HKU Med

Microbiome for Gut Health: A modern tool and a target in the effort to address AMR

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Disclosure

- NO financial disclosure
- My presentation should not directly reflect the opinions of the following committees I serve;
  - HKU-AMR Working Group
  - Scientific Steering Committee of Institut Pasteur International Network (COS-RIIP)
  - klebNET International Network

Microbial World

- 5 X 10^{30} bacteria on Earth

Whitman et al. 1998. PNAS 95:6578

Microbes in Animals

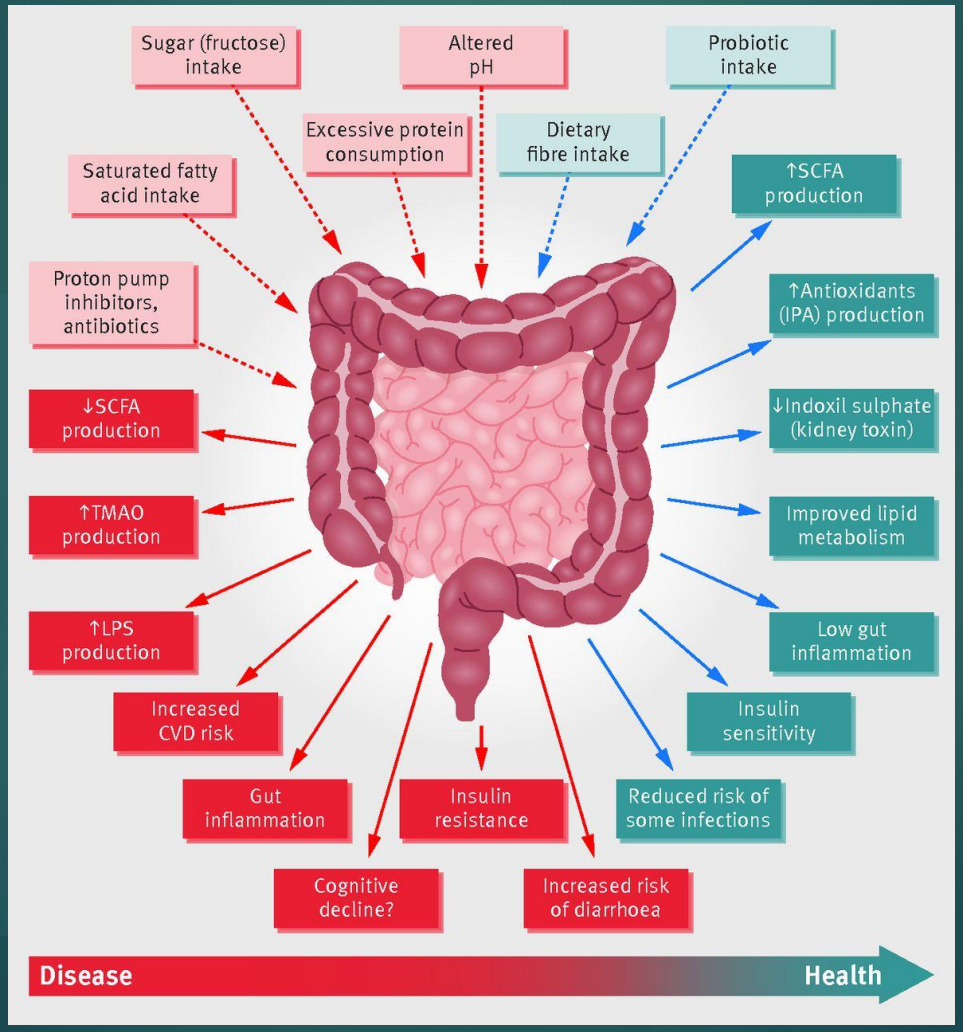
Whitman et al. 1998. PNAS 95:6578

Table 4. Total number of prokaryotes in some representative animals

Animal	Organ	Cells/ml or cells/g	Organ contents*	No. of animals†	No. of cells, $\times 10^{23}$
Human	Colon	3.2×10^{11}	220 g	5.6×10^{9}	3.9
Cattle	Rumen	2.1×10^{10}	106 liter	1.3×10^{9}	29.0
Sheep and goats	Rumen	4.4×10^{10}	12 liter	1.7×10^{9}	9.0
Pigs	Colon	5.4×10^{10}‡	9 liter	8.8×10^{8}	4.3
	Cecum	2.8×10^{10}‡	1 liter	8.8×10^{8}	0.3
Domestic birds§	Cecum	9.5×10^{10}	2 g	1.3×10^{10}	0.024
Termites	Hindgut	2.7×10^{6}¶		2.4×10^{17}	6.5

