Concept of Lung microbiome – role in health and disease

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- What is Microbiome?
- Methods to study.
- Healthy lung Microbiome.
- Factors influencing.
- Alterations in a diseased state.
- Recent interest in Fungal Microbiome and effect on disease phenotype.

What is Microbiome?

- **Microbiome -** The community of microbes and their gene content in an enviroment niche.

- **Virome** – The Viral microbiome.

- **Mycobiome** – The Fungal microbiome.

Introduction

- The Lung for decades considered sterile.
- Actually , NOT !
- Bacterial burden enhances risk of exacerbations and disease progression.
- Host pathogen interaction believed to affect disease course .
- Host immune response believed to shape the Microbiome.
- So interest in the role of microorganisms residing in mucosal sites (i.e., Microbiome) and the associated host immune response has emerged.

Some relevant terminology

- **Operational taxonomic unit (OTU) –** closely related gene sequences to represent a unit of bacteria (taxon) – 16sRNA sequence clusters sharing 97% sequence identity.

- **Taxon –** grouping of microbes at a taxonomic level such as genus or species.

- **Richness –** number of different taxa in a community.

- **Evenness –** equality of distribution among taxa in a community.

- **Alpha diversity** : the within sample diversity that incorporates both richness and evenness – within sample measurement of how many distinct microbes are present and how evenly they are distributed.

- **Beta diversity** : compositional differences between two or more microbial communities – measure of difference in composition between 2 samples.

- **Dysbiosis** – deviation from normal healthy microbiome

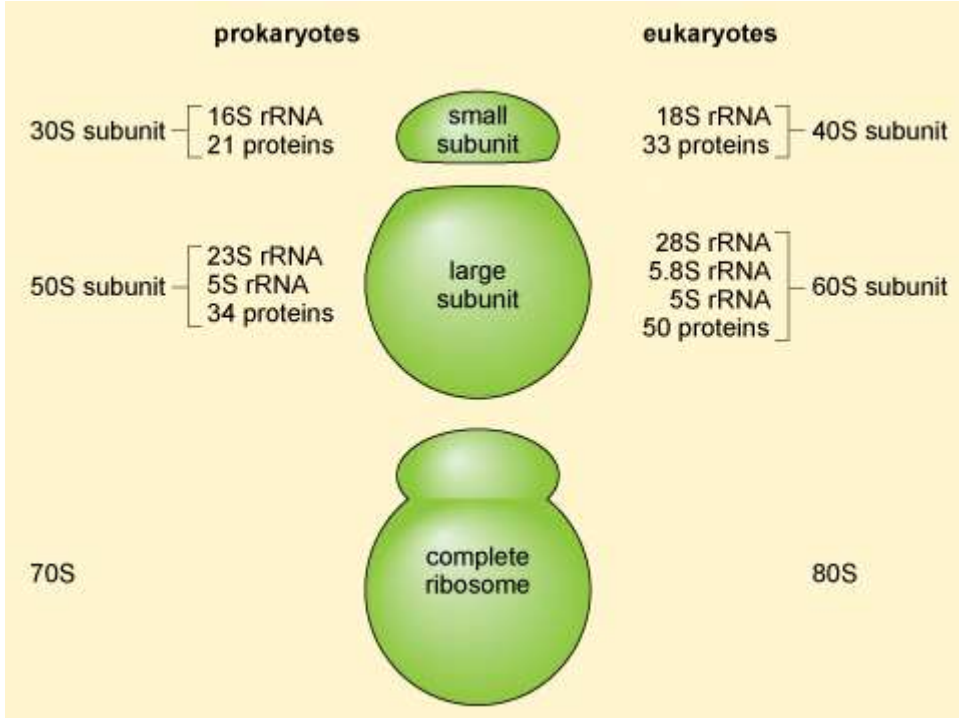
Methods

- **Samples:** Sputum, BAL, Protective Specimen Brush, Lung tissue .

- **Targeted 16S rRNA gene analysis by amplification** – This 16S rRNA gene analysis is used only for bacterial identification. within the 16S rRNA are *hypervariable regions (V1-V9)* whose sequences vary between bacteria. Drawback is the inability to differentiate live & dead microbes. Identifies at genus- species level.

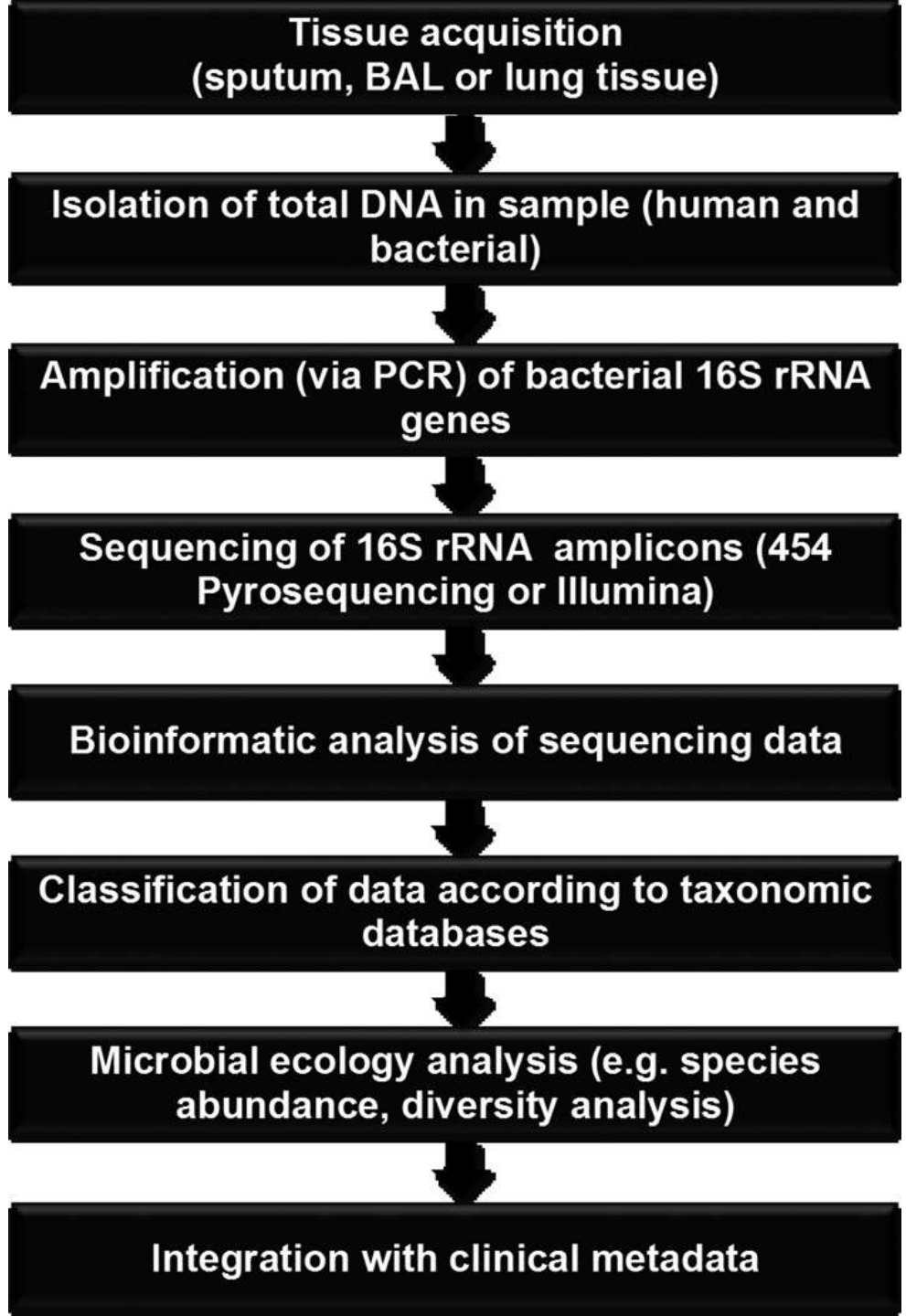
- **18SRNA and ITS (internal transcribed spacer)-** used for fungal study. 18SRNA are found in eukaryotes and in fungi.

Structure of Ribosome



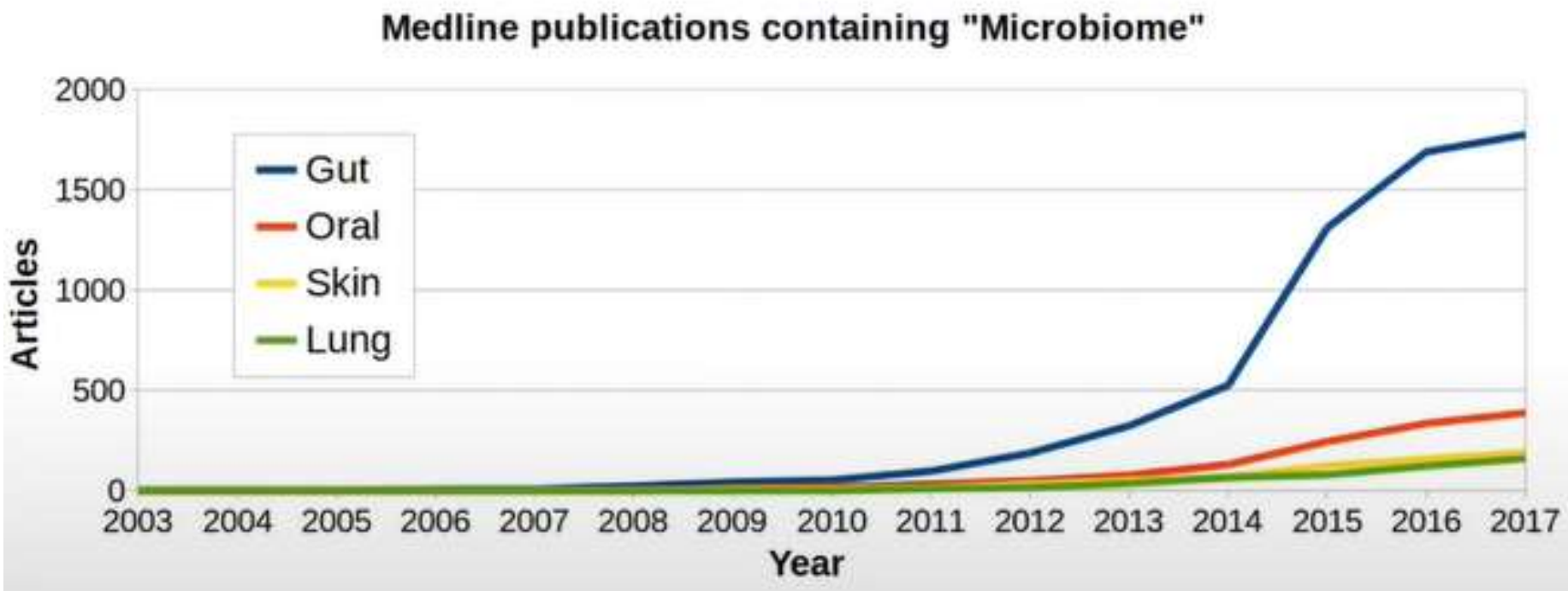
Other methods

- **Shotgun Metagenomic Sequencing** – sequencing all DNA/RNA, can be used to profile viruses/bacteria/fungi. It also helps us to understand metabolic functions/virulence/resistance. It identifies at species – strains level.
- Its drawback is the large amount of HOST DNA in sample which makes the data acquisition difficult and expensive.
- **Droplet Digital PCR**
- Culture-independent microbiological techniques based on DNA/RNA sequencing has revealed that the respiratory tract was never sterile as previously assumed for decades


Tissue acquisition
(sputum, BAL or lung tissue)
Isolation of total DNA in sample (human and bacterial)
Amplification (via PCR) of bacterial 16S rRNA genes
Sequencing of 16S rRNA amplicons (454 Pyrosequencing or Illumina)
Bioinformatic analysis of sequencing data
Classification of data according to taxonomic databases
Microbial ecology analysis (e.g. species abundance, diversity analysis)
Integration with clinical metadata

Is the lung sterile??

- Lack of microbial exposure?
- Lack of microbial metabolism?
- Lack of microbial replication?
- Lack of microbial colonization?
- Lack of studies?


Medline publications containing "Microbiome"
2000
1500
1000
500
0
Articles
Gut
Oral
Skin
Lung
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

NOW

- Who is there?
- What are they doing?
- Do they impact the host?
- HOW?
- Therapeutic interventions?

Microbiome of Healthy Lung

- Lung is contiguous with the microbe rich URT flora
- We inhale from a non sterile environment.
- The bacterial community of lungs are similar (but subtle differences) to the upper respiratory tract (URT) flora and supraglottic region.
- Found to be constant amongst healthy individuals.
- Common phyla are Bacteroidetes, Firmicutes.
- Genera - *Streptococcus sp*, *Prevotella sp* & *Veillonella sp*.

