

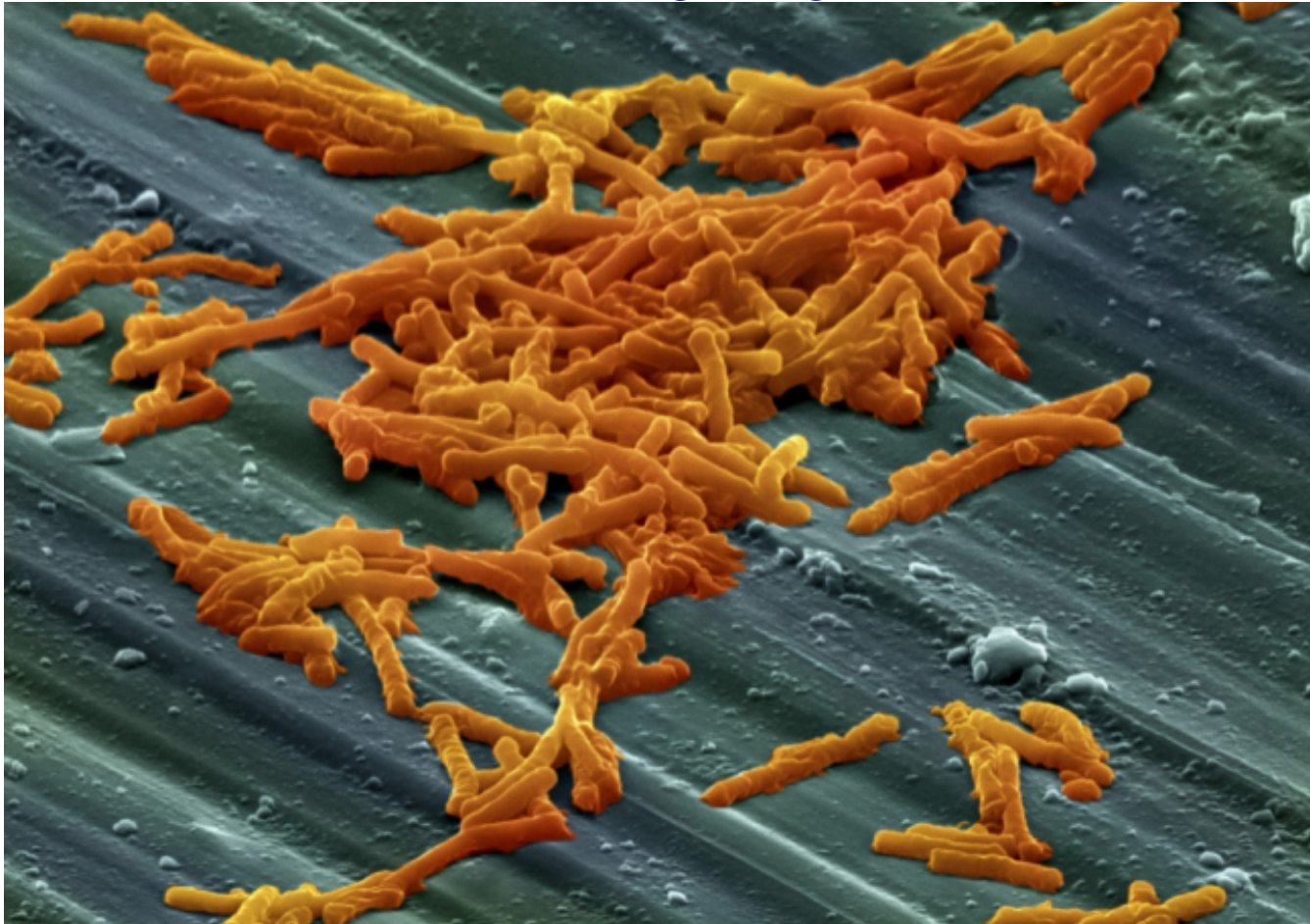
Faecal transplantation: alchemy or therapy?

