Non antibiotic treatment of hospital-acquired pneumonia

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What for ?

Optimized antimicrobial therapy to solve the problem ?

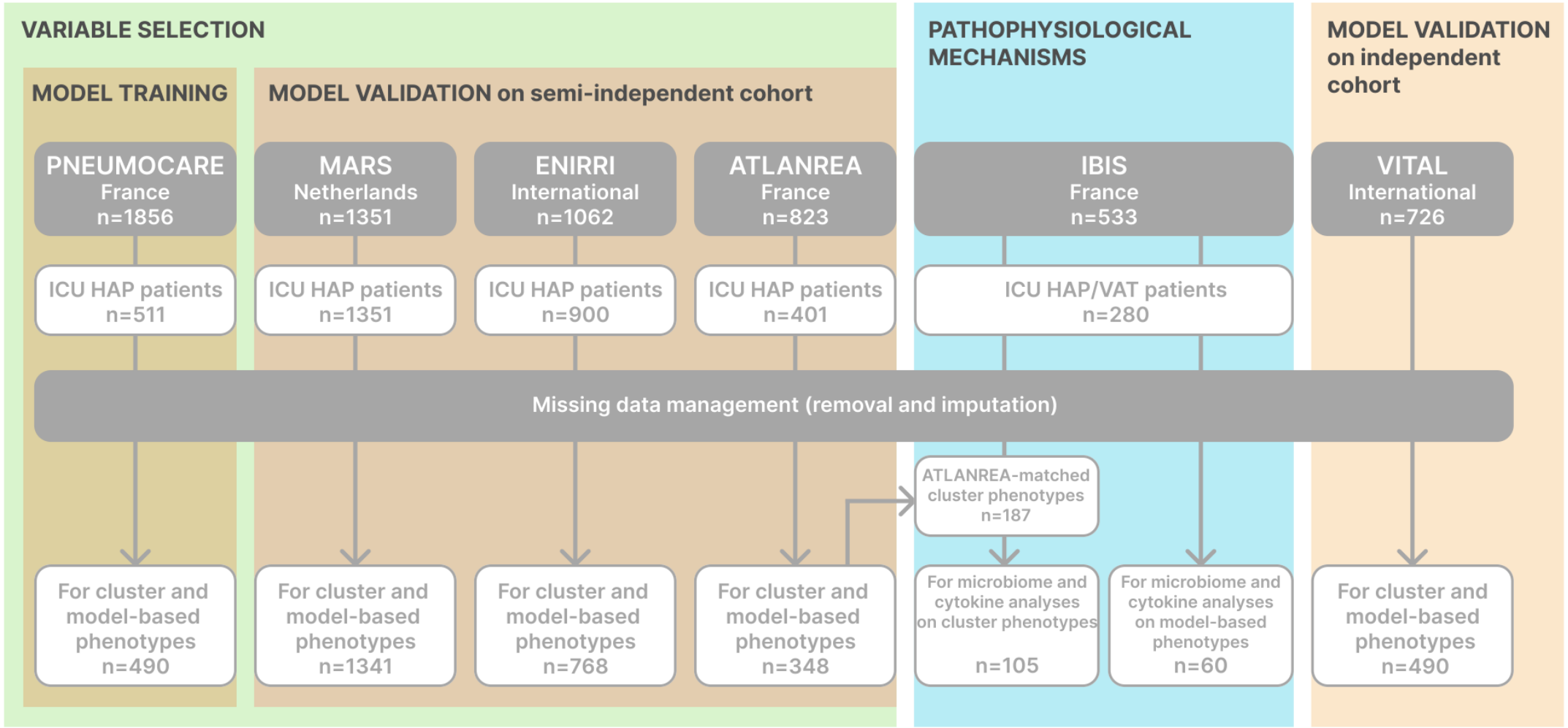
A multifaceted strategy to optimize pharmacokinetics of antimicrobial therapy in patients with hospital-acquired infections—a monocentre quality improvement project

Lagarde et al. JAC 2023

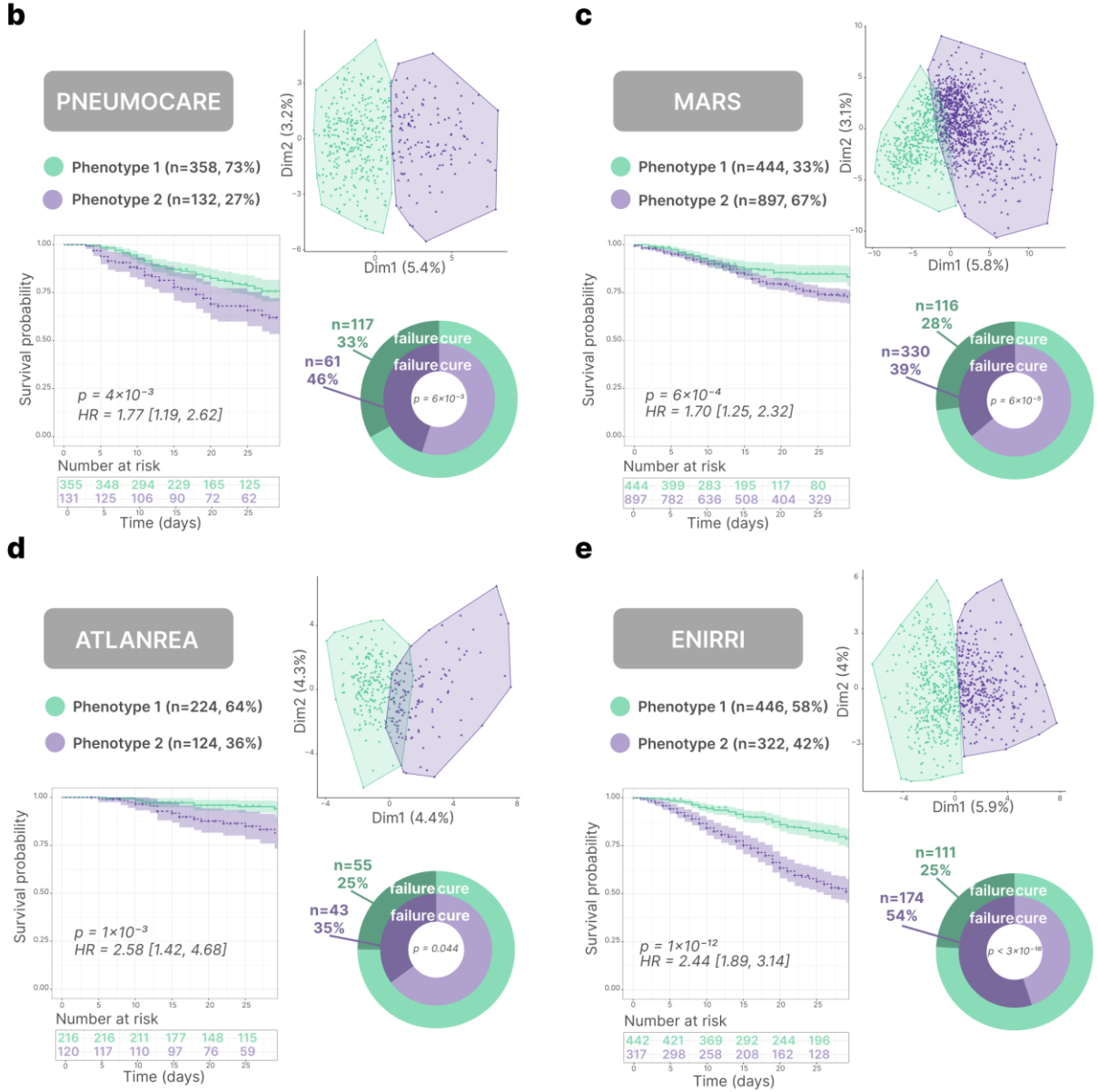
	Pre-intervention group *N*=58	Intervention group *N*=140	*P* values
Continuous intravenous infusion, *N* (%)	Not recorded	30 (21.4%)	/
Therapeutic drug monitoring, *N* (%)	12 (20.3%)	83 (58.6%)	<0.0001
Target achievement, *N* (%)			
Meet the targets	6 (50%)	40 (48.2%)	0.51
Under-dosage[a]	3 (25%)	14 (16.9%)	0.49
Overdose[b]	2 (16.7%)	28 (33.7%)	0.23
Dose adaptation of antimicrobial therapy, *N* (%)	3 (5.2%)	17 (12.2%)	0.13
Increase of the daily dose	1 (1.7%)	5 (3.6%)	0.49
Decrease of the daily dose	2 (3.5%)	12 (8.6%)	0.20
De-escalation of the spectrum after bacterial identification, *N* (%)	3 (25%)	20 (24.1%)	0.94

	Pre-intervention group *N*=58	Intervention group *N*=140	Adjusted hazard ratio (95%CI)
Secondary outcomes			*P* values
Treatment failure, *N* (%)	22 (37.9)	36 (25.7)	0.07
Relapse	11 (18.9)	18 (12.8)	0.28
Recurrence	11 (18.9)	18 (12.8)	0.21
Duration of invasive mechanical ventilation, days, mean (SD)	21 (29)	15 (16)	0.15[b]
ICU length of stay, days, mean (SD)	32 (35)	25 (22)	0.39[b]

Treatment failure : a worldwide matter



Treatment failure : a worldwide matter



An incomplete understanding of the pathophysiology ?

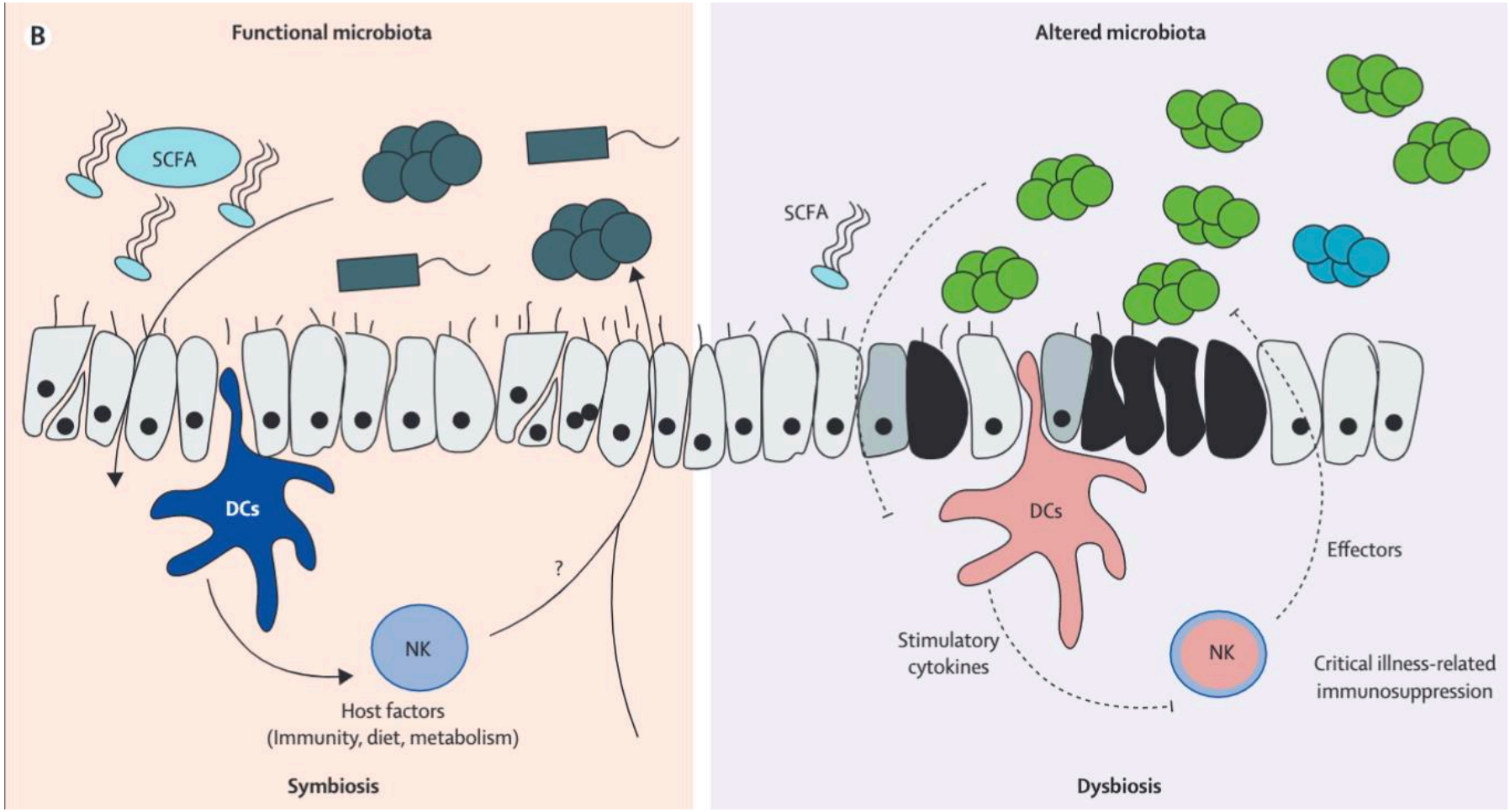
Weak association between clinical and microbiological cures