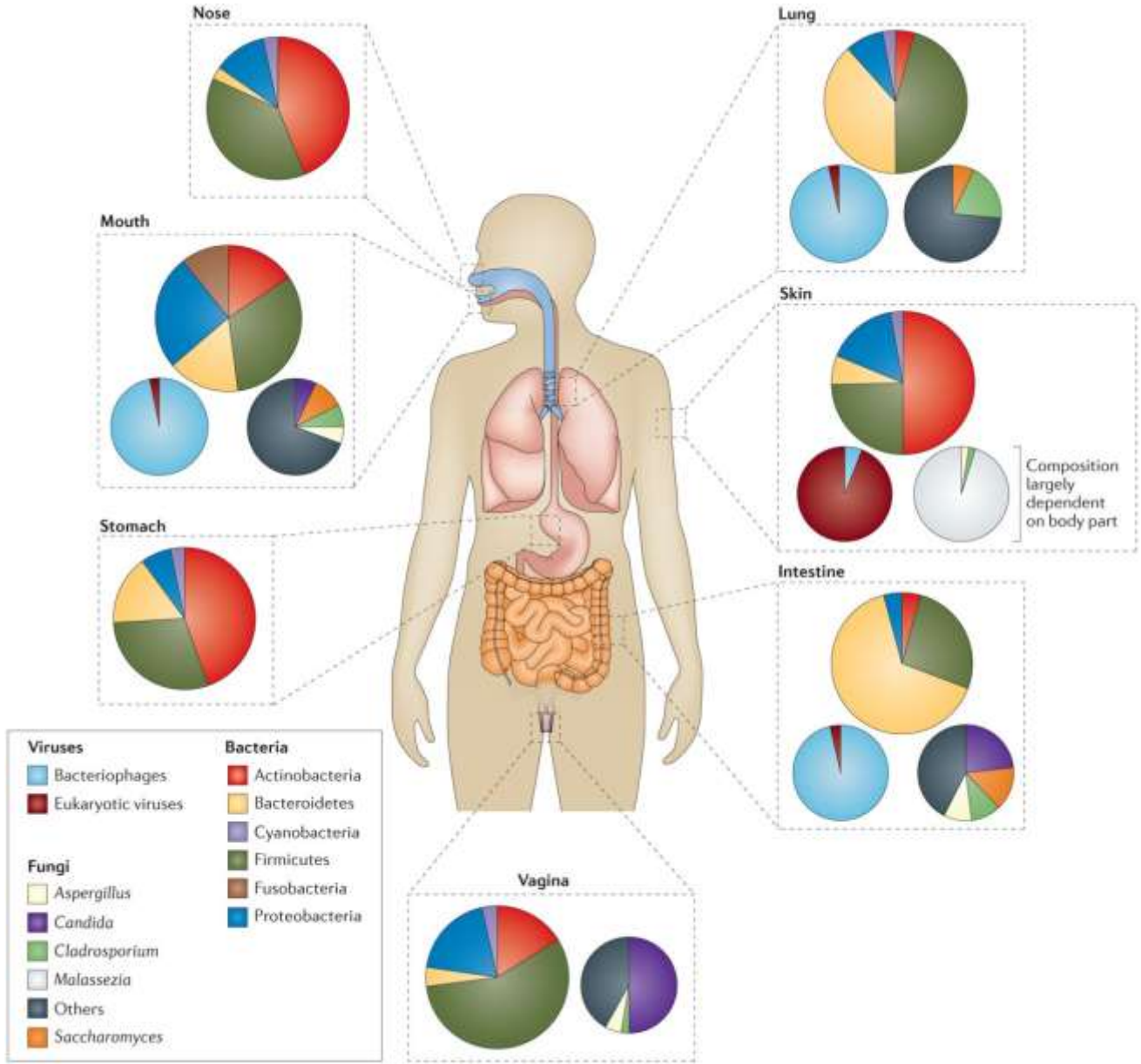
- Healthy lung defense mechanisms: keep effective clearance and differential clearance of microbes, and allow local replication.

- Lung Microbiome in comparison to gut Microbiome is a relatively a low bio mass.(10x3-10x5 vs 10x11 – 10x12/gm of tissue)

- Gut Microbiome also influences the systemic host immunity tone which naturally effects the lung local immunity , termed as the GUT-LUNG AXIS.

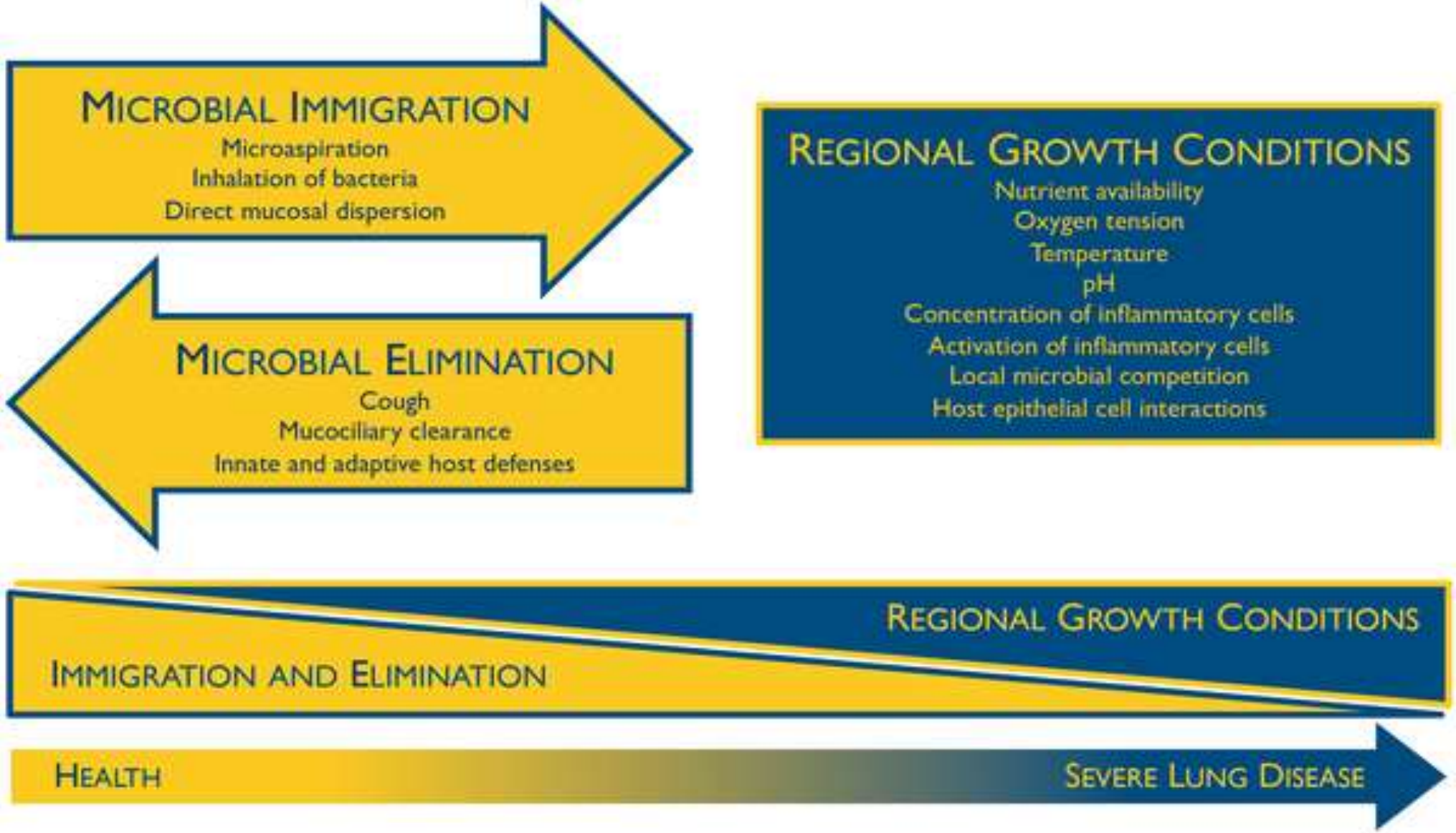
- Fungal Mycobiome are low biomass with less number of taxa.
- Fungal walls are difficult to lyse and biases in 18S and ITS primers.
- Mycobiome is generally built from environmental fungi.
- Common organisms are *Basidiomycetes, Saccharomyces, Candida Penicillium, Aspergillus* & *Cladosporium*.
- *Pneumocystis* is inconsistently identified at low levels in healthy people.

- Anelloviridae- is the most common virus (non pathogenic & found only in humans), along with some Bacteriophages. Rarely some Herpes and Papilloma virus.
- Viruses have no universally shared sequence. Either Metagenomic Shotgun Sequencing or Targeted gene methods.


Nose
Lung
Mouth
Skin
Composition largely dependent on body part
Stomach
Intestine
Vagina
Viruses
Bacteriophages
Eukaryotic viruses
Fungi
Aspergillus
Candida
Cladrosporium
Malassezia
Others
Saccharomyces
Bacteria
Actinobacteria
Bacteroidetes
Cyanobacteria
Firmicutes
Fusobacteria
Proteobacteria

Factors influencing lung “Microbiome”

- Immigration from Upper Respiratory Tract (URT) – micro aspiration.
- Microbial elimination
- Local microbial replication
- Lung microbiome is a result of microbial influx, clearance and local reproduction .



Dickson RP, Huffnagle GB (2015) The Lung Microbiome: New Principles for Respiratory Bacteriology in Health and Disease. PLoS Pathog 11(7): e1004923. doi:10.1371/journal.ppat.1004923

Review TRENDS in Microbiology Vol.12 No.12 December 2004

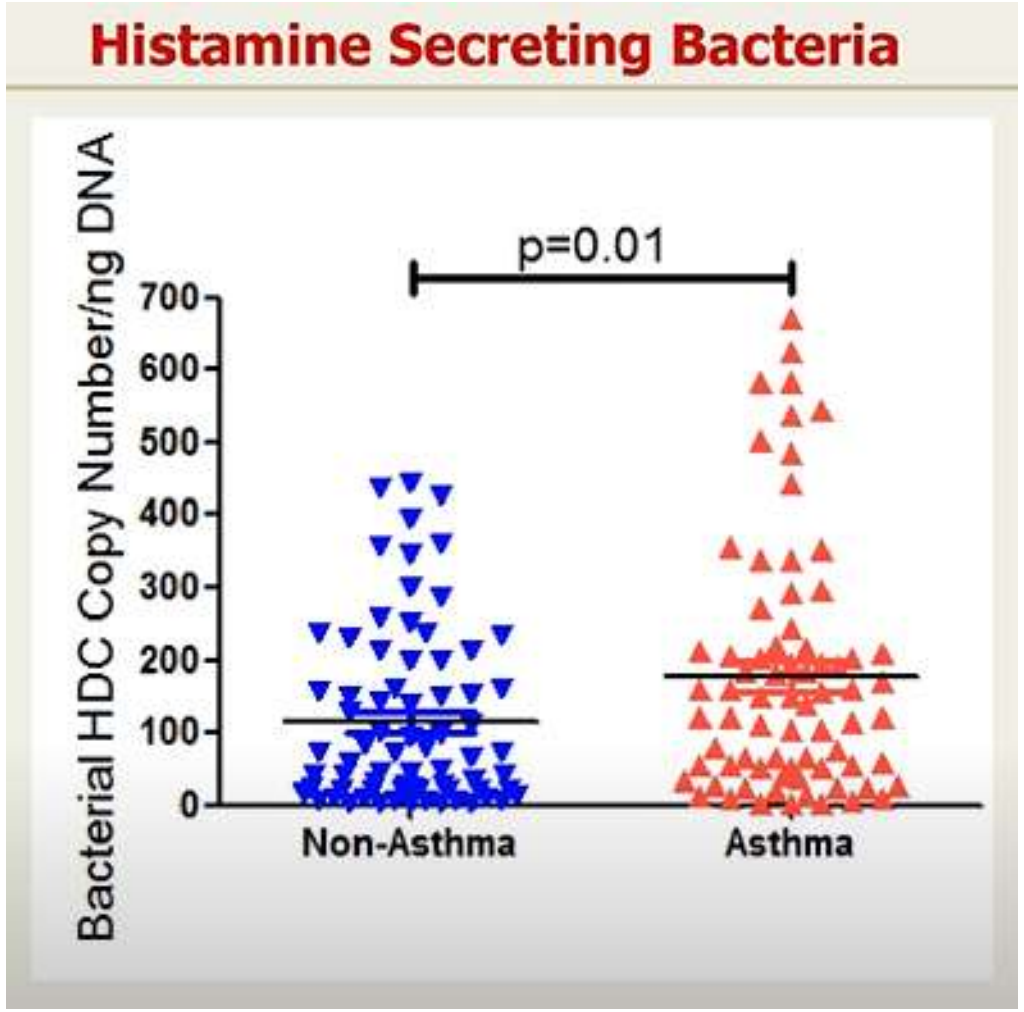
ELSEVIER

Does the microbiota regulate immune responses outside the gut?

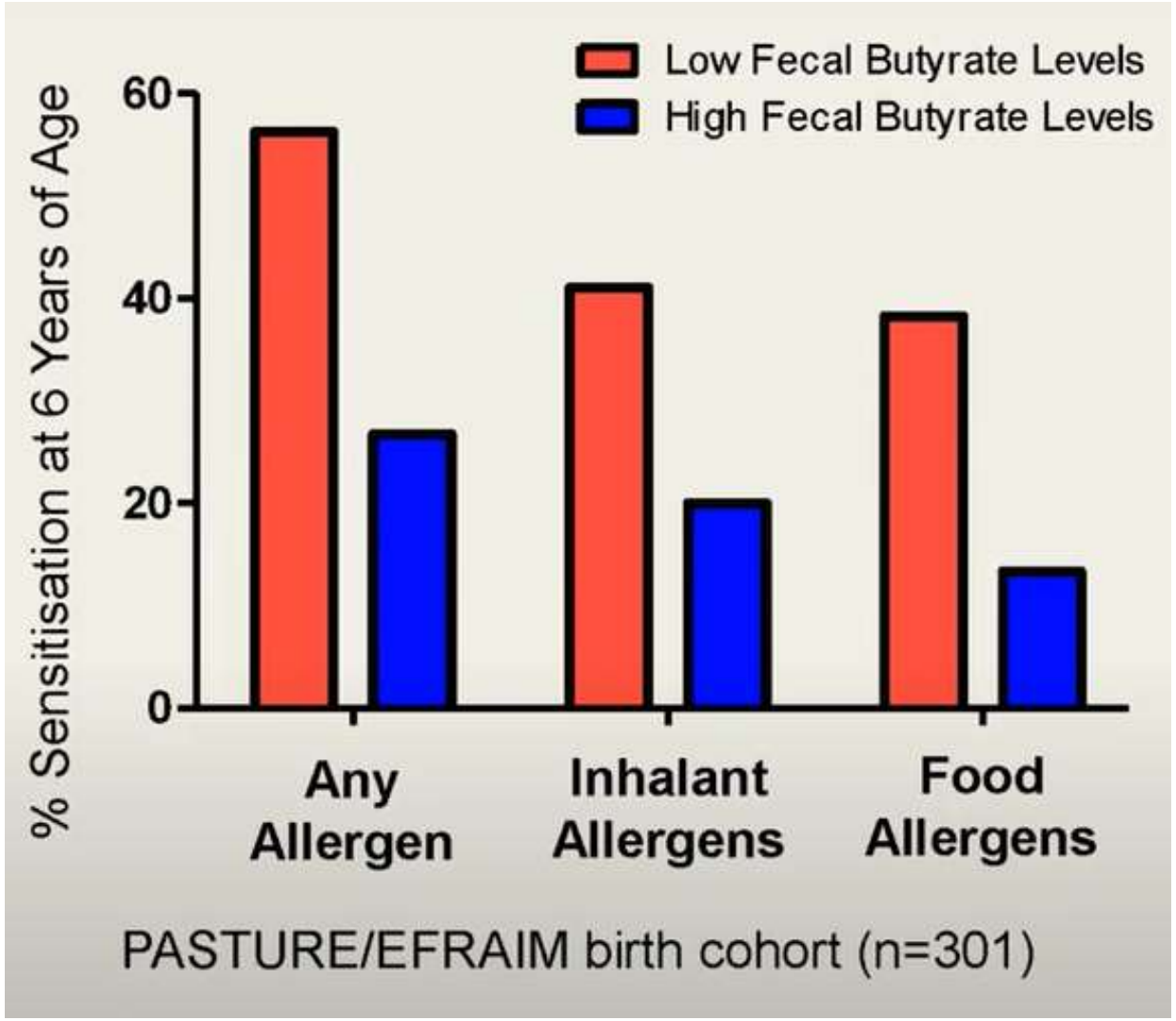
Mairi C. Noverr[1] and Gary B. Huffnagle[1,2]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109-0642, USA
[2]Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI 48109-0642, USA

