Can we use bugs as drugs? Fixing the gut with Microbial Ecosystem Therapeutics

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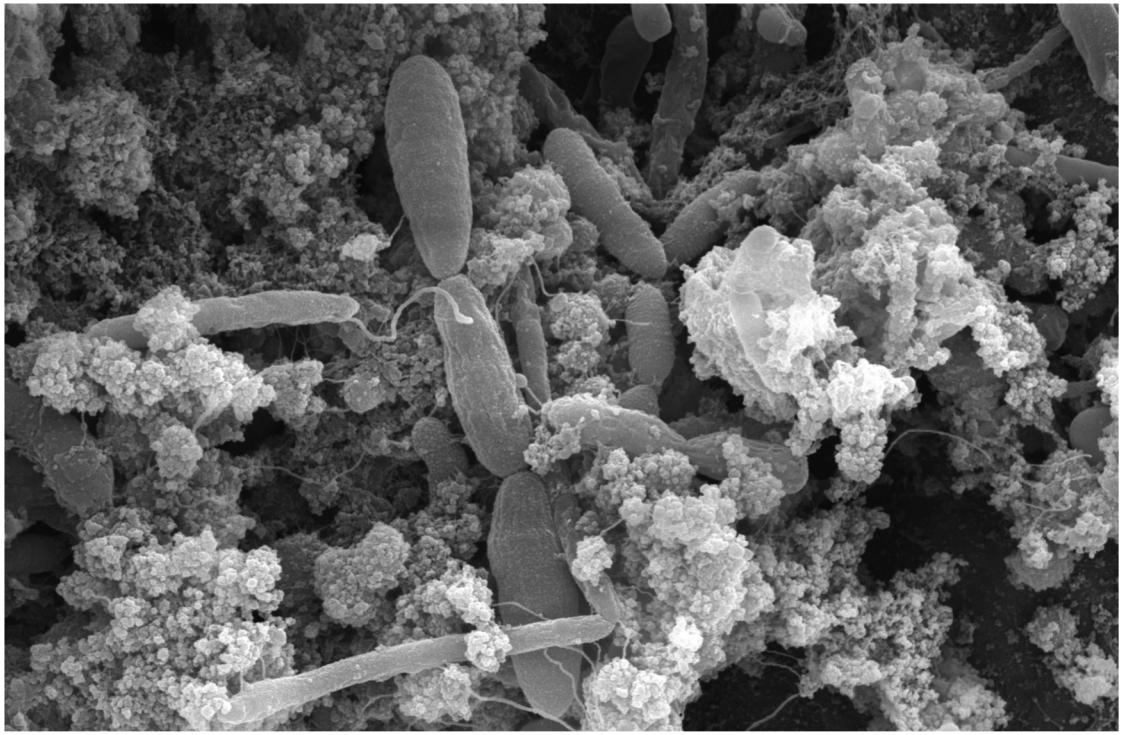
University of Guelph

Lifelong Learning Markham – online webinar

May 4th 2020



Gut microbes digesting a kernel of corn. SEM credit: Dr. Amber Park, U of G

What is your gut microbiome …and why is it so important?

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

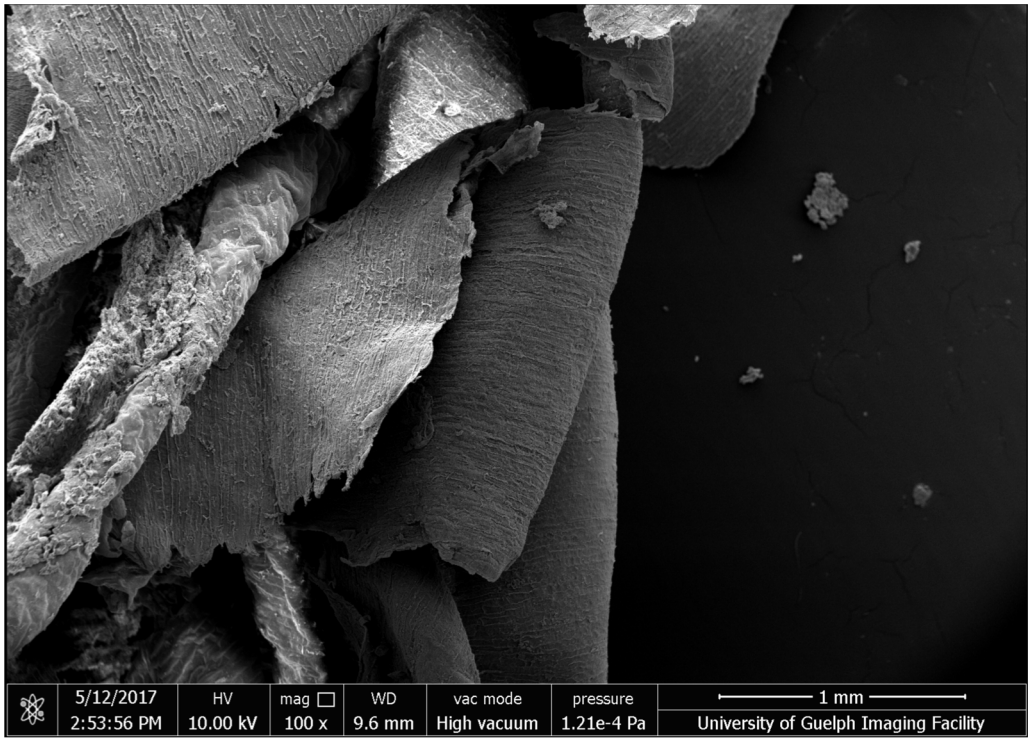
Sender, Fuchs and Milo
doi: https://doi.org/10.1101/036103

