinal tract as entry route for hantavirus infection. *Front Microbiol* 2017;**8**:1721.
108. Mossel EC, Ramig RF. A lymphatic mechanism of rotavirus extraintestinal spread in the neonatal mouse. *J Virol* 2003;**77**:12352—6.
109. Ghazarian L, Diana J, Beaudoin L, Larsson PG, Puri RK, van Rooijen N, et al. Protection against type 1 diabetes upon Coxsackievirus B4 infection and iNKT-cell stimulation: role of suppressive macrophages. *Diabetes* 2013;**62**:3785—96.
110. Knowles B, Silveira CB, Bailey BA, Barott K, Cantu VA, Cobian-Guemes AG, et al. Lytic to temperate switching of viral communities. *Nature* 2016;**531**:466—70.
111. Li W, Yao G, Cai H, Bai M, Kwok LY, Sun Z. Comparative genomics of in vitro and in vivo evolution of probiotics reveals energy restriction not the main evolution driving force in short term. *Genomics* 2021;**113**:3373—80.
112. Paterson JS, Smith RJ, McKerral JC, Dann LM, Launer E, Goonan P, et al. A hydrocarbon-contaminated aquifer reveals a Piggyback-the-Persistent viral strategy. *FEMS Microbiol Ecol* 2019;**95**.
113. Shkoporov AN, Khokhlova EV, Stephens N, Hueston C, Seymour S, Hryckowian AJ, et al. Long-term persistence of crAss-like phage crAss001 is associated with phase variation in Bacteroides intestinalis. *BMC Biol* 2021;**19**:163.
114. Van Goethem MW, Swenson TL, Trubl G, Roux S, Northen TR. Characteristics of wetting-induced bacteriophage blooms in biological soil crust. *mBio* 2019;**10**.
115. Miernikiewicz P, Klopot A, Soluch R, Szkuta P, Keska W, Hodyra-Stefaniak K, et al. T4 phage tail adhesin Gp12 counteracts LPS-induced inflammation in vivo. *Front Microbiol* 2016;**7**:1112.
116. Barr JJ, Auro R, Furlan M, Whiteson KL, Erb ML, Pogliano J, et al. Bacteriophage adhering to mucus provide a non-host-derived immunity. *Proc Natl Acad Sci U S A* 2013;**110**:10771—6.
117. Parent K, Wilson ID. Mycobacteriophage in Crohn's disease. *Gut* 1971;**12**:1019—20.
118. Nguyen S, Baker K, Padman BS, Patwa R, Dunstan RA, Weston TA, et al. Bacteriophage transcytosis provides a mechanism to cross epithelial cell layers. *mBio* 2017;**8**.
119. Gogokhia L, Buhrke K, Bell R, Hoffman B, Brown DG, Hanke-Gogokhia C, et al. Expansion of bacteriophages is linked to aggravated intestinal inflammation and colitis. *Cell Host Microbe* 2019;**25**:285—299 e8.
120. Van Belleghem JD, Clement F, Merabishvili M, Lavigne R, Vaneechoutte M. Pro- and anti-inflammatory responses of peripheral blood mononuclear cells induced by Staphylococcus aureus and Pseudomonas aeruginosa phages. *Sci Rep* 2017;**7**:8004.
121. Eriksson F, Tsagozis P, Lundberg K, Parsa R, Mangsbo SM, Persson MA, et al. Tumor-specific bacteriophages induce tumor destruction through activation of tumor-associated macrophages. *J Immunol* 2009;**182**:3105—11.
122. Dar HH, Anthonymuthu TS, Ponomareva LA, Souryavong AB, Shurin GV, Kapralov AO, et al. A new thiol-independent mechanism of epithelial host defense against Pseudomonas aeruginosa: iNOS/NO(*) sabotage of theft-ferroptosis. *Redox Biol* 2021;**45**:102045.
123. Przerwa A, Zimecki M, Switala-Jelen K, Dabrowska K, Krawczyk E, Luczak M, et al. Effects of bacteriophages on free radical production and phagocytic functions. *Med Microbiol Immunol* 2006;**195**:143—50.
124. Uhr JW, Dancis J, Franklin EC, Finkelstein MS, Lewis EW. The antibody response to bacteriophage phi-X 174 in newborn premature infants. *J Clin Invest* 1962;**41**:1509—13.
125. Gorski A, Wazna E, Dabrowska BW, Dabrowska K, Switala-Jelen K, Miedzybrodzki R. Bacteriophage translocation. *FEMS Immunol Med Microbiol* 2006;**46**:313—9.
126. Frenkel D, Solomon B. Filamentous phage as vector-mediated antibody delivery to the brain. *Proc Natl Acad Sci U S A* 2002;**99**:5675—9.