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From me, to poo, to you: The faecal transplants fighting *C. difficile*



By [Ross McGuinness](#)

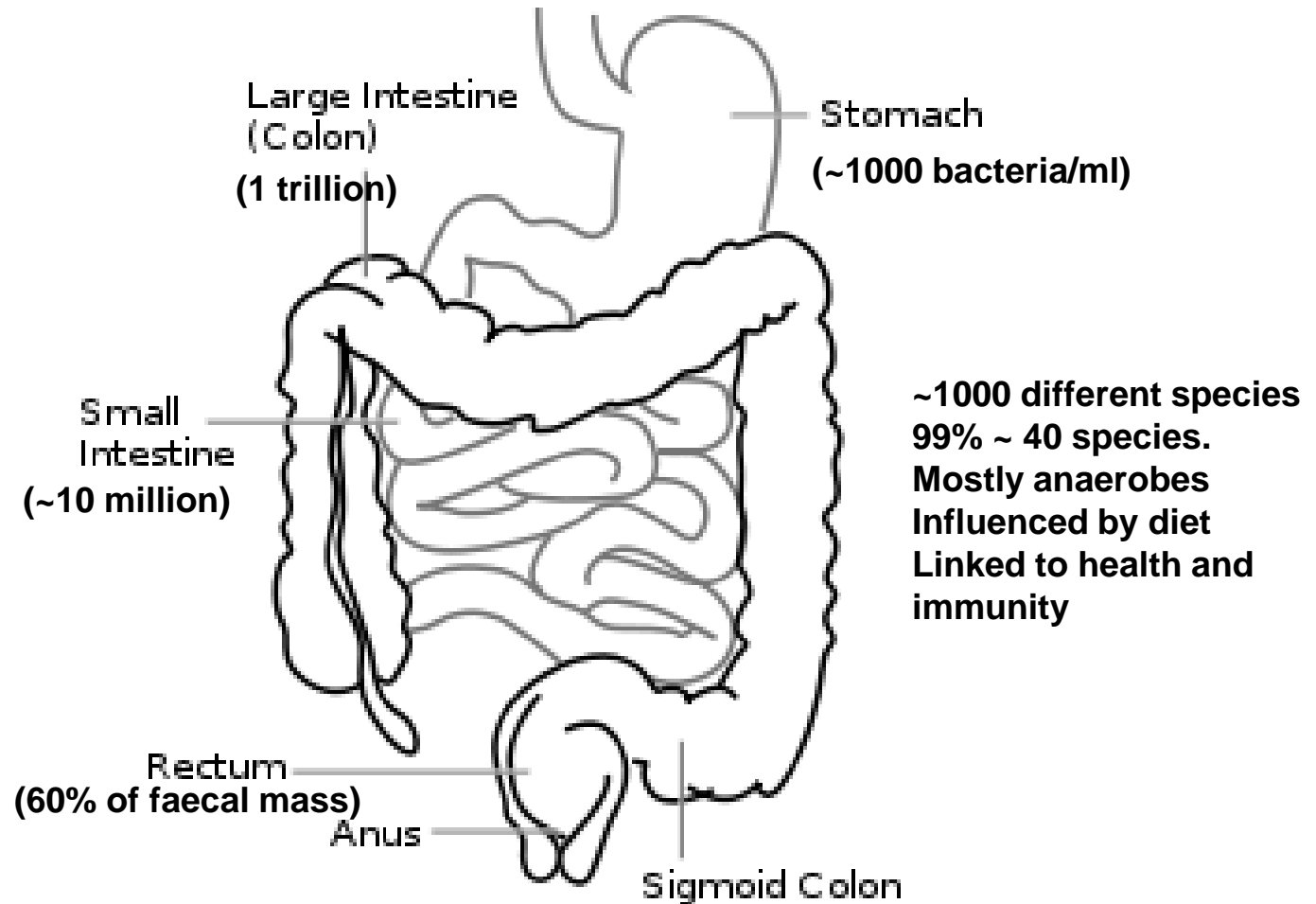


Writer of In Focus
features at Metro

**Clostridium difficile, above, causes severe diarrhoea
(Picture: Annie Cavanagh)**

National Blood Service

Human Intestine



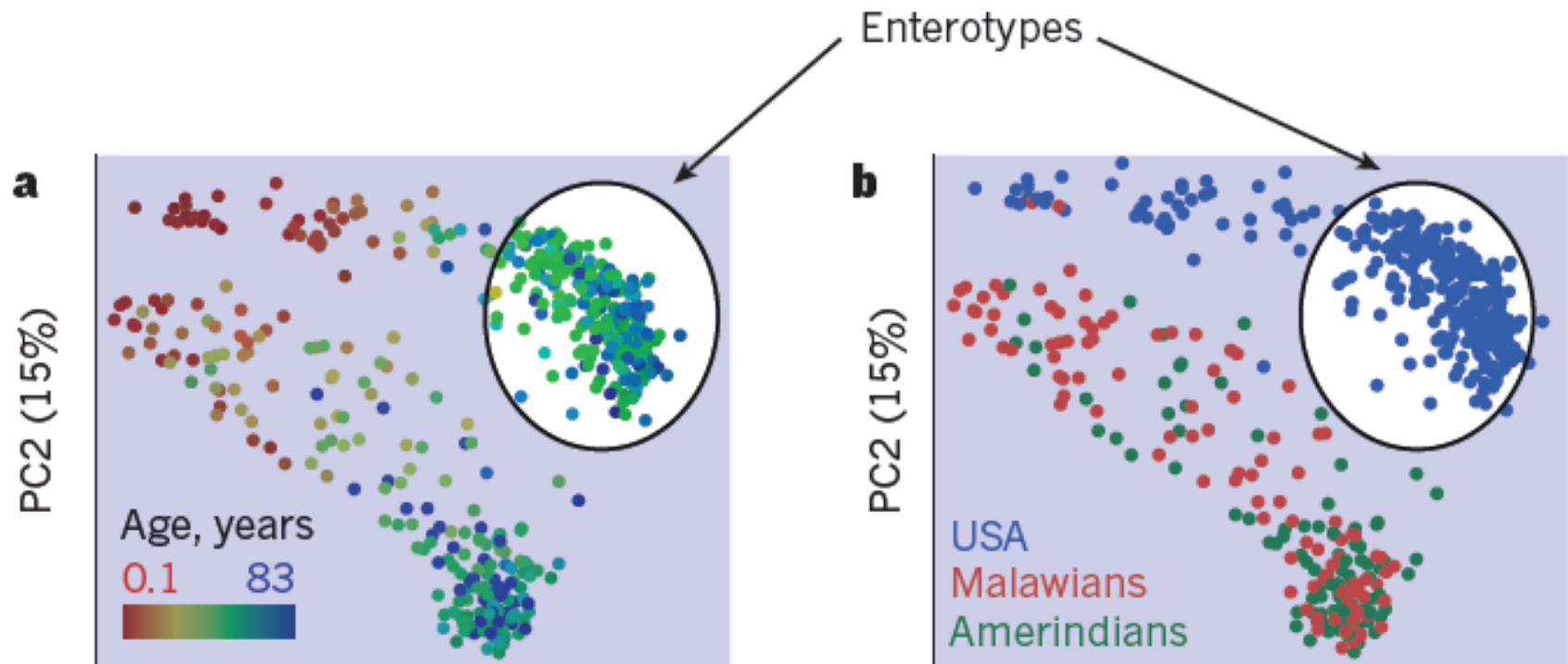
Health and gut microbiota

- Supplying nutrients to host
- Development of immune system and function
- Protect against infection by excluding pathogenic bacteria
- Protect enterocytes from acute inflammatory response in infections
- Epigenetic activators of gene expression

Human gut microbiota

- Bacteria constitute ~ 60% of faecal mass
- Complex community of 100 trillion archaeal and bacterial phyla; most diverse in body
- 90% Firmicutes (*Ruminococcus*, *Clostridium*, *Lactobacillus*) and Bacteroidetes (*Bacteroides*, *Prevotella*, *Xylanibacter*)
- Minor: Actinobacteria (*Bifidobacterium*), Proteobacteria (coliforms), Verrucomicrobia
- Broad range of substrate utilization, carbohydrates, SCFA, vitamin metabolism; promote energy harvest from diet

