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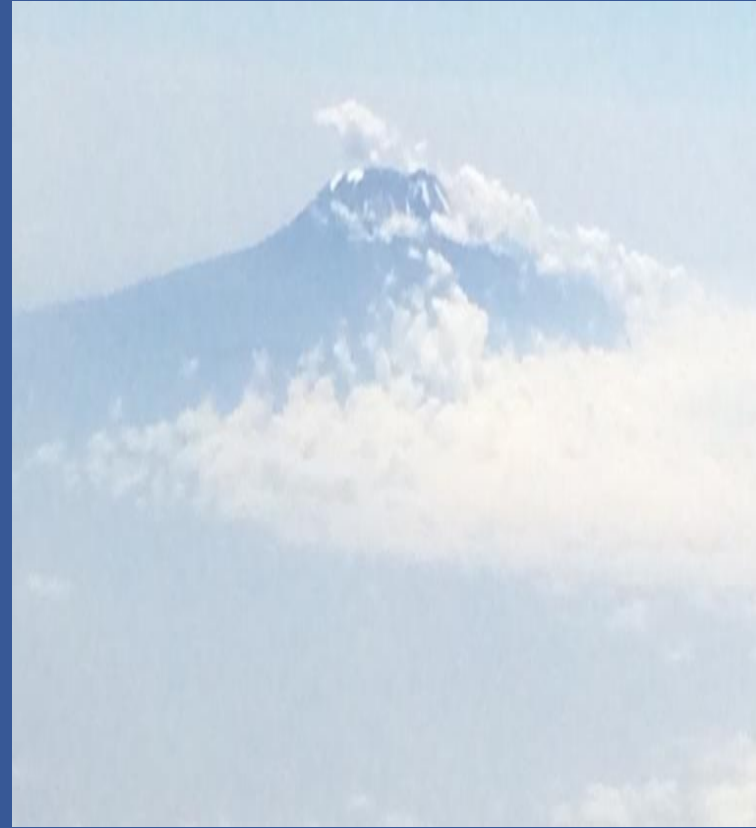
Faculty of
Health Sciences

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

The Microbiome in Allergic Disease

Robin J Green

PhD, DSc



Conflict of Interest

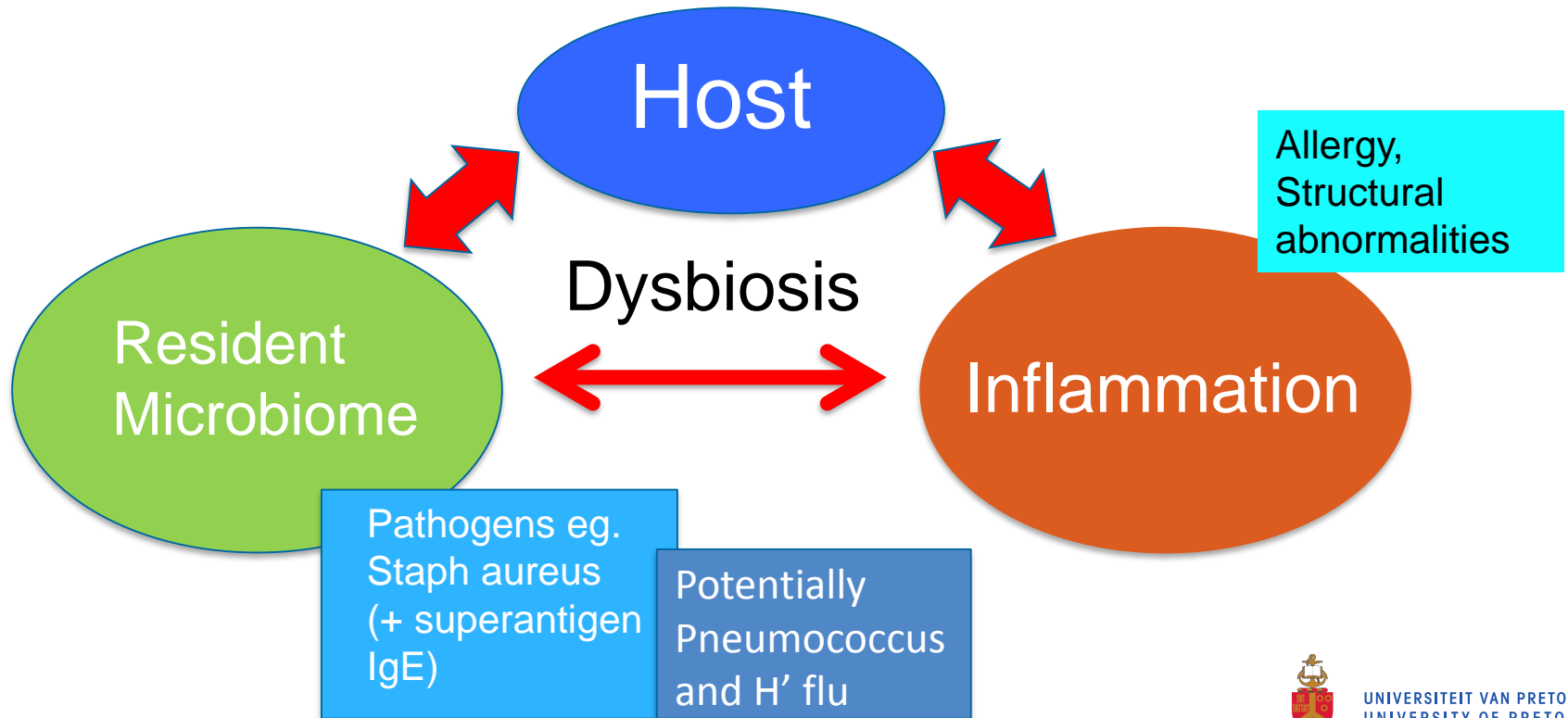
- Executive Member: CMSA
- Speakers Bureau: Abbott/Abbvie, Actavis, Aspen/GSK, AstraZeneca, Cipla, Dr Reddy's, MSD, Nestle, Pfizer, Pharmaplan, Roche, Sanofi, Wyeth
- Advisory Board: Abbott/Abbvie, Aspen/GSK, AstraZeneca, MSD, Pfizer, Pharmaplan, Roche, Sanofi
- Research Grants: Abbott, Discovery Health, MSD, NRF, ALLSA



