Solving the Enigma: The Immune System in the Context of Complex Microbial Communities

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Microbes in blood are recognized as a clear sign of disease

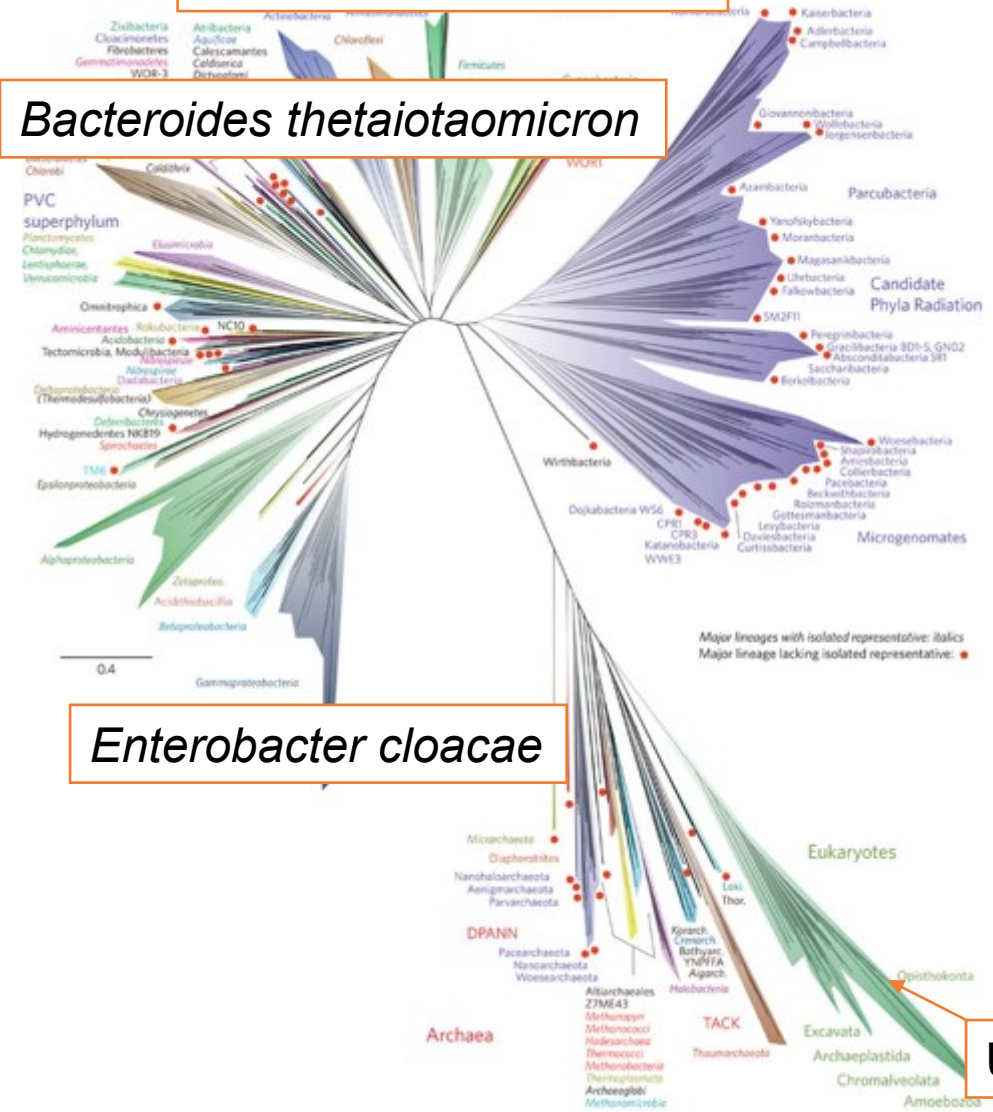
and ideally should be rapidly and completely eliminated…