Human microbial diversity and enterotypes

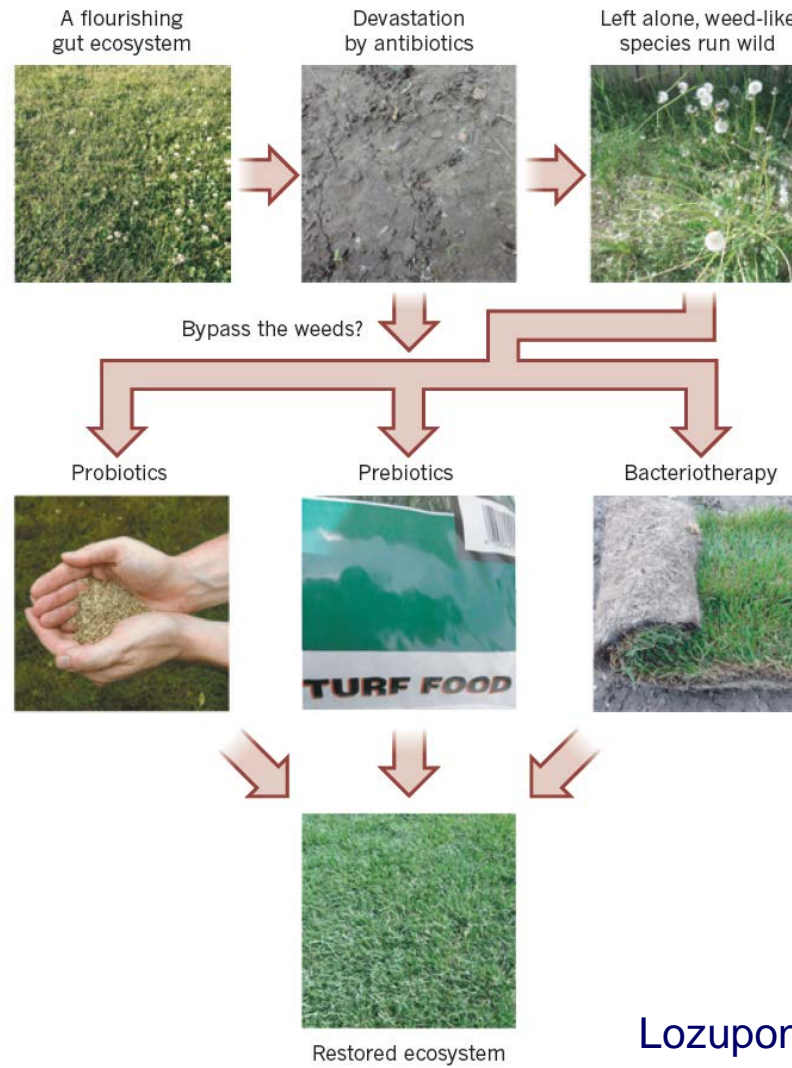


Lozupone et al. Nature 2012;489:220

Conditions linked to faecal microbiota

- Diarrhoea
- *C. difficile* pseudomembranous colitis
- Irritable bowel
- Ulcerative colitis
- Crohn's
- Coeliac
- Colorectal cancer
- Cardiovascular
- Type 2 diabetes (blood insulin sensitivity)
- Obesity (Colonic fermentation products)
- Neurological (Parkinson's, MS)
- Anxiety/Depression

Maintaining our gut microbial lawn



Lozupone et al. Nature 2012;489:220

C. difficile

- Present in about 3% of healthy
- Common cause of antibiotic associated diarrhoea
- Affects mostly elderly in geriatric wards (outbreaks)
- Profuse diarrhoea due to bacterial toxins increasing gut motility → dehydration, electrolyte imbalance
- In UK current CDI reports c.15,000 cases p.a (2000 deaths in 2011)
- 15-30% relapse rate, frequency increases with number of relapses
- Conventional treatment: vancomycin, fidamoxacin, or metronidazole + bowel lavage

Faecal microbiota transplantation (FMT)