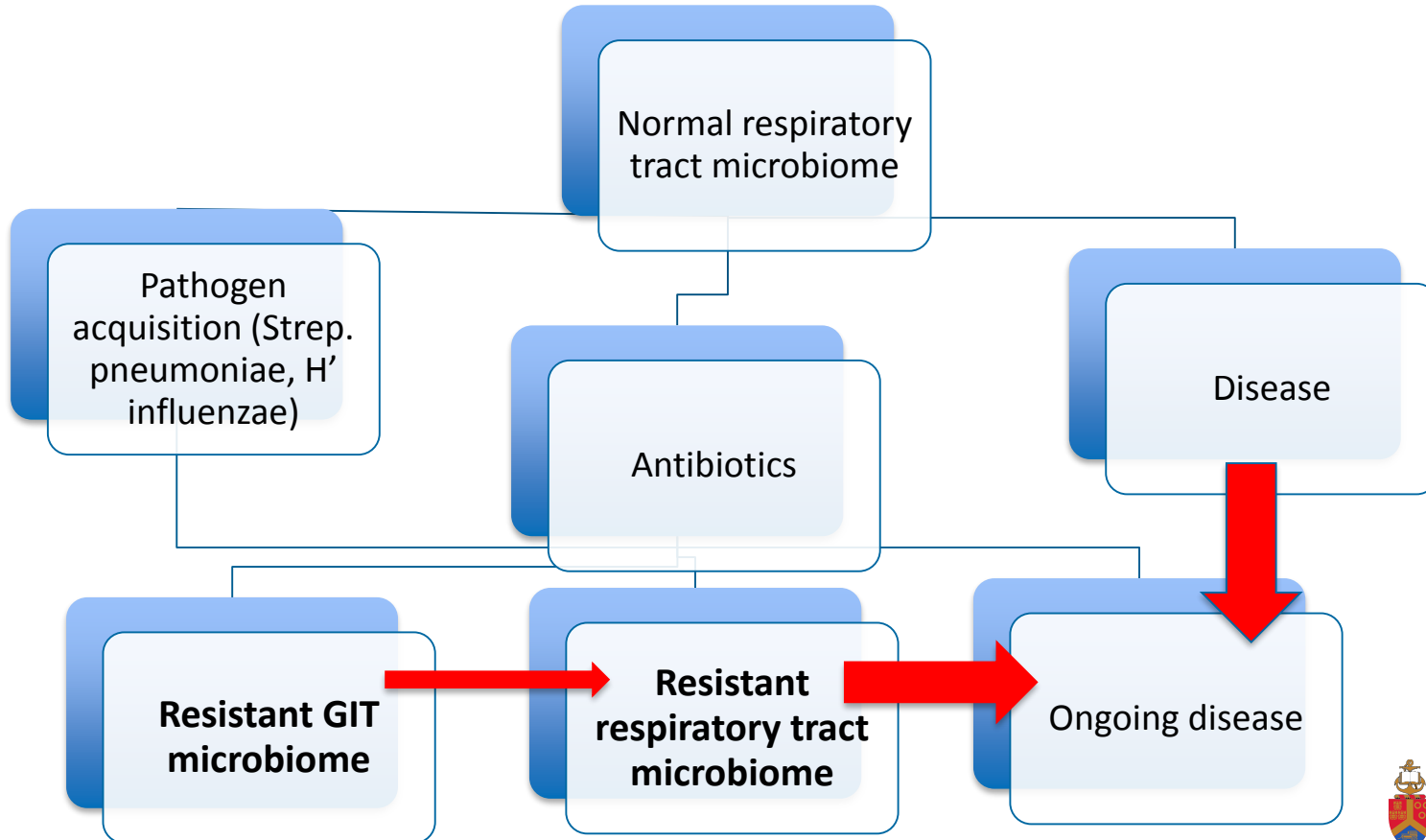
Introduction

- The microbiome is the microbial organisms that inhabit every system of the body
- The resident microbial pan-genome outnumbers that of humans by at least 100 x in functional gene content
- They contribute to metabolic capacity, **drive immune development** and afford mucosal protection
