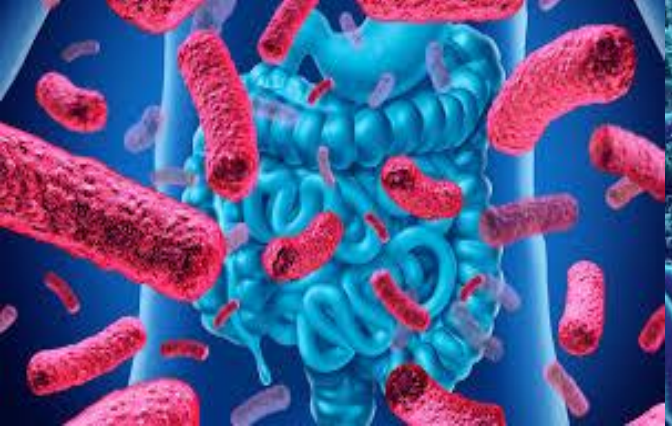


Μικροβίωμα πνεύμονα και παροξύνσεις

Ροβίνα Νικολέττα
Επίκουρη καθηγήτρια Πνευμονολογίας - Εντατικής Θεραπείας
ΕΚΠΑ
Α Πανεπιστημιακή Πνευμονολογική Κλινική
ΝΝΘΑ «η Σωτηρία»

Ορολογία

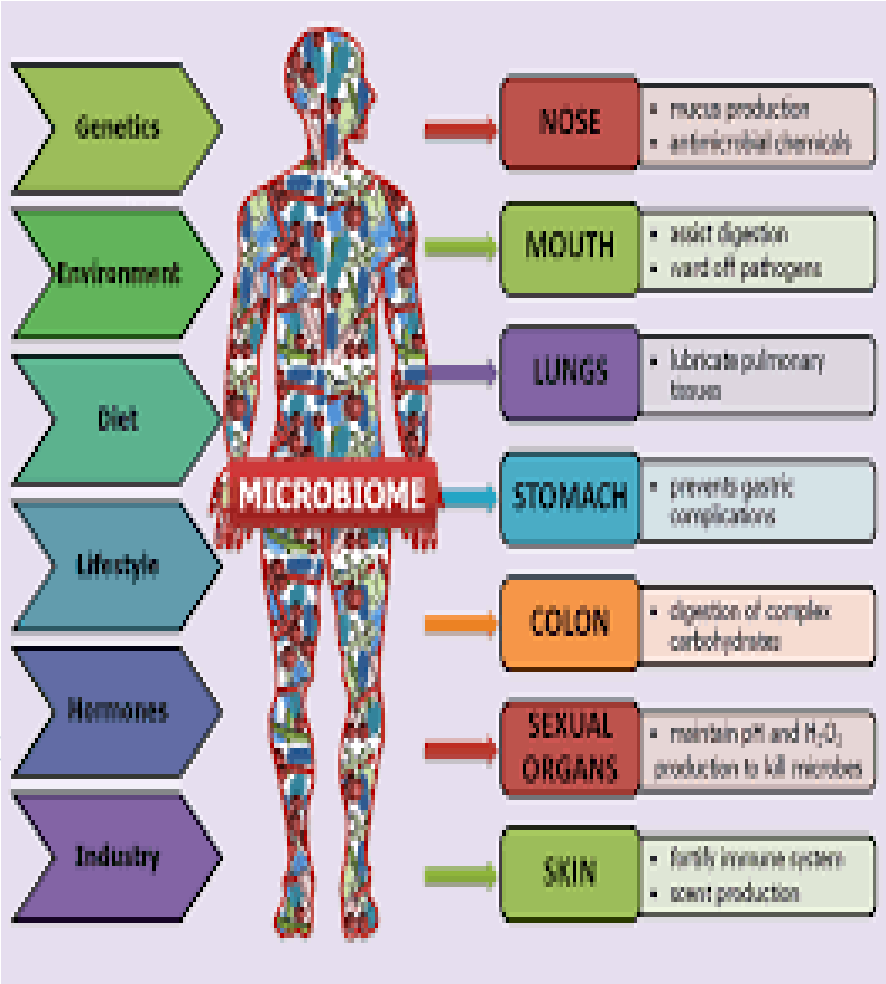
Microbiota: το σύνολο των μικρο-οργανισμών που διαβιούν στο ανθρώπινο σώμα

Microbiome: οι γενετικές πληροφορίες (γενώματα) και οι επαγώμενες φυσικο-χημικές ιδιότητες των γονιδιακών προϊόντων των μικροβιακών κοινοτήτων (microbiota)

Human microbiome: το μικροβίωμα των εσωτερικών και εξωτερικών βιότοπων του ανθρώπινου σώματος

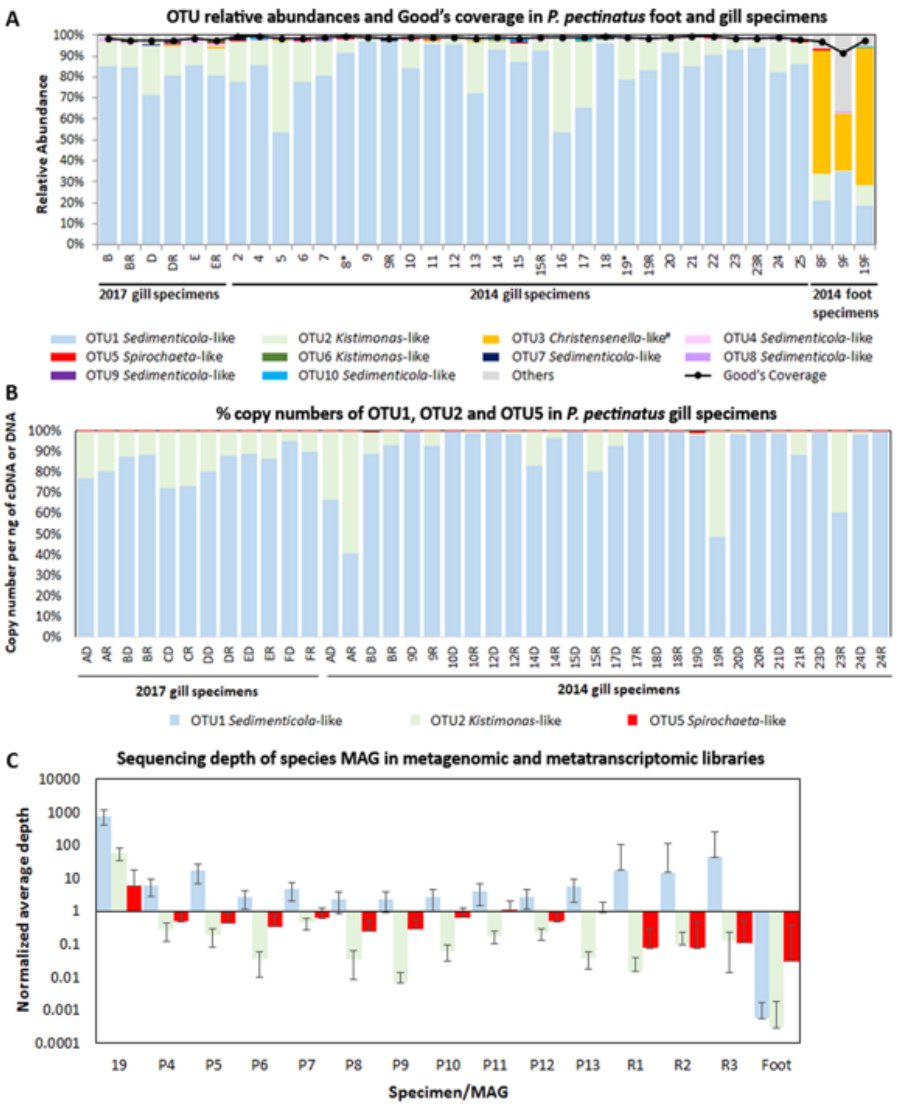
Συμβίωση: η αλληλεπίδραση ξενιστή και μικροβίων που επιφέρει αμοιβαία οφέλη και στα δυο μέρη

Δυσβίωση: αλλαγή στη σύνθεση της μικροβιακής κοινότητας που διαμορφώνεται από τις τοπικές οικολογικές συνθήκες και γενικά, σχετίζεται με μειωμένη αλληλεπίδραση ξενιστή-μικροβίων



Ορολογία ταξινόμησης

Domain	Bacteria
Phylum	Proteobacteria
Class	Gammaproteobacteria
Order	Enterobacteriales
Family	Enterobacteriaceae
Genus	Escherichia
Species	Escherichia coli



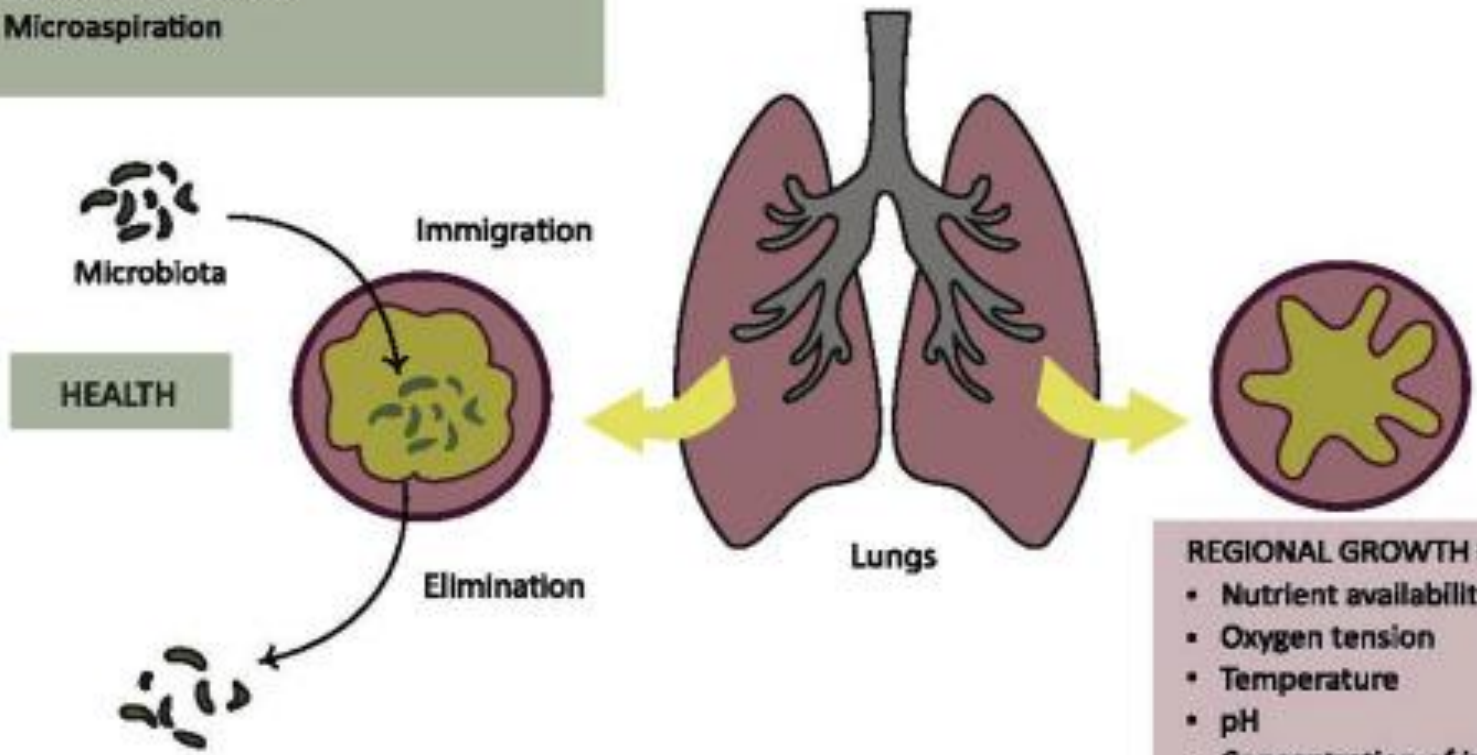
Han et al. Thorax 2013

Οι υγιείς πνεύμονες δεν είναι στείροι, είναι αποικισμένοι από παθογόνα που βρίσκονται σε μια δυναμική ισορροπία εναπόθεσης/κάθαρσης

Εναπόθεση, ανάπτυξη

MICROBIAL IMMIGRATION

- Direct mucosal dispersion
- Inhalation of bacteria
- Microaspiration



REGIONAL GROWTH CONDITIONS

- Nutrient availability
- Oxygen tension
- Temperature
- pH
- Concentration of inflammatory cells
- Activation of inflammatory cells
- Local microbial competition
- Host epithelial cell interactions

