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Antimicrobial resistance and the microbiome

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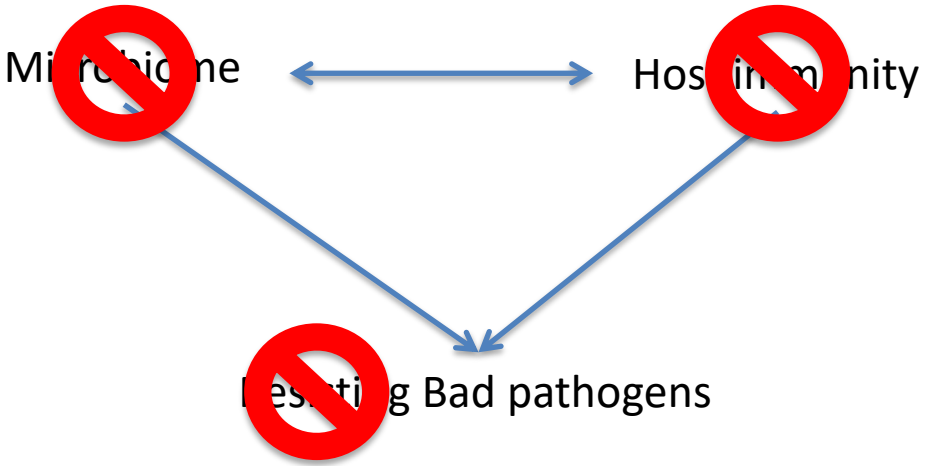
Conflicts of interest

- I have no conflicts of interest related to this presentation


Mi ro bio me
Hos in m nity
Bad pathogens

Lung Microbiome data

- Alpha diversity
  - Number of bacteria in a given area of an individual
- Beta diversity
  - How much diversity between individuals across a group
- Types and amounts of individual bacteria

- Nuances in technique “old” 16S, next gen deep sequencing etc
- Virome .. Fungome ..
- Gut microbiome …

Question 1

- From a microbiome point of view, how close are sputum samples to what is grown in the distal lung?
- A – identical
- B – 90% similar
- C – 50% similar
- D – <50% similar

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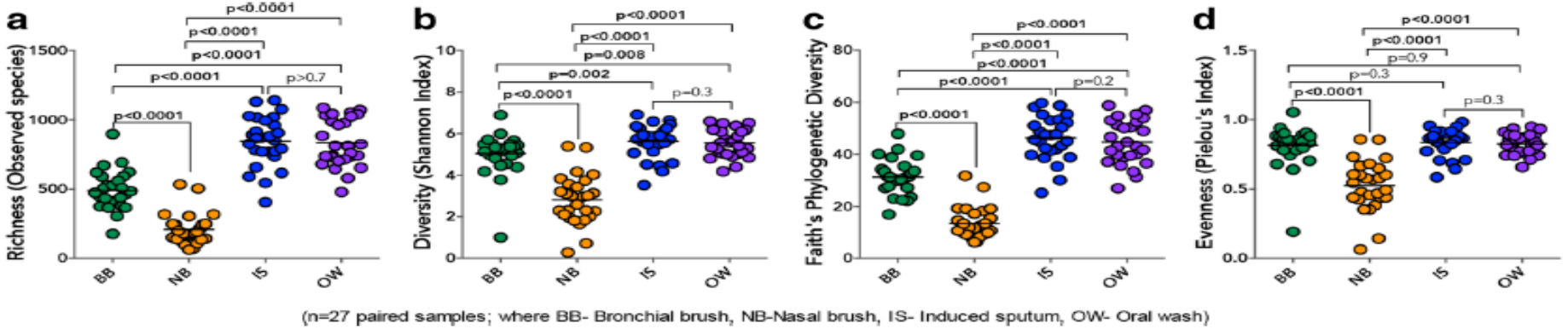
Is microbiome data from sputum samples really representative of what is the airways?



(n=27 paired samples; where BB- Bronchial brush, NB-Nasal brush, IS- Induced sputum, OW- Oral wash)

Fig. 1 Alpha diversity in the microbiota of different specimen types demonstrating that the upper airway harbors significantly sparser bacterial communities than the lower airways or the oral cavity. **a** Bacterial richness as indicated by the total number of taxa detected in each sample type. **b** Shannon index of bacterial diversity in each sample type. **c** Phylogenetic Faith's index of bacterial diversity in each sample type. **d** Pielou's index of community evenness in each sample type. Statistical significance was determined using Wilcoxon matched-pairs signed rank test

Durack et al Microbiome 2018

Pragman et al Microbiome 2018

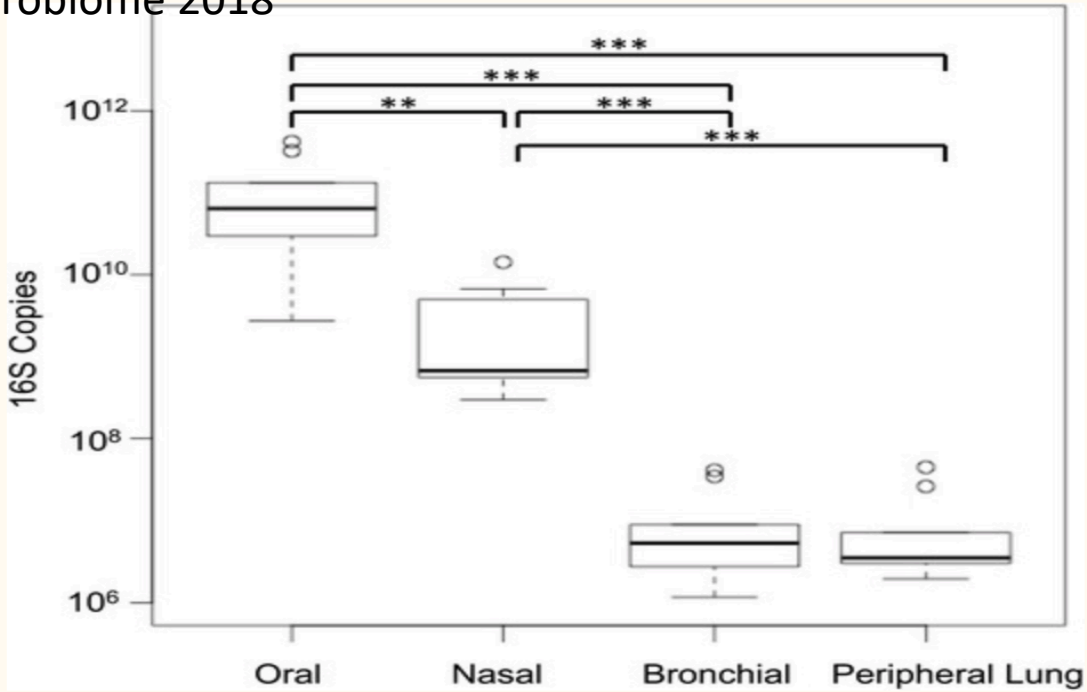
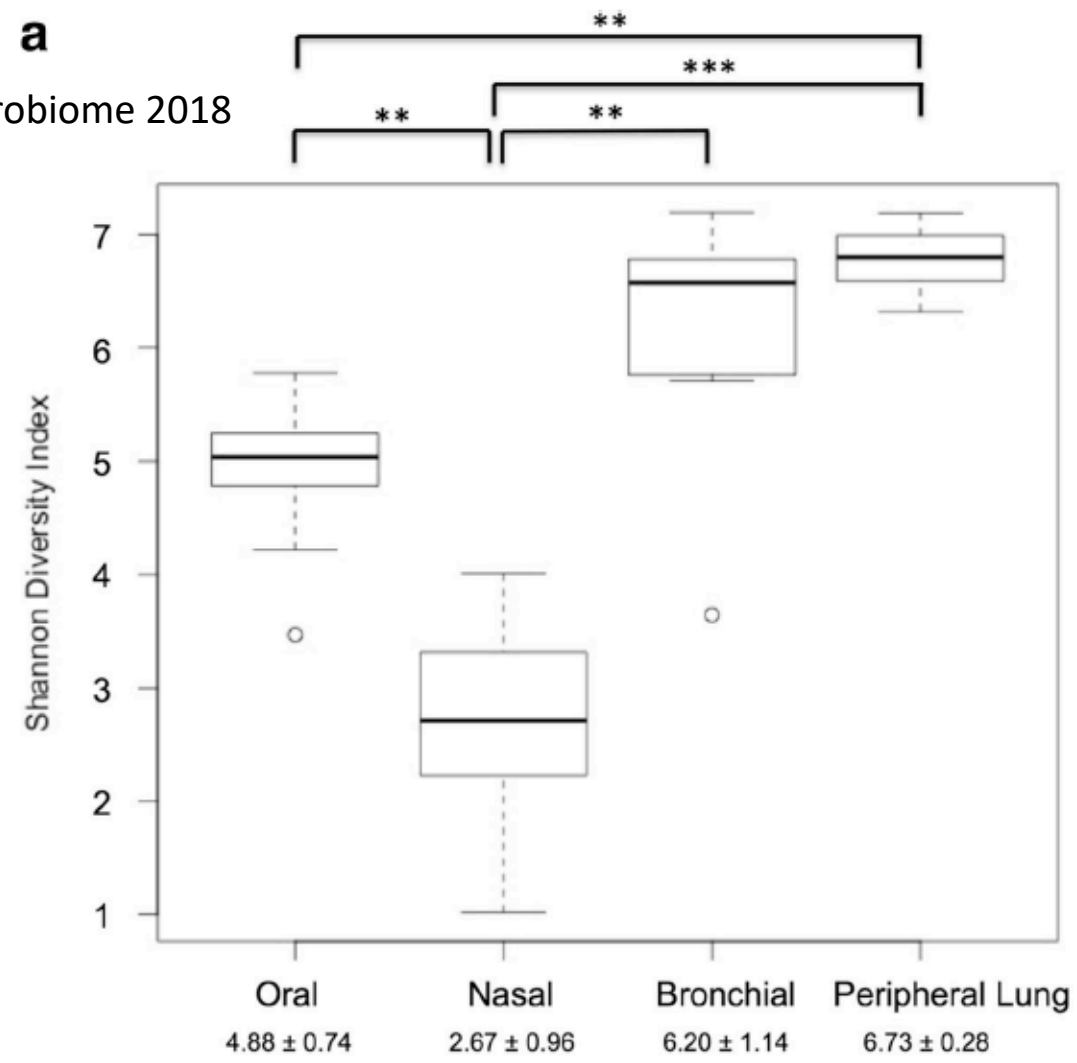