127. Zhang H, Stevens RH. Intrinsic resistance of Enterococcus faecalis strains to PhiEf11 phage endolysin is associated with the presence of PhiEf11 prophage. *Arch Virol* 2021;**166**:249—58.
128. Rossmann FS, Racek T, Wobser D, Puchalka J, Rabener EM, Reiger M, et al. Phage-mediated dispersal of biofilm and distribution of bacterial virulence genes is induced by quorum sensing. *PLoS Pathog* 2015;**11**:e1004653.
129. Freeman VJ. Studies on the virulence of bacteriophage-infected strains of Corynebacterium diphtheriae. *J Bacteriol* 1951;**61**:675—88.
130. Nakamura K, Ogura Y, Gotoh Y, Hayashi T. Prophages integrating into prophages: a mechanism to accumulate type III secretion effector genes and duplicate Shiga toxin-encoding prophages in Escherichia coli. *PLoS Pathog* 2021;**17**:e1009073.
131. Faruque SM, Mekalanos JJ. Phage-bacterial interactions in the evolution of toxigenic Vibrio cholerae. *Virulence* 2012;**3**:556—65.
132. Maiques E, Ubeda C, Campoy S, Salvador N, Lasa I, Novick RP, et al. beta-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in Staphylococcus aureus. *J Bacteriol* 2006;**188**:2726—9.
133. Levin BR, Bull JJ. Population and evolutionary dynamics of phage therapy. *Nat Rev Microbiol* 2004;**2**:166—73.
134. Yan W, Banerjee P, Xu M, Mukhopadhyay S, Ip M, Carrigy NB, et al. Formulation strategies for bacteriophages to target intracellular bacterial pathogens. *Adv Drug Deliv Rev* 2021;**176**:113864.
135. Roach DR, Donovan DM. Antimicrobial bacteriophage-derived proteins and therapeutic applications. *Bacteriophage* 2015;**5**:e1062590.
136. Chan BK, Sistrom M, Wertz JE, Kortright KE, Narayan D, Turner PE. Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. *Sci Rep* 2016;**6**:26717.
137. Shen Y, Loessner MJ. Beyond antibacterials - exploring bacteriophages as antivirulence agents. *Curr Opin Biotechnol* 2021;**68**:166—73.
138. Louie T. Nature's therapy for recurrent Clostridium difficile diarrhea. Interview by Paul C. Adams. *Can J Gastroenterol* 2008;**22**:455—6.
139. Freitag TL, Hartikainen A, Jouhten H, Sahl C, Meri S, Anttila VJ, et al. Minor effect of antibiotic pre-treatment on the engraftment of donor microbiota in fecal transplantation in mice. *Front Microbiol* 2019;**10**:2685.
140. Spindelboeck W, Halwachs B, Bayer N, Huber-Krassnitzer B, Schulz E, Uhl B, et al. Antibiotic use and ileocolonic immune cells in patients receiving fecal microbiota transplantation for refractory intestinal GvHD: a prospective cohort study. *Ther Adv Hematol* 2021;**12**:20406207211058333.
141. Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. *Gastrointest Endosc* 2013;**78**:240—9.
142. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *Am J Gastroenterol* 2014;**109**:1065—71.
143. Tian H, Ge X, Nie Y, Yang L, Ding C, McFarland LV, et al. Fecal microbiota transplantation in patients with slow-transit constipation: a randomized, clinical trial. *PLoS One* 2017;**12**:e0171308.
144. Allegretti JR, Elliott RJ, Ladha A, Njenga M, Warren K, O'Brien K, et al. Stool processing speed and storage duration

do not impact the clinical effectiveness of fecal microbiota transplantation. *Gut Microb* 2020;**11**:1806—8.
145. Fang H, Fu L, Wang J. Protocol for fecal microbiota transplantation in inflammatory bowel disease: a systematic review and meta-analysis. *BioMed Res Int* 2018;**2018**:8941340.
146. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. *Aliment Pharmacol Ther* 2017;**46**:479—93.
147. Tang G, Yin W, Liu W. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: a meta-analysis? *Diagn Microbiol Infect Dis* 2017;**88**:322—9.
148. Jiang ZD, Jenq RR, Ajami NJ, Petrosino JF, Alexander AA, Ke S, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: a randomized clinical trial. *PLoS One* 2018;**13**:e0205064.
149. Schwartz M, Gluck M, Koon S. Norovirus gastroenteritis after fecal microbiota transplantation for treatment of Clostridium difficile infection despite asymptomatic donors and lack of sick contacts. *Am J Gastroenterol* 2013;**108**:1367.
