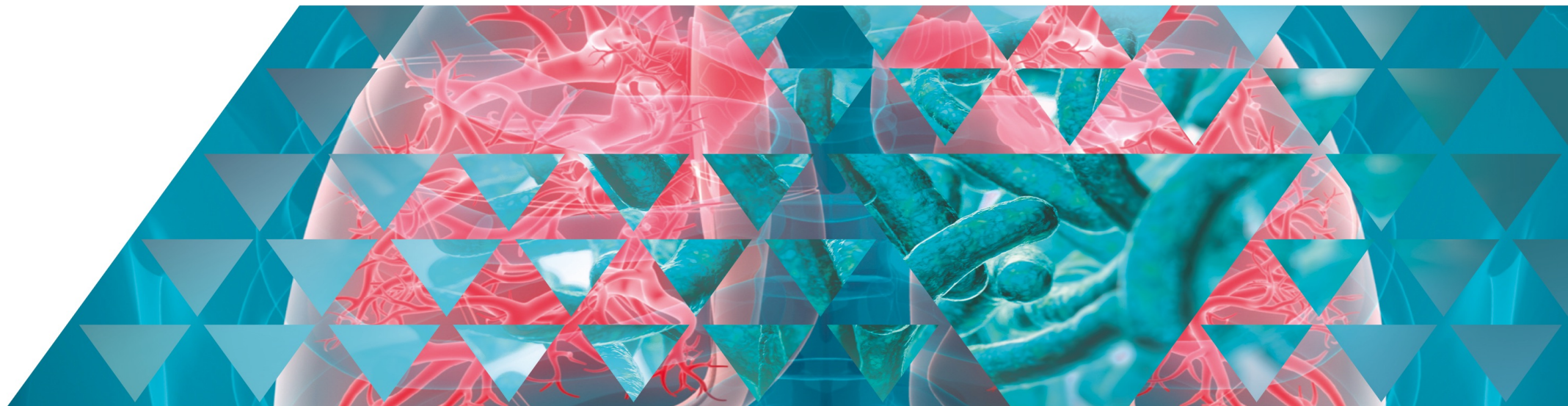




# Host-targeted **A**pproaches for **P**revention and treatment *of* **H**ospital-**A**cquired **P**neumonia



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847782.

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## Respiratory microbiome modulation and pneumonia

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**Nantes Université, UMR 1064 – CR2TI, France**

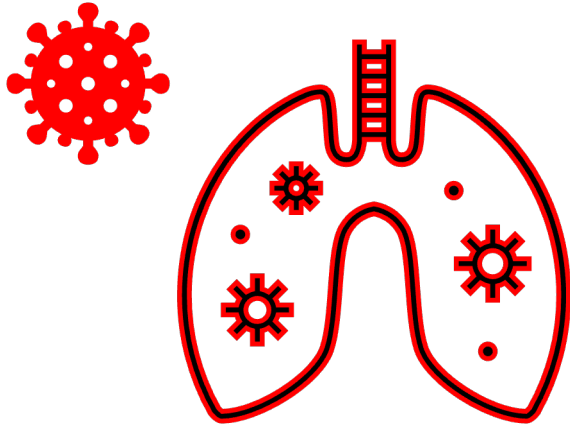
**CHU Nantes, Service d'Anesthésie Réanimation chirurgicale,**

**University of Melbourne, Dpt Microbiology and Immunology**

e-mail: [antoine.roquilly@chu-nantes.fr](mailto:antoine.roquilly@chu-nantes.fr)

Twitter [@RoquillyAntoine](https://twitter.com/RoquillyAntoine)

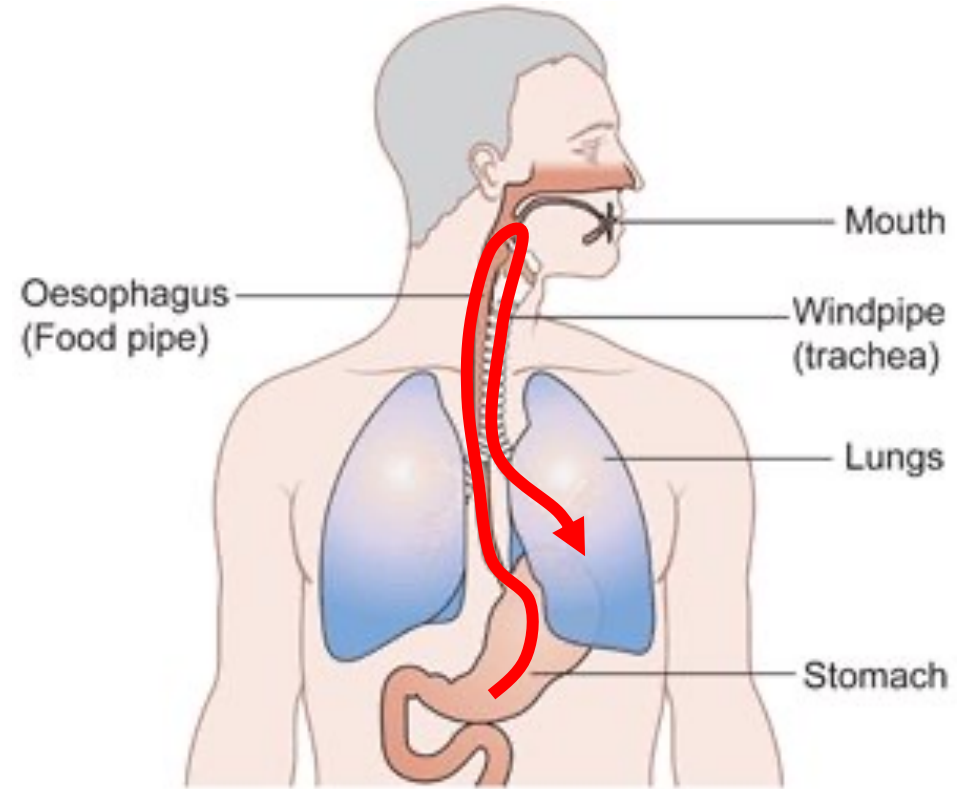
# Causes of pneumonia : classical view



Encounter with virulent pathogens

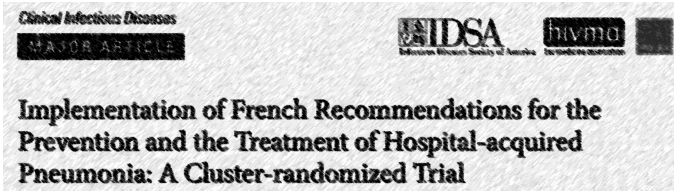


Cross- contamination

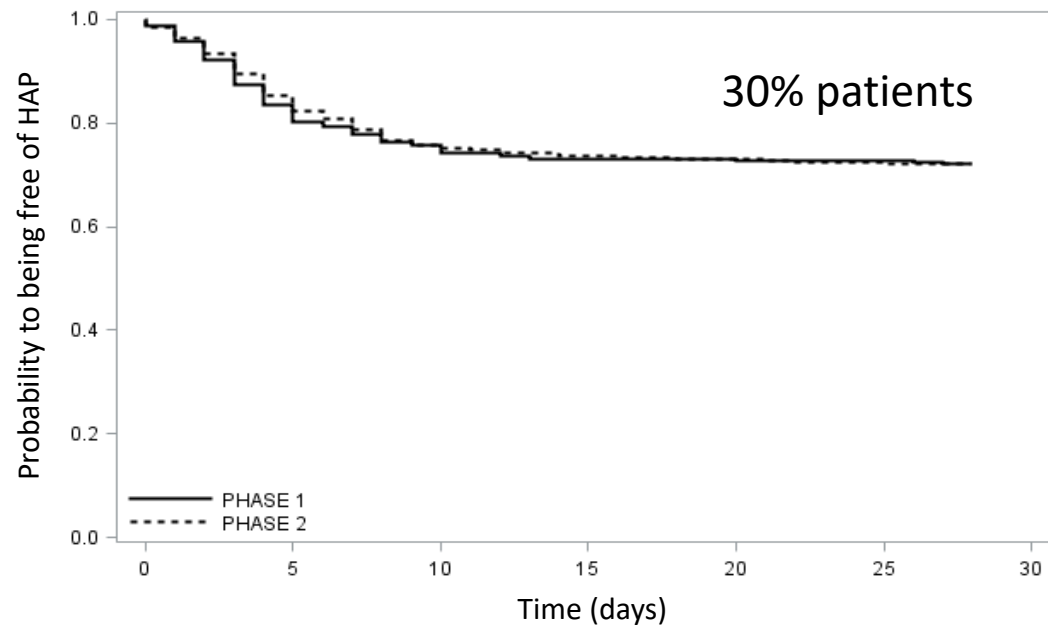


Colonization from digestive tract

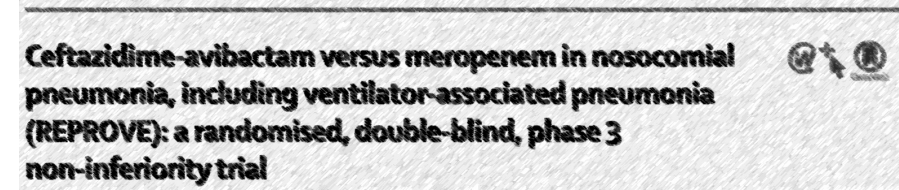
# Treatment failures, a **false understanding** of the pathophysiology?