Images: Wikipedia

Meanwhile in the intestine… the intestinal microbiome

Roseburia, Clostridiales

Bacteroides thetaiotaomicron

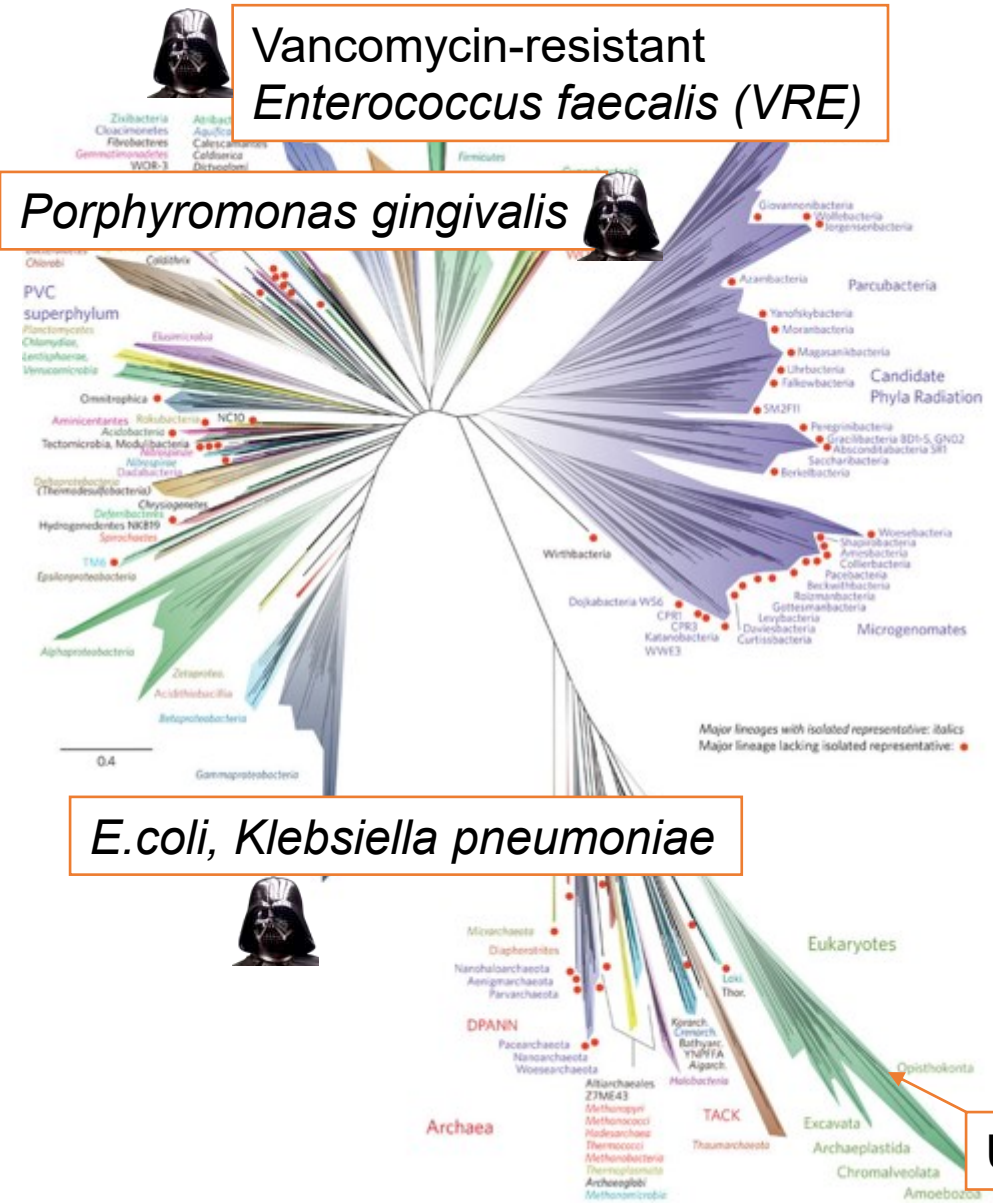


Enterobacter cloacae

Us, mushrooms

Nature Microbiology 1, Article number: 16048 (2016)

