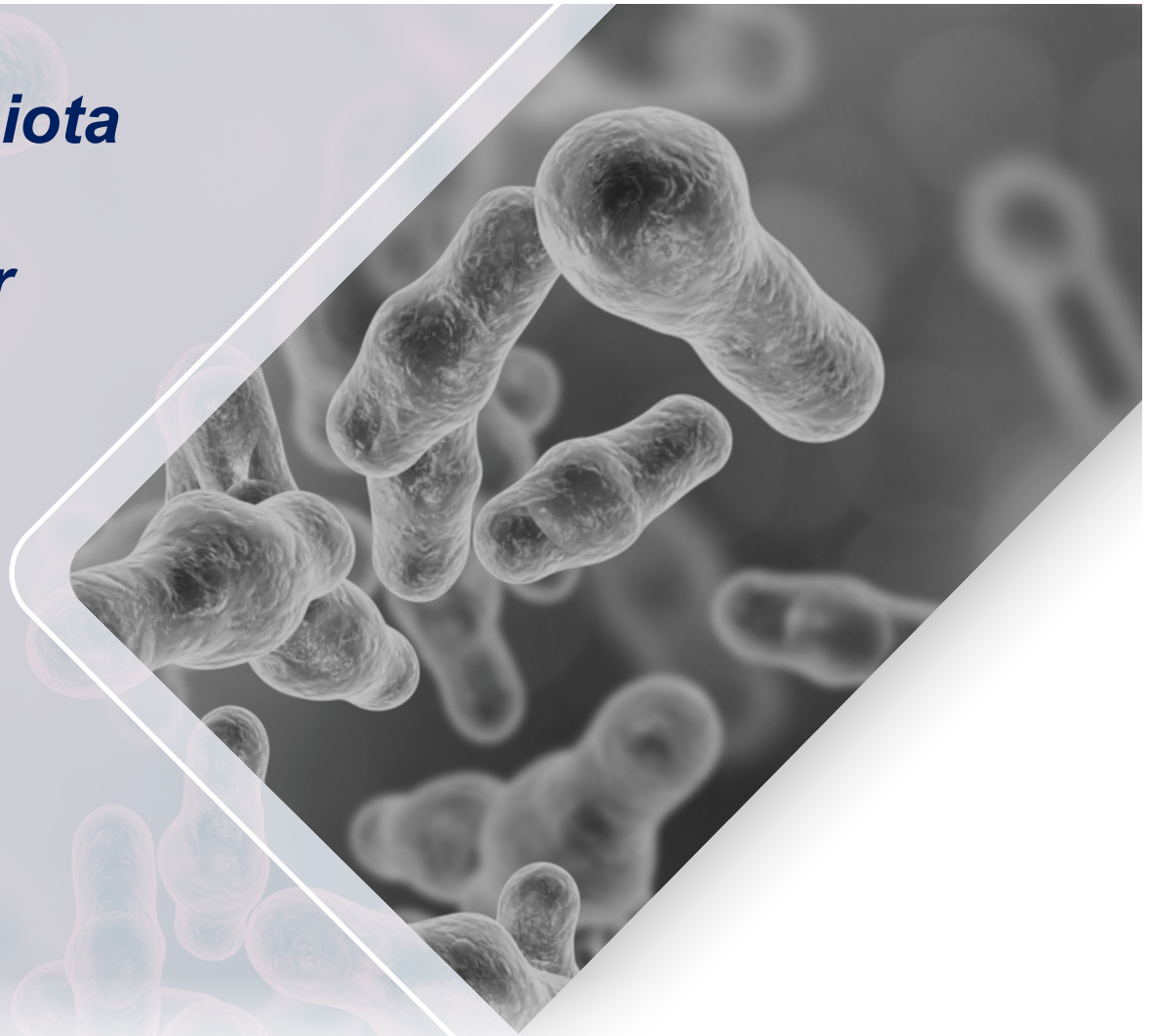
# *The use of Faecal Microbiota Transplant (FMT) as treatment for recurrent or refractory Clostridioides difficile Infection*



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**Hosted by Jim Gauthier**

# Disclosures

Consultancy and/or speaker fees:

AstraZeneca, Enterobiotix, Tillotts, Vedanta

# Learning objectives

- Understand epidemiology and risk factors for recurrent Clostridioides difficile Infection
- Understand the human gut microbiome and its importance in colonisation resistance
- Describe the principles of Faecal Microbiota Transplant (FMT) and the evidence to support its use
- Understand when and how FMT is used in clinical practice, including its risks and benefits
- Be aware of developments in regulation and FMT-like products / Live Biotherapeutic Products (LBPs) in development

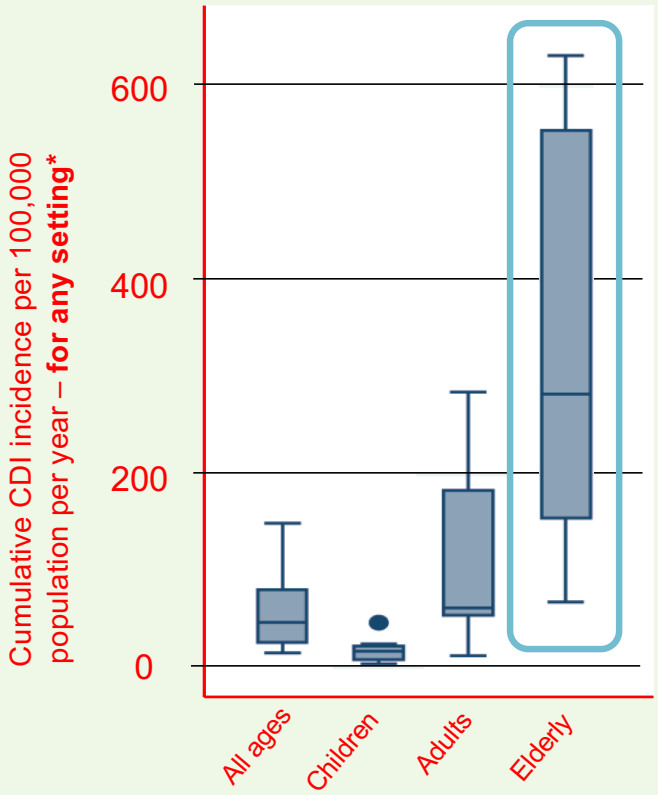
# Global incidence of *C. difficile* infection (CDI)

Data from Balsells et al. 2019

Cumulative incidence rate for all ages is **49.36 per 100,000 per year**

Disproportionately affects the elderly (>65 years): **323.32 per 100,000 per year**

**Over 80%** CDI deaths occur in those >65 years




* = for both hospital and community-based settings

Balsells (2019)

# Risk factors for CDI

| Antibiotic exposure | Older age | A recent stay at hospital or nursing home | Immunosupression | Previous history of *C. difficile* infection |
|---|---|---|---|---|
| People are 7 to 10 times more likely to get *C. difficile* infection | Immune senescence<br>Gut microbiome<br>Comorbid conditions<br>Use of antibiotics | Shared facilities may increase the risk of environmental contamination | e.g HIV/AIDS, cancer, or organ transplant patients | Up to a 25% recurrence rate |

**CDI**: *C. difficile* infection

Gould 2015

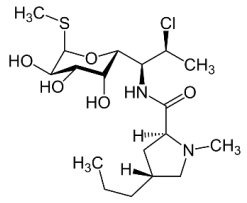
# Antibiotic-associated diarrhoea and CDI

Broad-spectrum antibiotics deplete the gut microbiota which increases the risk of CDI

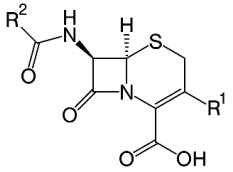
**Antibiotic-associated diarrhoea** occurs in up to **25%** of people treated with antibiotics

20-30% of antibiotic associated diarrhoea is due to CDI

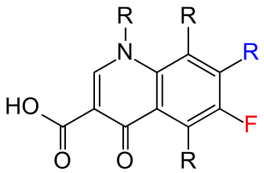
clindamycin



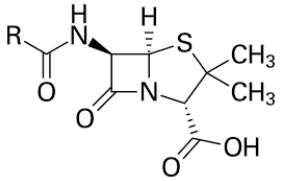
cephalosporins



fluoroquinolones



broad-spectrum penicillins



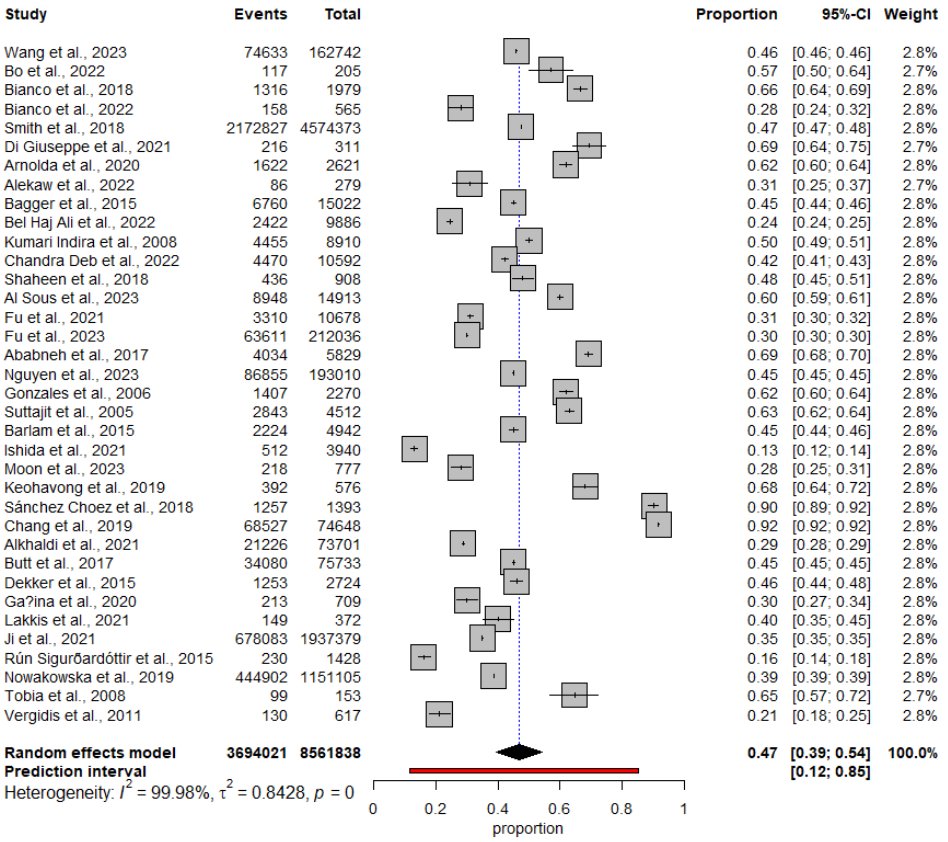
**CDI:** *Clostridioides difficile* infection

NICE CKS, Diarrhoea – antibiotic associated (2021)

# Appropriateness of antimicrobial prescription for outpatient respiratory tract infection: meta-analysis, 2024

- Among 36 studies, the proportion of inappropriate prescriptions exceeded 50% in 11 studies, whereas the remaining 25 studies reported a proportion below 50%
- Lowest level of inappropriate prescription was reported in a study conducted in Japan, with a rate of 13%.
- Highest rate of inappropriate prescription reported in a study from Ecuador was 90.25%.

