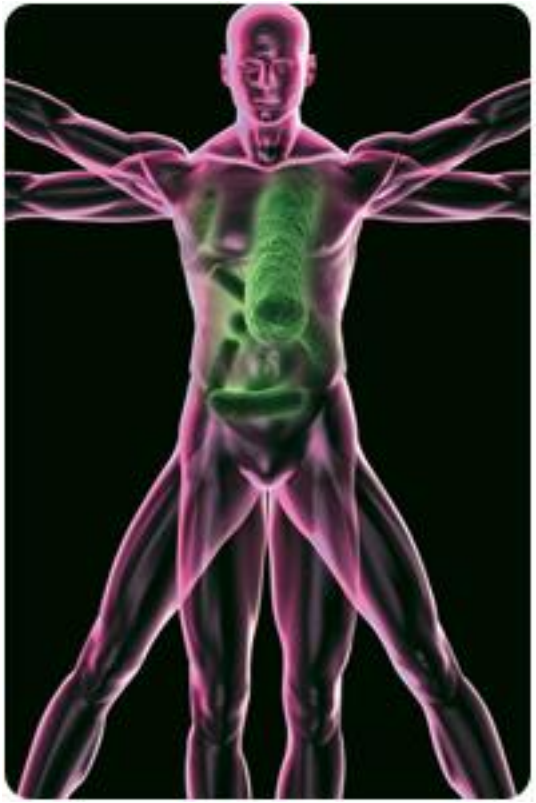
Antibiotic use and the gut microbiota: damage control

Emma Allen-Vercoe

Professor,

University of Guelph



IPAC workshop
April 27th 2018

Presenter disclosure

- **I am co-founder and CSO of Nubiyota LLC,** a company founded to commercialize Microbial Ecosystem Therapeutics, which I will mention in this talk

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BETTER ECOSYSTEM, BETTER HEALTH

We are not human!

We are *super-organisms* of human and microbial cells
We exist in a delicate host : microbe equilibrium

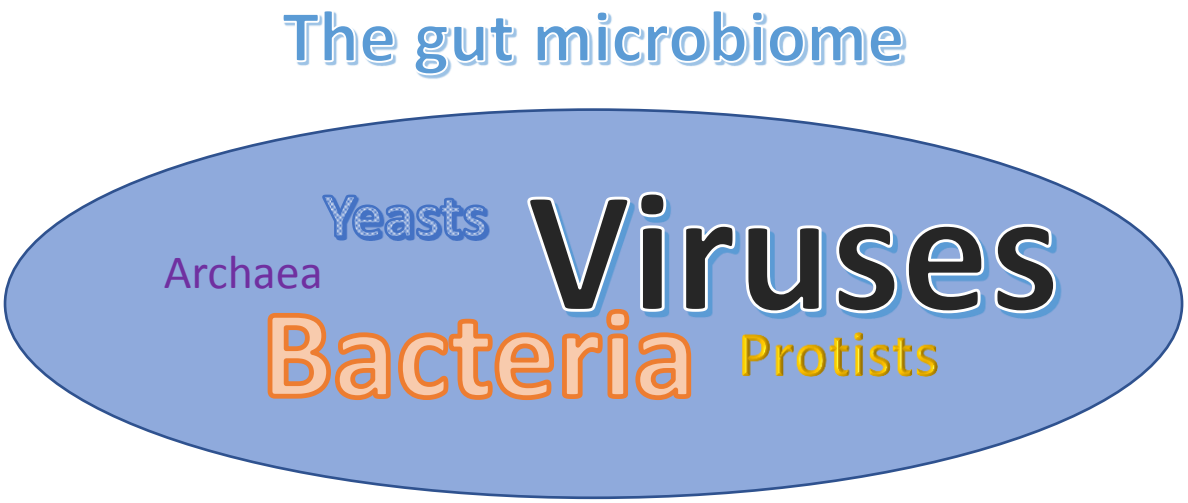
How human *are* we?

- ‘Reference human'
  - 70 kilograms, 20–30 years old, 1.7 metres tall
- ~30 trillion human cells
- 39 trillion bacterial cells

Human **1 : 1.3** Bacteria

Sender, Fuchs and Milo
doi: https://doi.org/10.1101/036103

Most of these microbes live in our gut



- Each gram of feces contains ~ 10^{11} bacterial cells
  - ~200 species

That's 10 trillion cells in the average bowel movement!

Everyone is different

http://farm9.staticflickr.com

Gut microbial ecosystems are highly variable in composition and abundance profiles between people

Ecosystem biodiversity drives overall health

High diversity of species:

- Healthy ecosystem
- Balance
- Functional redundancy
  - High gene count
- Resistance to damage

Low diversity of species:

- Sick ecosystem
- Imbalance
- Functional disability
  - Low gene count
- Susceptibility to damage