Meanwhile in the intestine… the intestinal microbiome



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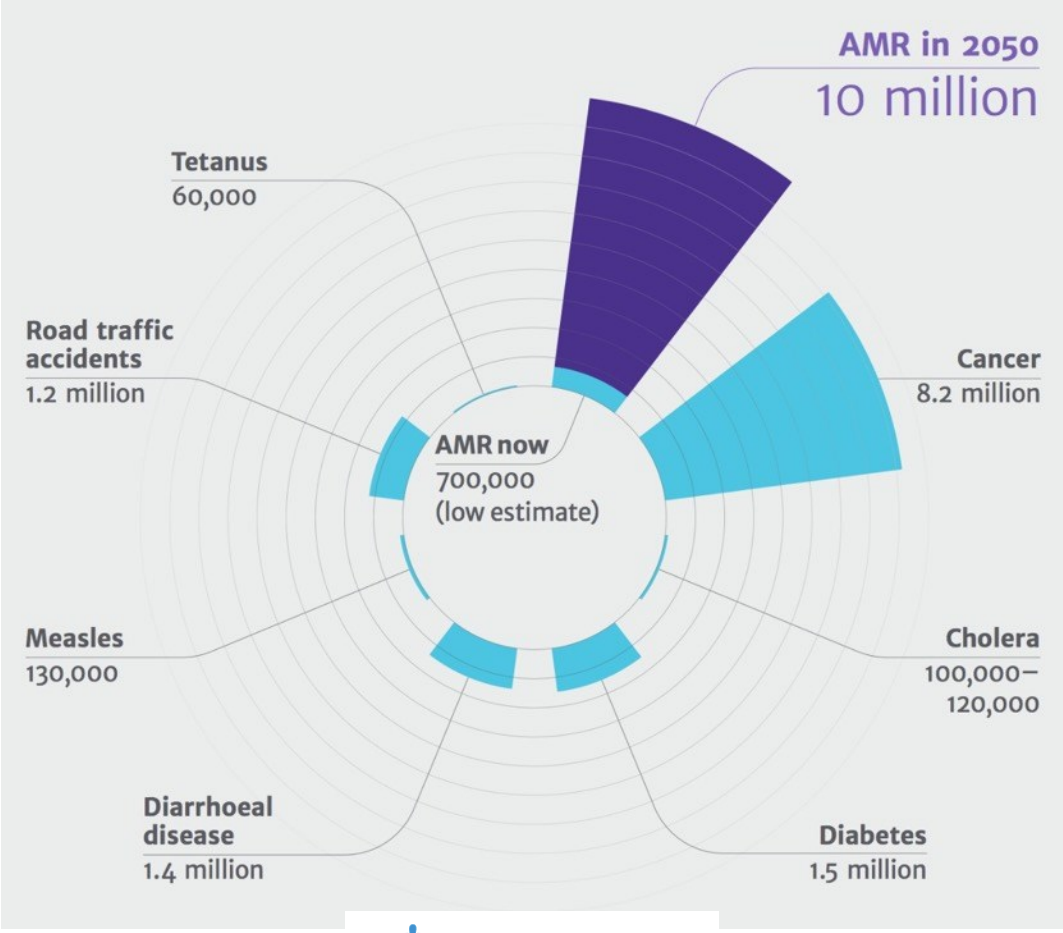
Why should you care about controlling opportunistic pathogens in your intestine?