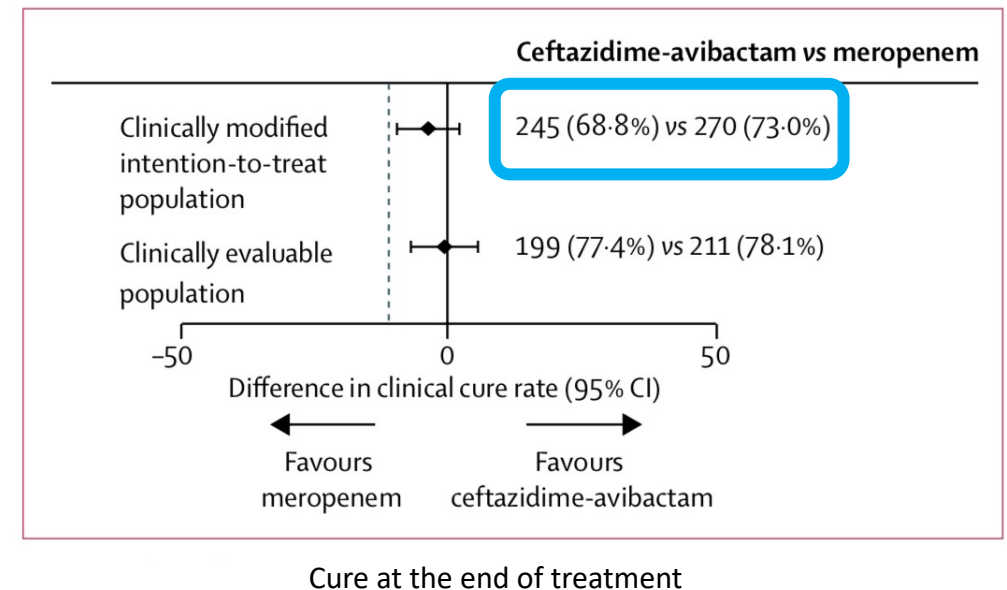
Roquilly et al. CID 2021



500.000 HAP every year in Europe  
(ECDC 2017)



Torres et al. Lancet Infect Dis 2018

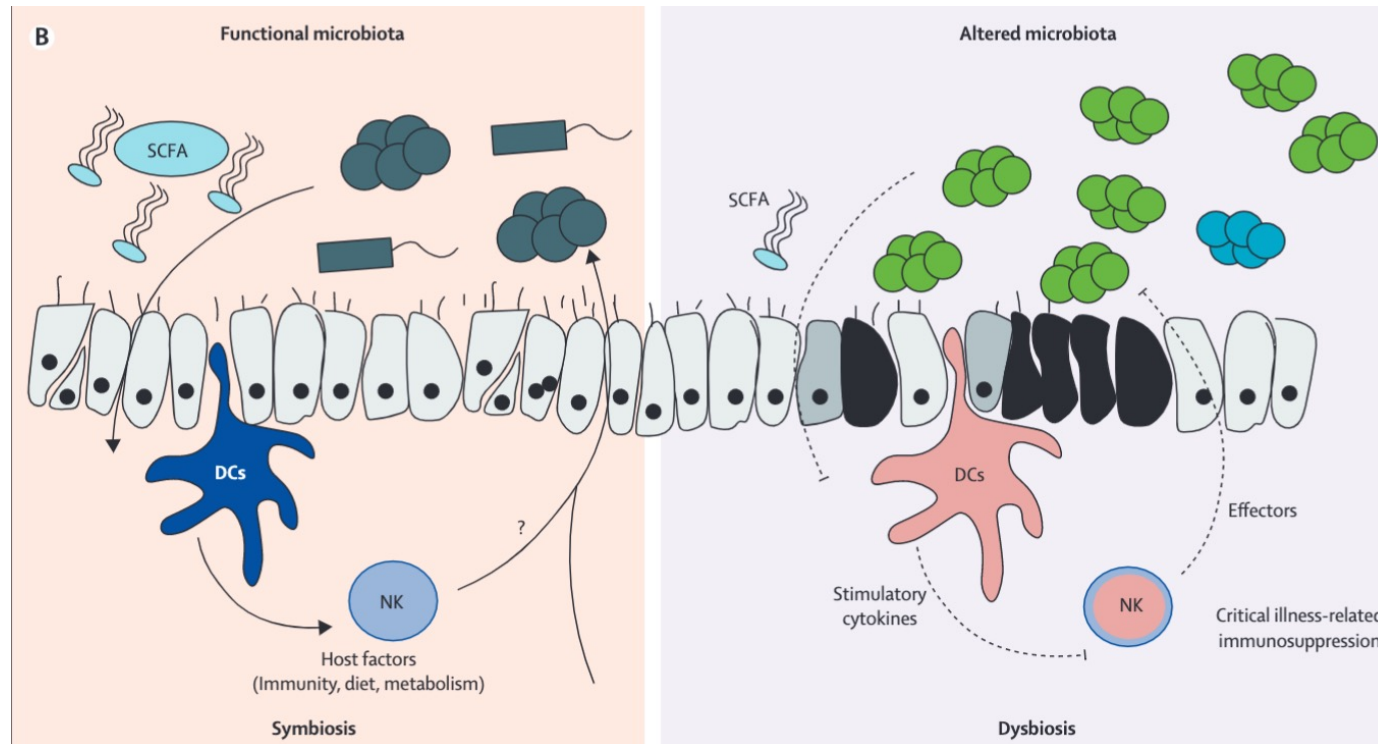


30% of treatment failure

# Pathophysiology and sepsis or sepsis ?

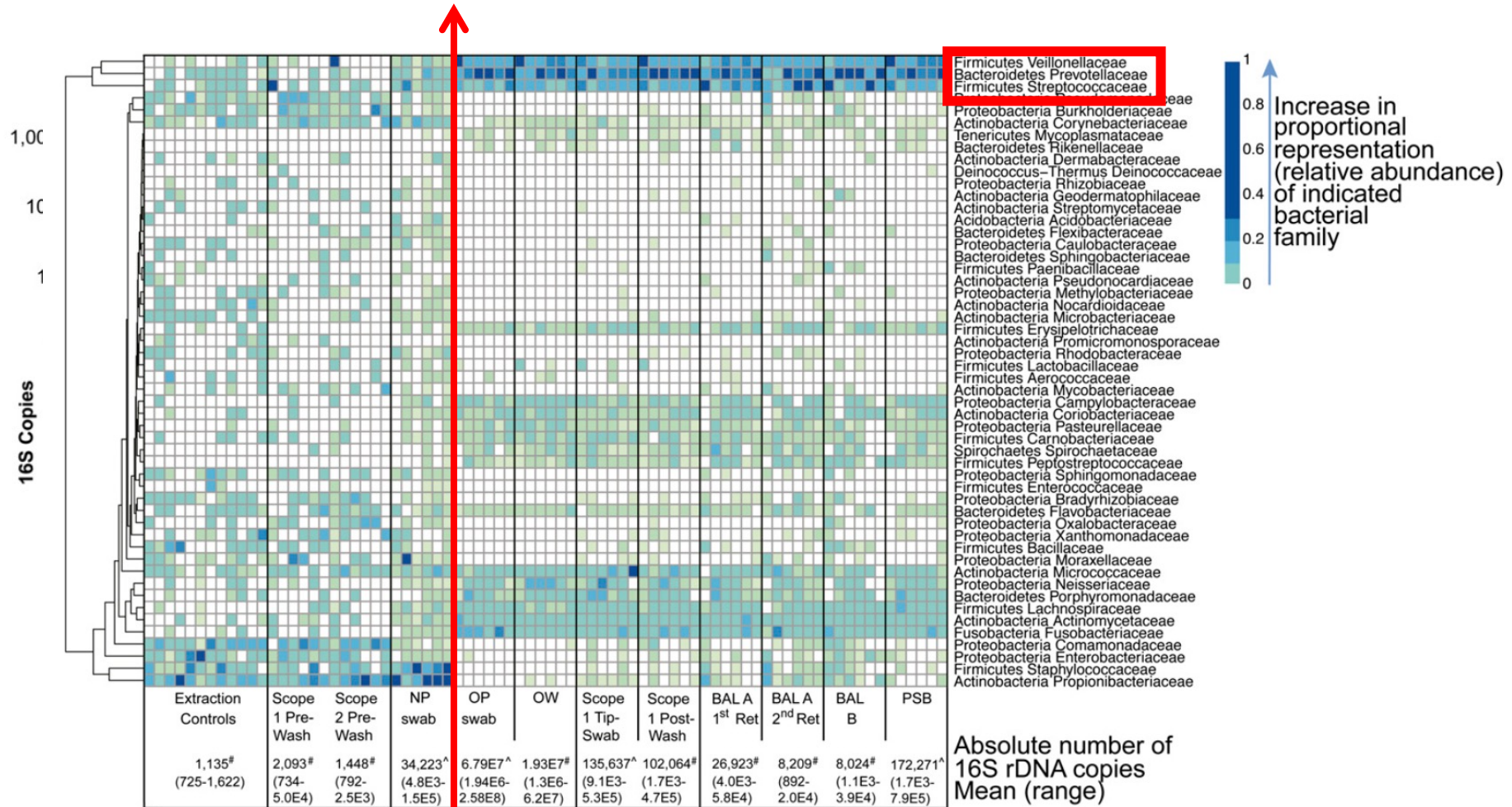
1. Heterogeneity starts by differentiating **infections of a sterile tissue from mucosal infections**

2. **Dysbiosis**, a refined concept of mucosal infection pathophysiology



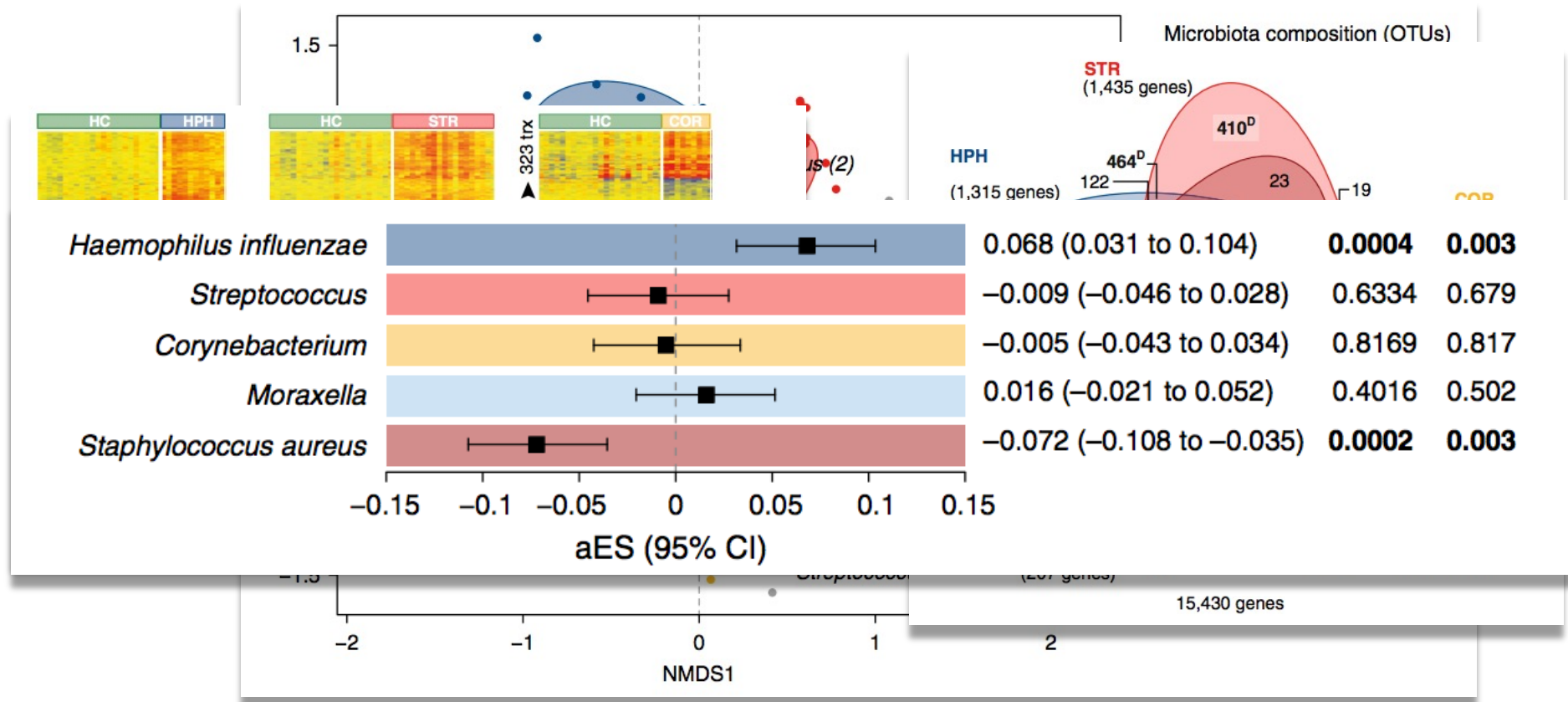
# Respiratory microbiota

## What can we learn? – healthy lungs



NP : nasopharynx    OP : Oropharynx

# The respiratory microbiota challenges the concept of the “dominant bacteria”



Exemple of a viral pneumonia (Respiratory Syncytial Virus Infection)

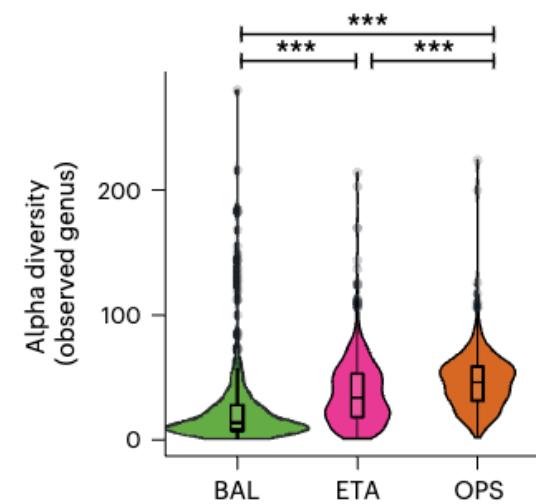
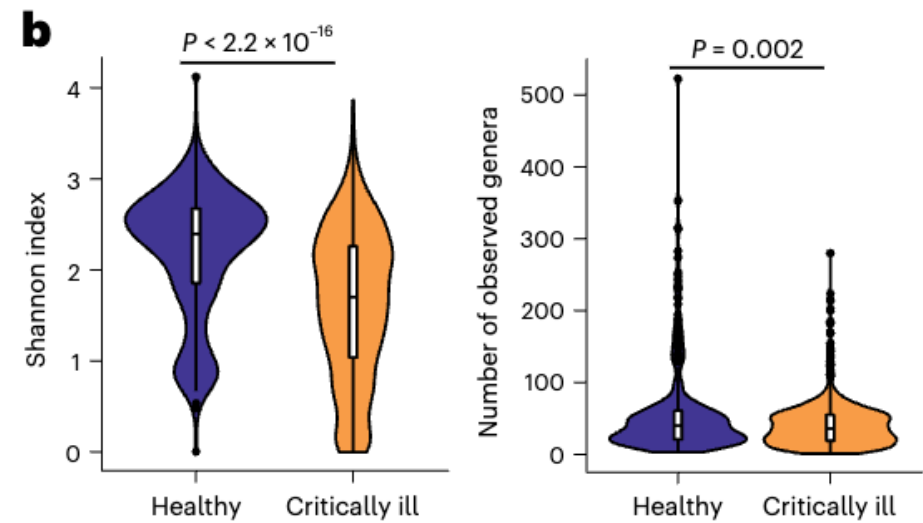
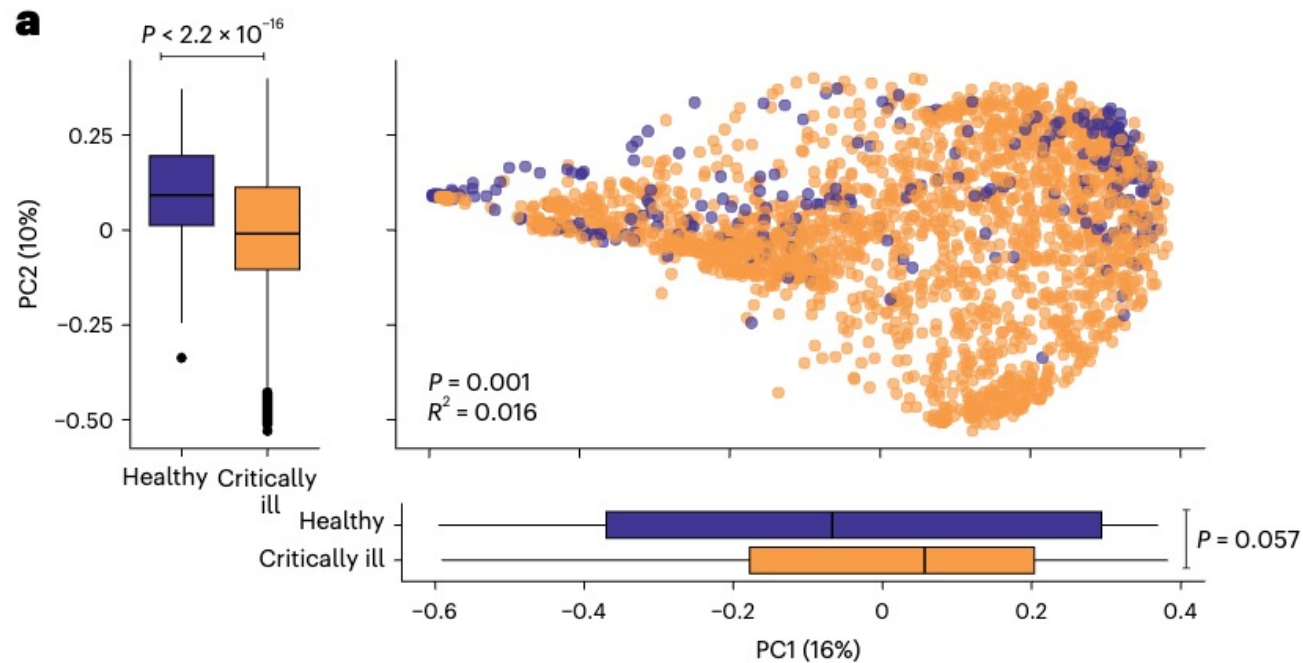
# Robust airway microbiome signatures in acute respiratory failure and hospital-acquired pneumonia

Received: 17 May 2023

Accepted: 27 September 2023

Published online: 13 November 2023

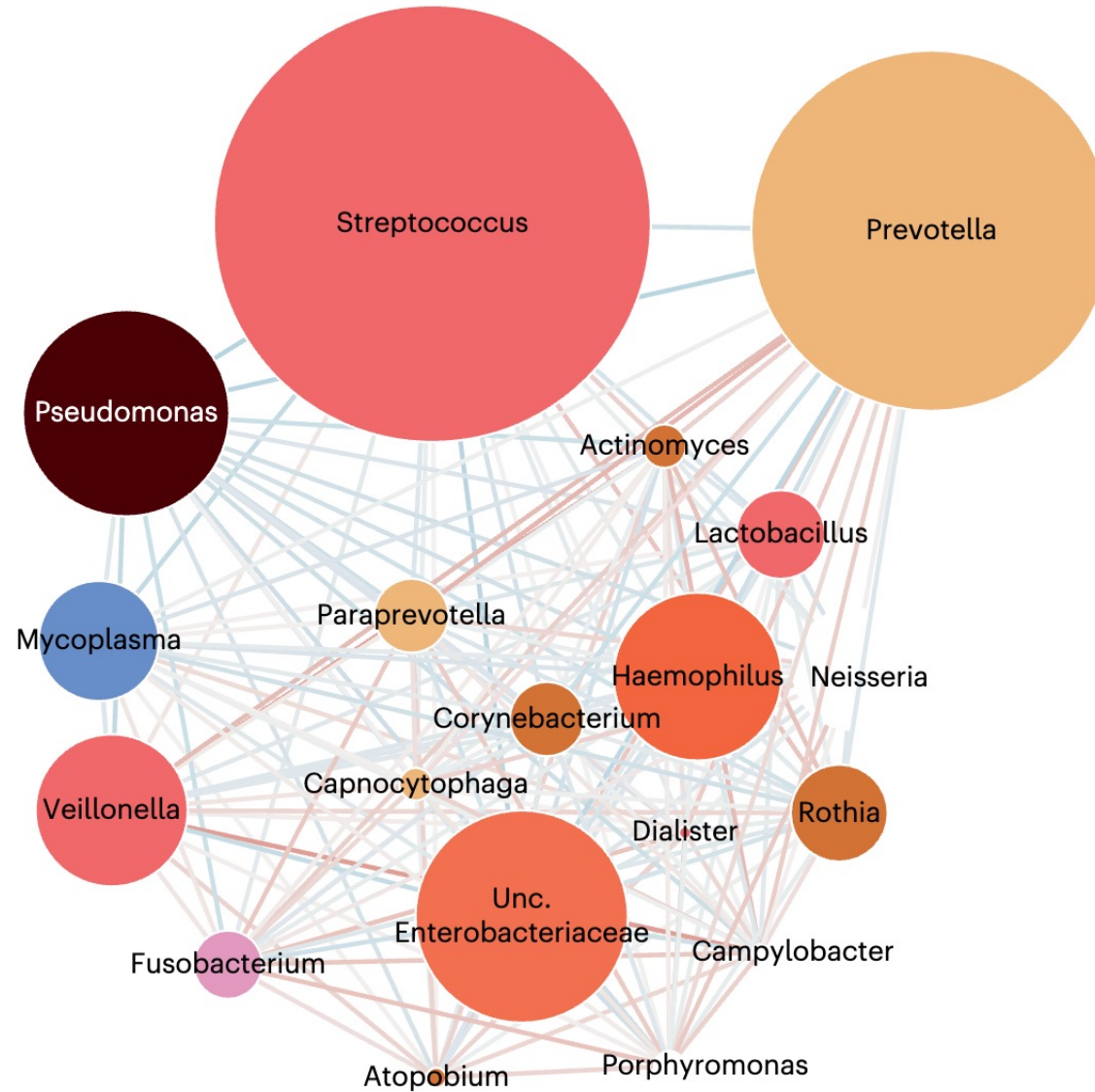
Emmanuel Montassier<sup>1,2</sup>✉, Georgios D. Kitsios<sup>3,4</sup>, Josiah E. Radder<sup>3,4</sup>,  
 Quentin Le Bastard<sup>2</sup>, Brendan J. Kelly<sup>5</sup>, Ariane Panzer<sup>6</sup>, Susan V. Lynch<sup>6</sup>,  
 Carolyn S. Calfee<sup>7</sup>, Robert P. Dickson<sup>8,9,10</sup> & Antoine Roquilly<sup>1,11,12</sup>✉