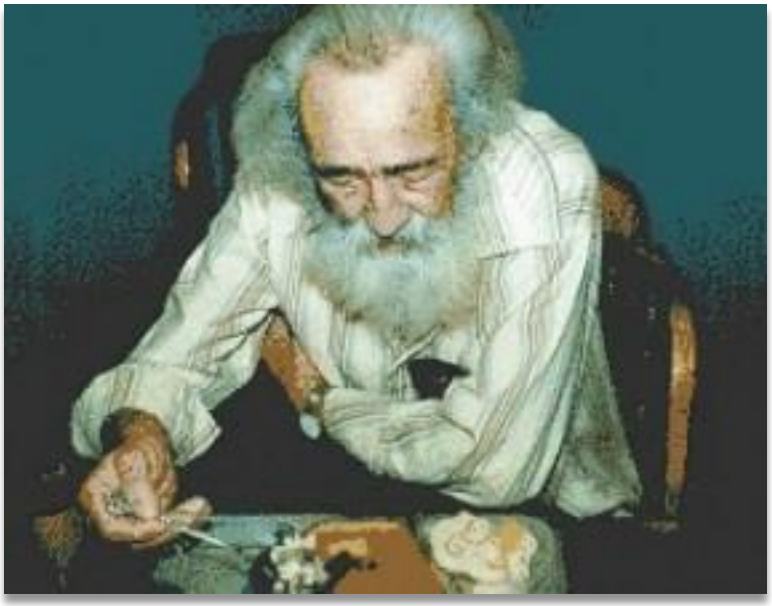
This is also true at the microbial scale

Remarkably…

The bacterial community in your gut remains stable from

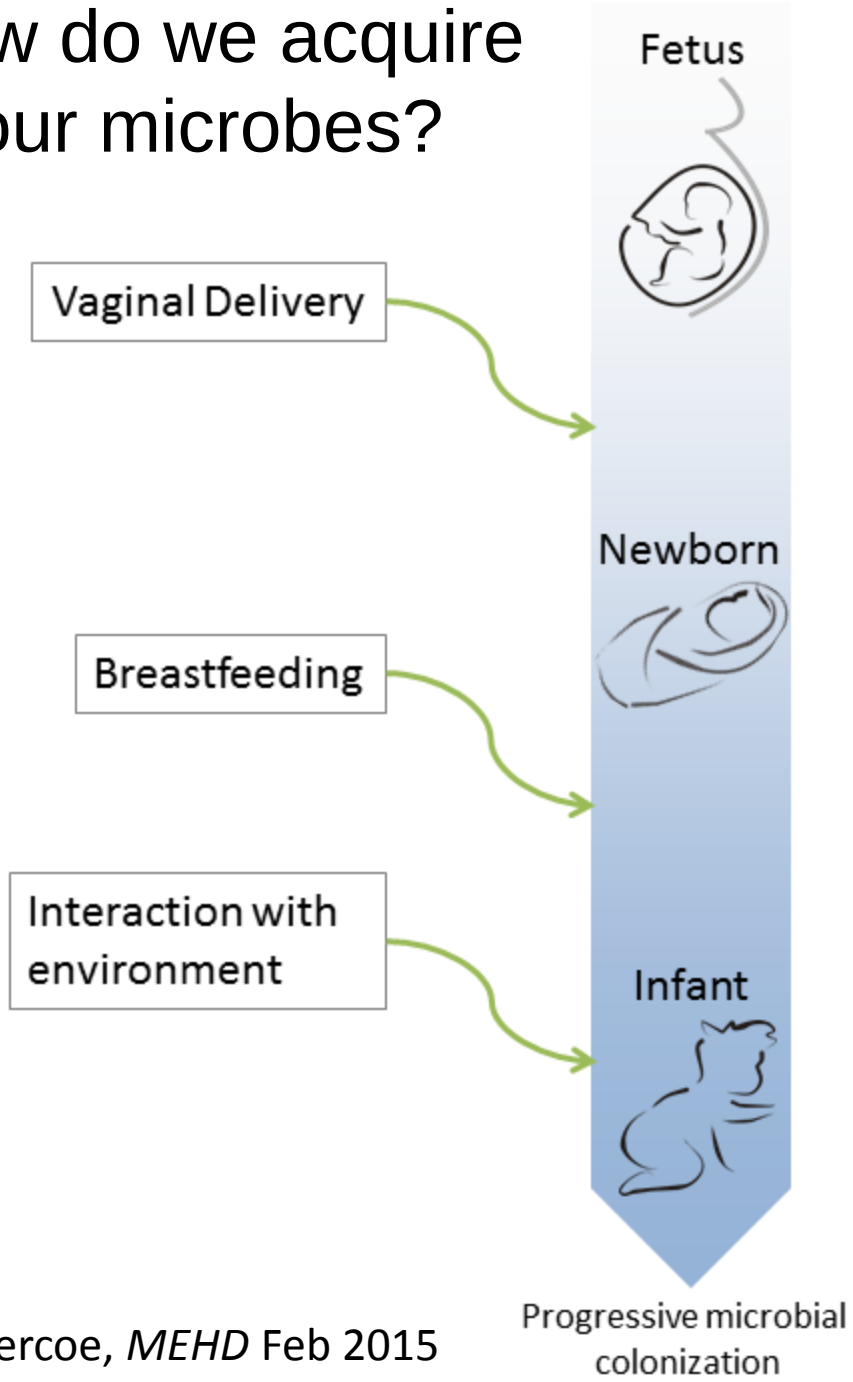
- weaning…

- …to old age



And we are only just starting to understand this homeostasis

How do we acquire our microbes?