But then,
why don't we look like bacteria?

- Bacterial cells are much, much smaller than human cells
  - On average 1/100 to 1/1000 of the size
  - Each gram of feces contains ~ 10^{11} bacterial cells

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

Series of scanning electron micrographs of a corn kernel retrieved from a poop sample



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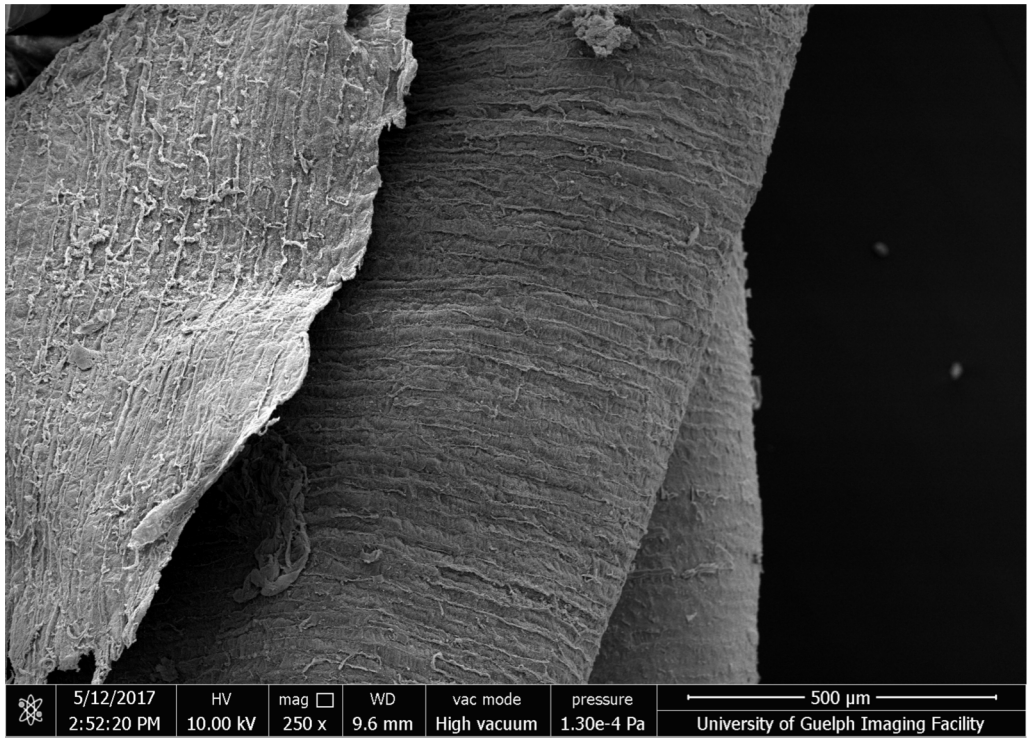

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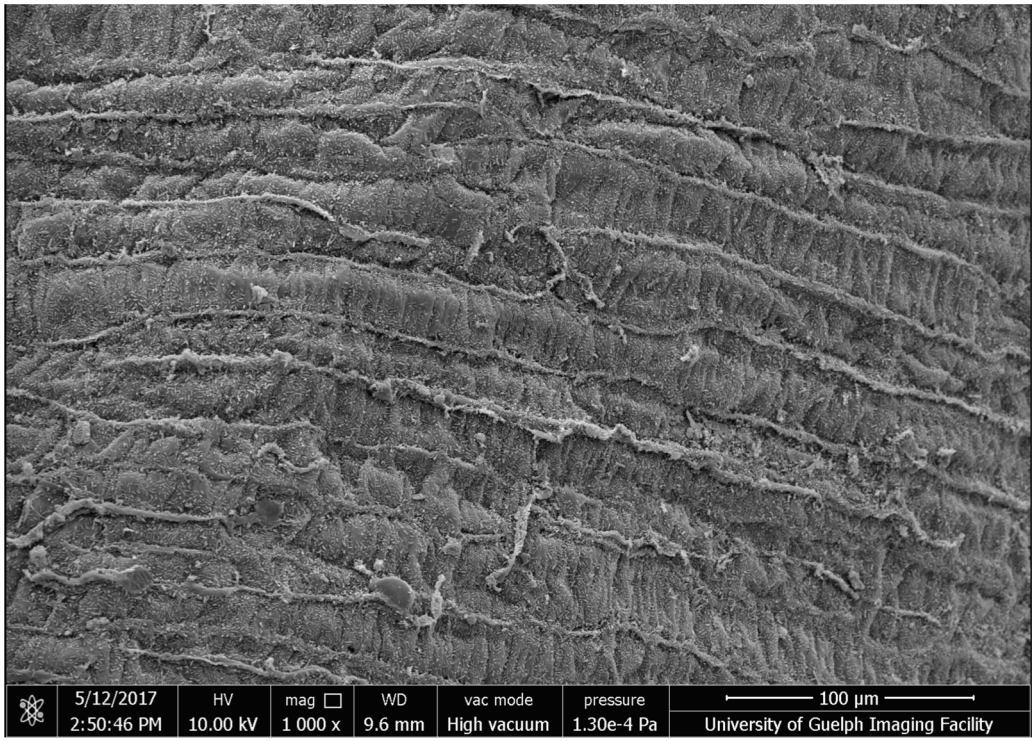