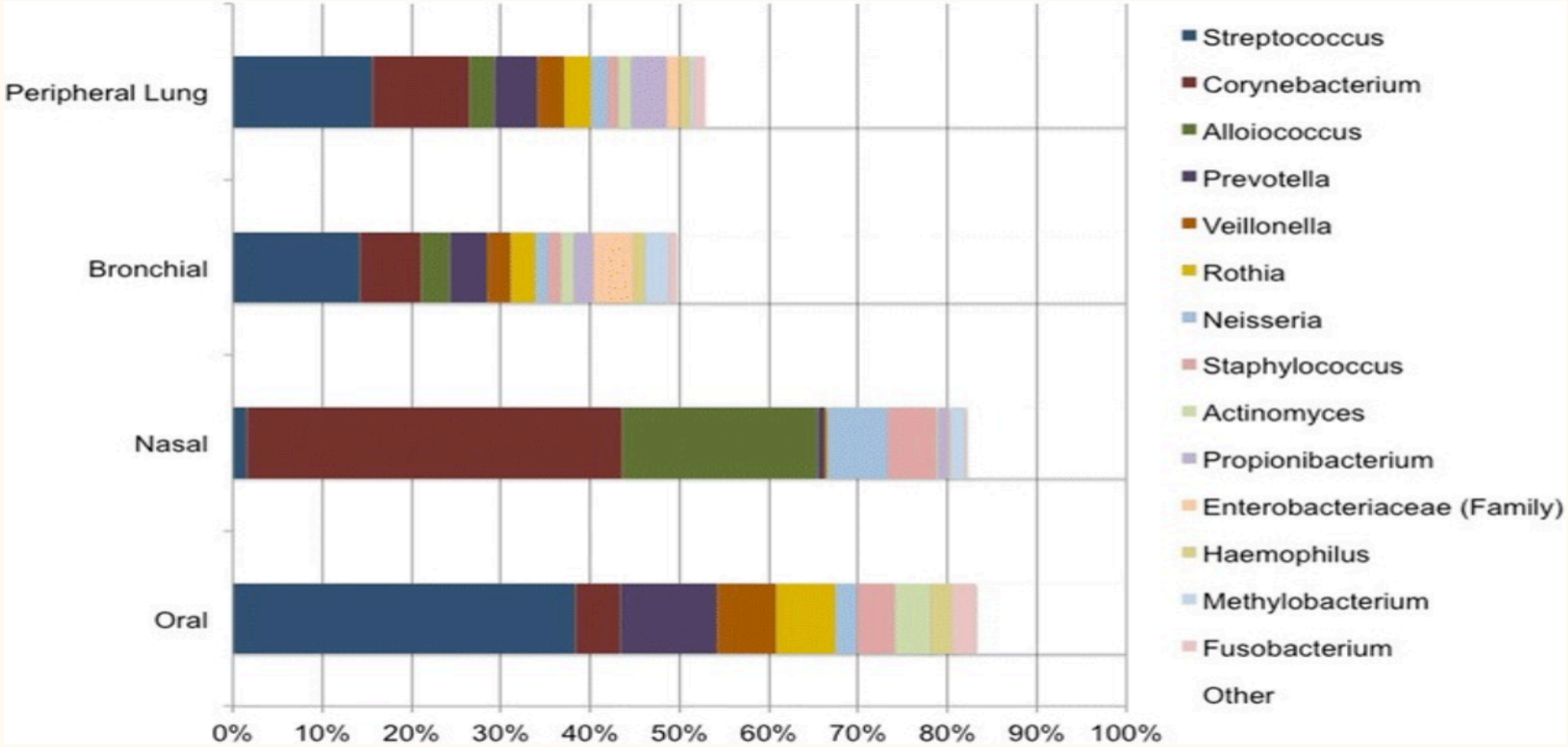
Fig. 2

Bronchial and lung tissue microbiota contain two- to fourfold fewer 16S rRNA gene copies than oral and nasal microbiota. Results of 16S rRNA gene qPCR for each sample were determined. 16S rRNA gene copy data were grouped by site. Bronchial and lung tissue microbiota 16S rRNA gene copy numbers were similar. The generalized estimating equations demonstrated an overall $p < 0.001$. Paired t tests with Holm correction demonstrated that all pairwise tests were significant with the exception of the bronchial-peripheral lung comparison. The oral-nasal comparison resulted in $p = 0.004$ (**), with the remaining significant comparisons demonstrating p values of < 0.001(***)

Pragman et al Microbiome 2018

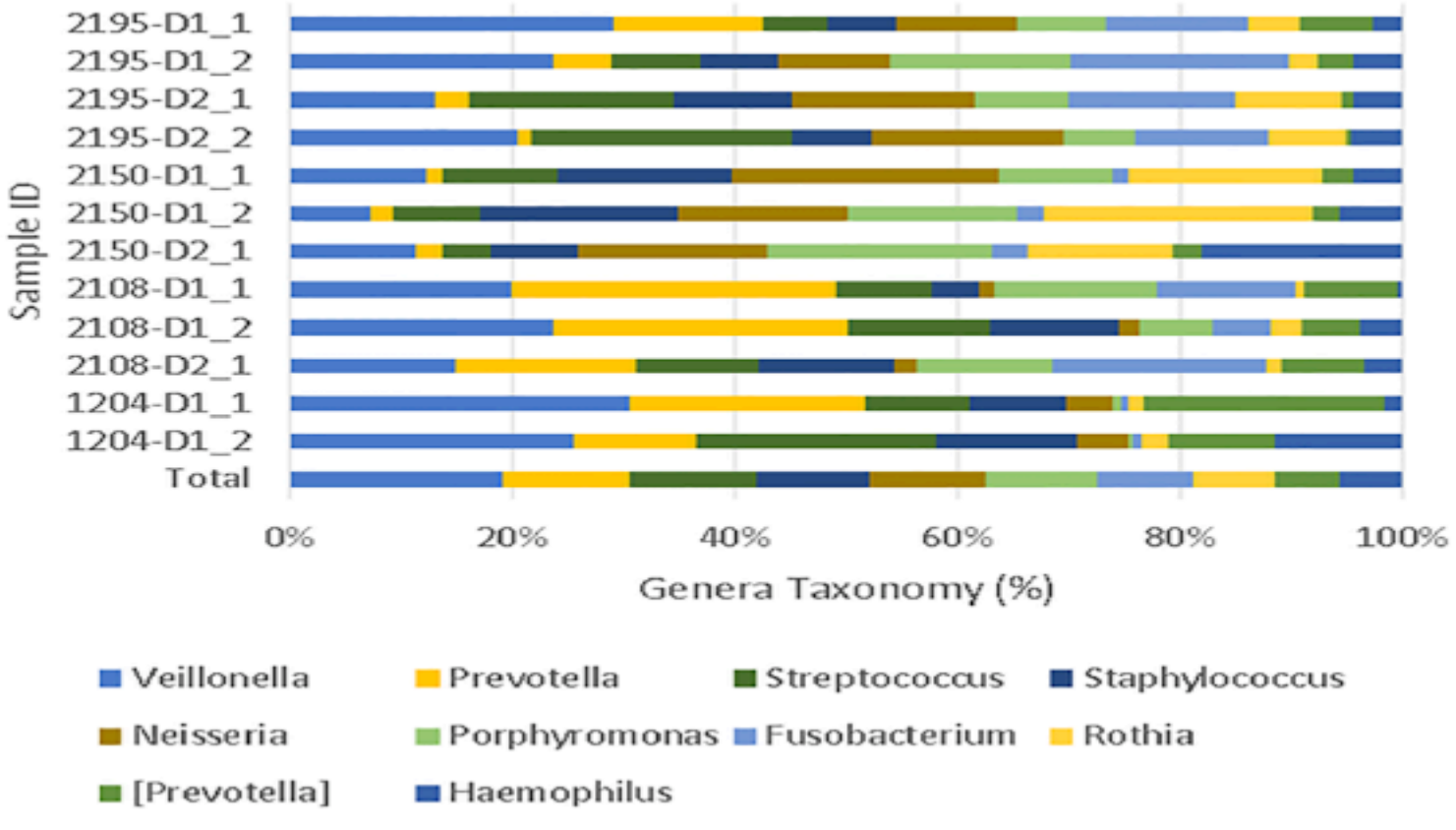


Pragman et al Microbiome 2018



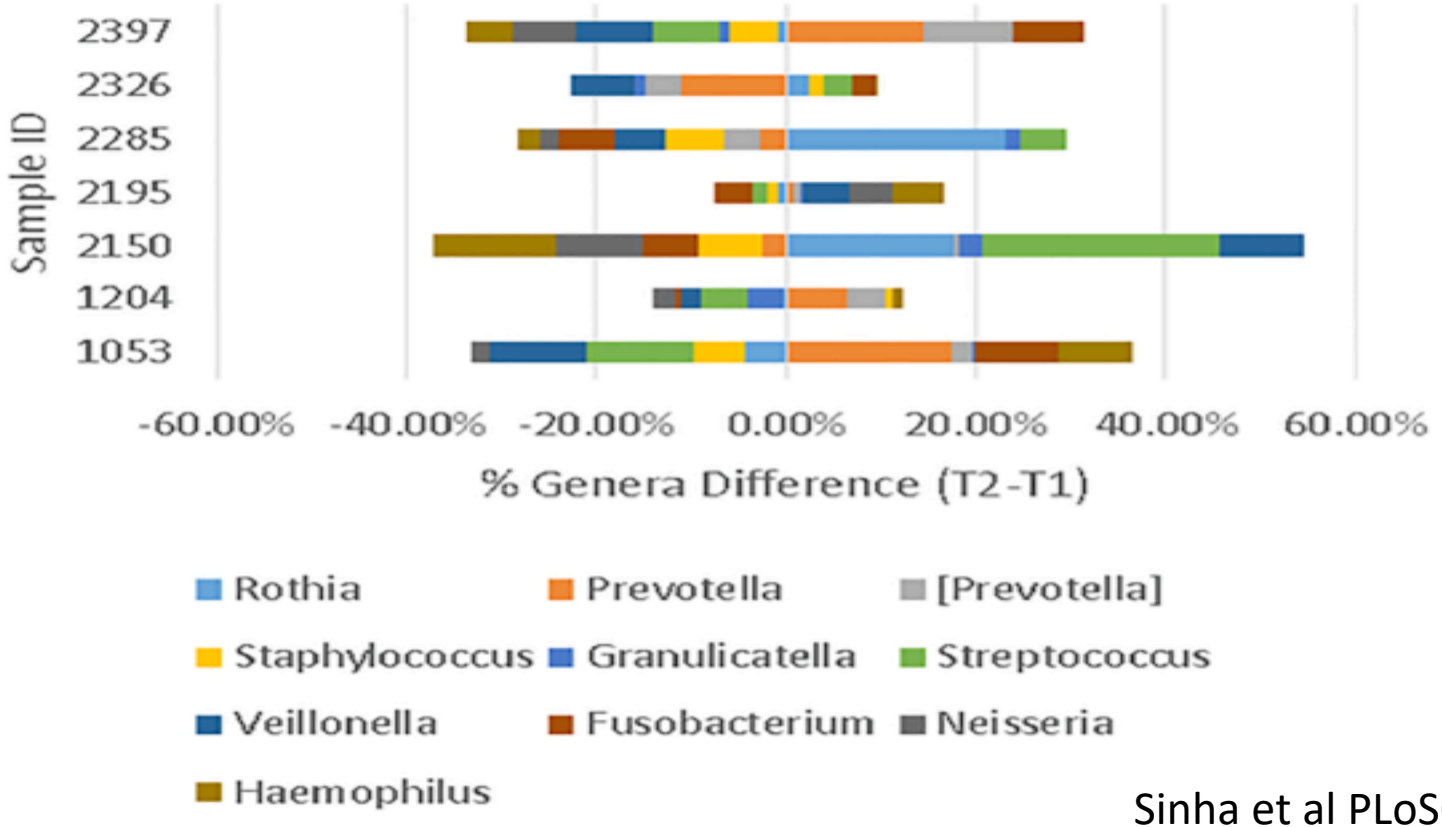
Is the microbiome stable in stable patients?