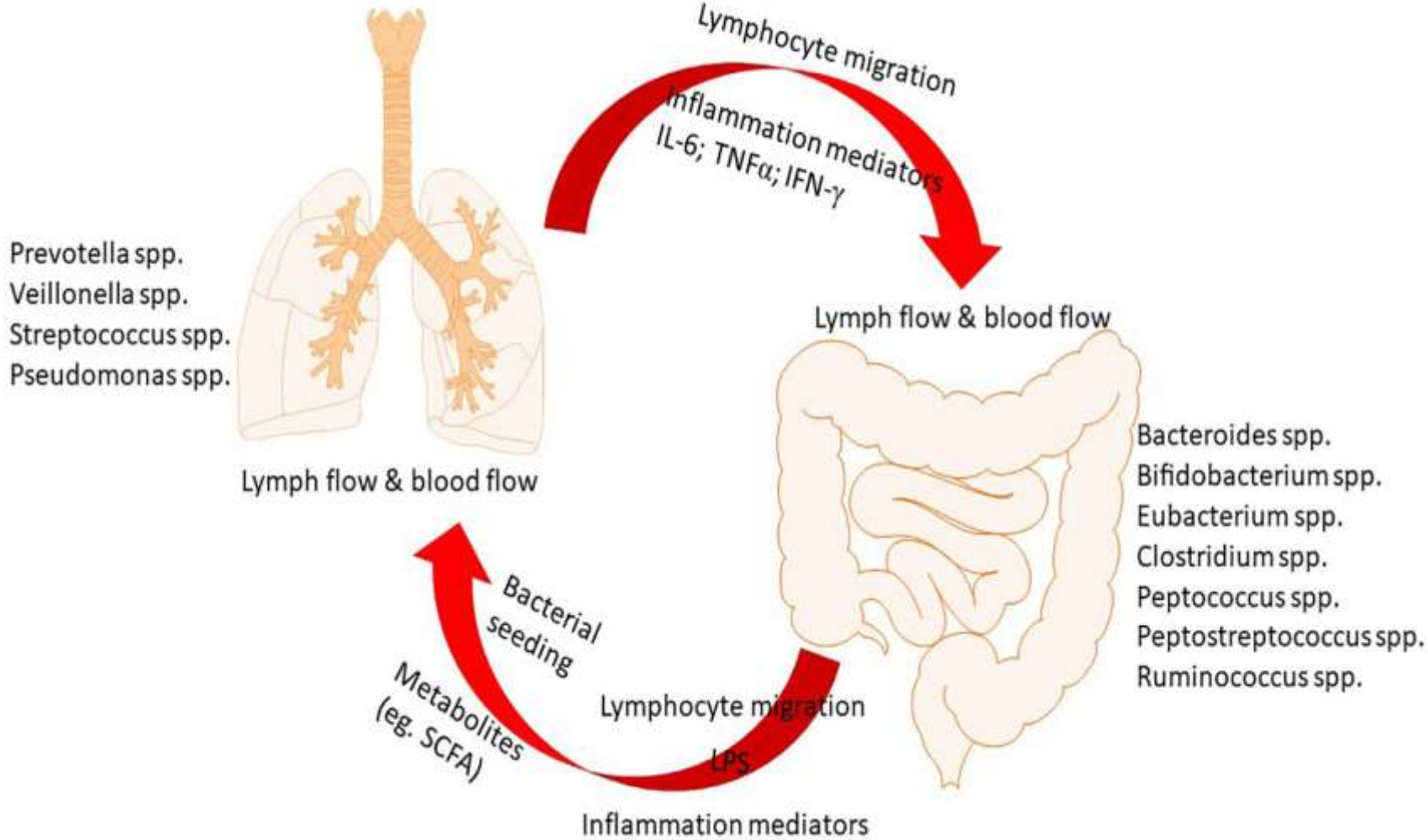
Perturbations in the gastrointestinal (GI) microbiota composition that occur as a result of antibiotics and diet in "westernized" countries are strongly associated with allergies and asthma ("hygiene hypothesis").



Barcik W etal., Histamine-secreting microbes are increased in the gut of adult asthma patients. J Allergy Clin Immunol. 2016 Nov;138(5):1491-1494.e7.



Roduit and Frei et al., Allergy 2018


Lymphocyte migration
Inflammation mediators
IL-6; TNFα; IFN-γ
Prevotella spp.
Veillonella spp.
Streptococcus spp.
Pseudomonas spp.
Lymph flow & blood flow
Lymph flow & blood flow
Bacteroides spp.
Bifidobacterium spp.
Eubacterium spp.
Clostridium spp.
Peptococcus spp.
Peptostreptococcus spp.
Ruminococcus spp.
Bacterial seeding
Metabolites (eg. SCFA)
Lymphocyte migration
LPS
Inflammation mediators

Dysbiosis of Lung Microbiome

- Increased aspiration and dysbiotic URT flora
- Decreased clearance as in immune dysfunction, mucosal defects and architectural distortion as in Cystic Fibrosis, Bronchiectasis and Fibrosis.
- Ineffective coughing
- Innate and adaptive host response
- Increased local replication may be due to increased nutrients in edema fluid or excessive mucus.
- Does dysbiosis initiate inflammation or is a result of it or BOTH?

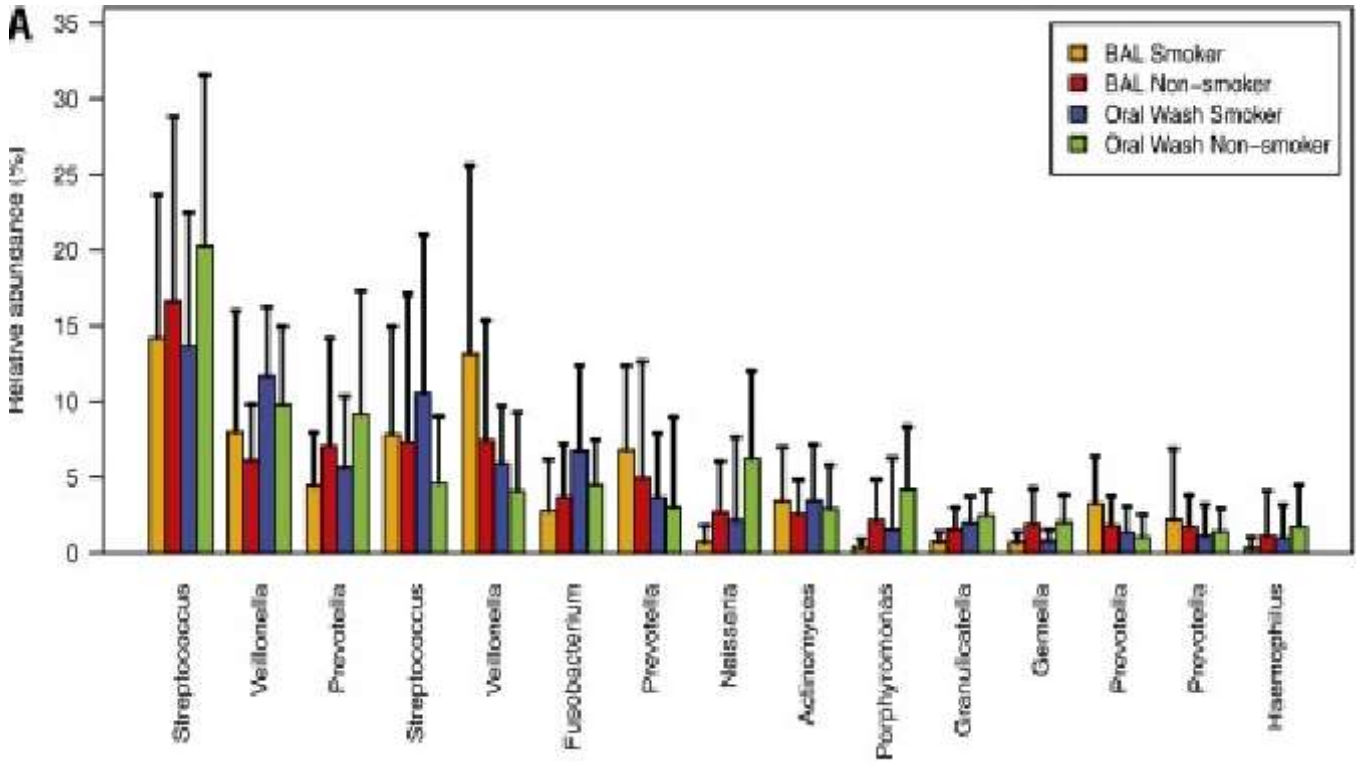
Host Defense – Microbe Interaction

Mood	Microbial behaviour
a) Content	a) Commensal – mechanical barrier and mucocilliary escalator
b) Irritated	b) Replication – innate immunity, macropahges and lymphoid cells.
c) Interested	c) Invasion – Inflammation - macrophages / PMN
d) Angry	d) Tissue invasion / replication in phagocytes – antigen specific immunity: DC; T and B lymphocytes.
e) Frustated	e) Persistence – macrophages ; Lymphocytes and NK cells

Fishmans Pulmonary Disease and Disorder 5th edition table 121-1

Importance in diseased state

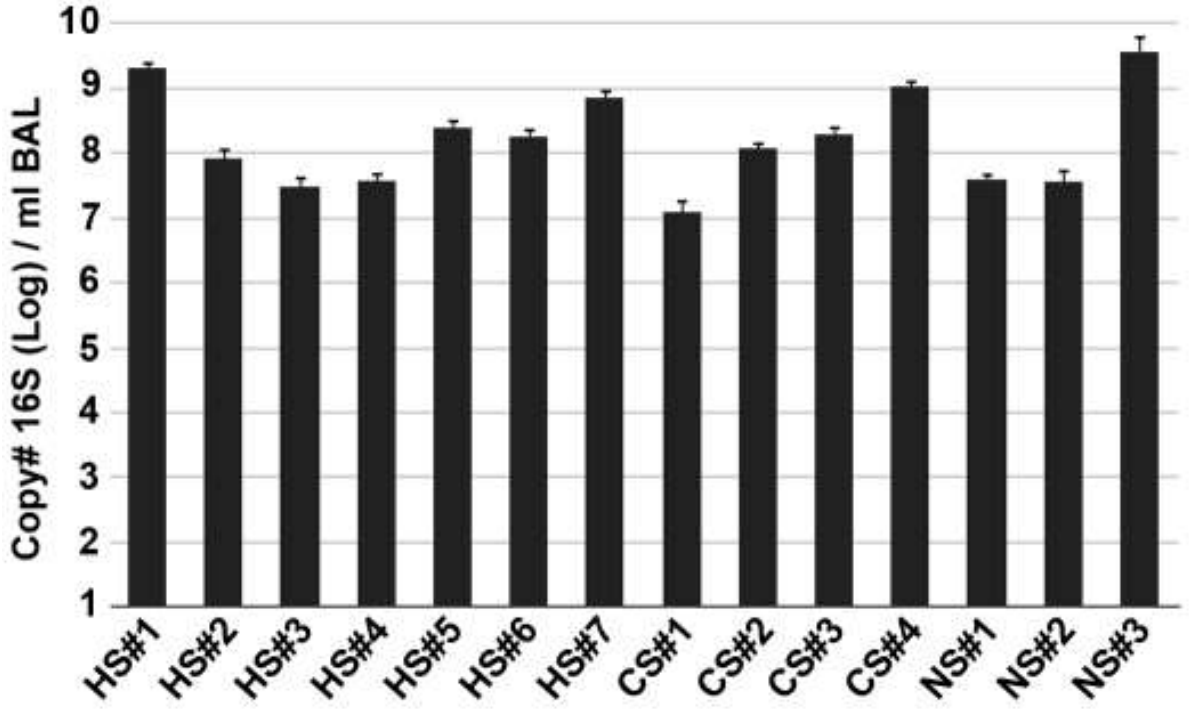
Comparison of the respiratory microbiome in healthy nonsmokers and smokers



- " The mouth microbiome differs in nonsmokers and smokers, but lung communities were not significantly altered by smoking."

Morris A et al., Am J Respir Crit Care Med . 2013 May 15;187(10):

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



- This study disclosed heterogeneity in the bacterial communities between HS subjects that was similar to that seen in healthy NS and mild COPD patients.

Erb-Downward JR et al. PLoS One. 2011 Feb 22

Disordered Microbial Communities in the Upper Respiratory Tract of Cigarette Smokers.

- ”The distributions of several genera were systematically altered by smoking in both the oro- and nasopharynx, and there was an enrichment of anaerobic lineages associated with periodontal disease in the oropharynx”

Charlson ES et al., PLoS One. 2010 Dec 20

- Information on long term effects of smoking in healthy subjects is scarce.
- Oropharyngeal dysbiosis have been reported, preliminary data- it doesn’t revert on quitting smoking.
- Difference in the oral microbiome in current and former smokers with and without disease needs to be studied.
- Exposure to tobacco smoke results in proximal microbiome changes but is not reflected distally, at least in healthy individuals.