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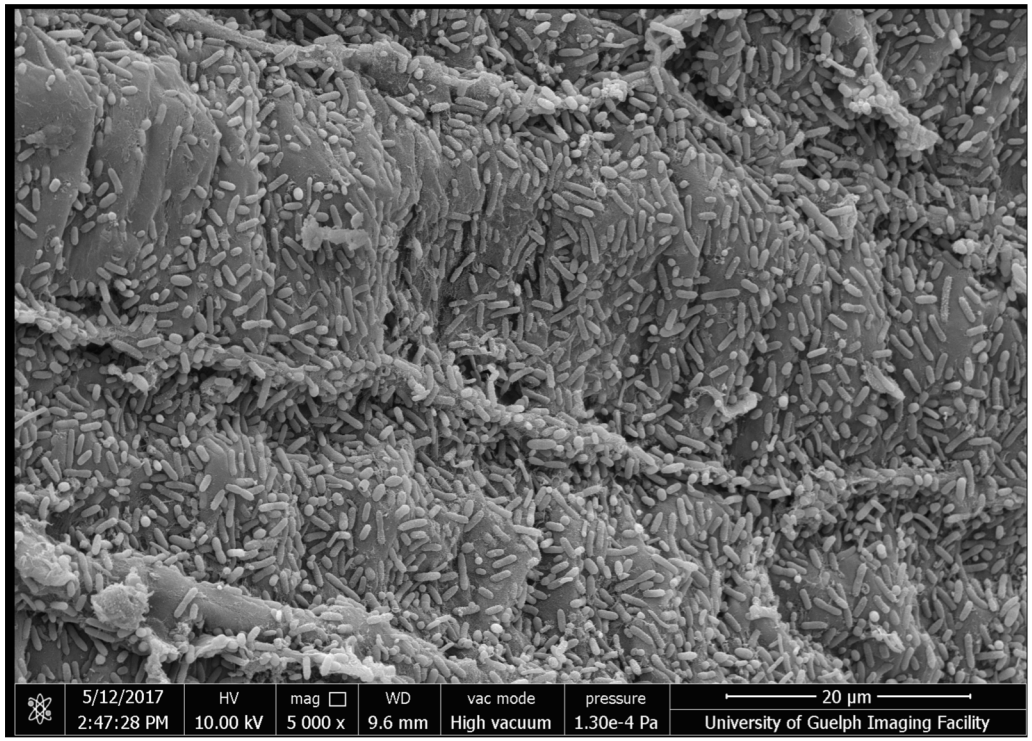

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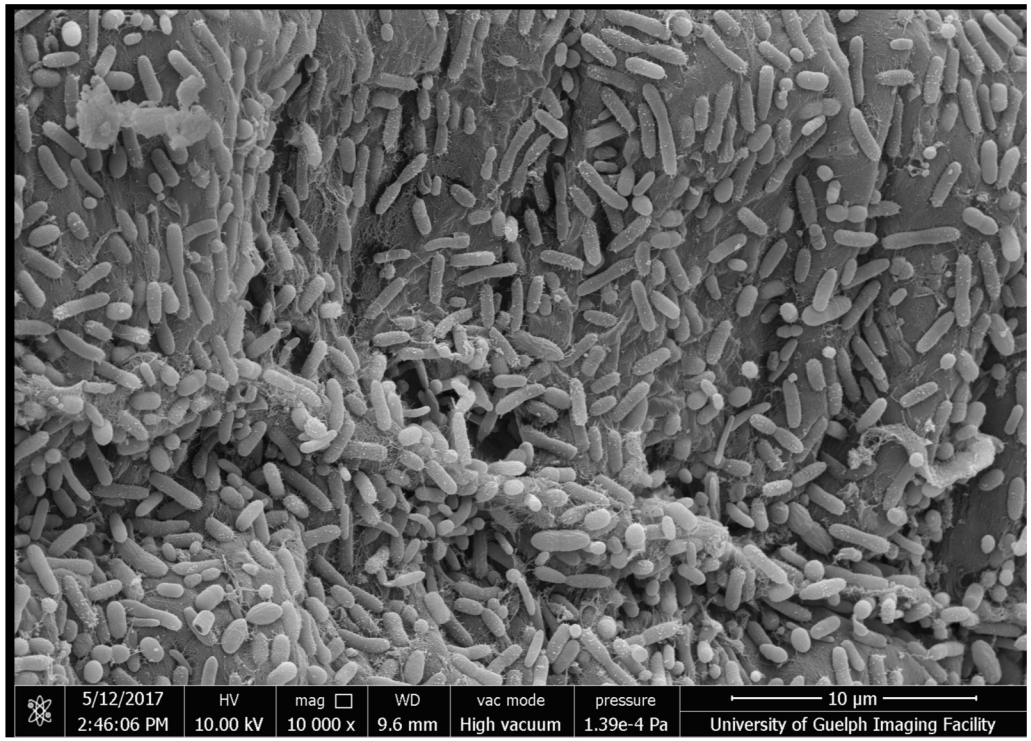