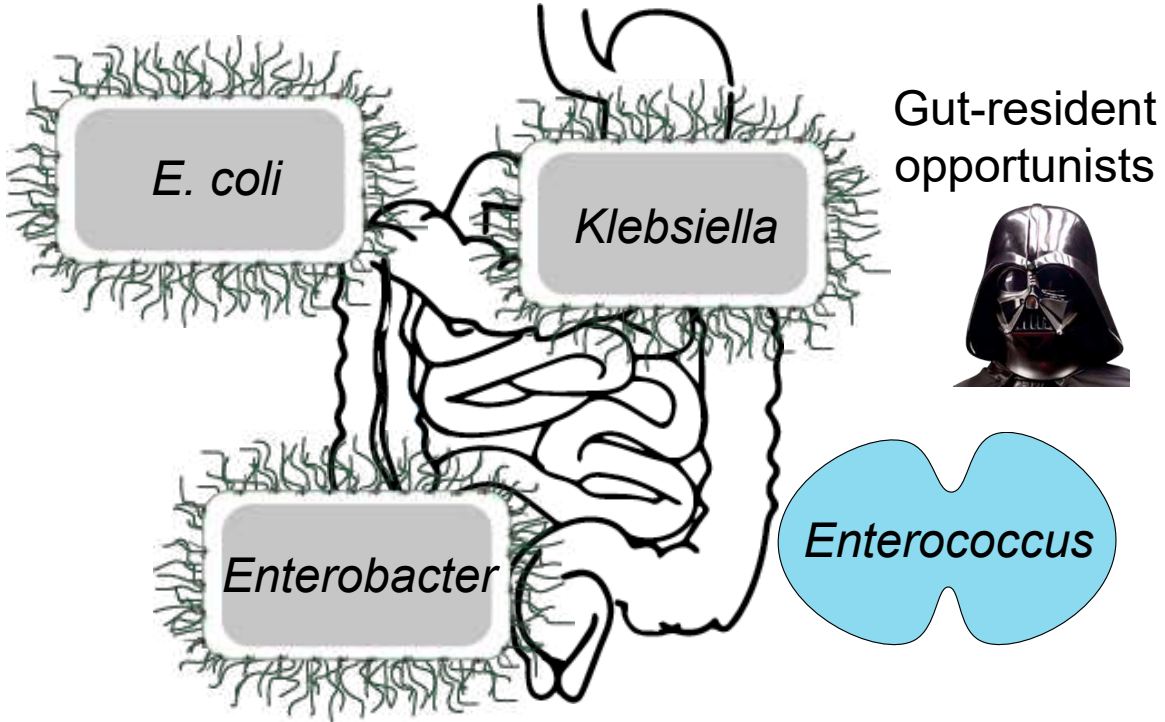


World Health Organization

Antimicrobial resistance will kill 10M per year by 2050

Estimated health care costs > $100 trillion

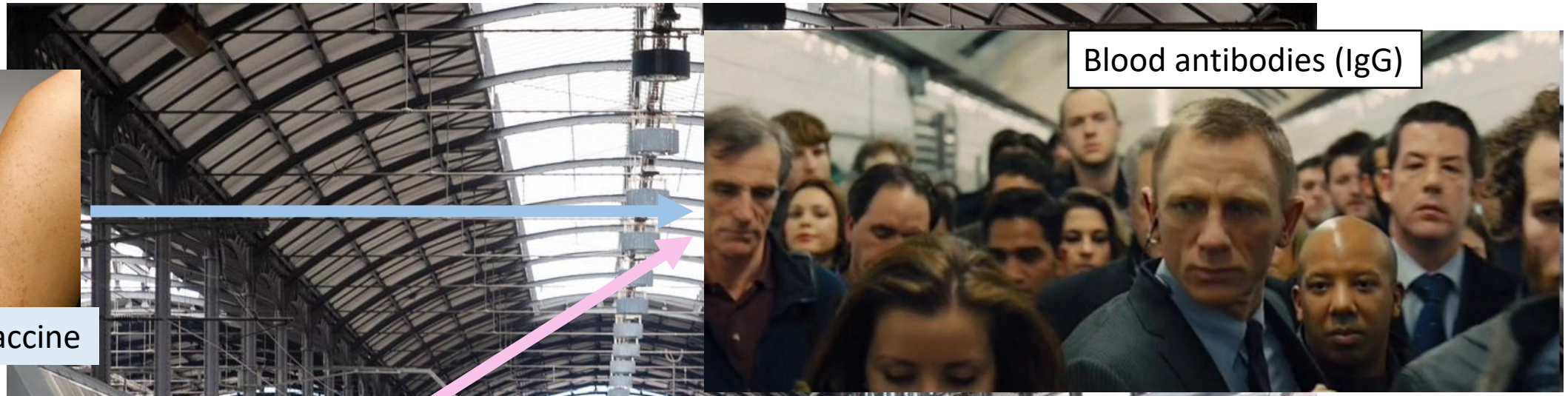
ESKAPEE pathogens – virulent, multi-drug resistant



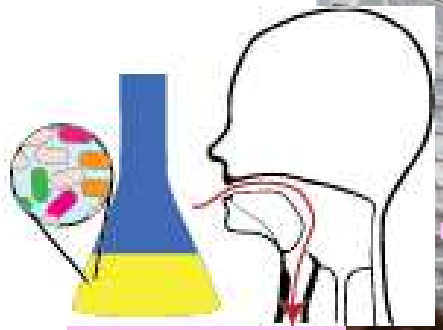
Gut-resident opportunists

Immune mechanisms targeting intestinal bacteria

intramuscular vaccine



Blood antibodies (IgG)