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Torres et al. Lancet Infect Dis

	Patients with clinical cure (clinically evaluable population)			Patients with favourable microbiological response* (extended microbiologically evaluable population)		
	Ceftazidime-avibactam (n=257)	Meropenem (n=270)	% difference (95% CI)	Ceftazidime-avibactam (n=125)	Meropenem (n=131)	% difference (95% CI)
Enterobacteriaceae						
Klebsiella pneumoniae	31/37 (83·8%)	39/49 (79·6%)	4·2 (–13·49 to 20·50)	29/37 (78·4%)	39/49 (79·6%)	–1·2 (–19·60 to 15·96)
Enterobacter cloacae	20/21 (95·2%)	7/11 (63·6%)	31·6 (4·79 to 61·30)	18/21 (85·7%)	7/11 (63·6%)	22·1 (–8·07 to 53·69)
Escherichia coli	8/11 (72·7%)	14/18 (77·8%)	–5·1 (–39·26 to 25·79)	10/11 (90·9%)	16/18 (88·9%)	2·0 (–29·11 to 26·44)
Proteus mirabilis	11/11 (100·0%)	7/8 (87·5%)	12·5 (–16·54 to 48·07)	9/11 (81·8%)	6/8 (75·0%)	6·8 (–30·73 to 46·51)
Serratia marcescens	10/12 (83·3%)	8/8 (100·0%)	–16·7 (–45·58 to 19·48)	9/12 (75·0%)	5/8 (62·5%)	12·5 (–27·47 to 51·82)
Enterobacter aerogenes	4/6 (66·7%)	2/5 (40·0%)	26·7 (–31·92 to 70·73)	5/6 (83·3%)	3/5 (60·0%)	23·3 (–31·30 to 68·33)
Gram-negative pathogens other than Enterobacteriaceae						
Pseudomonas aeruginosa	27/42 (64·3%)	27/35 (77·1%)	–12·8 (–32·25 to 8·01)	18/42 (42·9%)	14/35 (40·0%)	2·9 (–19·13 to 24·32)
Haemophilus influenzae	10/11 (90·9%)	11/13 (84·6%)	6·3 (–26·19 to 36·09)	11/11 (100·0%)	12/13 (92·3%)	7·7 (–20·08 to 34·00)
Gram-positive aerobes						
Staphylococcus aureus	11/14 (78·6%)	16/22 (72·7%)	5·8 (–25·24 to 32·67)	5/14 (35·7%)	17/22 (77·3%)	–41·6 (–67·04 to –8·36)

Dysbiosis, a refined concept of mucosal infection physiopathology



Roquilly et al. Lancet respir Med 2019

Respiratory microbiome and pneumonia

Respiratory microbiome alterations in ICU patients

Article

https://doi.org/10.1038/s41591-023-02617-9

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

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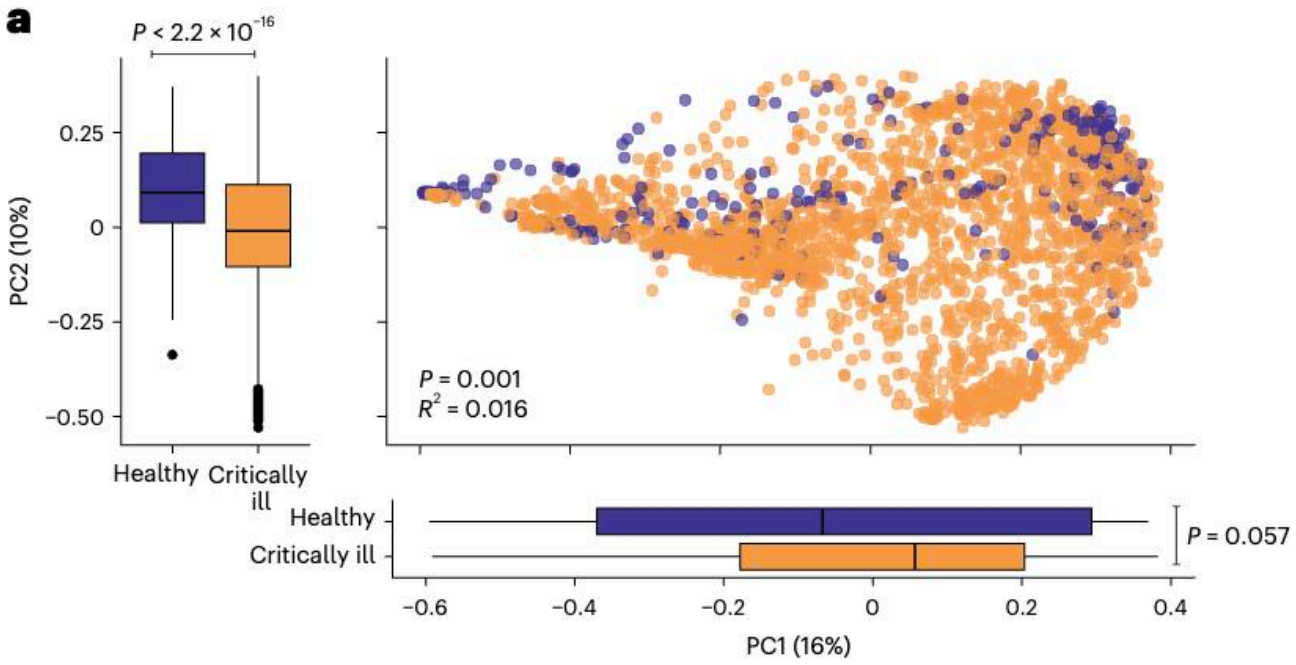
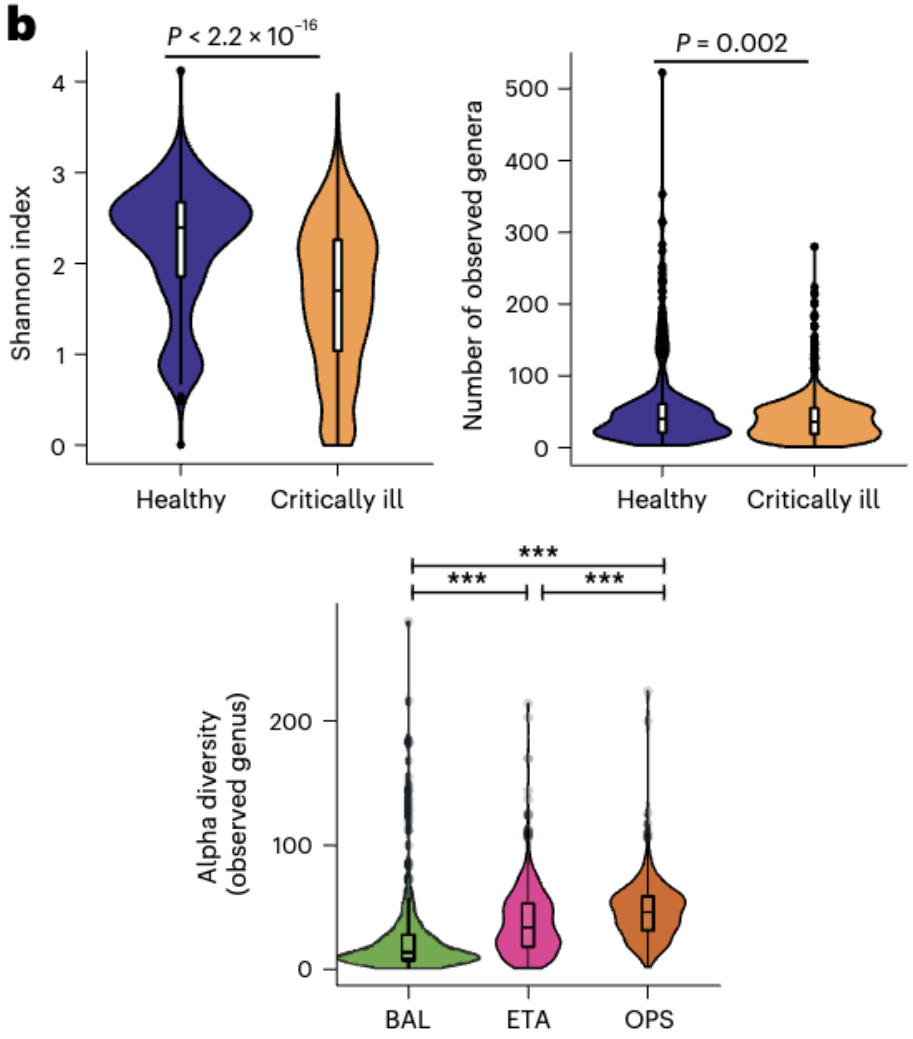
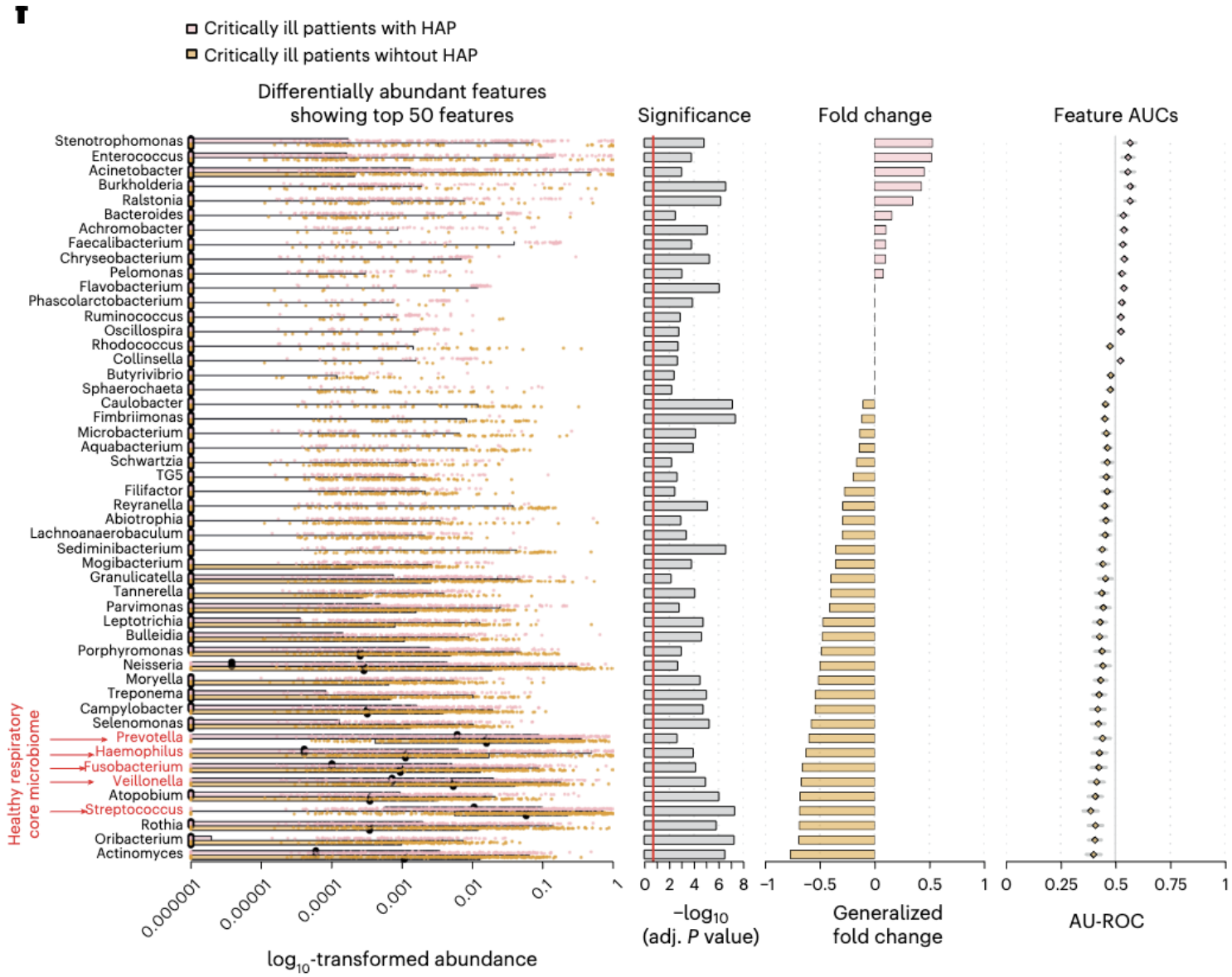
Emmanuel Montassier[1,2], Georgios D. Kitsios[3,4], Josiah E. Radder[3,4], Quentin Le Bastard[2], Brendan J. Kelly[5], Ariane Panzer[6], Susan V. Lynch[6], Carolyn S. Calfee[7], Robert P. Dickson[8,9,10] & Antoine Roquilly[1,11,12]