COPD patients with twinned samples 1 day apart



Sinha et al PLoSOne2018

Change over 9 months



Sinha et al PLoSOne2018

Having diversity is good

Having bad bugs is bad

Low diversity is bad, bad bugs is bad

- Filho et al AJRCCM 2018
- 102 subjects at discharge from hospital with AECOPD
- 19 deaths over 1 year
- Non-survivors lower alpha diversity
- Survivors was enriched with Rothia, Prevotella, Veillonella, Fusobacterium, and Actinomyces (genera frequently identified as oral commensals)
- Non-survivors was enriched with Staphylococcus and Escherichia-Shigella.
- Staph associated with 7.3X increased risk of 1-year mortality
- No Veillonella associated with 13.5X increased risk of 1-year mortality

Lower FEV_1 associated with lower diversity in patients with COPD

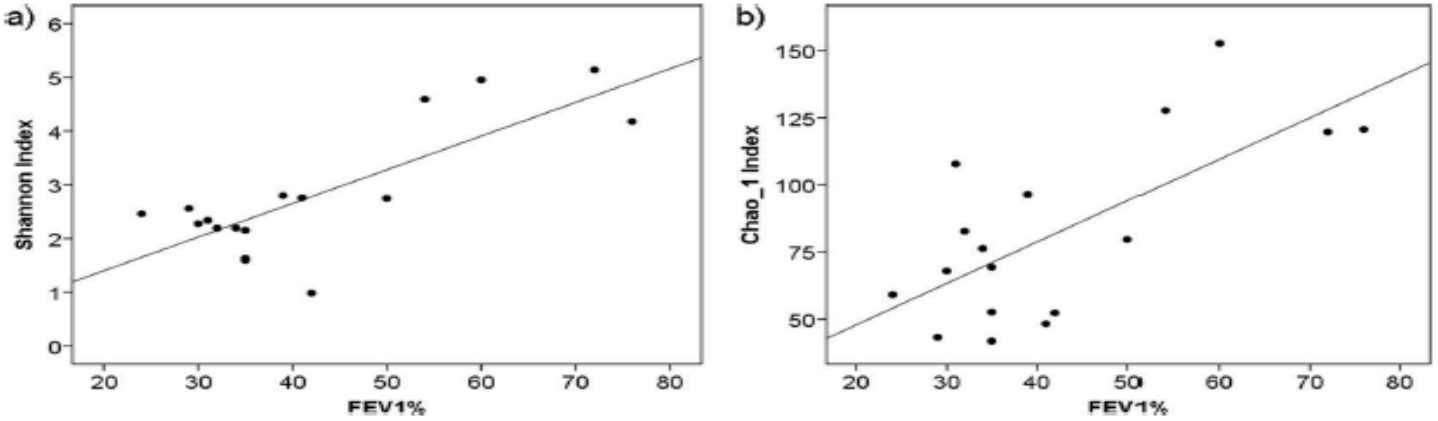
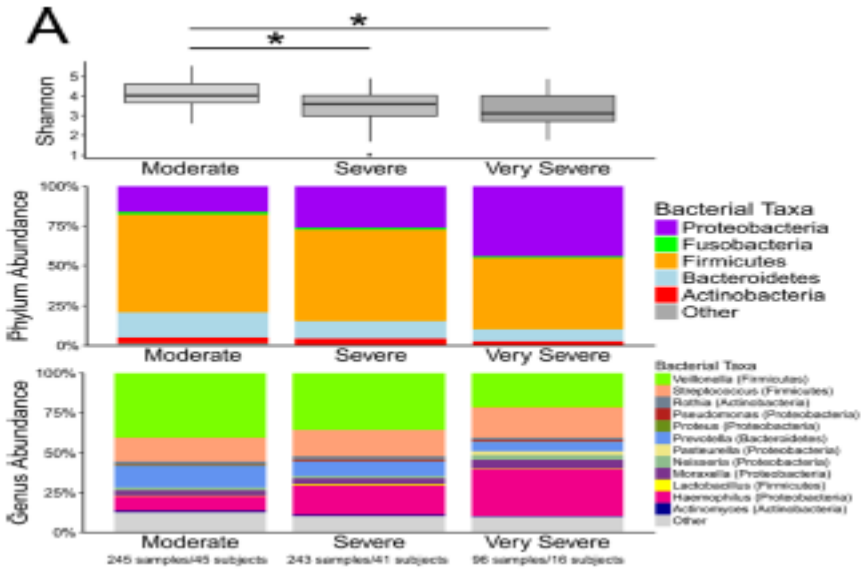


FIG 5 Microbiome diversity in chronic obstructive pulmonary disease (COPD) patients according to lung function by the Shannon index (a) and Chao1 index (b) ($P = 0.029$, $\rho = 0.53$; $P = 0.028$, Spearman correlation test).

Garcia-Nunez et al J Clin Micro 2014

Worse COPD, lower diversity, more bad bugs

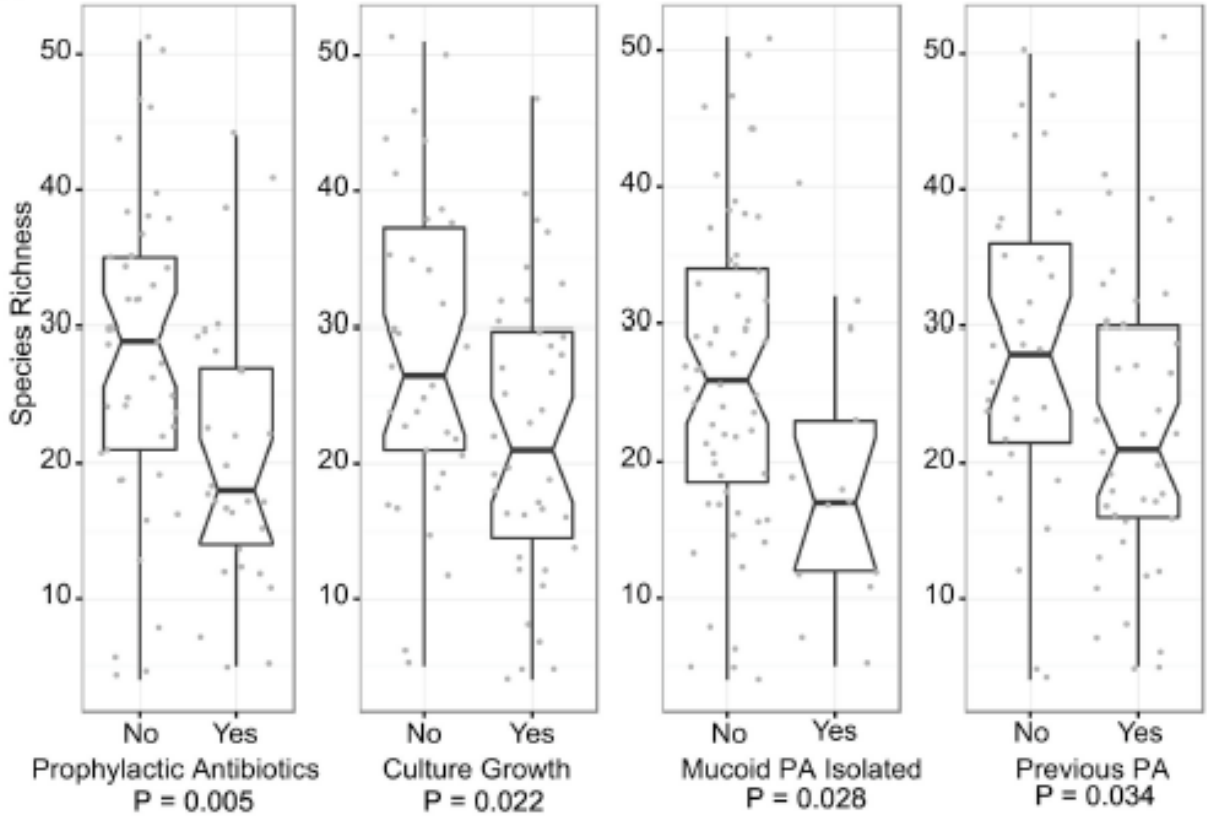


	Severe vs Moderate	Very Severe vs Moderate	Very Severe vs Severe
% Proteobacteria		↑*	↑*
% Bacteroidetes	↓*	↓*	
% Firmicutes			
% *Haemophilus*		↑*	
% *Prevotella*	↓*	↓*	
% *Veillonella*		↓*	↓*
% *Streptococcus*			
% *Moraxella*			