Toh & Allen-Vercoe, *MEHD* Feb 2015

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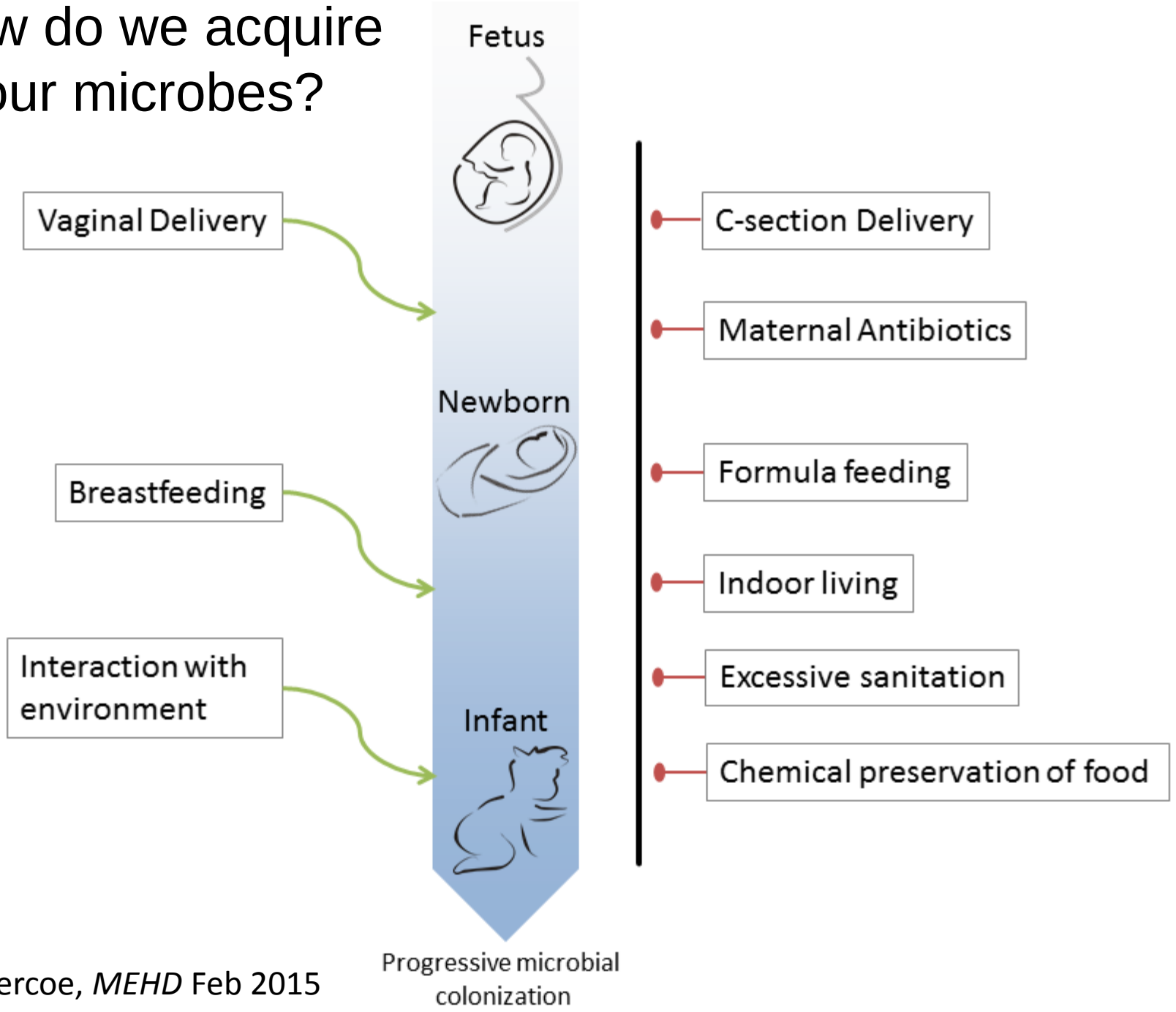
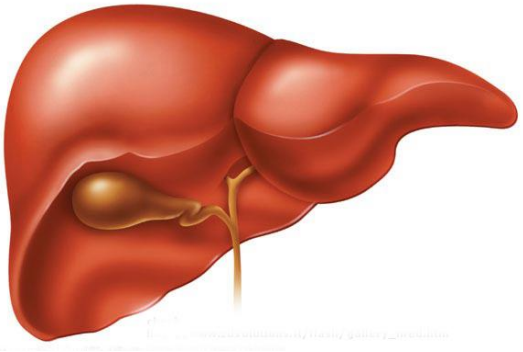


Toh & Allen-Vercoe, *MEHD* Feb 2015

What do our gut microbes do for us?