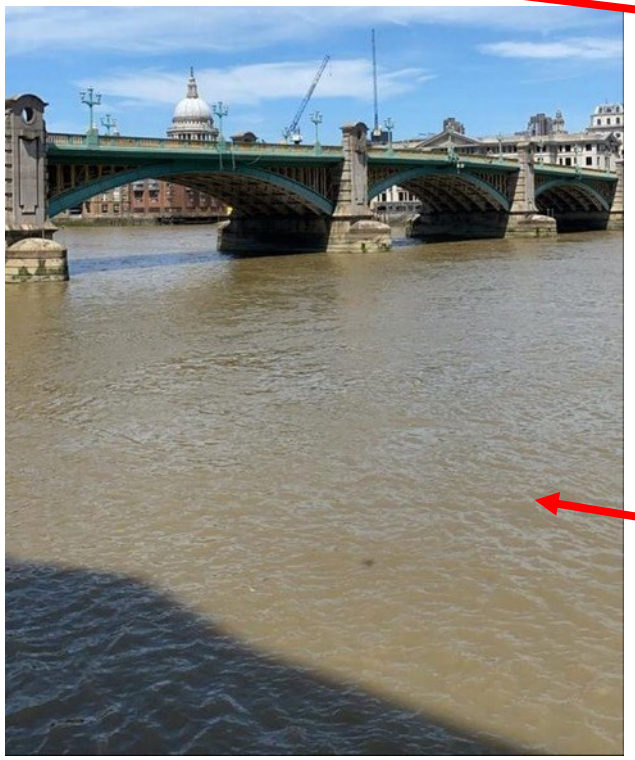
Oral vaccine

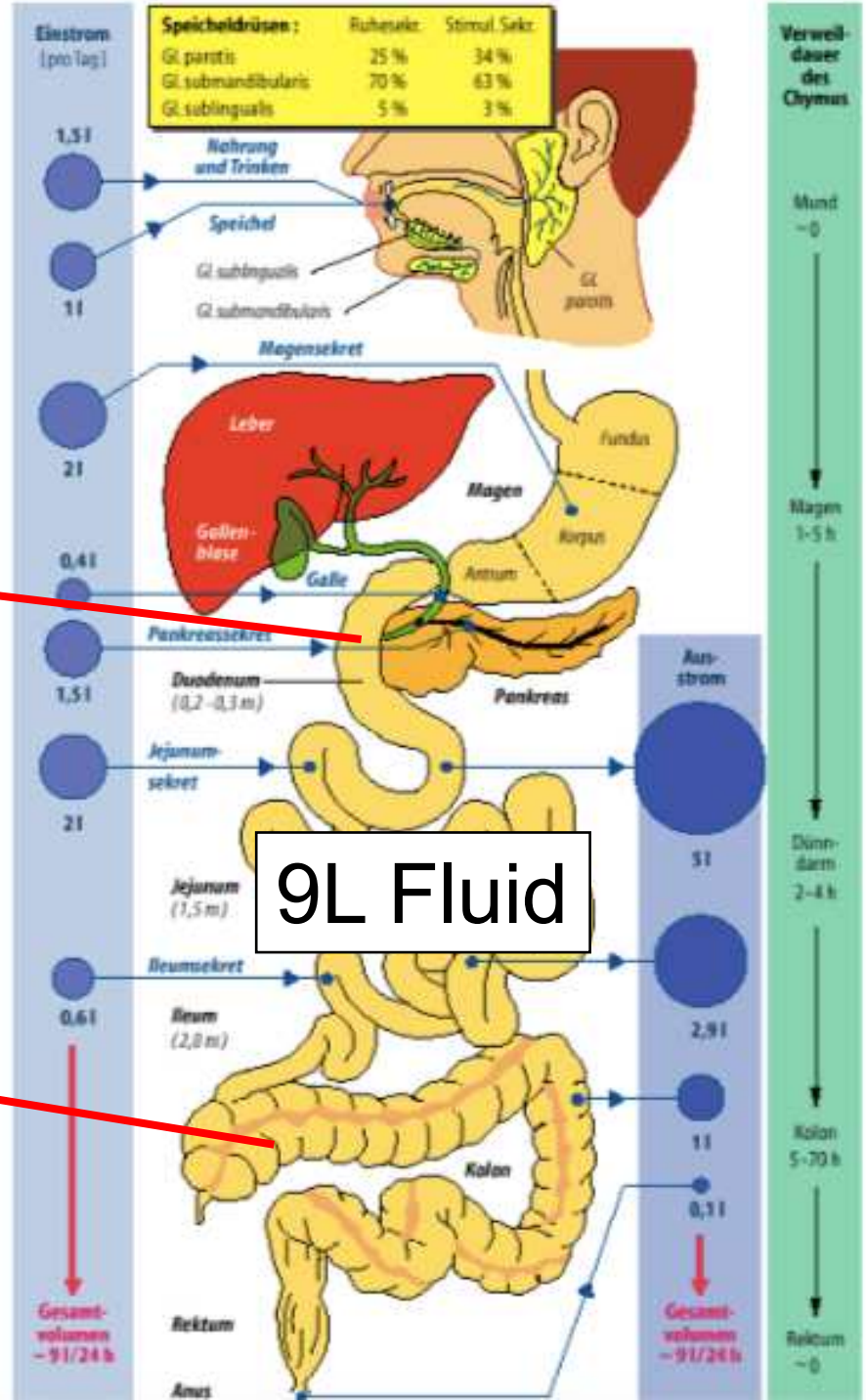
Intestinal antibodies (IgA)