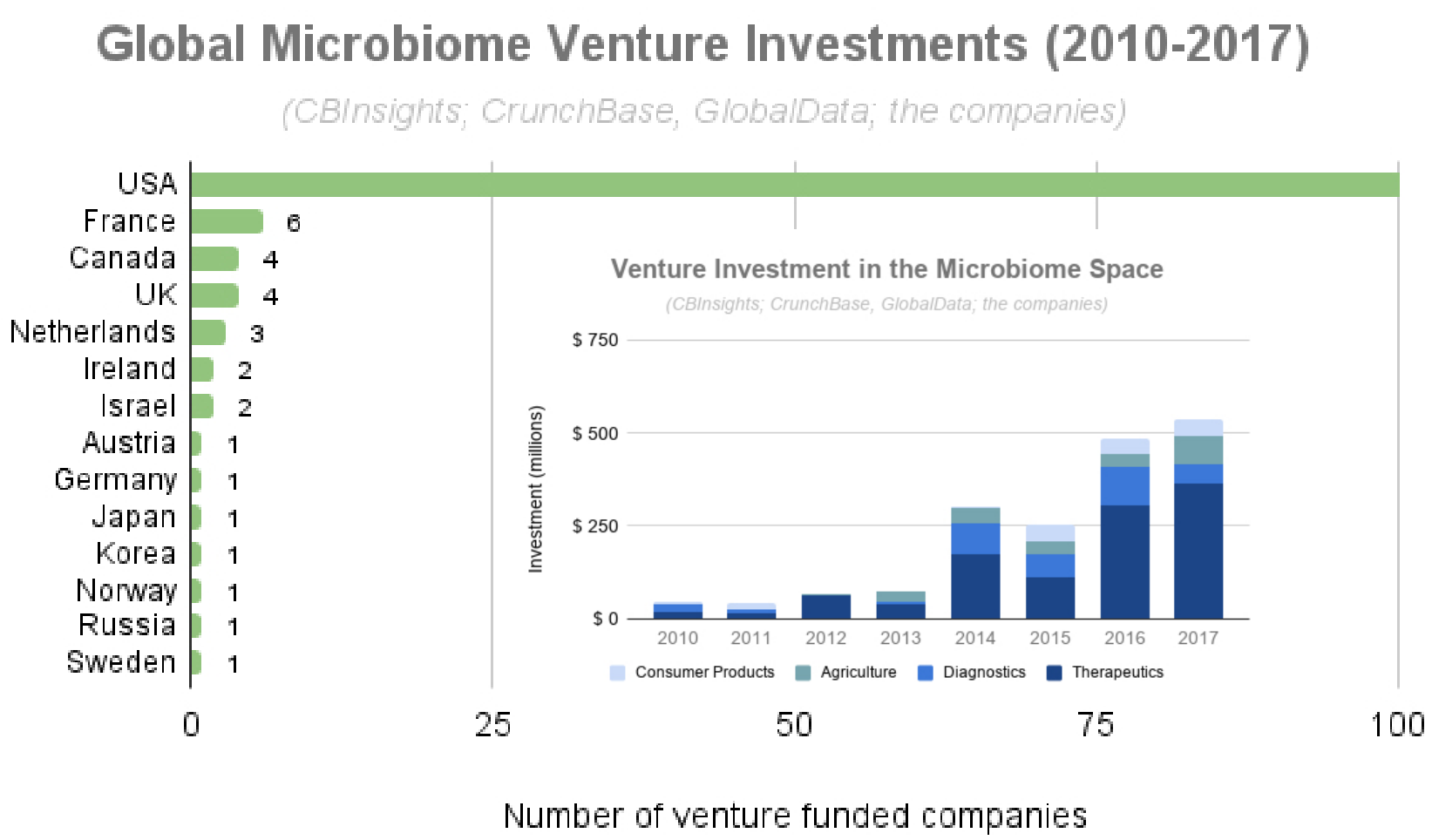
Functions of Human Gut Microbiome

Gut Microbiome in Health and Disease

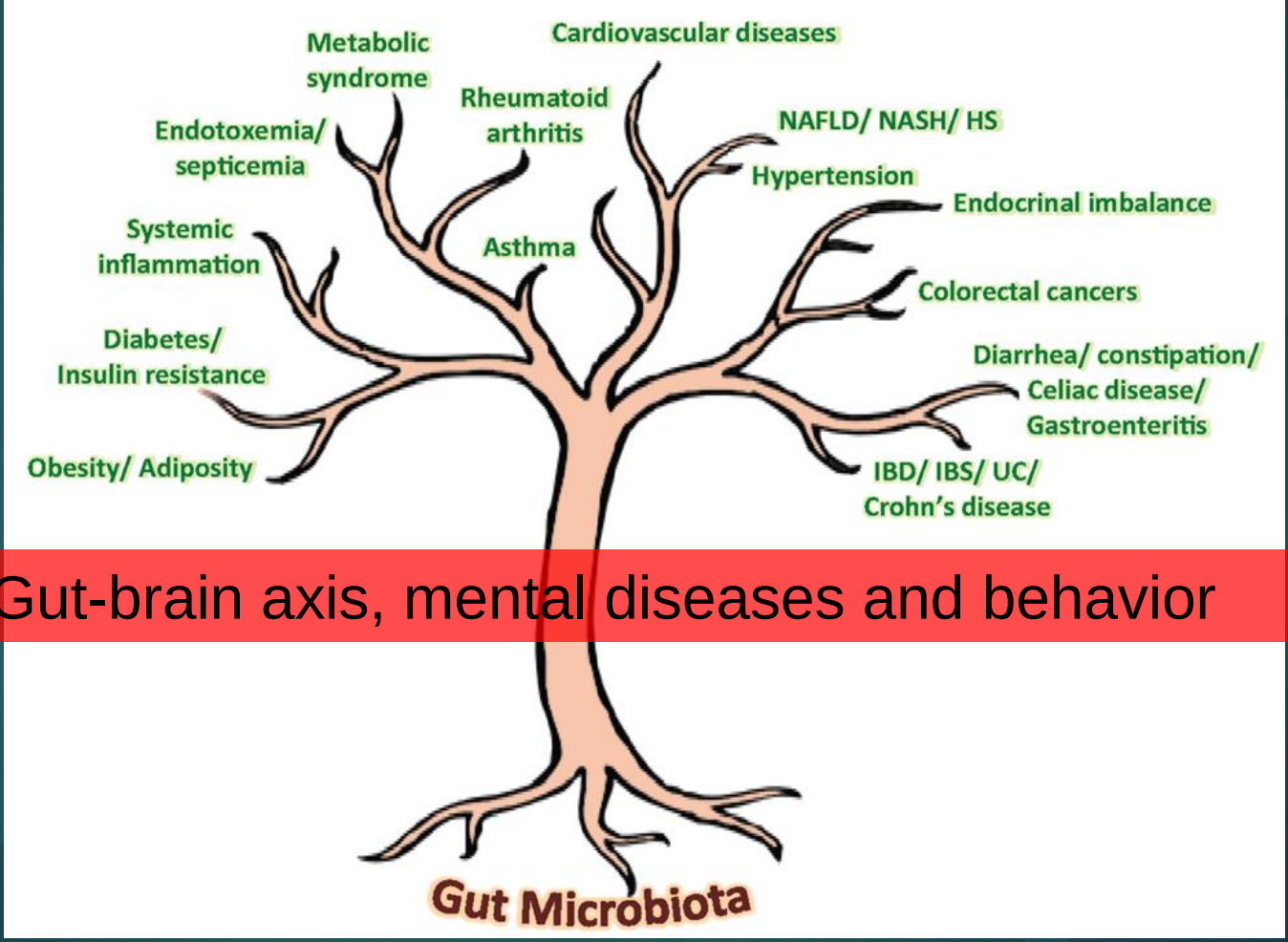


Valdes et al. 2018. BMJ 361:k2179

Investing In Microbiome – A Look Back Into The Future

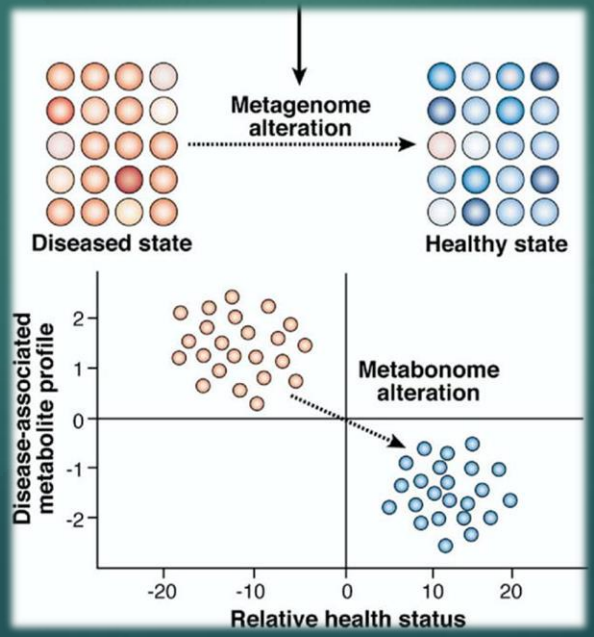


Gut Microbiota-Associated Diseases

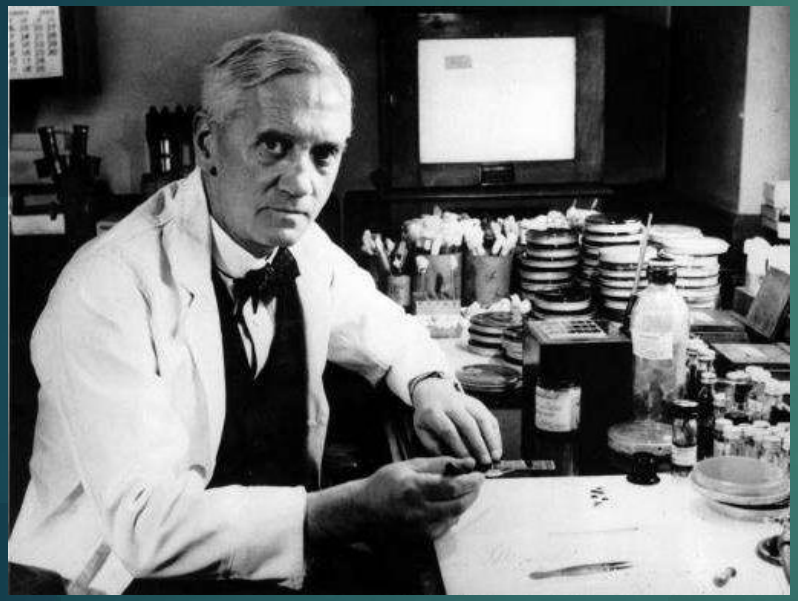


Restoring Healthy Gut Microbiome

- Fecal Microbiome Transplant (FMT)
- Engineered Consortia
- **Antibiotics**
- Prebiotics
- Probiotics
- Peptides
- Phage Therapy
- Bioactive compounds
- Postbiotics
- Microbial Enzymes

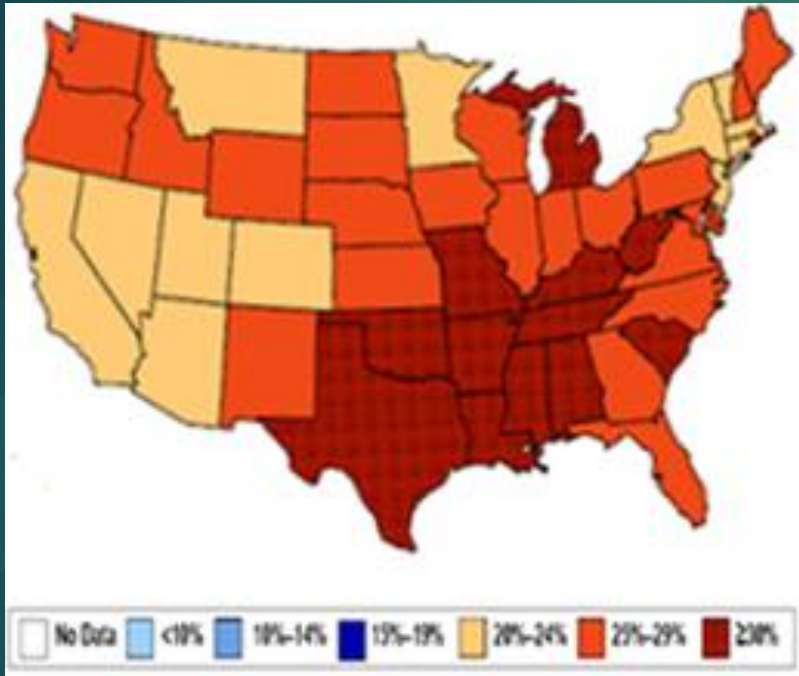


Discovery of Antibiotics



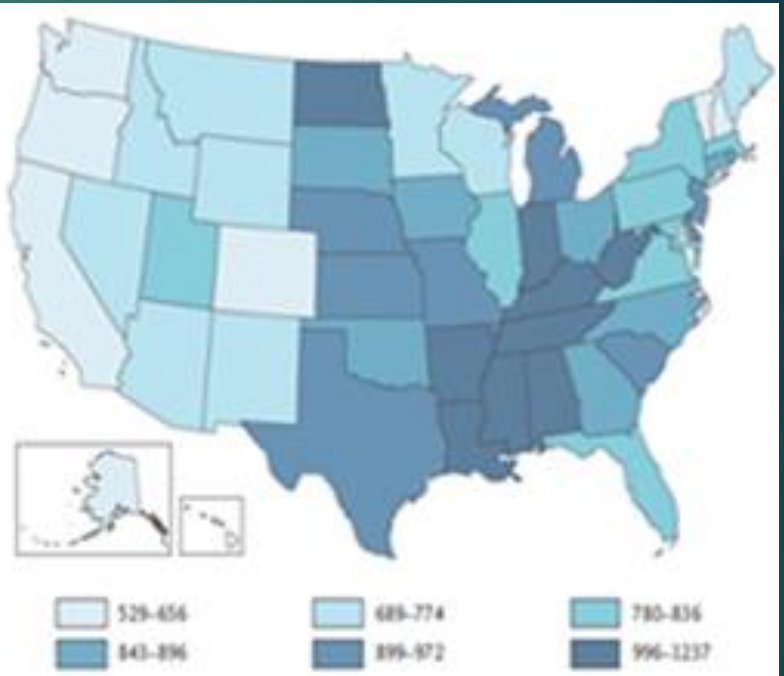
Sir Alexander Fleming (1881-1955)

Collateral Damage Of Antibiotic Use?