- Immune system regulation
- Calorie extraction from foods
- Crowd out potential pathogens
- Make some vitamins and cofactors
- Improve intestinal function
- Remove toxins and carcinogens

- As important to us as a liver
  - A virtual organ

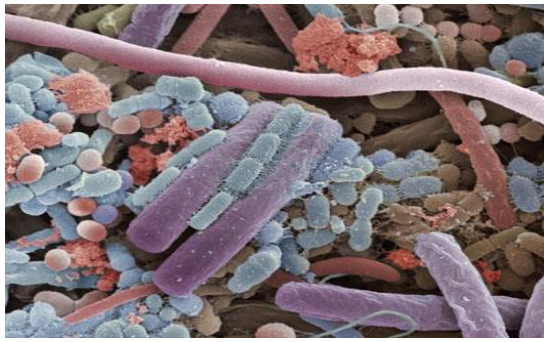
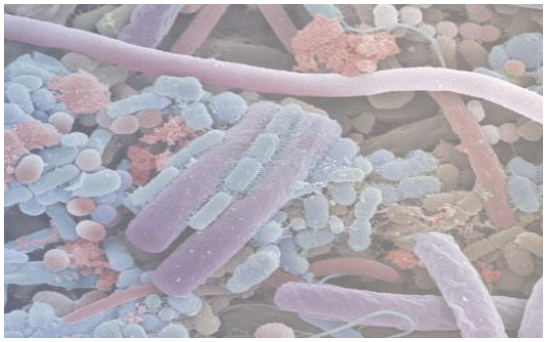


Our microbes are vitally important…

- But we are working very hard to exterminate them!

Are we damaging our health by eroding microbiome diversity?

- Hygiene hypothesis (Strachan, 1989)
  - Lack of exposure to certain infectious agents during childhood drives allergic disease
- Old friends hypothesis (Rook, 2003)
  - Humans are dependent on a co-evolved microbiome to educate the immune system and prevent inflammatory disease
- Missing microbiota hypothesis (Blaser &Falkow, 2009)
  - Loss of microbiota generally compounds over generations, and *recent changes in lifestyle* have greatly exacerbated this loss

- Many studies have shown:
  - Gut microbiota changes significantly with antibiotic use
  - Takes a long time afterwards to return to baseline
  - Sometimes does not return to baseline at all
  - Repeated ‘hits’ cause vast changes from which the ecosystem does not recover

Looft *et al*., PNAS 2012; Robinson & Young Gut Microbes. 2010; Jakobsson *et al*. PLoS One. 2010; Antonopoulos *et al*., Infect Immun. 2009; Dethlefsen *et al*. PLoS Biol. 2008; Heinsen *et al*. Gut Microbes 2015; Nobel *et a*l., Nat Comm. 2015

The average person in the U.S. will receive 10-20 courses of antibiotics by the time he or she is 18 years old

Examples of diseases associated with reduced gut microbiota diversity
(published research)

Inflammatory bowel diseases

Infant colic

Eczema

Autism

Colorectal cancer

Allergic asthma

Celiac disease

Obesity

Neonatal necrotizing enterocolitis

Irritable Bowel Syndrome

***Clostridioides difficile* infection**

- Lack of microbial diversity
- Loss of ‘keystone’ species
- Overgrowth of opportunistic pathogens
- Poor diet/lifestyle
- Drug interactions

“Dysbiosis”

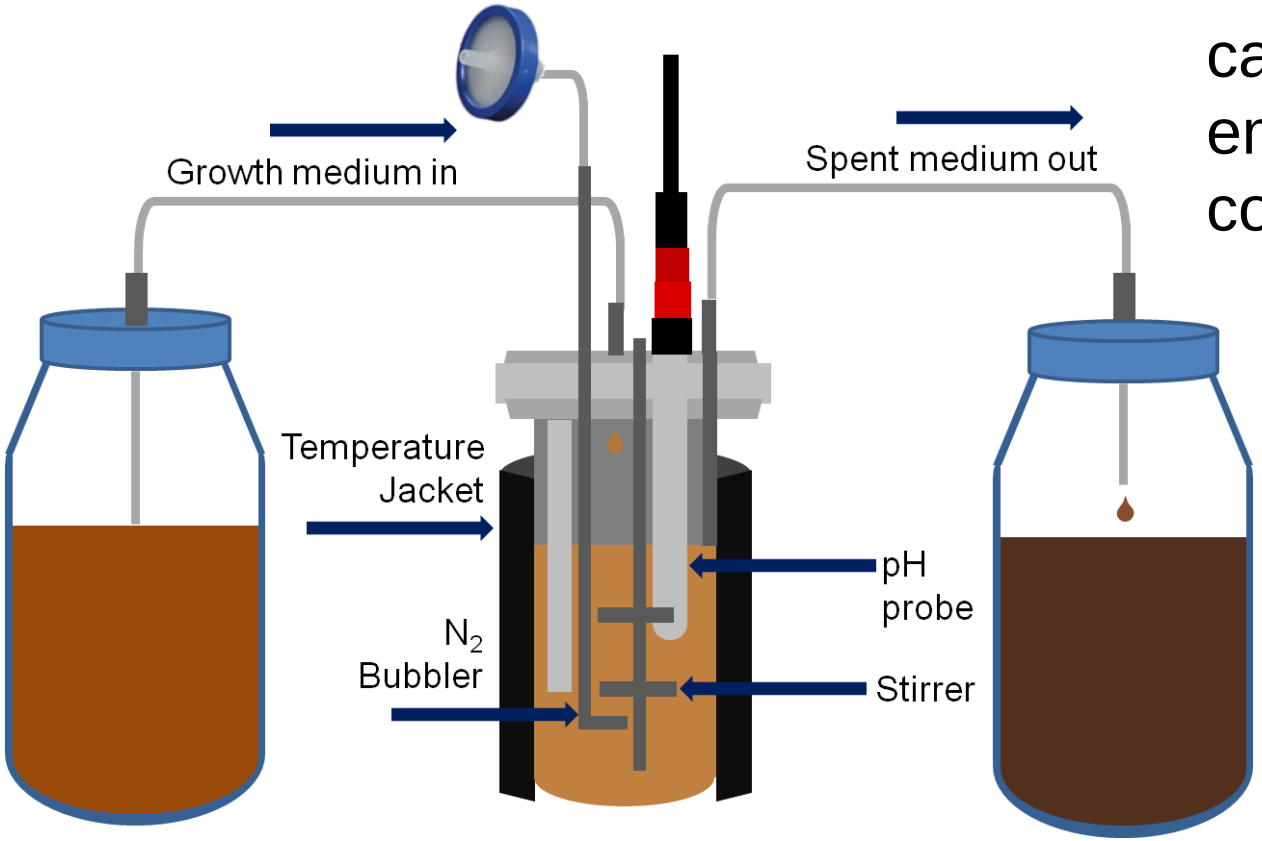
Looking inside the black box is the key to understanding disease