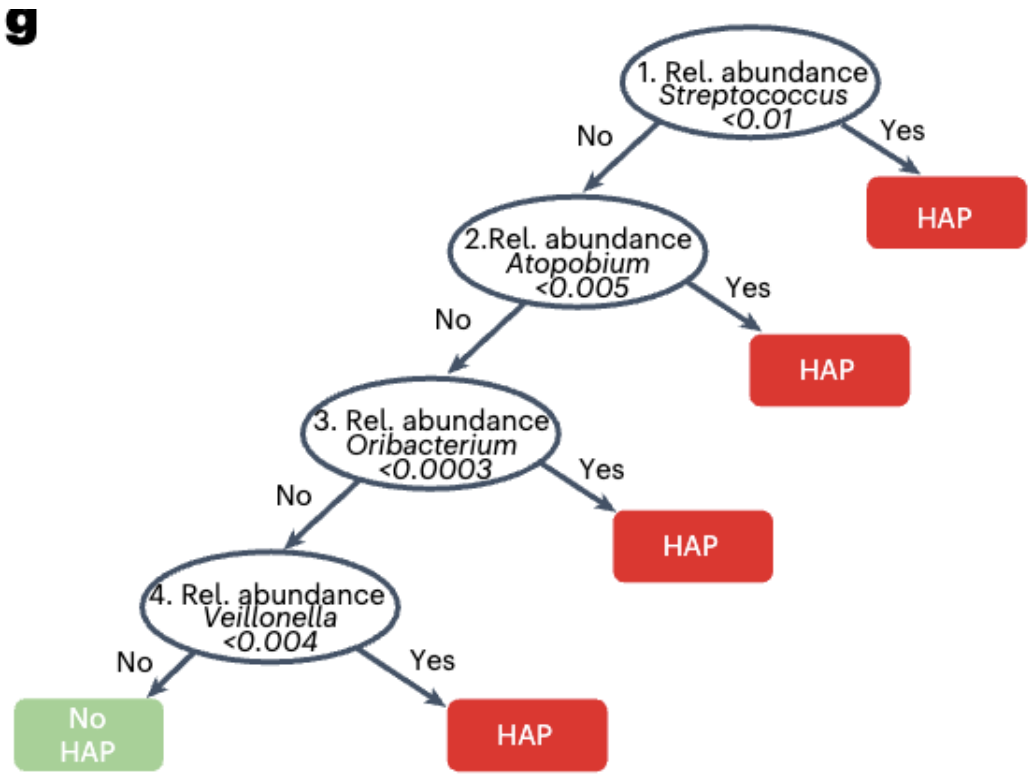


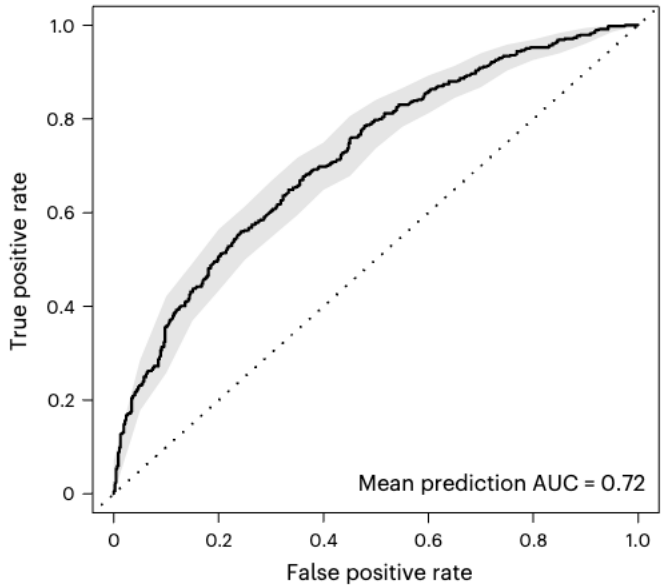


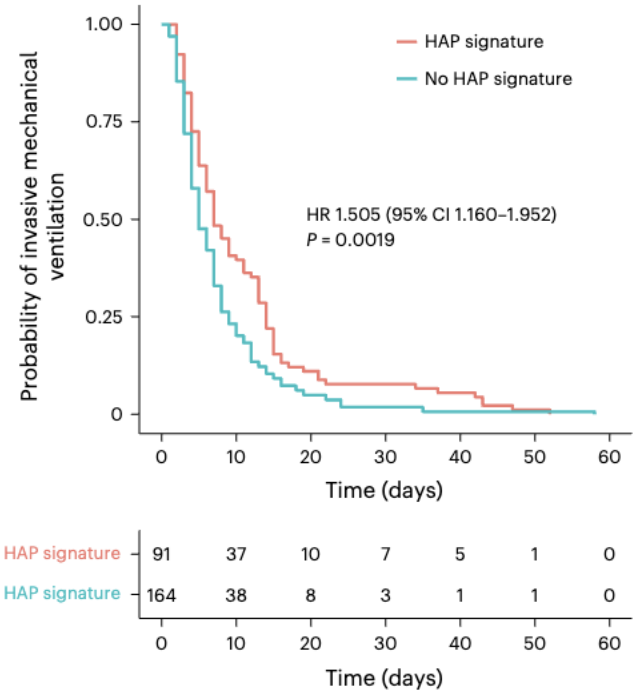
Respiratory microbiome alterations associated with HAP