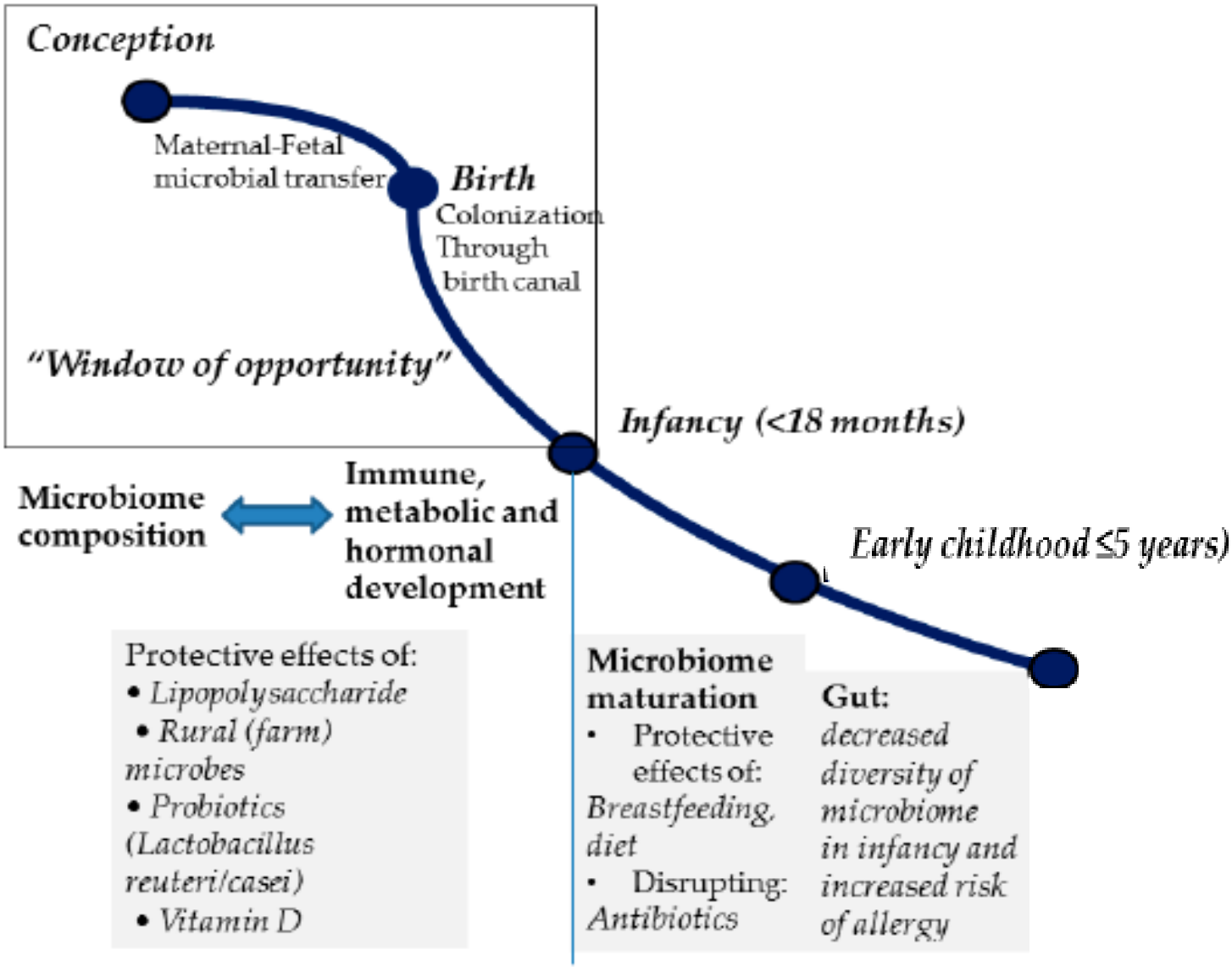
Κάθαρση, θάνατος

MICROBIAL ELIMINATION

- Cough
- Mucociliary clearance
- Innate and adaptive host defenses

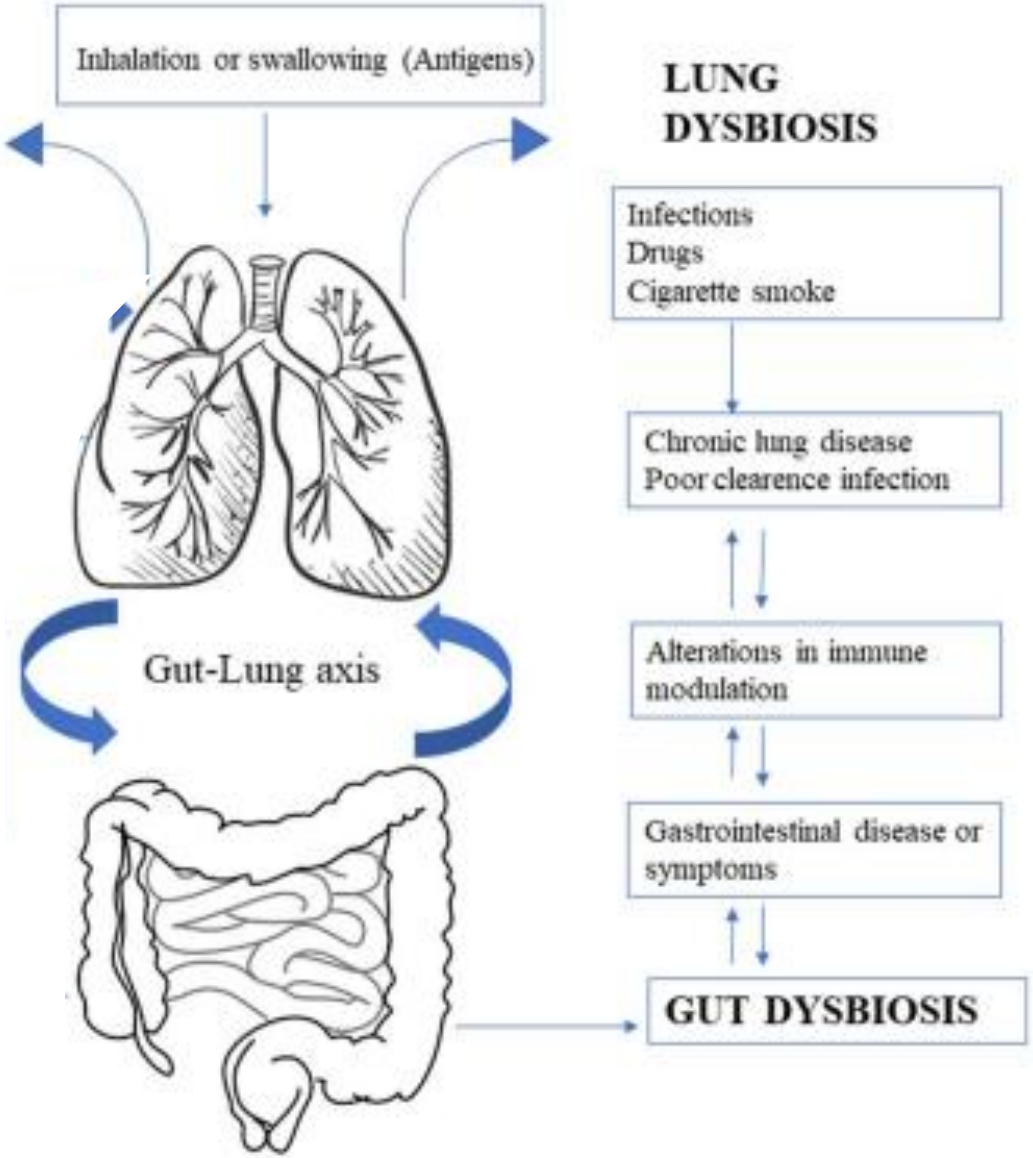
Chellappan et al Chem Biol Interact. 2019 Sep 1;310:108732

Η φυσική εξέλιξη στην μορφοποίηση του μικροβιώματος

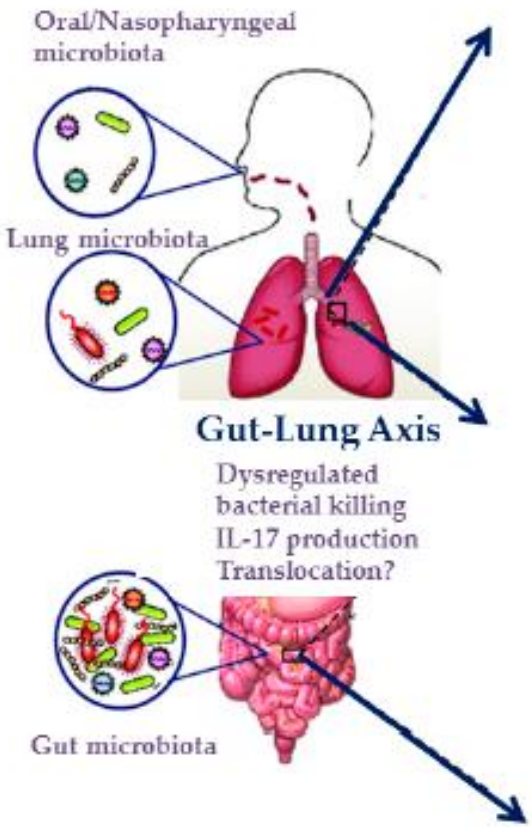


Loverdos et al. Clin. Med. **2019**, *8*(11), 1967

Gut–lung axis



Fabbrizzi et al. Intern Emerg Med. 2019 Nov;14(8):1241-1250

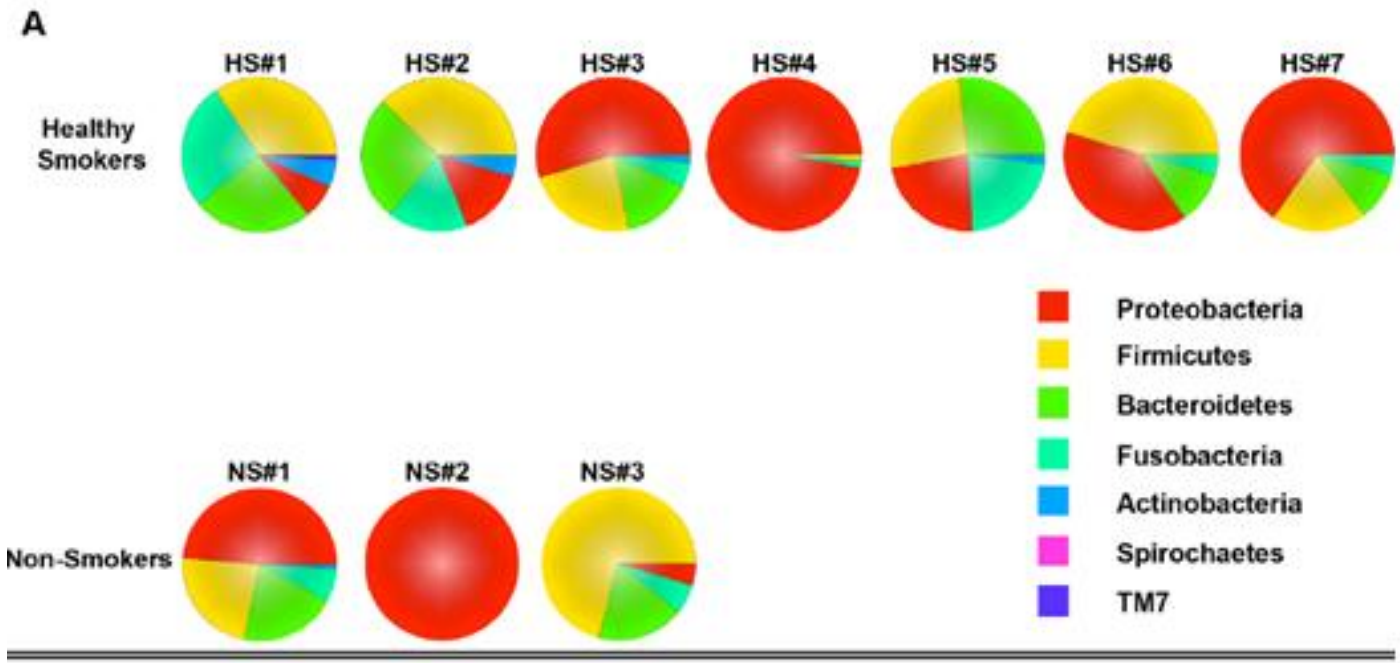


Loverdos et al. Clin. Med. **2019**, *8*(11), 1967

Μικροβιακή χλωρίδα των υγιών πνευμόνων

Αρκετές μελέτες έχουν χαρακτηρίσει το μικροβίωμα του υγιούς πνεύμονα με τα συχνότερα φύλα σε μεγάλη ανάπτυξη να είναι τα Bacteroides, Firmicutes και Proteobacteria.