Images: Wikipedia

Why is sticking things together useful?

Intestinal content flows!





9L Fluid

Sticking -> aggregation -> efficient loss via flow

Moor..Slack. Nature 2017, Diard…Slack. Science 2017

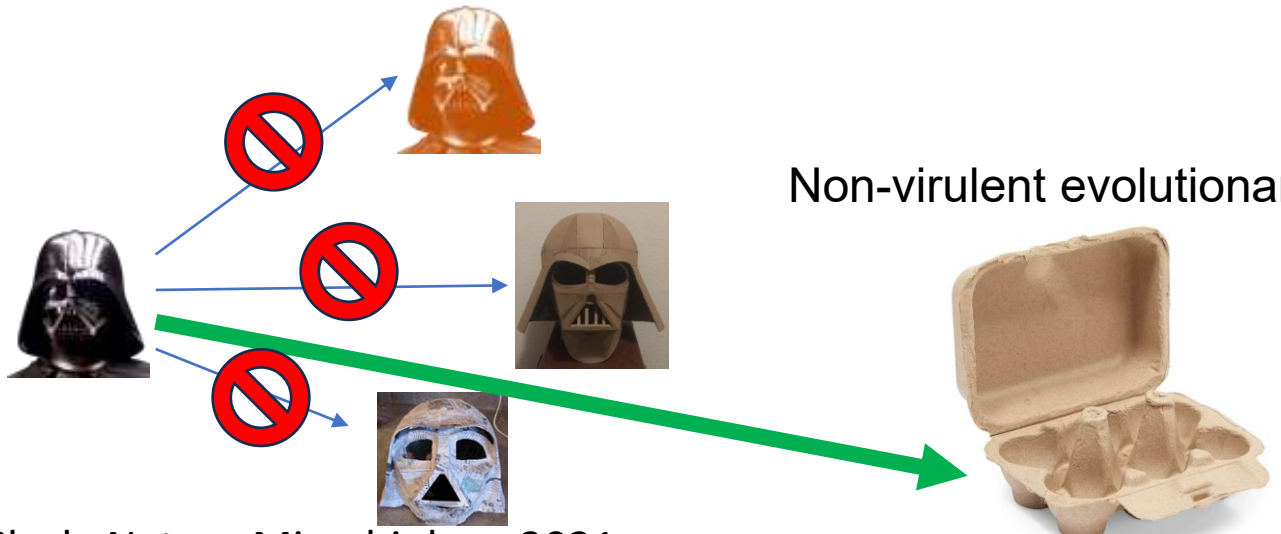
Just clearing gut bacteria faster is not enough.