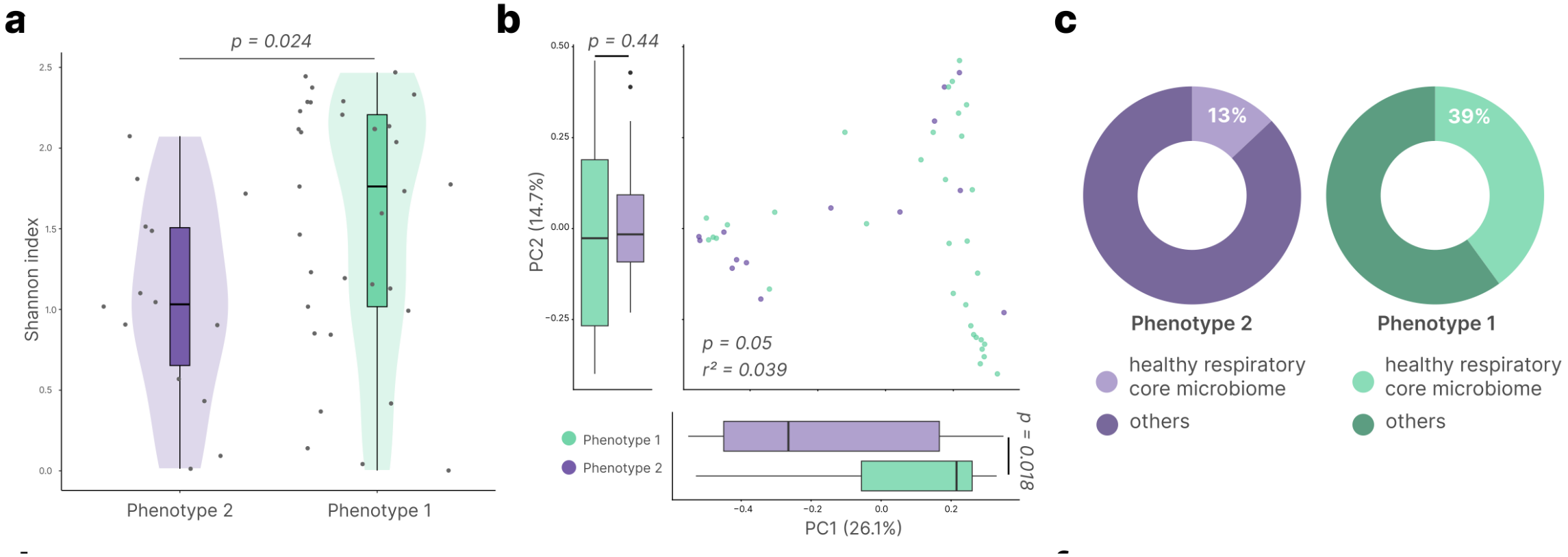


Human readable signature

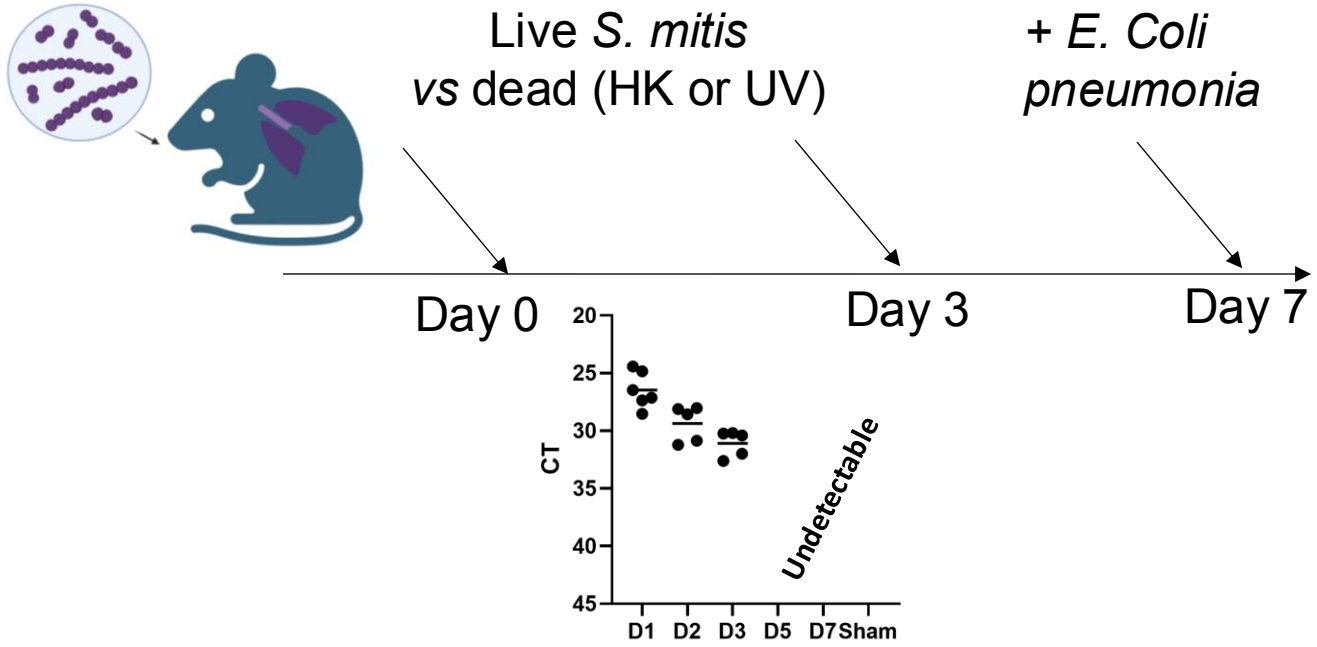


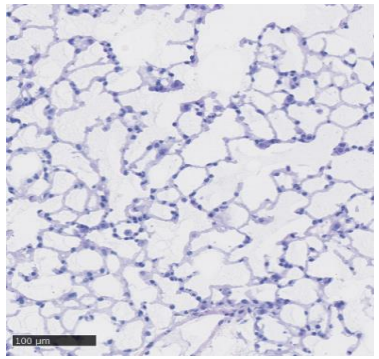


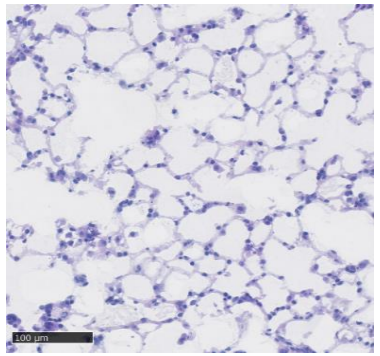


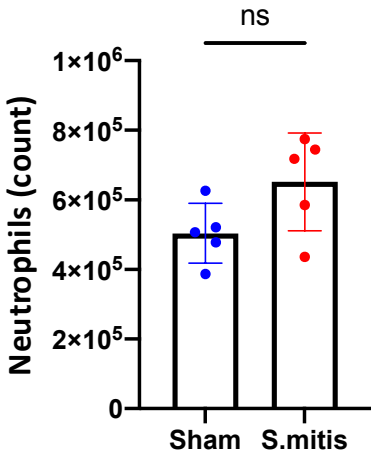

a
p = 0.024
Shannon index
2.5
2.0
1.5
1.0
0.5
0.0
Phenotype 2
Phenotype 1
b
p = 0.44
PC2 (14.7%)
0.50
0.25
0.00
−0.25
p = 0.05
r² = 0.039
Phenotype 1
Phenotype 2
p = 0.018
−0.4
−0.2
0.0
0.2
PC1 (26.1%)
c
13%
39%
Phenotype 2
Phenotype 1
healthy respiratory core microbiome
others
healthy respiratory core microbiome
others

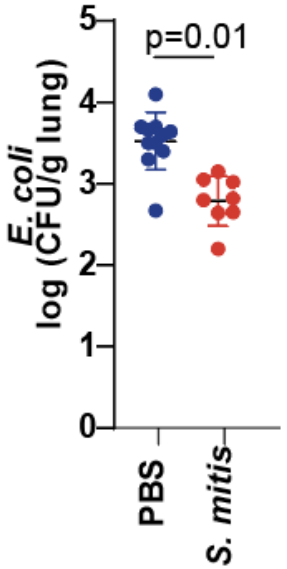
Effects of a single commensal bacterial taxa as a proof of concept

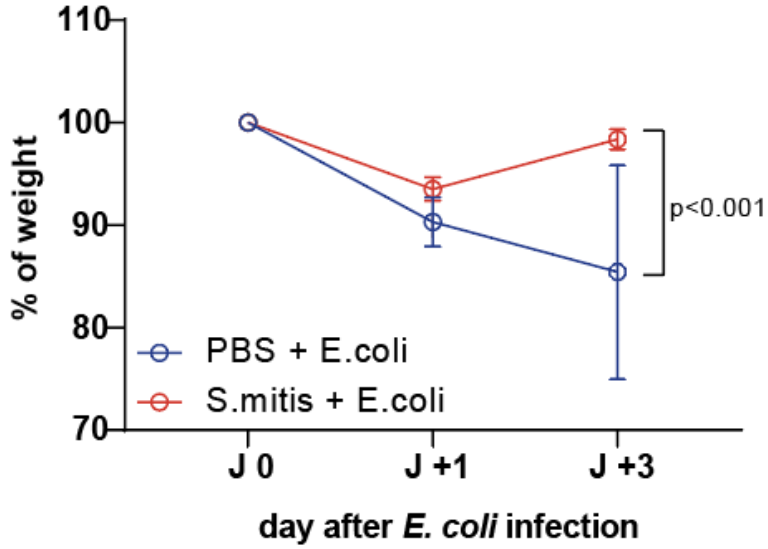








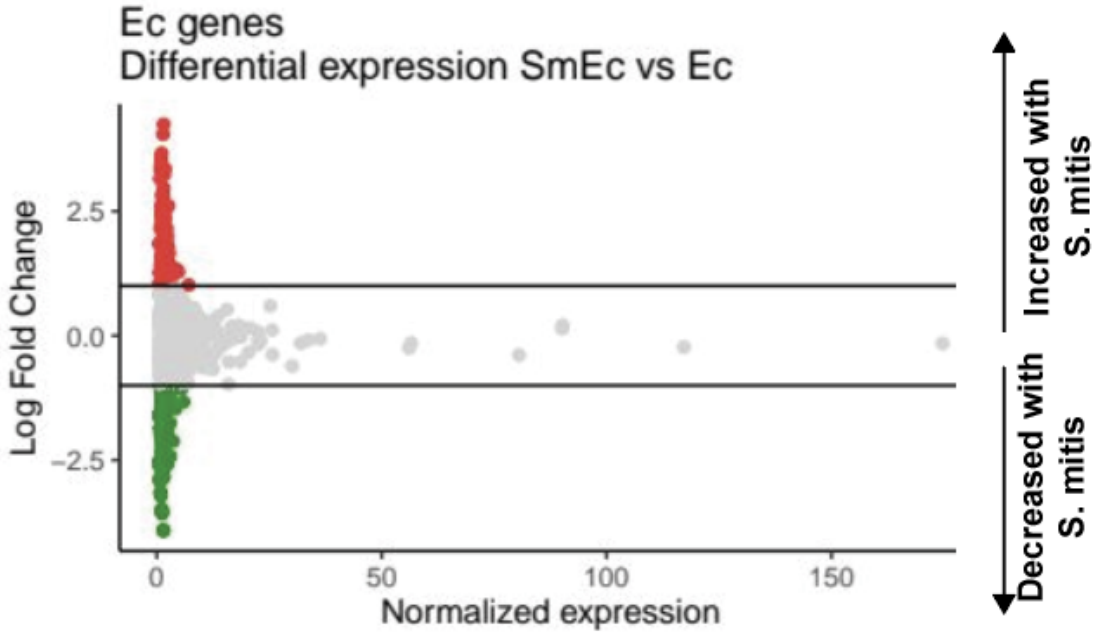


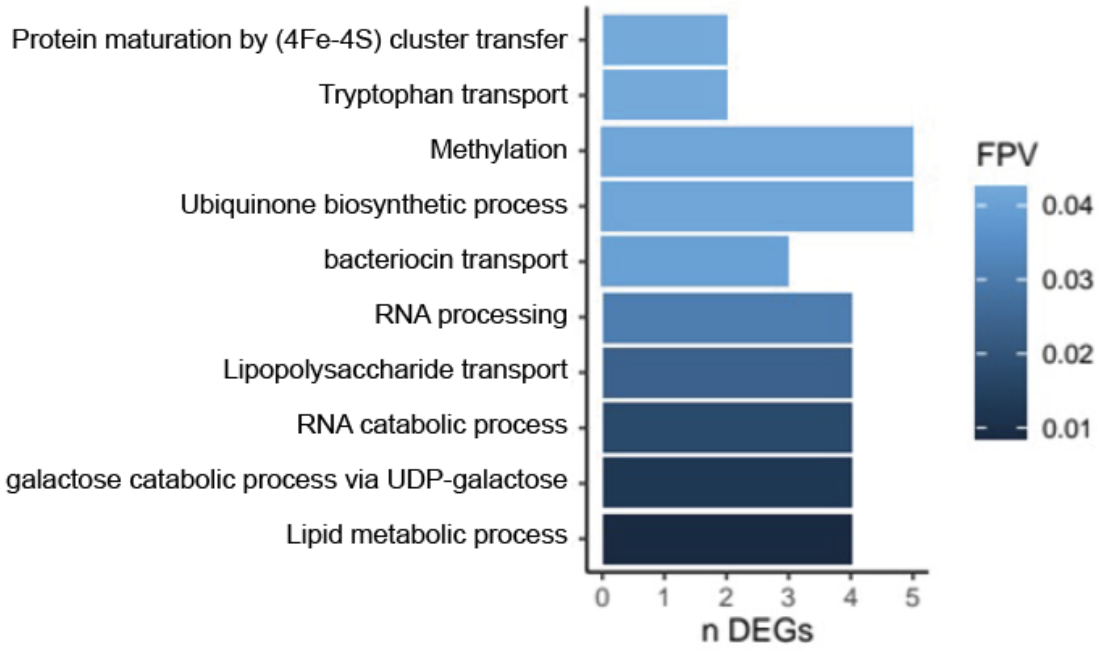


Personal unpublished data

How does it work ?