Το βακτηριδιακό μικροβίωμα των υγιών αποτελείται από έναν κοινό πυρήνα μικροβίων που περιλαμβάνει ως συχνότερα είδη τα: Pseudomonas, Streptococcus, Prevotella, Fusobacterium, Haemophilus, Veillonella, and Porphyromonas

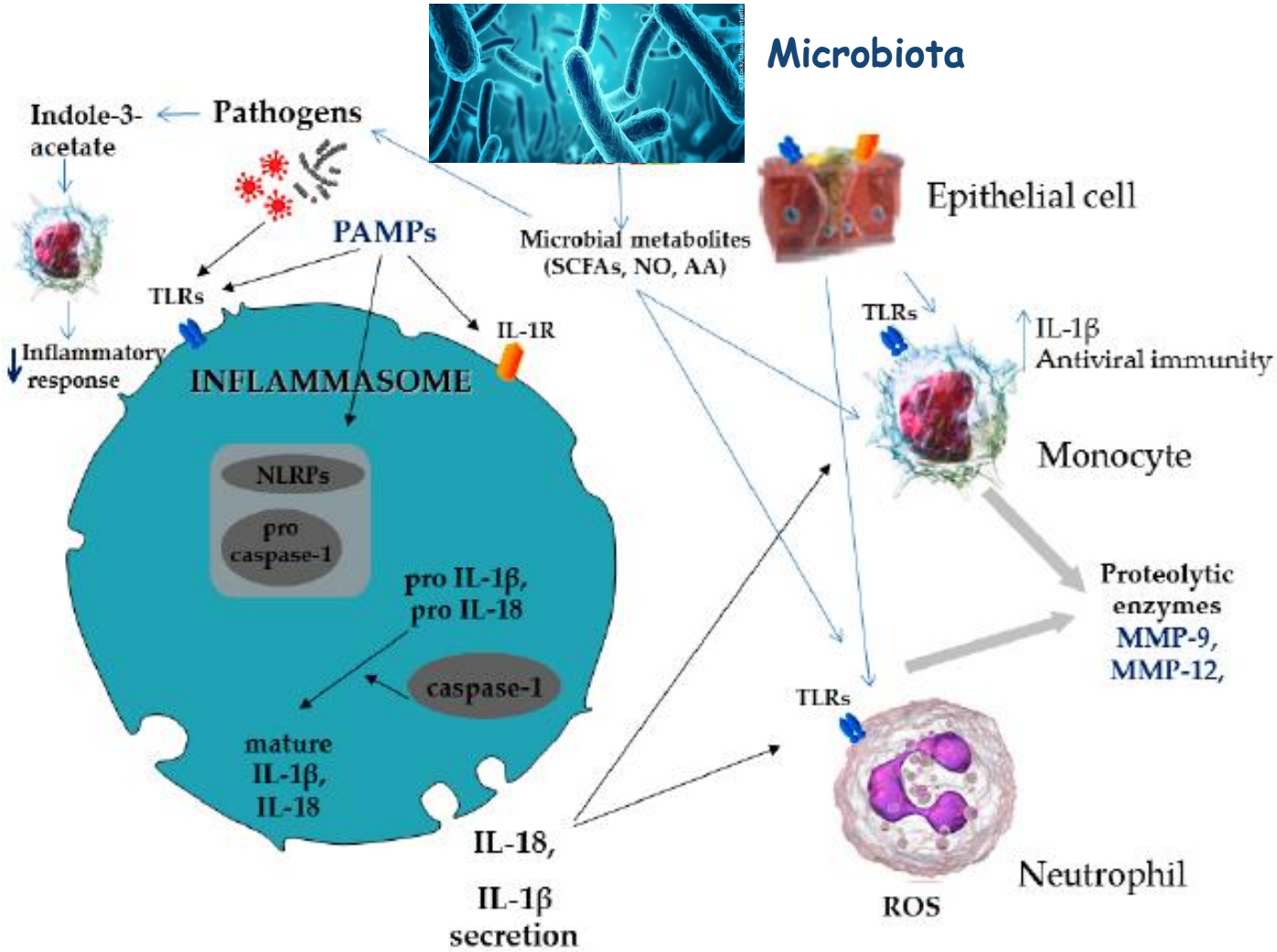


Han KM, et al. Thorax. 2012;67(5):456-463
Erb-Downward JR, et al. PloS one. 2011; 6(2):e16384
Charlson ES, et al. PloS one. 2012; 7(9):e42786.
Charlson ES, et al. Am J Respir Crit Care Med. 2011; 184(8):957-963.

Τι αλλάζει στη νόσο;

Ο κύκλος δυσβίωσης-φλεγμονής

Η φλεγμονή επάγεται μέσω αλληλεπίδρασης των μοριακών προτύπων αναγνώρισης παθογόνων (PAMP) – με τους υποδοχείς προτύπων αναγνώρισης (PRR) στέλνοντας σήματα σε διάφορα μονοπάτια

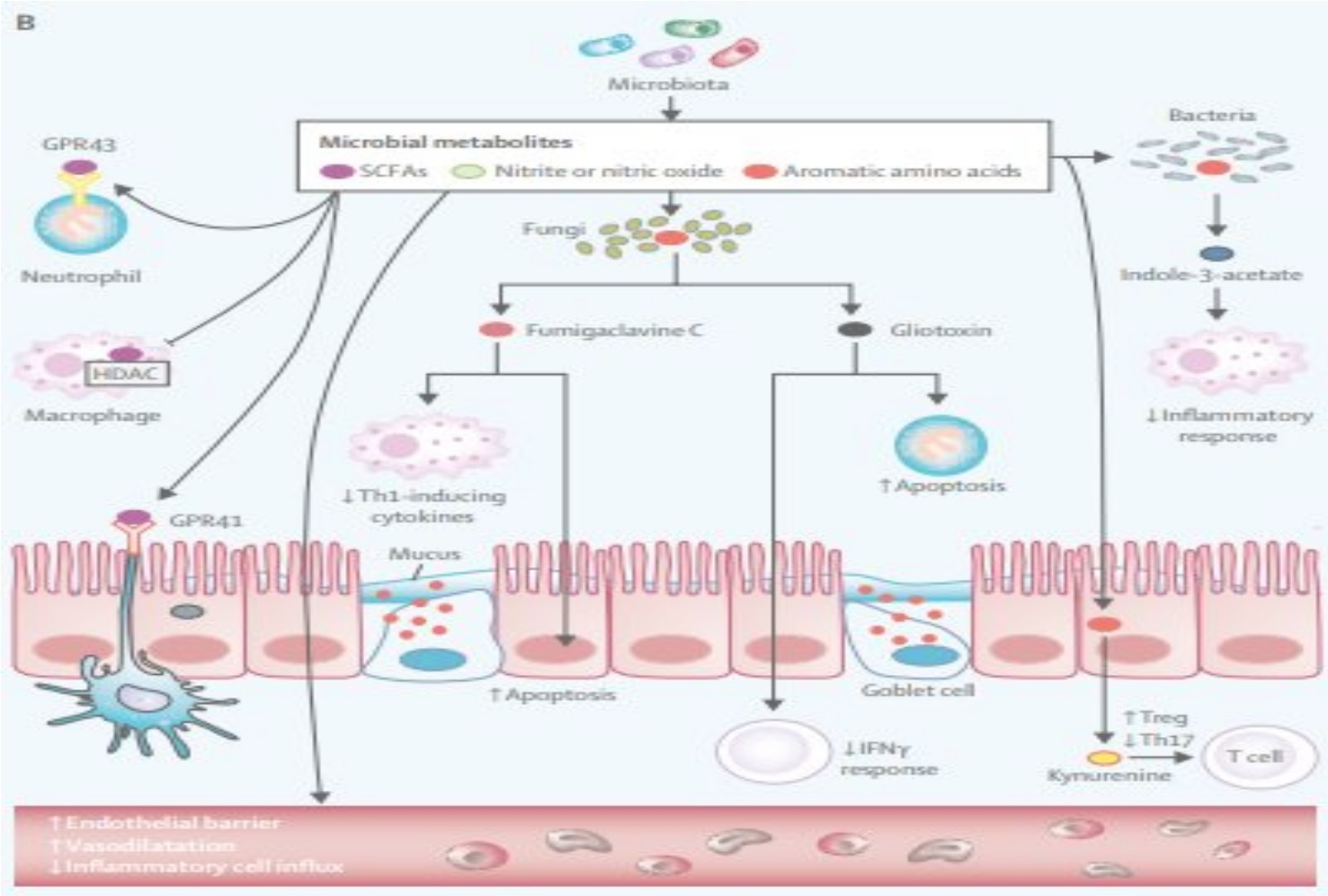


Loverdos et al. Clin. Med. **2019**, *8*(11), 1967

The microbiome in respiratory disease 2

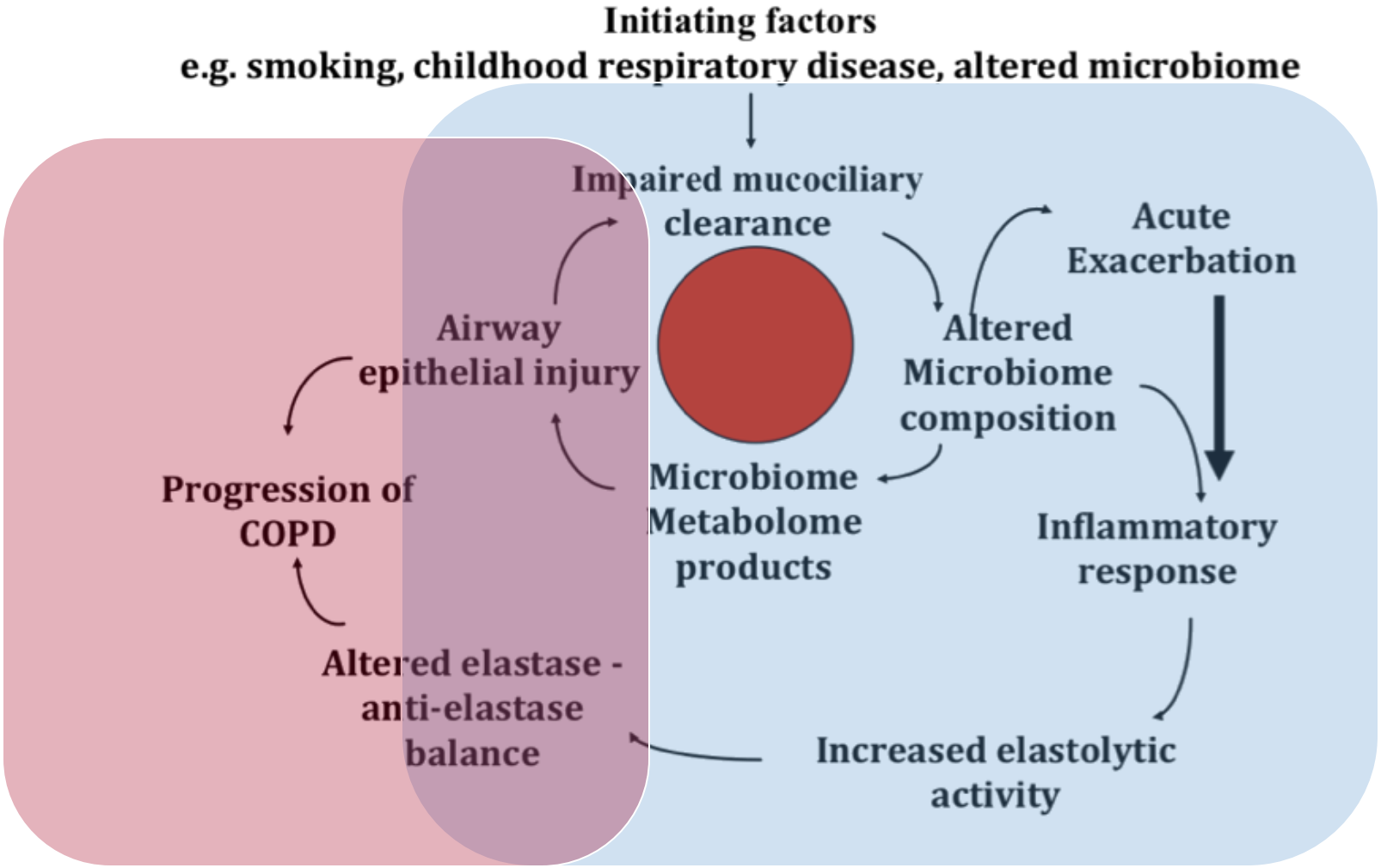
Functional effects of the microbiota in chronic respiratory disease

Kurtis F Budden*, Shakti D Shukla*, Saima Firdous Rehman, Kate L Bowerman, Simon Keely, Philip Hugenholtz, Darius P H Armstrong-James, Ian M Adcock, Sanjay H Chotirmall, Kian Fan Chung, Philip M Hansbro



Lancet Respir Med. 2019 Oct;7(10):907-920

Vicious Circle Hypothesis Revised

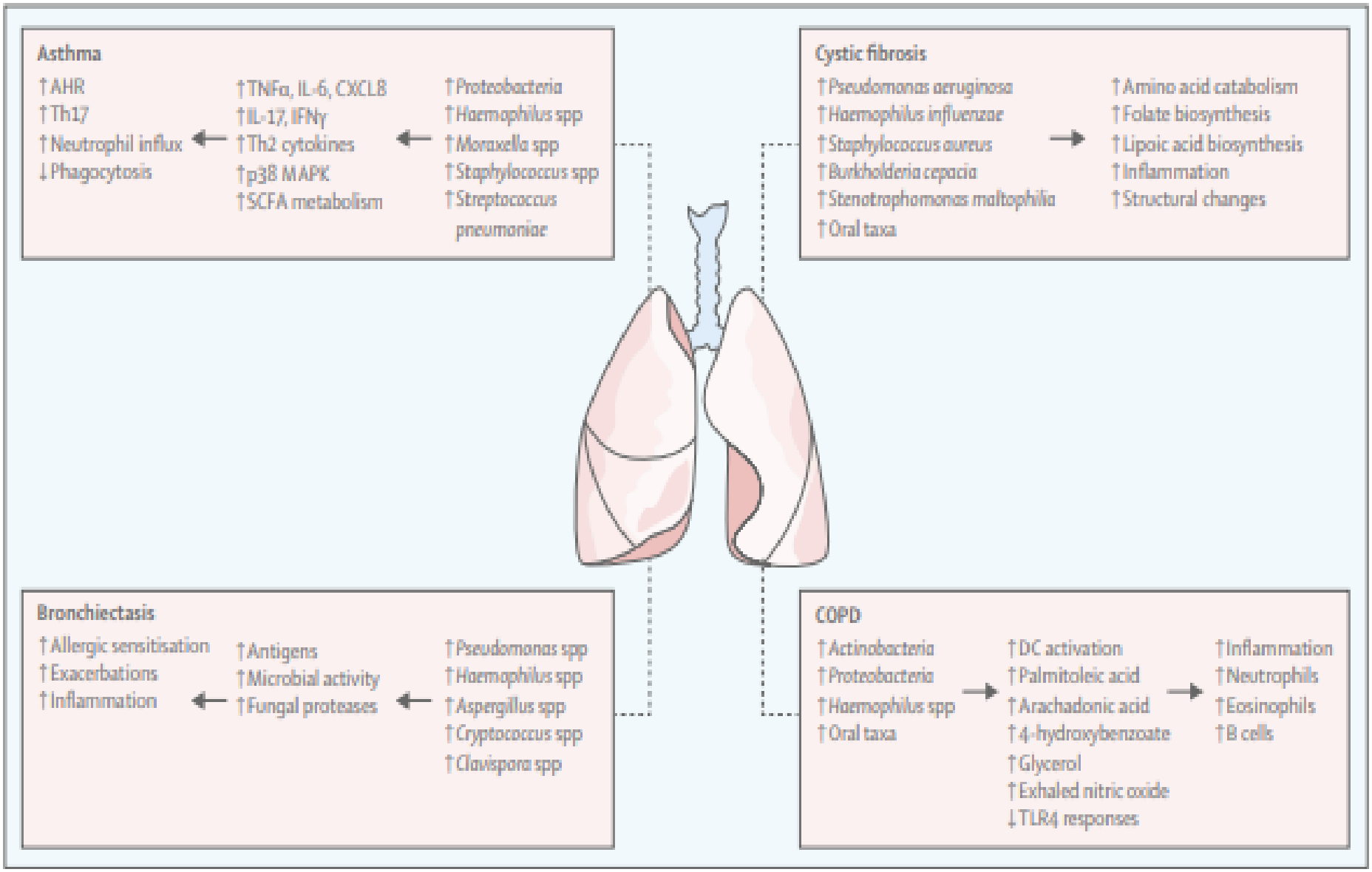


Η διαταραχή του οικοσυστήματος οδηγεί σε αλλαγή της σύστασης του μικροβιώματος, το οποίο επάγει περαιτέρω τη φλεγμονή