Cleared bacteria leave a gap in the ecosystem

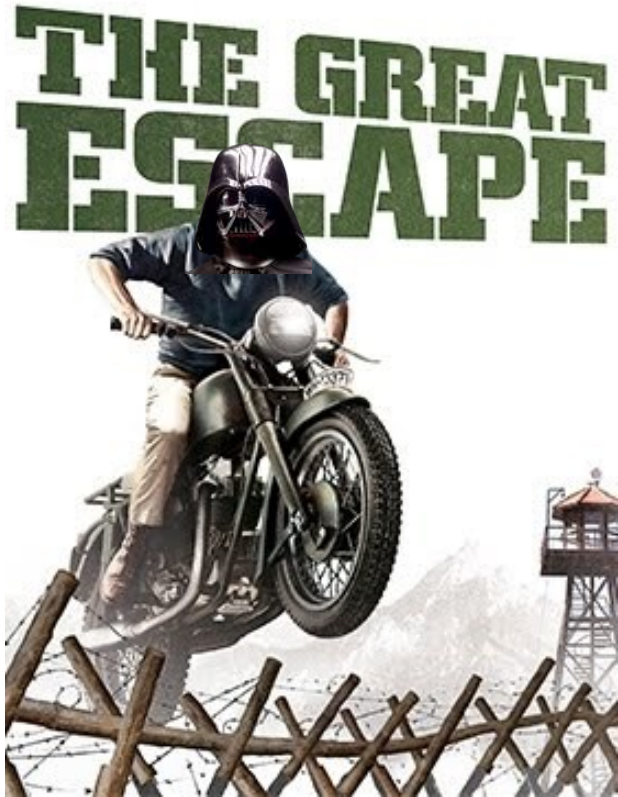
Huge pathogen populations – Strong selection

Rapid evolution of immune escape

“Evolutionary trap vaccines”



Non-virulent evolutionary trade-off



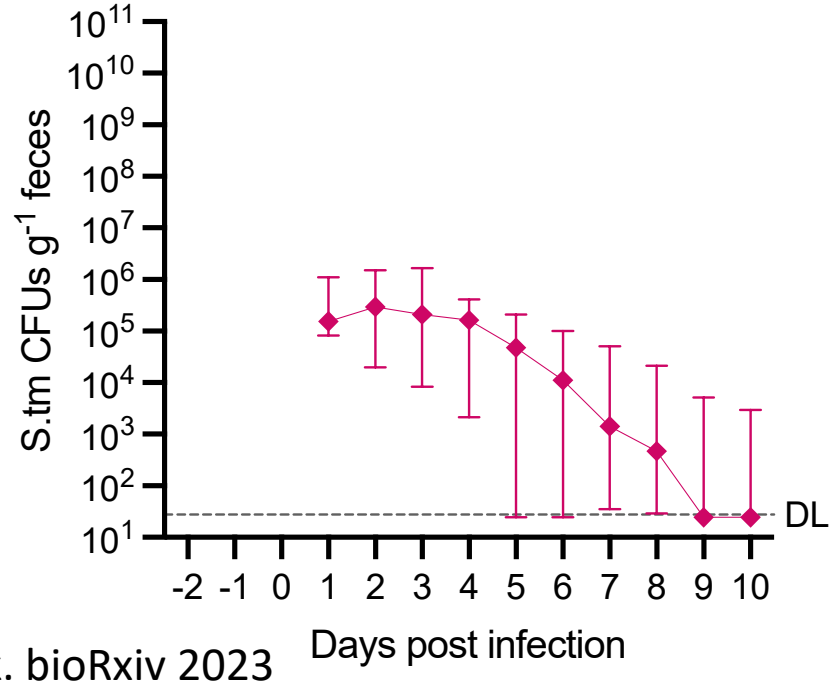
Diard…Slack. Nature Microbiology 2021

Manipulating evolution = altering the outcome of competition

Instead of relying on bacterial evolution, we can introduce benign competitor bacteria into the microbiota…

Sterilizing immunity in the intestine

Vacc. + Comp.



Lentsch…Diard, Slack. bioRxiv 2023

Complete replacement of an unwanted bacterium by a derisable strain/species

➔ Preventing infection

➔ **Microbiota Engineering!**

Functional Microbiome diagnostics → Rational vaccine design and next-gen probiotic selection → Rational microbiome engineering

3-5 years: Vaccinations to eliminate *Salmonella* risk in livestock rearing

10 years: Microbiota engineering strategies to prevent/ameliorate diseases of known gut microbiota-derived etiology
e.g. *E. coli* sepsis, inborn errors of metabolism

10-25 years: Microbiota engineering strategies to prevent/ameliorate complex diseases
e.g. food allergy, obesity, autoimmunity

What I hope you've learned

- Many of our gut microbes are involved in defending us. "Kill all of them" is not a great strategy in the gut

- Fundamental understanding -> Novel ways to prevent disease