Bacteria-bacteria interactions

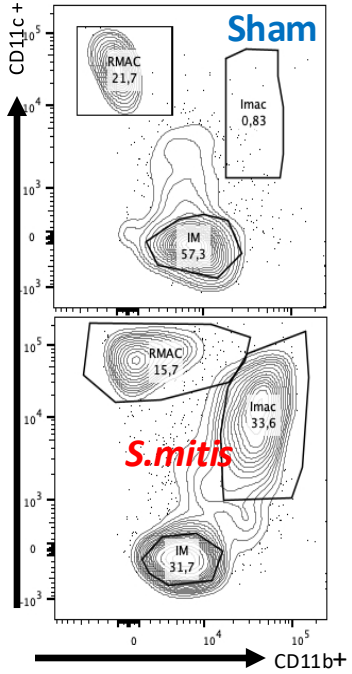


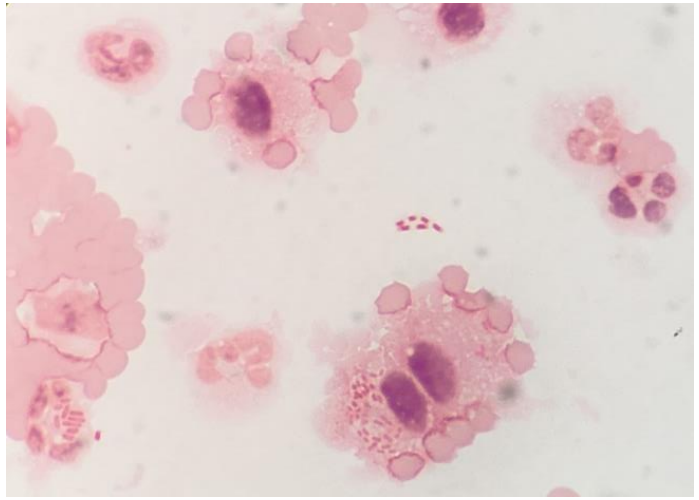


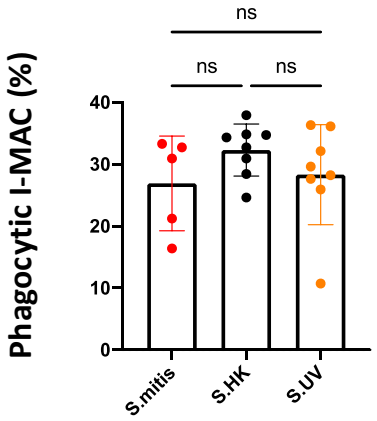
Personal unpublished data

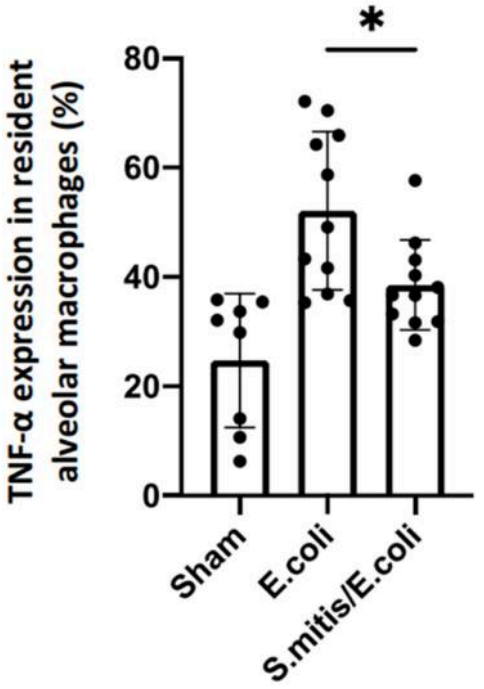
How does it work ?