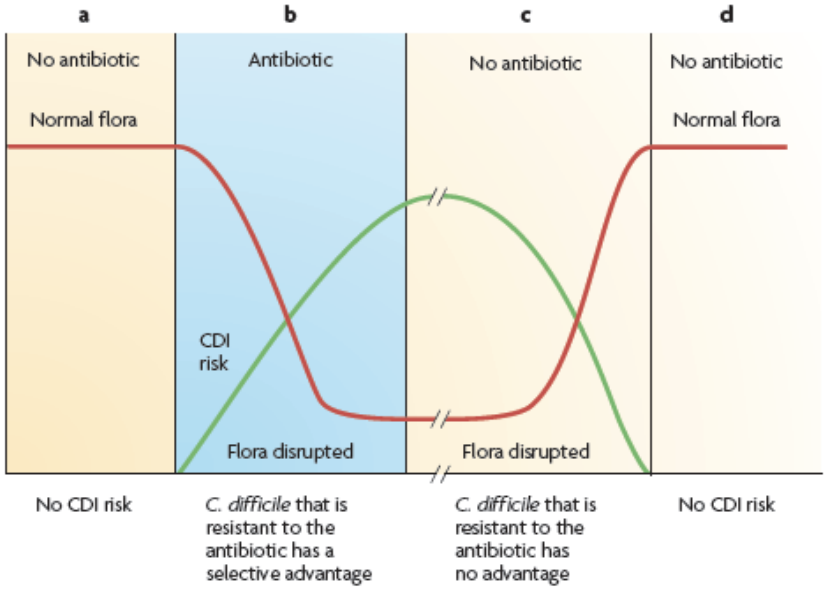
**Overall pooled prevalence of inappropriate antimicrobial prescription was 45% (95% CI 0.38–0.52, PI 0.12–0.82, I 2=99.9%)**




Events = antimicrobials, Total = sample size

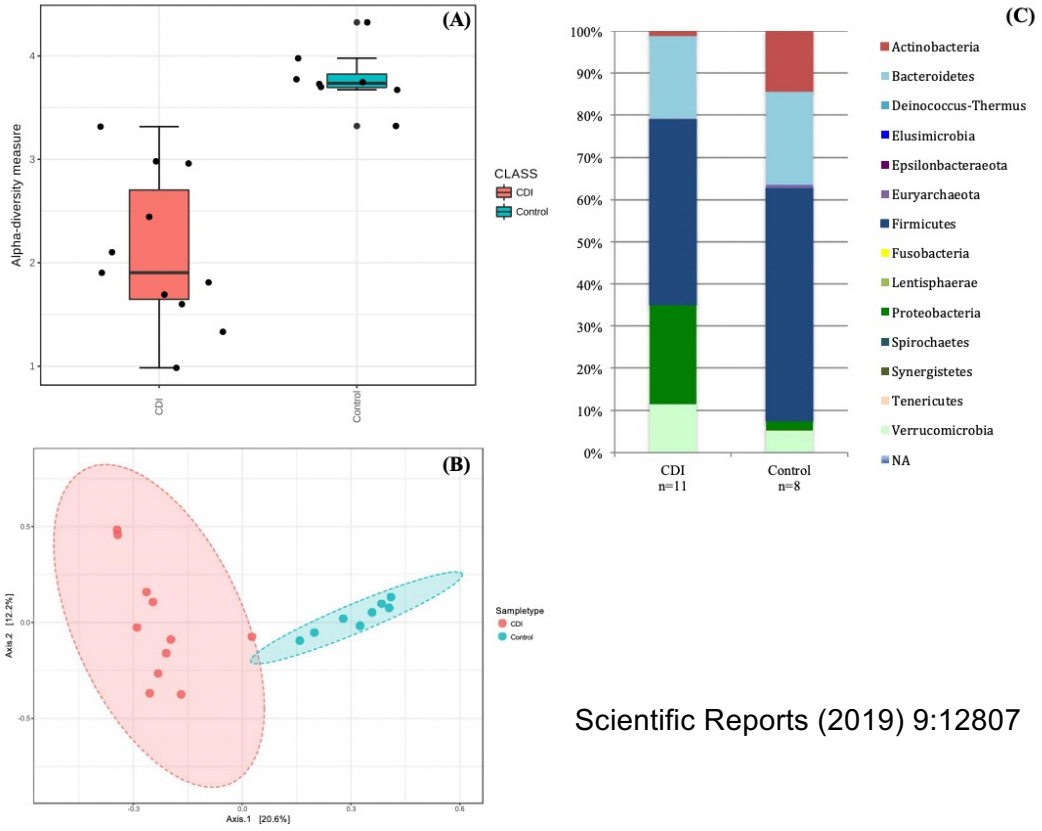
https://pmc.ncbi.nlm.nih.gov/articles/PMC11378372/

# Decreased Diversity of the Faecal Microbiome in rCDI




Patients with recurrent *CDI* have decreased phylogenetic richness

After antibiotics some bacteria remain disrupted for prolonged periods
(up to a year following treatment with clindamycin or after H. pylori eradication therapy)



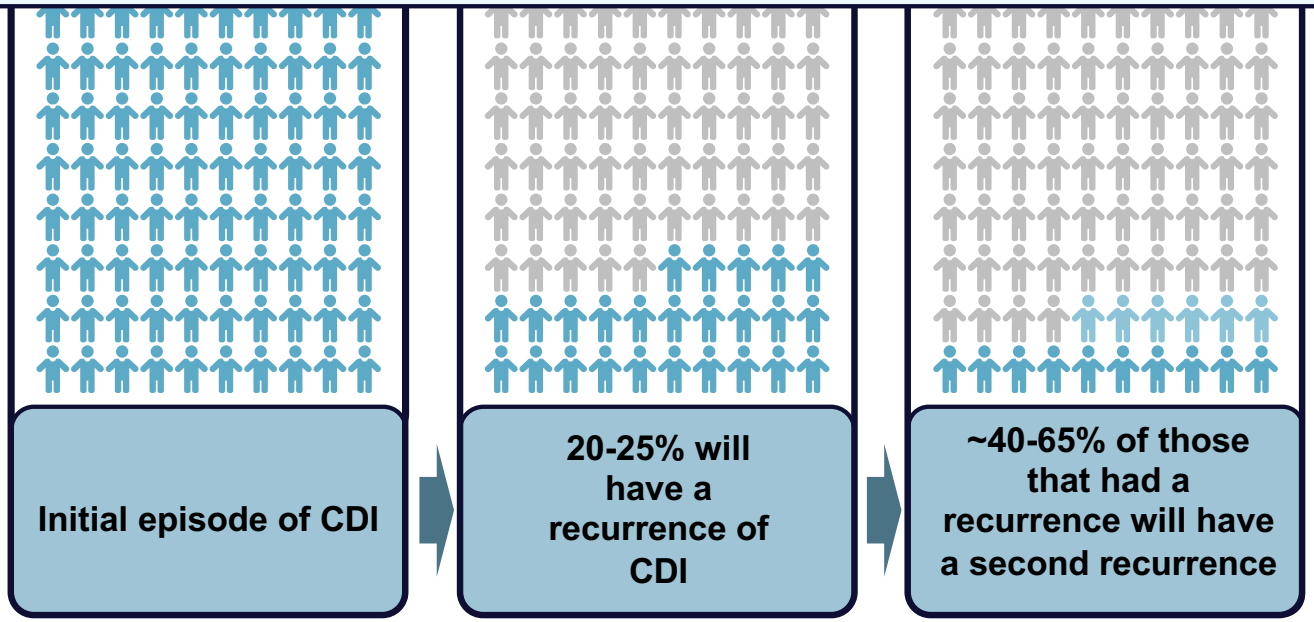

Scientific Reports (2019) 9:12807

**Figure 2.** (**A**) Shannon index, p = 9.0334e-06 (t-test), (**B**) PCoA, (**C**) Phyla repartition between CDI group and control group in metagenomic analysis[49].

*Chang JY, et al. J Infect Dis 2008:197;435-8*
*Sadowsky et al. The Fecal Bacteria, 2011*
*Zaura et al. mBio 6:6 Nov/Dec 2015*

# The incidence of recurrent CDI:
## Prevention requires consideration and effective management of the first episode

According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
**'the most important problem in treating CDI is the high recurrence rate'**

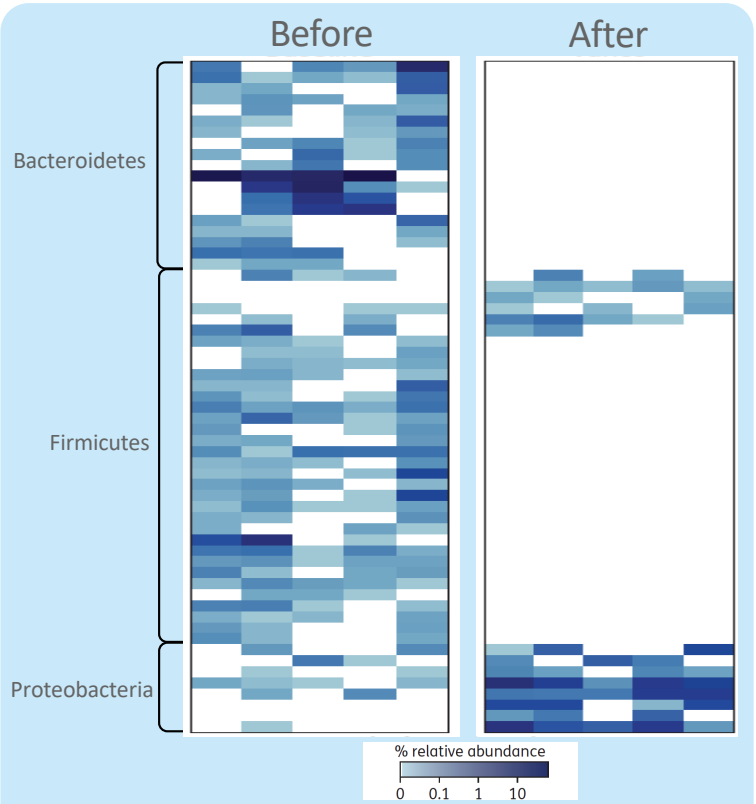



**A subset of patients will develop multiple recurrences**

Meehan (2016), Sheitoyan-Pesant (2016), Bauer (2009)

**CDI:** *Clostridiodes difficile* infection

# Vancomycin: negative impact on gut microflora



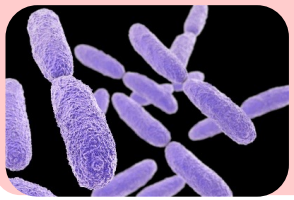

Heat map showing abundance of microflora bacteria before and after vancomycin treatment

Isaac et al. 2017 utilized high-throughput sequencing to analyse the effects of vancomycin on the faecal human microbiota up to 22 weeks post-antibiotic cessation. This was a study in treatment-naïve, new onset rheumatoid arthritis patients, not in patients with CDI.
9 patients received vancomycin, with 12 in the control group.

**Vancomycin** has **negative, long-term effects on the gut microflora**

**22 weeks after** vancomycin treatment **only 39 ±21.9%** of the most abundant groups of gut microflora bacteria had recovered

**Vancomycin** depletes most intestinal microbiota genera (including Bacteroidetes, most of the Firmicutes phyla, *Faecalibacterium* and *Ruminococcus*)



This is accompanied by a vast expansion of Proteobacteria associated with infectious processes (e.g. *Klebsilella, Escherichial / Shigella)*

Significant disruption to the colonic microflora and the colonisation resistance it provides can increase susceptibility to recurrent CDI

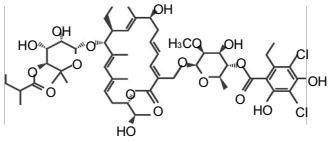
Chilton (2014), Isaac (2017)

# Fidaxomicin: limited effect on gut microflora

**Mechanism of action of fidaxomicin[1]**

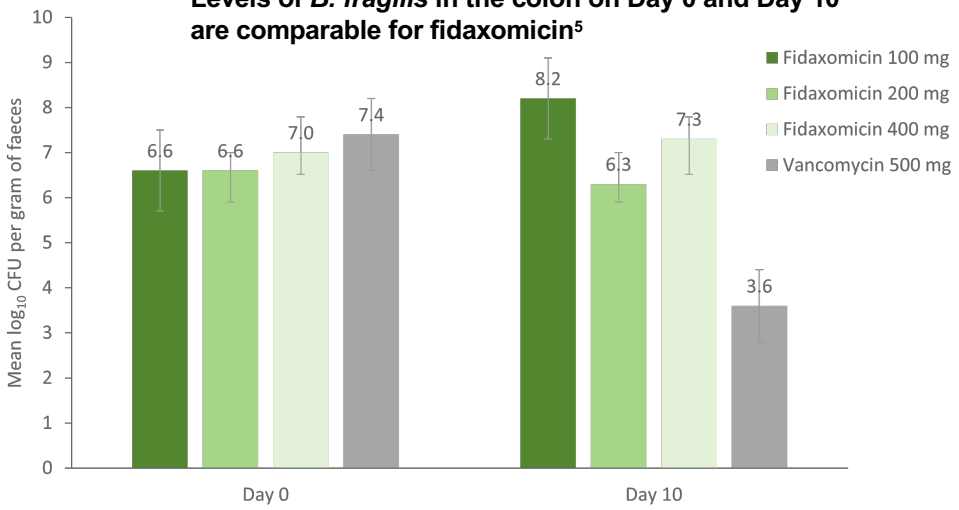
- Inhibition of bacterial RNA polymerase
- Acts in the initiation stage of RNA synthesis
- Activity is highly specific to *C. difficile*
- Active metabolite OP-1118 has activity against *C. difficile*

**Fidaxomicin**



**Fidaxomicin has little or no activity against gram-negative aerobic and anaerobic bacteria, but demonstrates high activity against *C. difficile*[2-4]**