* : P-value < 0.05

Mayhew et al Thorax 2017

Lower diversity in bad prognostic phenotypes of bronchiectasis



Cox et al PLoSOne 2017

Neutrophilic asthma has less alpha diversity

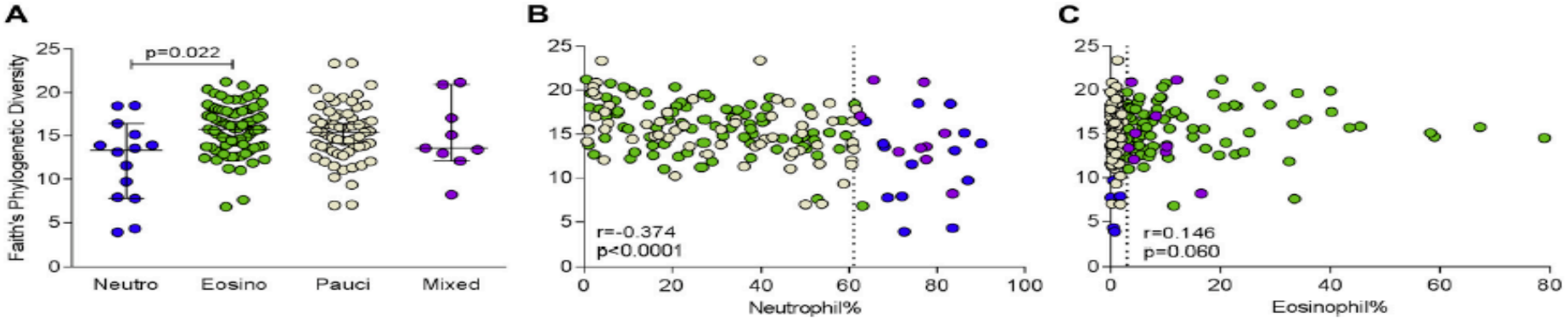
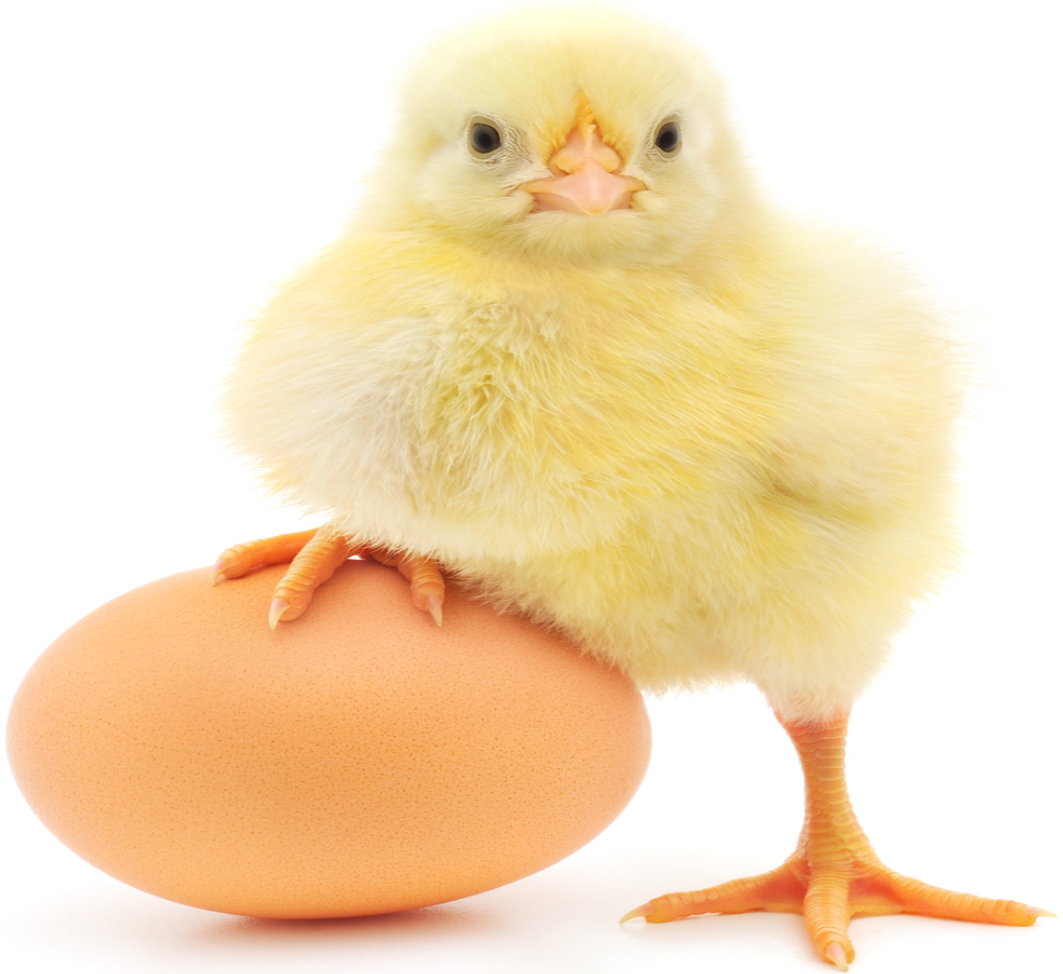


FIG 1. Faith's phylogenetic diversity is significantly associated with sputum neutrophilia but not eosinophilia. **A**, Patients grouped by asthma phenotype. **B**, Neutrophil percentage. The *dotted line* at 61% neutrophils indicates the phenotype cutoff point. **C**, Eosinophil percentage. The *dotted line* at 3% eosinophils indicates the phenotype cutoff point. Colors represent the asthma phenotype: blue is greater than 61% neutrophils, green is greater than 3% eosinophils, yellow is less than 61% neutrophils and less than 3% eosinophils (paucigranulocytic), and purple is both greater than 61% neutrophils and greater than 3% eosinophils (mixed). Statistical significance was assessed by using the Kruskal-Wallis 1-way ANOVA with the Dunn *post hoc* test (Fig 1, *A*) or Spearman rank correlation (Fig 1, *B* and *C*).

Taylor et al JACI 2018



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Antibiotics obviously disturb the microbiome – for months

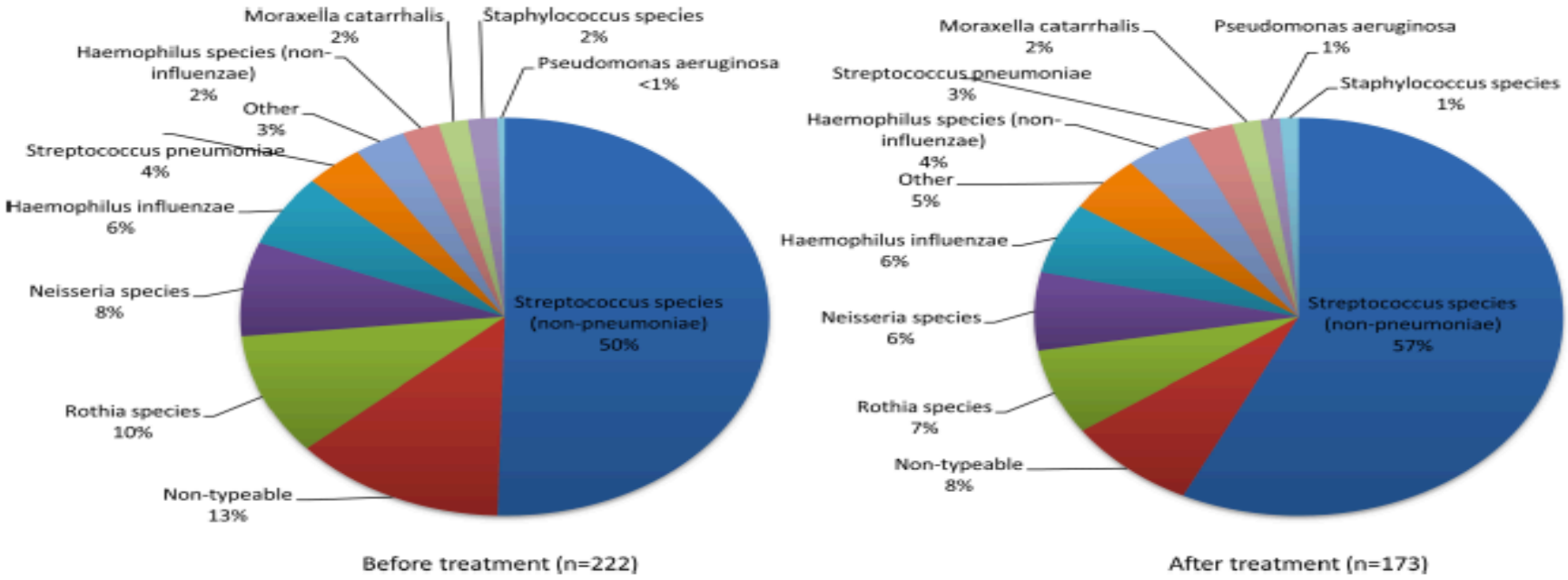


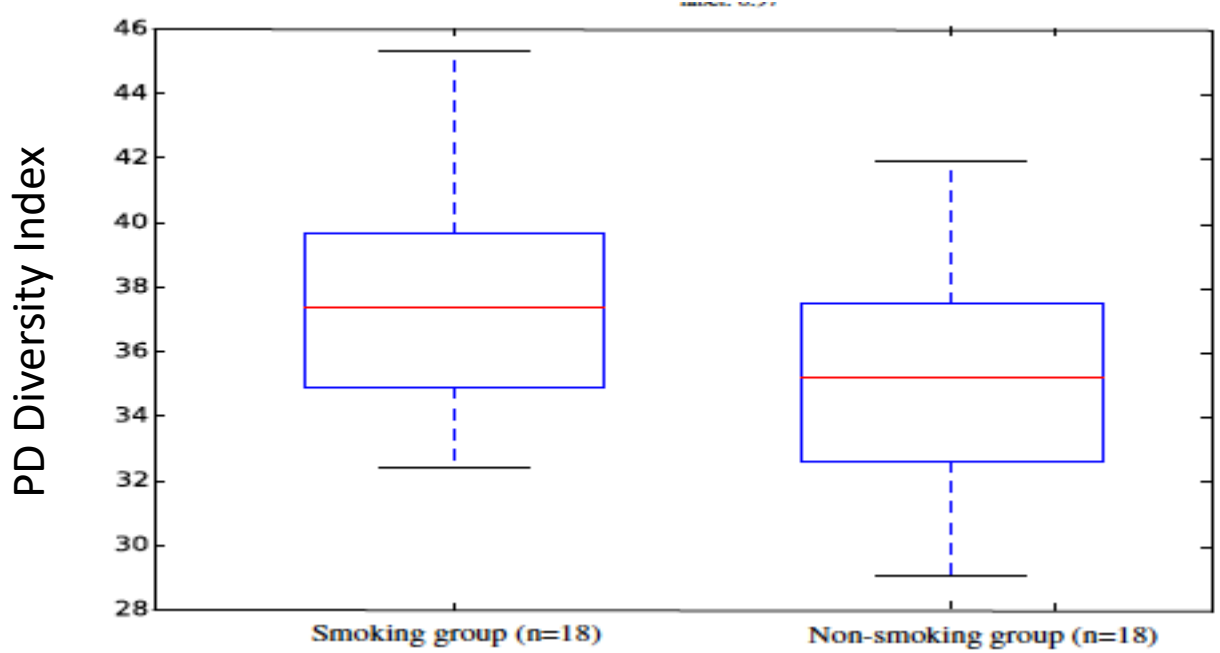
Figure 2 Species breakdown of all cultured isolates (n=395) before and after treatment.