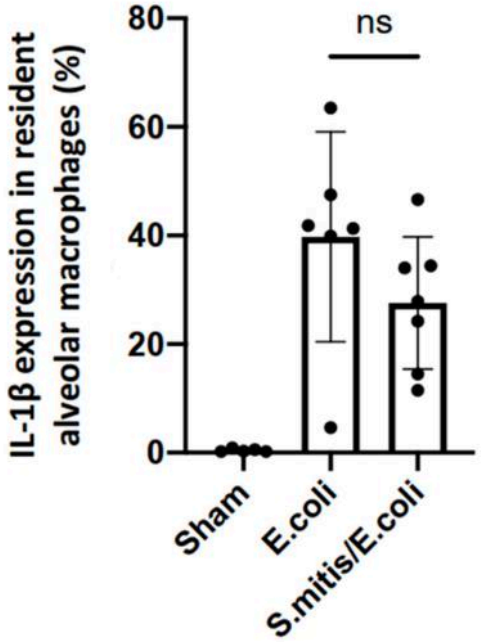
Bacteria-immune cell interactions



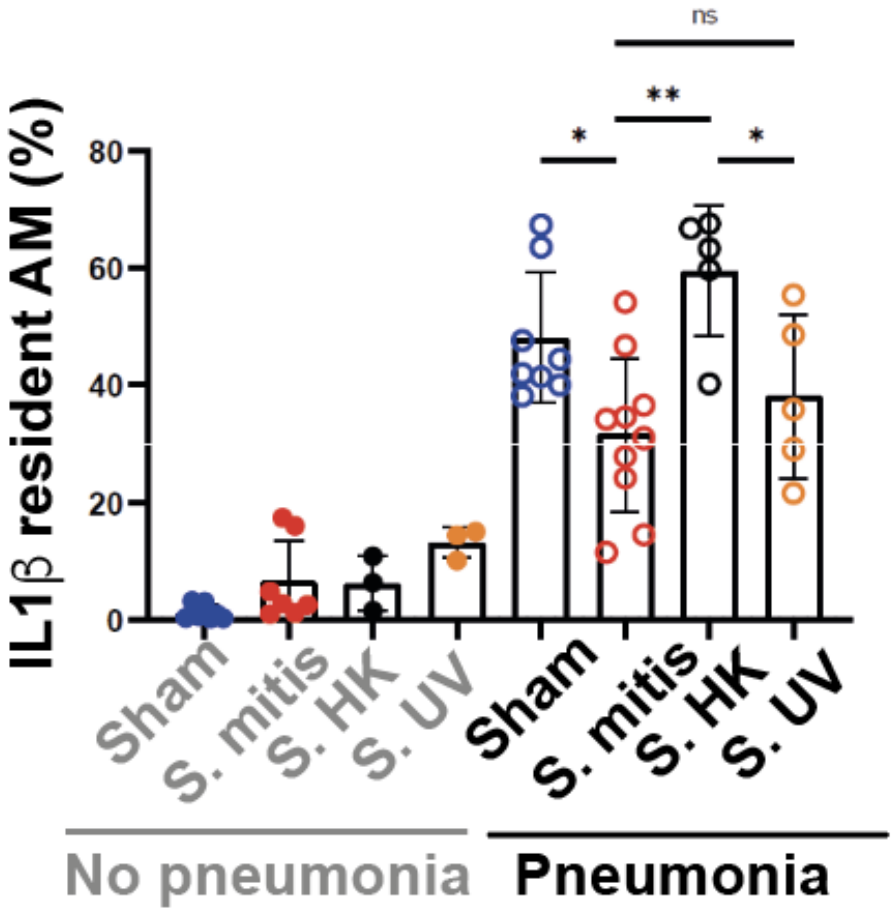


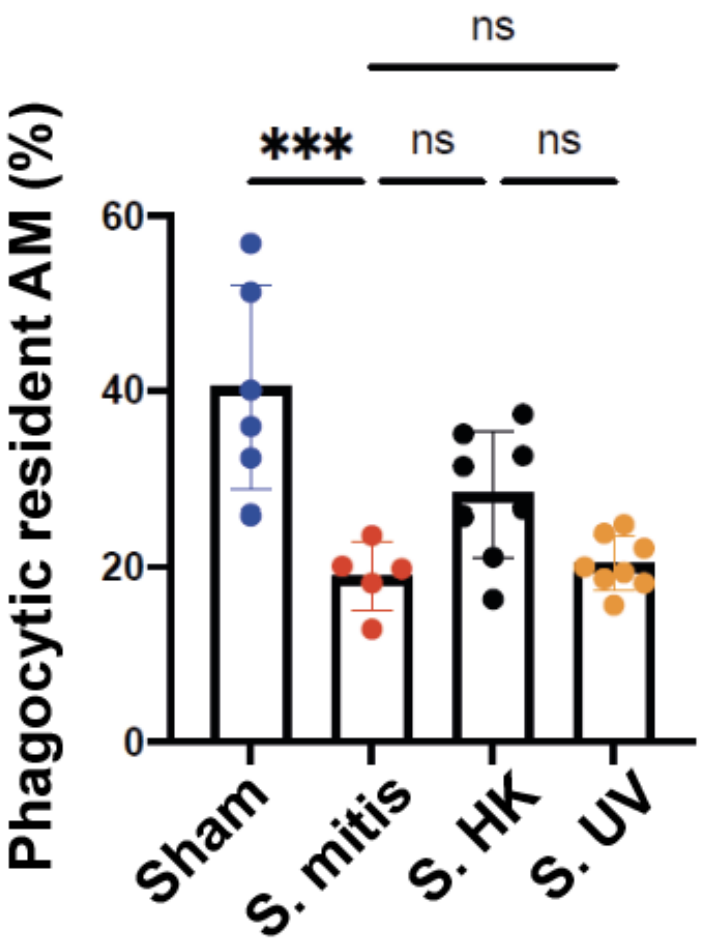






Metabolic activity of S. mitis is key

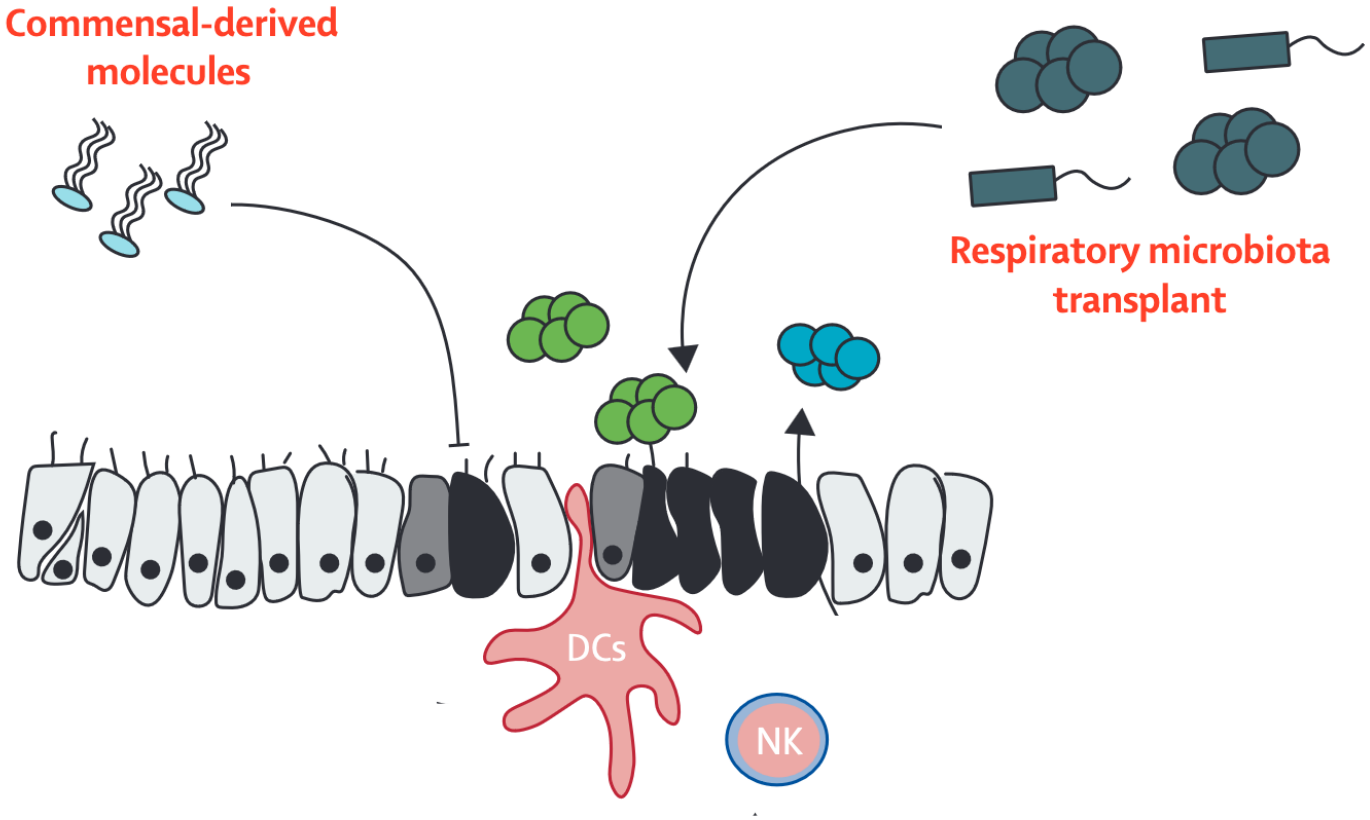




Proposed innovative therapeutical solution

Probiotic cocktail (dead ?)
Streptococcus mitis
+ other (??)

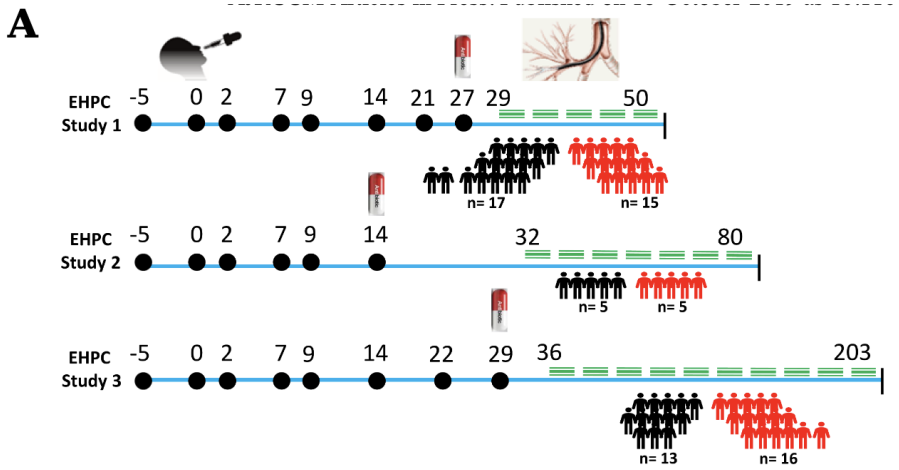
Associated with metabolites
Lactate acid
+ other (??)