Sethi and Murphy NEJM 2008

Mammen and Sethi Respirology 2016

Η αλλαγή της σύστασης του μικροβιώματος επάγει περαιτέρω τη φλεγμονή



Lancet Respir Med. 2019 Oct;7(10):907-920

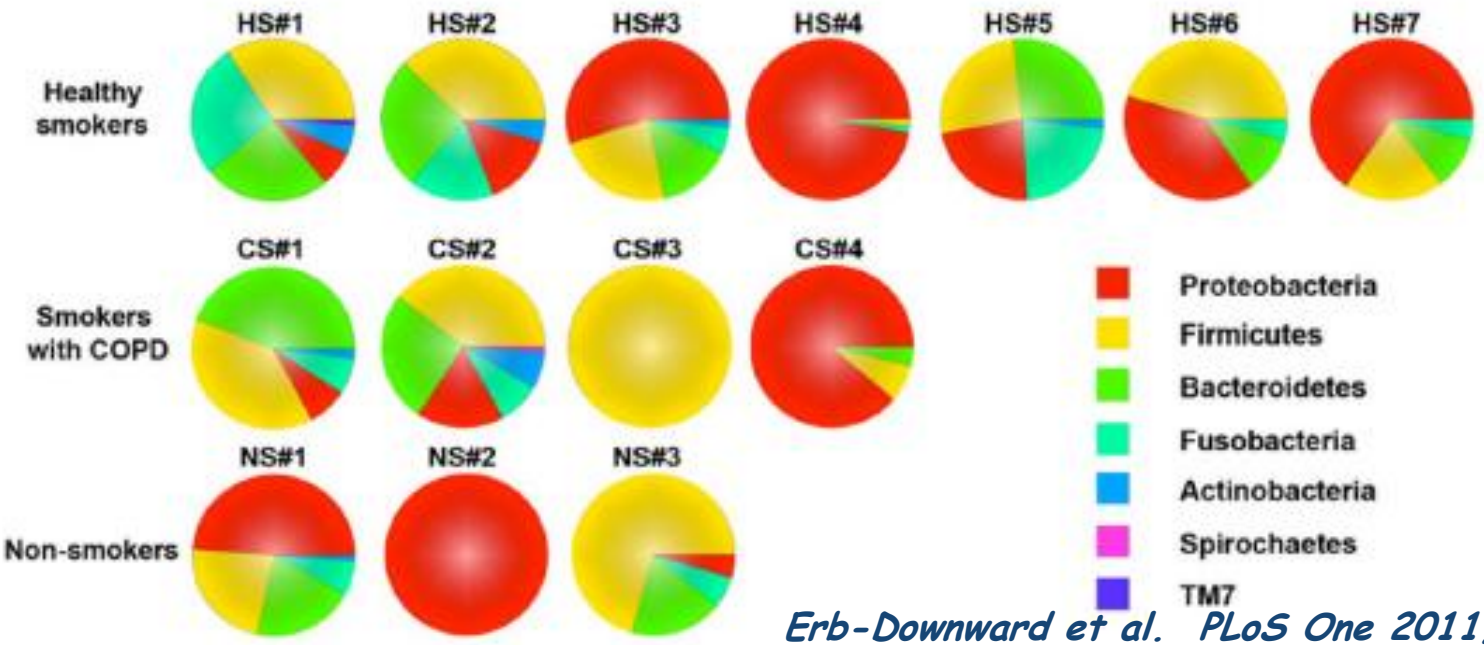
Τι συμβαίνει στις παροξύνσεις;

OPEN ACCESS Freely available online PLoS one

Analysis of the Lung Microbiome in the "Healthy" Smoker and in COPD

John R. Erb-Downward[1], Deborah L. Thompson[1], Meilan K. Han[1], Christine M. Freeman[1,2], Lisa McCloskey[1,2], Lindsay A. Schmidt[1], Vincent B. Young[1], Galen B. Toews[1,2], Jeffrey L. Curtis[1,2], Baskaran Sundaram[1], Fernando J. Martinez[1], Gary B. Huffnagle[1*]

Το μικροβιακό φορτίο αυξάνεται στους πνεύμονες στον οποίο απαντάμε διάφορες βακτηριδιακές τάξεις που δεν απαντώνται στο στοματικό βλεννογόνο. Επιλεκτικές πιέσεις στους πνεύμονες ευνοούν μάλλον την παραμονή των μικροβίων, τον αποικισμό και την ανάπτυξή τους

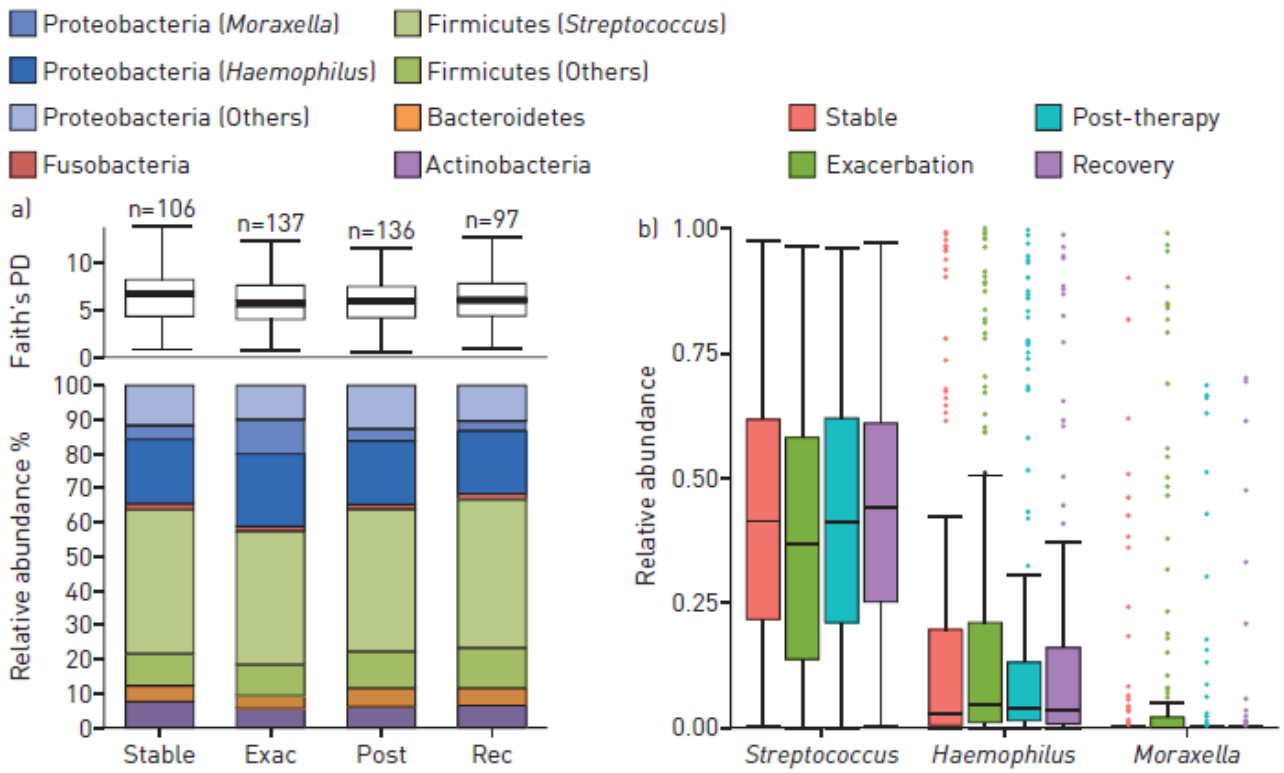


Erb-Downward et al. PLoS One 2011;6(2):e16384

Lung microbiome dynamics in COPD exacerbations

Zhang Wang[1,7], Mona Bafadhel[2,7], Koirobi Haldar[3,6], Aaron Spivak[1], David Mayhew[1], Bruce E. Miller[4], Ruth Tal-Singer[4], Sebastian L. Johnston[5], Mohammadali Yavari Ramsheh[3], Michael R. Barer[3], Christopher E. Brightling[3,6,8] and James R. Brown[1,8]

16S ribosomal RNA survey of the lung microbiome on 476 sputum samples collected from 87 subjects with COPD at four visits defined as stable state, exacerbation, 2 weeks post-therapy and 6 weeks recovery



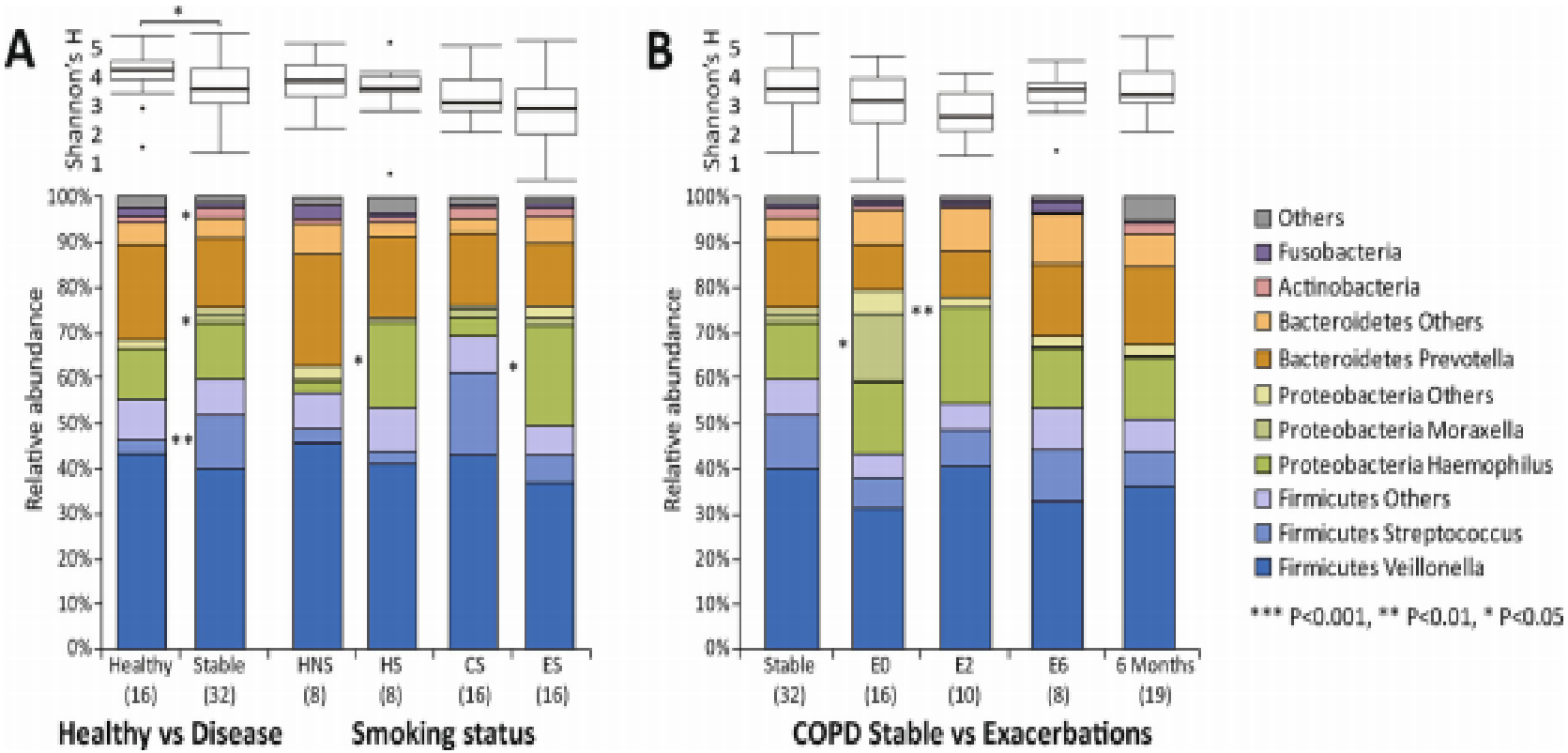
Dysbiosis of sputum microbiome was observed with significantly increased relative **abundance of Moraxella in COPD** versus healthy subjects and during **COPD exacerbations**