Brill et al COPD 2015

Cigarette smoking changes the microbiome

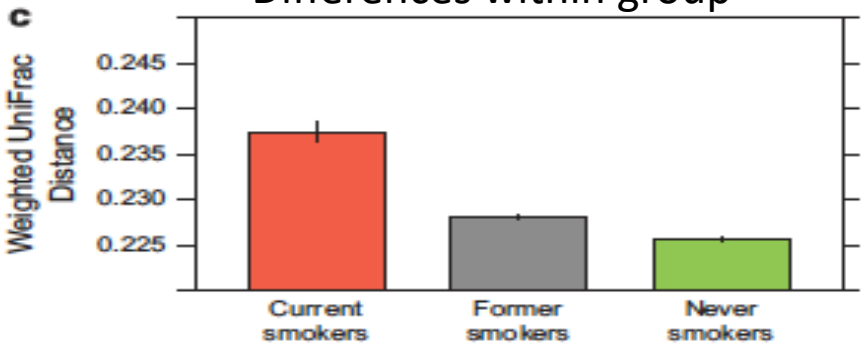
Smoking increases diversity in mice but the diversity is more “bad” bugs

Zhang et al Respir Res 2018

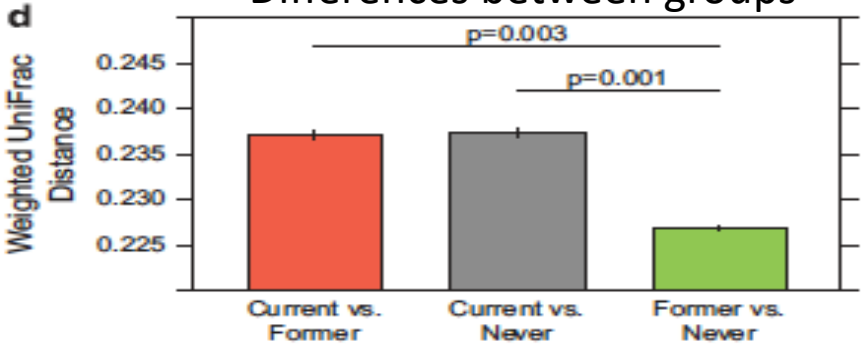


Smoking is associated with more diversity in humans too!

Differences within group



Differences between groups



Wu et al ISME 2016

Oral microbiome in 1200 individuals

Table 2 Median relative abundances of selected taxa according to smoking status in four data sets

Taxa	*CPS-II-a (n = 203)*	*CPS-II-b (n = 340)*	*PLCO-a (n = 261)*	*PLCO-b (n = 400)*	*Meta P-value[a] (q-value[b])*	*Meta P-value[c] (q-value[d])*	
						Current vs Never	*Former vs Never*
Proteobacteria (phylum)							
Never	13.18	13.42	10.43	7.4			
Former	10.97	12.55	7.59	7.21			
Current	7.15	2.63	3.62	4.28			
P-value[e]	0.02	0.003	9.29E−06	0.007	2.29E−09 (1.15E−08)	1.05E−07 (5.24E−07)	0.27 (0.60)
Betaproteobacteria (class); Proteobacteria (phylum)							
Never	3.15	2.35	2.8	1.86			
Former	2.15	2.22	2.05	2.28			
Current	0.13	0.24	0.28	0.65			
P-value[e]	2.18E−05	5.07E−05	2.27E−08	0.0007	3.88E−16 (5.05E−15)	1.02E−07 (1.02E−06)	0.17 (0.92)
Gammaproteobacteria (class); Proteobacteria (phylum)							
Never	8.93	8.52	5.23	4.01			
Former	7.02	8.5	3.89	3.96			
Current	6.34	1.87	2.47	2.38			
P-value[e]	0.17	0.03	0.001	0.02	5.57E−06 (3.62E−05)	5.73E−05 (0.0003)	0.52 (0.92)
Flavobacteriia (class); Bacteroidetes (phylum)							
Never	0.46	0.38	0.24	0.29			
Former	0.49	0.39	0.21	0.31			
Current	0.10	0.15	0.08	0.17			
P-value[e]	0.01	0.04	0.001	0.33	6.11E−05 (0.0003)	0.003 (0.009)	0.31 (0.92)
Actinobacteria (phylum)							
Never	10.59	10.10	15.18	11.62			
Former	11.16	9.30	13.81	11.53			
Current	13.65	13.88	17.46	11.55			
P-value[e]	0.35	0.62	0.36	0.71	0.47 (0.59)	0.02 (0.04)	0.87 (0.87)
Coriobacteriia (class); Actinobacteria (phylum)							
Never	0.36	0.28	0.28	0.33			
Former	0.51	0.33	0.22	0.29			
Current	0.40	0.46	0.51	0.42			
P-value[e]	0.41	0.26	0.02	0.10	0.004 (0.01)	0.01 (0.02)	0.67 (0.92)

[a]Meta-analysis *P*values from Kruskal–Wallis tests within each of the four data sets, calculated using *Z*-score methods.
[b]False discovery rate adjusted *q*-values were calculated based on the meta-analysis *P*-values from Kruskal–Wallis tests.
[c]Meta-analysis *P*values from polytomous logistic regression models within each of the four data sets, calculated using *Z*-score methods. Age (continuous value) and sex (male, female) were controlled for in the polytomous regression models.
[d]False discovery rate adjusted *q*-values were calculated based on the meta-analysis *P*-values from polytomous logistic regression models.
[e]*P*-values are based on nonparametric Kruskal–Wallis test of current, former and never smokers.

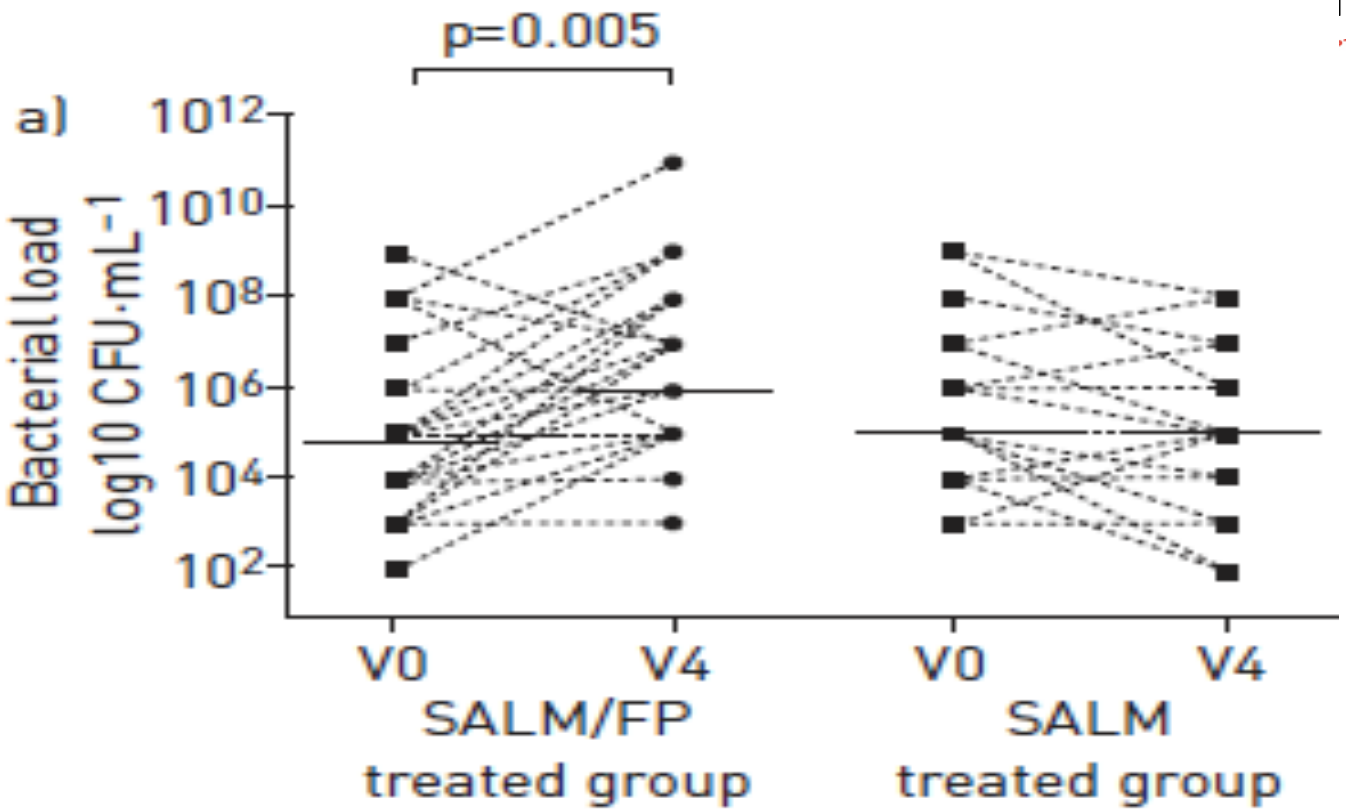
Wu et al ISME 2016

The biggest change with cigarette smoking is the loss of “healthy” bacteria

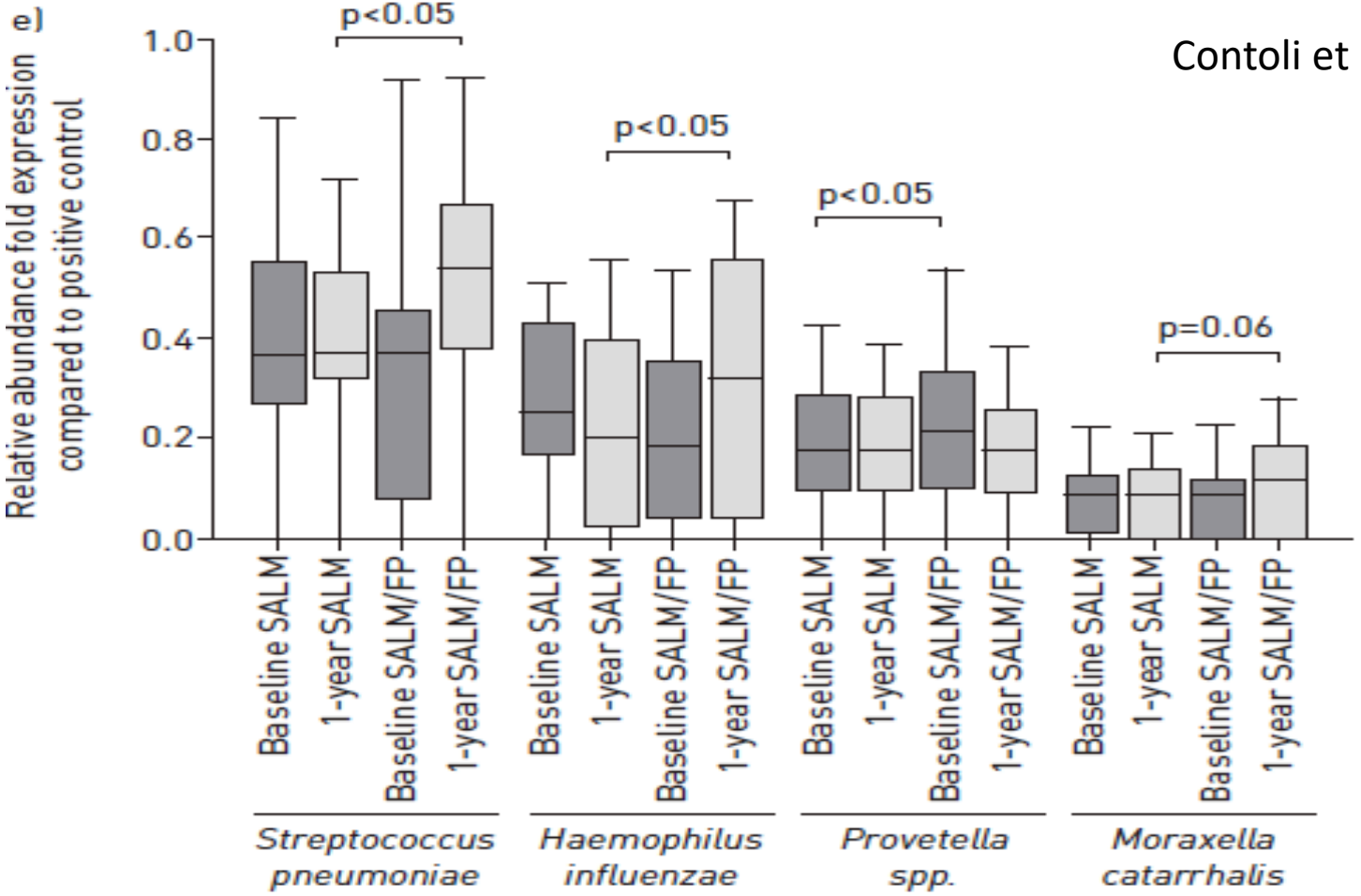
60 patients with stable COPD randomised to 12 months of FP 500/Sal 50 or Sal 50