Asthma / COPD

- Fostered by epidemiologic studies reporting an association between the development of bronchitis or pneumonia during community outbreaks of *Chlamydophila pneumoniae* and adult-onset asthma.

- Multiple studies observing an association between early childhood antibiotic exposure and subsequent development of asthma and allergies, prompted speculation that disruption of the normal Microbiome may be having a role in the pathogenesis of these conditions.

ORIGINAL ARTICLE

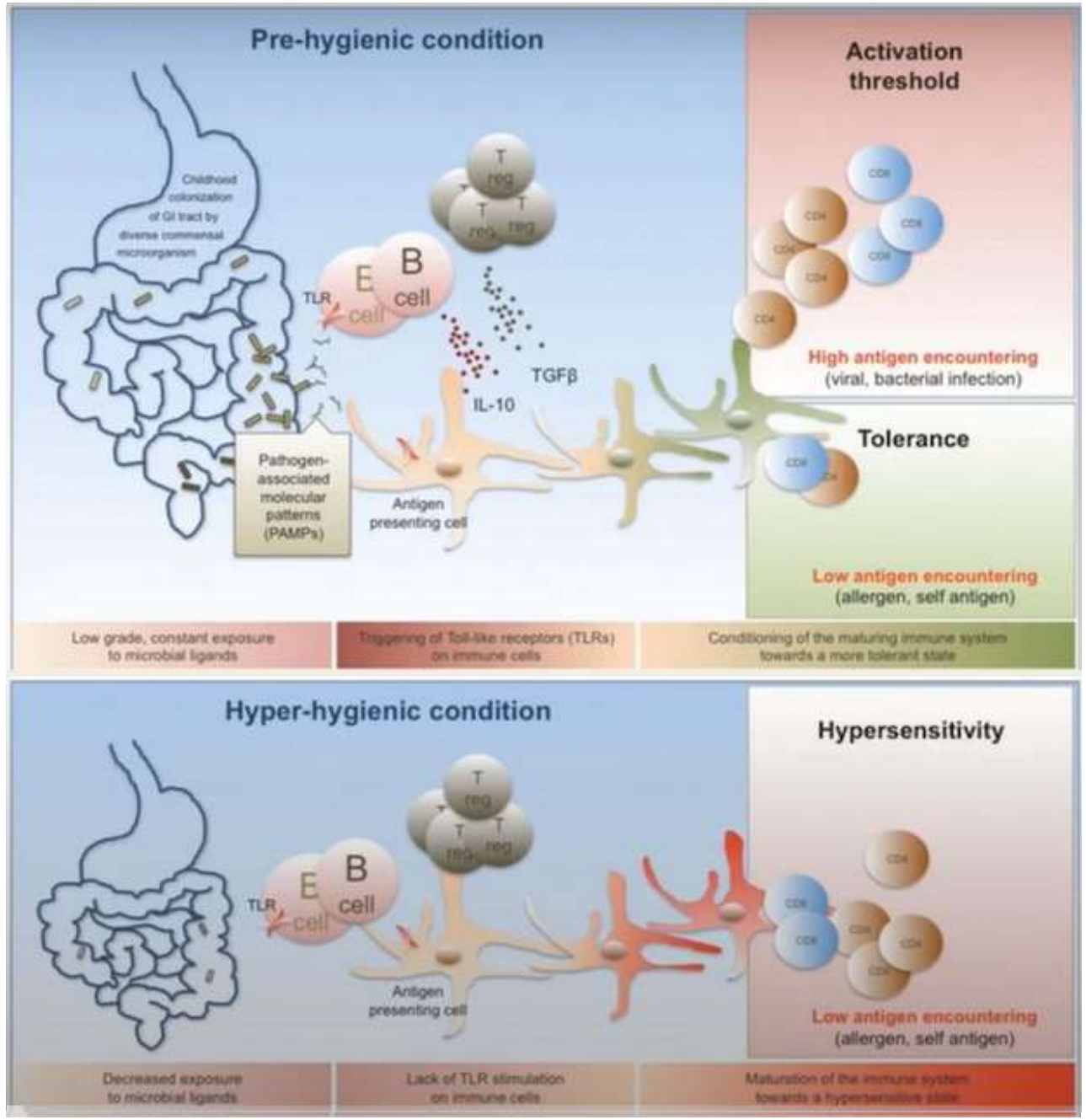
Childhood Asthma after Bacterial Colonization of the Airway in Neonates

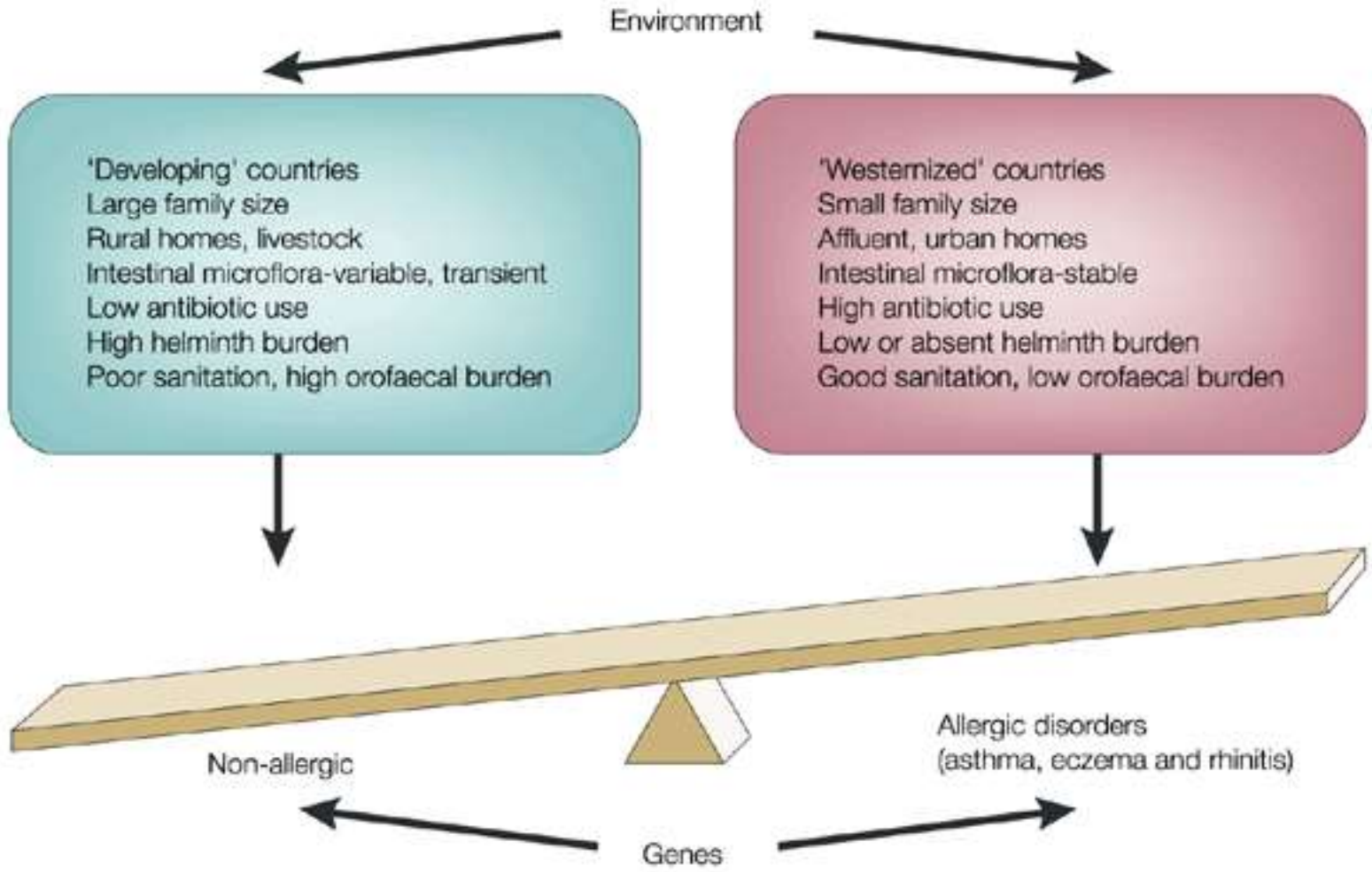
Hans Bisgaard, M.D., D.M.Sc., Mette Northman Hermansen, M.D., Frederik Buchvald, M.D., Ph.D., Lotte Loland, M.D., Ph.D., Liselotte Brydensholt Halkjaer, M.D., Ph.D., Klaus Bønnelykke, M.D., Martin Brasholt, M.D., Andreas Heltberg, M.D., Nadja Hawwa Vissing, M.D., Sannie Vester Thorsen, M.Sc., Malene Stage, M.Sc., and Christian Bressen Pipper, M.Sc., Ph.D.

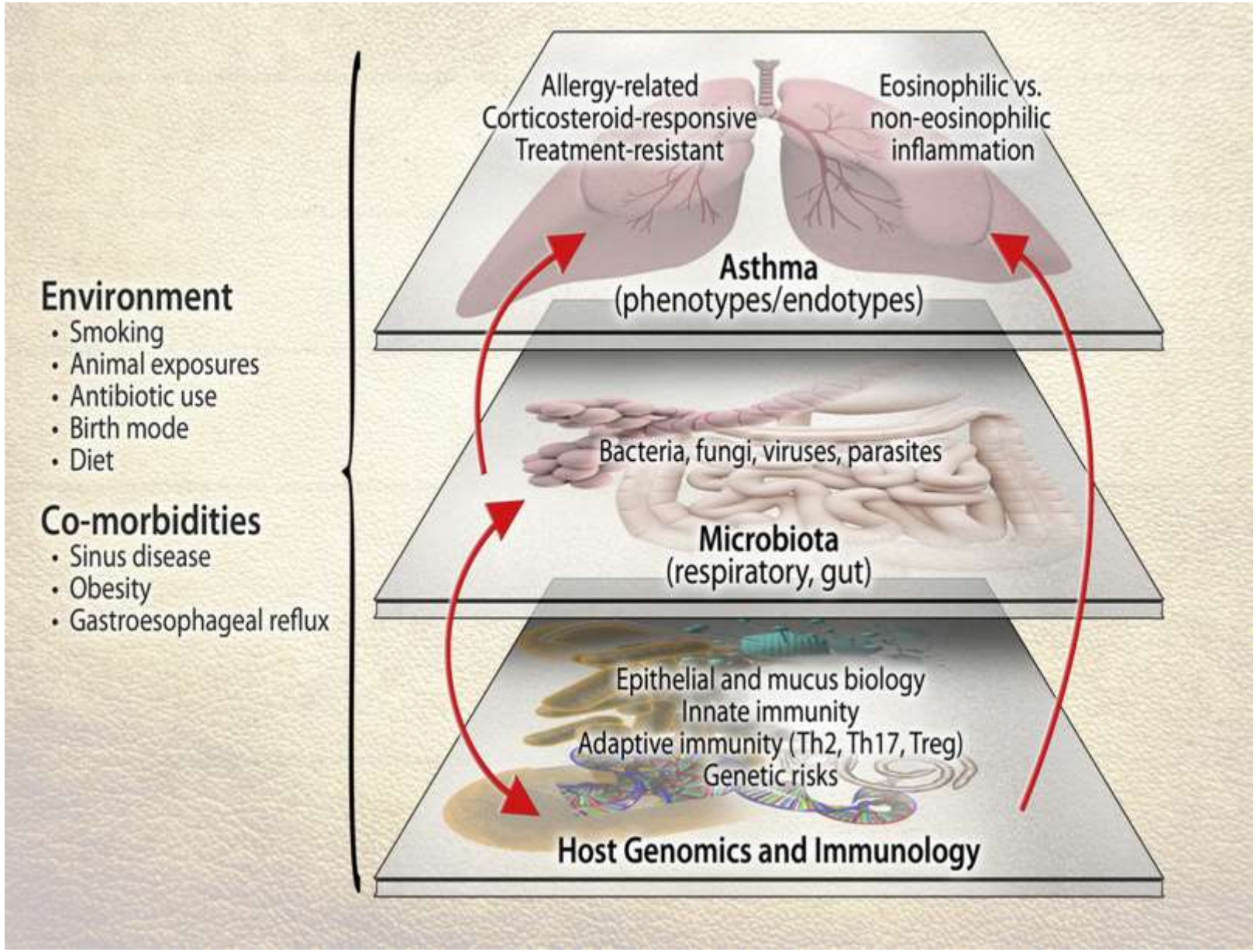
- Hypopharyngeal samples were cultured from 321 neonates at 1 month age.
- Twenty-one percent of the infants were colonized with *S. pneumoniae, M. catarrhalis, H. influenzae*, or a combination of these organisms.
- Colonizers were associated