- Disturbances in microbiome are associated with many inflammatory and autoimmune diseases
- There may be solutions to supplement normal biomes

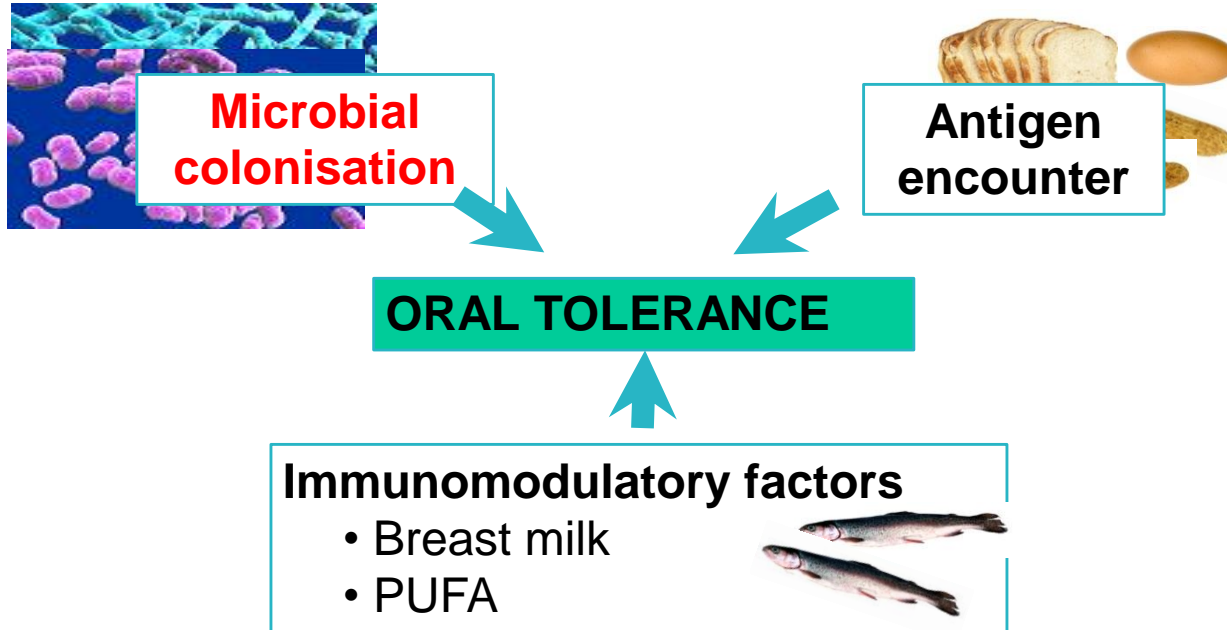
Microbiome – Inflammation Interaction



The Microbiome Problem



Origins of Allergy

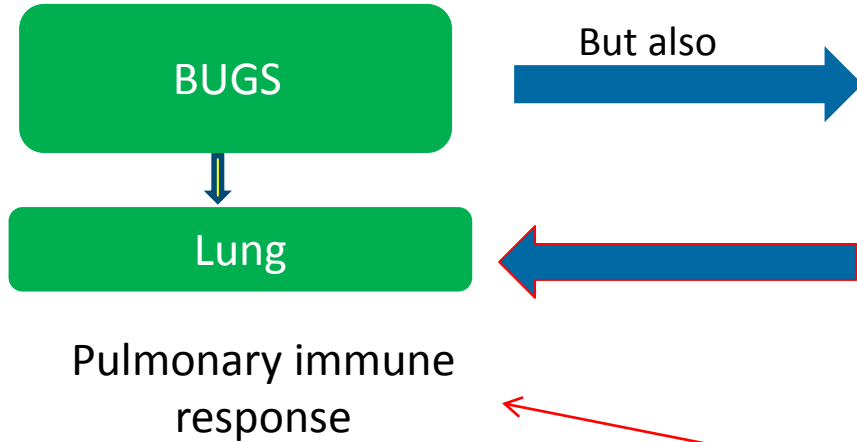


AIM OF INTERVENTIONS:

Promote **favourable conditions** for normal **tolerance** during **critical period** of immune development

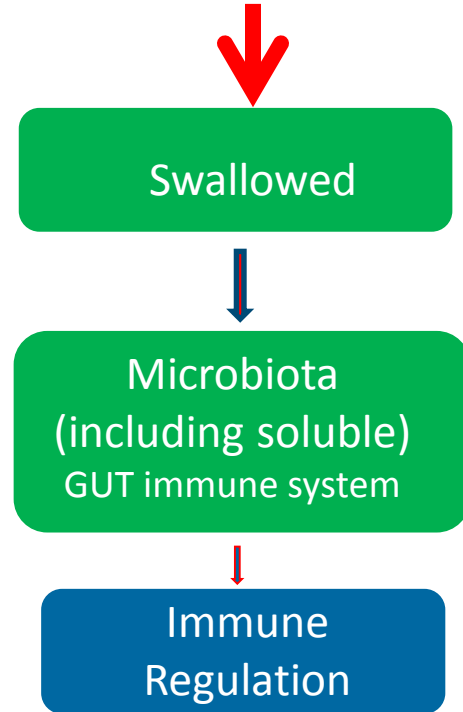


GUT - Airway Axis



But also →

Lactobacilli Bifidobacter



←

←



The Hygiene Hypothesis

- Term first coined in 1989 by Professor David Strachan (St George's, University of London, London, United Kingdom).
- Derived from his study showing that a child's risk of developing allergic rhinitis ("hay fever") was inversely related to the number of older siblings in the family
- Microbial exposure in early life protects against allergic rhinitis, eczema, and asthma

Strachan DP. Br Med J 1989;299:1259–60



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The Hygiene Hypothesis

Better terms may be:

"microbial hypothesis" (avoiding an overemphasis on cleanliness)

"old friends hypothesis" (implying that microbes that were beneficial for immune system development have been eliminated or replaced)

"biodiversity hypothesis" or "biome depletion"



GUT Microbial Diversity and Asthma

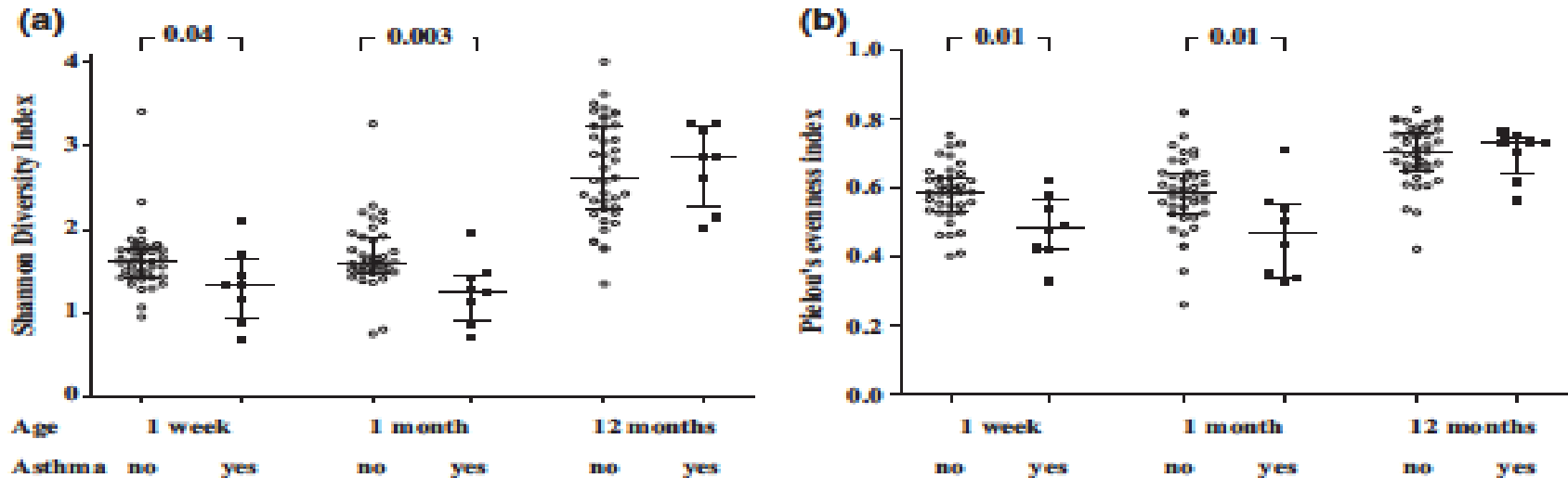
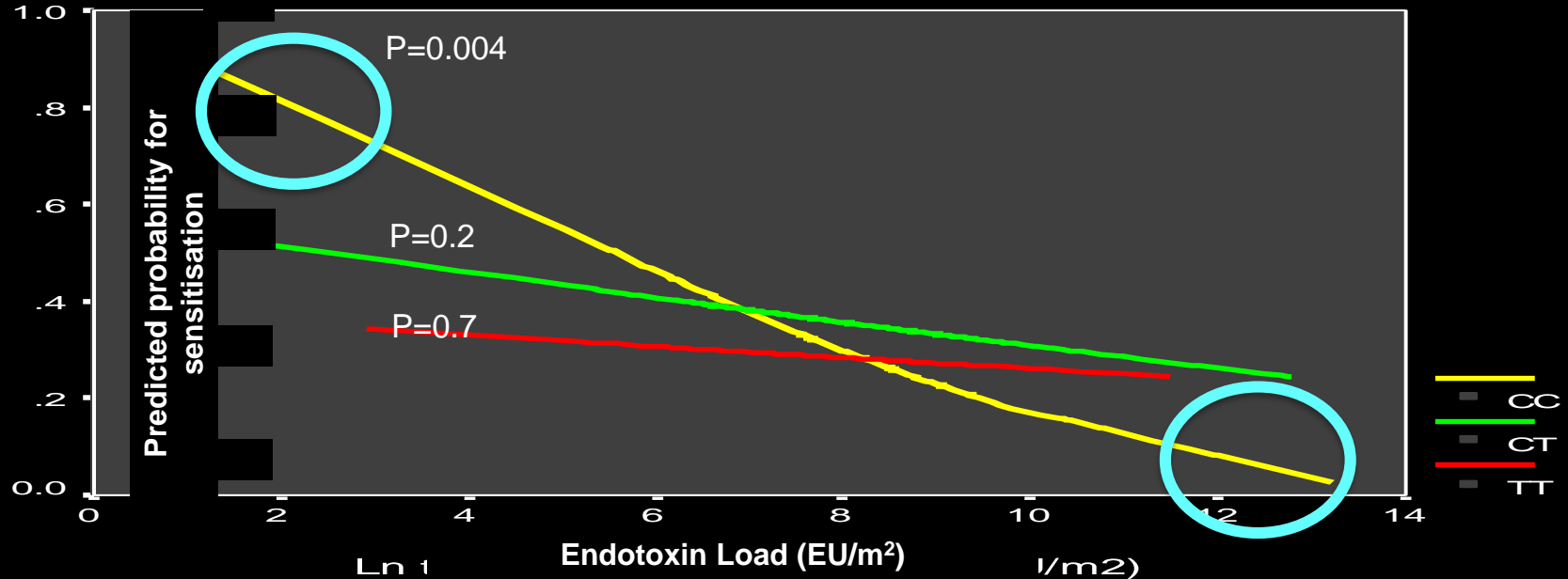