Obesity trends in US Adults, 2010

Source: CDC Behavioral Risk Factor Surveillance System.

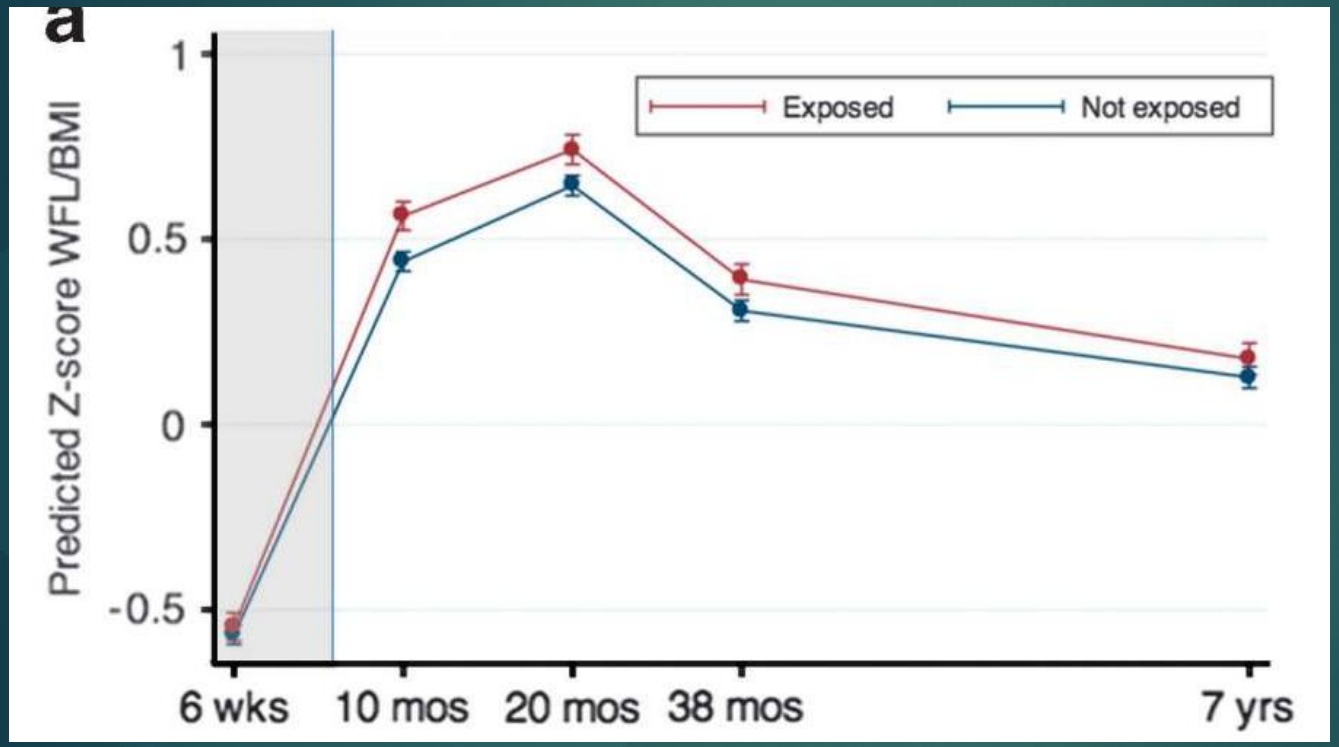


Antibiotic prescriptions per 1000 persons, 2010

Source: L Hicks, TH Taylor, RJ Hunkler. NEJM 2013, 368:1461.

Petschow et al. 2013. Ann N.Y. Acad Sci. 1-7

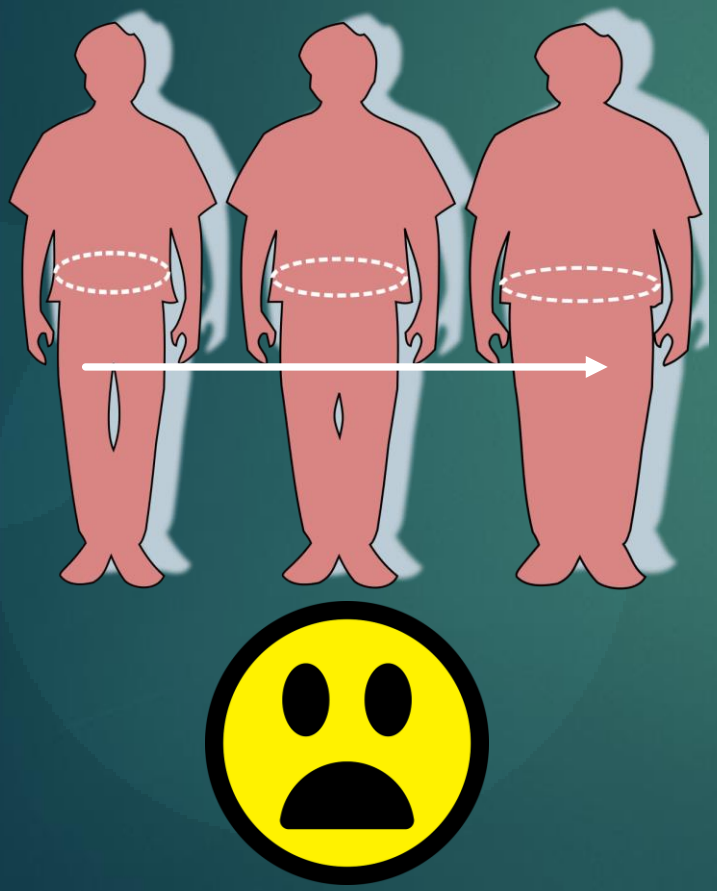
Collateral Damage Of Antibiotic Use?