- First used in China to treat diarrhoea in 4C
- 16C range of stool products for diarrhoea, fever, constipation etc! 17C used in veterinary medicine
- Faecal enema for treatment of pseudomembranous colitis (1958)
- To 2013 about 400 FMT cases reported worldwide most commonly for CDI
- Recipient's stool flora closely resembles donor stool 2 weeks after FMT, persists for about a month

Donor screen

- Medical history (GI)
- Excluded hospitalisation or antibiotic treatment (3 months); ? previous transfusion, transplant
- Serology: Hepatitis A,B,C (?E), HIV, HTLV, CMV, EBV; syphilis, *H. pylori*
- Culture: *Salmonella*, *Shigella*, *Campylobacter*, *Aeromonas*, *Vibrio*, *E. coli* O157, *C. difficile*
- *C. difficile* toxins
- Microscopy for ova cysts and parasites

Donor stool

- 50 -200 g of fresh stool
- Homogenized, filtered
- Bacteria centrifuged or whole sample
- Re-suspended in 10% glycerol/saline
- Frozen at -80°C (weeks)
- Diluted to 250 ml, delivered by enema, colonoscope or nasojejunal tube
- Single or repeated administration

FMT recipient

- Gut decontamination (vancomycin, metronidazole, rifampicin)
- Bowel lavage
- Loperamide to maximise contact time of infusate in colon
- Outcomes for CDI: reduction in frequency of motions, prevention of relapse

Outcomes

- High response rates (>80%) for CDI
- Randomized controlled trial showed 81% FMT response versus 31% for standard (vancomycin and/or bowel lavage). Trial closed early owing to unacceptable rates of recurrence in control groups (van Nood et al. *NEJM* 2013;**368**:407)
- Some evidence of durable change in bacterial flora long term
- Anecdotal reports of variable success in other conditions (100% UC, 50% IBD)

Issues of FMT as therapy

- Potential for transfer of pathogens from donor
- Screening efficiency for viruses, bacteria, fungi, parasites, 'unknown pathogens'
- Family and spouse as donors might give better tolerance of microbiota but possible predisposition to infection
- Recipient status; risk of subsequent transmission of occult infection?
- Yuck factor and logistics

Synthetic microbiota

- Defined cultured bacterial content
- Ensure strains free of antibiotic resistance and virulence genes
- Customised profiles of species according to specific imbalance identified in recipient
- Freezing/lyophilisation – transport
- Marker DNA sequences to allow tracking of retention in donor; opportunist infection and possible transmission!
- But, not as effective as total stool!

FMT potential

- Increasing number of reports implicating gut microbes in IBD and life style associated conditions (obesity, type 2 diabetes)
- Some evidence of benefit for ulcerative colitis but not Crohns
- Combination with pro- and pre-biotics
- Limited by efficiency of microbiota profiling
- Need for systematic clinical trials of donor and synthetic materials to refine protocols for use

FMT: Drug or tissue

- Non profit Stool Bank launched in USA, 2012
- May 2013, FDA proposed regulating FMT as 'drug'.
- Requested physicians to submit specific application before use but abandoned 6 weeks later
- February 2014; lobby for reclassification as 'tissue'
- NICE recommendation for CDI, April 2014
- Much interest in commercialization of faeces- derived products – therefore a 'drug'
- Health Canada calls for rigorous donor screening, better standardisation of material
- DIY- You Tube!!
- www.thepowerofpoop.com

Possible transmission of infection

- Two cases of norovirus gastroenteritis documented 2 and 12 days post FMT
- No evidence of direct transfer from donor to recipient
- *Blastocystis hominis* diarrhoea (asymptomatic donor)
- Colitis case with bloody diarrhoea following DIY FMT with stool from wife and 10-month old. Possible *C. difficile*, *E. coli* O157, *K. oxytoca* or CMV. (NEJM 2014;371:668-75).

Conclusion and issues

- Growing evidence of efficacy of FMT for CDI
- Several trials for other conditions underway
- Need to establish effective standards for donor screens
- Optimal preparation of donor stool
- Influence of nonbacterial factors on efficacy
- Most beneficial species profiles for dysbiotic conditions
- Wider use of metagenomic analysis to monitor changes in microbiota
- Influence of commercial market, pressure groups, self administration as treatment panacea for life style associated conditions

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