Fig. 1. The Shannon diversity index (a) and Pielou's evenness index (b) of the gut microbiota in stool samples at 1 week, 1 and 12 months of age in infants with (black circles) and without (clear circles) asthma at 7 years of age. The 25th, 50th and 75th percentiles are indicated. Groups were compared using Mann-Whitney *U*-test.

CD 14 Promoter Polymorphism, Endotoxin Exposure and Sensitisation



Promoting Healthy GUT Probiotic Bugs

- Vaginal Birth (Children born by C-section are at increased risk of allergy)
- Birth out of hospital
- Birth and infancy on a farm
- Avoid unnecessary antibiotics
- ? Probiotic supplementation



Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children

Michelle M. Stein, B.S., Cara L. Hrusch, Ph.D., Justyna Gozdz, B.A., Catherine Igartua, B.S., Vadim Pivniouk, Ph.D., Sean E. Murray, B.S., Julie G. Ledford, Ph.D., Mauricius Marques dos Santos, B.S., Rebecca L. Anderson, M.S., Nervana Metwali, Ph.D., Julia W. Neilson, Ph.D., Raina M. Maier, Ph.D., Jack A. Gilbert, Ph.D., Mark Holbreich, M.D., Peter S. Thorne, Ph.D., Fernando D. Martinez, M.D., Erika von Mutius, M.D., Donata Vercelli, M.D., Carole Ober, Ph.D., and Anne I. Sperling, Ph.D.
N Engl J Med 2016; 375:411-421 | August 4, 2016 | DOI: 10.1056/NEJMoa1508749

Despite the similar genetic ancestries and lifestyles of Amish and Hutterite children, the prevalence of asthma and allergic sensitization was 4 and 6 times as low in the Amish

Median endotoxin levels in Amish house dust was 6.8 times as high



Probiotic Supplementation

- The current role of probiotic supplementation is unclear
- Studies supporting benefit of probiotics in prevention, and studies that fail to support benefit.
- The ultimate answer to the probiotic strategy may well depend on actual bacterial strains (not all organisms have equal benefit), dose, viability and timing of intervention
- There is insufficient evidence at present to give a clear recommendation