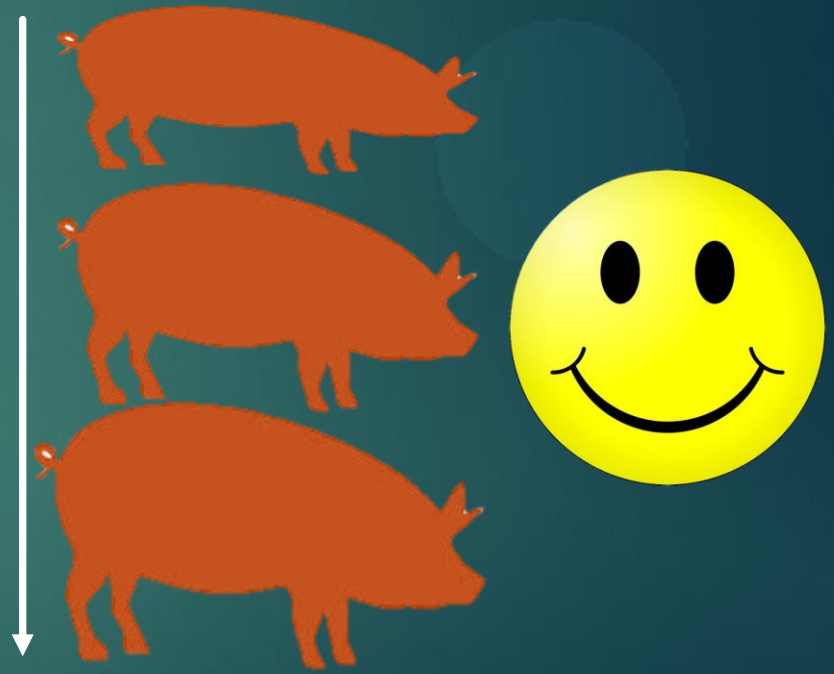


Prof. Martin J. Blaser
Rutgers University

Transande et al. 2013. Intl J Obesity 37:16-23

Obesity in Human vs Livestock Animals



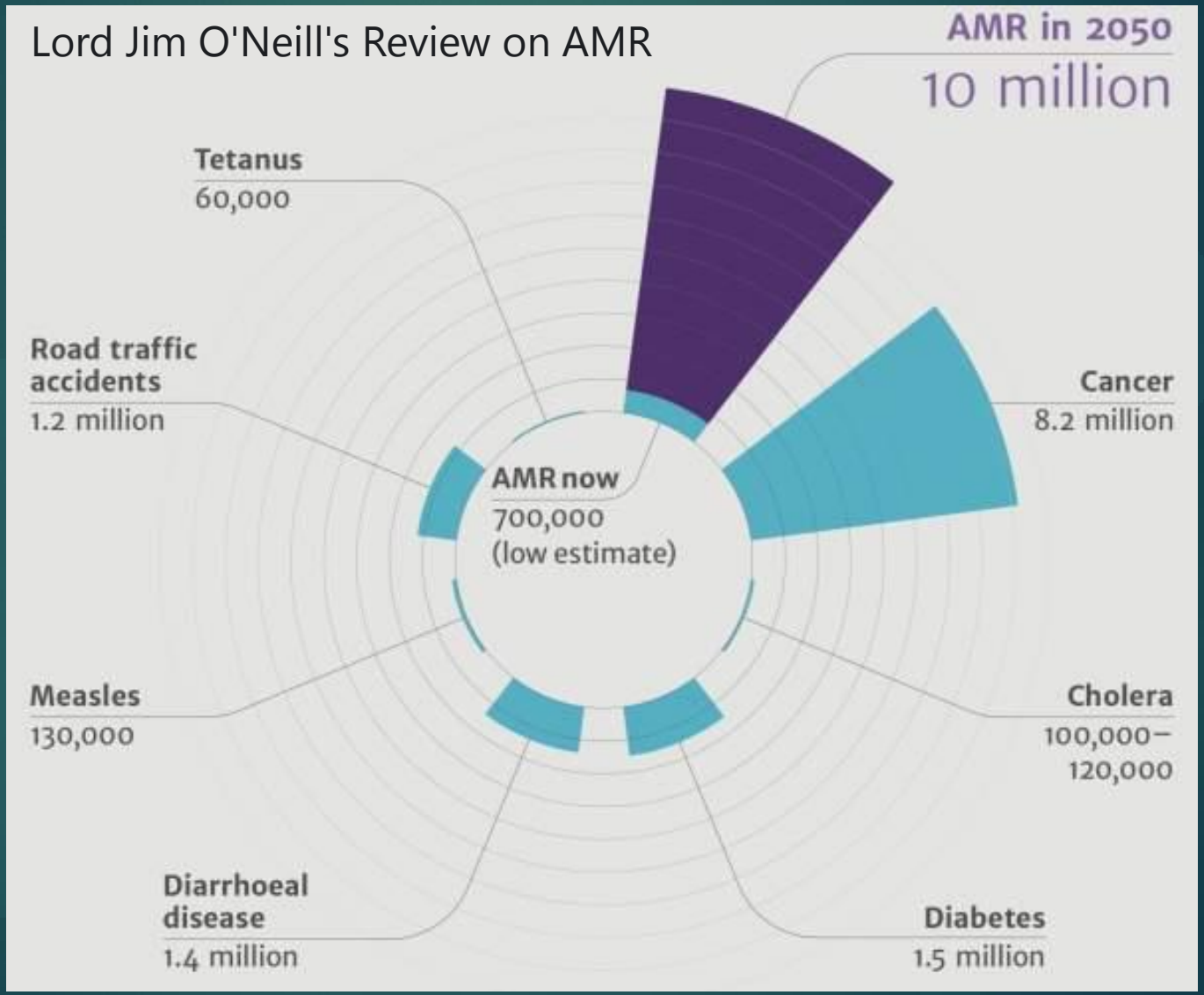


Another Collateral Damage Of Antibiotic Use?

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the **drug** make them **resistant**."

~Alexander Fleming

Post-antibiotic Era



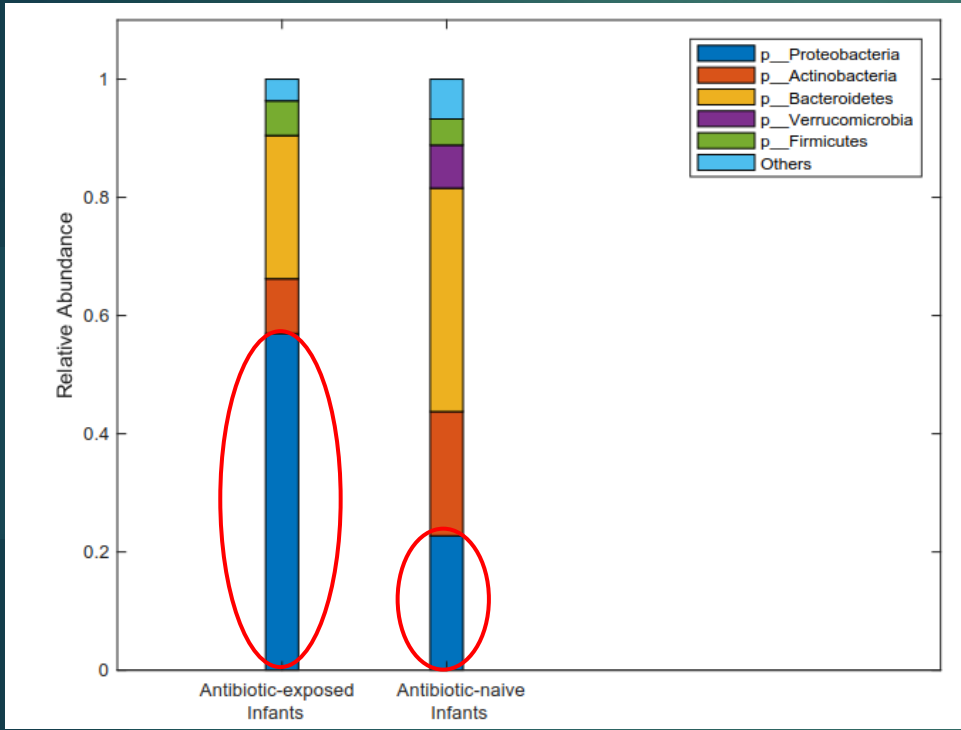
Causes of AMR

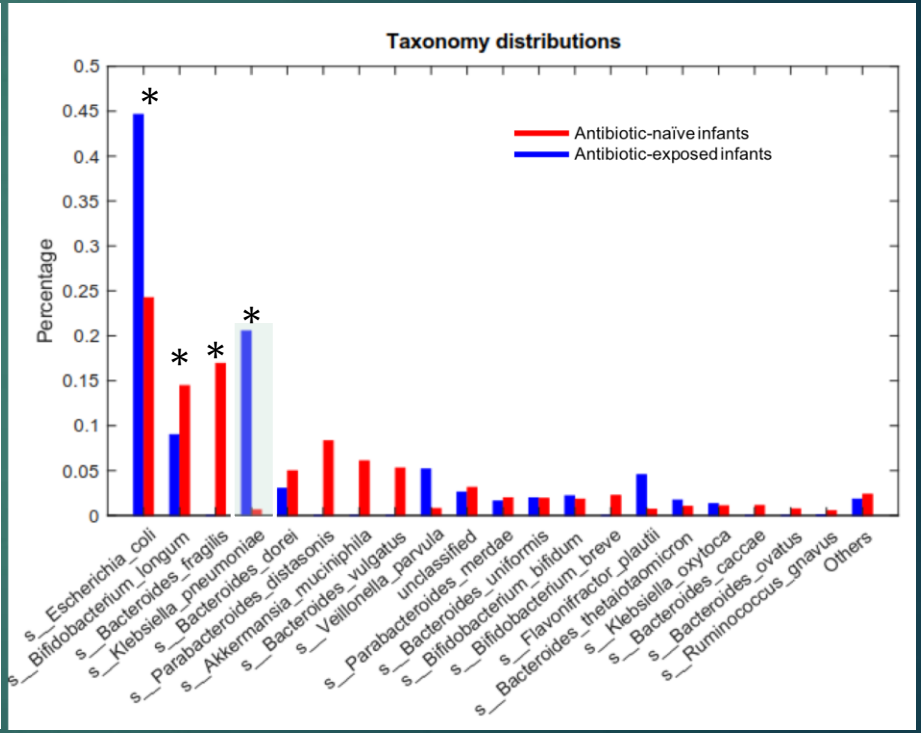
www.who.int/drugresistance

#AntibioticResistance

World Health Organization

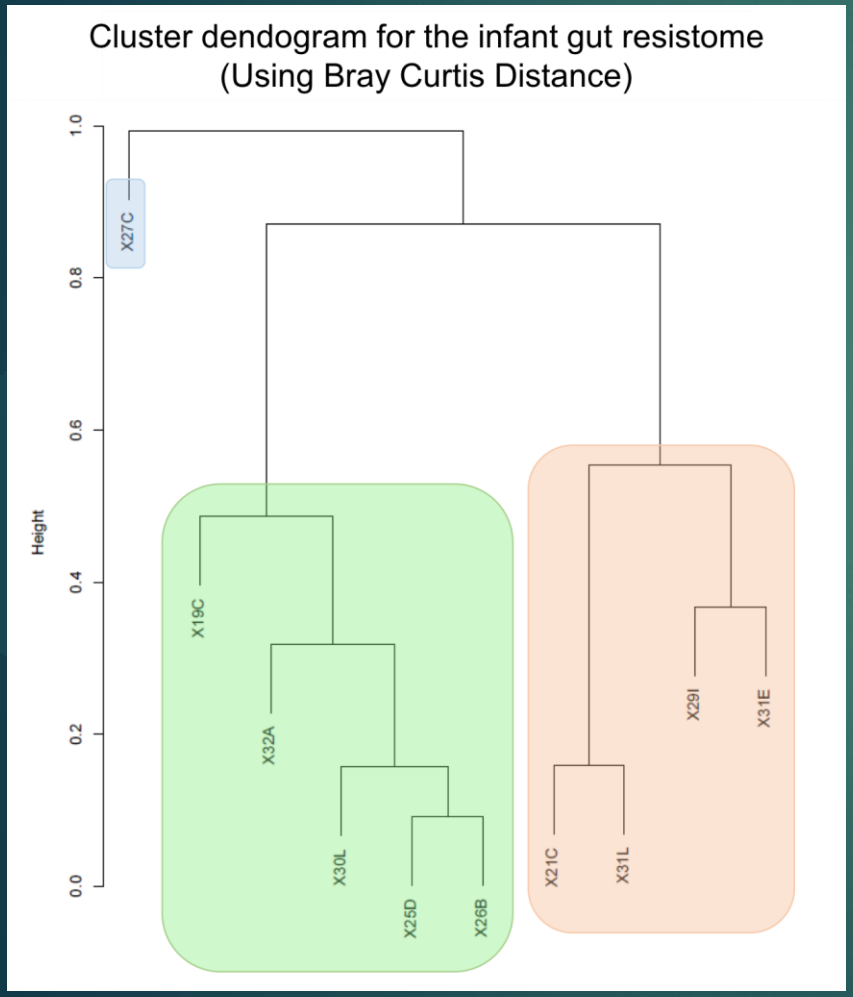
Impact of Early-life Antibiotic Exposure on Gut Microbiome