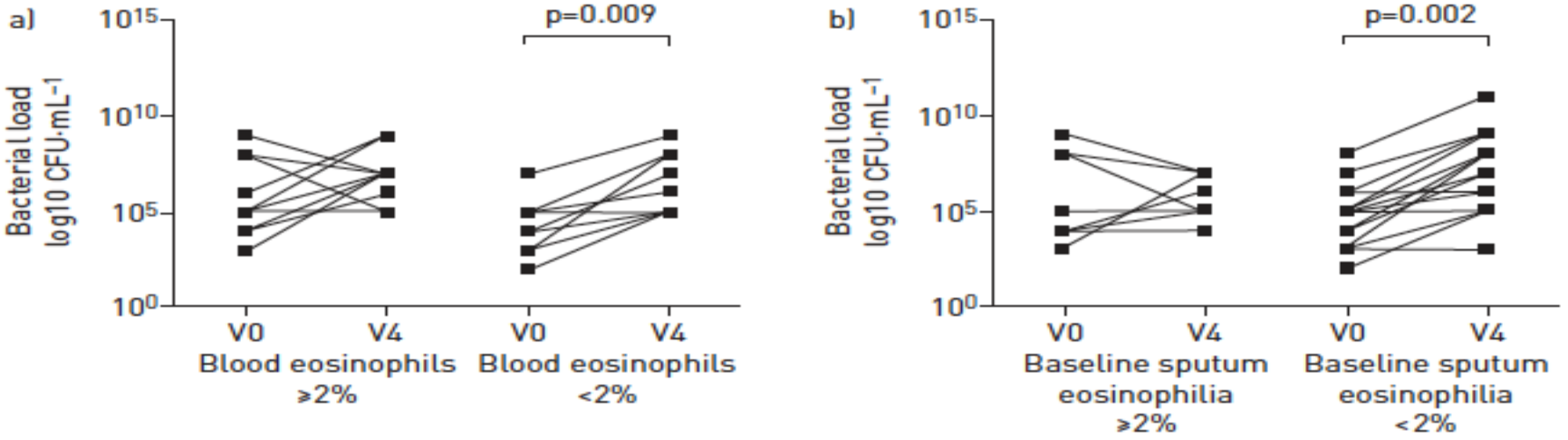
- Contoli et al ERJ 2017
- ICS group had
  - higher bacterial load
  - More pathogenic bacteria
- ICS microbiome changes only observed in patients with blood eosinophil levels <=2%

ERJ 2017


p=0.005
a)
Bacterial load
log10 CFU·mL-1
10^12
10^10
10^8
10^6
10^4
10^2
V0
V4
SALM/FP
treated group
V0
V4
SALM
treated group

Contoli et al ERJ 2017





Contoli et al ERJ 2017

Inhaled corticosteroids seem to drive the microbiome in an unhealthy direction – at least in those with low blood eosinophil counts

Adverse impacts on the lung microbiome

- Antibiotics
- Smoking
- Immune suppressants (?including ICS)
- Viral Infections
- Structural lung disease
- Gut microbiome

Antimicrobial resistance

- Patient level factors driving an unhealthy microbiome that “opens the door”
- Societal level factors driving higher exposure risks

Question 2

- What is the biggest risk of pneumonia?
- A – Having COPD
- B – Airline travel in the past 3 months
- C – Having regular contact with pre-school age children
- D – Smoking cigarettes more than 5/day

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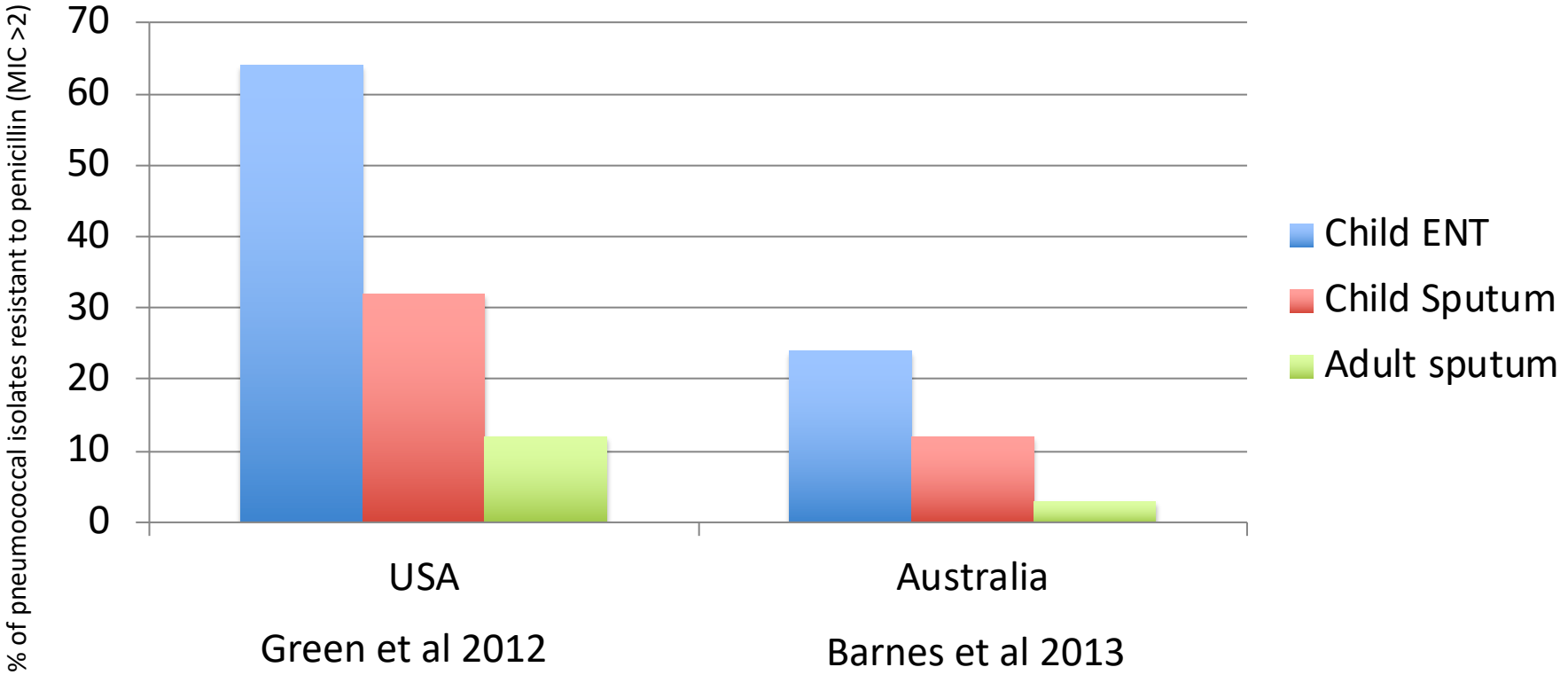
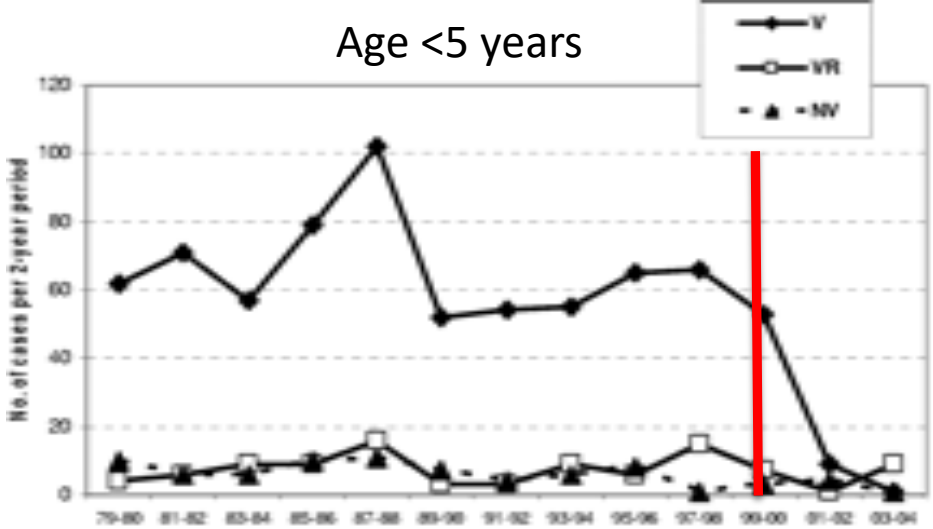
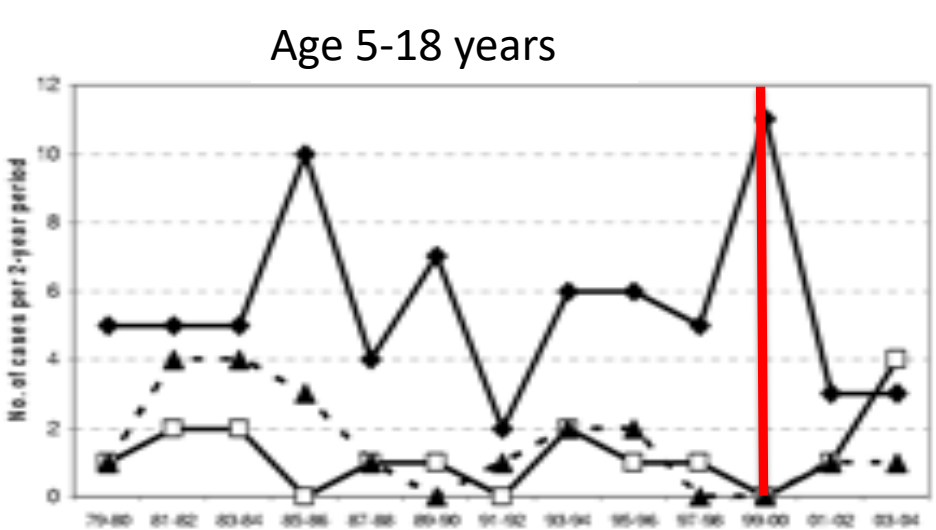
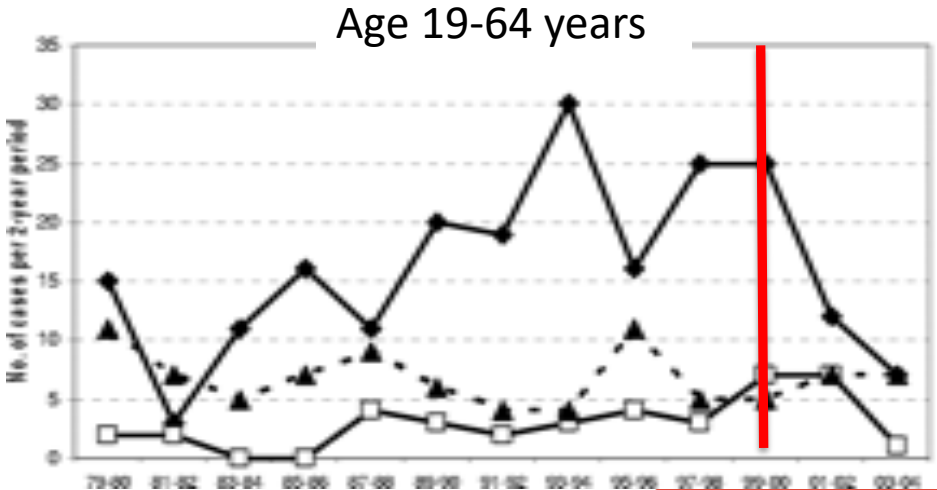
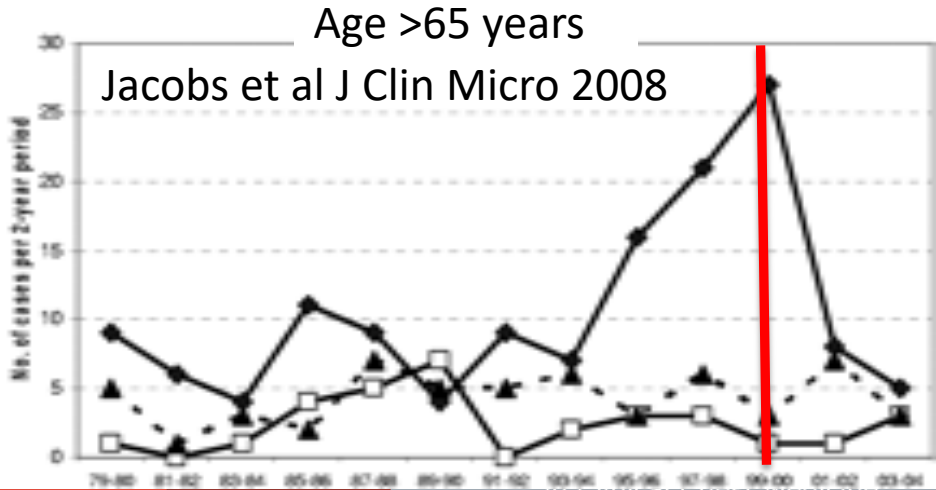
The resistance osmotic gradient