**Levels of *B. fragilis* in the colon on Day 0 and Day 10 are comparable for fidaxomicin[5]**

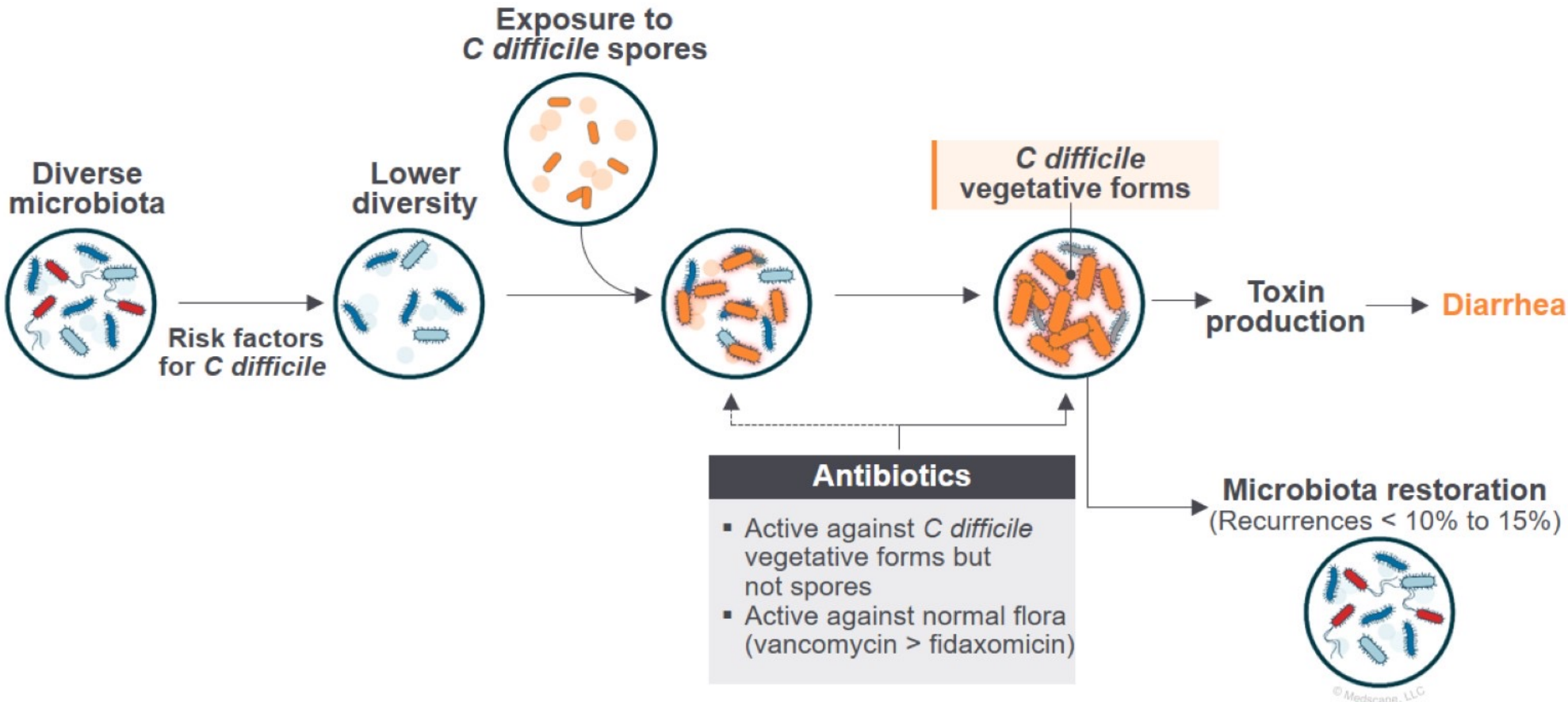



Fidaxomicin preserves the intestinal microbiome and does not cause further gut dysbiosis

Abx, antibiotic; *C. difficile, Clostridioides difficile*; CDI, *C. difficile* infection; MIC, minimum inhibitory concentration; RNA, ribonucleic acid

*1. Zhanel GG et al. Can J Infect Dis Med Microbiol 2015;26:305-312; 2. Credito K & Appelbaum P. Antimicrob Agents Chemother 2004;48:4430–4; 3. Finegold SM et al. Antimicrob Agents Chemother 2004;48:4898–902; 4. Nerandzic MM et al. Clin Infect Dis 2012;55(Suppl. 2):S121–6; 5. Louie TJ et al. Antimicrob Agents Chemother 2009;53:261–3; 6. Louie TJ et al. Clin Infect Dis 2012;55(Suppl 2):S132-42*

# Model of Microbiota Restoration




Adapted from Khanna S. J Intern Med. 2021;290:294-309.

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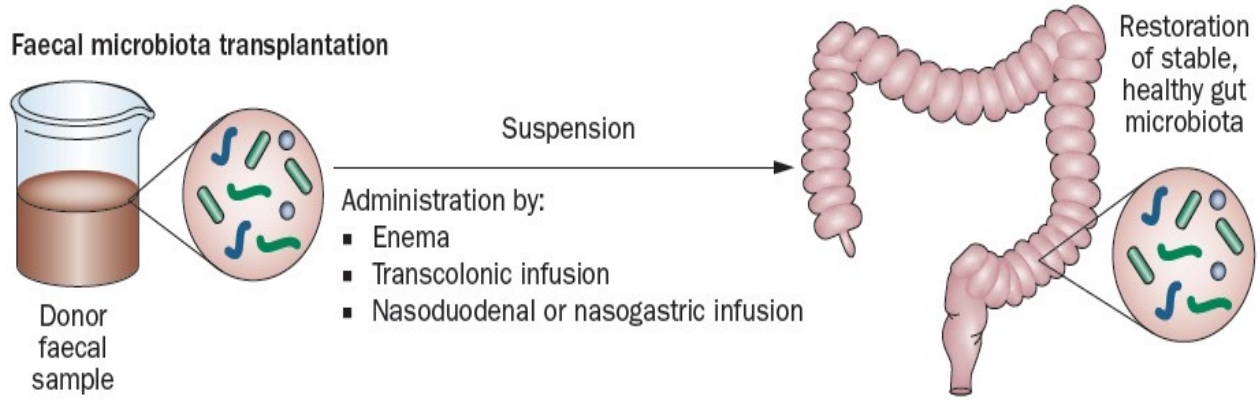
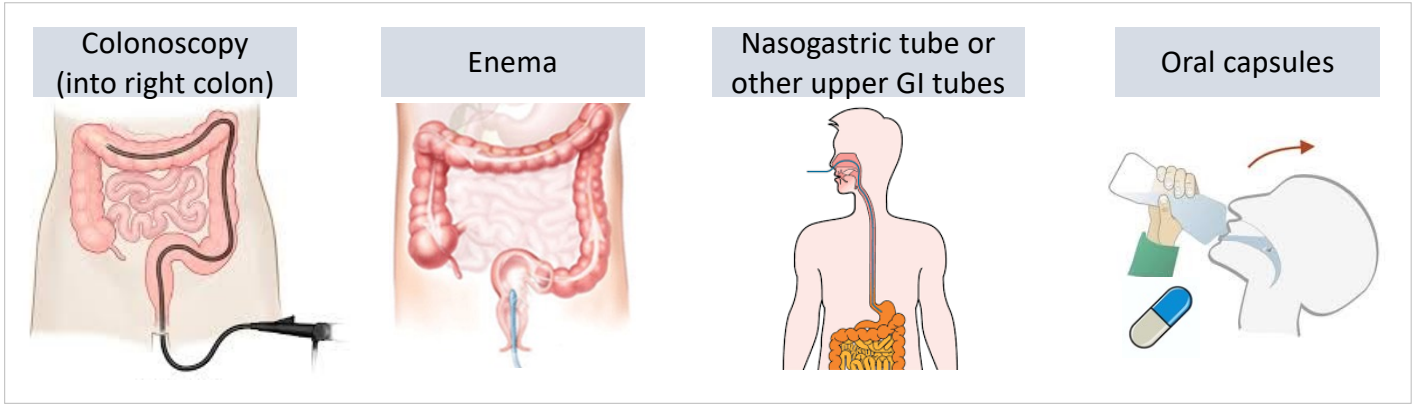
# Faecal Microbiota Transplantation (FMT)

Rationale: A perturbed imbalance in intestinal microbiota (dysbiosis) is associated with or causes disease and can be corrected by re-introduction of donor faeces



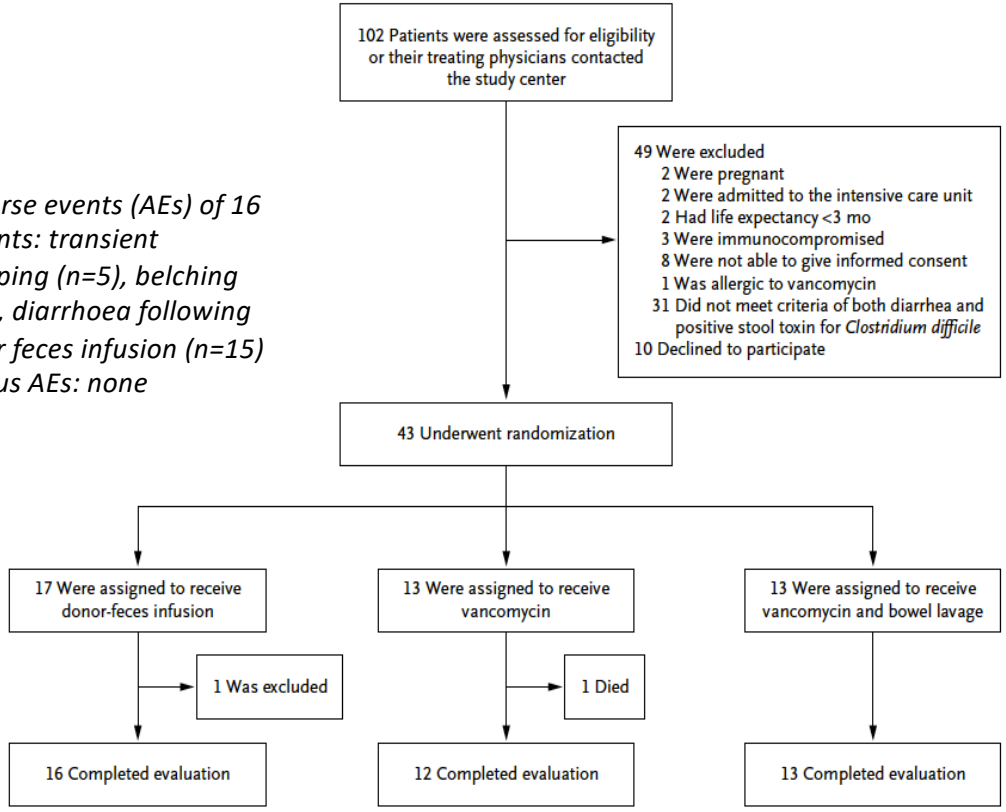



# Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

van Nood et al. NEJM 2013 368:5, 407-15

Patients randomly assigned to: initial vancomycin regimen, followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen; or a standard vancomycin regimen with bowel lavage.

*Adverse events (AEs) of 16 patients: transient cramping (n=5), belching (n=3), diarrhoea following donor feces infusion (n=15)*
*Serious AEs: none*




The primary end point was the resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks.

**Because most patients in both control groups had a relapse the data and safety monitoring board advised termination on the trial**