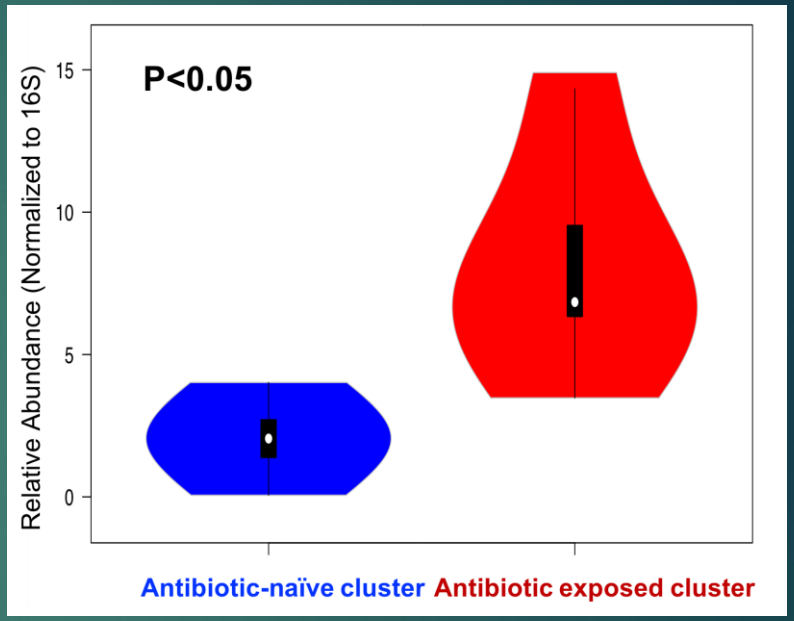




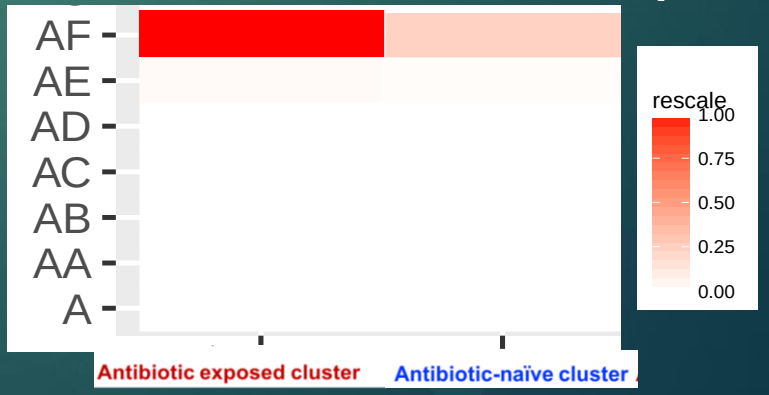
Tun et al. Unpublished data

Impact of Early-life Antibiotic Exposure on Gut Resistome





AF= Antibiotic Efflux Pump



Tun et al. Unpublished data

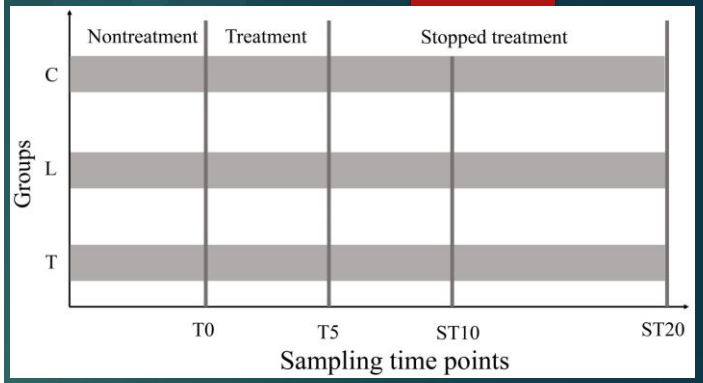
Xiong et al. Microbiome (2018) 6:34
https://doi.org/10.1186/s40168-018-0419-2

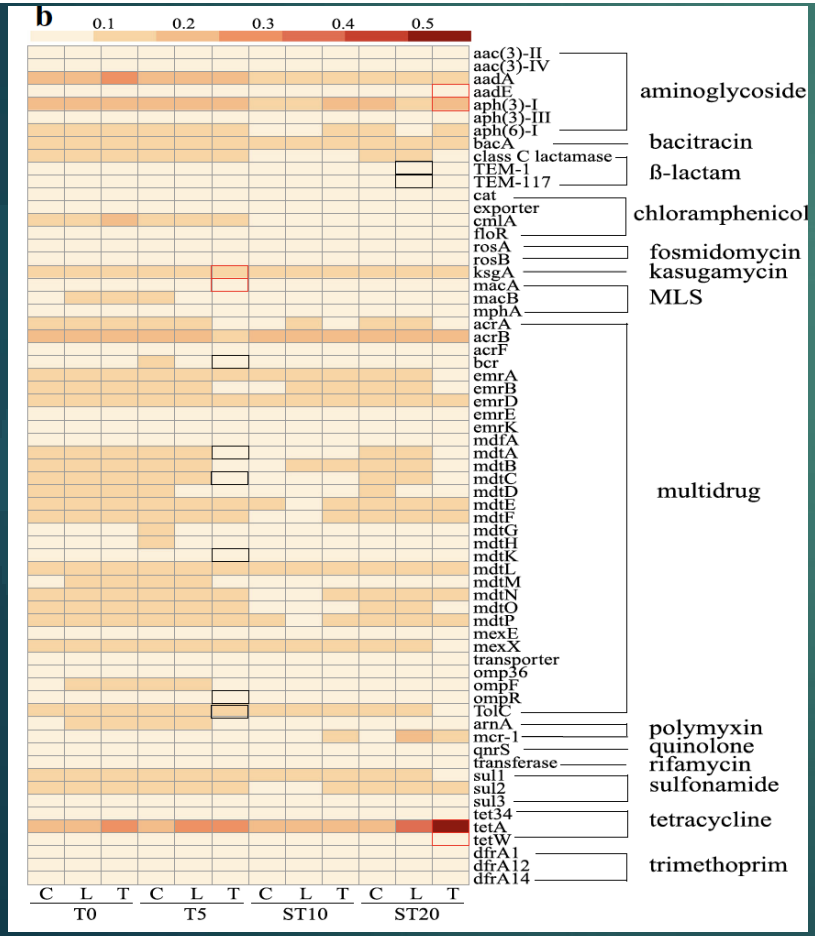
Microbiome

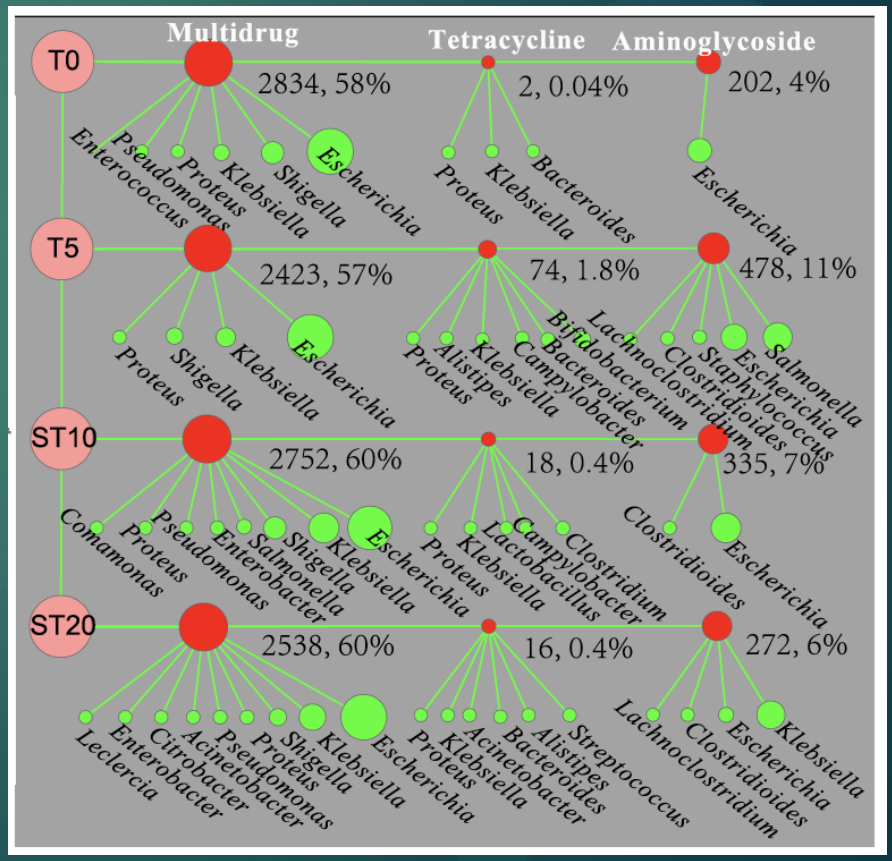
RESEARCH Open Access

Antibiotic-mediated changes in the fecal microbiome of broiler chickens define the incidence of antibiotic resistance genes