150. Hohmann EL. Faecal microbiota transplantation: more screening for old and new pathogens. *Lancet Infect Dis* 2021;**21**:587—9.
151. Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. *Aliment Pharmacol Ther* 2021;**53**:33—42.
152. Dawwas GK, Brensinger CM, Vajravelu RK, Wu Q, Kelly CR, Laine L, et al. Long-term Outcomes Following Multiply Recurrent Clostridioides difficile Infection and Fecal Microbiota Transplantation. *Clin Gastroenterol Hepatol* 2022;**20**:806—816 e6.
153. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012;**107**:1079—87.
154. Borody T, Leis S, Campbell J, Torres M, Nowak A. Fecal microbiota transplantation (FMT) in multiple sclerosis (MS): 942. *Official journal of the American College of Gastroenterology | ACG*. 2011;**106**:S352.
155. Ooijevaar RE, van Nood E, Goorhuis A, Terveer EM, van Prehn J, Verspaget HW, et al. Ten-Year follow-up of patients treated with fecal microbiota transplantation for recurrent clostridioides difficile infection from a randomized controlled trial and review of the literature. *Microorganisms* 2021;**9**.
156. Collyer R, Clancy A, Borody T. Faecal microbiota transplantation alleviates symptoms of depression in individuals with irritable bowel syndrome: a case series. *Medicine in Microecology* 2020;**6**.
157. El-Salhy M, Winkel R, Casen C, Hausken T, Gilja OH, Hatlebakk JG. Efficacy of Fecal Microbiota Transplantation for Patients With Irritable Bowel Syndrome at 3 Years After Transplantation. *Gastroenterology* 2022;**163**:982—994 e14.
158. OpenBiome. FDA Approval of microbiome-based therapy expands access for patients. OpenBiome Continues Distribution Fecal Microbiota Transplantation (FMT). Available: https://openbiome.org/feature/fda-approval-of-microbiome-based-therapy-expands-access-for-patients-openbiome-continues-distribution-of-fecal-microbiota-transplantation-fmt/ [Accessed 25 January 2023].
159. OpenBiome. OpenBiome Announces new collaboration with the university of Minnesota to treat patients with recurrent C. difficile infections. Available: https://openbiome.org/feature/openbiome-announces-new-collaboration-with-the-university-of-minnesota-to-treat-patients-with-recurrent-c-difficile-infections/[Accessed 25 January 2023].
160. He J, He X, Ma Y, Yang L, Fang H, Shang S, et al. A comprehensive approach to stool donor screening for faecal microbiota transplantation in China. *Microb Cell Factories* 2021;**20**:216.
161. Ianiro G, Porcari S, Bibbo S, Giambo F, Quaranta G, Masucci L, et al. Donor program for fecal microbiota transplantation: a 3-year experience of a large-volume Italian stool bank. *Dig Liver Dis* 2021;**53**:1428—32.
162. Terra DAA, Vilela EG, Silva ROS, LeAo LA, Lima KS, Passos R, et al. Structuring a fecal microbiota transplantation center in a university hospital in Brazil. *Arq Gastroenterol* 2020;**57**:434—58.
163. Terveer EM, van Beurden YH, Goorhuis A, Seegers J, Bauer MP, van Nood E, et al. How to: establish and run a stool bank. *Clin Microbiol Infect* 2017;**23**:924—30.
164. MICROBIOMA.ORG. World's first microbiota SUPERDONOR bank. Established in. *Int Availability* 2017. Available: https://microbioma.org/en/home-eng/. [Accessed 25 January 2023].
165. AMILI. Advancing Human health through microbiome science. Available: https://www.amili.asia/[Accessed 25 January 2023].
166. Biome Bank. Available: https://www.biomebank.com/ [Accessed 25 January 2023].
167. Netherlands Donor Feces Bank. Nieuws & media. Available: https://www.ndfb.nl/nieuws.html [Accessed 25 January 2023].
168. TML Science. FMT manufacturing and stool bank. Available: https://tml.science/[Accessed 25 January 2023].
169. OpenBiome. OpenBiome Announces new direct testing for SARS-CoV-2 in fecal microbiota transplantation (FMT) preparations and release of new inventory. Available: https://openbiome.org/feature/openbiome-announces-new-direct-testing-for-sars-cov-2-in-fecal-microbiota-transplantation-fmt-preparations-and-release-of-new-inventory/[Accessed 25 January 2023].
170. Asia Microbiota Bank. Announcement from February, 2020: the Asia Microbiota Bank has closed down operations temporarily due to the risk of Covid-19. AMB has not experienced any Covid-19 infection. This operational closing is a precautionary measure. Available: https://asiabiobank.com/ [Accessed 25 January 2023].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.02.005.