Eur Respir J 2016; 47: 1082-1092

Airway host-microbiome interactions in chronic obstructive pulmonary disease

Zhang Wang[1,2], Barbara Maschera[3], Simon Lea[4], Umme Kolsum[4], David Michalovich[3], Stephanie Van Horn[5], Christopher Traini[5], James R. Brown[1*], Edith M. Hessel[3†] and Dave Singh[4†]

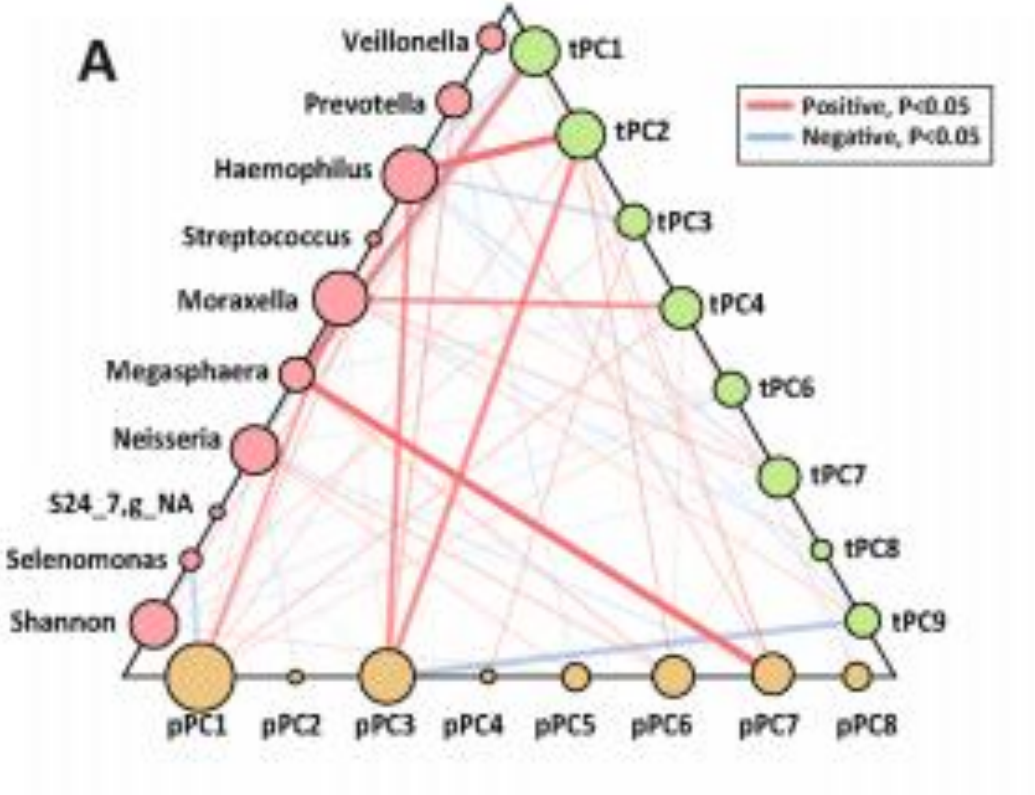
Moraxella-associated host responses were primarily related to exacerbations



Respir Res. 2019 Jun 6;20(1):113

Airway host-microbiome interactions in chronic obstructive pulmonary disease

Zhang Wang[1,2], Barbara Maschera[3], Simon Lea[4], Umme Kolsum[4], David Michalovich[3], Stephanie Van Horn[5], Christopher Traini[5], James R. Brown[1*], Edith M. Hessel[3†] and Dave Singh[4†]



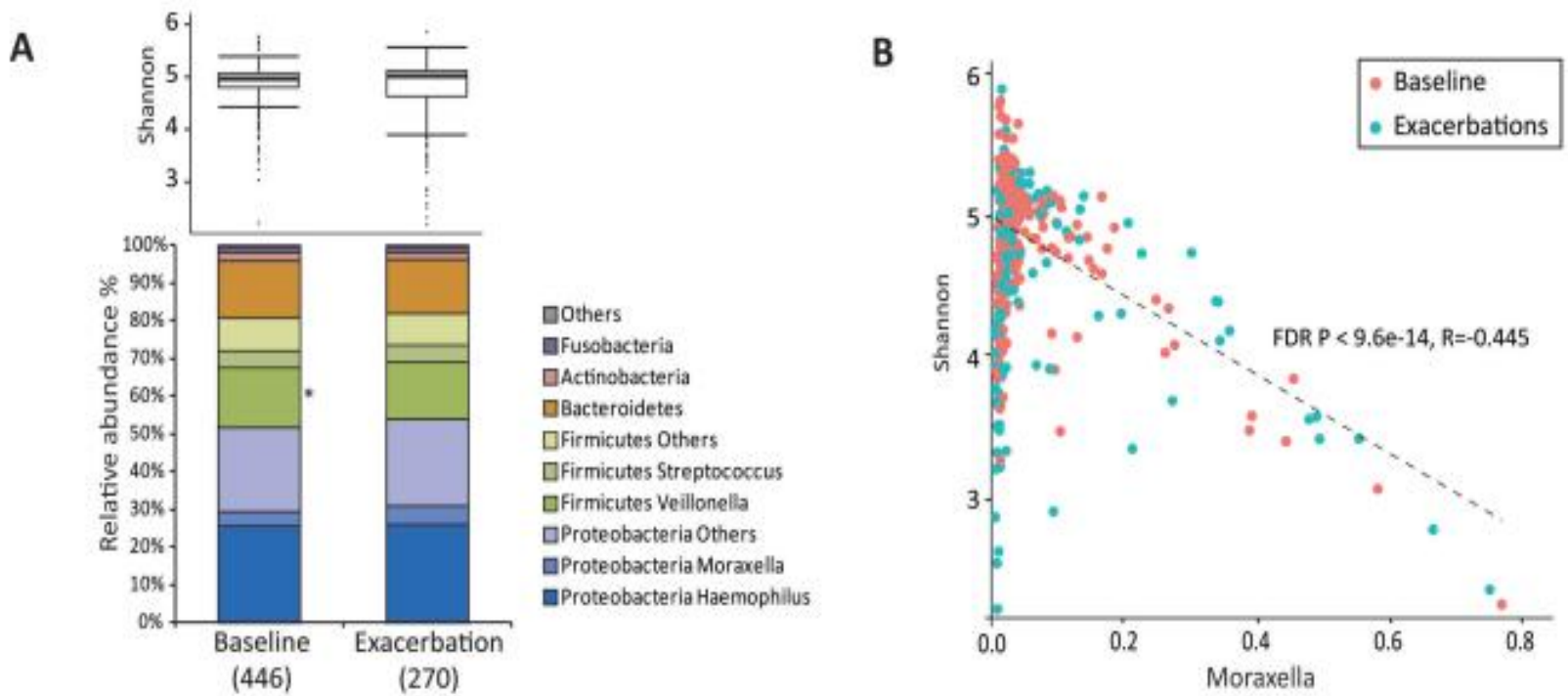
Multivariate modeling on sputum microbiome, host transcriptome and proteome profiles revealed that **significant associations between Moraxella and Haemophilus, host interferon and pro-inflammatory signaling pathways and neutrophilic inflammation**

Respir Res. 2019 Jun 6;20(1):113

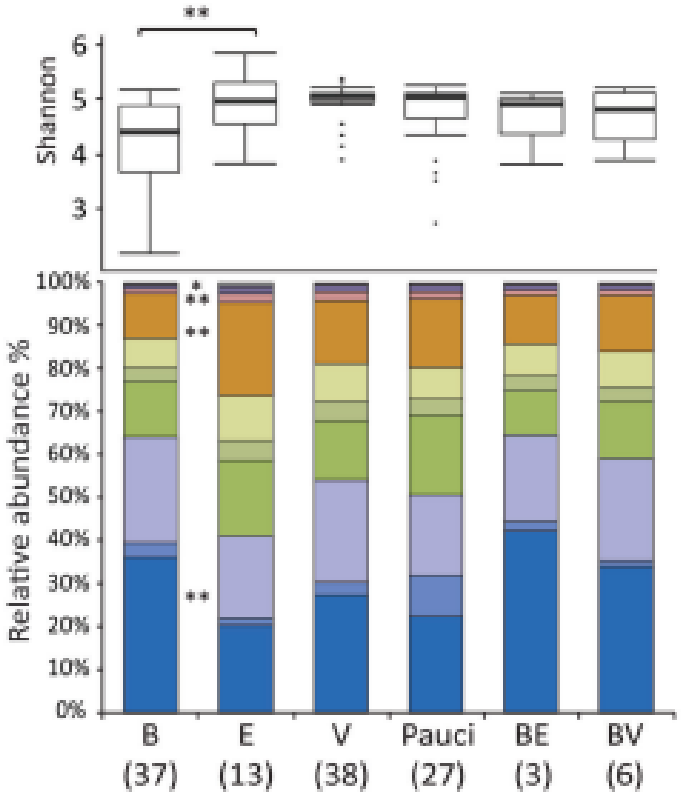
THORAX

Sputum microbiome temporal variability and dysbiosis in chronic obstructive pulmonary disease exacerbations: an analysis of the COPDMAP study

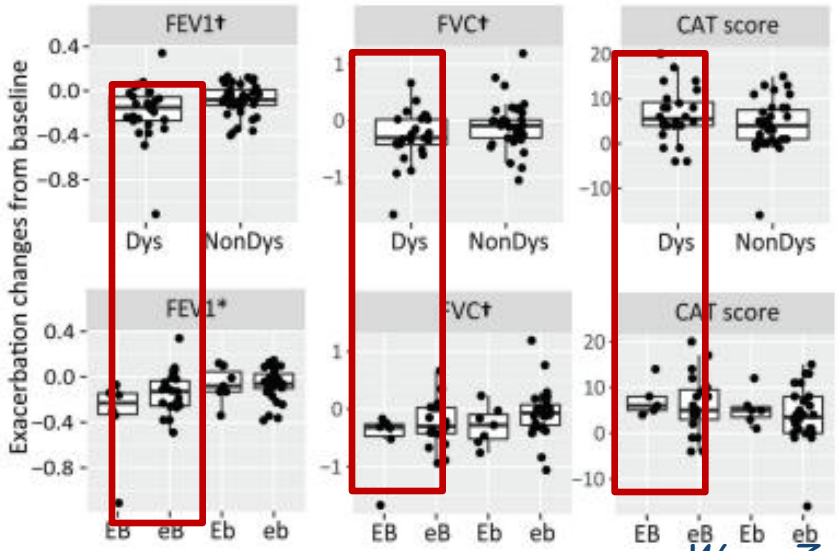
Zhang Wang, Richa Singh, Bruce E Miller, Ruth Tal-Singer, Stephanie Van Horn, Lynn Tomsho, Alexander Mackay, James P Allinson, Adam J Webb, Anthony J Brookes, Leena M George, Bethan Barker, Umme Kolsum, Louise E Donnelly, Kylie Belchamber, Peter J Barnes, Dave Singh, Christopher E Brightling, Gavin C Donaldson, Jadwiga A Wedzicha and James R Brown



Wang Z, et al. Thorax 2017;0:1-8.



Microbial dysbiosis is a feature of **some exacerbations** and its presence, especially in concert with **eosinophilic inflammation**, is associated with **more severe exacerbations** indicated by a **greater fall in lung function**

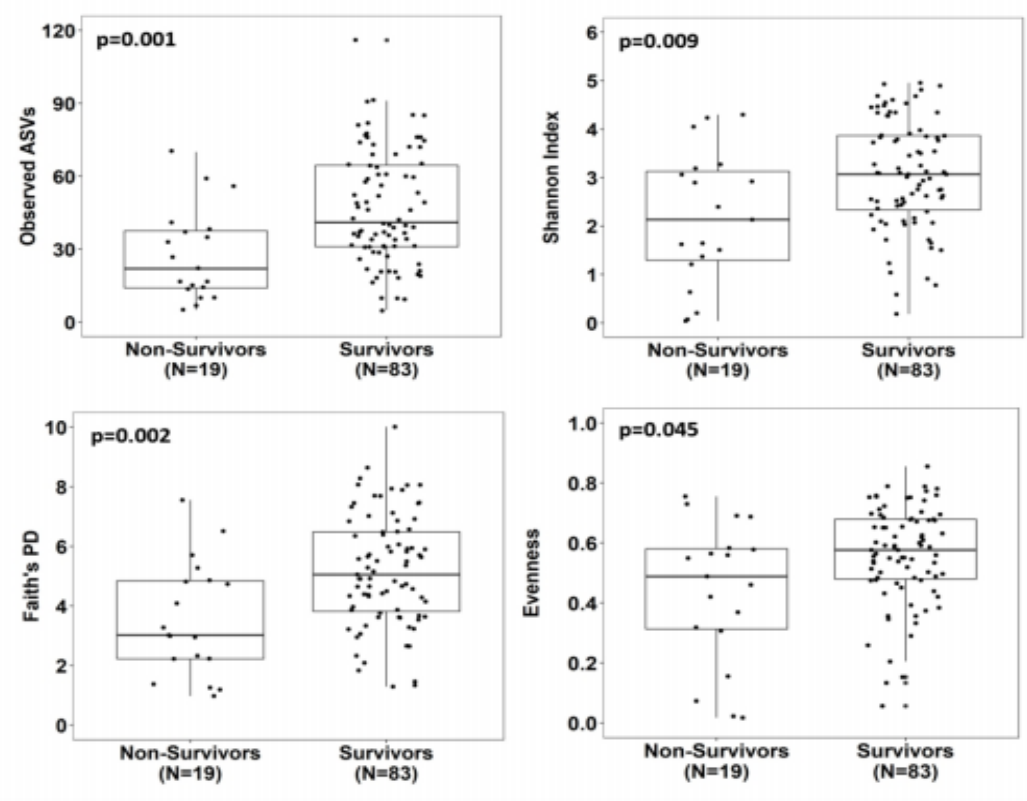


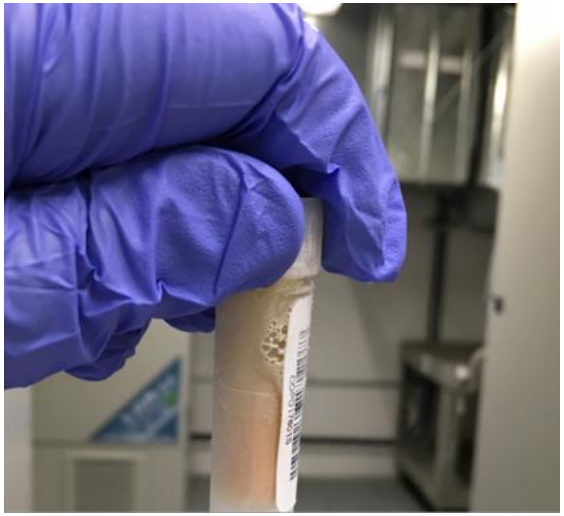
Dys: Dysbiosis
NonDys: Non-Dysbiosis
† 0.05 < P < 0.1
* P < 0.05

EB: Eosinophil+Dysbiosis
eB: Non-eosinophil+Dysbiosis
Eb: Eosinophil+Non-dysbiosis
eb: Non-eosinophil+Non-dysbiosis

Wang Z, et al. Thorax 2017;0:1-8.