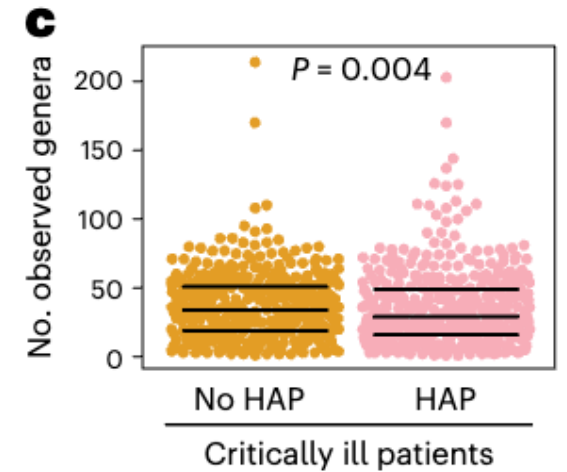
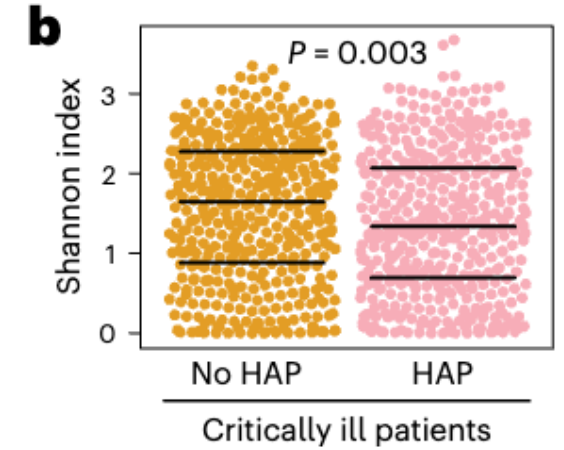
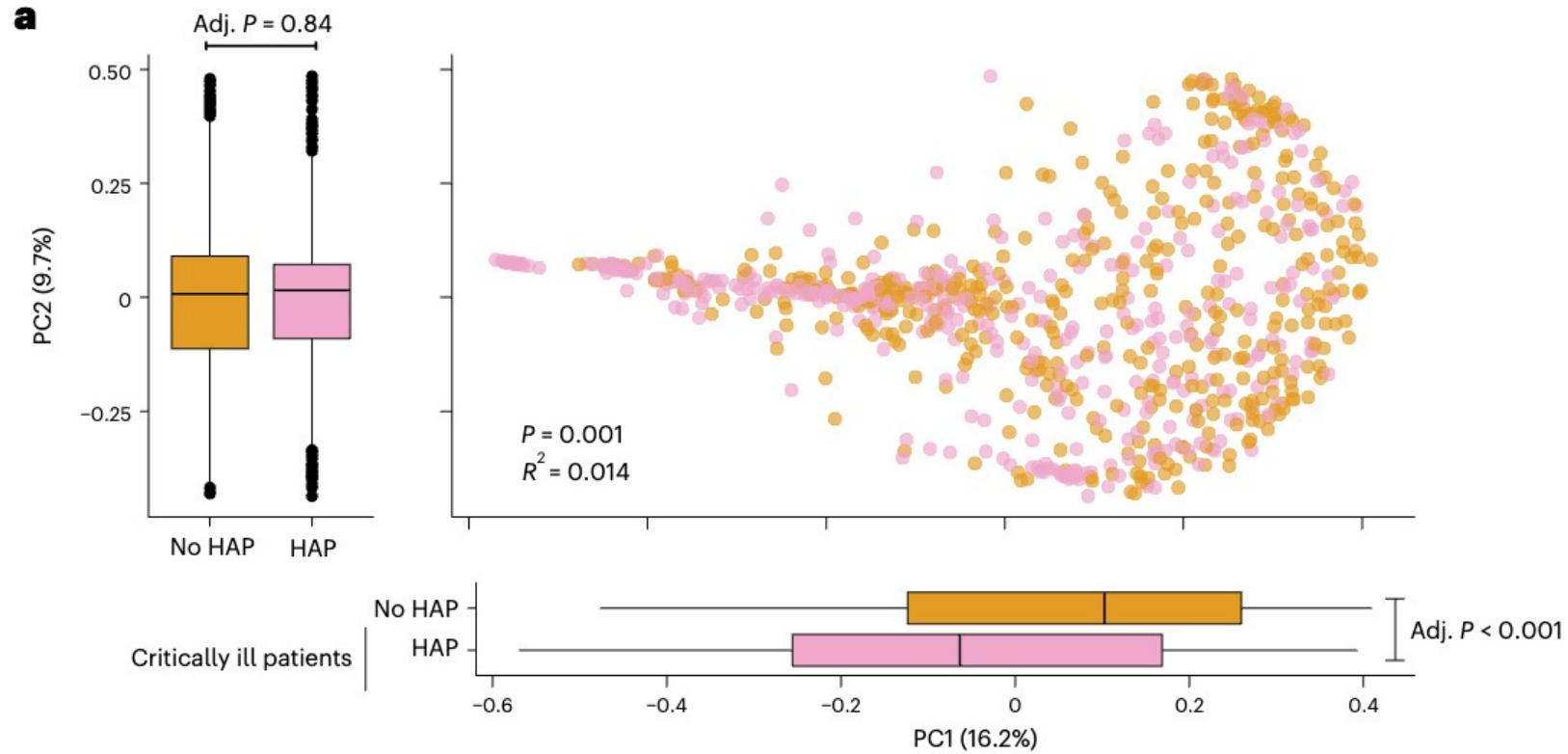