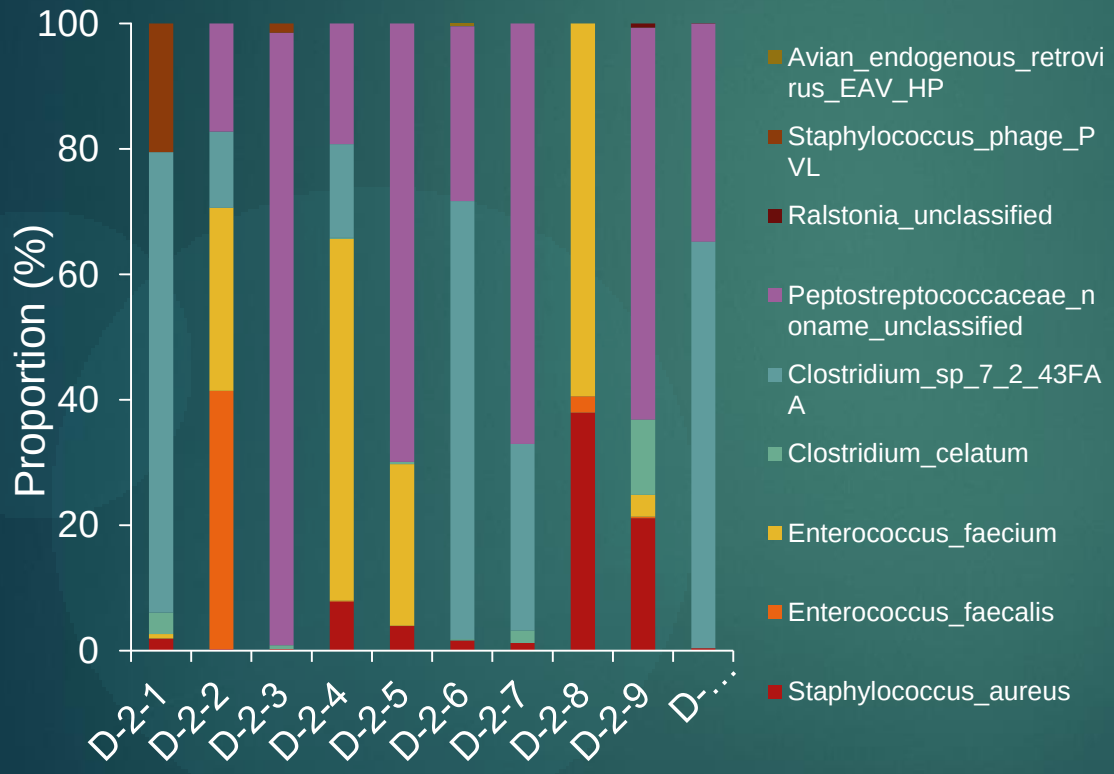
Wenguang Xiong[1,2], Yulin Wang[2], Yongxue Sun[1], Liping Ma[2], Qinglin Zeng[1], Xiaotao Jiang[2], Andong Li[2], Zhenling Zeng[1*] and Tong Zhang[2*]

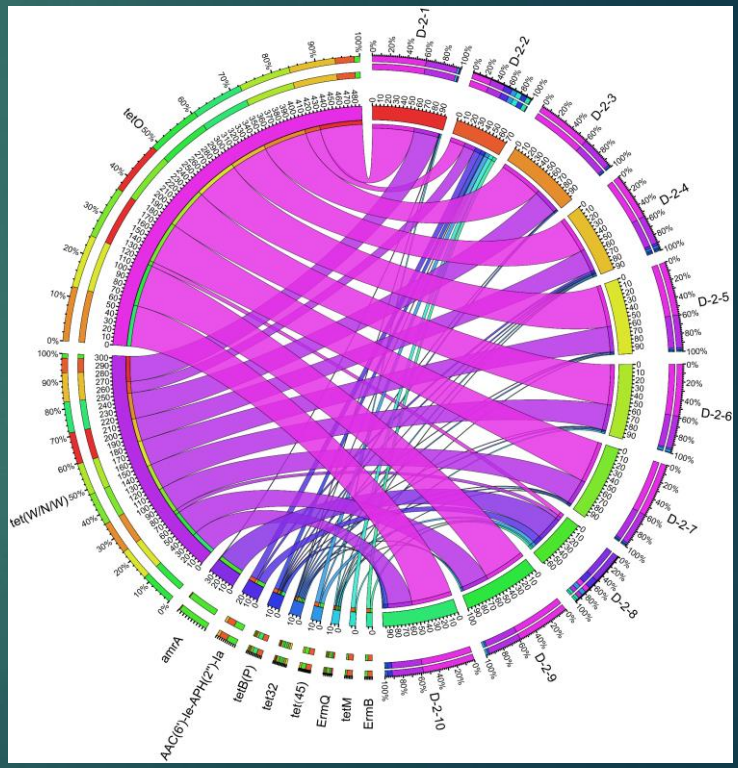






Microbiome and Resistome of Day-old chicks (DOCs)

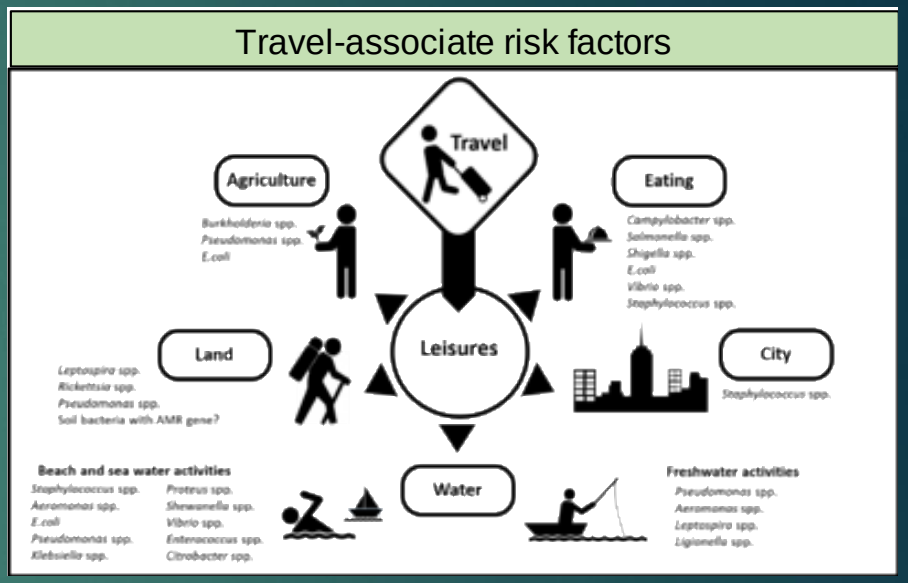




Zhang et al. Unpublished data

Association between Gut Dysbiosis and AMR Acquisition???

- No strong scientific evidence has been reported.
- Thus, we tested the question in our Prospective Cohort of Hong Kong Travelers.