Sputum Microbiome is Associated With 1-Year Mortality Following COPD Hospitalizations

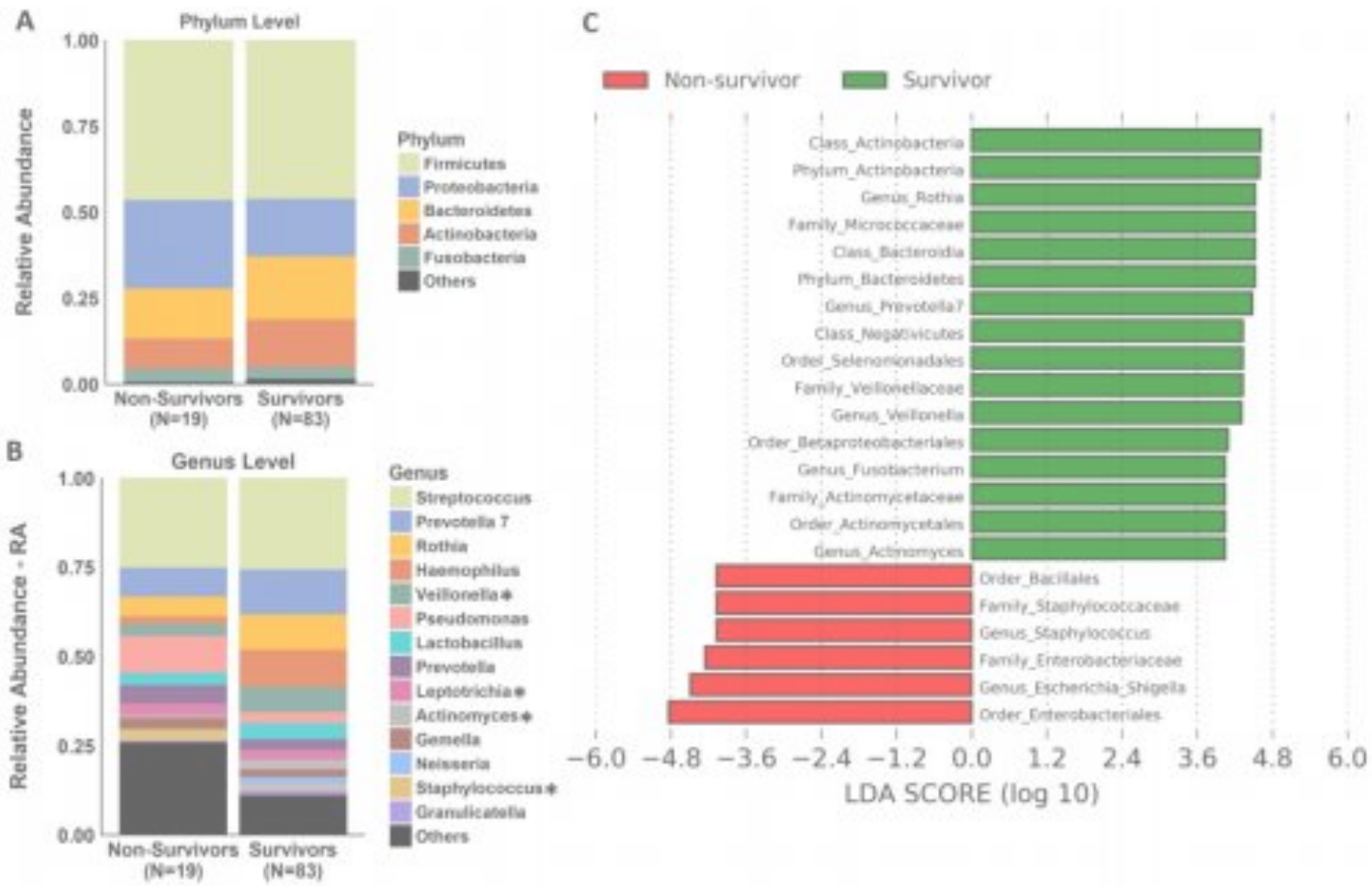




Significantly lower values of alpha diversity (Richness, Shannon Index, Evenness, and Faith's Phylogenetic Diversity) among non-survivors (n=19, 18.6%) compared to survivors (n=83, 81.4%).

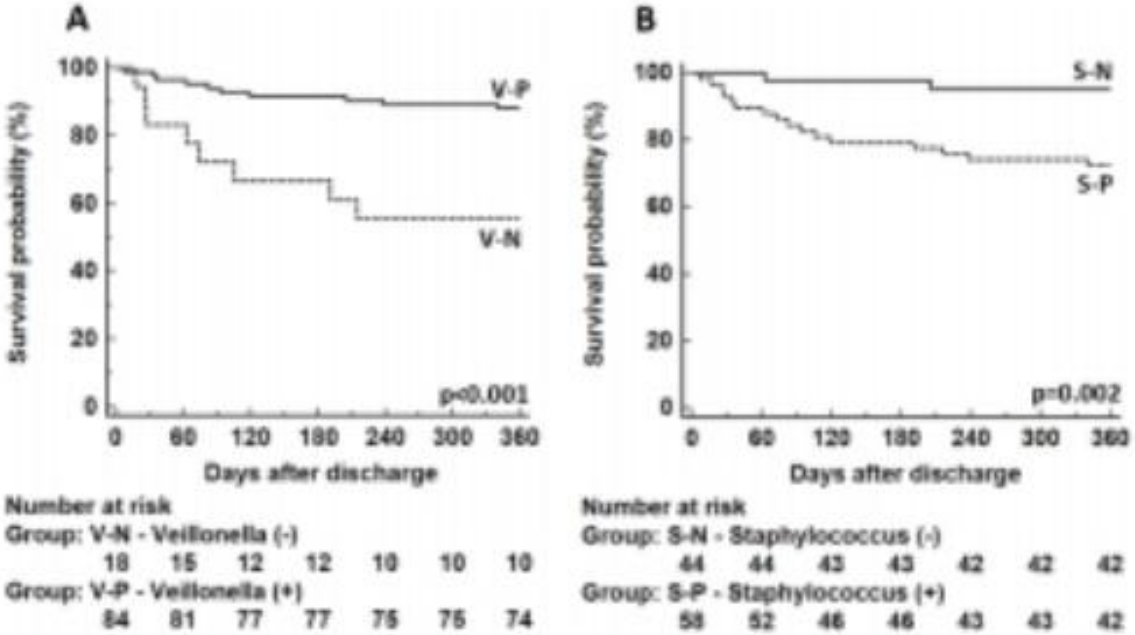
Am J Respir Crit Care Med. 2019 May15;199(10):1205-1213

Veillonella, Actinomyces, and Leptotrichia showed a higher relative abundance in survivors, whereas Staphylococcus predominated in non-survivors.



Am J Respir Crit Care Med. 2019 May15;199(10):1205-1213

Lower survival among patients in whom sputum samples were negative for Veillonella (HR: 13.5, 95% CI: 4.2 – 43.9, p<0.001) or positive for Staphylococcus (HR: 7.3, 95% CI: 1.6 – 33.2, p=0.01)



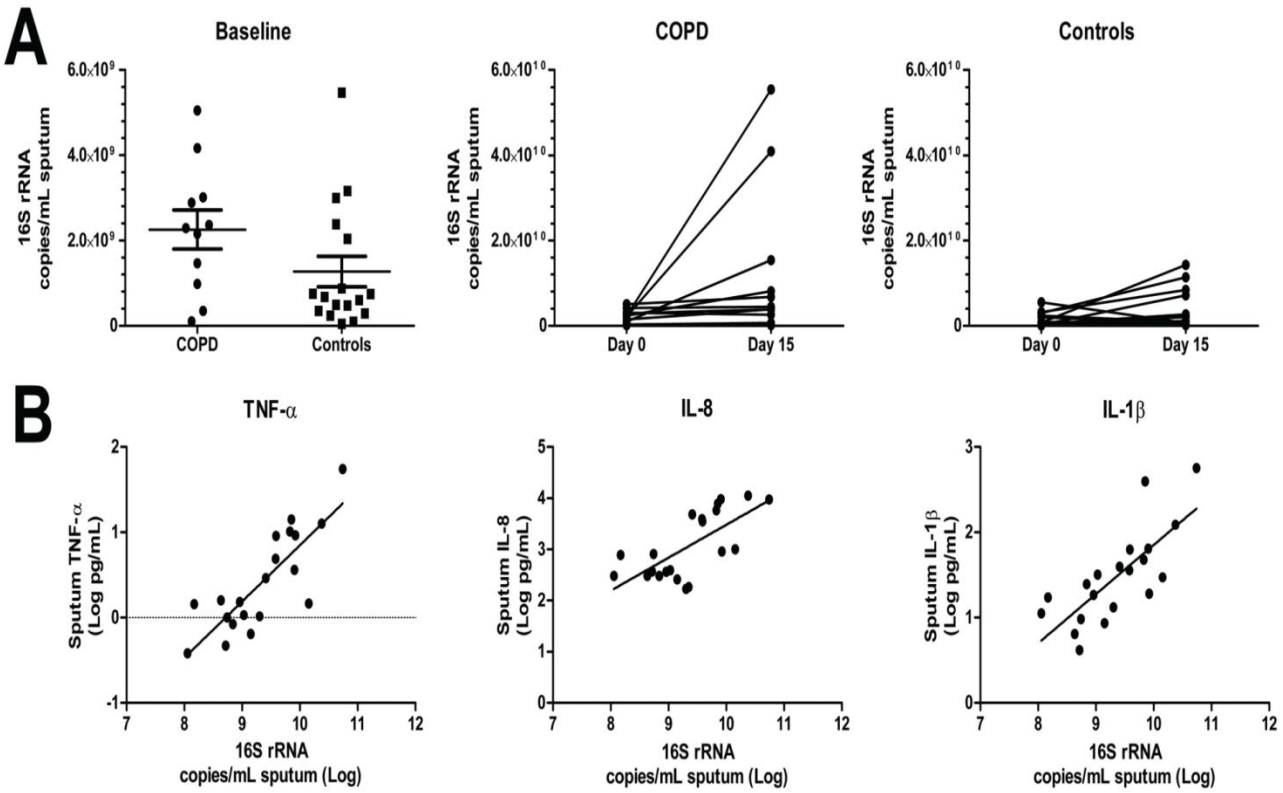
The microbiome profile of sputum in AECOPD is associated with 1-year mortality and may be used to identify subjects with a poor prognosis at the time of hospitalization

Am J Respir Crit Care Med. 2019 May15;199(10):1205-1213

Outgrowth of the Bacterial Airway Microbiome after Rhinovirus Exacerbation of Chronic Obstructive Pulmonary Disease

Philip L. Molyneaux[1,2], Patrick Mallia[1,2,3], Michael J. Cox[1,2], Joseph Footitt[1,2,3†], Saffron A. G. Willis-Owen[1], Daniel Homola[1], Maria-Belen Trujillo-Torralbo[1,2,3], Sarah Elkin[1,3], Onn Min Kon[1,2,3], William O. C. Cookson[1,2], Miriam F. Moffatt[1,2*], and Sebastian L. Johnston[1,2,3*]

After rhinovirus infection, there is a rise in bacterial burden and a significant outgrowth of Haemophilus influenzae from the existing microbiota of subjects with COPD