# The respiratory microbiota

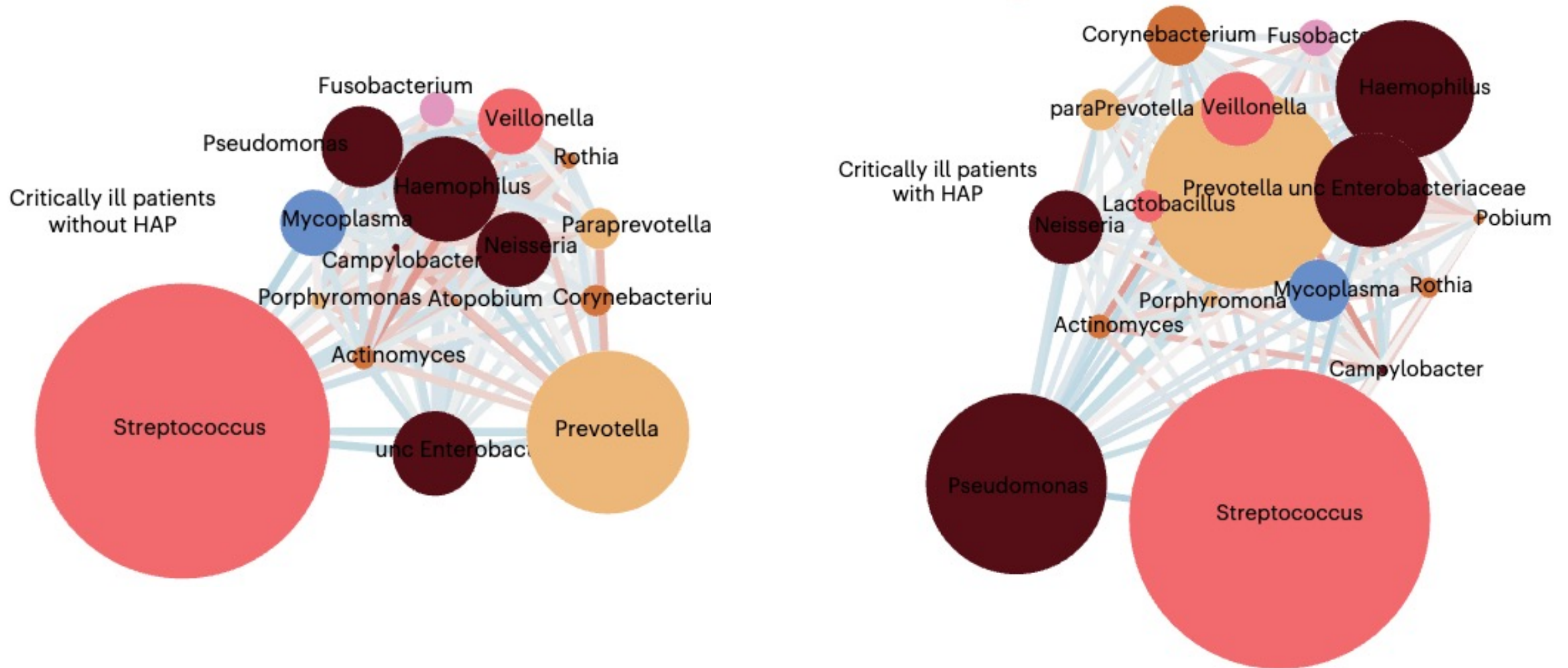
*Healthy respiratory microbiome core*



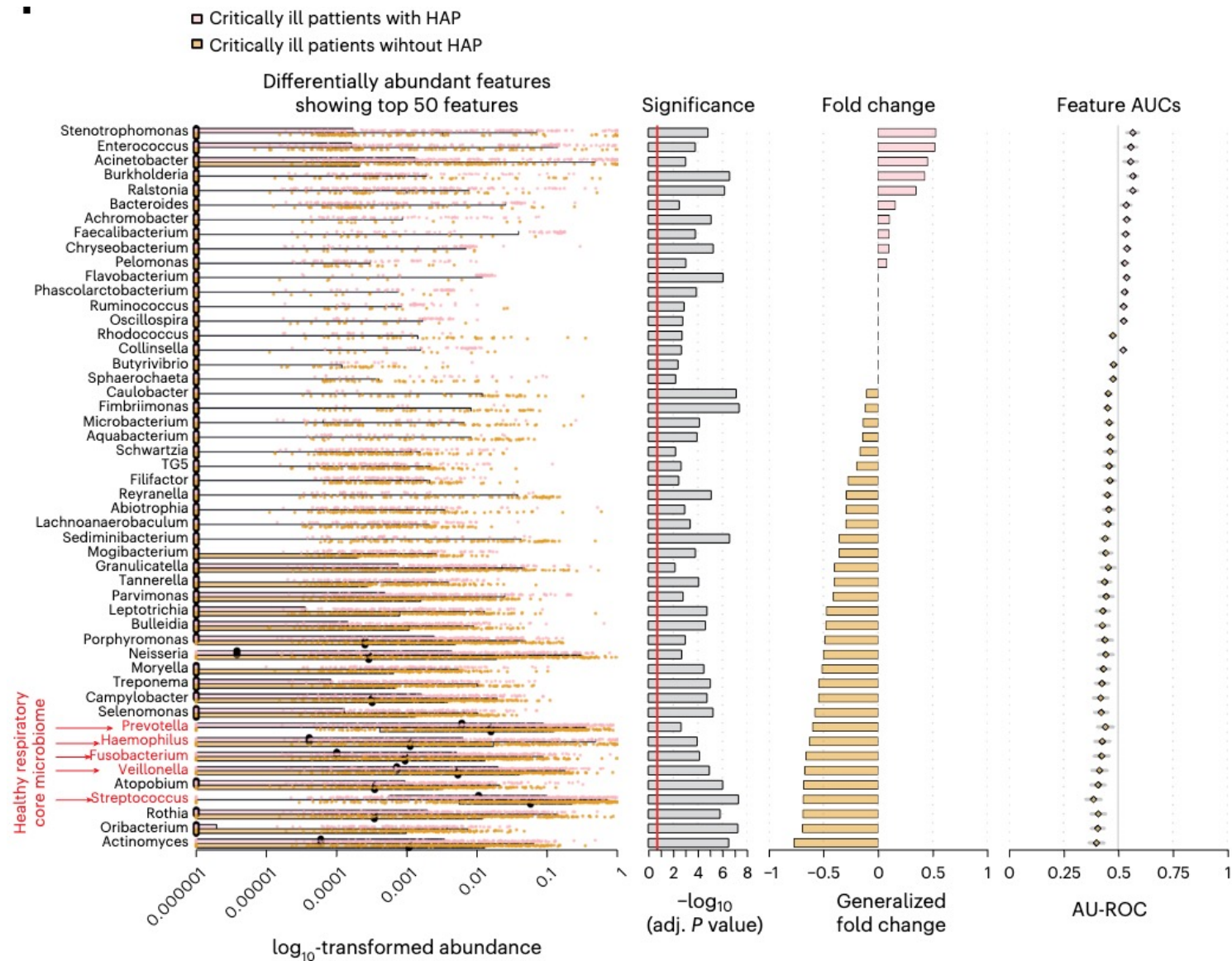
# Respiratory dysbiosis in HAP patients



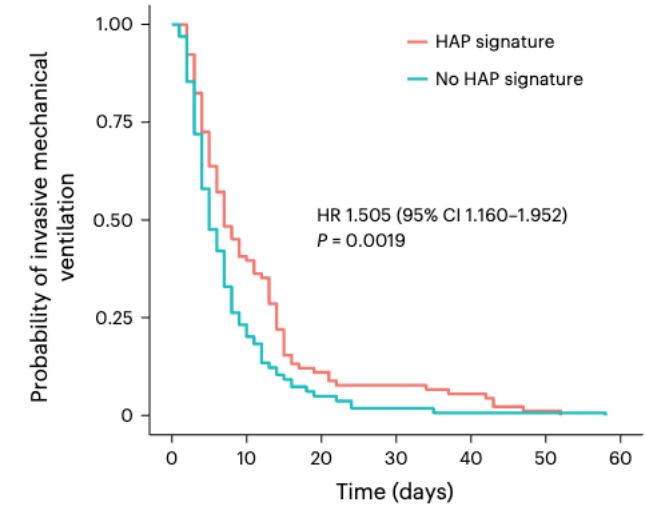
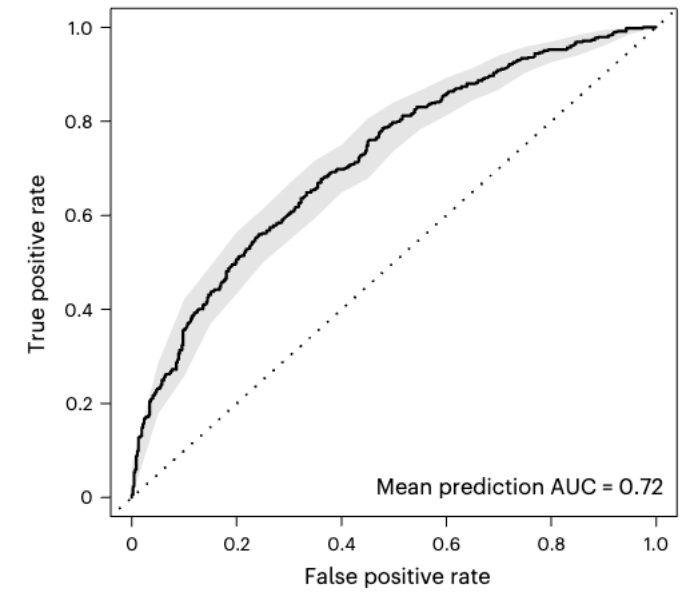
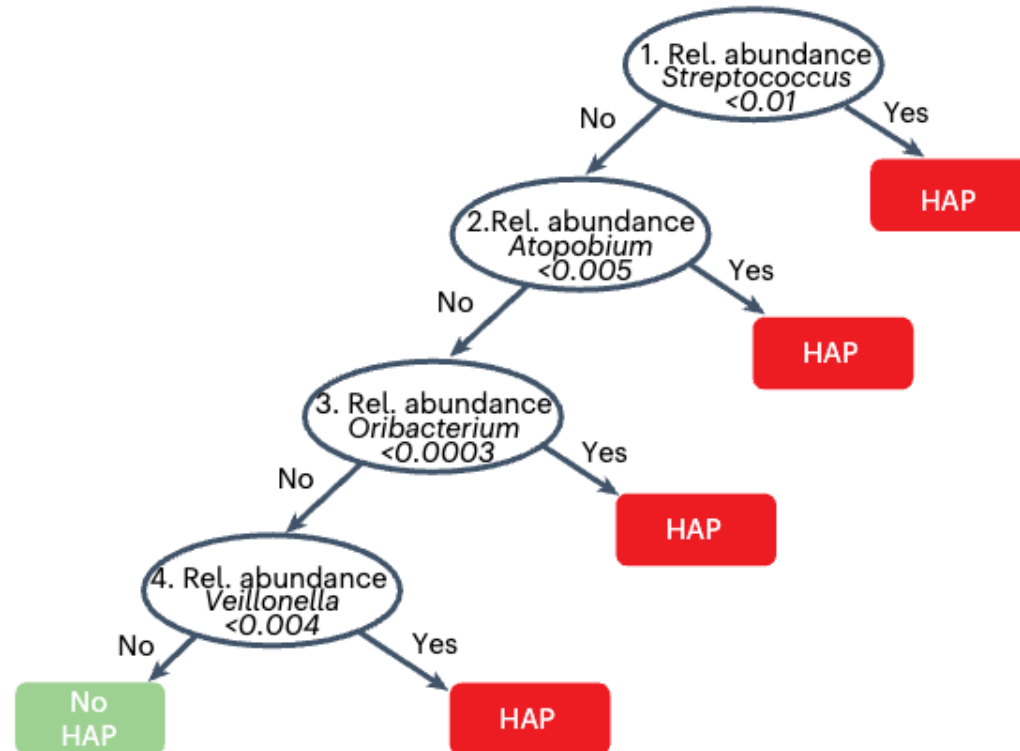
# Respiratory dysbiosis in HAP patients



# Respiratory microbiome top features associated with HAP

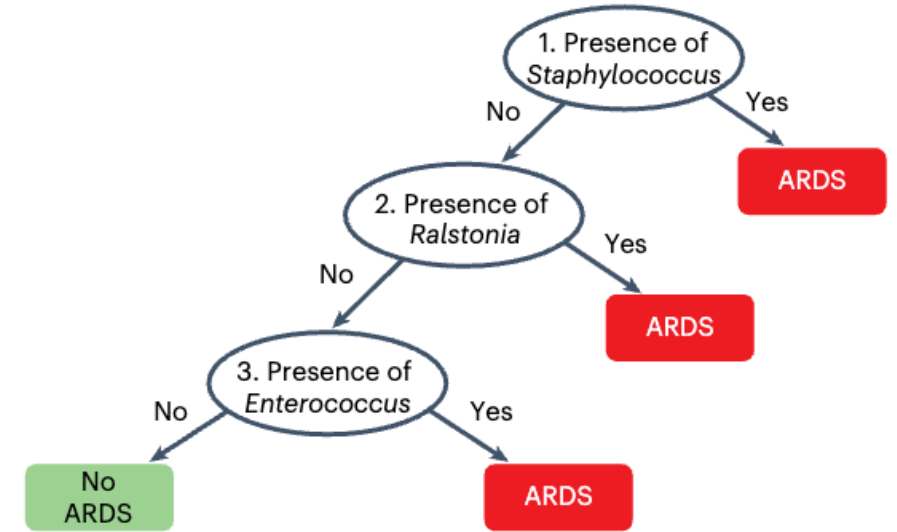
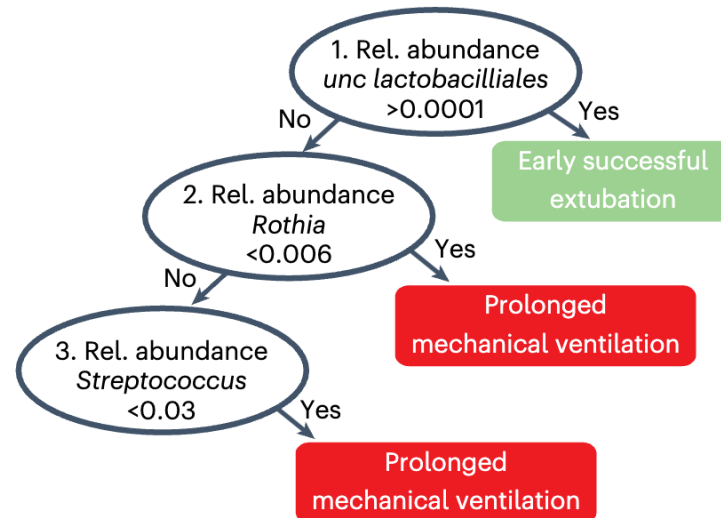
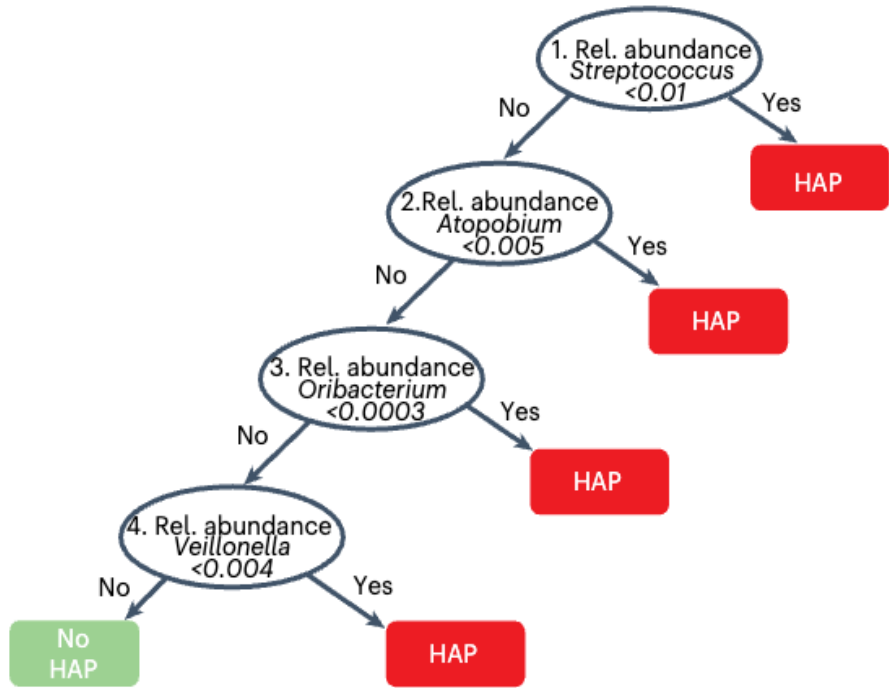


# Simple respiratory microbiome signature



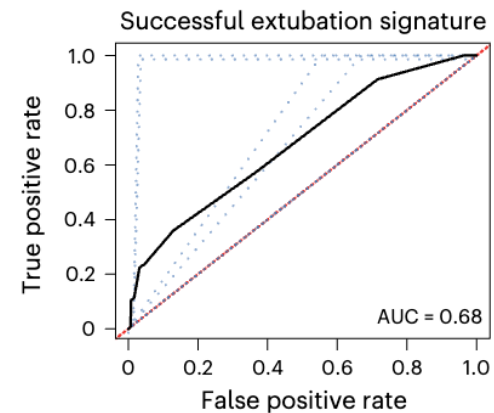
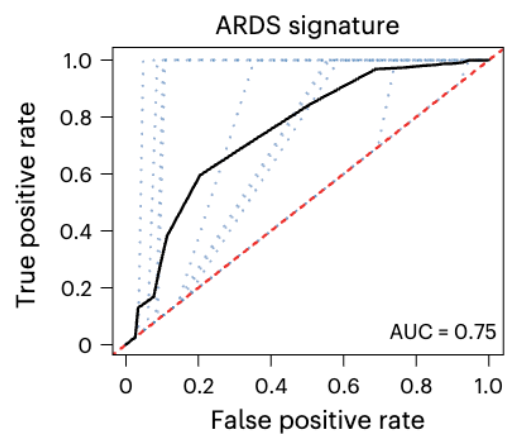
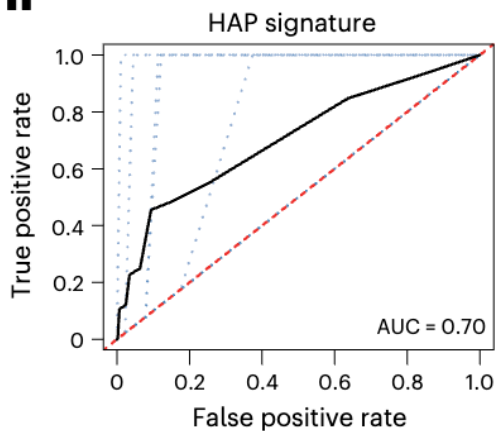
HAP signature	91	37	10	7	5	1	0
No HAP signature	164	38	8	3	1	1	0
	0	10	20	30	40	50	60
	Time (days)						

# Simple microbiome signatures for HAP, prolonged MV, ARDS

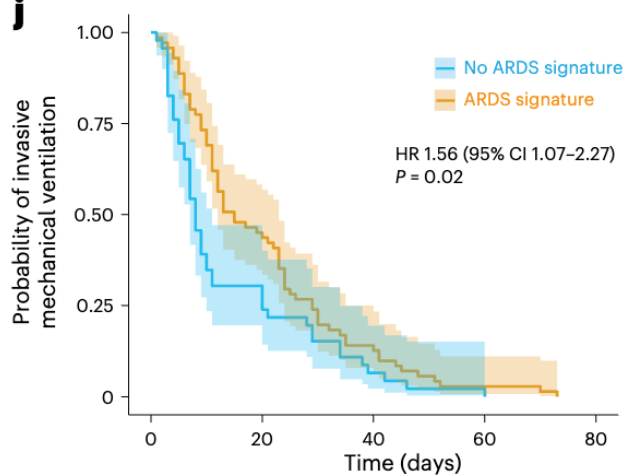


# Robust signatures

■



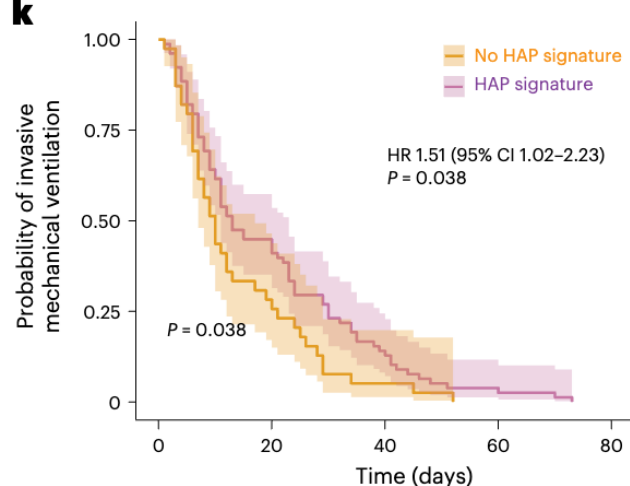
**j**



Number at risk

Time (days)	0	20	40	60	80
ARDS signature	71	32	10	2	0
No ARDS signature	46	14	3	1	0

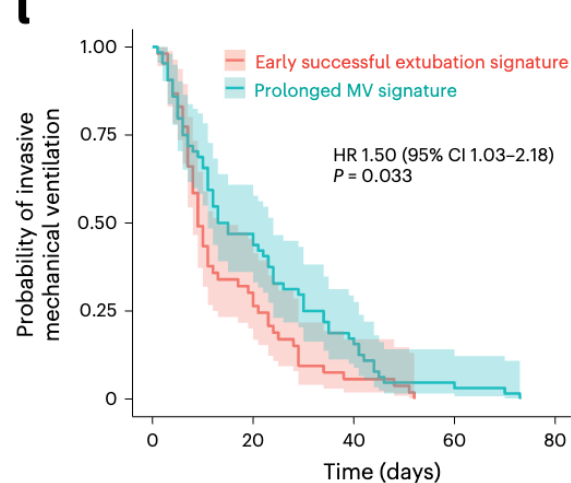
**k**



Number at risk

Time (days)	0	20	40	60	80
HAP signature	78	35	11	3	0
No HAP signature	39	11	2	0	0