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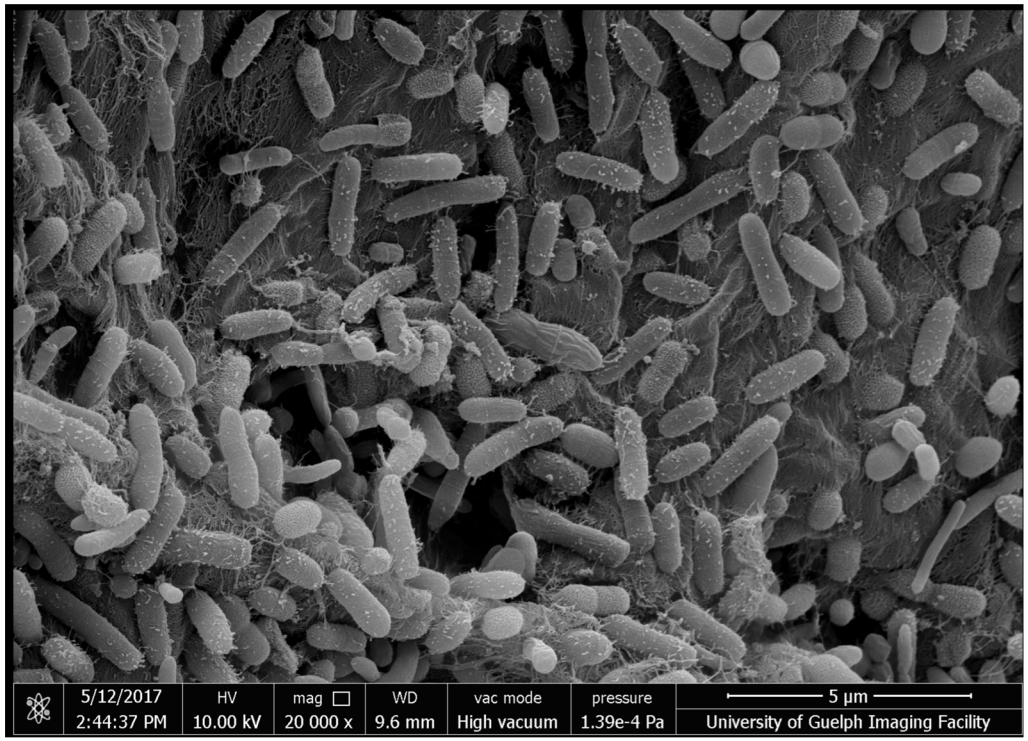

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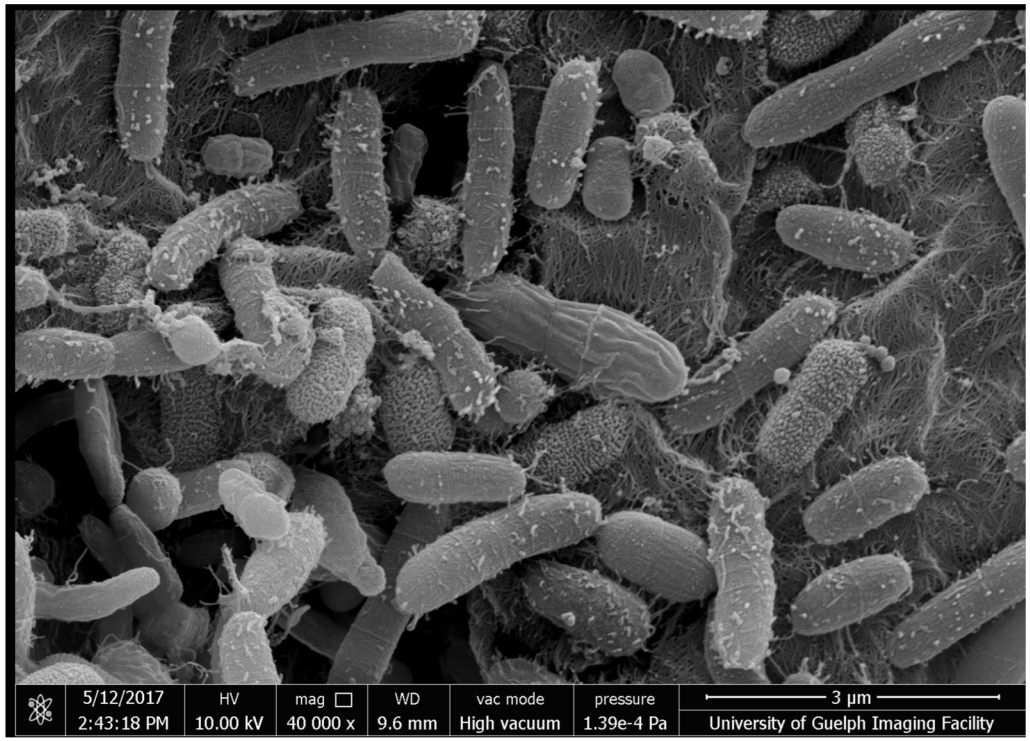