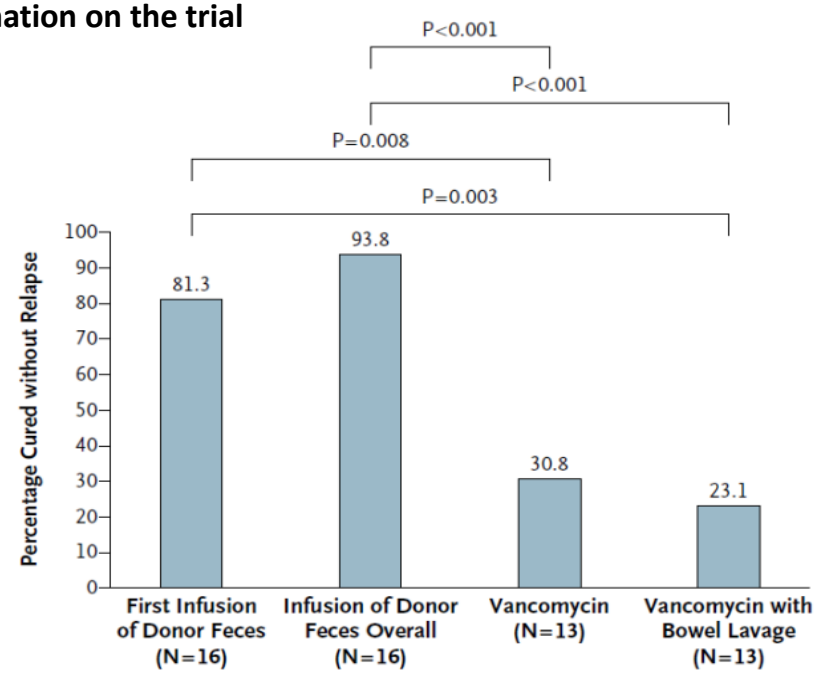
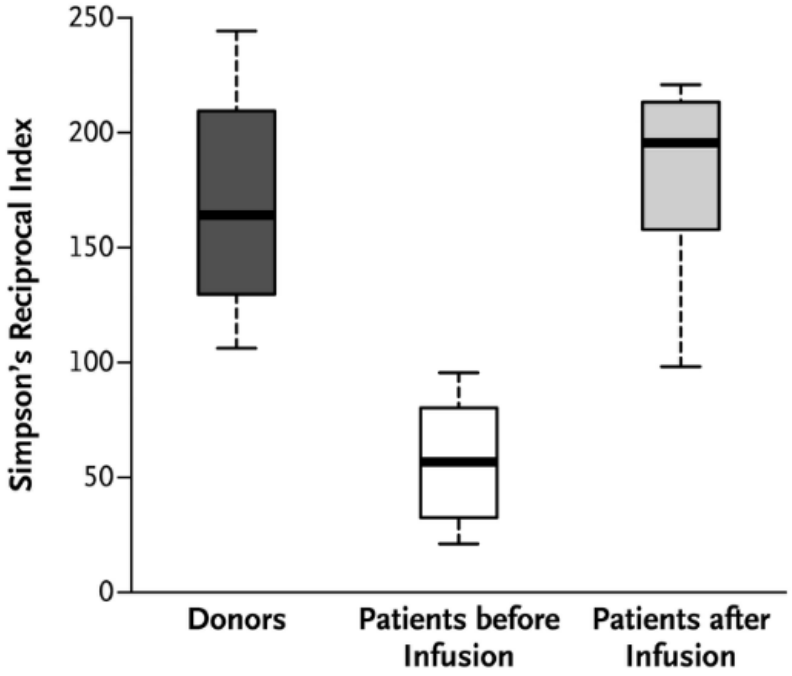
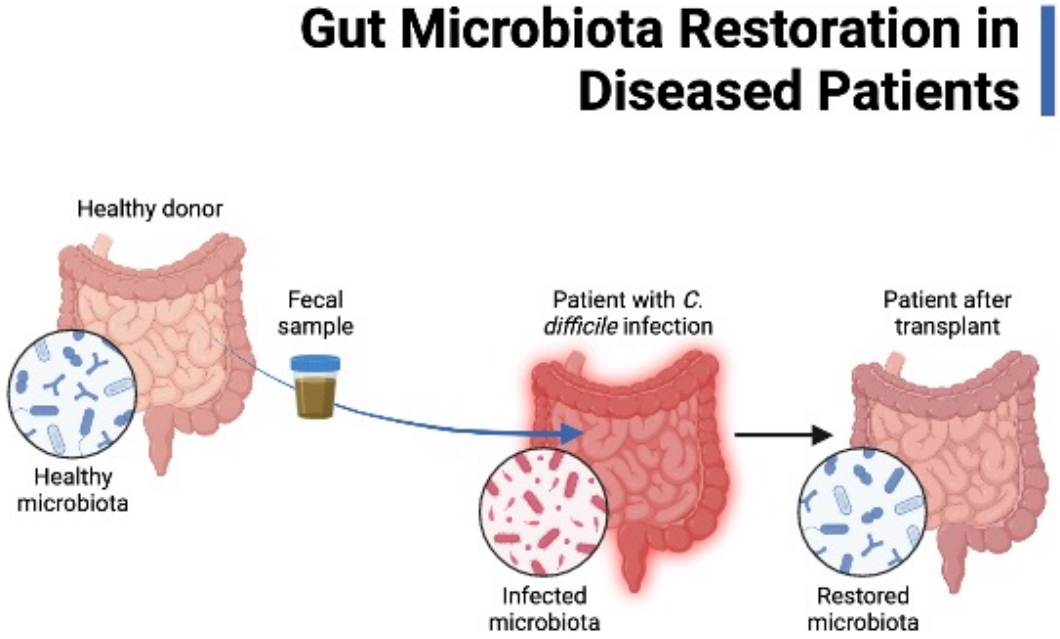



**Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.**

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

- FMT effectively reduces rCDI and increases gut microbiota diversity[1]




CI, confidence interval; FMT, faecal microbiota transplant; LBP, live biotherapeutic product; rCDI, recurrent CDI; Wk, week

*1. Van Nood E et al. NEJM 2013;368:407-15; 2. Feuerstadt P et al. NEJM 2022;386:220-29*

# FMT: Efficacy rCDI Clinical Trials

| Clinical Trial | Nº Participants | FMT Efficacy | Route |
|---|---|---|---|
| Van Nood et al, 2013[1] | 42 (16 FMT/13 VAN/13 VAN + Lav) | 93.8% | NDT |
| Youngster et al, 2014[2] | 20 (10 colono/10 NGT) | 90% | Colono/NGT |
| Cammarota et al, 2015[3] | 39 (FMT 20, VAN 19) | 90% | Colono |
| Lee et al, 2016[3] | 232 (FMT fresh 118/frozen 114) | 83.5%/85.1% | Enema |
| Jiang et al, 2017[3] | 72 (Fresh 25/Lio 23/Frozen 24) | 87% | Colono |
| Hota et al, 2017[3] | 30 (16 FMT/12 VAN) | 43.75% | Enema |
| Kelly et al, 2016[3] | 46 (Donor 22/Autologous 24) | 90.9%/62.5% | Colono |
| Oreinstein et al, 2016[3] | 31 FMT enema | 87.1% | Enema |
| Dubberke et al, 2018[3] | 127 (2 FMT 41/1 FMT 42/Placebo 44) | 89%/67%(2/1 FMT) | Enema |
| Ianiro et al, 2018[3] | 56 (28 FMT-S /28 FMT–M) | 75%/100% | Colono |
| Hvas 2019[4] | 64 (24 FMT/24 FDX/16 VAN) | 92% | Colono/NYT |

Adapted from 1. van Nood E et al. NEJM 2013;368:407-15; 2. Youngster I et al. JAMA 2014;312(17):1772-8;
3. Pomares Bascuñana RA et al. Lett Appl Microbiol 2021;73,149-158; 4. Hvas CL et al. Gastroenterology 2019;156:1324-1332.

FMT, faecal microbiota transplantation; FMT-M, FMT-faecal microbiota transplant multiple; FMT-S, FMT-single; LAV, lavage; Lio, lyophilised; NDT, nasoduodenal tube; NGT, nasogastric tube; NYT, nasojejunal tube; R-CDI, recurrent *Clostridioides difficile* infection, VAN, vancomycin.

# FMT: Efficacy rCDI Clinical Trials

| Clinical Trial | Nº Participants | FMT Efficacy | Route |
|---|---|---|---|
| Kao et al, 2017[1] | 116 (57 FMT Capsules/Colono) | 96.2% | Capsules/Colono |
| Garza-González et al, 2019[2] | 21 (13 FMT/8 FMT *Lactobacillus*) | 92.3% | Capsules |
| Baunwall et al, 2022[3] | 42 (21 FMT/21 Placebo) Early 1º R-CDI or 2º R-CDI | 90.5% | Capsules |
| Drekonja et al, 2025[4] | 153 (76 FMT, 77 Placebo) | 67.1% | Capsules |

1. Pomares Bascuñana RA et al. Lett Appl Microbiol 2021;73,149-158.
2. Garcia-Gonzalez E et al. Can J Gastroenterol Hepatol 2019;2019:4549298.
3. Baunwell SMD et al. Lancet Gastroenterol Hepatol 2022;12:1083-1091.
4. Drekonja DM et al. Clin Infect Dis 2025;80:52-60

FMT, faecal microbiota transplantation; FMT Caps, FMT Capsules; R-CDI, recurrent *Clostridioides difficile* infection.

# Stool Banks

OPENBIOME

www.openbiome.org

NDFB
Nederlandse Donor Feces Bank

www.ndfb.nl

Human Biome Institute

MBiotix HBI Caps

MIKROBIOTA JELITOWA

www.human-biome.com

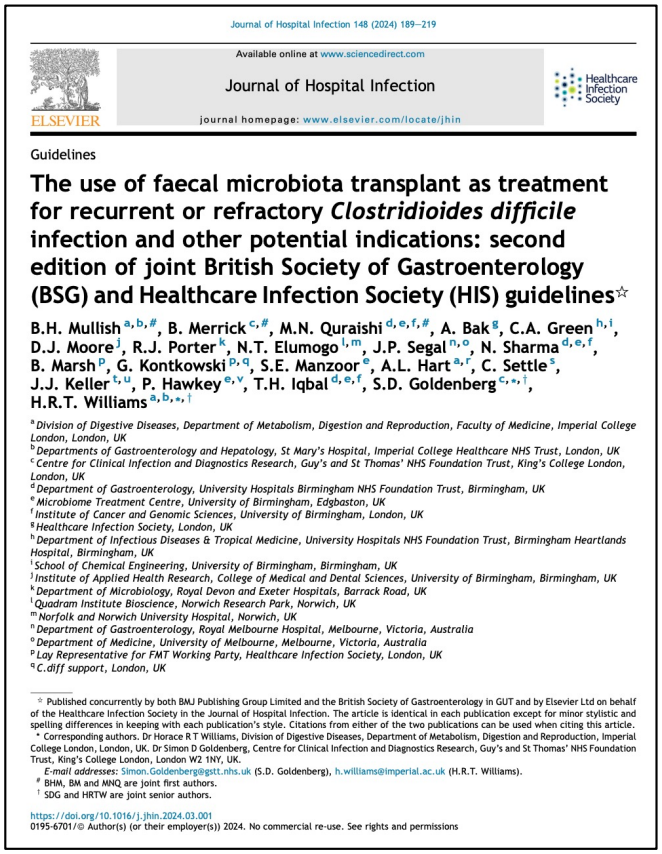

Asia Microbiota Bank

www.asiabiobank.com


www.cefta.com

EnteroBiotix

www.enterobiotix.com



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Guidelines

# The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridioides difficile* infection and other potential indications: second edition of joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines☆

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Guideline

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**ABSTRACT**

The first British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS)-endorsed faecal microbiota transplant (FMT) guidelines were published in 2018. Over the past 5 years, there has been considerable growth in the evidence base (including publication of outcomes from large national FMT registries), necessitating an updated critical review of the literature and a second edition of the BSG/HIS FMT guidelines. These have been produced in accordance with National Institute for Health and Care Excellence-accredited methodology, thus have particular relevance for UK-based clinicians, but are intended to be of pertinence internationally. This second edition of the guidelines have been divided into recommendations, good practice points and recommendations against certain practices. With respect to FMT for *Clostridioides difficile* infection (CDI), key focus areas centred around timing of administration, increasing clinical experience of encapsulated FMT preparations and optimising donor screening. The latter topic is of particular relevance given the COVID-19 pandemic, and cases of patient morbidity and mortality resulting from FMT-related pathogen transmission. The guidelines also considered emergent literature on the use of FMT in non-CDI settings (including both gastrointestinal and non-gastrointestinal indications), reviewing relevant randomised controlled trials. Recommendations are provided regarding special areas (including compassionate FMT use), and considerations regarding the evolving landscape of FMT and microbiome therapeutics.

**PATIENT SUMMARY**

Faecal microbiota transplant (FMT), sometimes also known as stool or poo transplantation, can be an effective treatment for patients with *C. difficile* (commonly known as *C. diff*) infection (CDI). It is usually given when the infection comes back after antibiotic treatment (relapse), or occasionally if antibiotics do not work (refractory). It is not fully understood how FMT helps patients with CDI, but it is thought it is partly to do with restoring beneficial gut microorganisms (eg, bacteria) and the chemicals (eg, metabolites) they produce.

The first British Society of Gastroenterology (BSG)/Healthcare Infection Society (HIS) guidelines on the use of FMT for *C. diff* were published in 2018, and since this time, new evidence has become available. This has prompted this second edition of the guidelines. Key recommendations focus on which patients should be offered FMT, when it should be offered and the best ways to administer it. The guidelines also describe important considerations for screening of stool donors to ensure the safety and success of FMT. Two further topics are focused on in this second edition. One is the evidence for the use of FMT for conditions other than CDI, including irritable bowel syndrome (IBS), ulcerative colitis and Crohn's disease, as well as conditions outside of the gut, such as obesity and metabolic syndrome. The second topic considers patients with conditions in which there are no other treatment options available to them, and if they can be offered FMT: this is called compassionate use.