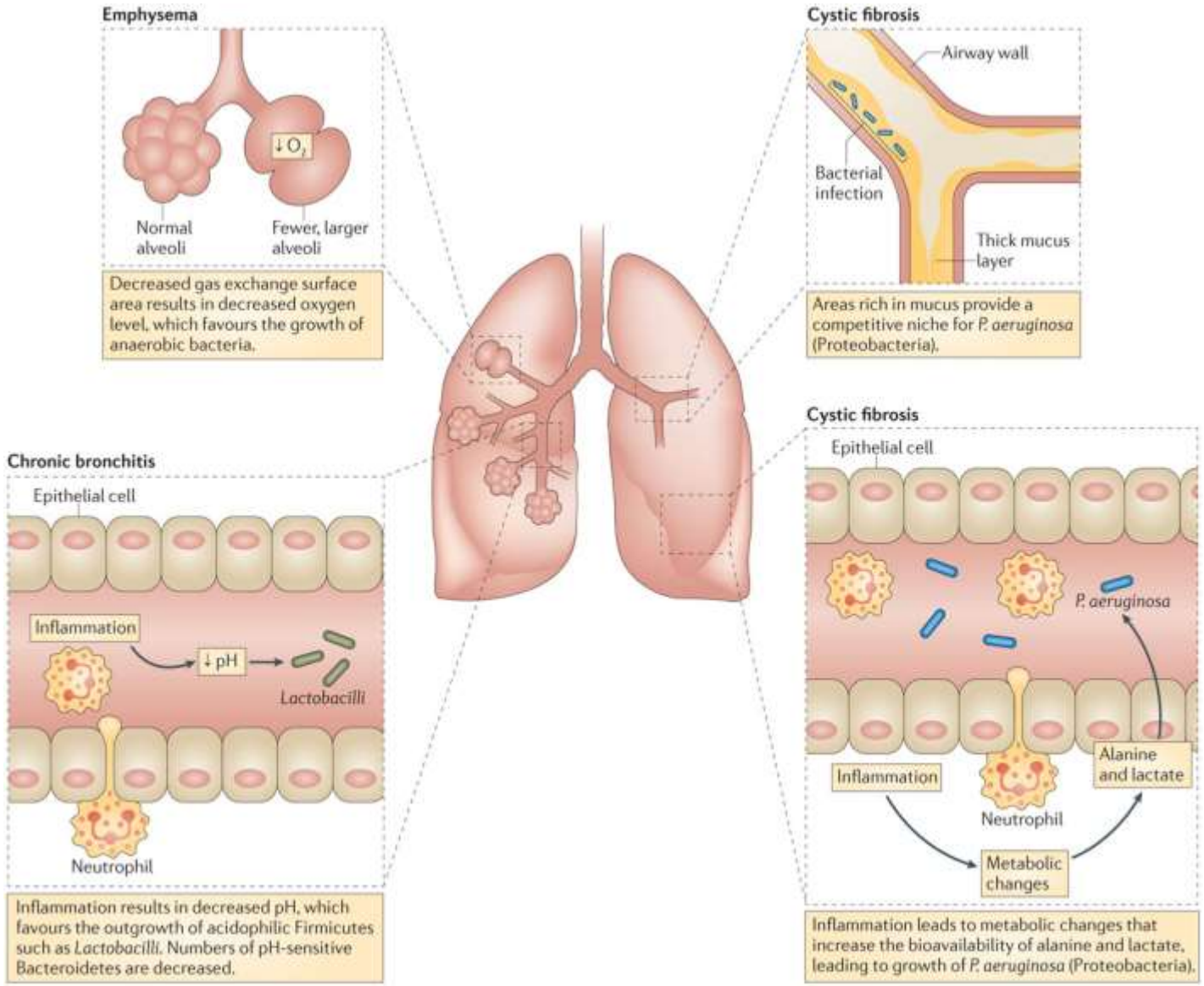
1. Significant wheezing, acute exacerbation , hospitalization for wheezing
2. High Total IgE and eosinophilia by 4 years of age
3. Prevalence of asthma and B2 agonist reversibility by 5 years of age more in colonizers.

Bisgaard H et al., N Engl J Med. 2007 Oct 11;357(15):1487-95


Pre-hygienic condition
Activation threshold
Childhood colonization of GI tract by diverse commensal microorganism
T reg
B cell
TLR
TGFβ
IL-10
Pathogen-associated molecular patterns (PAMPs)
Antigen presenting cell
High antigen encountering (viral, bacterial infection)
Tolerance
Low antigen encountering (allergen, self antigen)
Low grade, constant exposure to microbial ligands
Triggering of Toll-like receptors (TLRs) on immune cells
Conditioning of the maturing immune system towards a more tolerant state
Hyper-hygienic condition
Hypersensitivity
Low antigen encountering (allergen, self antigen)
Decreased exposure to microbial ligands
Lack of TLR stimulation on immune cells
Maturation of the immune system towards a hypersensitive state


Environment
'Developing' countries
Large family size
Rural homes, livestock
Intestinal microflora-variable, transient
Low antibiotic use
High helminth burden
Poor sanitation, high orofaecal burden
'Westernized' countries
Small family size
Affluent, urban homes
Intestinal microflora-stable
High antibiotic use
Low or absent helminth burden
Good sanitation, low orofaecal burden
Non-allergic
Allergic disorders
(asthma, eczema and rhinitis)
Genes


Environment
• Smoking
• Animal exposures
• Antibiotic use
• Birth mode
• Diet
Co-morbidities
• Sinus disease
• Obesity
• Gastroesophageal reflux
Allergy-related
Corticosteroid-responsive
Treatment-resistant
Eosinophilic vs.
non-eosinophilic
inflammation
Asthma
(phenotypes/endotypes)
Bacteria, fungi, viruses, parasites
Microbiota
(respiratory, gut)
Epithelial and mucus biology
Innate immunity
Adaptive immunity (Th2, Th17, Treg)
Genetic risks
Host Genomics and Immunology


Emphysema
↓ O_2
Normal alveoli
Fewer, larger alveoli
Decreased gas exchange surface area results in decreased oxygen level, which favours the growth of anaerobic bacteria.
Cystic fibrosis
Airway wall
Bacterial infection
Thick mucus layer
Areas rich in mucus provide a competitive niche for *P. aeruginosa* (Proteobacteria).
Chronic bronchitis
Epithelial cell
Inflammation
↓ pH
Lactobacilli
Neutrophil
Inflammation results in decreased pH, which favours the outgrowth of acidophilic Firmicutes such as *Lactobacilli*. Numbers of pH-sensitive Bacteroidetes are decreased.
Cystic fibrosis
Epithelial cell
P. aeruginosa
Inflammation
Neutrophil
Alanine and lactate
Metabolic changes
Inflammation leads to metabolic changes that increase the bioavailability of alanine and lactate, leading to growth of *P. aeruginosa* (Proteobacteria).

Disordered Microbial Communities in Asthmatic Airways

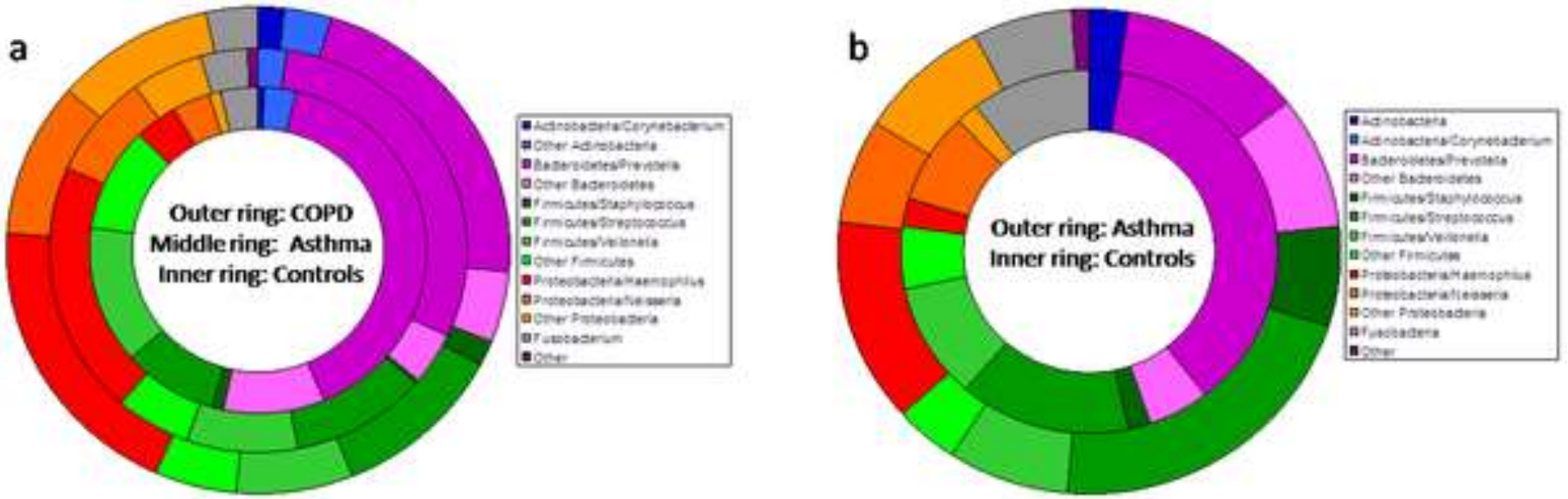
- Compared the Microbiome of oral, nasal and BAL specimens of patients with asthma to that of patients with Chronic Obstructive Pulmonary Disease and healthy controls

- The bronchial tree was not sterile.

- It contained a mean of 2,000 bacterial genomes per cm2 surface sampled.

- Pathogenic Proteobacteria, particularly Haemophilus spp., were much more frequent in bronchi of adult asthmatics or patients with COPD than controls.

Hilty M, et al. PLoS One. 2010 Jan 5



Hilty M, Burke C, Pedro H, Cardenas P, Bush A, et al. (2010) PLoS ONE 5(1): e8578. doi:10.1371/journal.pone.0008578

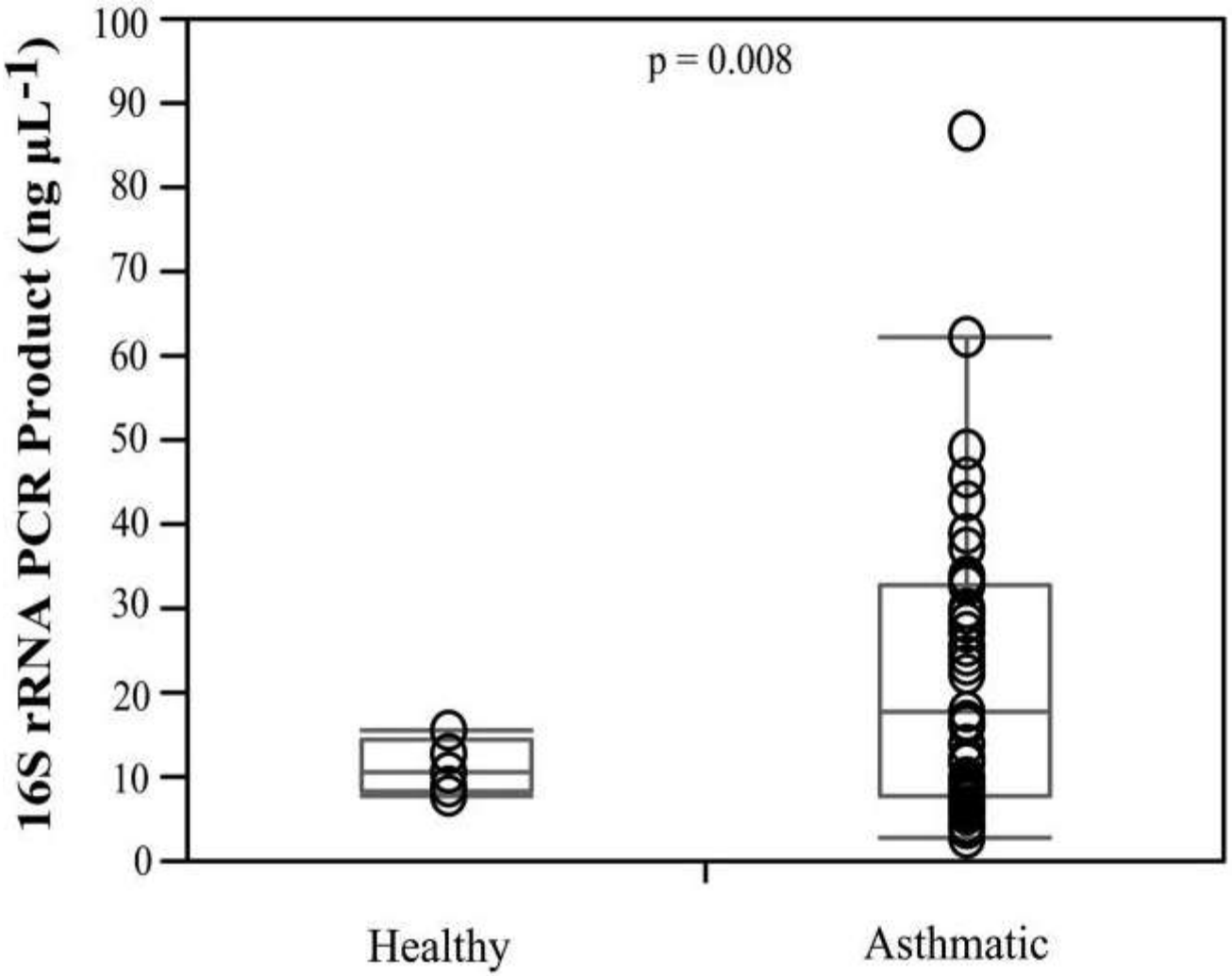
Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma.