DISEASE

The human gut microbiota is a complex microbial ecosystem

Its function and behaviour is *best studied as a whole*

The human colon is a type of ‘bioreactor’…



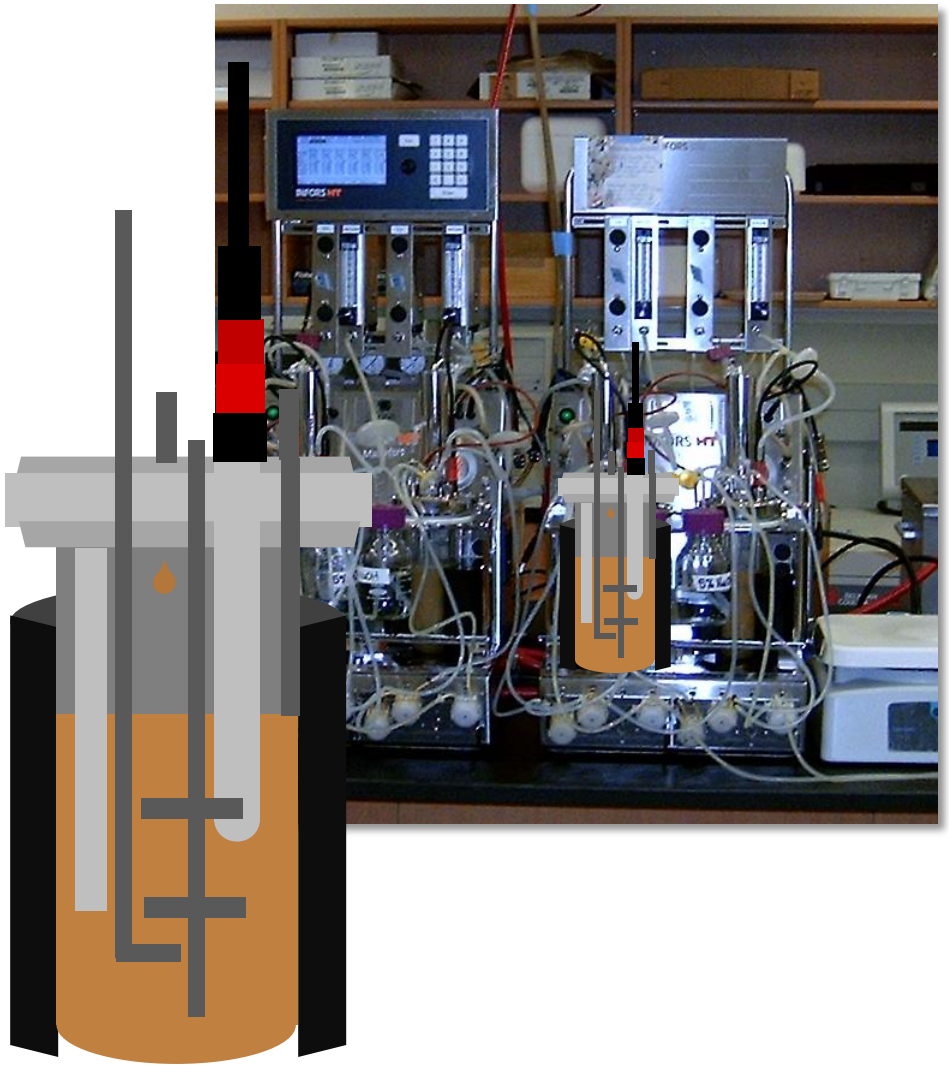
…thus, bioreactors can be used to emulate the human colonic environment

•Seeded with fresh feces or defined communities and set to model the ecosystem of the colon

•Host-free system

•Can be used to ‘culture the unculturable’

•Can support whole gut microbial ecosystems for several weeks at a time



- We can model the gut microbiota under different stress conditions
- We can try to protect against the effects of stress

When most people think of gut microbes, they think of the good and the bad…

- **The Good**
- Lactic Acid Bacteria (LAB)
  - E.g. *Bifidobacterium* and *Lactobacillus* spp.
- Butyrate-producing bacteria
  - E.g. *Faecalibacterium prausnitzii, Roseburia* spp.

- **The Bad**
- Opportunistic pathogens
  - *E. coli*
  - *Clostridioides difficile*
  - *Bacteroides fragilis*
- Sulfate-reducing bacteria
  - E.g. *Desulfovibrio* spp.