Poonsuk et al. 2019. Travel Med Infect Dis. Under Review

Flow chart of study design

HKU staffs and students

Registration system

Pre-travel sample and questionnaire

Travel

Post-travel sample and questionnaire

Fecal sample

Bacterial culture and Antibiotic Susceptibility Testing

Microbiome and Resistance gene study

Questionnaire

Travel information

Isolation on ESBL selective agar

Identification genus and species of isolates using MALDI-Toff

AST
Disk Diffusion test

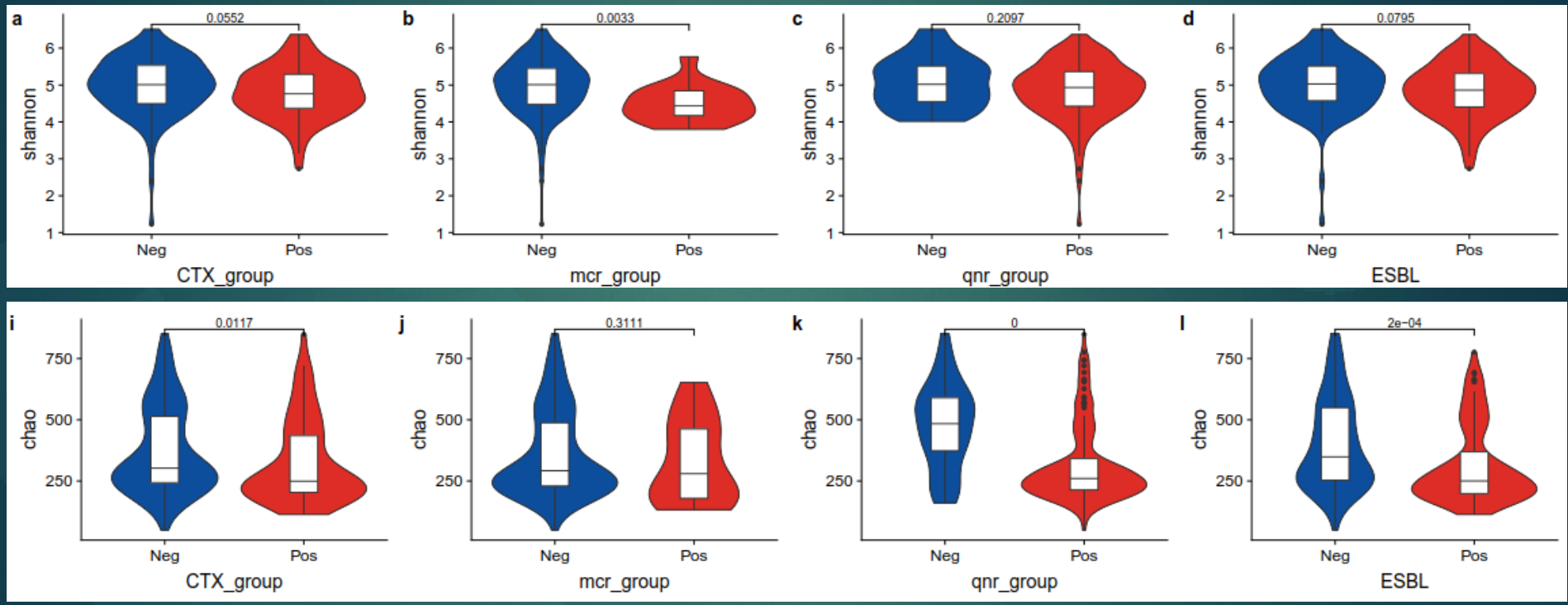
DNA extraction

Microbiome analysis and Resistance genes analysis

Identification of travel-associated risk factors for the acquisition of AMR genes/bacteria

Inclusion criteria: Hong Kong travelers (≥18 years) who travel abroad for a minimum of one night stay

Association between gut microbiome diversity and AMR



- Loss of species richness/diversity of gut microbiome is associated with AMR acquisition.

Liang & Poonsuk et al. Unpublished data

What are the alternatives to antibiotics (ATA) left for us?

Fecal Microbiome Transplant (FMT)

Engineered Consortia

~~**Antibiotics**~~

Prebiotics

Probiotics

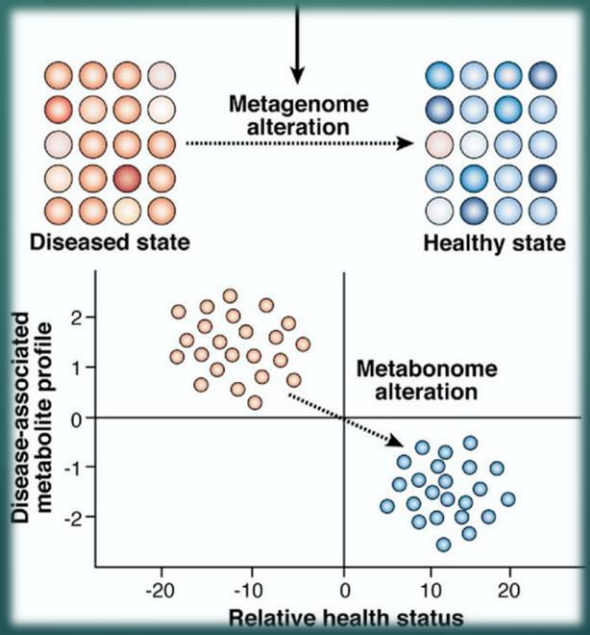
Peptides

Phage Therapy

Bioactive compounds

Postbiotics

Microbial Enzymes

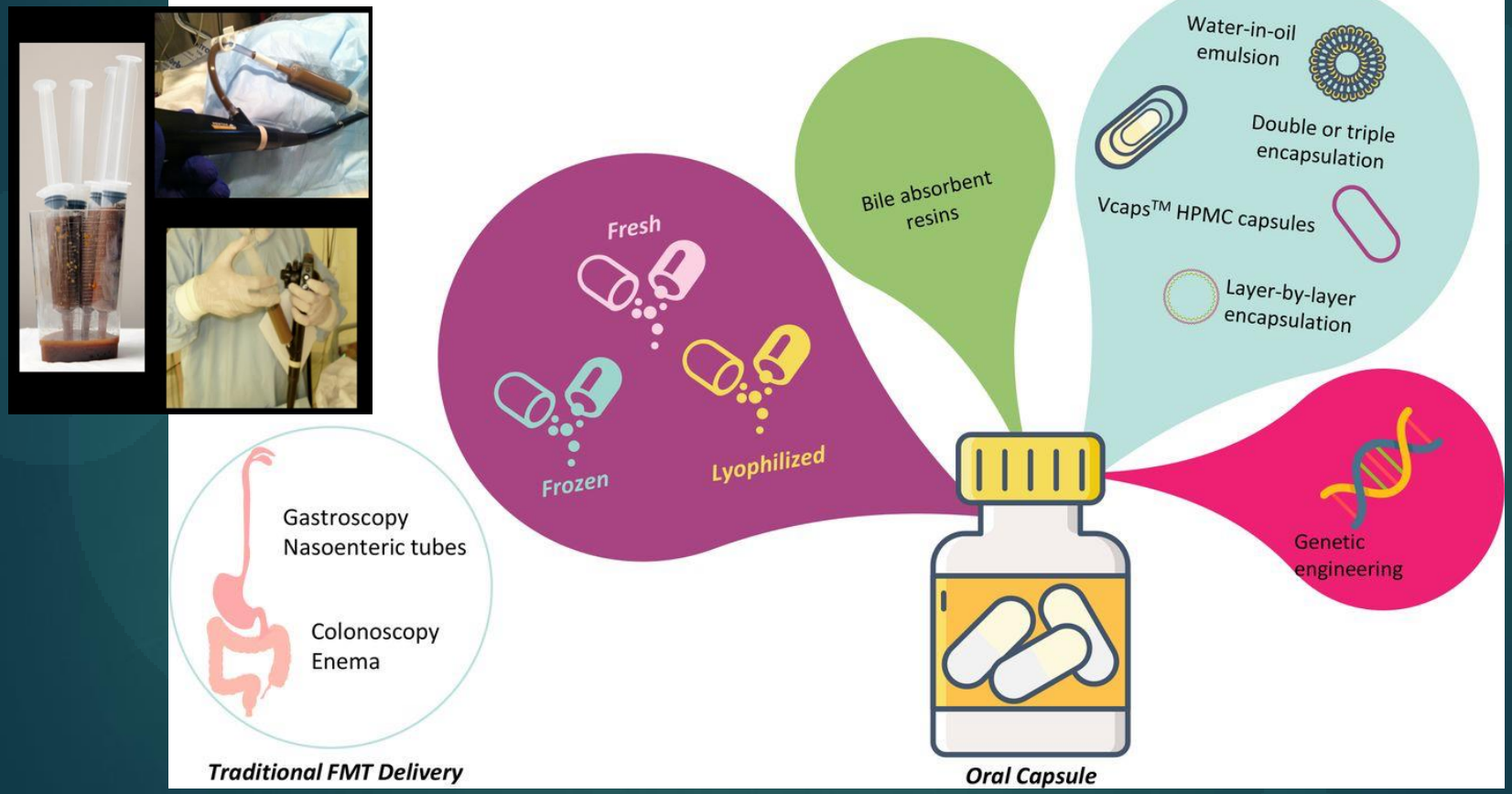


Fecal Microbiome Transplant (FMT) in the History

- 4th Century (Ge Hong):
  - Oral human fecal suspension ("yellow soup") for severe diarrheal illnesses, food poisoning
- 16th Century (Li Shinzen): fermented fecal solution, dry feces - treated fever, severe diarrhea, vomiting and constipation
- 17th Century: Veterinary medicine
  - Fecal transfer for horses with diarrhea
- 1958: FMT enema
  - Eismann, et al. 4 patients

  with pseudomembranous colitis
  - "Dramatic" response within 48 hours

Current FMT Delivery Methods



Fecal Microbiome Transplant (FMT)

- Successfully used to treat recurrent *C. difficile* infection.
- Use in other GI disorders and extra-GI diseases are underway.
- Several barriers remain;
  - Characteristics of Healthy Microbiome?
  - Long-term safety of the recipient
  - Donor selection
  - Need high quality control
  - Inconsistencies among different studies

3 unresolved issues in FMT!

- Transplants should be adequately screened for potentially harmful bacteria. These should include virulence factors and resistance genes. The screening procedures also need to be continuously updated as new resistance genes or virulence factors are identified.
- Patients should be adequately informed about the procedure and the risks involved, especially the most vulnerable patients. The transplants are complex mixtures of bacteria that we still only know a fraction about.
- Appropriate patient groups need to be identified. Are there comorbidities that affect the safety of fecal microbiota transplants?