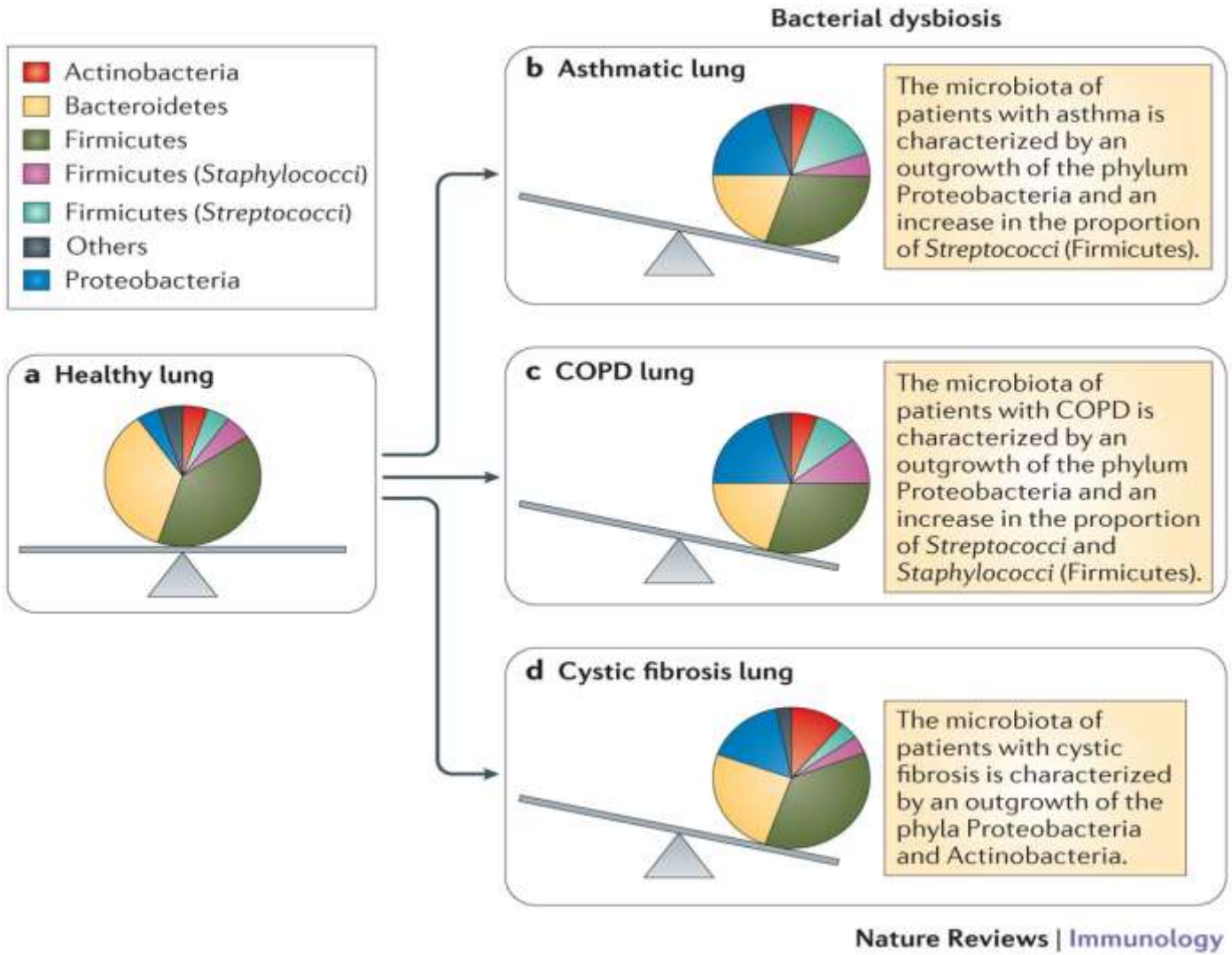
•Compared the lung microbiota (obtained by bronchoscope using protected specimen brushes) of 65 poorly-controlled asthmatics with that of 10 control subjects

•Found both increased bacterial burden and bacterial diversity among the asthmatic subjects.

•Increased *Proteobacteriae* among asthmatics, and a positive correlation between the presence of numerous species (*Comamonadacea, Sphingomonadaceae and Oxalobacteraceae*) and the severity of bronchial hyperresponsiveness.

Huang YJ et al., J Allergy Clin Immunol. 2011 Feb


16S rRNA PCR Product (ng µL-1)
100
90
80
70
60
50
40
30
20
10
0
p = 0.008
Healthy
Asthmatic



Nature Reviews | Immunology

Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment

- Bacterial communities in protected bronchial brushings from 42 atopic asthmatic subjects, 21 subjects with atopy but no asthma, and 21 healthy control subjects
- Asthmatic subjects were uniquely enriched in members of the *Haemophilus*, *Neisseria, Fusobacterium*, and *Porphyromonas* species and the *Sphingomonodaceae* family and depleted in members of the Mogibacteriaceae family and Lactobacillales order.
- Subjects with type 2-high asthma harbored significantly lower bronchial bacterial burden.
- Baseline *Streptococcus, Fusobacteria* and *Sphingomonas* predicted response to ICS.

Durack J et al., J Allergy Clin Immunol. 2017 Jul

Sputum Microbiome Is Associated with 1-Year Mortality after Chronic Obstructive Pulmonary Disease Hospitalizations

- Sputum samples from 102 patients hospitalized because of AECOPD.
- The Microbiome profile was assessed through sequencing of 16S rRNA gene.
- Observed significantly lower values of α-diversity among non survivors.
- The survivors had a higher relative abundance of *Veillonella*; in contrast, non-survivors had a higher abundance of *Staphylococcus*.

Leitao Filho FS etal., Am J Respir Crit Care Med. 2019 May 15;199(10).

Environmental fungal sensitisation associates with poorer clinical outcomes in COPD

- Patients with stable COPD (n=446) and non-diseased controls (n=51) were prospectively recruited across three countries (Singapore, Malaysia and Hong Kong) and screened against a comprehensive allergen panel including house dust mites, pollens, cockroach and fungi.

- Fungal sensitization associates with frequent exacerbations, and unsupervised clustering reveals a “highly sensitized fungal predominant” subgroup demonstrating significant symptoms, frequent exacerbations and poor lung function.

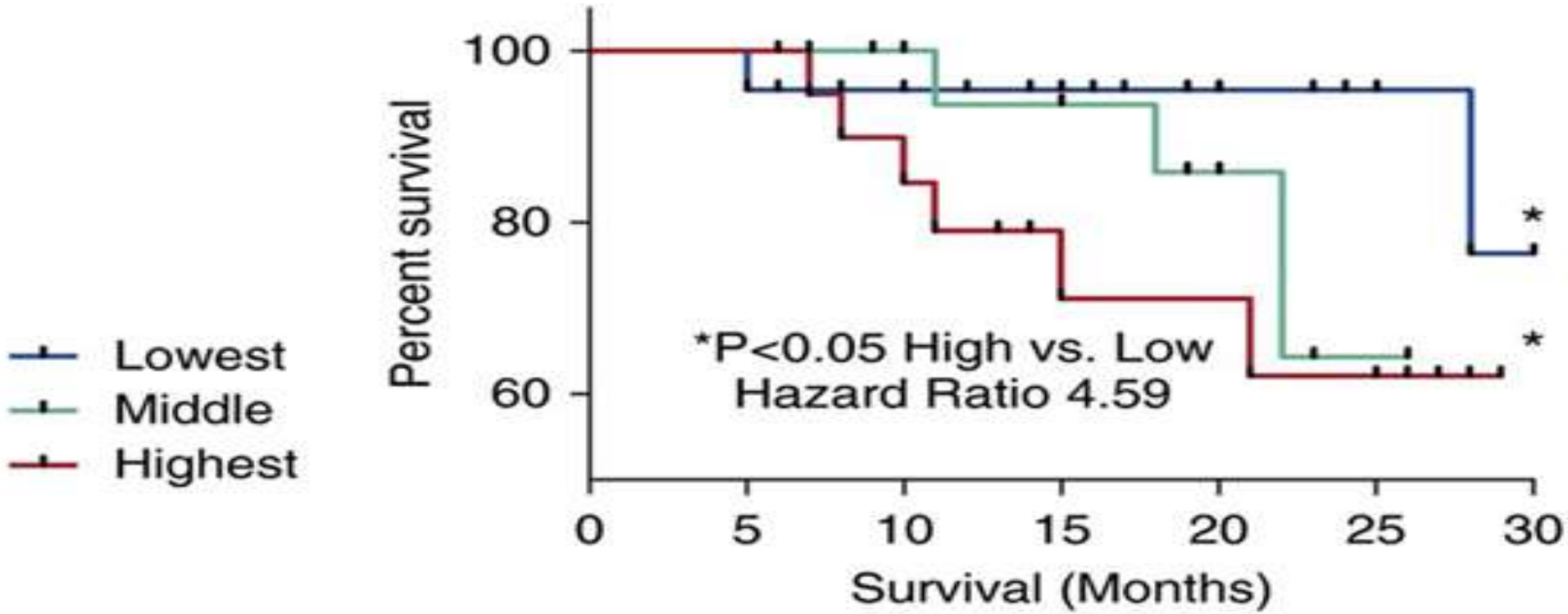
Tiew PY et al. Eur Respir J. 2020 Aug 27;56(2):2000418.

ILD

The role of bacteria in the pathogenesis and progression of Idiopathic Pulmonary Fibrosis.

- 65 well-defined IPF patients and 44 controls
- Two fold higher bacterial load in IPF BALF compared with control subjects .
- Significant association between patients with higher BALF bacterial load and disease progression at six months (defined by a decline in forced vital capacity (FVC) by 10%, or death) compared with controls .

Molyneaux PL et al., Am J Respir Crit Care Med. 2014 Oct 15



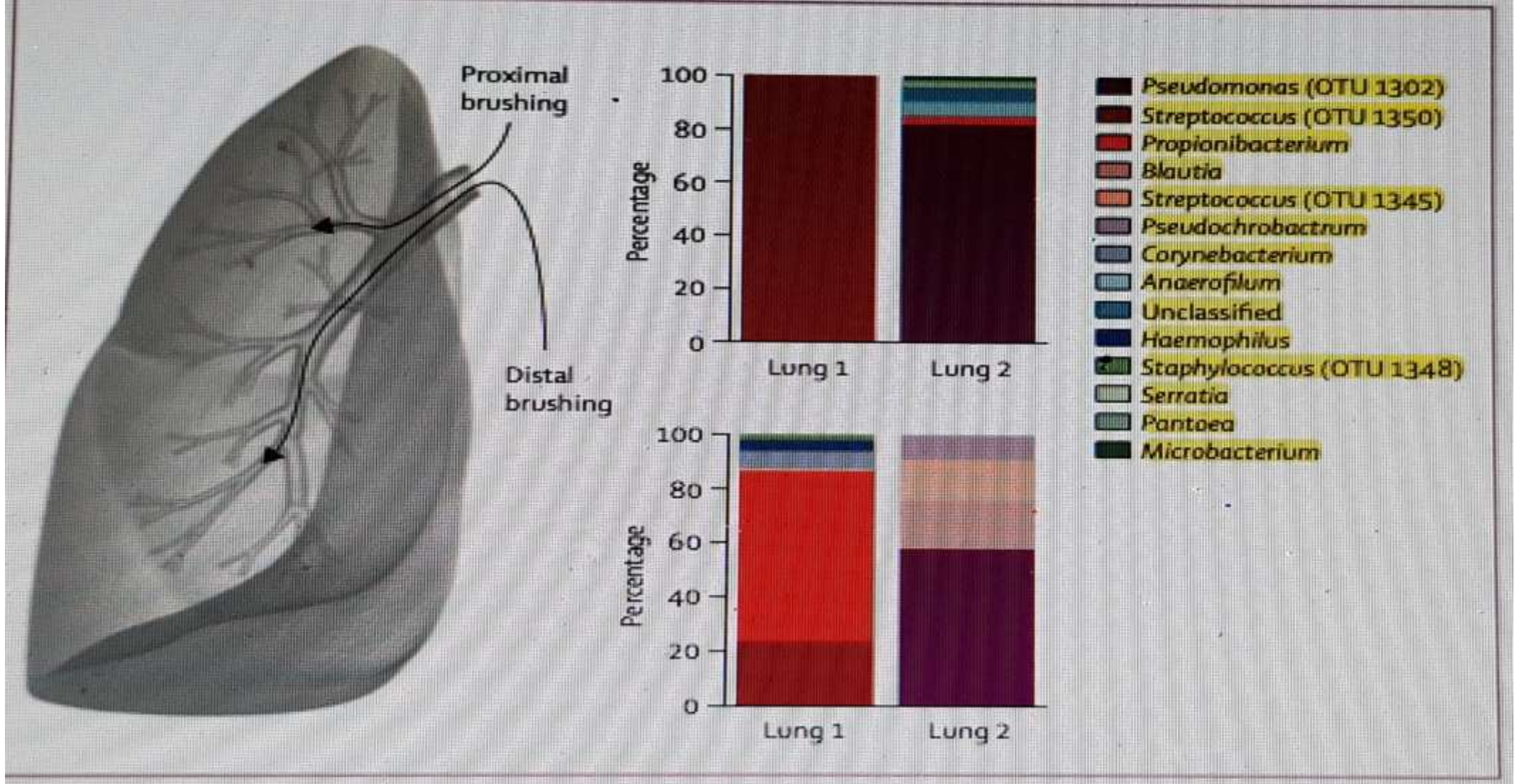
Number at Risk

High Bacterial Burden	22	22	17	10	8	7	0
Middle Bacterial Burden	21	21	17	13	10	1	0
Low Bacterial Burden	22	22	19	15	10	6	4

Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study

- Correlating Outcomes with Biochemical Markers to Estimate Time-progression in Idiopathic Pulmonary Fibrosis (COMET) study.
- The most prevalent OTUs (operational taxonomic unit) in IPF patients were *Prevotella, Veillonella & Cronobacter sp.*
- The preliminary data suggest progression of idiopathic pulmonary fibrosis is associated with the presence of specific members within the Staphylococcus (OTU 1348) and Streptococcus (OTU 1345) genera.
- They proposed lung microbiome as a biomarker for disease progression and severity.

Han MK et al.Lancet Respir Med. 2014 Jul



igure 2: Percentage relative abundance of OTUs in lung explants

roximal and distal airway brushings were taken from two lung explants after the lungs were removed from two atients with idiopathic pulmonary fibrosis. Lung 1 had 100% relative abundance of *Streptococcus* OTU 1350 in he proximal brushing. In the distal brushing, *Streptococcus* OTU 1350 and OTU 1345 relative abundance was 3·89% and 0·81%, respectively. *Staphylococcus* OTU 1348 was also identified in the distal brush at 1·86% relative bundance. Lung 2 had neither *Streptococcus* nor *Staphylococcus* OTUs in the proximal brush, but the distal brush ad 15·29% relative abundance of *Streptococcus* OTU 1345. OTU=operational taxonomic unit.