Airway Microbiota and Asthma Link

End point and bacterial species	Hazard Ratio	Adjusted HR
First wheezy episode		
Strep pneumoniae	1.54	1.53 (0.97 – 2.40)
H influenzae	1.49	1.27 (0.82 – 1.97)
Persistent wheeze		
Strep pneumoniae	1.71	1.41 (0.65 – 3.07)
H influenzae	2.85	2.73 (1.36 – 5.48)
Acute severe exacerbations of wheeze		
Strep pneumoniae	1.80	2.02 (0.79 – 5.17)
H influenzae	3.23	3.78 (1.36 – 5.48)
Hospitalization for wheeze		
Strep pneumoniae	1.90	2.33 (0.72 – 7.54)
H influenzae	3.81	4.09 (1.65 – 10.15)



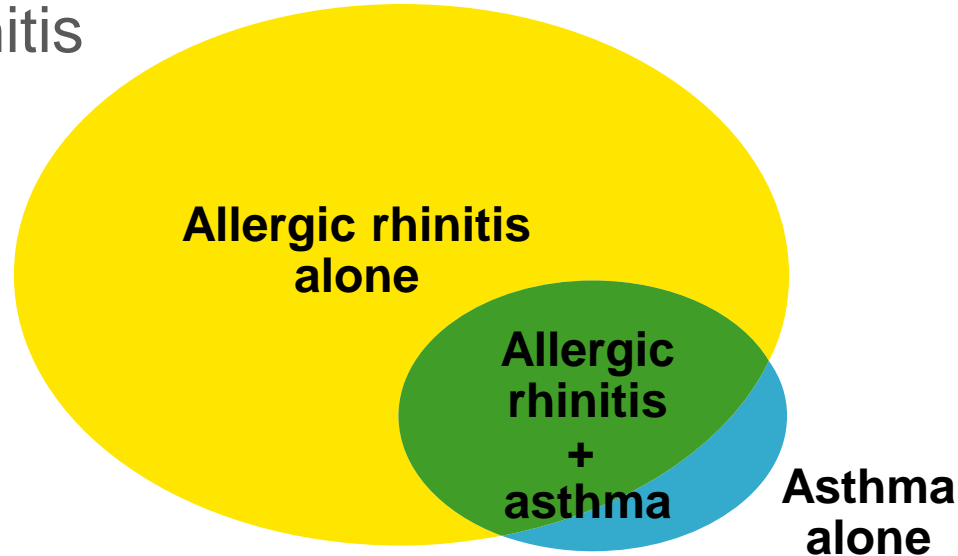
Airway Microbiota and Asthma Link

Outcome	Colonized	Not Colonized	OR
Asthma at 5 yrs			
Yes	17 (33%)	20 (10%)	4.57 (2.18 – 9.57)
No	35	188	

Bisgaard H, et al. N Eng J Med 2007;357:1487-95

Most Patients with Asthma Have Allergic Rhinosinusitis

Approximately **80%** of asthmatics have allergic rhinitis



Gene-wide Microbiome Studies - Confounders

- Antibiotic use
- Steroid use
- Sampling method
- Exacerbations
- Variability in constitutive epithelial host defense molecule secretion based on the region of the nose and sinuses



16S rRNA Gene Wide Sequencing

- Anaerobic bacteria (Diaphorobacter, Peptoniphilus) in 78% and 72% of CRS cases, respectively, but not identified in control cases
- ***S. aureus* was found in half of the CRS cases, while it was detected in all controls**



16S rRNA Gene Wide Sequencing

Pseudomonas

Citrobacter

Haemophilus

Propionibacterium

Staphylococcus

Streptococcus



Microbiome in Specific Co-morbidities

- The sinus microbiome of CRS patients with asthma had significant differences compared with non-asthmatic CRS cases
- Phylum level in asthmatic CRS cases was more similar to controls than non-asthmatic patients with CRS
- Furthermore, at the genus level, *Prevotella*, which had a relative abundance of only 1.5% in controls and 0.6% in asthmatic CRS cases, had a significantly higher relative abundance of 7.7% in non-asthmatic CRS
- A similar pattern was observed for *Staphylococcus*, which had a trend towards a lower abundance in CRS compared to controls, but a trend towards higher abundance in non-asthmatics within the CRS group