The Ugly: it really is not that clear-cut!

Some microbes are like bad teenagers in a subway station…

In a crowded environment they tend to behave well

When the crowds are gone, they tend to start behaving in antisocial ways

Fixing dysbiosis with probiotics

- If you take an antibiotic, you can just cancel the negative effects out by using a probiotic, right?
  - Nope!
- Many types and strains of probiotics
- Many manufacturers, some legitimate, most not
- Many over-inflated claims
- Very little actual science

From a typical probiotic website: "There are ov… …rent types of bacteria in the digestive system; the two most pr… …Lactobacilli and Bifidobacterium. Bifidobacterium … …t prevalent bacteria in the large intestine, while Lactobacilli … …st prevalent in the small intestine. As we age, studies show th… …s of Bifidobacterium decline, while harmful pathogenic ba… …ase. This is one of the main reasons that intestinal ailments increa… …as we age."

WRONG, WRONG, WRONG!!!

The layperson's view of probiotics…

Myth 1:
Probiotics found in food are the same kinds of species that are found in the gut

Myth 2:
Probiotics colonize the gut

The microbial ecologist's view of probiotics

Normal gut microbiota

Colon: 100 billion to 1 trillion cells per gram of poop

VS.

Probiotic

2-15 billion cells per capsule

My advice: do careful research or consult reputable sources for info

http://www.probioticchart.ca/

3
NEW INDICATIONS FOR 2015

Clinical Guide to PROBIOTIC SUPPLEMENTS

AVAILABLE IN CANADA: 2015 Edition

Indications, Dosage Forms, and Clinical Evidence to Date

Author: Dragana Skokovic-Sunjic BScPhm RPh NCMP

Reviewers: Dr. Vivien Brown MDCM CCFP FCFP NCMP,
Dr. Bradley C. Johnston PhD, Iris Krawchenko BScPhm RPh,
Dr. John Marshall MD MSc FRCPC AGAF, Dr. Tom Smiley BScPhm PharmD

Medical Editor: Ivana Sunjic BSc

Download for free **PROBIOTIC mobile app**

ANDROID APP ON Google play

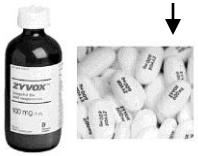
Download on the App Store

Prebiotics

- ‘Food’ for your gut microbes
- Typically non-digestible* fibre compounds
  - *your microbes digest them just fine!
- Not a one-size-fits-all approach
  - But sold that way!
  - No simple solution – fibre supplements not diverse enough
  - Could be used more cleverly
- Are we entering the era of matching foods to gut microbiota ‘types’?
- *How* do we do that?

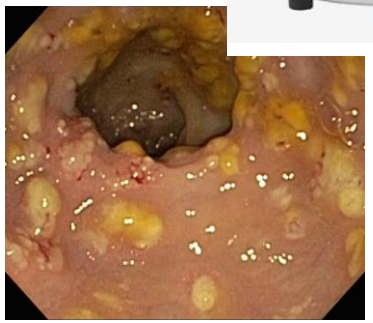
C. difficile infection: a man-made disease

Normal colon
C.difficile absent or numbers low



Antibiotics
-clindamycin
-cephalosporins
-ampicillin

Reduction in normal Gut microbes
C.difficile grows to high numbers



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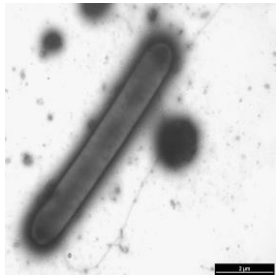

C. Carlucci, A-V lab, 2012

...n of ...and B

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Ulceration of colon

Death

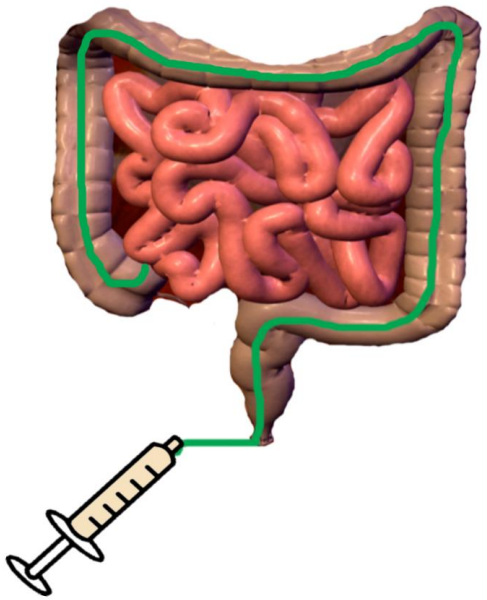
Vancomycin or metronidazole

Symptoms abate

Cessation of therapy

Return to normal

But poop does not make great medicine, so…



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Petrof *et al. Microbiome* 2013, **1**:3
http://www.microbiomejournal.com/content/1/1/3