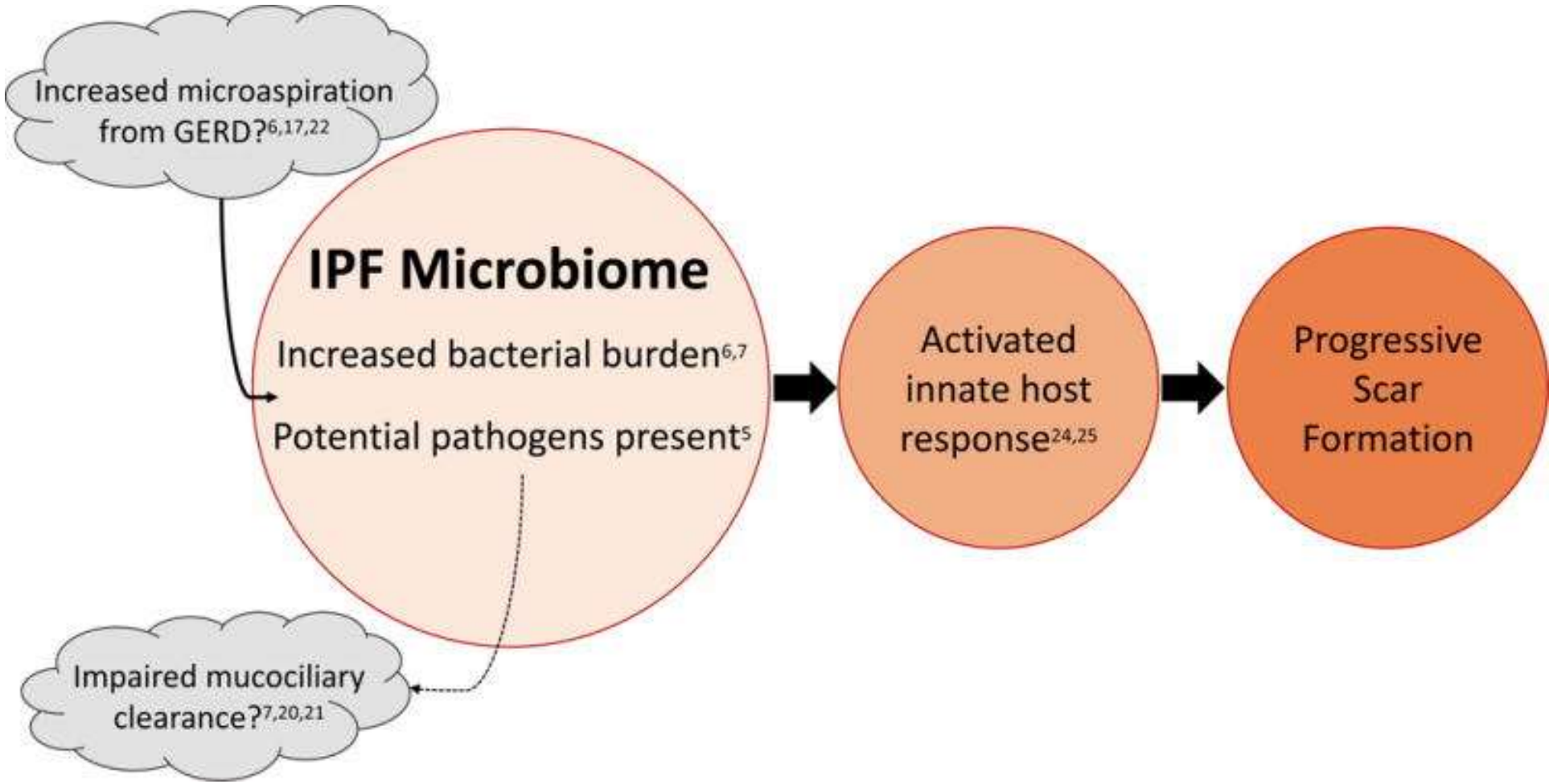
Metagenomic analysis of bronchoalveolar lavage samples from patients with idiopathic interstitial pneumonia

- First culture non dependent study in 2010, used PCR techniques studied Microbiomes in 17 patients

- In 5 patients, who grew *P. jerovecii*, the bacterial presence was negative ! (antagonisitic ???)

- *Streptococcus, Neisseria and Actinobacterium* sp. Genera were most common organisms isolated in the rest.

Friaza et al. J Microbiol Methods. 2010 Jul


Increased microaspiration from GERD?[6,17,22]
IPF Microbiome
Increased bacterial burden[6,7]
Potential pathogens present[5]
Impaired mucociliary clearance?[7,20,21]
Activated innate host response[24,25]
Progressive Scar Formation

Sarcoidosis

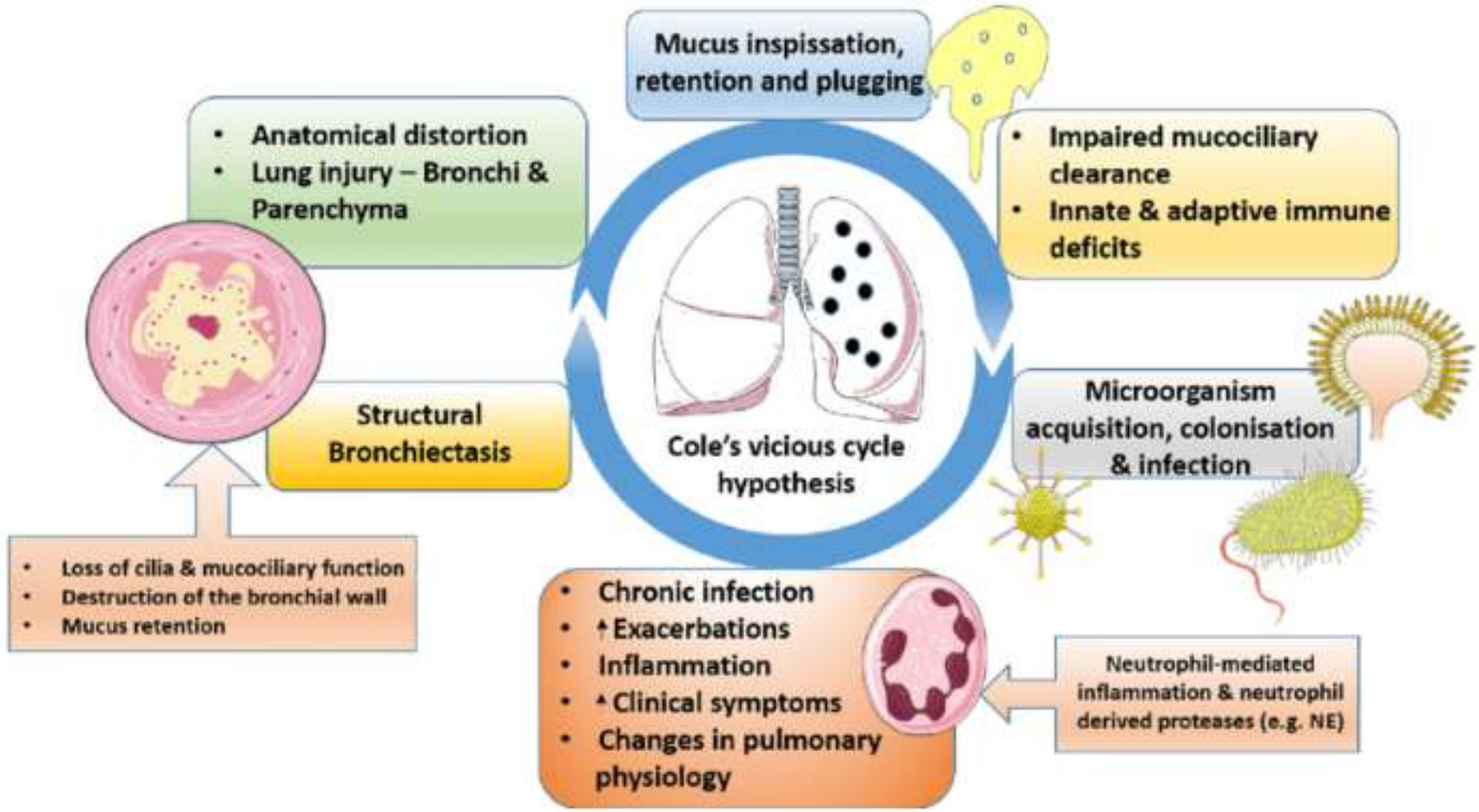
- In 2013 a meta analysis by Zhou et al. had shown increased risk of Sarcoidosis associated with *Propionibacterium acnes*.

- Rationale and Design of the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) Study.- a large observational study by NIH is ongoing. The primary objective of this study is identification of patterns in the lung Microbiome and association with disease severity and phenotype.

Lung Transplant

- Post lung transplant recipient lungs have higher biomass Microbiome.
- Mostly oral flora seen with decrease in alpha diversity.
- The dysbiosis here is patient specific and disease specific.
- In CF patients, *Pseudomonas sp* strains populate the graft in days.
- BOS has been found to be influenced by the Microbiome.
- BOS is exaggerated by oral flora and some studies demonstrate that *Pseudomonas* colonisation may be protective ???
- Herpes, CMV are important viral pathogens.
- *Aspergillus* causing anastomotic complications at ischemic surgical site and *Candida* infections are well documented.

Bronchiectasis


Mucus inspissation, retention and plugging
Impaired mucociliary clearance
Innate & adaptive immune deficits
Microorganism acquisition, colonisation & infection
Neutrophil-mediated inflammation & neutrophil derived proteases (e.g. NE)
Chronic infection
↑ Exacerbations
Inflammation
↑ Clinical symptoms
Changes in pulmonary physiology
Cole's vicious cycle hypothesis
Structural Bronchiectasis
Anatomical distortion
Lung injury – Bronchi & Parenchyma
Loss of cilia & mucociliary function
Destruction of the bronchial wall
Mucus retention

Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial

- In the BLESS (Bronchiectasis and Low-dose Erythromycin Study) study, low-dose erythromycin (400 mg, twice daily) was given to stable bronchiectasis patients for 48 weeks.
- Erythromycin did not result in significant changes in microbiome composition in patients with a *Pseudomonas*-dominated microbiome, but significantly reduced the rate of pulmonary exacerbations compared to placebo in this group.
- Erythromycin reduced 24-hour sputum production and attenuated lung function decline.
- Erythromycin increased the proportion of macrolide-resistant oropharyngeal streptococci.

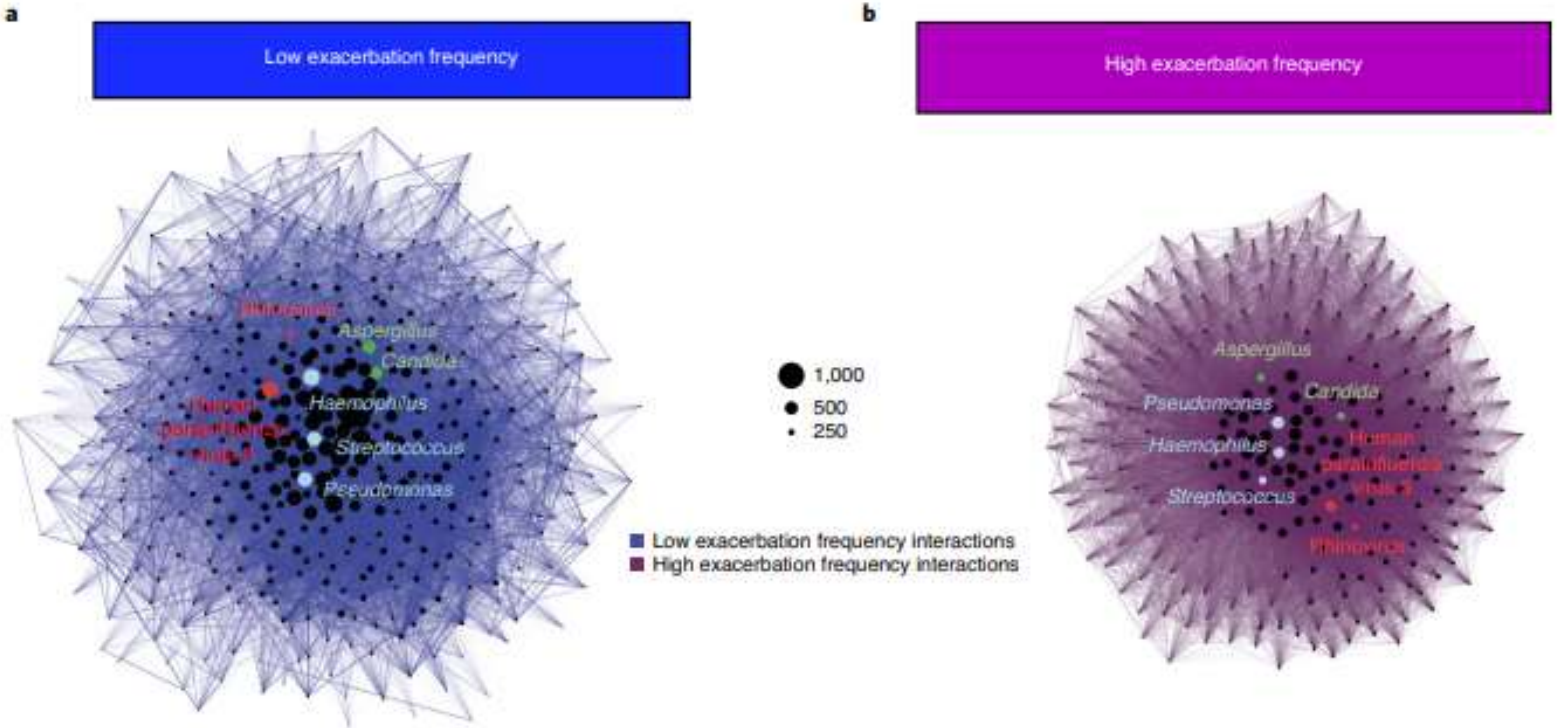
Serisier DJ et al., JAMA. 2013 Mar 27;309(12):1260-7.