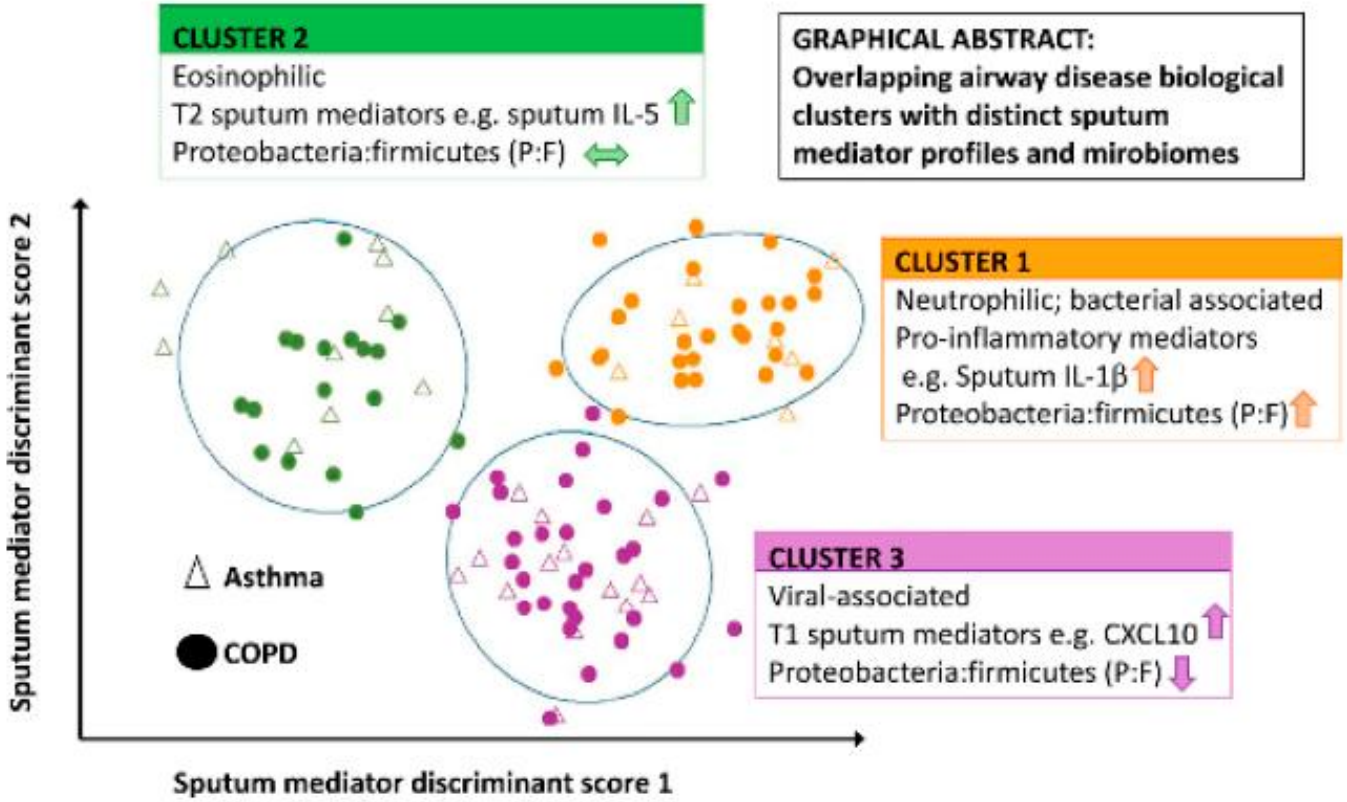


Am J Respir Crit Care Med. 2013 Aug 30

Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles

Check for updates

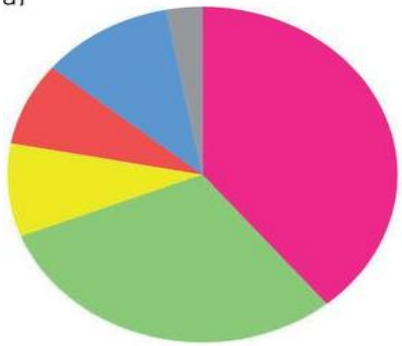
32 asthmatic patients and 73 patients with COPD assessed at exacerbation



Ghebre et al. Allergy Clin. Immunol. **2018**, 141, 2027–2036

ΒΡΟΓΧΕΚΤΑΣΙΕΣ

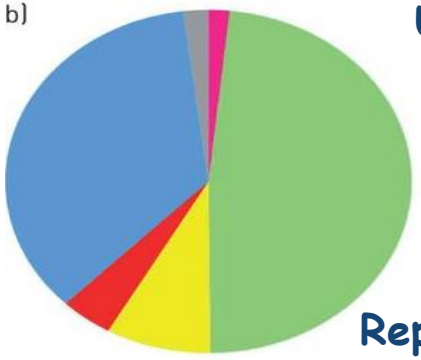
a)



European cohort study

- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Moraxella catarrhalis*
- Enterobacteriaceae
- NTM

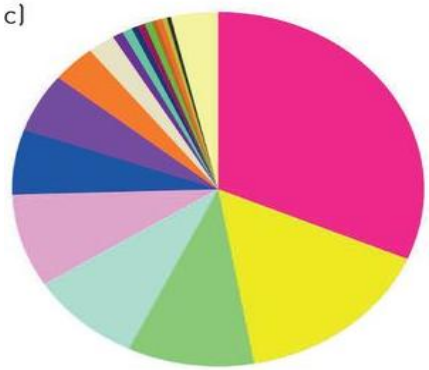
b)



US Bronchiectasis Registry

- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Moraxella catarrhalis*
- Enterobacteriaceae
- NTM

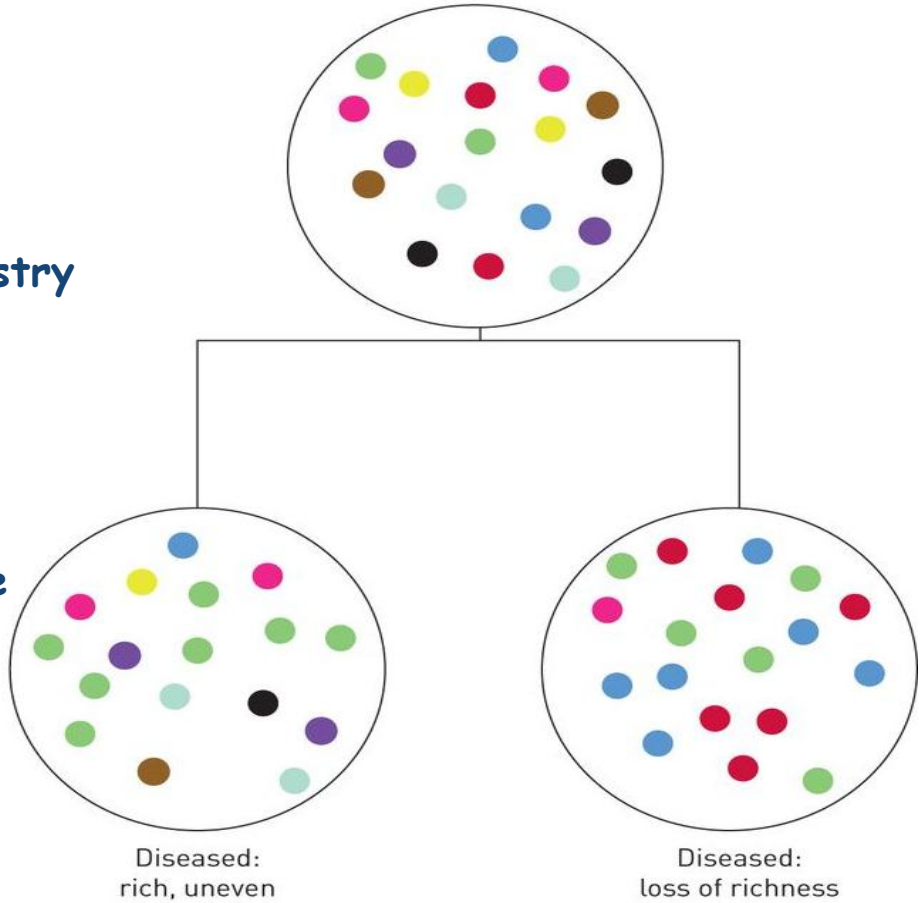
c)



Representative microbiome profile

- *Haemophilus influenzae*
- *Streptococcus*
- *Pseudomonas*
- *Prevotella*
- Gemellaceae
- *Neisseria*
- *Porphyromonas*
- *Veillonella*
- *Granulicatella*
- *Rothia*
- *Fusobacterium*
- *Aggregatibacter*

d)

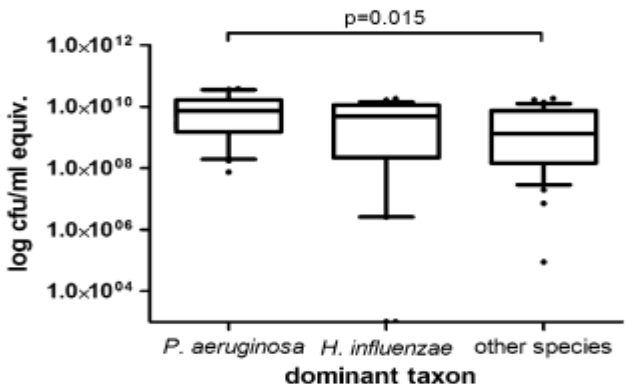


Richardson et al. Eur Respir Rev. 2019 Sep 4;28(153)

A Novel Microbiota Stratification System Predicts Future Exacerbations in Bronchiectasis

Geraint B. Rogers[1], Nur Masirah M. Zain[2], Kenneth D. Bruce[2*], Lucy D. Burr[1], Alice C. Chen[1], Damian W. Rivett[3], Michael A. McGuckin[1], and David J. Serisier[1,4*]

	n	Dominant Species Relative Abundance (%)	
		Median	IQR
All samples	96	82.1	52.3
Pseudomonas aeruginosa dominated	26	92.4	14.2
Haemophilus influenzae dominated	34	96.2	9.2
Dominated by another genus	36	37.6	26.0
Veillonella spp. dominated	10	35.4	12.2
Prevotella spp. dominated	9	36.8	19.8



Clinical Measure	Spearman's ρ	Significance (P *Value*)
Pre-BD FEV_1	−0.225	0.027
Post-BD FEV_1	−0.223	0.029
Bronchiectasis duration, yr	0.221	0.031
CRP	0.306	0.003
Sputum IL-8	0.585	<0.001
Sputum IL-1β	0.626	<0.001
Sputum neutrophils, absolute	0.240	0.031
Sputum neutrophils, %	0.347	0.001
Sputum macrophages, absolute	−0.340	0.002
Sputum macrophages, %	−0.389	<0.001
24-h sputum volume, g	0.370	0.002

Ann Am Thorac Soc. 2014 May;11(4):496-503

IPF

The Microbiome is Substantially Changed in IPF Lungs

COMET study[1]

Disease progression and increased mortality is associated with the presence of specific members of the Staphylococcus and Streptococcus genera and a shift in the lung microbiome (preliminary data from BAL samples)

Molyneaux et al.[2]

Confirmation of COMET: increased bacterial burden in BAL predicts decline in lung function and death

The lung microbiome is correlated with disease progression and is a biomarker for disease severity

Boehringer Ingelheim

1. Han M. K, et al. *Lancet Respir Med*. 2014;2(7):548-56.
2. Molyneaux P. L, et al. *AJRCCM*. 2014;190(8):906-13.

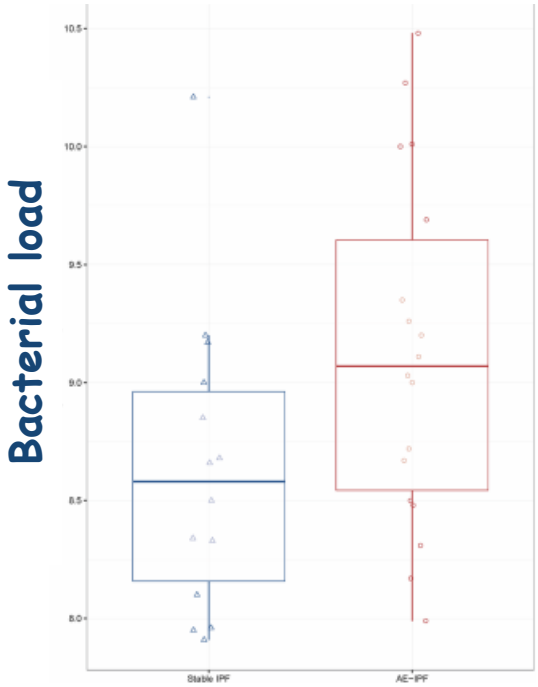
BAL = bronchoalveolar lavage

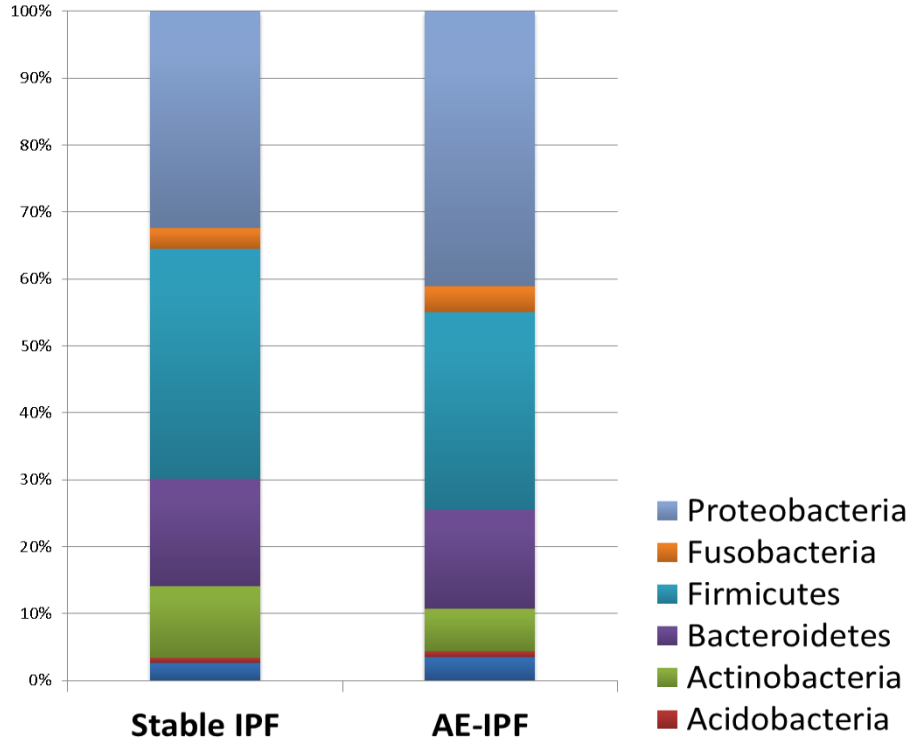
ATS Highlights 2015 Slide Kit. Sponsored by Boehringer Ingelheim; not reviewed or approved by ATS.