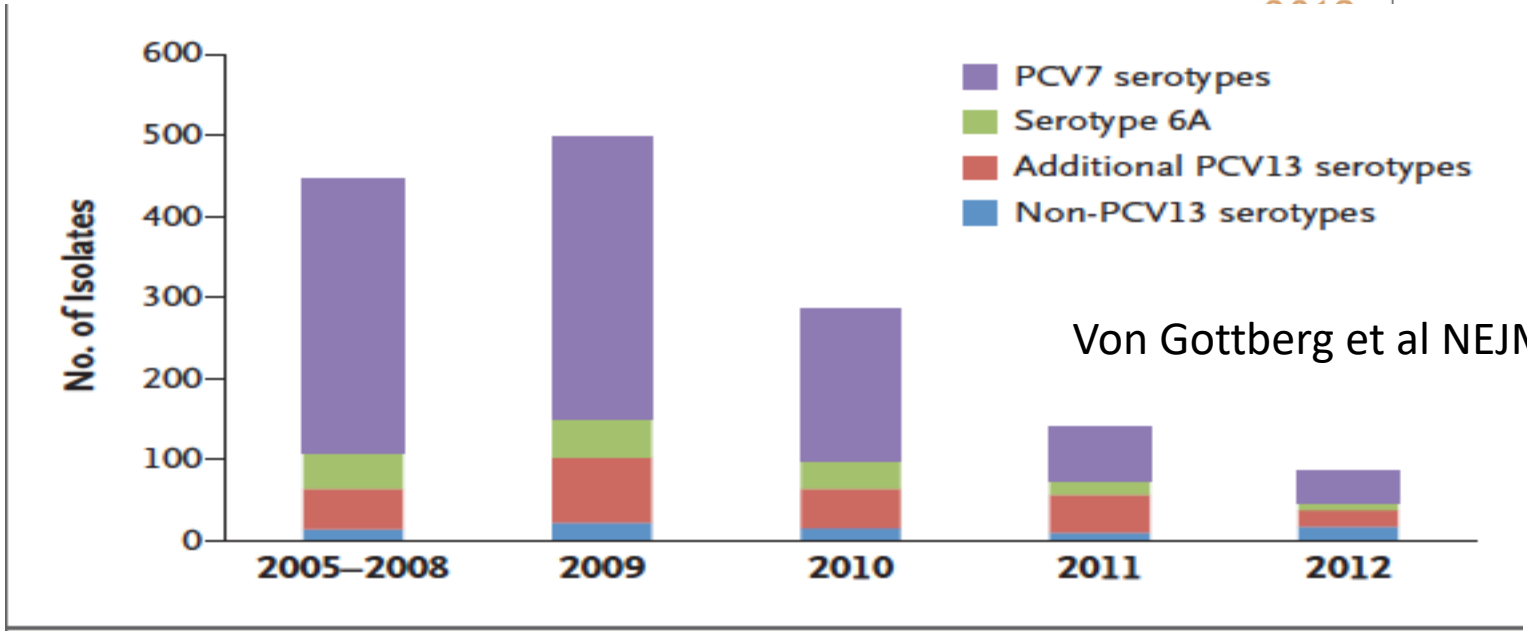








Jacobs et al J Clin Micro 2008

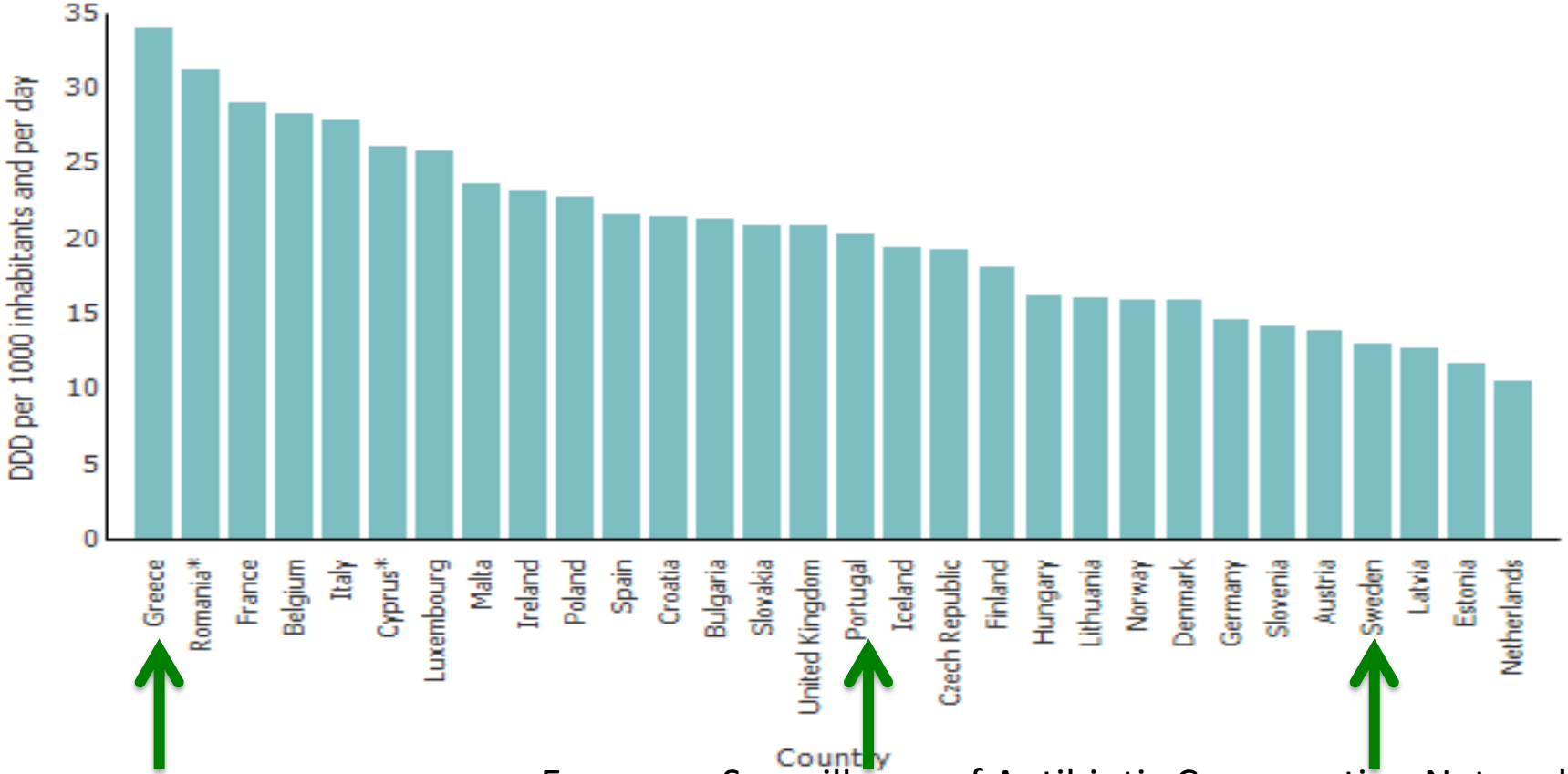


Von Gottberg et al NEJM 2014

Figure 4. Number of Penicillin-Nonsusceptible Isolates Causing Invasive Pneumococcal Disease among Children Younger than 2 Years of Age, According to Serotype.