**INTRODUCTION**

FMT (sometimes referred to by other names, including 'intestinal microbiota transplant/transfer'[1]) describes the transfer of minimally manipulated faeces from a healthy screened donor to a patient for the treatment of disease. FMT is now entering its second decade of use in modern mainstream medicine, with the first randomised trial reporting its utility following antibiotic treatment in recurrent CDI (rCDI) in 2013.[2] The first BSG/HIS-endorsed FMT guidelines were published in 2018,[3] and the interest continues to grow in the use of FMT, both



Mullish BH, et al. Gut 2024

# Donors

Live locally (must bring the donation within 2 hours)

Travel expenses only, no other payment

| Questionnaire screening (1/2): |
| --- |
| 1. Receipt of antimicrobials within the past 3 months |
| 2. Known prior exposure to HIV and/or viral hepatitis, and known previous or latent tuberculosis |
| 3. Risk factors for blood borne viruses, including high risk sexual behaviours, use of illicit drugs, any tattoo/body piercing/needlestick injury/blood transfusion/acupuncture, all within the previous 6 months |
| 4. Receipt of a live attenuated vaccine within the past 6 months |
| 5. Underlying GI conditions/symptoms (eg, history of IBD, irritable bowel syndrome (IBS), chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery), also including acute diarrhoea/GI symptoms within the past 2 weeks |
| 6. Family history of any significant GI conditions (eg, family history of IBD or colorectal cancer) |
| 7. History of atopy (eg, asthma, eosinophilic disorders) |

| Questionnaire screening (2/2): |
| --- |
| 8. Any systemic autoimmune conditions |
| 9. Any metabolic conditions, including diabetes and obesity |
| 10. Any neurological or psychiatric conditions, or known risk of prion disease |
| 11. History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia |
| 12. History of any malignancy |
| 13. Taking particular regular medications, or such medications within the past 3 months—that is, antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy. |
| 14. History of receiving growth hormone, insulin from cows or clotting factor concentrates. |
| 15. History of receiving an experimental medicine or vaccine within the past 6 months |
| 16. History of travel to tropical countries within the past 6 months |

| ***Pathogen screening (serology):*** |
| --- |
| Hepatitis A IgM |
| Hepatitis B (HBsAg and HBcAb) |
| Hepatitis C antibody |
| Hepatitis E IgM |
| HIV -1 and -2 antibodies |
| HTLV-1 and -2 antibodies |
| *Treponema pallidum* antibodies (*TPHA, VDRL)* |
| Epstein-Barr virus IgM and IgG* |
| Cytomegalovirus IgM and IgG* |
| *Strongyloides stercoralis* IgG |
| *Entamoeba histolytica* serology |

*Only recommended when treating immunosuppressed patients at risk of severe infection if exposed to CMV and EBV

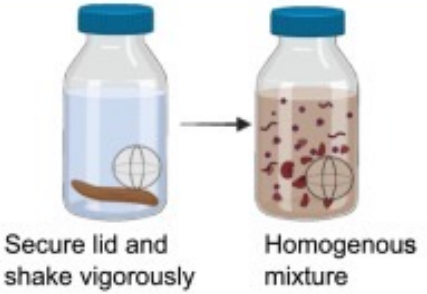
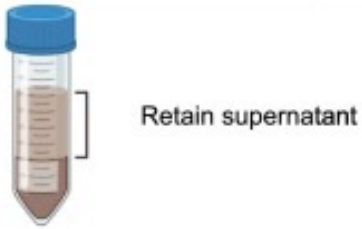
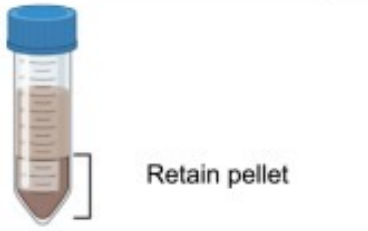
| ***General/ metabolic screening:*** |
| --- |
| Full blood count with differential |
| Creatinine and electrolytes |
| Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-GT and ALP) |
| C-reactive protein |

| ***Pathogen screening (stool):*** |
| --- |
| *Clostridium difficile* PCR |
| *Campylobacter, Salmonella,* and *Shigella* by standard stool culture and/ or PCR |
| Shiga toxin-producing *Escherichia coli* by PCR |
| Multi-drug resistant bacteria, at least carbapenemase-producing *Enterobacteriaceae* (CPE) and extended-spectrum beta-lactamases (ESBL)* |
| Stool ova, cysts and parasite analysis, including for *Microsporidia* |
| Faecal antigen for *Cryptosporidium* and *Giardia* |
| Acid fast stain for *Cyclospora* and *Isospora* |
| *Helicobacter pylori* faecal antigen |
| Norovirus, Rotavirus PCR |
| SARS-CoV-2 (plus nose/throat swab) |

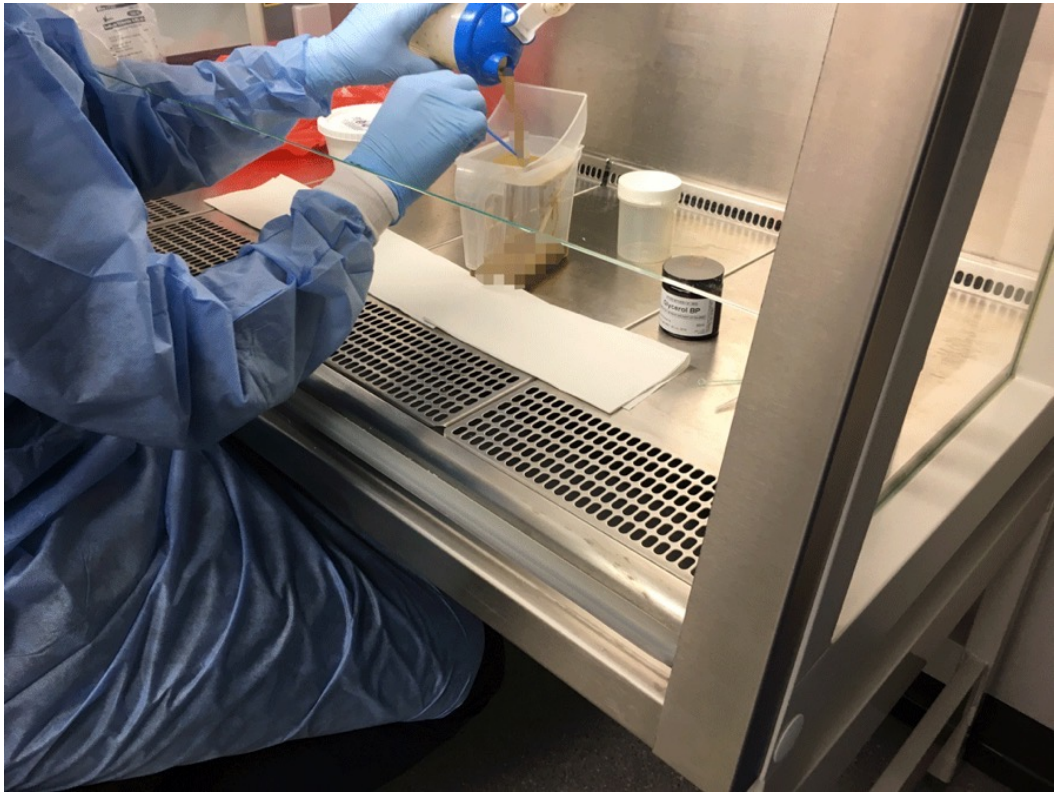
## Donor sample collection

Donor stool should be processed within 6 hours of defaecation

Secondary donor questions – new symptoms / risk factors including travel and new sexual partners

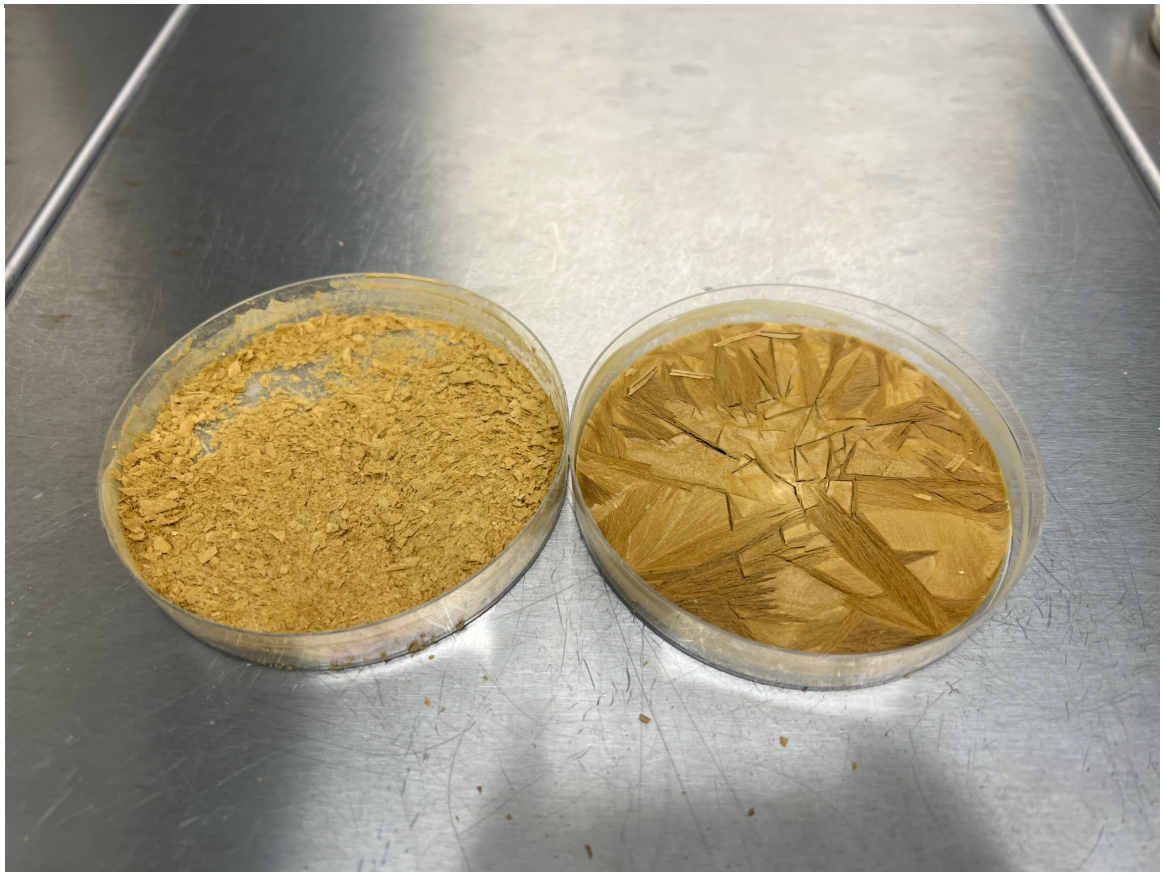
| Key Processing steps | | Purpose |
|---|---|---|
| **Step 1:**<br>Homogenize |  | Homogenise the stool and produce a disaggregated suspension to facilitate filtration |
| **Step 2:**<br>Filter the mixture |  | Remove extraneous material and collect the filtrate containing microorganisms |
| **Step 3:**<br>First centrifugation |  | Low centrifugation speed (400 *x g* for 10 minutes) to separate more stool material (pellet - discard) from the microorganisms in suspension (supernatant - retain) |
| **Step 4:**<br>Second centrifugation |  | Faster centrifugation speed (3000 *x g* for 25 minutes) to separate microorganisms (pellet – retain) from bulk solution (filtrate – discard) |





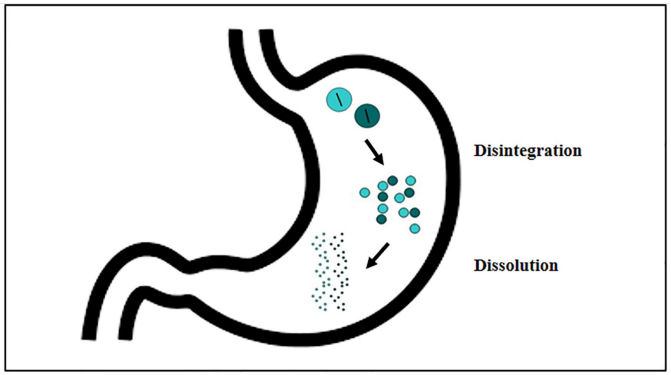
| | | |
|---|---|---|
| **Step 5:**<br><br>Add trehalose |  <br>5% trehalose of total volume in each tube<br><br>Transfer into 90mm sterile petri dishes and store at -80°C | Addition of a cryoprotectant to stabilise microbial cell membrane during the subsequent freeze-drying step. |
| **Step 6:**<br><br>Lyophilisation |  <br>**FREEZE DRY**<br>Min 12 hours,<br>-50°C, 0.05 millibars | Removal of water to produce a course powder containing microorganisms, small/soluble stool material and trehalose |
| **Step 7:**<br><br>Capsule filling |  | Hand filled into 5 Swedish Orange size 0 capsules (DRcaps®) |