Biodiversity in the gut is important

High diversity of species:

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

Low diversity of species:

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

Remarkably…

The bacterial community in your gut remains stable from

- weaning…

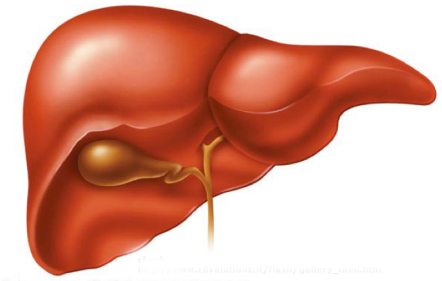
- …to old age

This is a combination of host and microbe-driven effects

What do our gut microbes do for us?

- Regulate the immune system
- Help to extract energy from foods
- Control potential pathogens
- Make some essential metabolites, including vitamins and cofactors
- Improve intestinal function
- Remove toxins and carcinogens

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

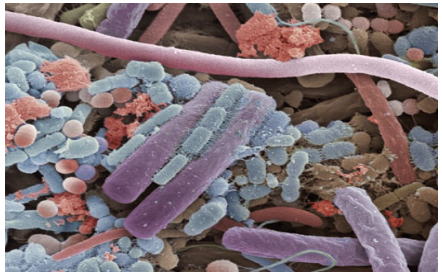
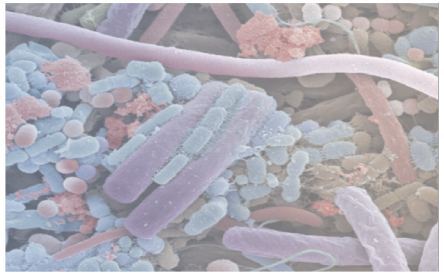


Are we damaging our health by eroding microbiome diversity?

- 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

‘Extinction events’ may impact health

- Hygiene hypothesis
  - We are preventing proper colonization by being too clean
- Missing microbiota hypothesis
  - We are disturbing proper colonization across generations through e.g. antibiotic use
- Antibiotic use (especially in early childhood) may be particularly problematic

- 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

Antibiotics save lives

- They are one of the miracles of modern medicine, and always will be
- But we have failed to understand the full consequences of their use…
- …And now we are suffering the consequences
  - Antibiotic resistance
  - Damage to the microbiota ‘organ’
  - Dependence of many livestock farming practices on antibiotic-induced growth promotion

In Ontario, in 2016, doctors prescribed 637 antibiotic courses per 1000 inhabitants

The additional impact of the Western diet

- Average Western diet:
  - rich in refined foods,
  - low in fermented foods, complex carbohydrates, fibre
- Refined foods are easily broken down in the upper GI tract
  - Thus very little left-over food makes it to the colon
- Colon is the site of most beneficial gut microbial activity
  - Starvation of this community can lead to ecosystem damage
  - ‘extinction events’ and reduced diversity