ARTICLES
https://doi.org/10.1038/s41591-021-01289-7
nature medicine
Check for updates

Integrative microbiomics in bronchiectasis exacerbations

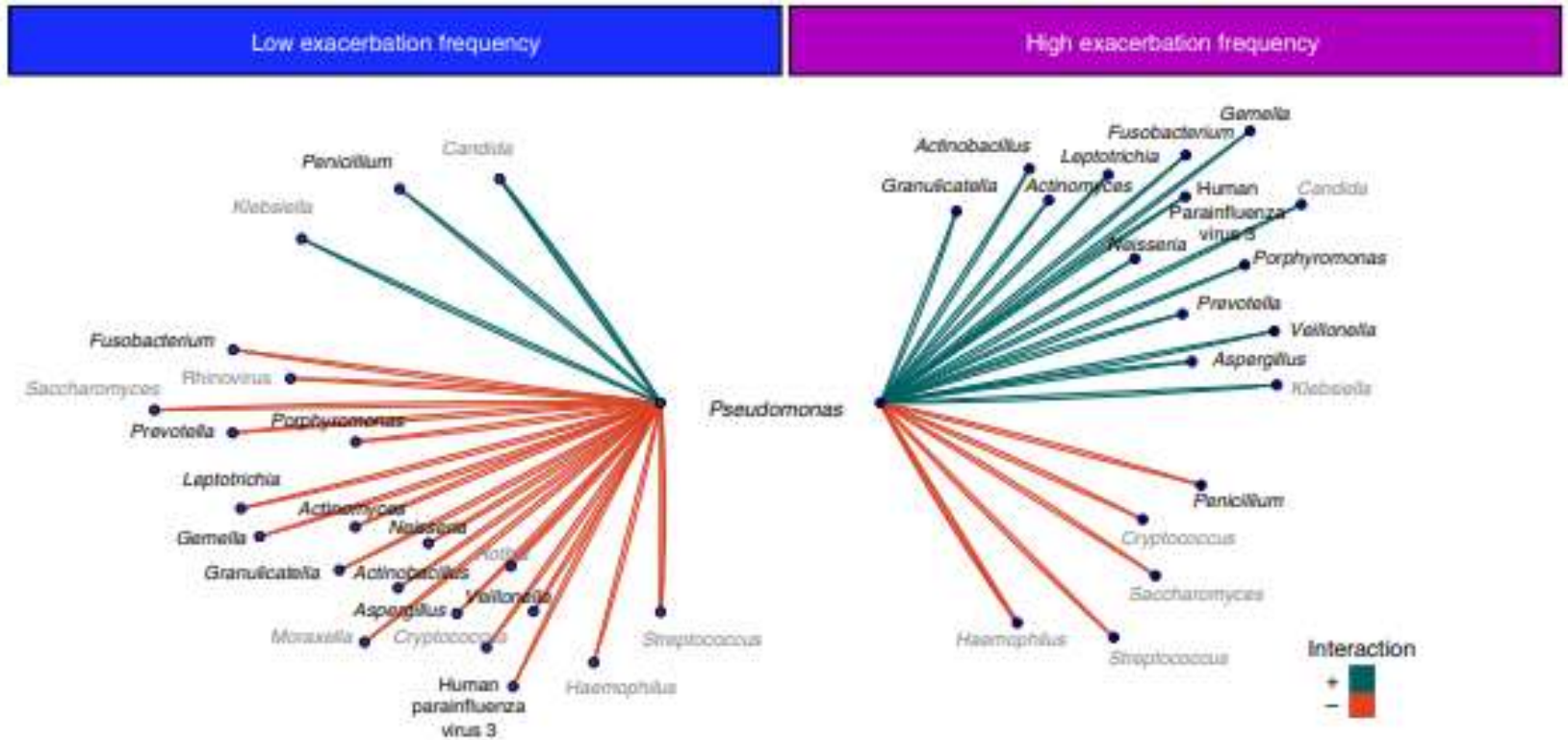
Mac Aogáin *et al.* Integrative microbiomics in bronchiectasis exacerbations. *Nat Med* **27**, 688–699 (2021)

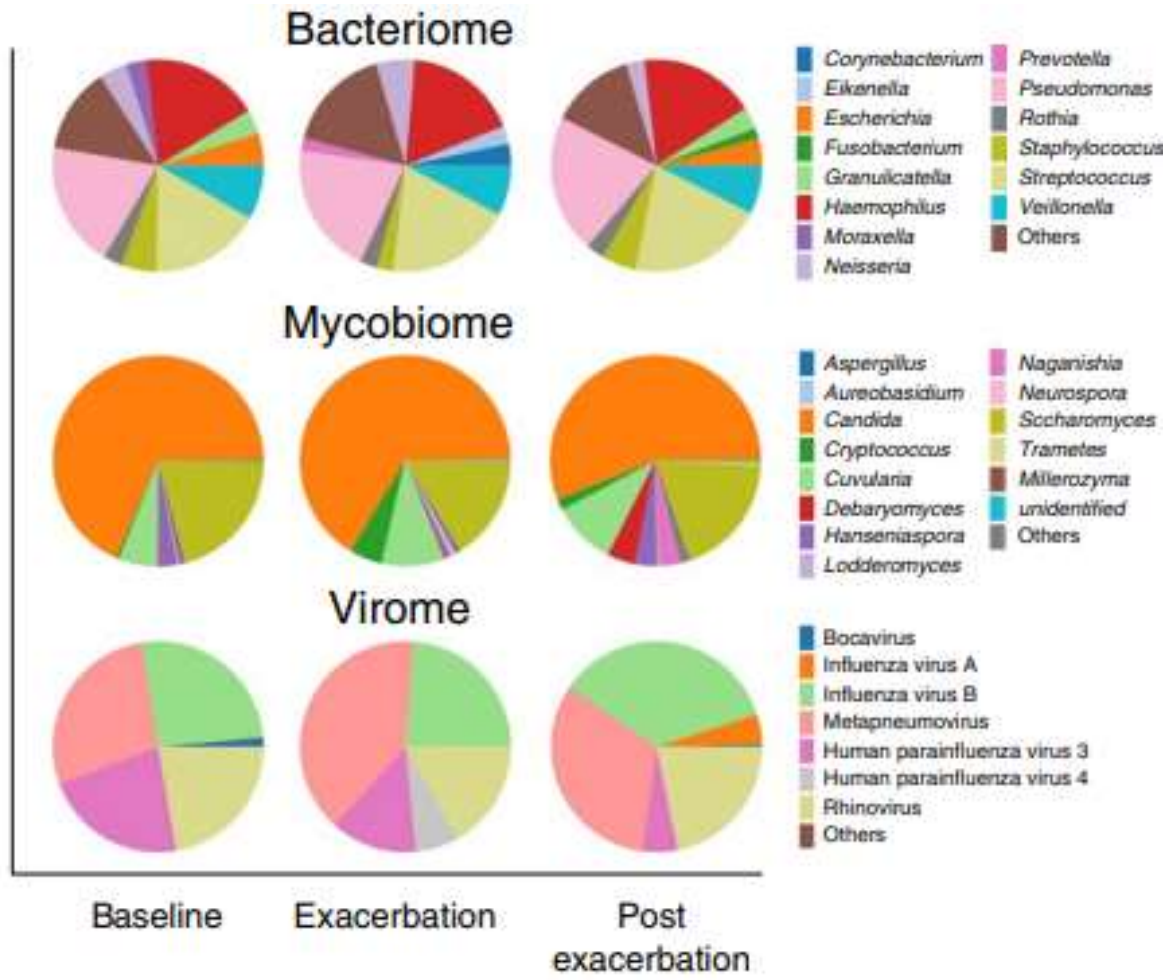
- Used a different approach to the Microbiome, including virus, bacteria and fungus using Weighted Similarity Network Fusion (WSNF) in Bronchiectasis patients, *“interactome”.*
- they used Shotgun Metagenomic Sequencing and 17 virus panel targeting respiratory virus.
- *Pseudomonas* and *Haemophilus* -dominant clusters had lower α-diversity and a more positive correlation with clinical features such as exacerbation.
- High airway viral load (especially Human Para Influenza Virus 3),

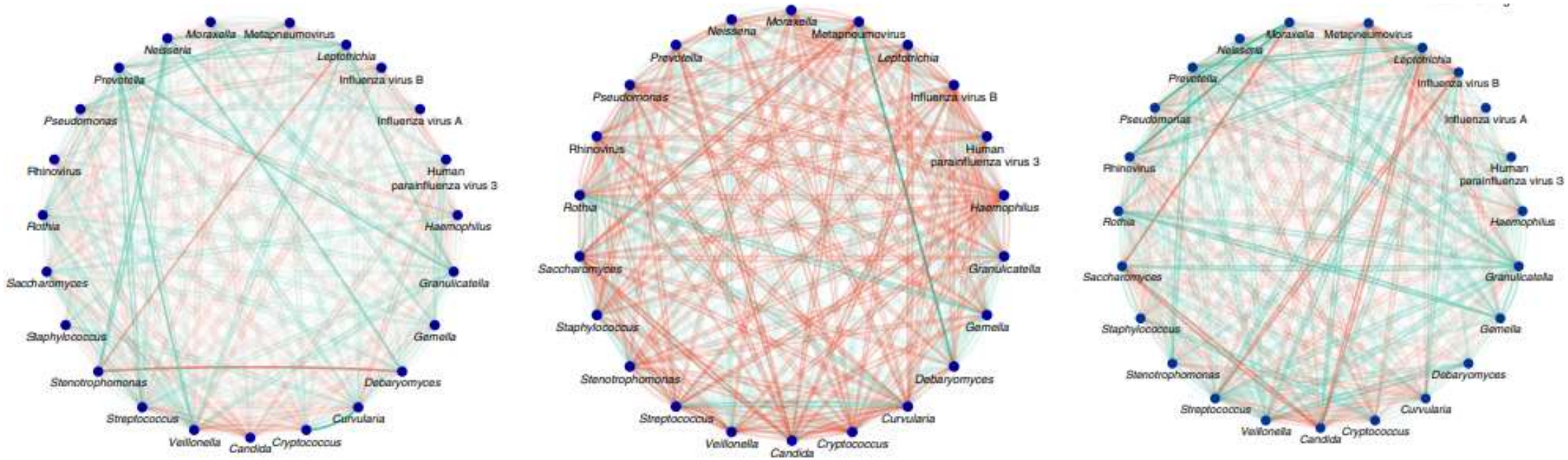


c

	Low exacerbation frequency	High exacerbation frequency	Percentage change
Total no. of microbes in network (no. of nodes)	455	243	–46.6
Total no. of interactions between microbes (no. of edges)	56,221	22,837	–59.4
Total no. of negative interactions as a proportion of total interactions (no. of negative edges)	14,646/56,221 (26%)	7,306/22,837 (32%)	(+6)


Low exacerbation frequency
High exacerbation frequency
Penicillium
Candida
Klebsiella
Fusobacterium
Saccharomyces
Rhinovirus
Prevotella
Porphyromonas
Leptotrichia
Actinomyces
Neisseria
Gemella
Granulicatella
Actinobacillus
Rothia
Veillonella
Aspergillus
Moraxella
Cryptococcus
Streptococcus
Human parainfluenza virus 3
Haemophilus
Pseudomonas
Gemella
Actinobacillus
Fusobacterium
Leptotrichia
Granulicatella
Actinomyces
Human parainfluenza virus 3
Candida
Neisseria
Porphyromonas
Prevotella
Veillonella
Aspergillus
Klebsiella
Penicillium
Cryptococcus
Saccharomyces
Haemophilus
Streptococcus
Interaction
+
−


Bacteriome
Corynebacterium
Eikenella
Escherichia
Fusobacterium
Granulicatella
Haemophilus
Moraxella
Neisseria
Prevotella
Pseudomonas
Rothia
Staphylococcus
Streptococcus
Veillonella
Others
Mycobiome
Aspergillus
Aureobasidium
Candida
Cryptococcus
Cuvularia
Debaryomyces
Hanseniaspora
Lodderomyces
Naganishia
Neurospora
Saccharomyces
Trametes
Millerozyma
unidentified
Others
Virome
Bocavirus
Influenza virus A
Influenza virus B
Metapneumovirus
Human parainfluenza virus 3
Human parainfluenza virus 4
Rhinovirus
Others
Baseline
Exacerbation
Post exacerbation


Moraxella
Metapneumovirus
Neisseria
Leptothrichia
Prevotella
Influenza virus B
Pseudomonas
Influenza virus A
Rhinovirus
Human parainfluenza virus 3
Rothia
Haemophilus
Saccharomyces
Granulicatella
Staphylococcus
Gemella
Stenotrophomonas
Debaryomyces
Streptococcus
Curvularia
Veillonella
Candida
Cryptococcus
Baseline versus exacerbation
Exacerbation versus post exacerbation

- *Pseudomonas* and *Hemophilus* dominant microbiome are found in more frequent exacerbator phenotype.
- Patients receiving macrolide in the presence of *Pseudomonas* have symptomatic change , and this is thought to be due to the drug's anti-inflammatory properties or the presence of co-infection.
- The use of macrolides may also have a role in modifying the *interactome* and behaviour of the microorganisms.

Lung microbiota predict Invasive Pulmonary Aspergillosis and its outcome in immunocompromised patients

- Characterise the lung microbiota in 104 immunocompromised patients using Bacterial 16S ribosomal RNA gene sequencing on Bronchoalveolar Lavage samples.
- Associations between lung dysbiosis in IPA and pulmonary immunity were evaluated by quantifying alveolar cytokines and chemokines and immune cells.
- Patients diagnosed with IPA had decreased alpha diversity,
- *Staphylococcus*, *Escherichia*, *Paraclostridium* and *Finegoldia* were found in increased abundance.

Hérivaux A, etal., Thorax. 2022 Mar;77(3):283-291.

Summarize

- A state of “dysbiosis” or imbalance in the microbial community may be recognized to characterize common airway diseases, including Asthma, COPD, Bronchiectasis and IPF.
- Once microbes enter a niche and become established, a balance must be struck that maintains functional homeostasis between the Microbiome and the host. When imbalance develops *dysbiosis* results.
- What is not clear is whether the differences in microbial community composition themselves mediate pathologic changes in the airways or whether they reflect differences in systemic immune function driven by differences in the development of the Microbiome in early life, when the immune system is most malleable.

- When healthy, the microbial load in the lungs is low and BAL samples contain a predominance of bacterial taxa also found in the mouth.

- When diseased, the microbial load in the lungs increases/changes and BAL samples often contain numerous bacterial taxa not found in the mouth, indicating selective pressures in the lungs for persistence, colonization and growth.

- More studies are needed to define link between disease phenotypes and the Microbiome.

Future Direction and Challenges

- Absence of studies from samples of microbiota from normal lungs.
- More reference data of microbes (including bacteria, fungi and virus)
- Synthesis of the data will require integrating the findings from careful study of phenotypic features of disease/health in the subjects studied and careful study of the microbiota of their respiratory tract with information gathered through “genomics” analysis of the host and the microbiome, genome and metabolome.
- Should altering lung Microbiome/*interactome* be seen as a potential therapy ?