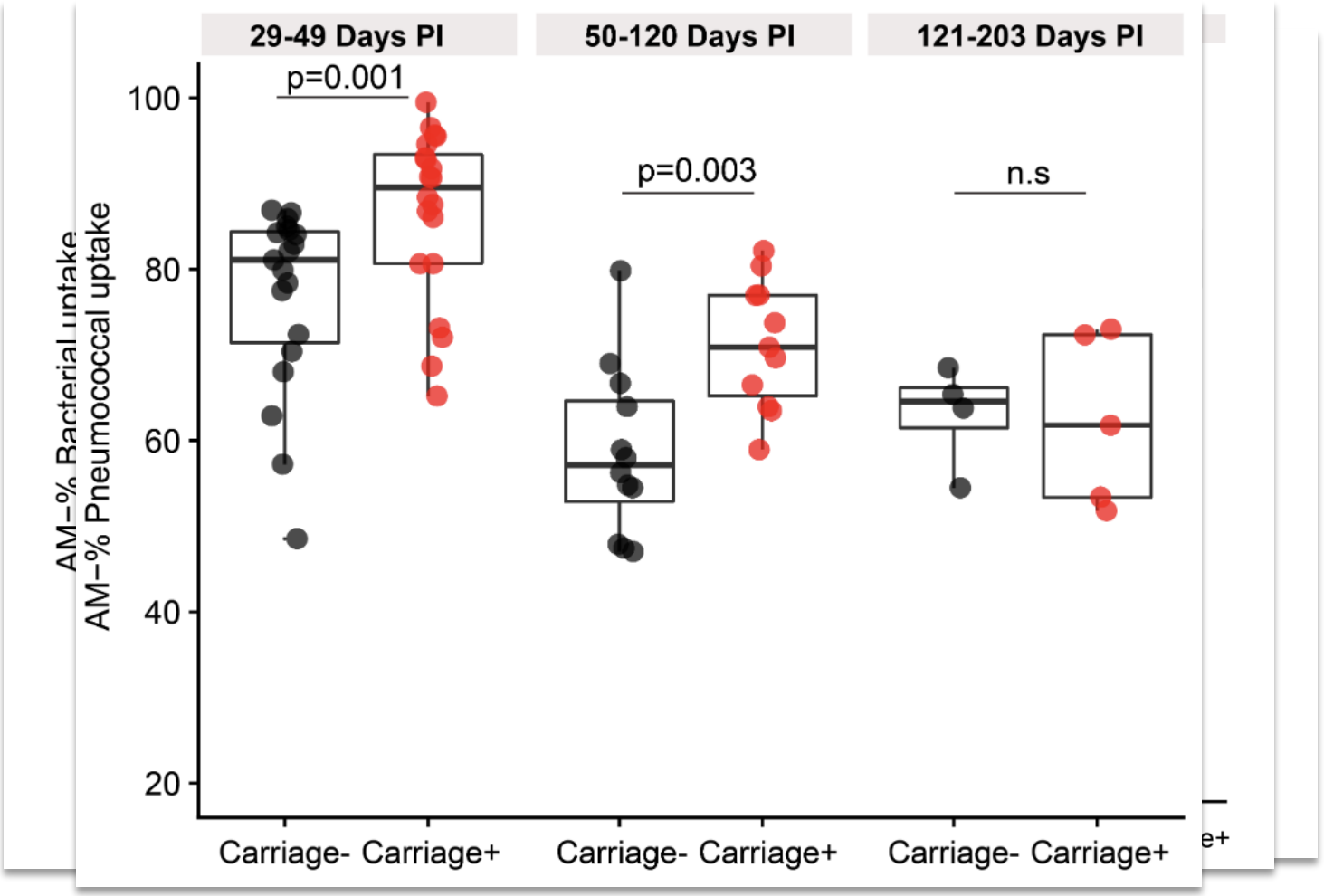


Roquilly et al. Lancet respir Med 2019

Microbiome enrichment to boost immunity

Proof of concept in humans





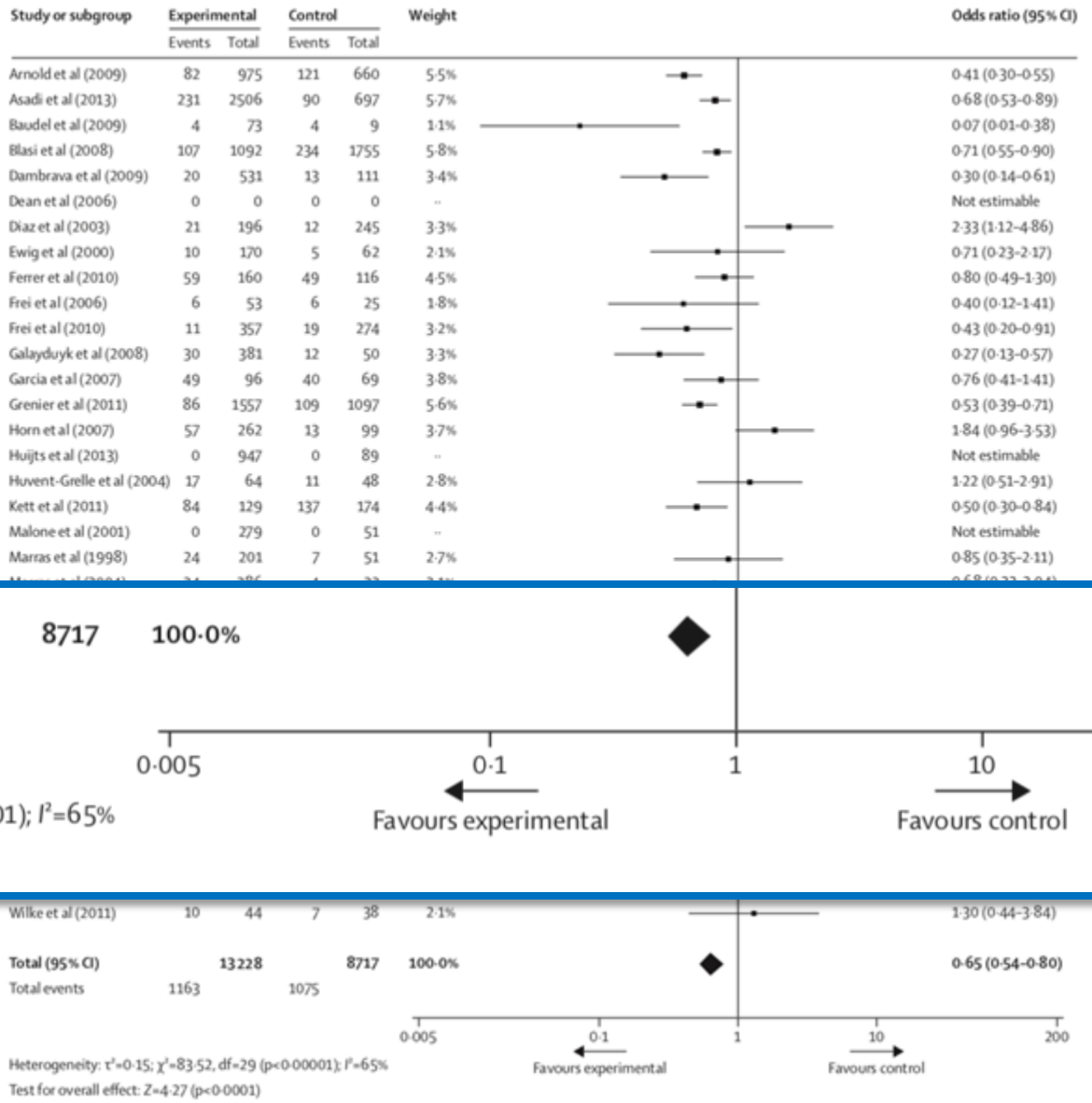
Mitsi *et al. AJRCCM 2019*

Microbiome failure

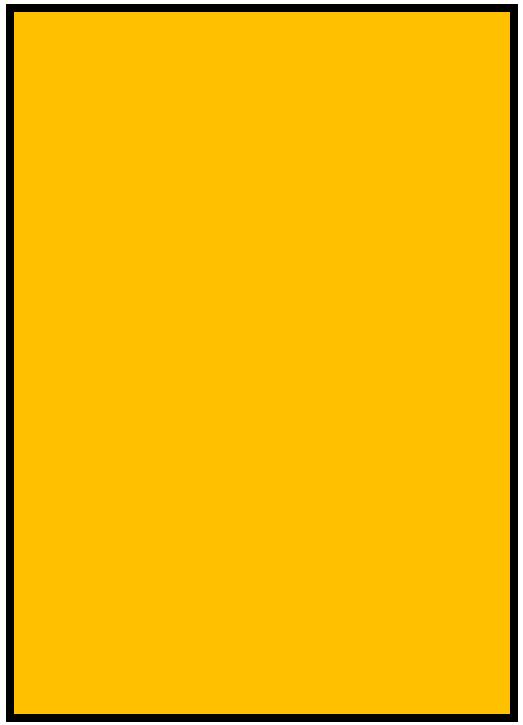
Proof of concept in humans

Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

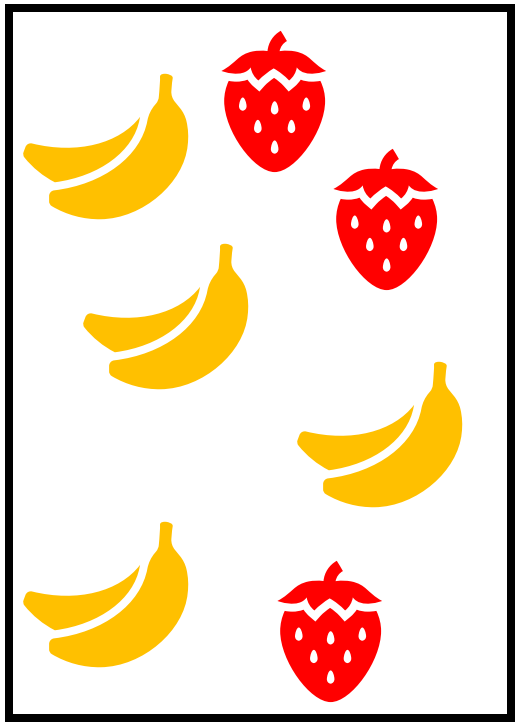
Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James W T Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins



One fits all ?



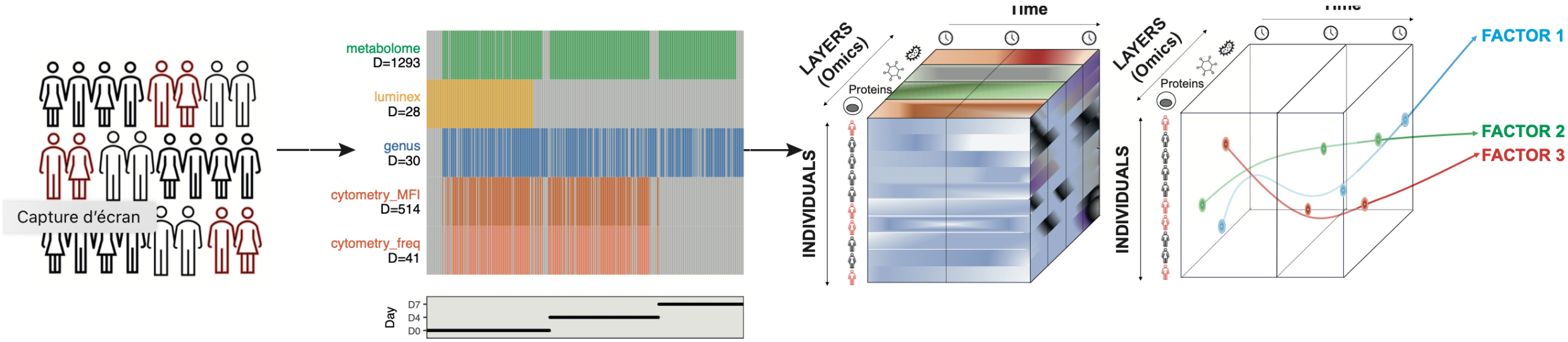
In vivo investigation of host-microbiome interactions



Pneumonia ----------▸ **Phenotypes Endotypes**

Hospital-acquired pneumonia heterogeneity

Temporo-spatial modelisation of host-microbiome interactions



158 BI patients
(73 with HAP, 23 with ARDS)

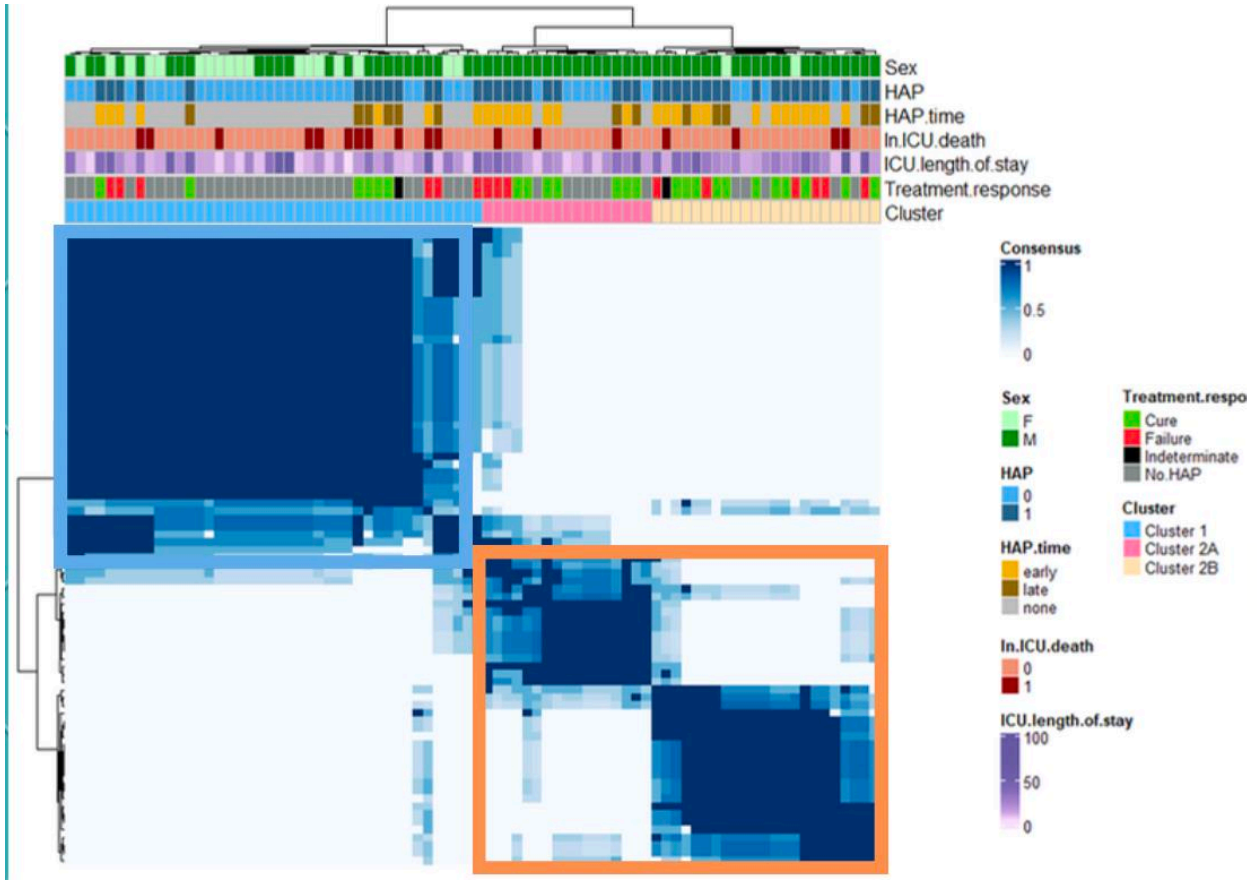
384 samples (blood and ETAs) collected upon admission, day 4 and day 7

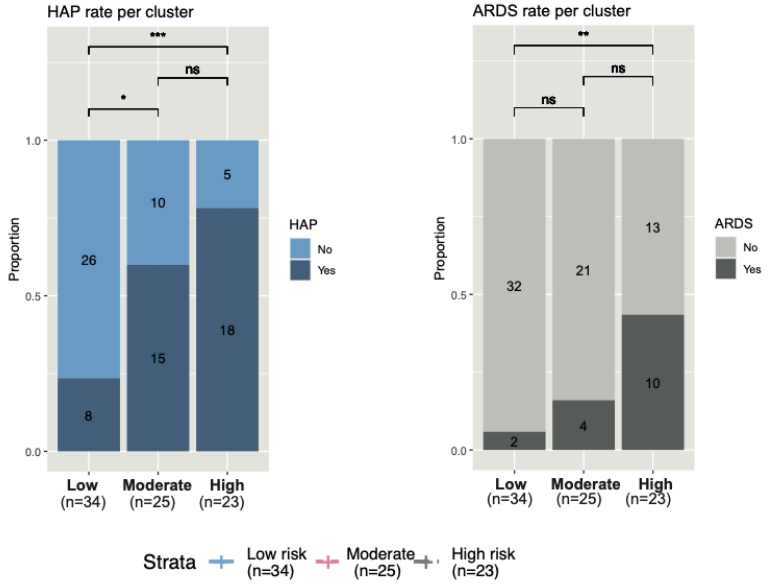
Identification of temporal and spatial patterns of variation (MEFISTO)

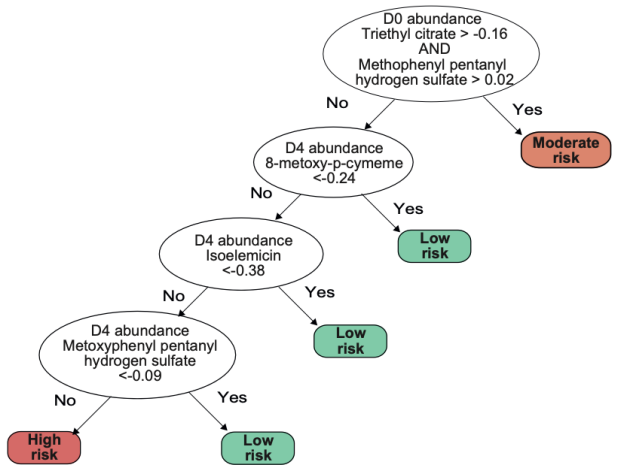
Personal unpublished data

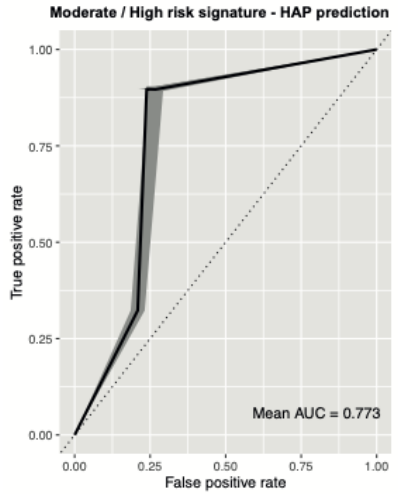
Hospital-acquired pneumonia heterogeneity