For example…

Artificial sweeteners…

…and artificial food emulsifiers

Damage your gut microbiota

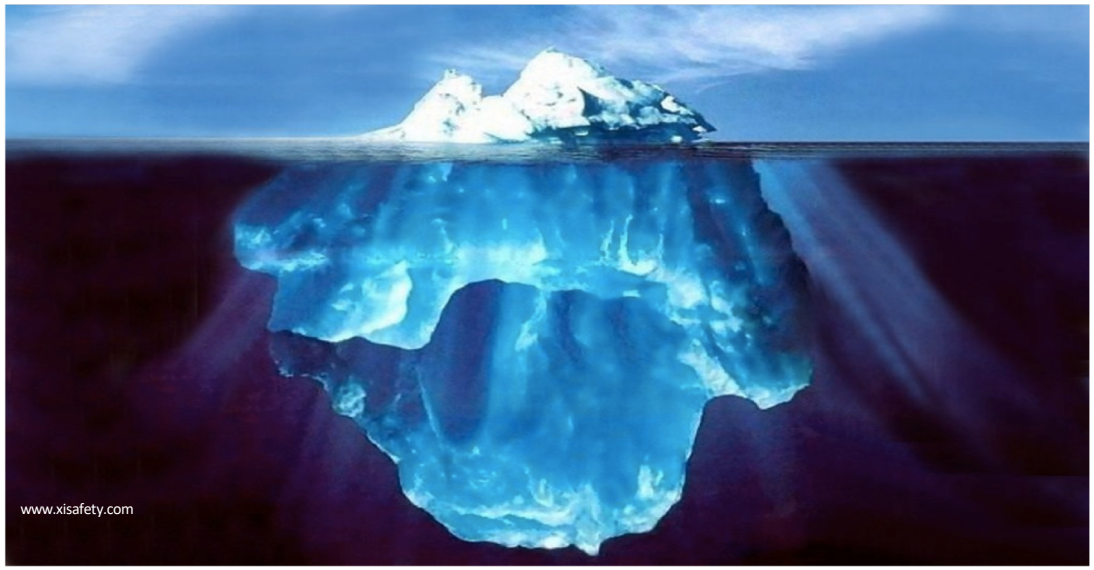
Chassaing *et al.*, doi 10.1038/nature14232, Suez *et al.*, doi: 10.1038/nature13793

What about common drug products?

- Why do some drugs work miracles in some patients and do nothing for others?
- We've been focusing on the wrong genome!
  - Remember, your gut microbiome carries out a great deal of metabolic 'work' for you!
- Everyone's gut microbiome is different… so predicting drug effects suddenly becomes a lot more complicated!
- There is a new era of pharmacology emerging: 'metagenomic toxicology'

What we *need to understand:*

- The safety of many food additives, supplements and drugs has NEVER been assessed taking into account our microbial passengers
  - we are just scratching the tip of the iceberg



Examples of diseases *associated* with altered 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

***C. difficile* infection**

Depression and anxiety

How do we know that Westerners have low gut diversity?

- We **can't** go back in time to look at microbiomes pre-antibiotics/refined foods
- We **can** look at indigenous peoples who have not had exposure to these things

Their gut microbiomes are much more diverse than ours!

Schnorr et al. Nat Commun. 2014 Apr 15;5:3654; Obregon-Tito et al. Nat Commun. 2015 Mar 25;6:6505.

The pervasive advertising message is

"<u>all</u> microbes are bad!"

But only a
tiny fraction
of microbes are
pathogens

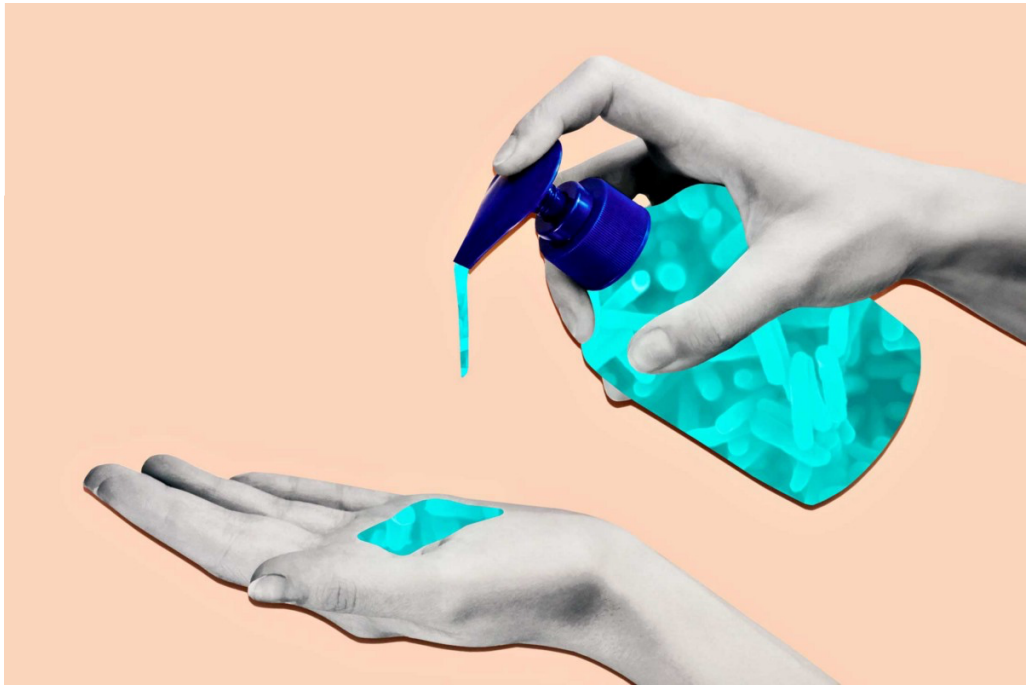
Antimicrobial practices don't discriminate between pathogens and microbiota

This situation is starting to change!