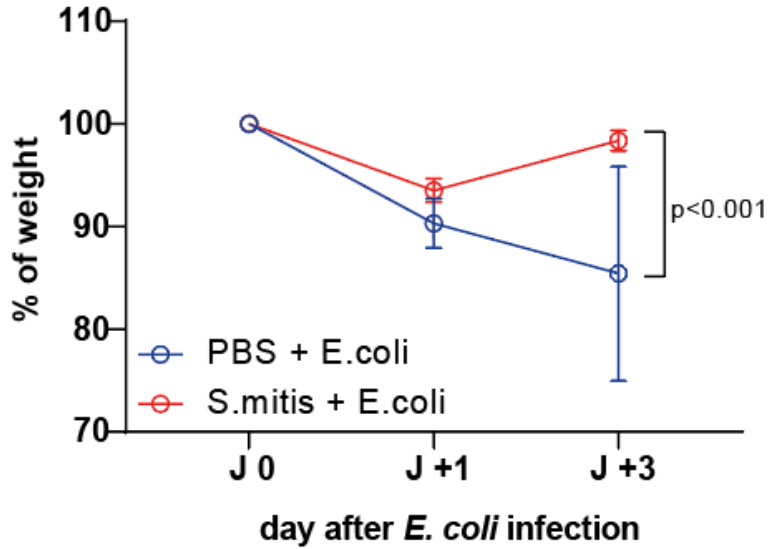
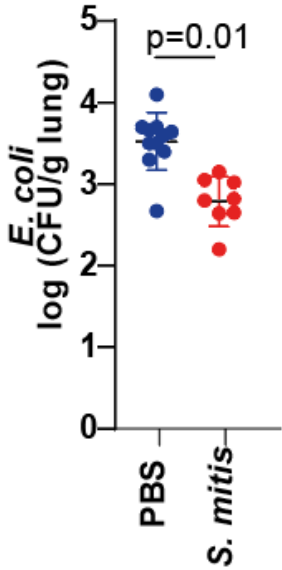
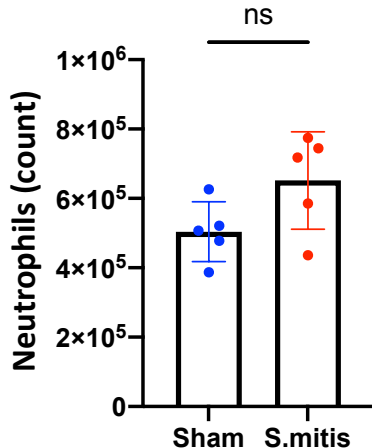
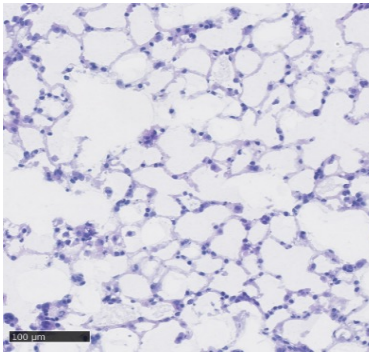
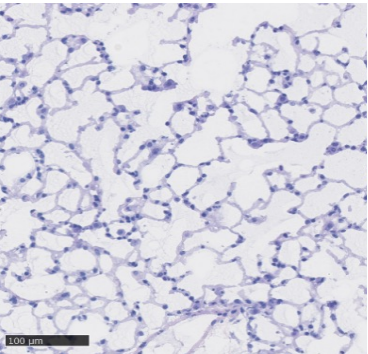
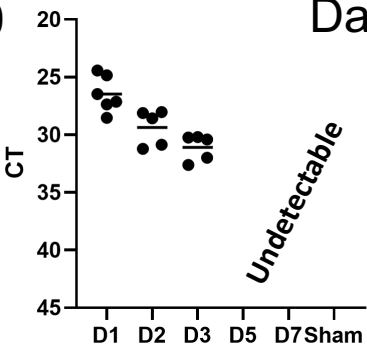
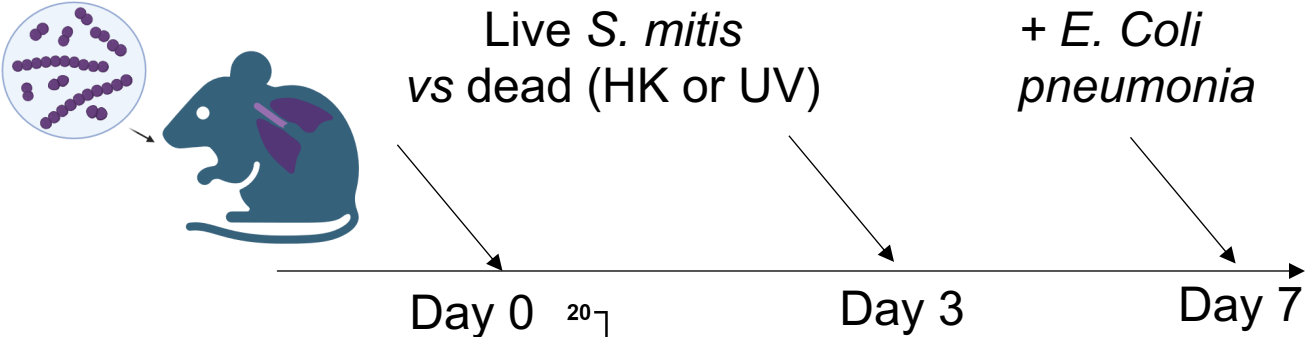
**l**



Number at risk

Time (days)	0	20	40	60	80
Early signature	53	16	3	0	0
Prolonged MV	64	30	11	3	0

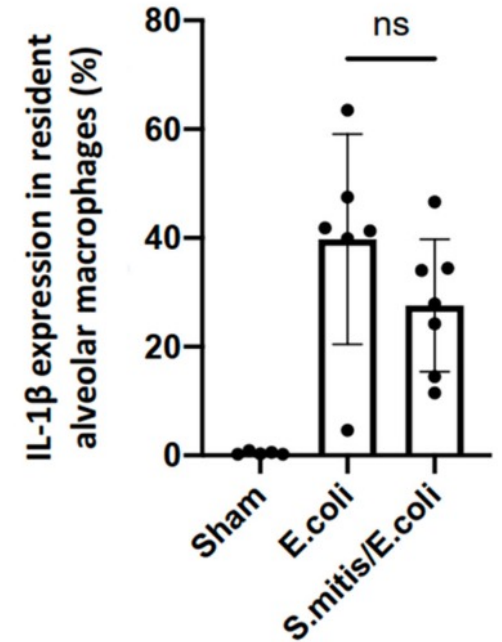
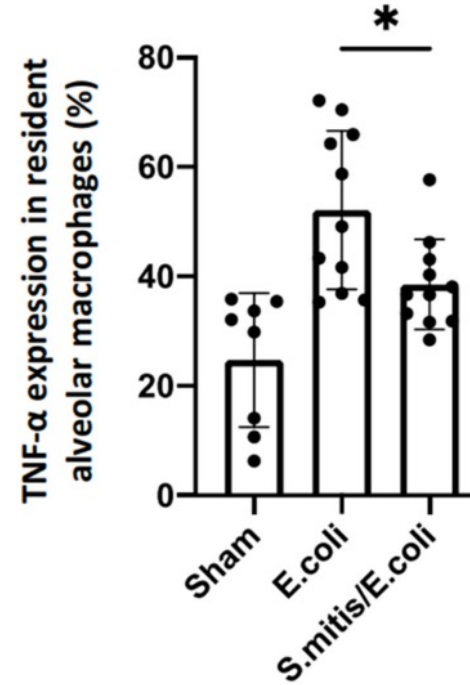
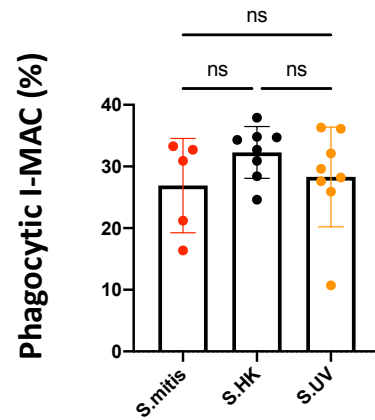
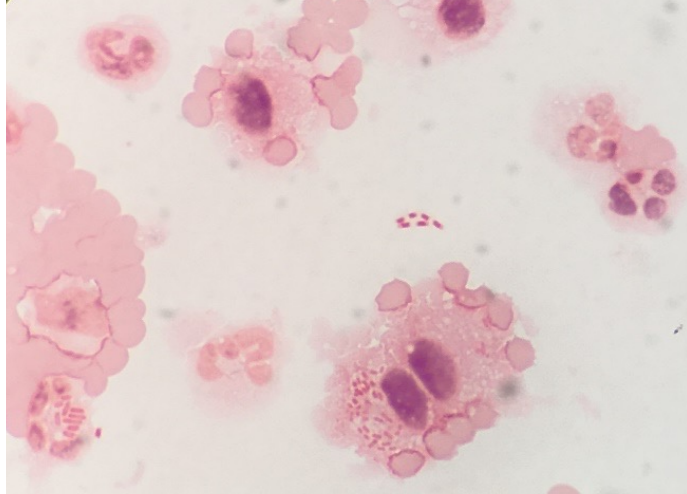
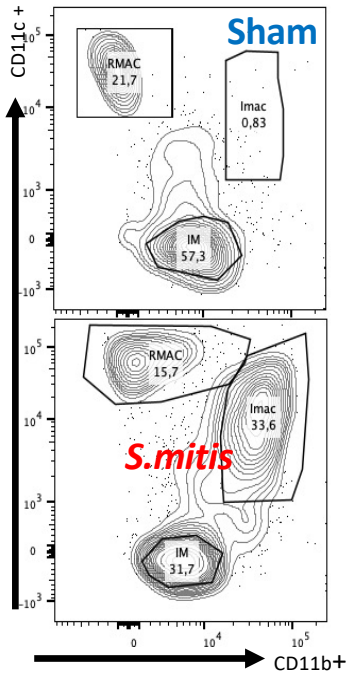
# Respiratory colonization improve response to pneumonia



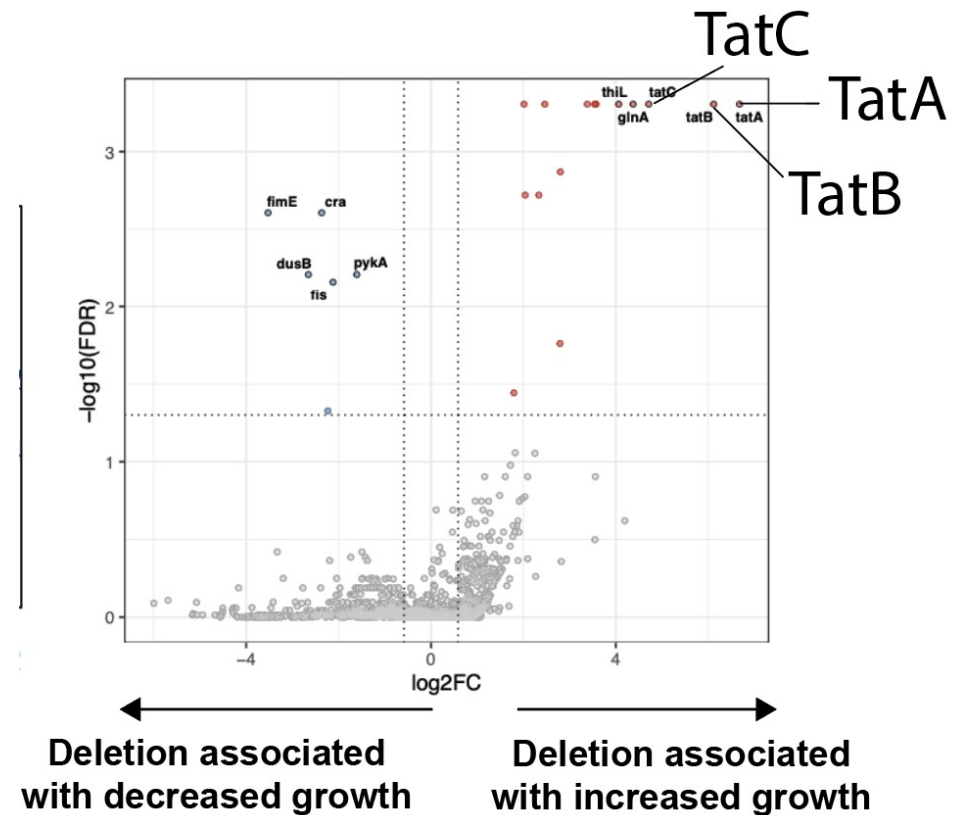
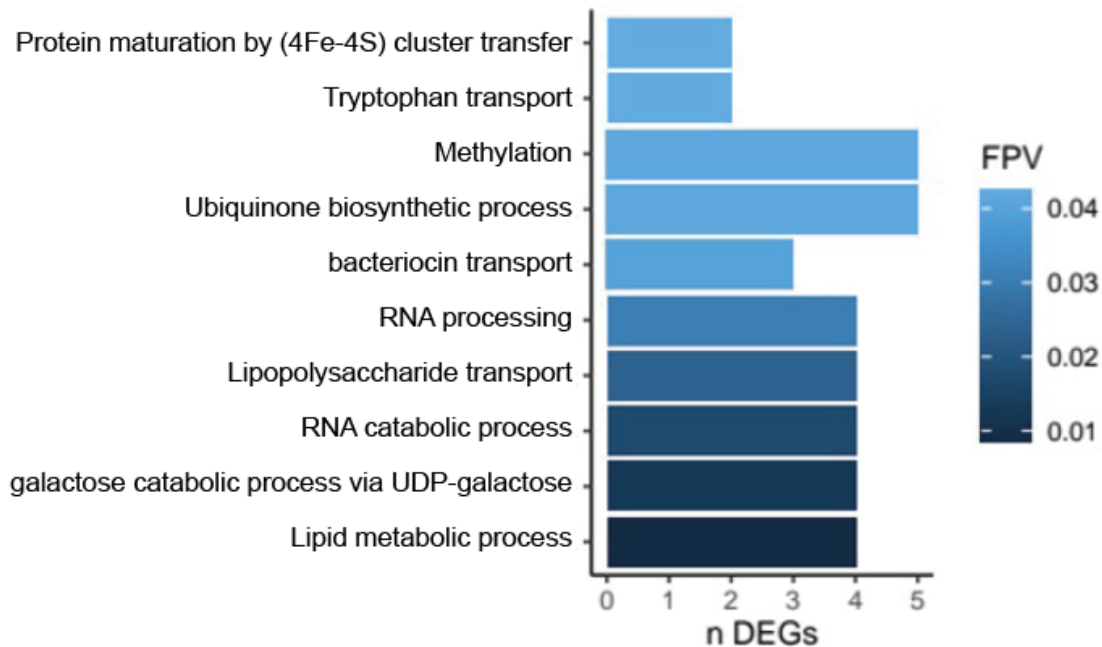
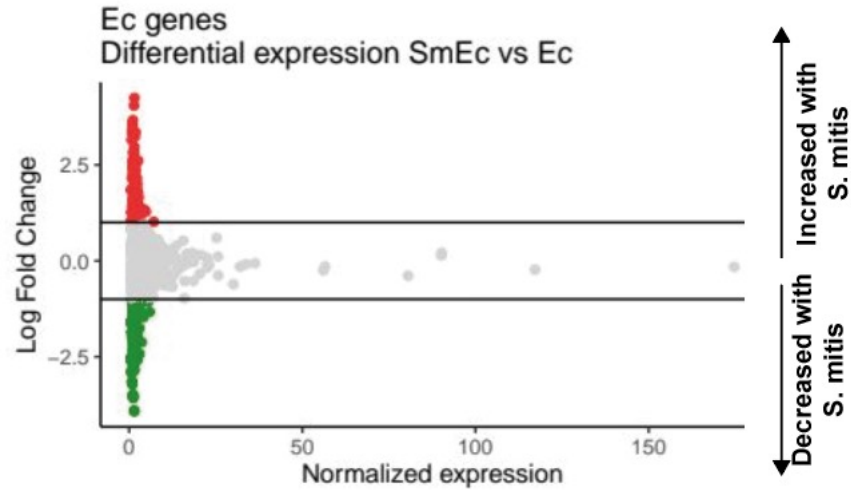
Personal unpublished data