Microbiome

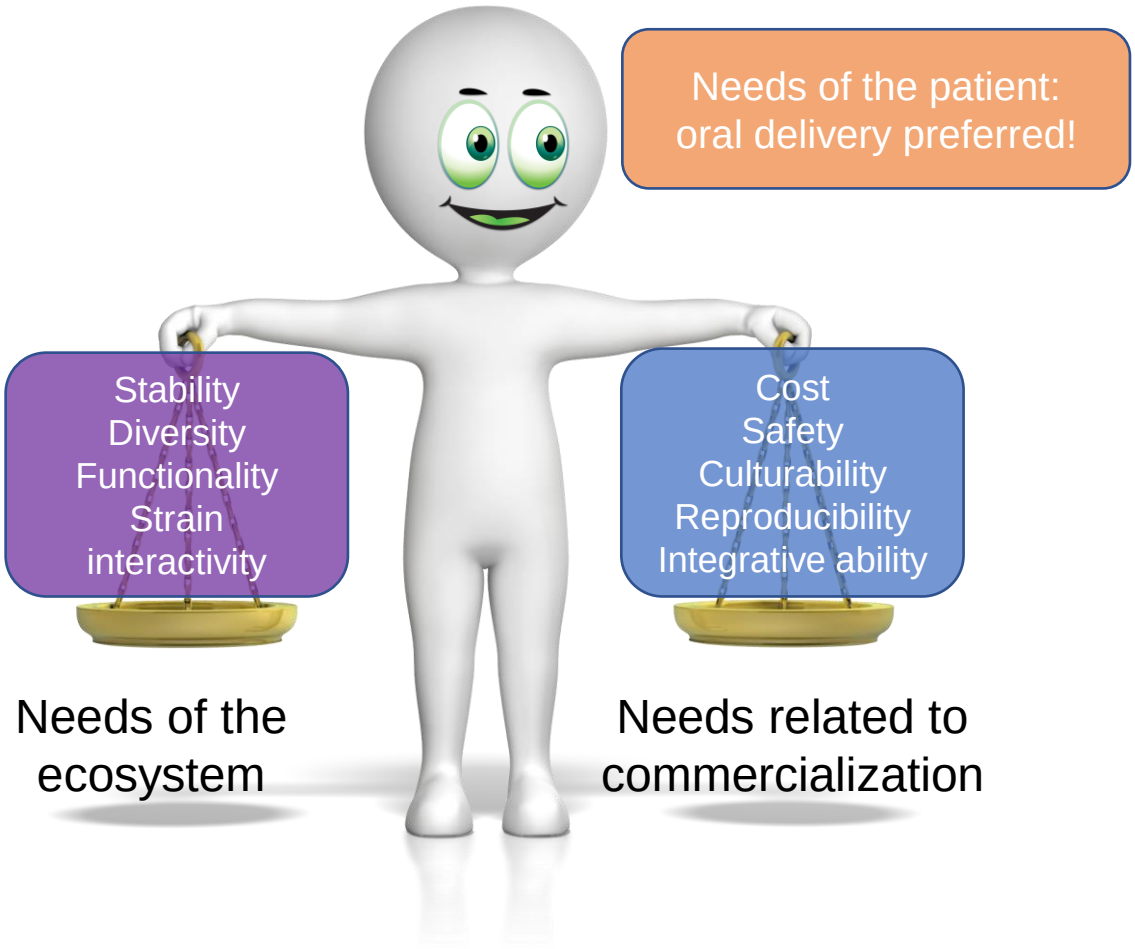
METHODOLOGY Open Access

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut

Elaine O Petrof[1*†], Gregory B Gloor[2†], Stephen J Vanner[1], Scott J Weese[3], David Carter[4], Michelle C Daigneault[5], Eric M Brown[5], Kathleen Schroeter[5] and Emma Allen-Vercoe[5]

- **MET-1 = 33 bacterial strains**
  - 1x100 mL dose via colonoscopy
  - Two cases of severe recurrent CDI treated
  - Both patients recovered within 48 h (and have remained *C. difficile*-free to date)
- Same concept as a 'fecal transplant'
- But instead of poop, we used a complex, defined ecosystem of *pure microbes*
  - Logical next step
- Because it's defined, we can monitor long-term effects

Which microbial species should be chosen?



Making a better MET

MET-1
Trialed as a novel probiotic
33 bacterial strains, 25 species
4 bacterial phyla included
Pure culture as a suspension of microbes for delivery via colonoscope

Making a better MET

MET-1	MET-2
Trialed as a novel probiotic	Developed as a first-in-class biologic drug
33 bacterial strains, 25 species	40 bacterial strains, 40 species
4 bacterial phyla included	5 bacterial phyla included
Pure culture as a suspension of microbes for delivery via colonoscope	Pure culture as stabilized, lyophilized capsules for oral delivery