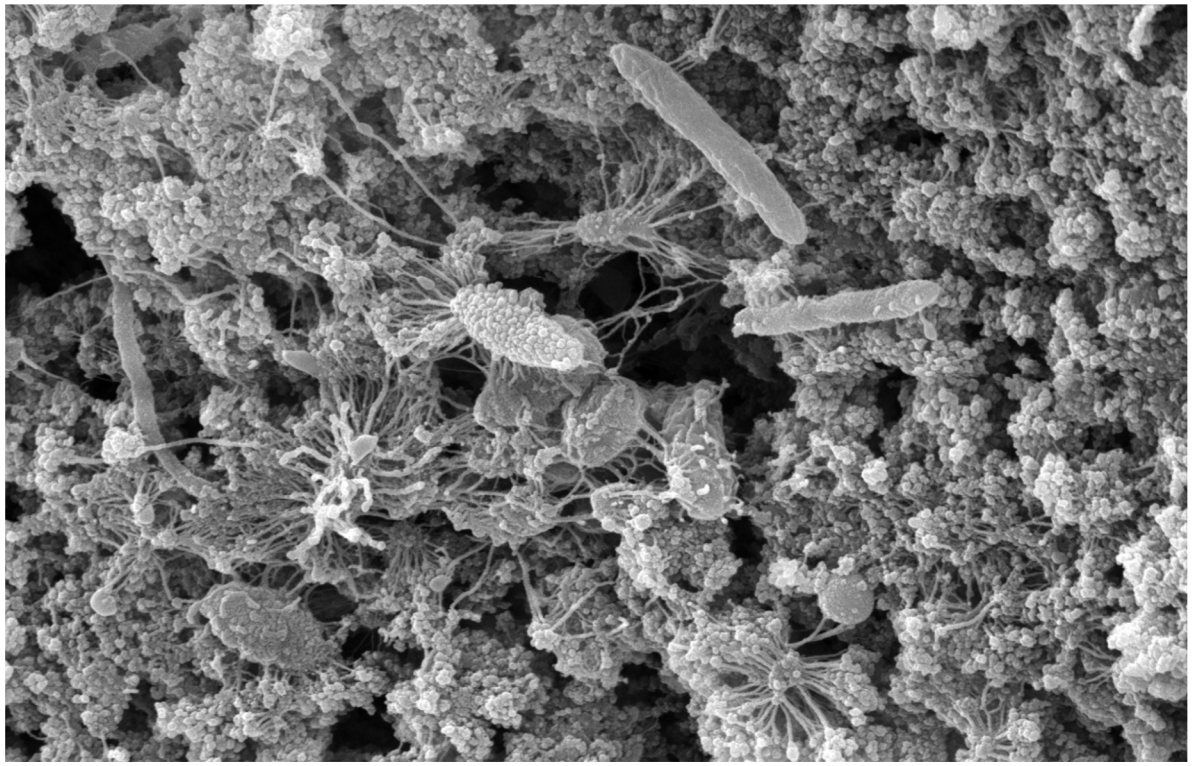
Germ-Killing Brands Now Want to Sell You Germs

The world's best-known antibacterial labels are pouring millions into probacterial health and beauty startups

Bloomberg Businessweek Follow
Apr 23 · 17 min read ★



What can we do to support gut microbiome health?



Gut microbes digesting a kernel of corn. SEM credit: Dr. Amber Park, U of G

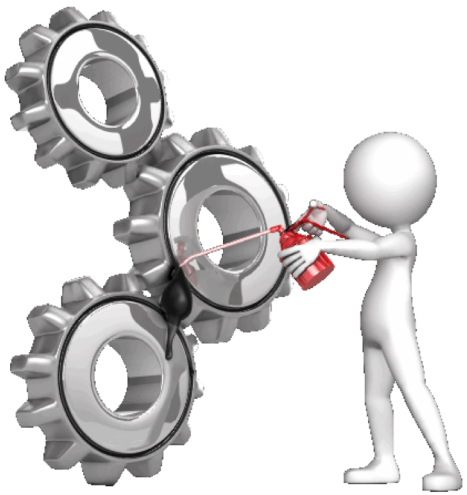
A number of activities seem to support a healthy gut microbiota

- Natural childbirth, breastfeeding
- Increased social exposure
- Regular exercise
- Outdoor activities
- Pet ownership (if the pet goes outdoors)
- Healthy diet
- Antibiotic and other drug use *only as appropriate*
- **These are most effective if adopted early in life**

Bloomfield et al. Perspect Public Health 2016 136:213-24; and many others!

How can we ‘fix’ dysfunctional gut microbial ecosystems?

Probiotics, prebiotics and beyond…



Can we fix 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

Study of 14 commercial probiotic products[1] showed:
"…many probiotic products contain unadvertised additional lactobacilli and bifidobacteria, whereas others are missing species listed on the product label."
Many probiotic capsules contain far fewer than the number of microbial cells advertised.