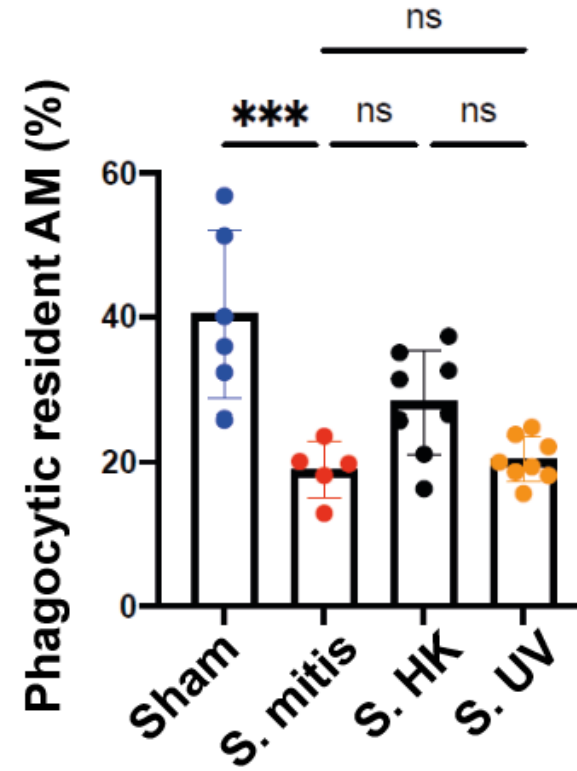
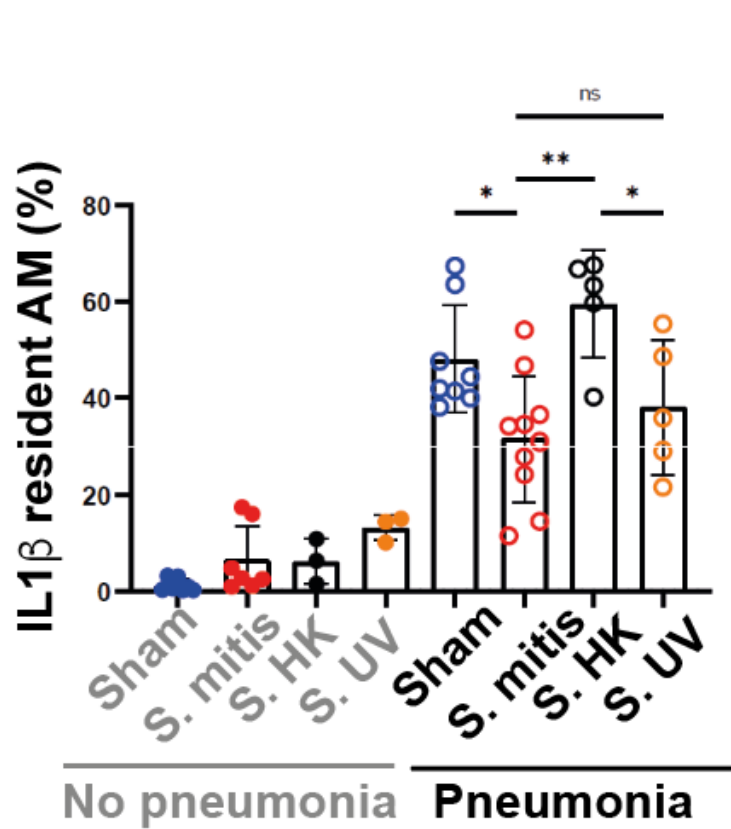
# *S. mitis* colonization modulates immune response to *E. coli* pneumonia



# *S. mitis* colonization modulates *E. coli* during pneumonia via TAT system

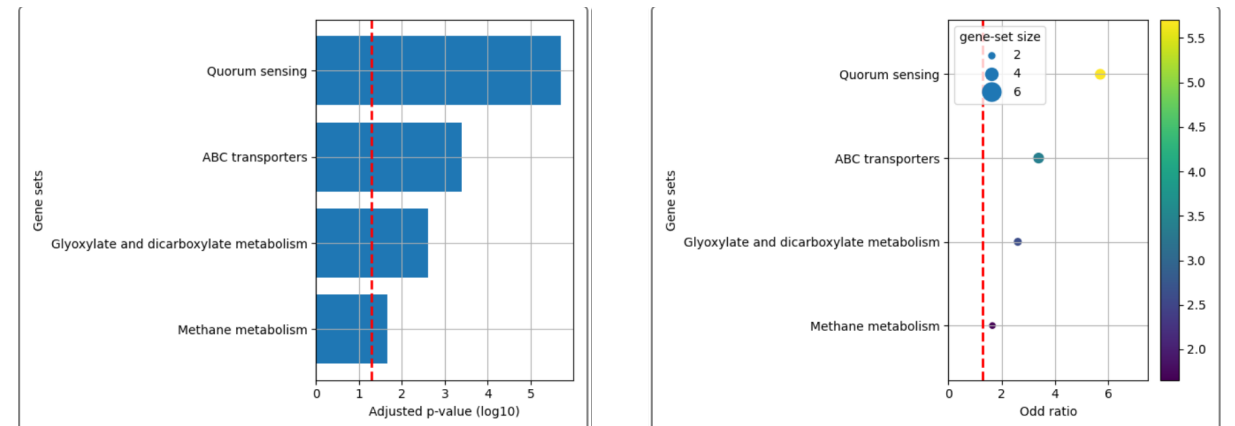
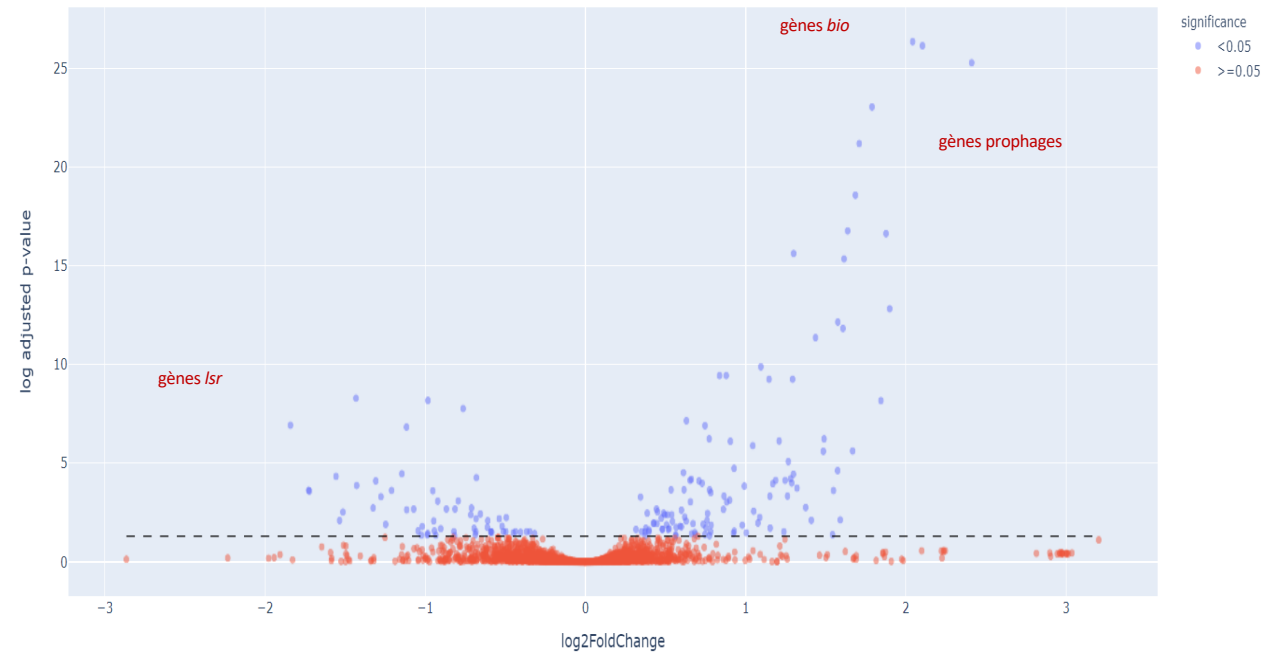
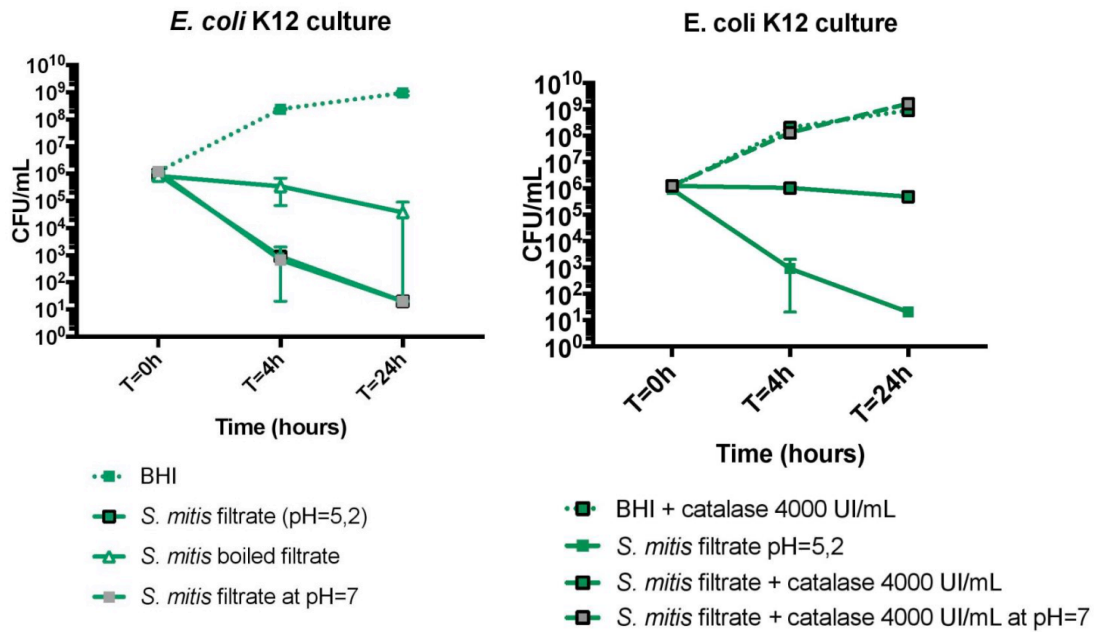


# Heat Shock killed *S. mitis* are less effective than living *S. mitis*



# S. mitis-derived products control bacteria growth and activity

## Streptococcus mitis (ATCC 49456) supernatant affects E. coli K-12



# S. mitis-derived metabolites

Quels métabolites **communs** entre :

- *S. mitis* 16H00 en Ae (= 4 points : MI16A1/MI16A2/MI16B1/MI16B2)

et

- *S. mitis* 24H00 en Ae (= 4 points : MI24A1/MI24A2/MI24B1/MI24B2)

et

- *S. oralis* 8H00 en Ae (= 4 points : OR8A1/OR8A2/OR8B1/OR8B2)

et

- *S. oralis* 16H00 en Ae (= 4 points : OR16A1/OR16A2/OR16B1/OR16B2)

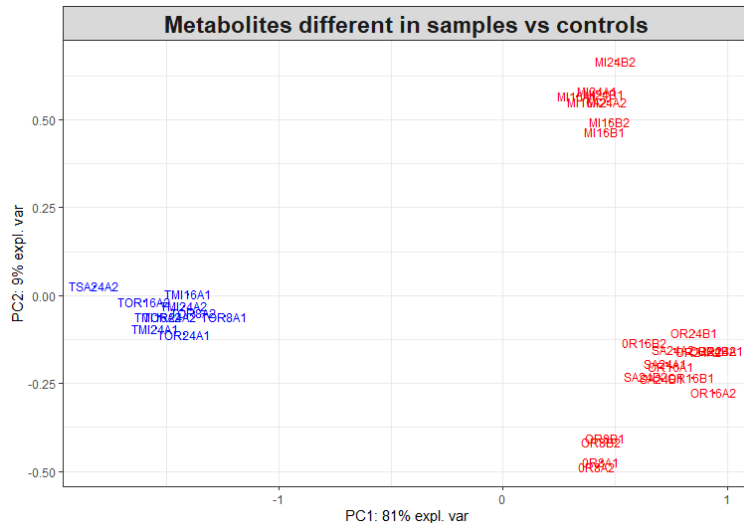
et

- *S. oralis* 24H00 en Ae (= 4 points : OR24A1/OR24A2/OR24B1/OR24B2)

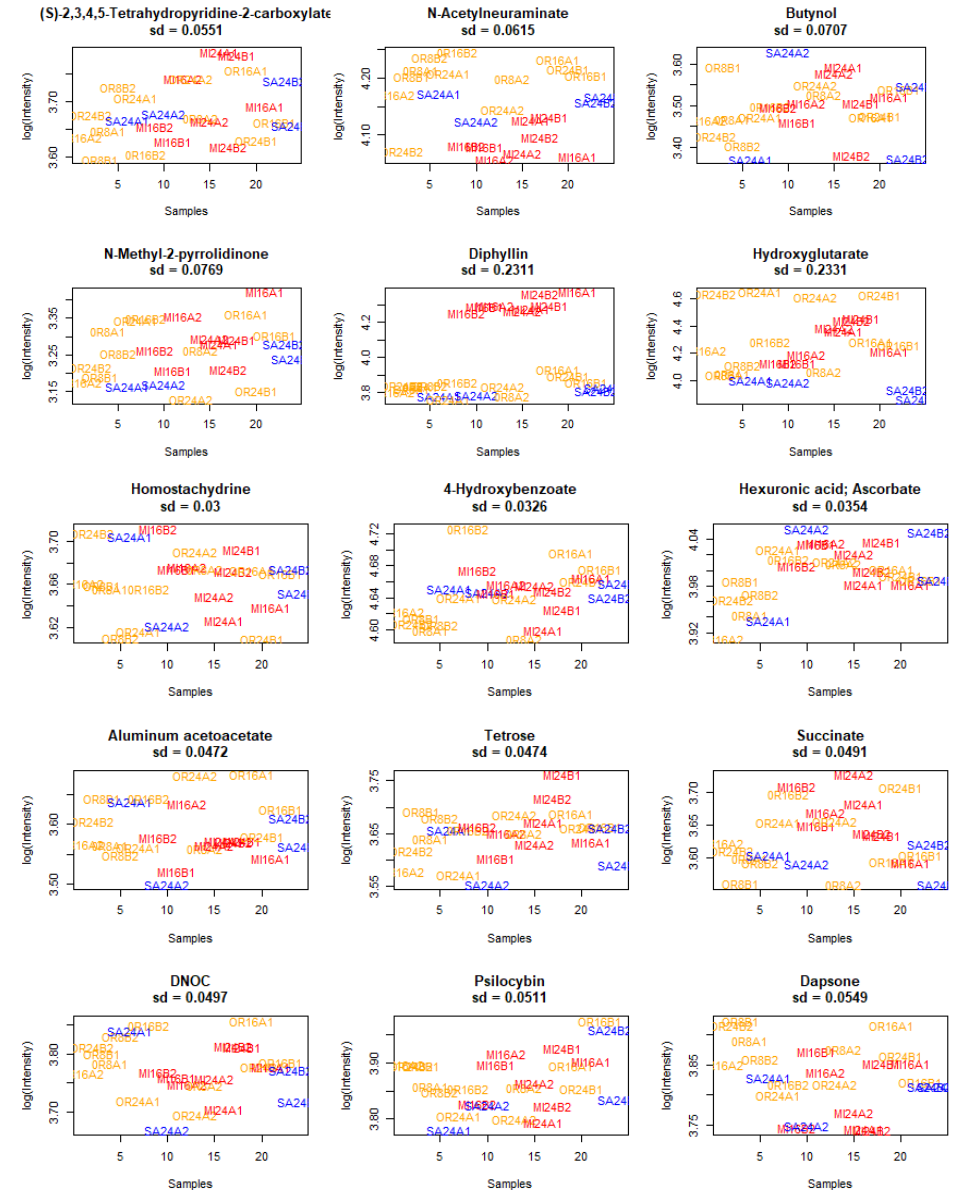
et

- *S. salivarius* 24H00 en Ae (= 4 points : SA24A1/SA24A2/SA24B1/SA24B2)