Use of FMT in Livestock- Need Cautions!!!

frontiers in Microbiology

REVIEW
published: 19 June 2018
doi: 10.3389/fmicb.2018.01328

Standardized Preparation for Fecal Microbiota Transplantation in Pigs

*Jun Hu[1,2,3†], Lingli Chen[1,2,3†], Yimei Tang[1,2,3], Chunlin Xie[1,2,3], Baoyang Xu[1,2,3], Min Shi[1,2,3], Wenyong Zheng[1,2,3], Shuyi Zhou[1,2,3], Xinkai Wang[1,2,3], Liu Liu[1,2,3], Yiqin Yan[1,2,3], Tao Yang[1,2,3], Yaorong Niu[1,2,3], Qiliang Hou[1,2,3], Xiaofan Xu[1,2,3] and Xianghua Yan[1,2,3]**

[1] State Key Laboratory of Agricultural Microbiology, College of Animal Sciences and Technology, Huazhong Agricultural University, Wuhan, China, [2] The Cooperative Innovation Center for Sustainable Pig Production, Wuhan, China, [3] Hubei Provincial Engineering Laboratory for Pig Precision Feeding and Feed Safety Technology, Wuhan, China

ELSEVIER

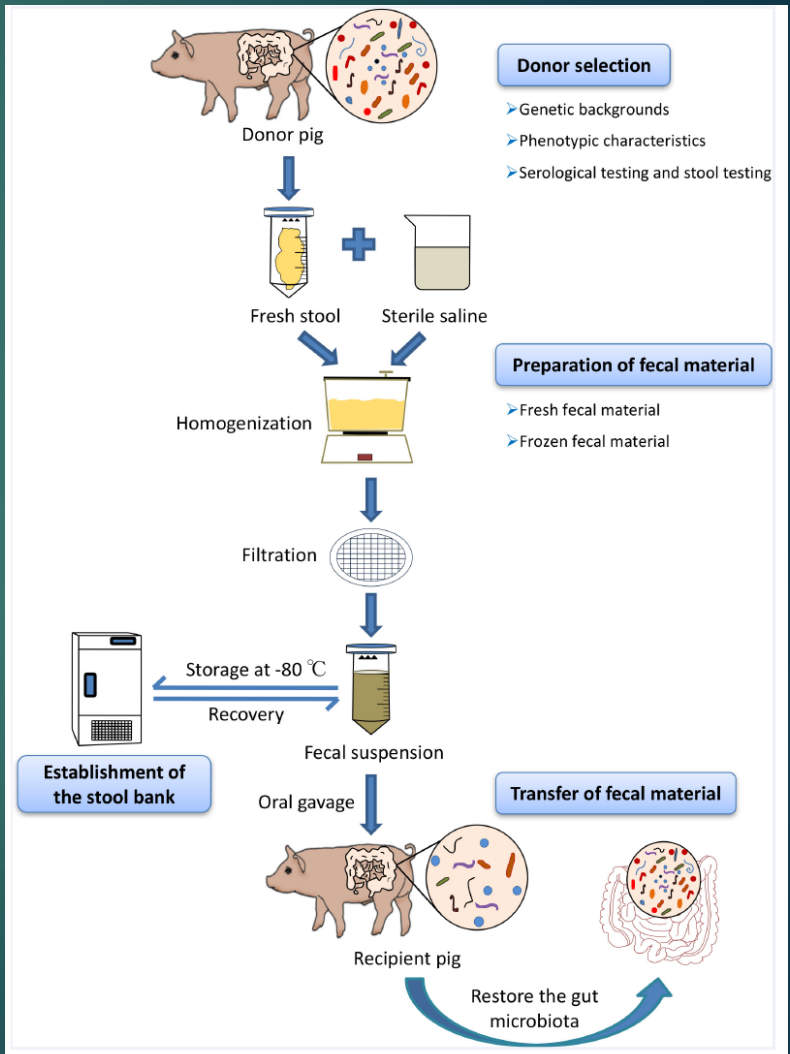
Veterinary Immunology and Immunopathology

Volume 206, December 2018, Pages 65-72

Review Paper

Fecal microbiota transplantation as a tool to treat and reduce susceptibility to disease in animals

Megan C. Niederwerder



What are the alternatives to antibiotics (ATA) left for us?

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~~**Antibiotics**~~

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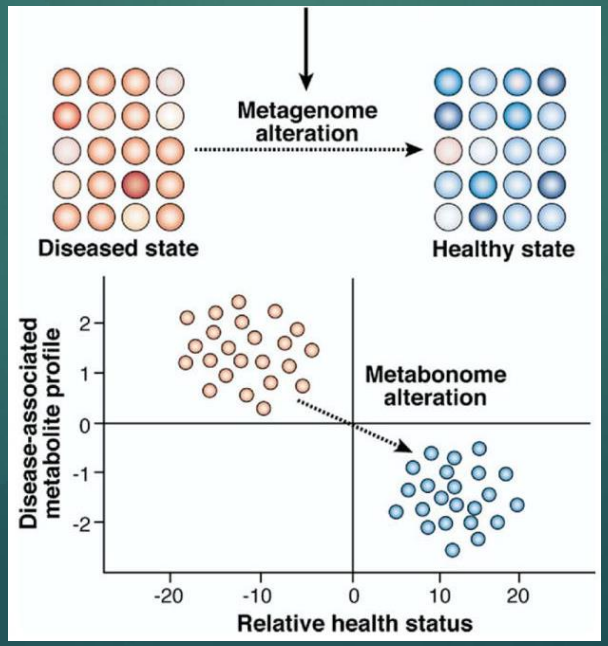


Contents lists available at ScienceDirect

Animal Nutrition

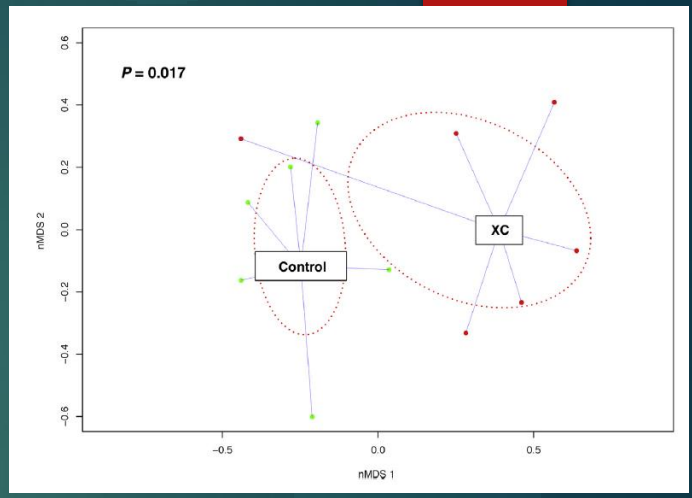
journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Original Research Article

Impact of xylanases on gut microbiota of growing pigs fed corn- or wheat-based diets

Zhengxiao Zhang [a, b], Hein M. Tun [a], Ru Li [a], Beatriz J.M. Gonzalez [a], Hannah C. Keenes [a], Charles M. Nyachoti [a], Elijah Kiarie [c], Ehsan Khafipour [a, b, *]

[a] Department of Animal Science, University of Manitoba, Winnipeg, MB, R3T 2N2, Canada
[b] Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, MB, R3T 2N2, Canada
[c] Department of Animal Bioscience, University of Guelph, Guelph, ON, N1G 2W1, Canada



XC: xylanase from *B. subtilis*

Table 1
Effects of different xylanase supplementations within basal diets on the apparent total tract digestibility of nutrients and VFA concentrations in the ileal and cecal digesta of piglets.[1]

Item	Corn-based diet[2]							Wheat-based diet[2]						
	Control	XA	XB	XC	XD	XE	SEM	Control	XA	XB	XC	XD	XE	SEM
Digestibility, %														
DM	71.04	73.26	70.42	68.93	68.81	68.75	1.65	71.90	73.79	75.35	79.18	73.73	73.81	1.77
GE	71.01	72.89	70.54	68.78	68.49	68.29	1.64	72.91	73.44	76.21	80.39	74.83	74.50	1.69
CP	70.98	73.78	72.45	70.02	72.70	71.86	1.88	73.70[a]	77.06[a,b]	80.31[a,b]	84.09[b]	78.11[a,b]	78.46[a,b]	1.68
Fat	50.29	58.30	50.73	52.94	41.92	50.24	7.08	31.63	26.72	39.40	17.70	53.51	47.21	12.25
VFA concentration, mmol/L														
Ileum	10.66	10.31	11.44	12.64	12.53	12.33	1.10	6.02	5.95	8.00	8.21	7.60	7.28	1.00
Cecum	42.75	46.80	39.15	42.53	43.84	44.25	4.76	42.59	40.52	42.67	35.40	33.80	34.79	4.07

SEM = standard error of the mean.
[a, b] Mean values within a row with different superscripts were significantly different ($P < 0.05$).
[1] Reported values are least-squares means.
[2] The basal diets were supplemented with or without 75 mg/kg of 1 of 5 types of xylanase supplements (xylanase A [XA], xylanase B [XB], xylanase C [XC], xylanase D [XD], and xylanase E [XE]) from various original microorganisms.

Take Home Messages

- Due to increasing awareness of AMR globally, we need to explore more about ATA for both human and animals.
- Optimizing gut health/microbiome is most desirable to maintain health and production in livestock agriculture.
- More scientific investigations are needed to build evidences for the choices of ATA.
- International organizations and scientific communities should develop regulations and recommendations to benchmark ATA available in the market.

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- Prof. Roberto
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- Dr. Wu Peng
- Dr. Herb Peng

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- Dr. Nigel Kwan (AFCD, HK)
- Dr. Garry Hor (AFCD, HK)

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Food and Health Bureau

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Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Research Grants Council of Hong Kong
香港 研究資助局

漁農自然護理署
Agriculture, Fisheries and Conservation Department

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