1 Marcobal et al. J Pediatr Gastroenterol Nutr. 2008 May;46(5):608-11.

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 CFU per mL

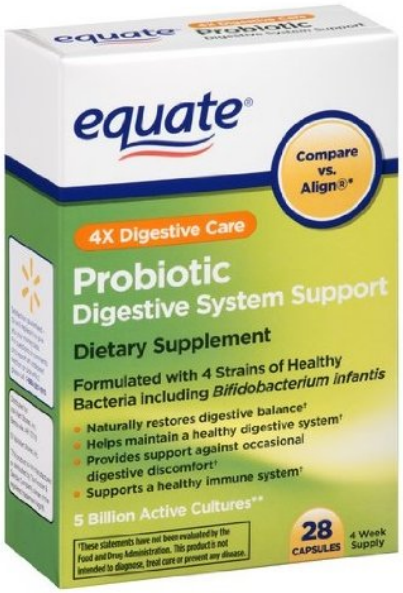
VS.

Probiotic

2-15 billion CFU per capsule

Strain is important, not just species!

Clinical evidence for efficacy
Probiotic species and *strain* clearly labeled



No clinical evidence for efficacy
Probiotic species, but no strain on the label

Be realistic…

- You would not expect to use a drug designed to treat diarrhea for the treatment of psoriasis
  - So don't assume probiotics are panaceas, either!
- Benefits seen in clinical trials are generally modest, at best
- But the risk of side effects is very low, so worth a try **IF** you pick the right probiotic!

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

http://www.probioticchart.ca/

AEProbio

Clinical Guide to Probiotic Products Available in Canada

Indications, Dosage Forms and Clinical Evidence to Date - 2020 Edition

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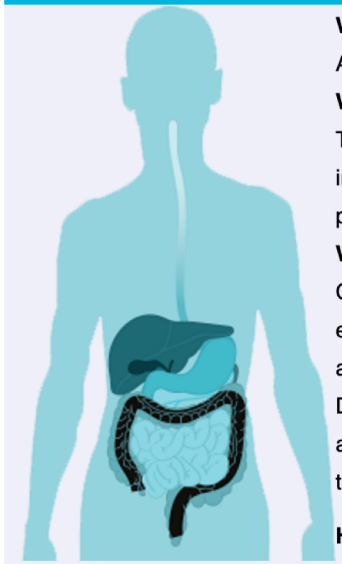
Introduction | Adult Health | Womens Health | Pediatric Health | Functional Foods | References | About



WHAT is this:

A Practice Tool to Assist with Clinical Decision Making for Appropriate Probiotic Therapy for Your Patients

WHO is the intended user:

This Clinical Guide is designed to translate scientific evidence available for probiotic products to practical, clinically relevant information. It is intended to be used as a clinical decision-making tool, enabling clinicians to easily select the appropriate product, dose, and formulation for a specific indication.

WHY is this needed:

Currently, the body of evidence for probiotic interventions is growing along with popular demand for these products. There is evidence to support the use of probiotic products for a variety of indications beyond gut health, however, applications and results are strain-specific.

Due to frequent changes in commercial availability of probiotic strains, new published evidence, and growing research, an annual review and updates of this Clinical Guide have been conducted since 2008. A general lack of adverse effects attributable to probiotics supports the widespread use of these products but an ongoing investigation is recommended.

HOW is this tool reviewed:

A systematic literature review using pre-defined inclusion criteria was undertaken to identify studies of defined clinical outcomes for specific probiotic strain(s). Commercially available products containing said strain(s) were identified, and the levels of evidence were used to rate the strength of expected benefit. This information was compiled into a chart format. Data were assessed by a group of independent expert reviewers.

In the case of probiotics, the clinical evidence must be linked to specific formulations as defined by genus, species, alphanumeric designation or strain, number of live bacteria present, the blend of probiotic strains present and finally, non-active ingredients present.

What about fecal transplants?

Use a healthy donor's microbes to replace your own…

- Fecal homogenate instilled into patient
  - Rectal enema
  - Colonoscopy
  - Nasoduodenal tube
  - "Crapsules" – encapsulated frozen or freeze-dried stool

- For *C.diff* infection, results in cure of the patient in >90% of cases
- Rapid resolution of disease
- Only rare recurrence of infection
- But there are risks associated with 'unknown microbes'

What if we could make FMT safer?

- Couldn't we just select pure microbes from healthy stool to create a microbial ecosystem therapeutic?

Well, we did!

- ‘MET-2’ is a new, first-in-class biologic drug
- A lyophilized, standardized ecosystem for oral delivery

Clinical trials underway for rCDI,
and several other indications

Not a probiotic – will be prescription only

NUBIYOTA
BETTER ECOSYSTEM, BETTER HEALTH

To help maintain health,
remember the gut microbiota 3 R's:

- Recognize that we are custodians of a hidden army of helpful microbes
- Respect what these microbes do for us
- Reinforce their beneficial activities

Acknowledgements

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Questions?

I found the problem, Mr. Smith. Instead of probiotics, you have been taking amateur biotics.