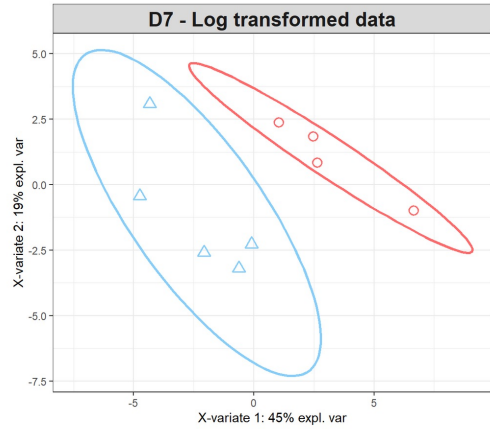
**et non présents** dans témoin BCC (= 12 points : TOR8A1/TOR8A2/  
TMI16A1/TMI16A2/TOR16A1/TOR16A2/TMI24A1/TMI24A2/TOR24A1/TOR24A2/TSA24A1/TSA24A2)



Metabolites with statistically different abundance  
between samples and control : n=44

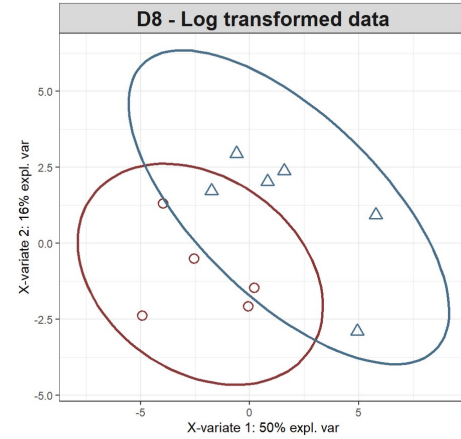


# *S. mitis* changes metabolome in respiratory fluid in vivo



**Uninfected**

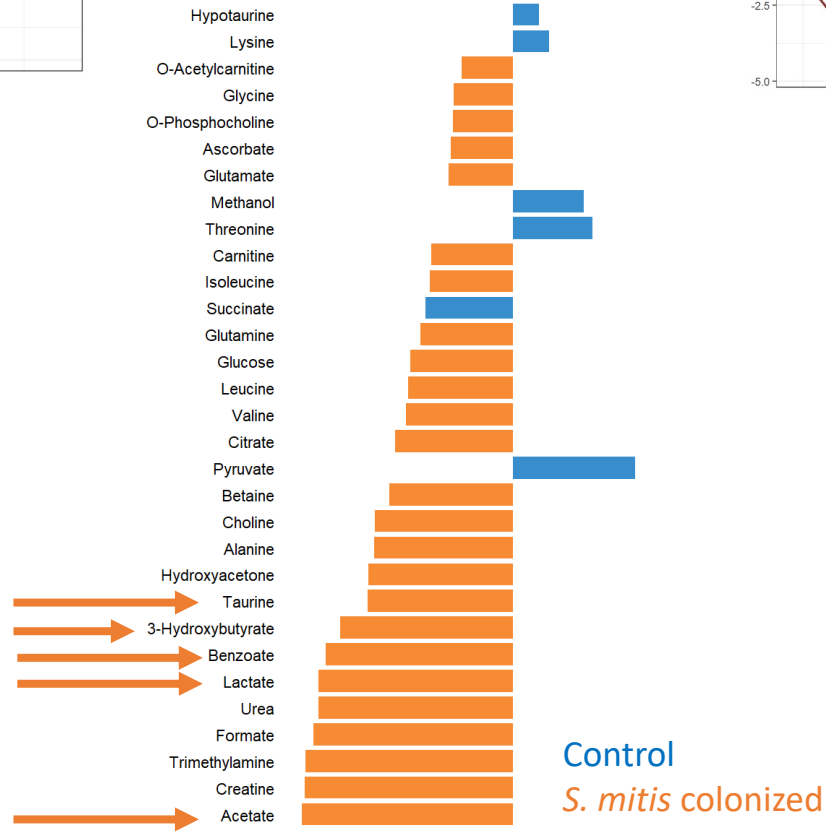
○ Control  
△ *S. mitis* colonized



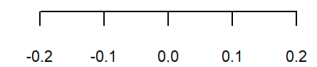
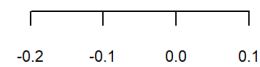
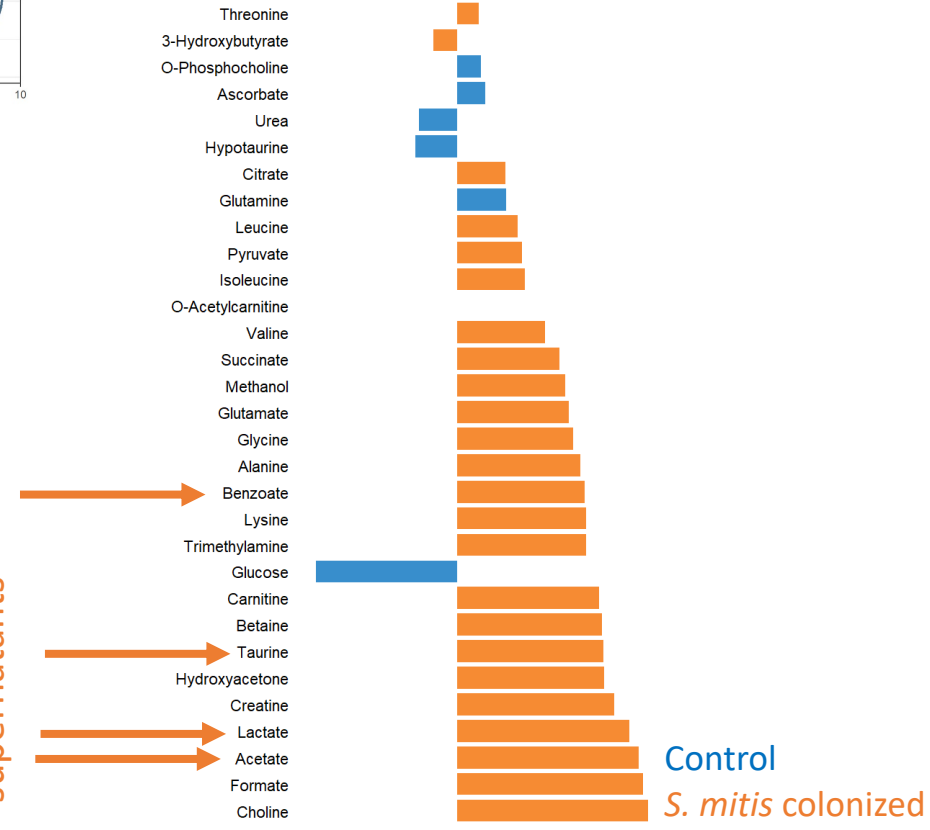
***E. coli* pneumonia**

○ Control  
△ *S. mitis* colonized

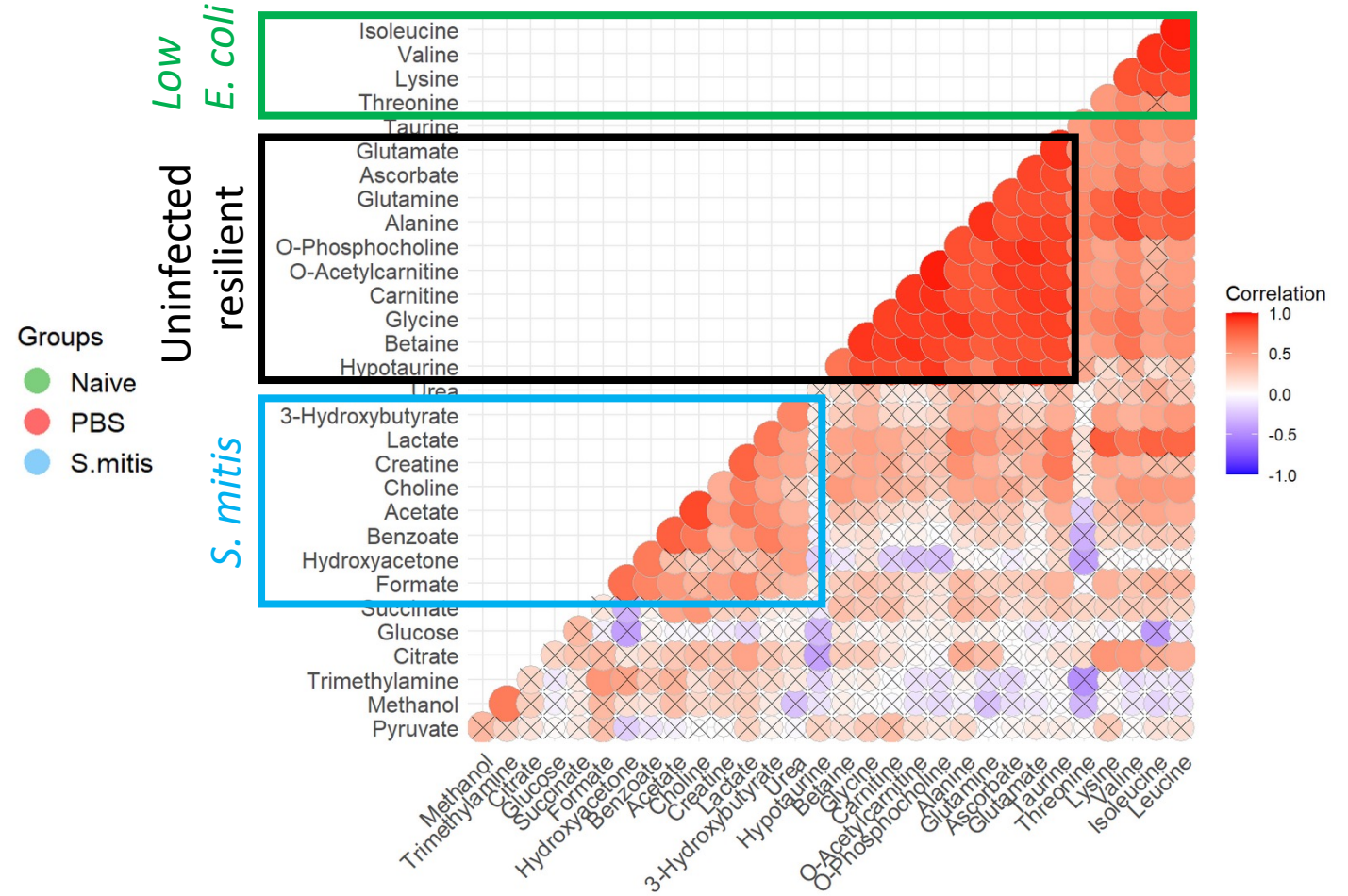
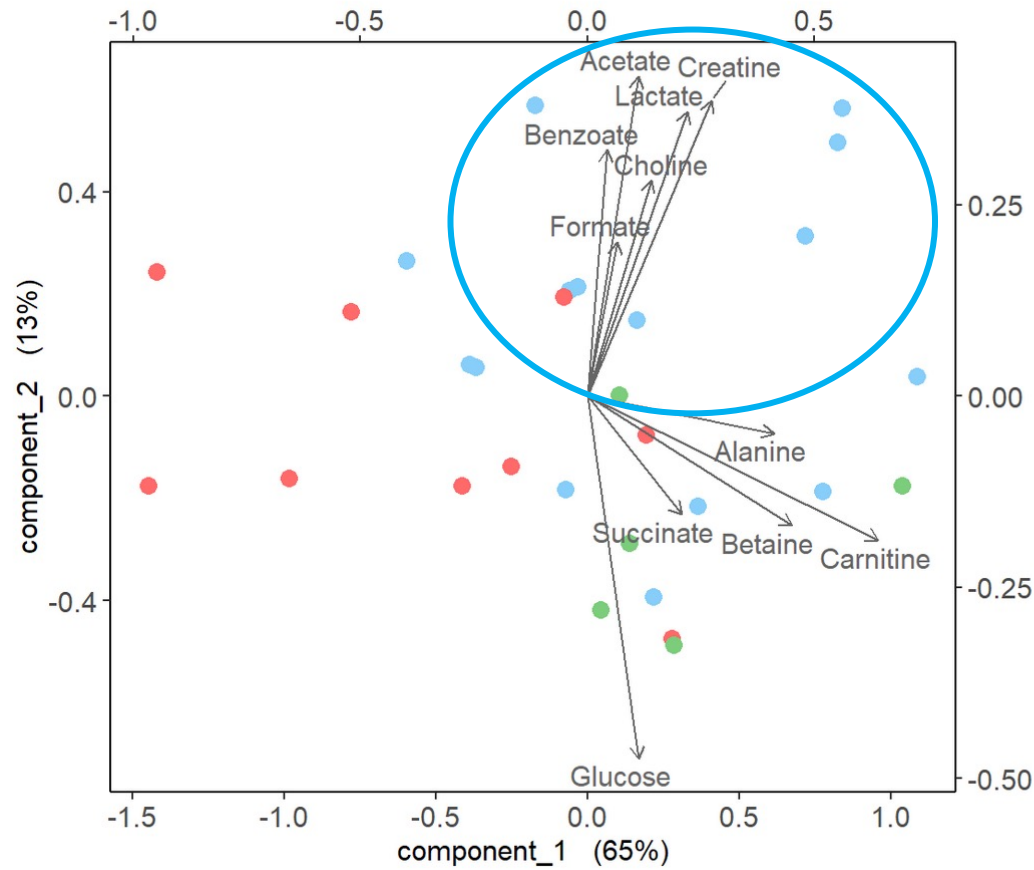
*Found in S. mitis*  
supernatants