LETTER TO THE EDITOR Open Access

Changes in the respiratory microbiome during acute exacerbations of idiopathic pulmonary fibrosis

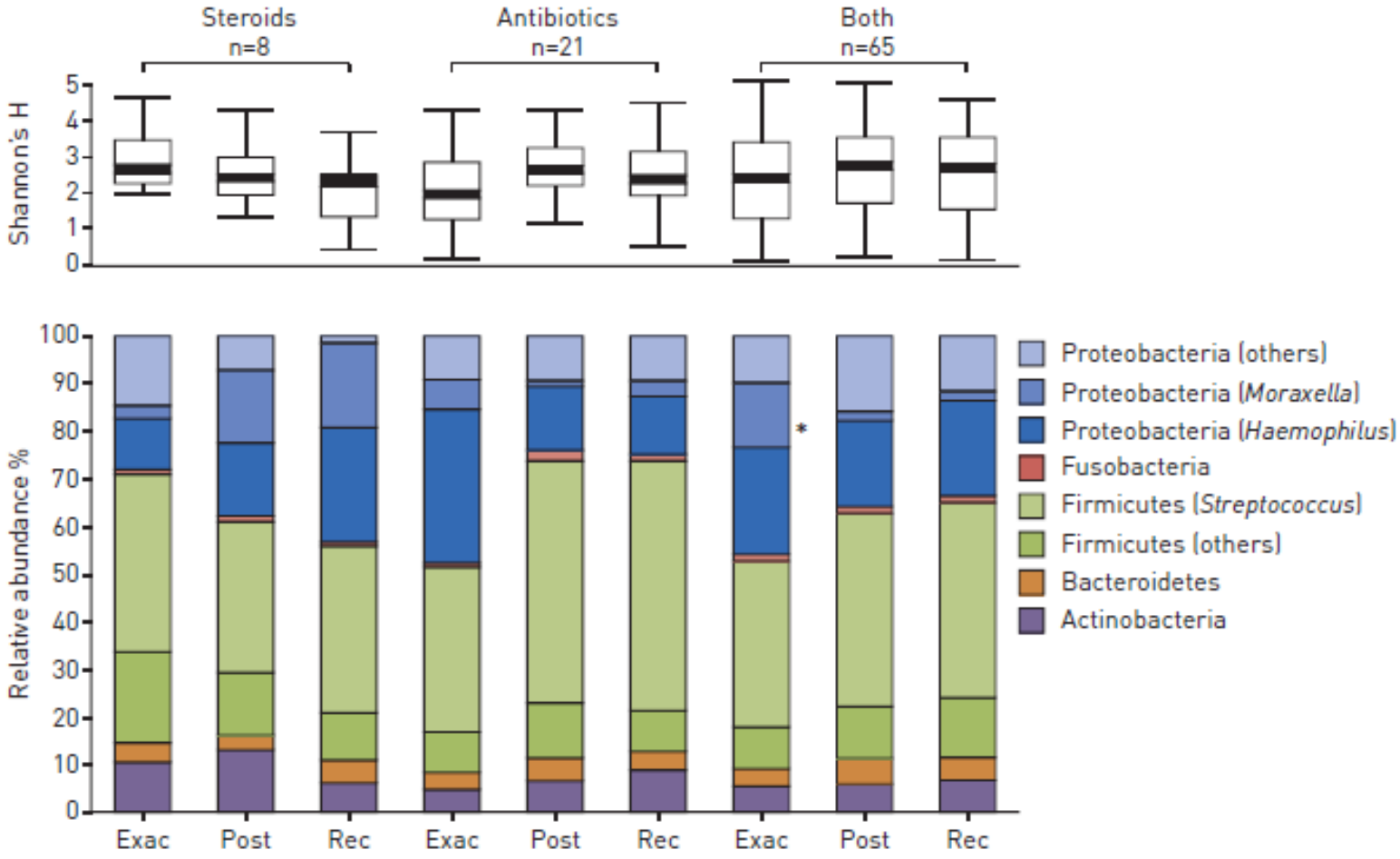
Philip L. Molyneaux[1,2], Michael J Cox[1], Athol U. Wells[2], Ho Cheol Kim[3], Wonjun Ji[3], William O. C. Cookson[1], Miriam F. Moffatt[1], Dong Soon Kim[3†] and Toby M. Maher[1,2,4*†]





Αντιμετώπιση παροξύνσεων και μικροβίωμα

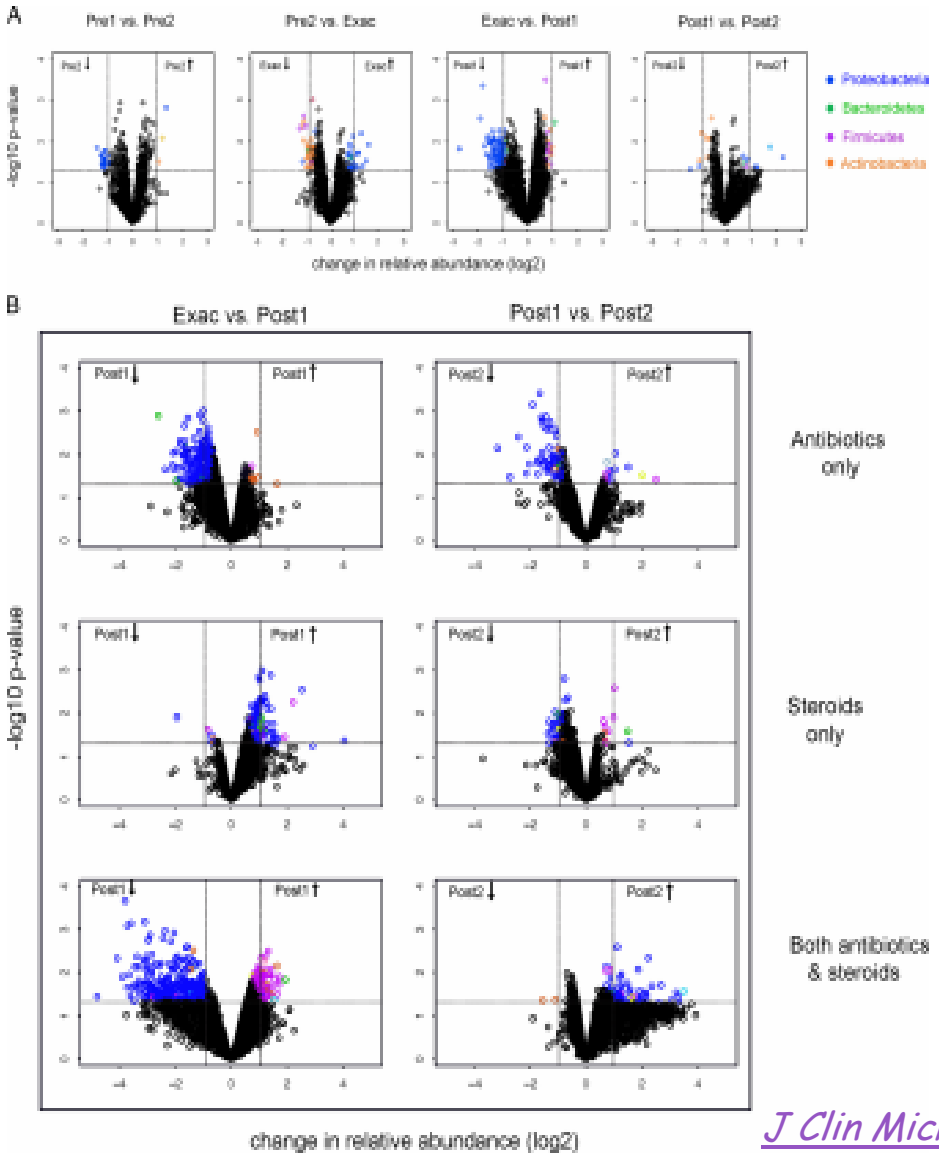
Επίδραση θεραπείας με αντιβιοτικά, στεροειδή ή συνδυασμό



Eur Respir J 2016; 47: 1082-1092

Airway Microbiome Dynamics in Exacerbations of Chronic Obstructive Pulmonary Disease

Yvonne J. Huang,[a] Sanjay Sethi,[b,c] Timothy Murphy,[c] Snehal Nariya,[a] Homer A. Boushey,[a] Susan V. Lynch[d]



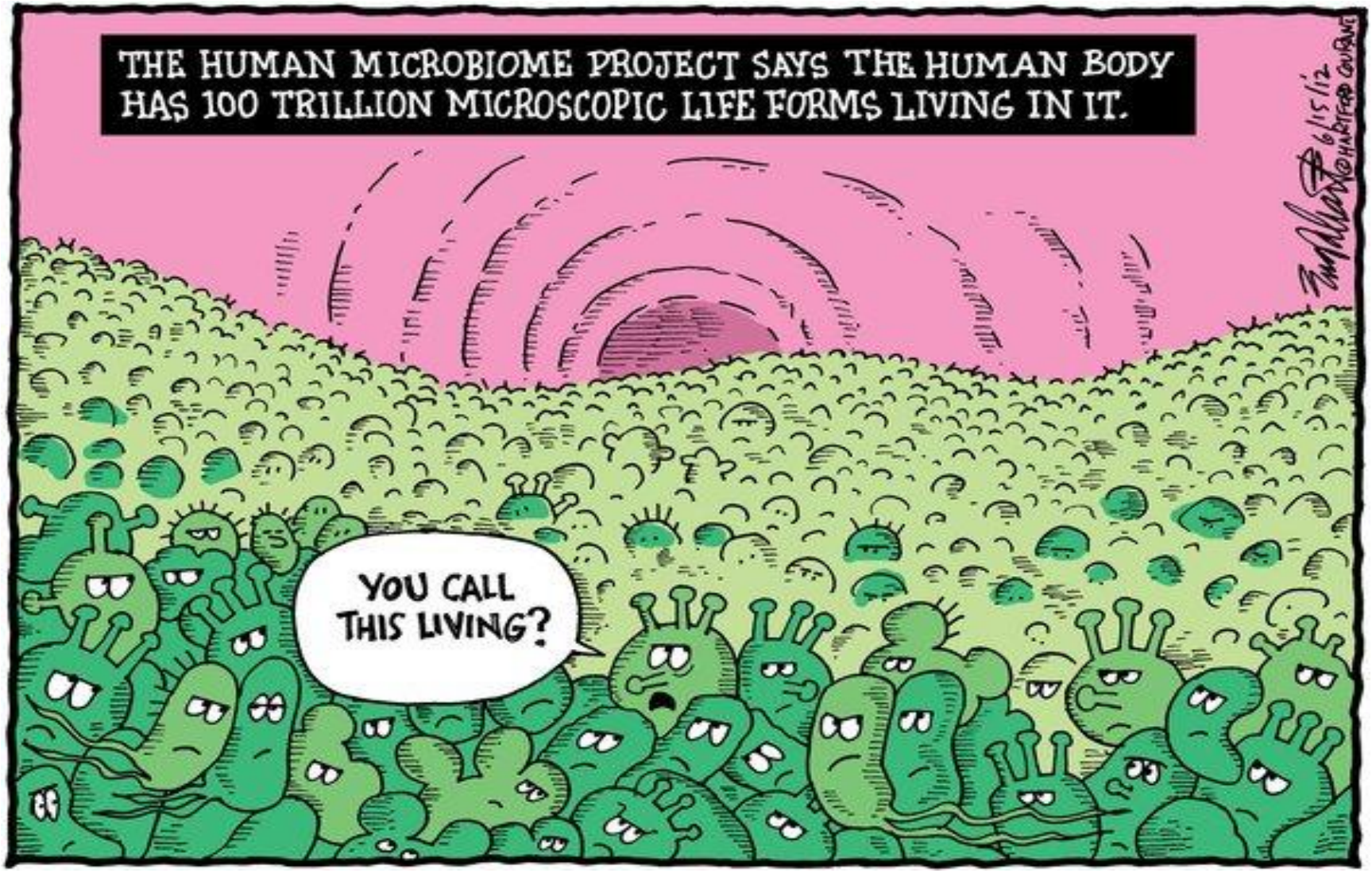
J Clin Microbiol. 2014 Aug;52(8):2813-23

Κλείνοντας..

- Η χρήση τεχνικών ανεξάρτητων της καλλιέργειας για την ταυτοποίηση των μικροβίων έχει διευρύνει την κατανόησή μας για τους ρόλους που παίζουν τα βακτήρια στις παροξύνσεις των χρόνιων αναπνευστικών νόσων

- Οι παροξύνσεις δεν είναι βακτηριδιακές λοιμώξεις των αεραγωγών, αλλά μάλλον περιστάσεις αναπνευστικής δυσβίωσης, αποδιοργάνωσης και δυσλειτουργίας του μικροβιακού οικοσυστήματος που πυροδοτεί περαιτέρω δυσλειτουργία της ανοσολογικής απάντησης και περαιτέρω δυσβίωση

- Έχει μεγάλη κλινική σημασία να διερευνηθεί ποια χαρακτηριστικά του αναπνευστικού μικροβιώματος συσχετίζονται με επόμενες παροξύνσεις και ποιοι θεραπευτικοί χειρισμοί που στοχεύουν στο μικροβίωμα μπορούν να είναι αποτελεσματικοί στη μείωση του ρυθμού τους



Ευχαριστώ για την προσοχή σας!