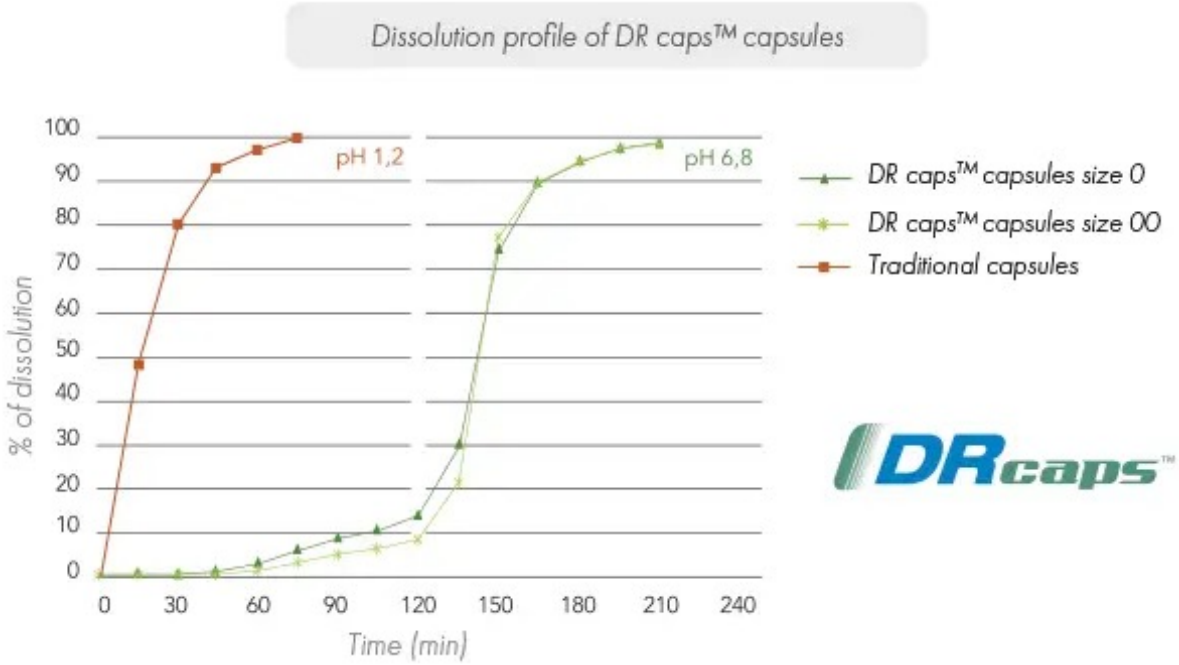

Kniplein
Vacuum Freeze Dryer




For Clinical Trial Use Only
PROMISE TRIAL
EudraCT number: 2022-000300-3
Chief Investigator: Professor Debbie Shawcross
College London, Denmark Hill, London

- Capsules
- Delayed release, pH dependent
- Dissolution at pH 6.8-7.2 (duodenum)




FDA U.S. FOOD & DRUG ADMINISTRATION

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# Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

Share Tweet Linkedin Email Print

Safety & Availability (Biologics)

Biologic Product Security

Blood Safety & Availability

CBER-Regulated Products:

**June 13, 2019**

The Food and Drug Administration (FDA) is informing health care providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation (FMT). The agency is now aware of bacterial infections caused by multi-drug resistant organisms (MDROs) that have occurred due to transmission of a MDRO from use of investigational FMT.

**Content current as of:**
06/13/2019

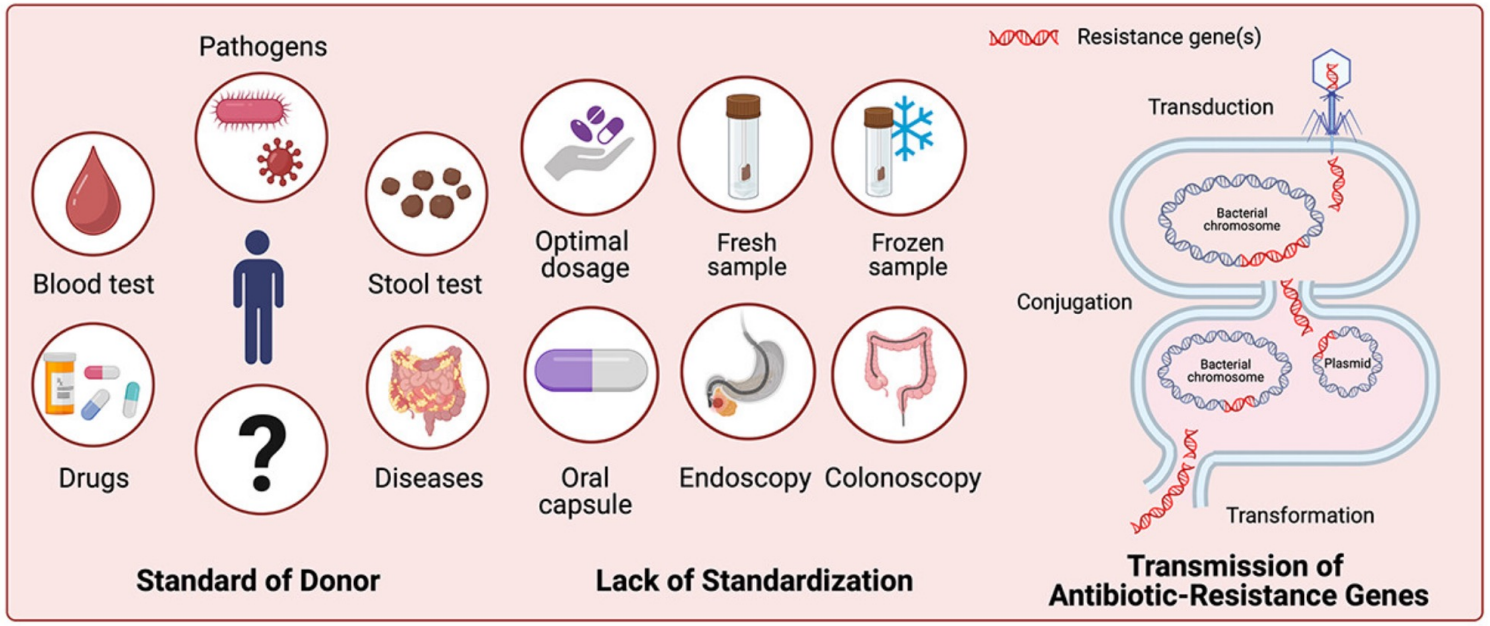
- Two immunocompromised adults who received FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E.coli)*.
- One of the individuals died.
- Donor stool not tested for ESBL-producing organisms prior to use.
- Stored preparations of FMT from this stool donor were subsequently tested and found to be positive for ESBL-producing *E. coli* identical to the organisms isolated from the two patients.

## Safety concerns

- Transmission of infection
- ?Transmission of risk of non-infectious disease:  metabolic syndrome, obesity etc. Uncertain and very difficult to study

# Challenges with ‘Traditional’ FMT

- Lack of standardisation / characterisation
- Problems with scalability > unequal access to products
- Safety concerns
- Uncertain regulatory oversight




Kim et al Gut Microbes 2024

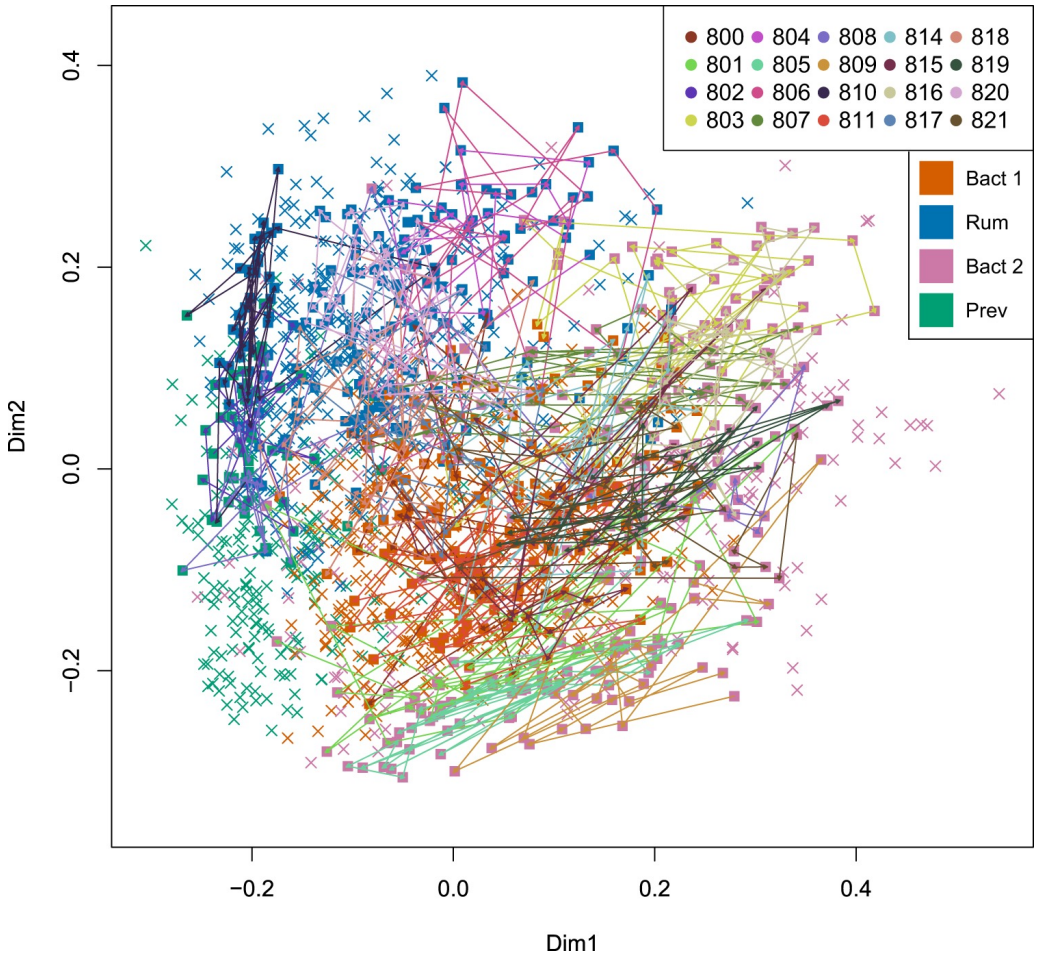
# Lack of standardisation / characterisation

- Organisms – bacteria / viruses / fungi
- Metabolites
- Significant intra-person and inter-person variation

For 78% of microbial genera, **day-to-day absolute abundance variation is substantially larger within than between individuals**, with up to 100-fold shifts over study period

Daily sampling of 20 healthy Belgian women over 6 weeks

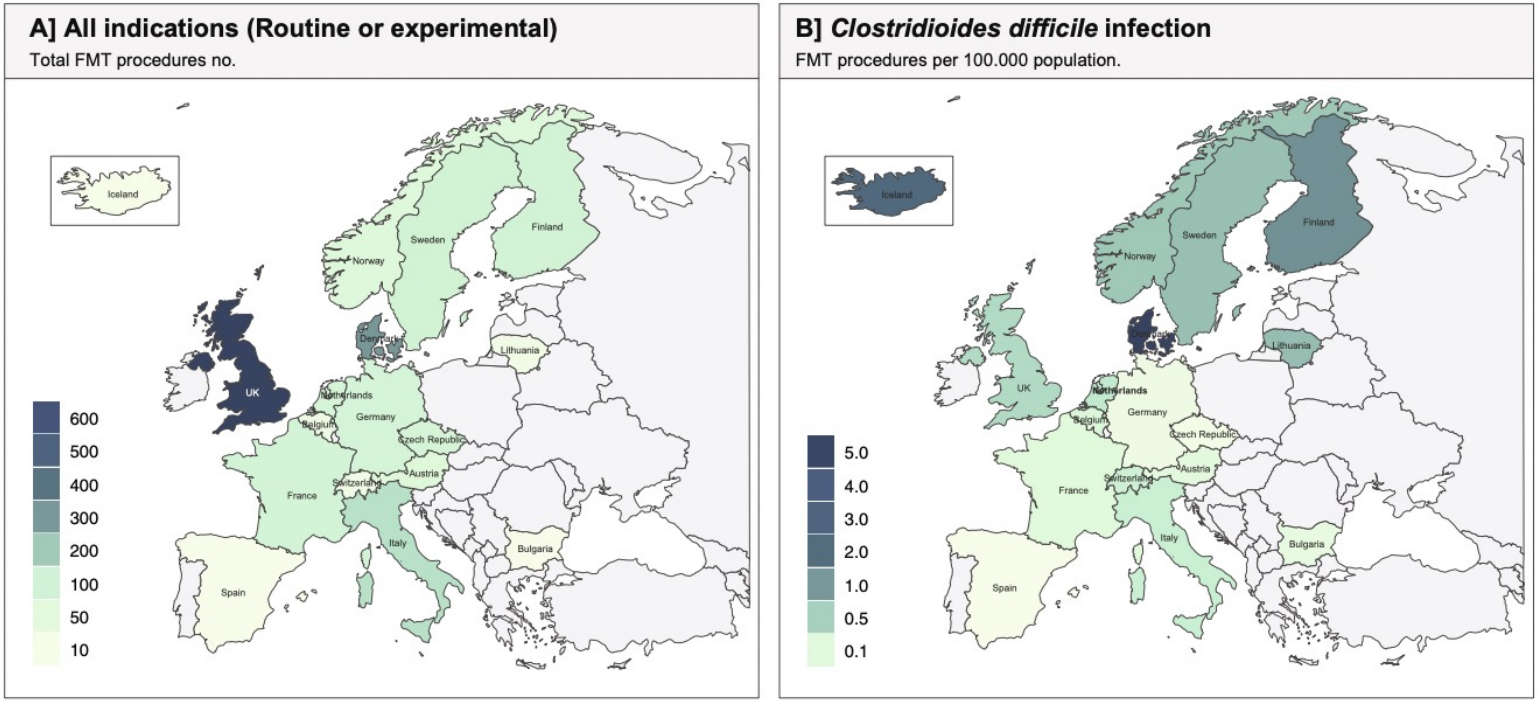
PCA analysis of study samples, arrows indicating temporal sampling sequence