Fungal Microbiome

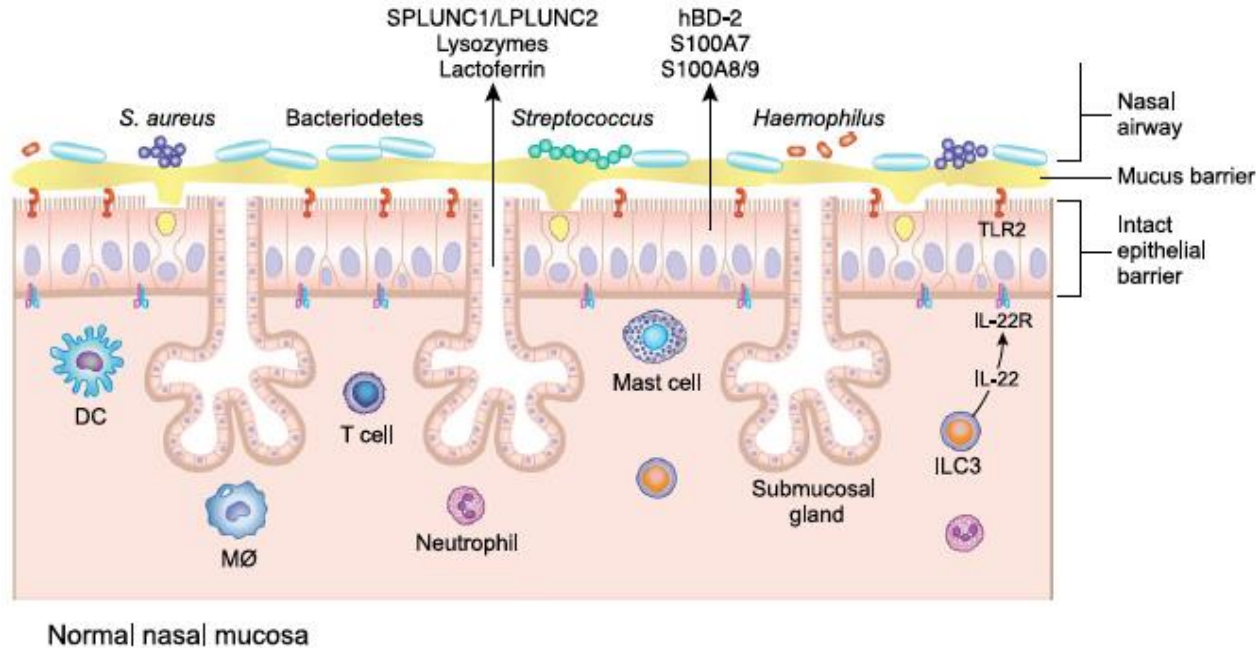
- There is a fungal microbiome in CRS
- Species differ in different studies
- Often found in normal controls
- Including Candida, Aspergillus, Mucor sp.



Viral Microbiome

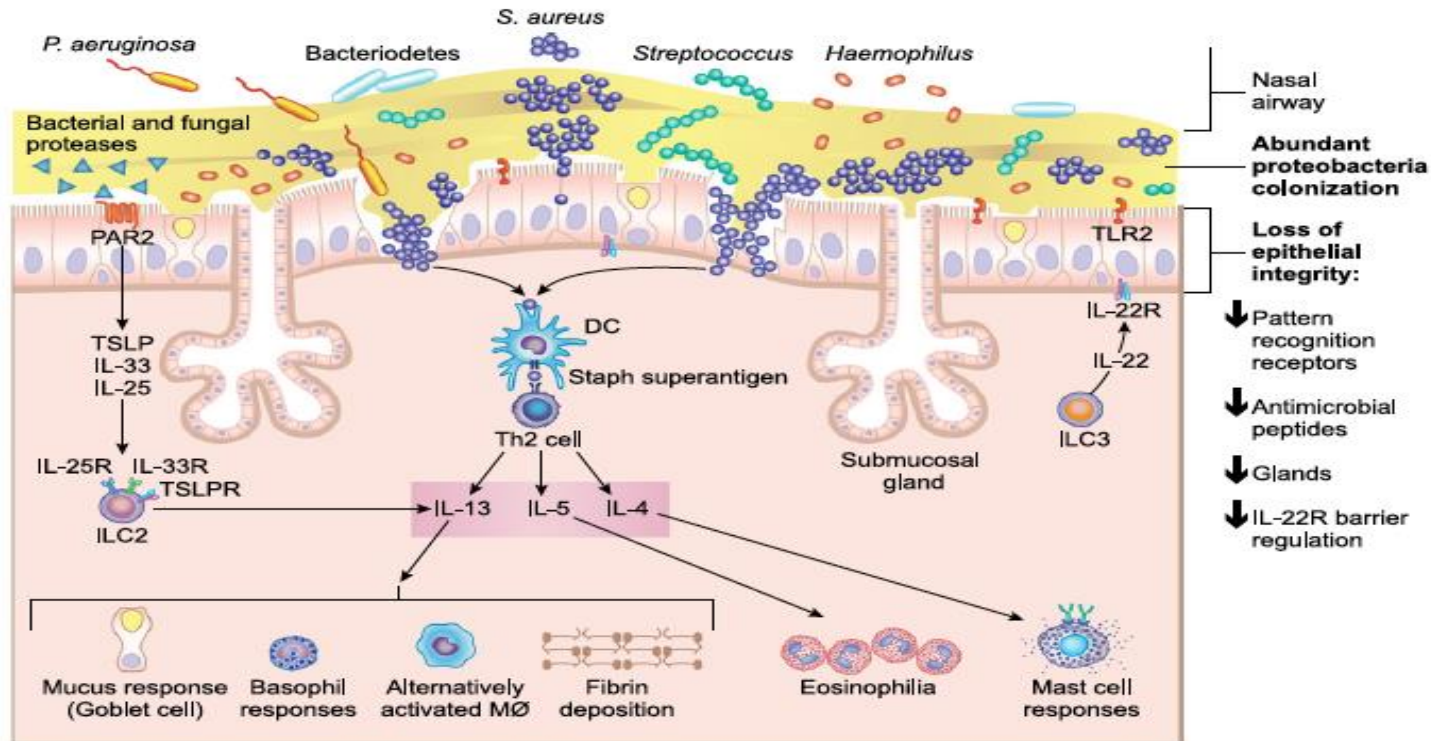
- Using multiplex PCR for respiratory viruses
- Viral nucleic acid sequences found in 64% of sinus scrapings and 50% of nasal lavage samples in the CRS group
- Significantly higher than controls (30% and 14% in scraping and lavage, respectively)
- Rhinovirus (RV) was the most frequently detected virus