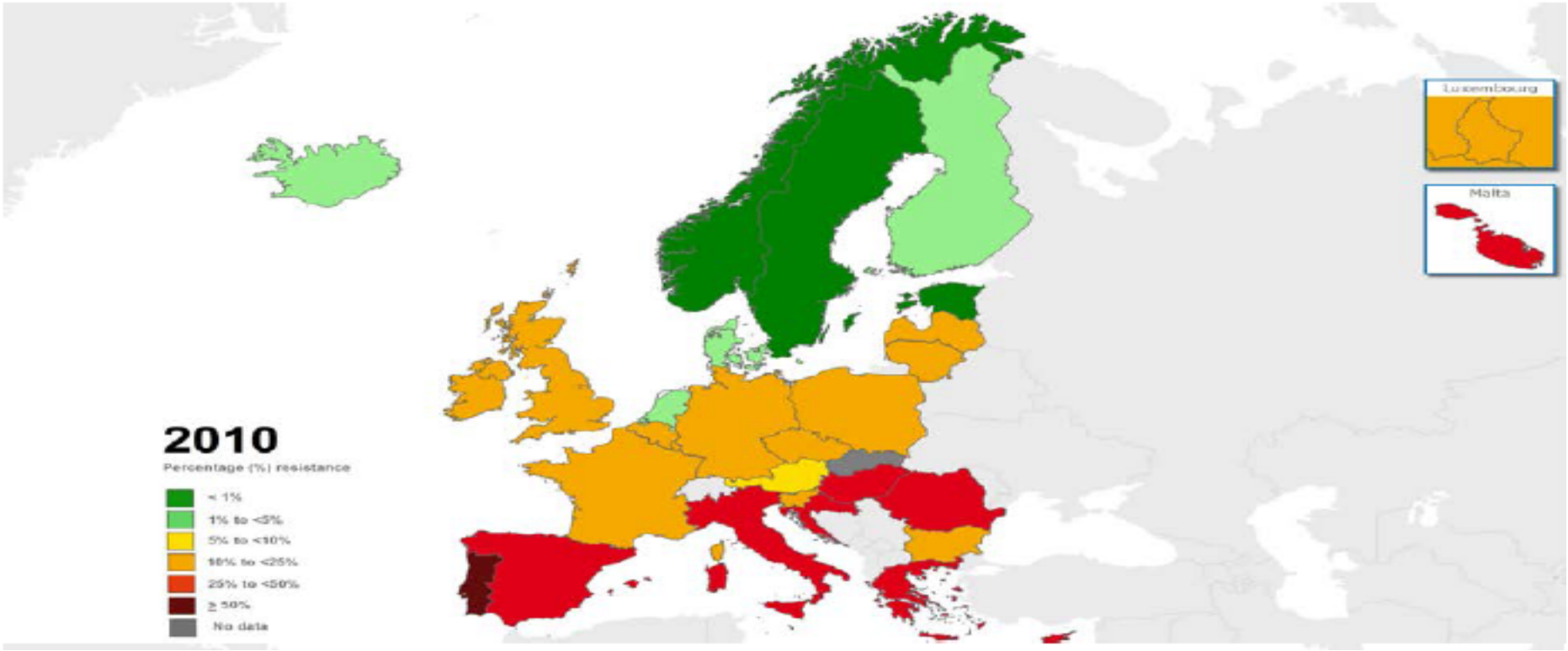
For common respiratory pathogens antibiotic resistance is primarily driven by antibiotic use in young children

Consumption of Antibacterials For Systemic Use (ATC group J01) in the community (primary care sector) in Europe, reporting year 2014



European Surveillance of Antibiotic Consumption Network

Figure 6. ***Staphylococcus aureus*: percentage of invasive isolates with resistance to meticillin (MRSA), EU/EEA, 2010 (top), 2013 (bottom)**



Hospital-acquired multi-drug resistant Gram-negatives

Klebsiella pneumonia carbapenemase (KPC) producers

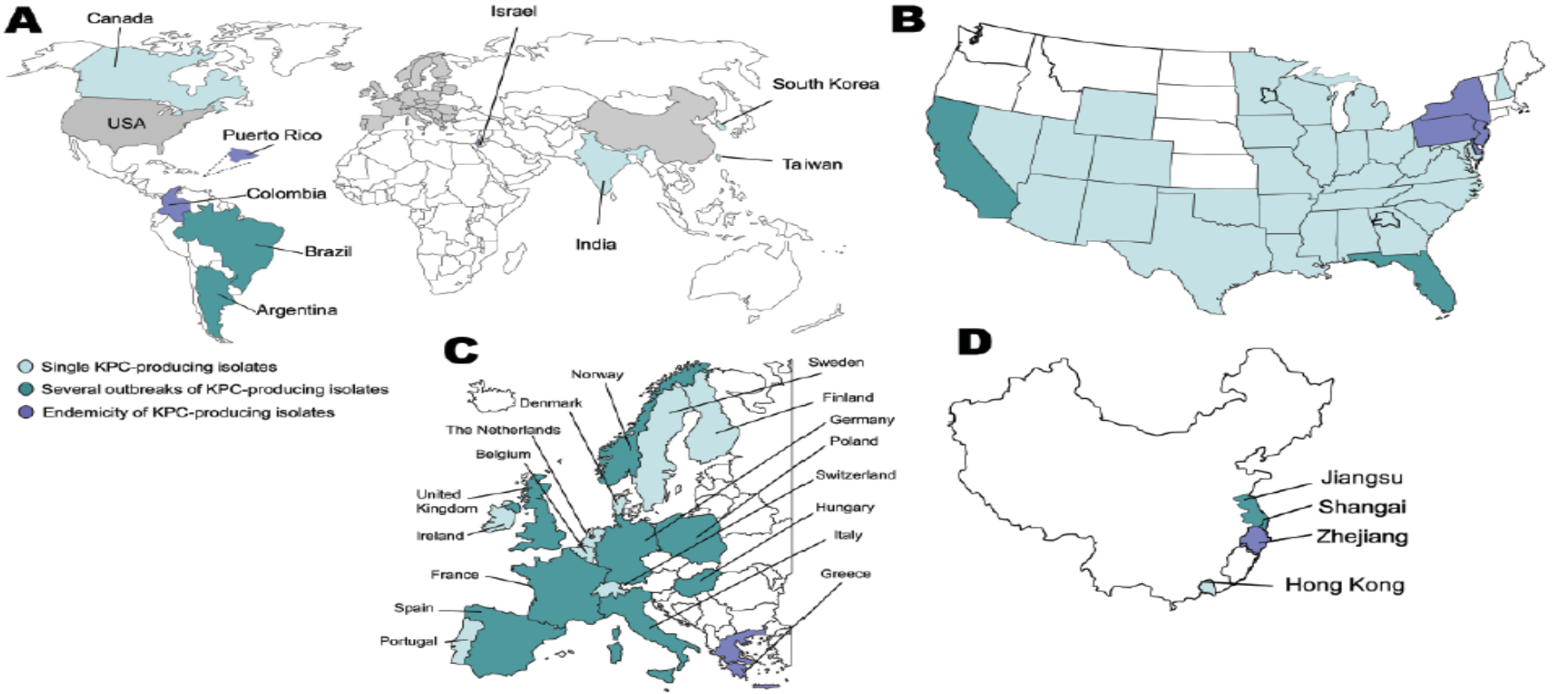


Figure 1. A) Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States; C) distribution in Europe; D) distribution in China.

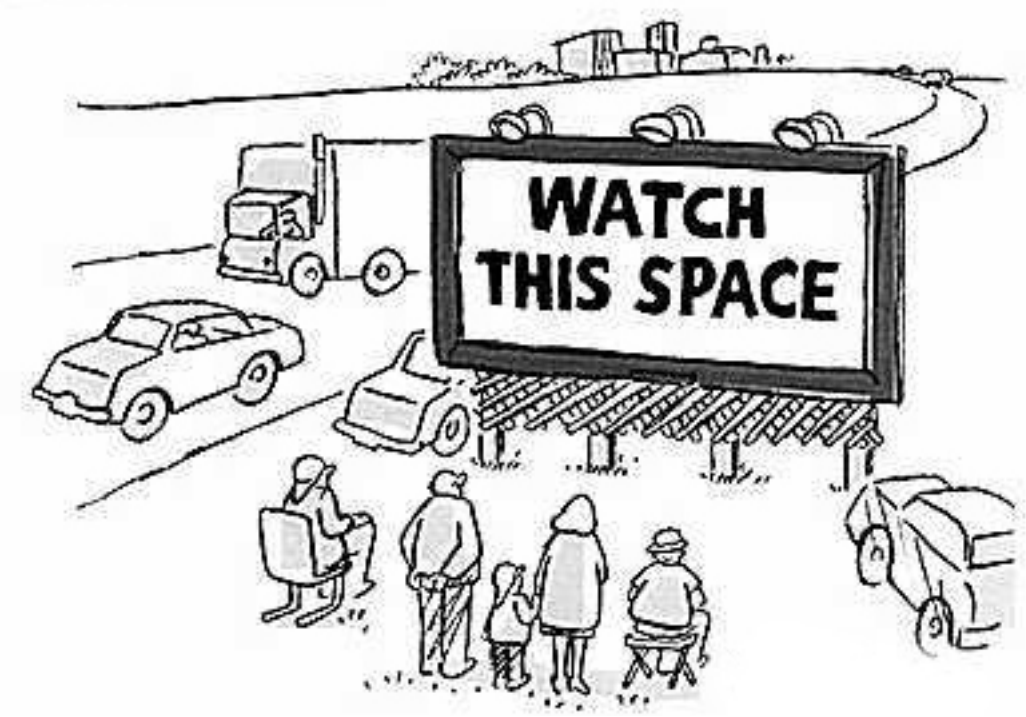
What is driving the multi-resistance problem?

- Intensive care
  - Prolonged mechanical ventilation
  - Patients with no effective immune response
  - Failure of infection control
- Increasing immunocompromised patient groups
- Cultural differences in End of life care
- Cohorting large populations of at-risk individuals
  - Inadequate infection control
- Over use of broad-spectrum antibiotics in first-line care (esp. carbapenems)
  - Inadequate antibiotic stewardship
- Incomplete antibiotic therapy (duration and/or dosing)
- Global health tourism

Can manipulating the microbiome help us with antimicrobial resistance?

- Maintain a healthy microbiome = less opportunity for damaging pathogens
- Can you restore a healthy microbiome if it is damaged?
  - Smoking data suggests you can
- Does restoring a healthy microbiome prevent disease progression?

- We now have to ask –
  - what is the impact of my treatment on the microbiome?
  - Can I minimise the impact?
  - Can I restore the microbiome to a more healthy profile?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THIS SPACE