Vandeputte et al Nature Comms 2021

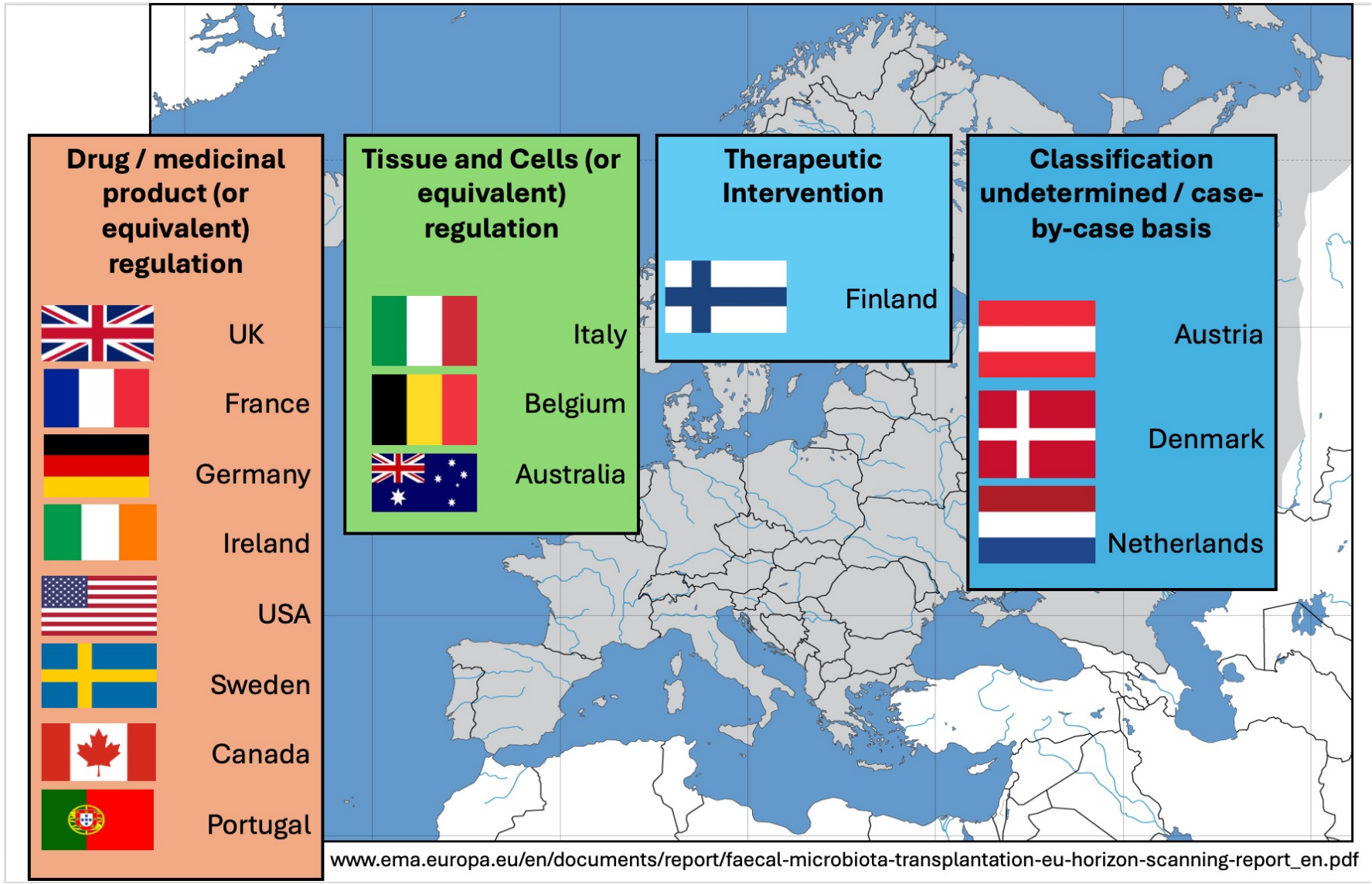
# Scalability / unequal access

The use of Faecal Microbiota Transplantation (FMT) in Europe:
A Europe-wide survey (2020)




Significant gap in FMT coverage: need to increase FMT production in Europe by at least 10-fold to meet demand

Baunwall et al. The Lancet Regional Health - Europe 9 (2021) 100181


Drug / medicinal product (or equivalent) regulation
UK
France
Germany
Ireland
USA
Sweden
Canada
Portugal
Tissue and Cells (or equivalent) regulation
Italy
Belgium
Australia
Therapeutic Intervention
Finland
Classification undetermined / case-by-case basis
Austria
Denmark
Netherlands
www.ema.europa.eu/en/documents/report/faecal-microbiota-transplantation-eu-horizon-scanning-report_en.pdf

# Substances of Human Origin (SoHO)

Official Journal
of the European Union

EN
L series

2024/1938

17.7.2024

**REGULATION (EU) 2024/1938 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

**of 13 June 2024**

**on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC**

**(Text with EEA relevance)**

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 168(4), point (a), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee ([1]),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure ([2]),

# Evolution of therapeutics targeting the gut microbiota

More complex, less standardised, variable composition, less manipulated

| | |
|---|---|
| **‘Traditional’ FMT, unlicensed** | Donor derived, poorly defined, variable composition<br>Full spectrum<br>Potential risk of pathogen transmission, food allergens<br>Poor scalability, unreliable supply<br>Enema required |
| **Licensed faecal microbiota products:** | |
| **- Fecal microbiota, live-jslm (Rebyota)** | |
| **- Fecal microbiota, spores live-brpk (Vowst)** | Donor derived<br>Fractionated: live purified Firmicutes spores<br>Bowel lavage required |
| **Defined bacterial consortia** | Non-donor derived, consistent composition, well defined<br>Scalable, reliable supply<br>Reduced/no risk of pathogen transmission |
| **Live biotherapeutics, single strains** | |

Less complex, more standardised, defined composition, more manipulated

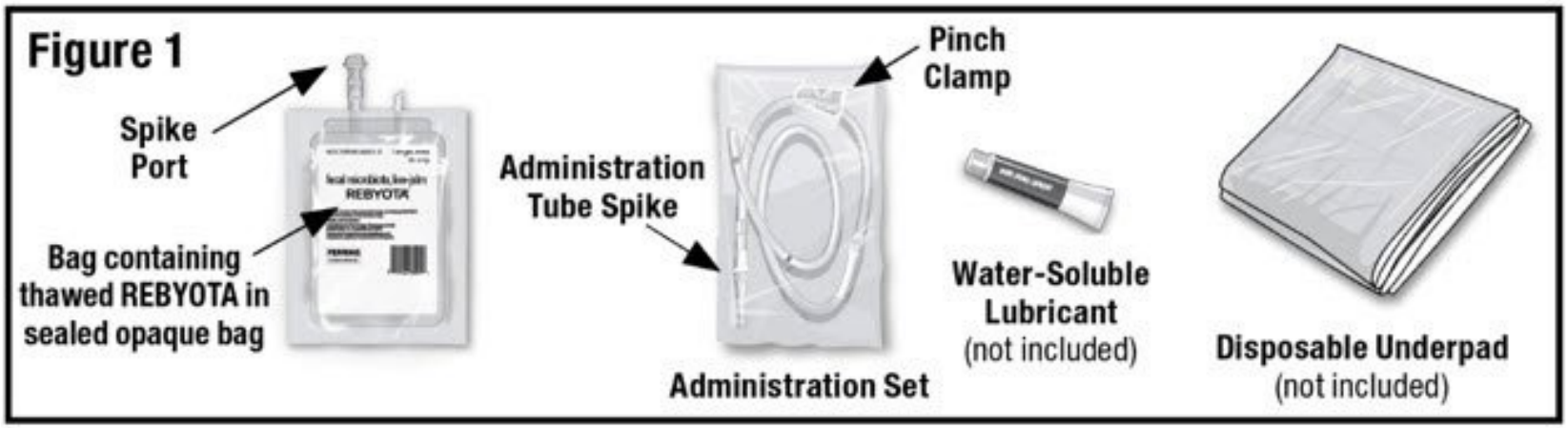
# Fecal microbiota, live-jslm (Rebyota)

- Full spectrum microbiota-based therapy
- Similar preparation to ‘traditional FMT’
- Administered as a single 150mL enema following SOC antibiotics (24-72h)
- No bowel preparation required
- Licensed FDA indication: Prevention of rCDI in adults ≥18 years following antibiotic treatment for recurrent CDI


Khanna et al. Drugs (2022) 82:1527–1538

# Fecal microbiota, live-jslm (Rebyota)

- Derived from single donor/not pooled
- 50g stool minimally manipulated and diluted in 0.9% NaCl and PEG
- Contains >$10^7$ organisms
- Cost = $9000

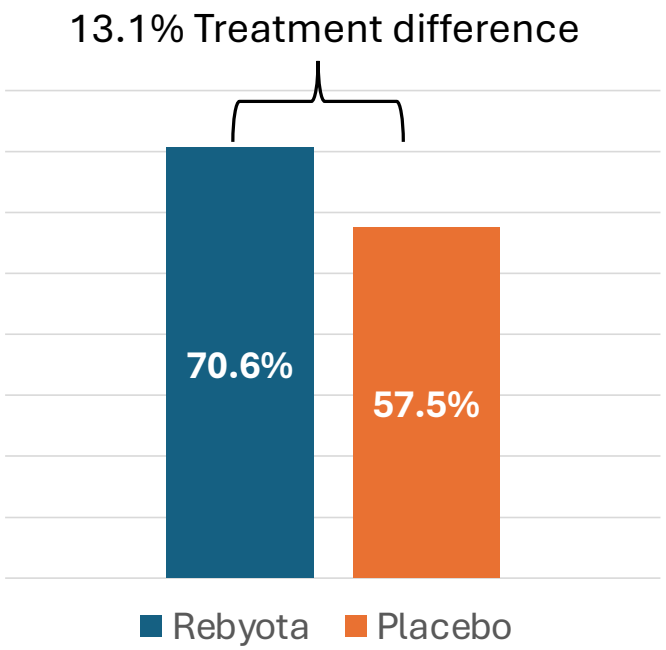


# Fecal microbiota, live-jslm (Rebyota)

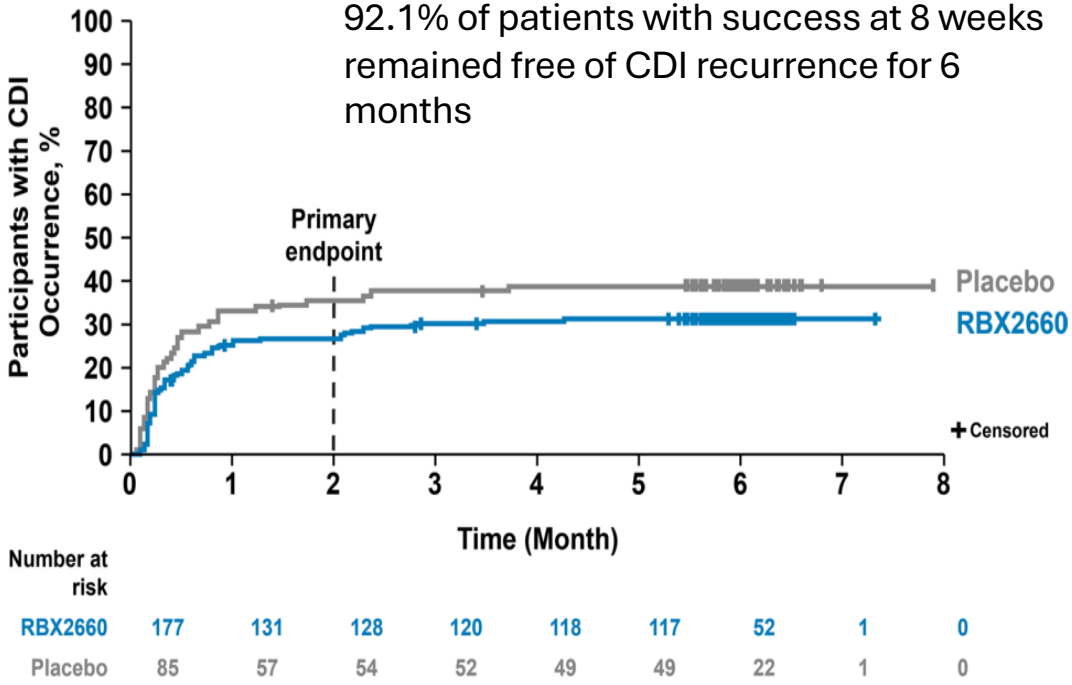
- Frozen at -80°C
- Thaw at room temperature 1 hour before patient arrives
- In-office administration by anyone trained in its administration