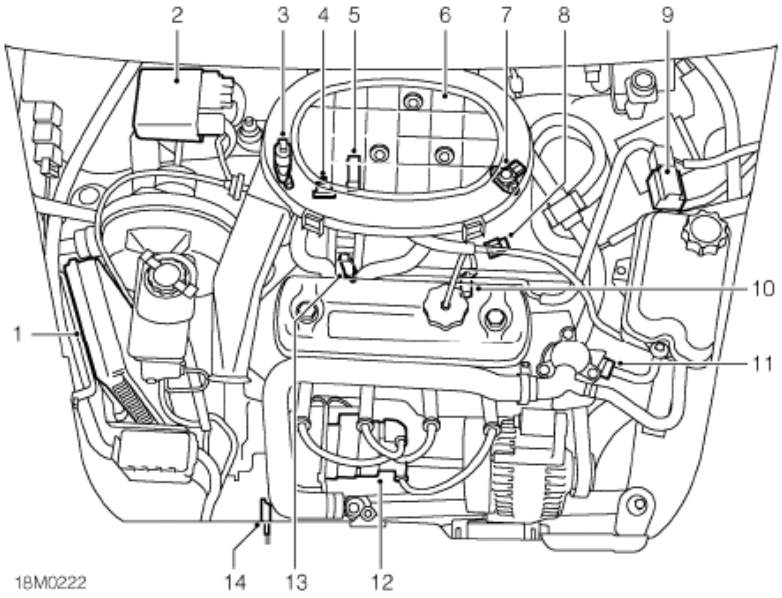
Enhanced safety

- Fecal transplants cannot be undone!
- Microbial species used for MET are confirmed generally sensitive to selected antibiotics
  - Can be removed if required
- Genomes are sequenced to check for absence of known virulence genes
- Because they are well-characterized, we can track each strain during and after treatment of a patient

Phase 1A trial currently underway

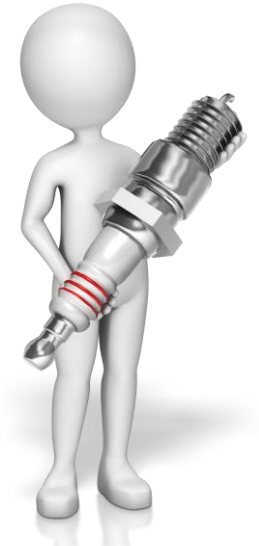
- For the treatment of recurrent *C. difficile* infection that has repeatedly failed to be resolved using antibiotic therapy

Moving towards the future:
How should we approach development of novel METs?



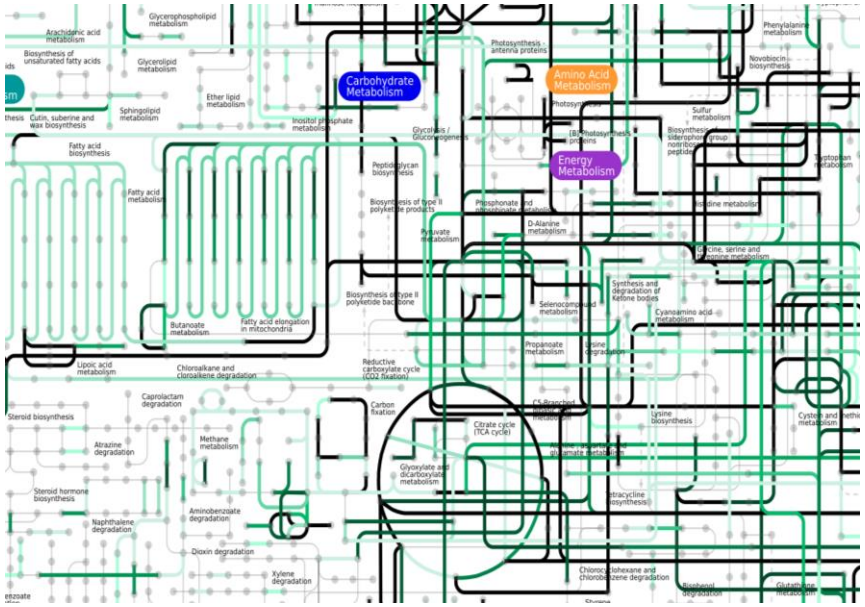
We need to look at the ‘emissions’

We need to look at the
gut microbial ‘engine’

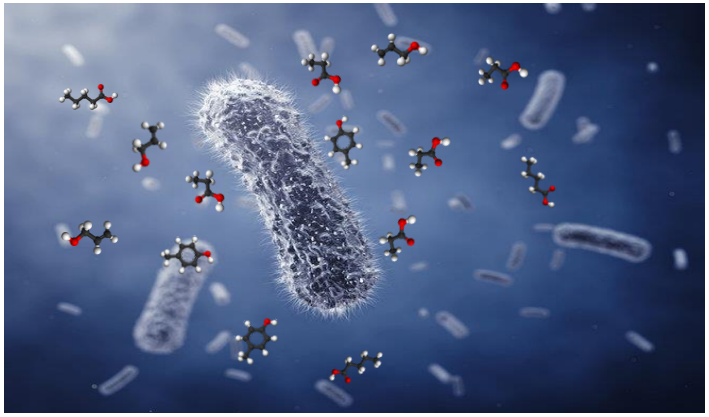


We need to replace the faulty parts to get the engine running optimally again

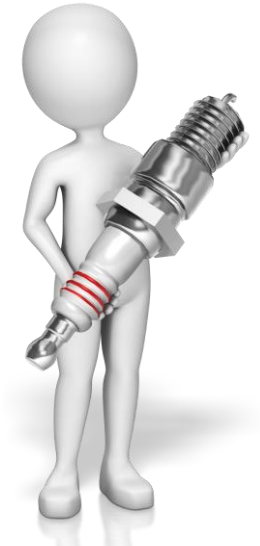
Moving towards the future:
How should we approach development of novel METs?



The ‘metagenome’



The ‘metabonome’



We need to replace missing functions to get the engine running optimally again

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