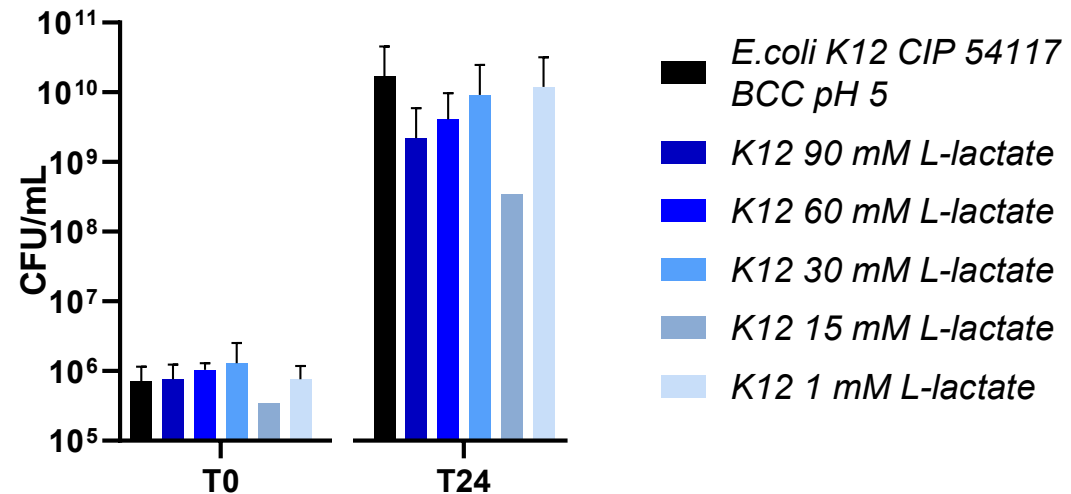
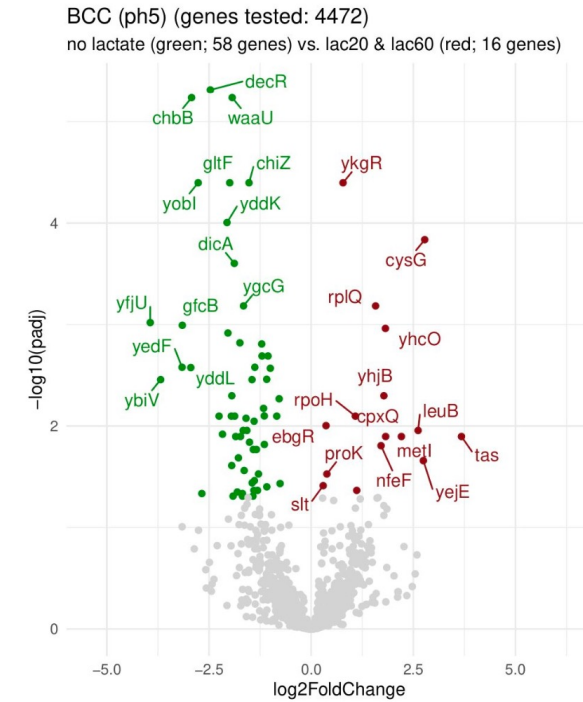
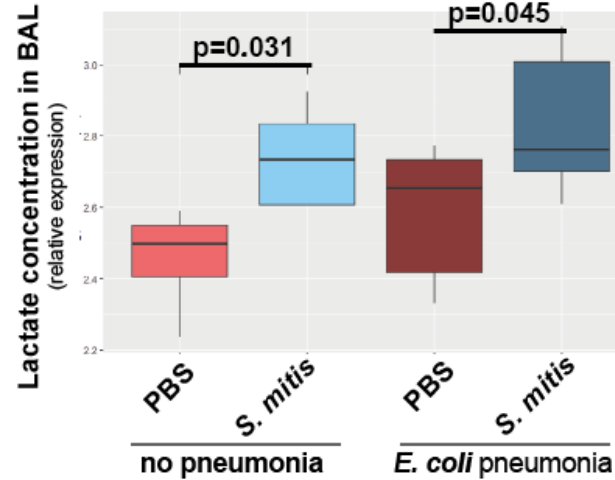
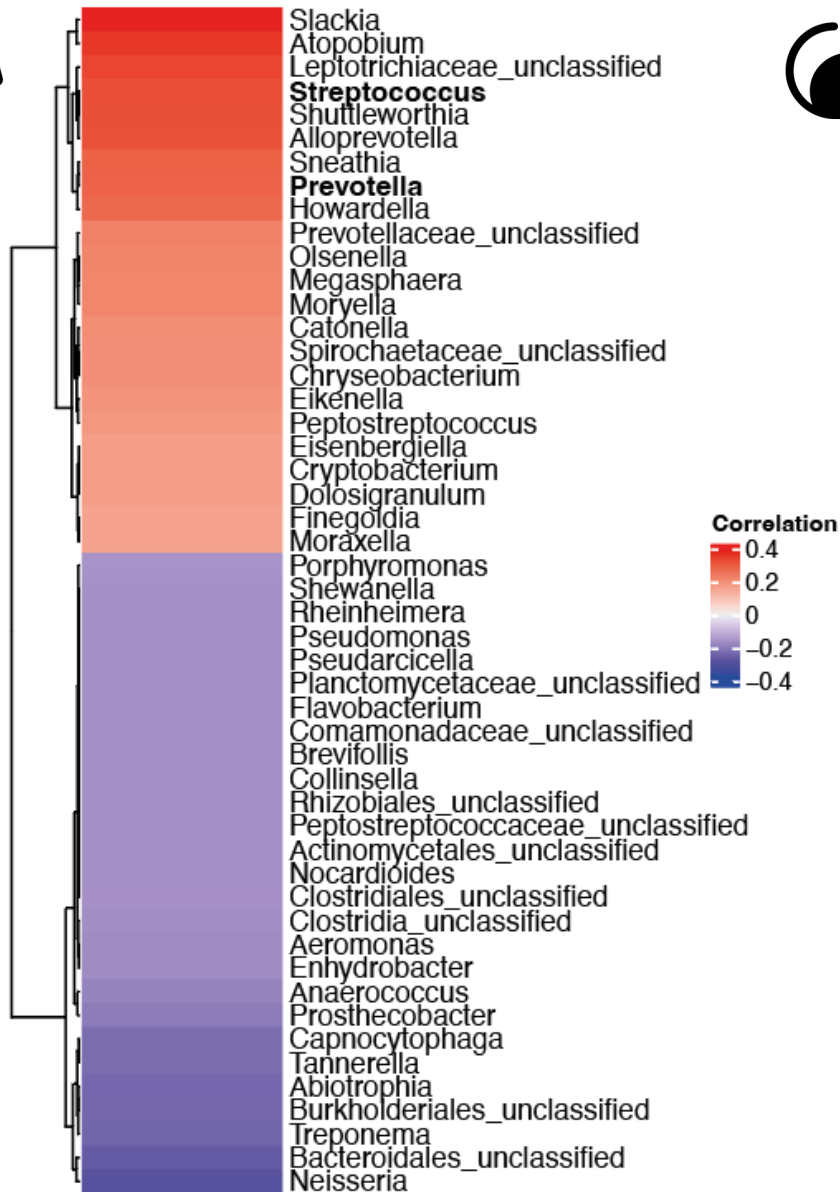
*Found in S. mitis*  
supernatants



# *S. mitis*-derived metabolite clusters *in vivo*



# *S. mitis*-derived lactate control bacteria growth in vitro





# Proposed innovative therapeutical solution

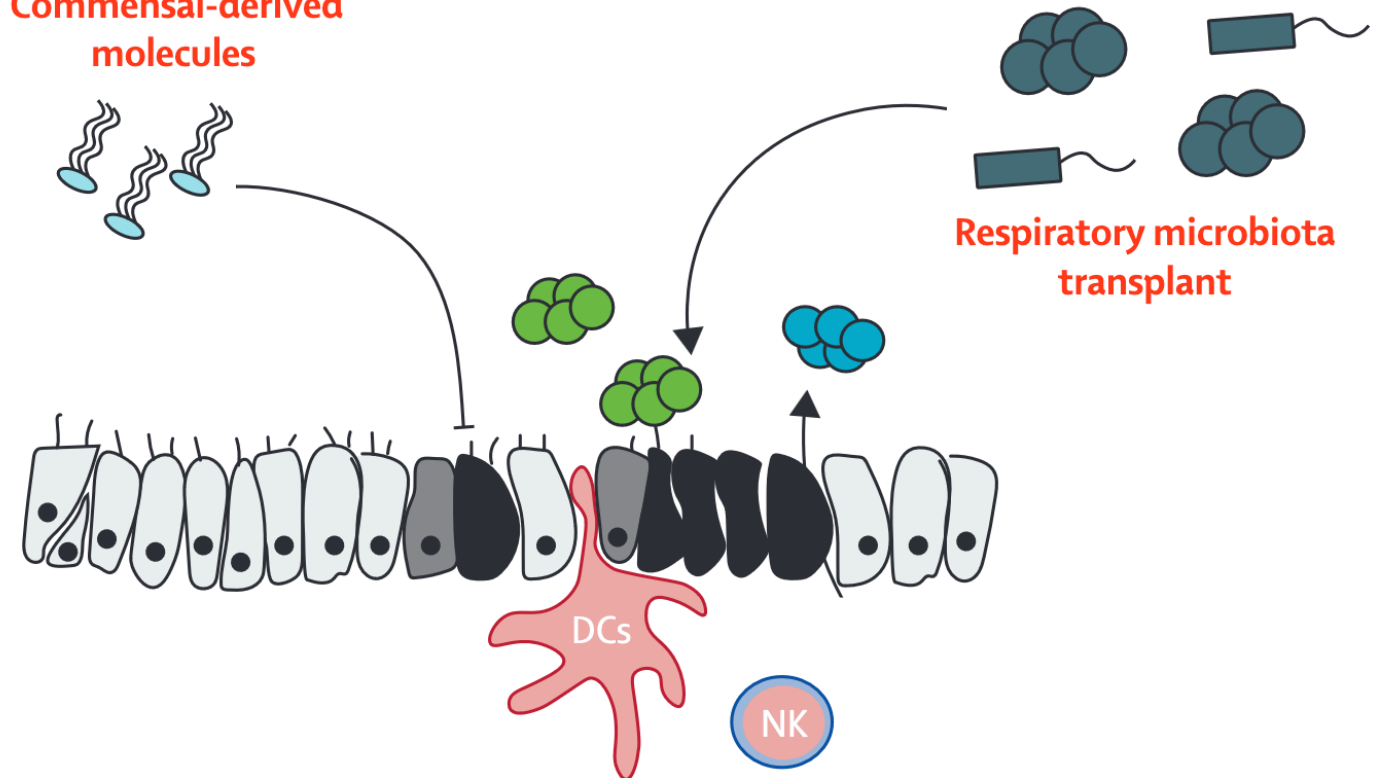
## Probiotic cocktail (dead ?)

*Streptococcus mitis*  
+ other (??)

## Associated with metabolites

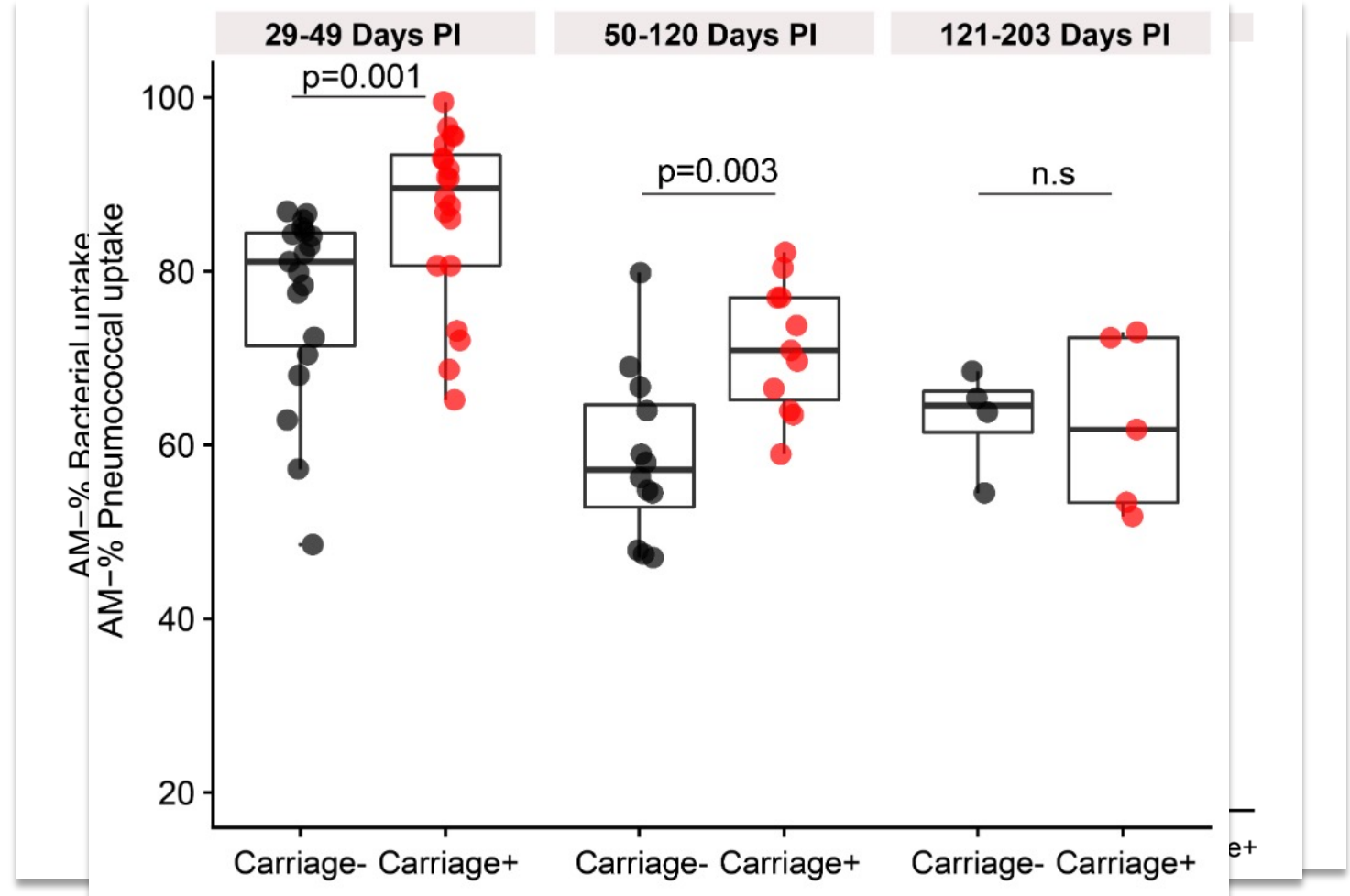
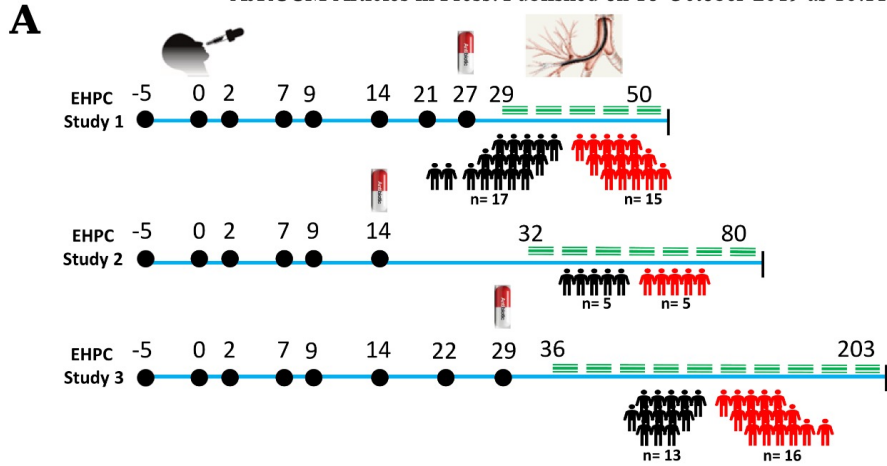
Lactate acid  
+ other (??)

Commensal-derived  
molecules



# Microbiome enrichment to boost immunity

*Proof of concept in humans*



# Conclusions

- Consider the « **site** » of infection
- Not only a matter of pathogens... take care of **unimportant bacteria**
- Commensal bacteria and « **immune tolerance** »
- Heterogeneity and **personalized** treatments
- In the future: tailored symbiotics?



**Symbiosis restauration**



### Team 6 - Pr Roquilly

- Jeremie Poschmann (PhD)
- Lise Cremet (PharmD, PhD)
- Emmanuel Montassier (MD, PhD)
- Aurelien Serandour (PhD)
- Alexis Broquet (PhD)
- Cédric Jacqueline (PhD)
- Victor Gourain (PhD)
- Debajyoti Sinha (PhD)
- Marion Davieau
- Virginie Le Mabeccque
- Sandie Delanou
- Cynthia Fourgeux
- Florian Martin
- Valeria Chahwane
- Melanie Petrier
- Pierre Martin



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- Pr Raphael Cinotti (MD, PhD)
- Pierre Joachim Mahe (MD)
- Yannick Hournant (MD)
- Mickael Vourc'h (MD, PhD)
- Delphine Flattres (TEC)
- Celine Lerebourg (TEC)
- Cecilia Lebel (TEC)
- Flavien Cornouille (TEC)



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### Collaboration with

- J. Villadangos (PDI & Bio21)**
- J. Mintern
- H. McWilliam
- J. Mintern
- M. Ashayeripannah