Khanna et al. Drugs (2022) 82:1527–1538

# Fecal microbiota, live-jslm (Rebyota)




92.1% of patients with success at 8 weeks remained free of CDI recurrence for 6 months




Using Bayesian analysis, the model-estimated treatment success rate was 70.6% with RBX2660 versus 57.5% with placebo

Khanna et al. Drugs (2022) 82:1527–1538

# SER-109 “Vowst™” (fecal microbiota spores, live-brpk) capsules

- Oral microbiome therapeutic containing live purified Firmicutes bacterial spores that limit C. difficile spore germination
- Derived from single donor stool treated with ethanol
- Dosage: 4 capsules taken on empty stomach once daily for 3 consecutive days
- Store at 2-25$^{o}$C, shelf life 36 months
- Antibiotic treatment should be completed 2 to 4 days before initiating therapy
- Drink 296 mL (10 oz) of magnesium citrate on day before and ≥ 8 h before taking first dose


Feuerstadt et al, N Engl J Med 2022; 386:220-229

# SER-109 “Vowst™”
# (fecal microbiota spores, live-brpk) capsules

FDA indications:
-2nd recurrence (3rd episode) following standard of care antimicrobial
-1st recurrence (2nd episode) in patients with high risk of recurrence:

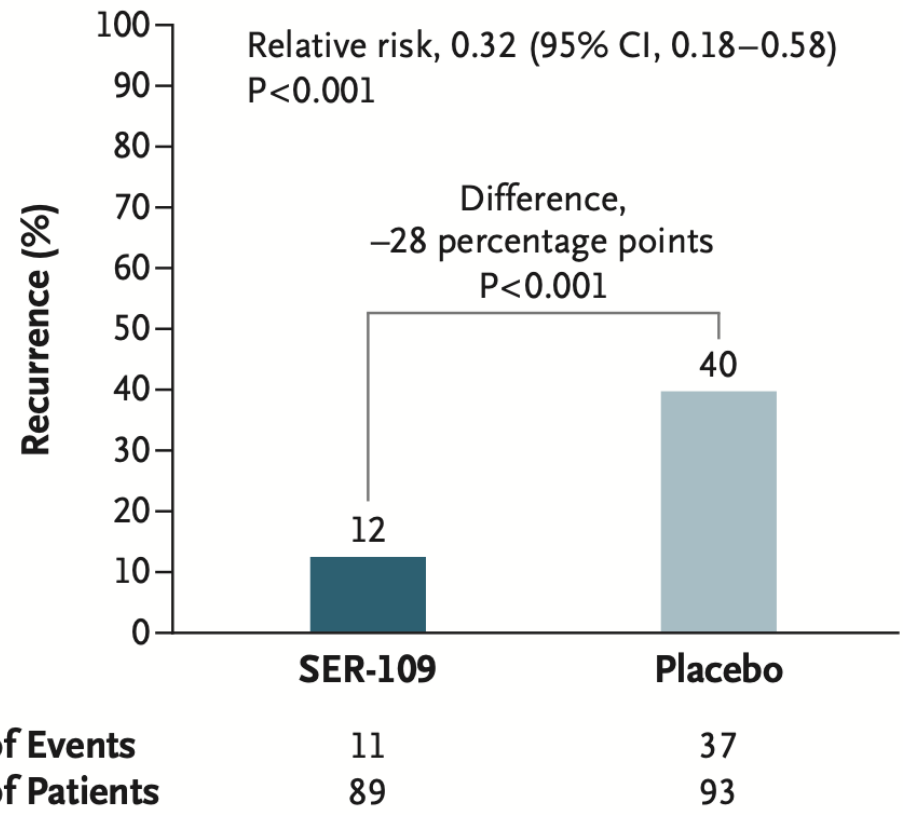
- Age >65
- Chronic PPI use
- Likely future concomitant antimicrobial requirement
- Resident in skilled nursing facility
- Significant hospital inpatient
- Severe underlying illness


Cost = $17,000

Feuerstadt et al, N Engl J Med 2022; 386:220-229

# SER-109 “Vowst™” (fecal microbiota spores, live-brpk) capsules

- Phase 3, double-blind, placebo-controlled trial assessed the efficacy of SER-109 in USA and Canada
- Study included patients with three or more C. difficile infections in the previous year
- 182 adults randomised to SER-109 or matching placebo

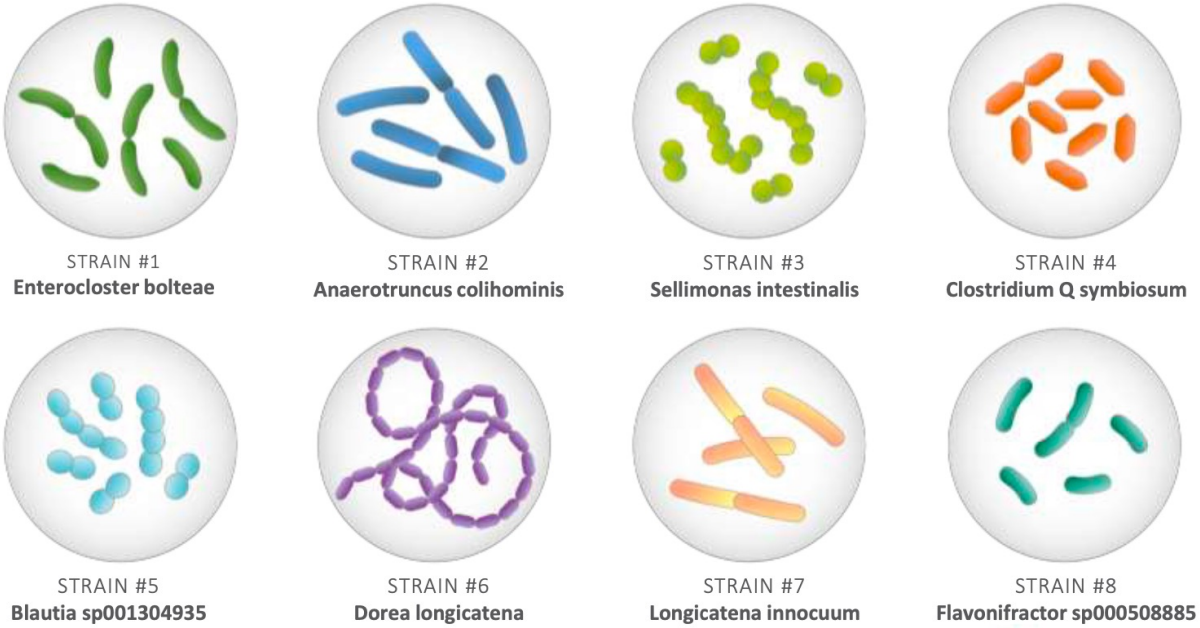



Feuerstadt et al, N Engl J Med 2022; 386:220-229

# Non- donor derived LBP Landscape (non-exhaustive)

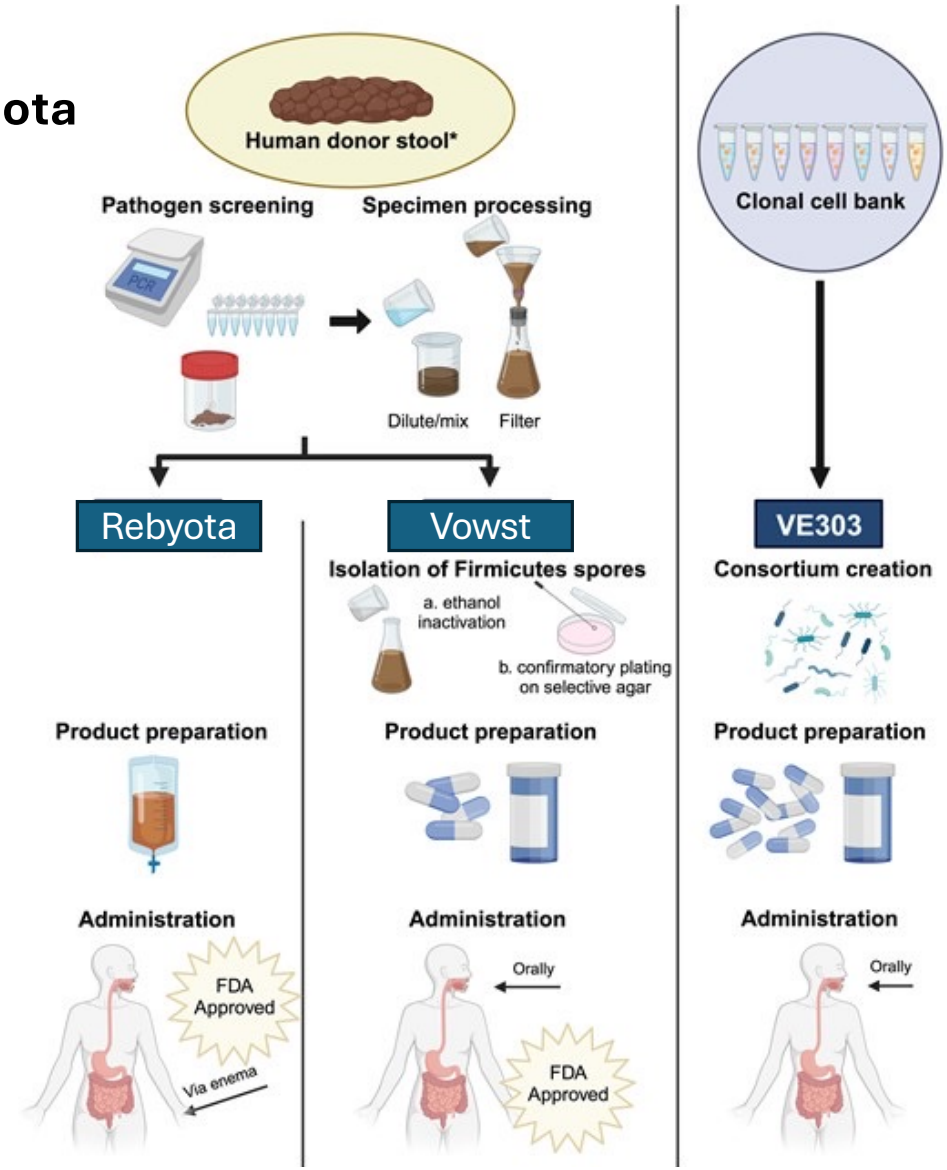
# VE303, Vedanta Biosciences

- Defined bacterial consortia, rationally selected
- 8 strains of Clostridiales originally isolated from healthy donor
- Manufactured from clonal cell bank (not donor derived)




Louie T, JAMA 2023; 329: 1356-66

## Faecal Microbiota Products




## Live Biotherapeutic Products

Gonzales-Lune A, CID 2023; 77: S487-96

# Conclusion

- CDI causes significant morbidity and mortality and has a high rate of recurrence
- Driven by changes in gut microbiota (decreased diversity)
- FMT is a way of restoring structure and function of ‘normal’ microbiota
- Manufacture of FMT relies on human volunteers who have been rigorously screened
- Problems with standardisation / characterisation / scalability / regulation
- FDA (+Heath Canada) approval of two new microbiota-based products for prevention of rCDI has significantly changed the treatment landscape
- Many non-donor derived LBPs (for a wide range of indications) are under investigation

United Nations | World Toilet Day 19 November

www.un.org/en/observances/toilet-day

Home | Background | Stories | Messages | Resources | UN Observances


**PHOTO:** UN-Water

# www.webbertraining.com

## NOVEMBER

11 ... The Use of Faecal Microbiota Transplant as Treatment for *Clostridium difficile*
Afro-European Teleclass
With Simon Goldenberg, UK

~~13 ... Solve the LTC Outbreak!~~
~~With Steven J. Schweon~~

19 ... Special Lecture for World Toilet Day

## DECEMBER

4 ... What's On a Surface Doesn't Stay On a Surface - The Dynamics and Risk of Microbial Resuspension From Surfaces
With Prof. Charles Gerba, US

16 ... Patience, Patients and Persistent Antimicrobial Resistance
Afro-European Teleclass
With Colm Dunne, UK

18 ... Empowering Patients to Prevent Healthcare-Associated Infections
With Dr. Curtis Donskey, US

Thanks to Teleclass Education

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