Mechanisms of Healthy Airway Microbiome Stability



Mahdavinia M, et al. Clin Exper Allergy 2015;46:21–41

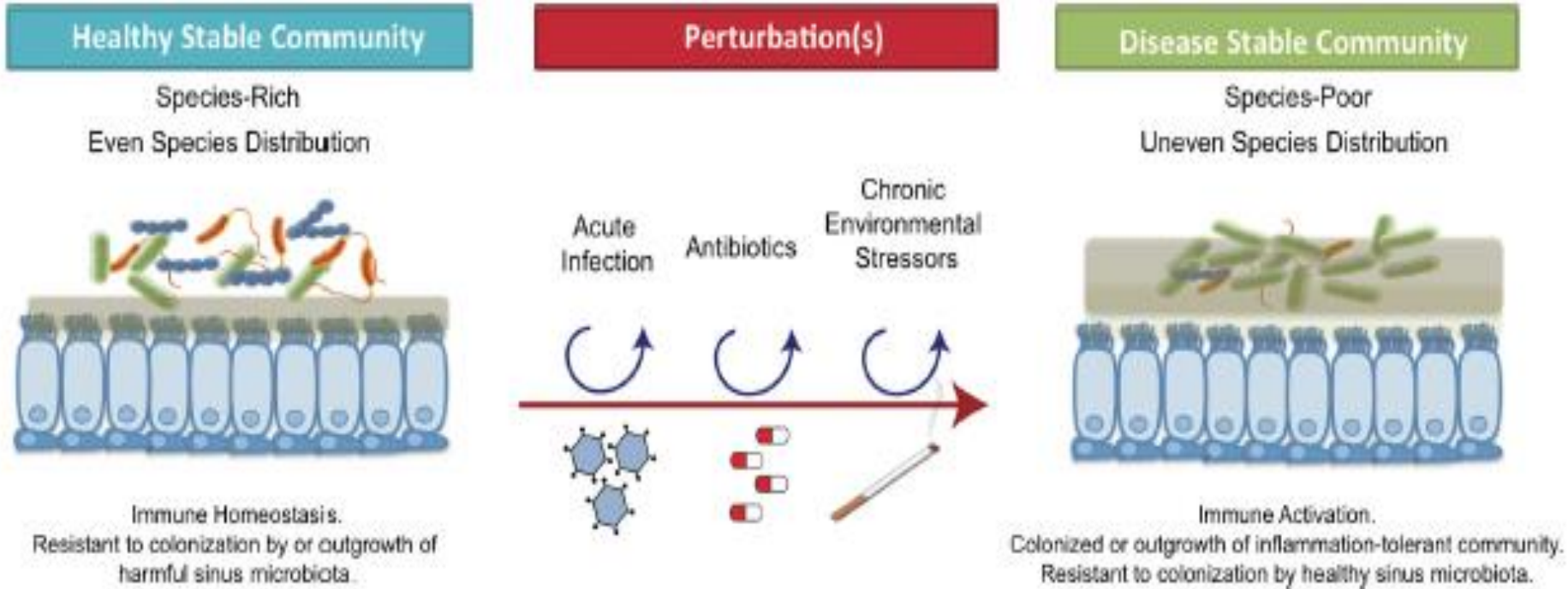
Disturbed Microbiome



Chronic rhinosinusitis (CRS)

Mahdavinia M, et al. Clin Exper Allergy 2015;46:21–41

From Health to Disease



Thank You

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