Metabolomic for HAP prediction







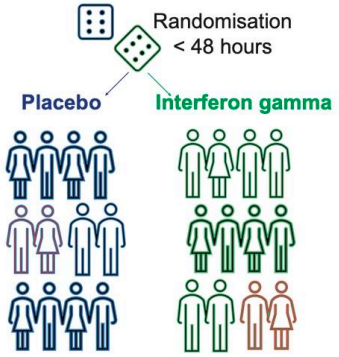


Personal unpublished data

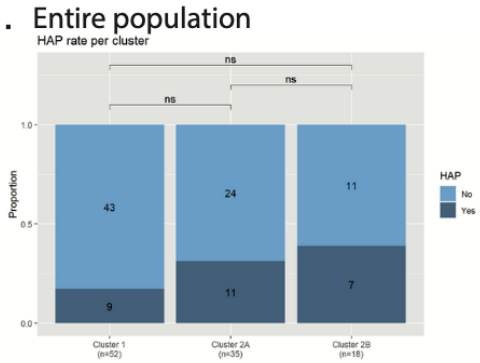
Hospital-acquired pneumonia heterogeneity

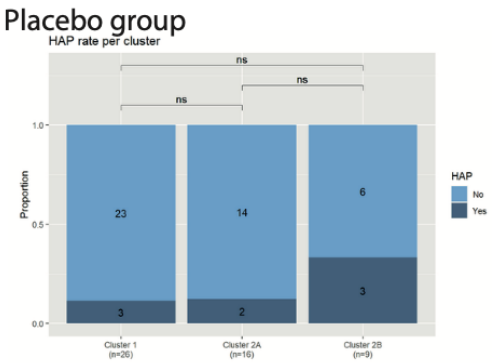
External validation

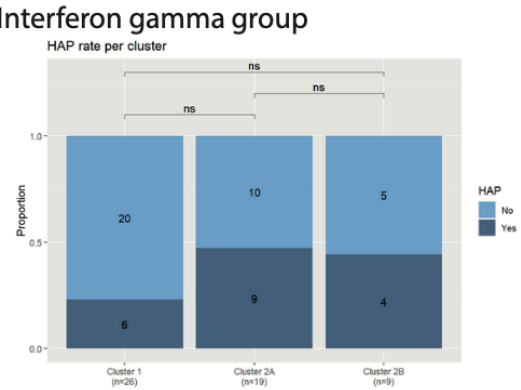
Randomized clinical trial (validation)

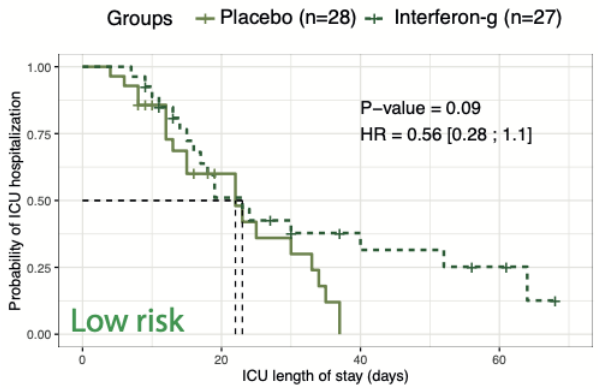


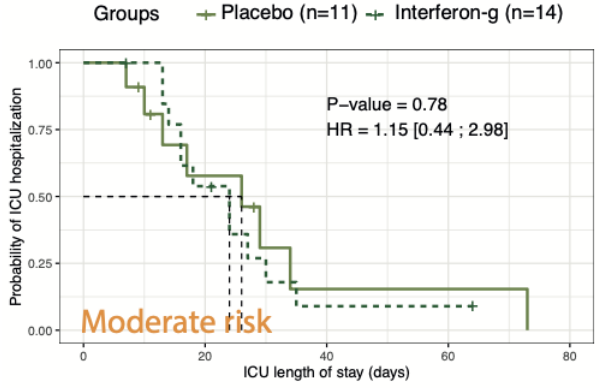
108 critically ill patients patients
(80% BI, 27 with HAP, 81 without HAP)

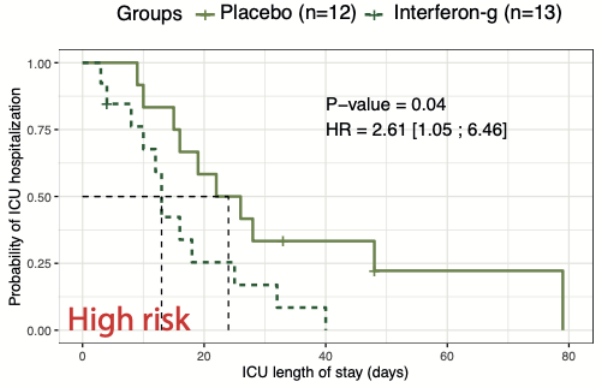


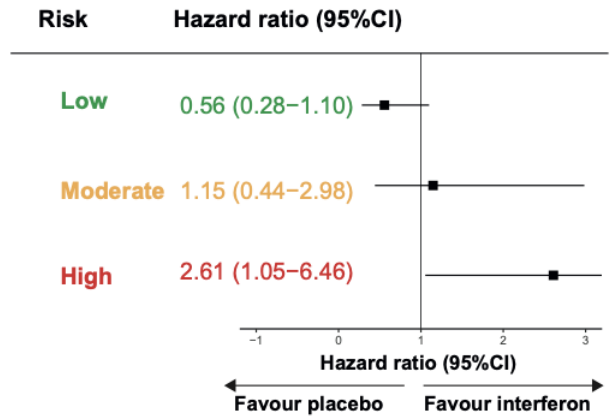












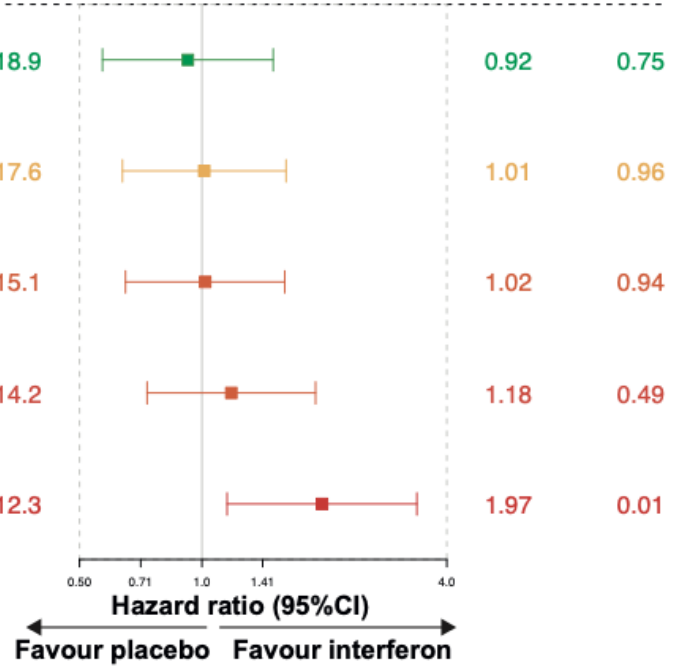
Personal unpublished data

Hospital-acquired pneumonia heterogeneity

In silico simulation to predict response to treatment

Varying the frequency of the risk phenotype in simulation

Dataset	N patients Placebo/IFNG	Mean duration mechanical ventilation Placebo/IFNG	Hazard Ratio	P–values
70% Low risk	46/54	16.9/18.9	0.92	0.75
70% Moderate risk	41/59	17/17.6	1.01	0.96
50% High risk	38/62	16.8/15.1	1.02	0.94
70% High risk	38/46	18.5/14.2	1.18	0.49
90% High Risk	31/35	19.2/12.3	1.97	0.01



Personal unpublished data

The interact project - Outcomes

- **Mission:** to better understand the regulation of a vital CHECKPOINT for mucosal inflammation regulation.
- **Vision:** revolutionising severe pneumonia treatment

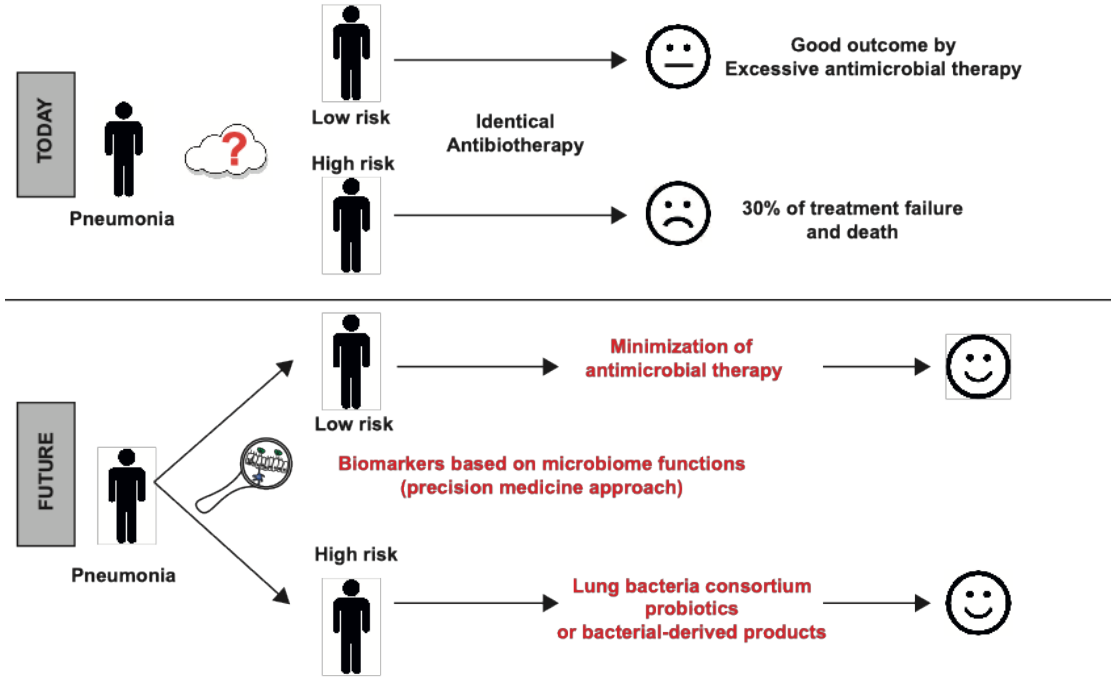
  ⇒ New therapeutical targets / potential drug intervention *(IP valorisation/start-up)*

  ⇒ Biomarkers for personalised, non-antimicrobial treatment

  ⇒ Multicenter randomized clinical trials for validation *(Roquilly et al. JAMA 2021, 2023, BMJ 2021)*

Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia

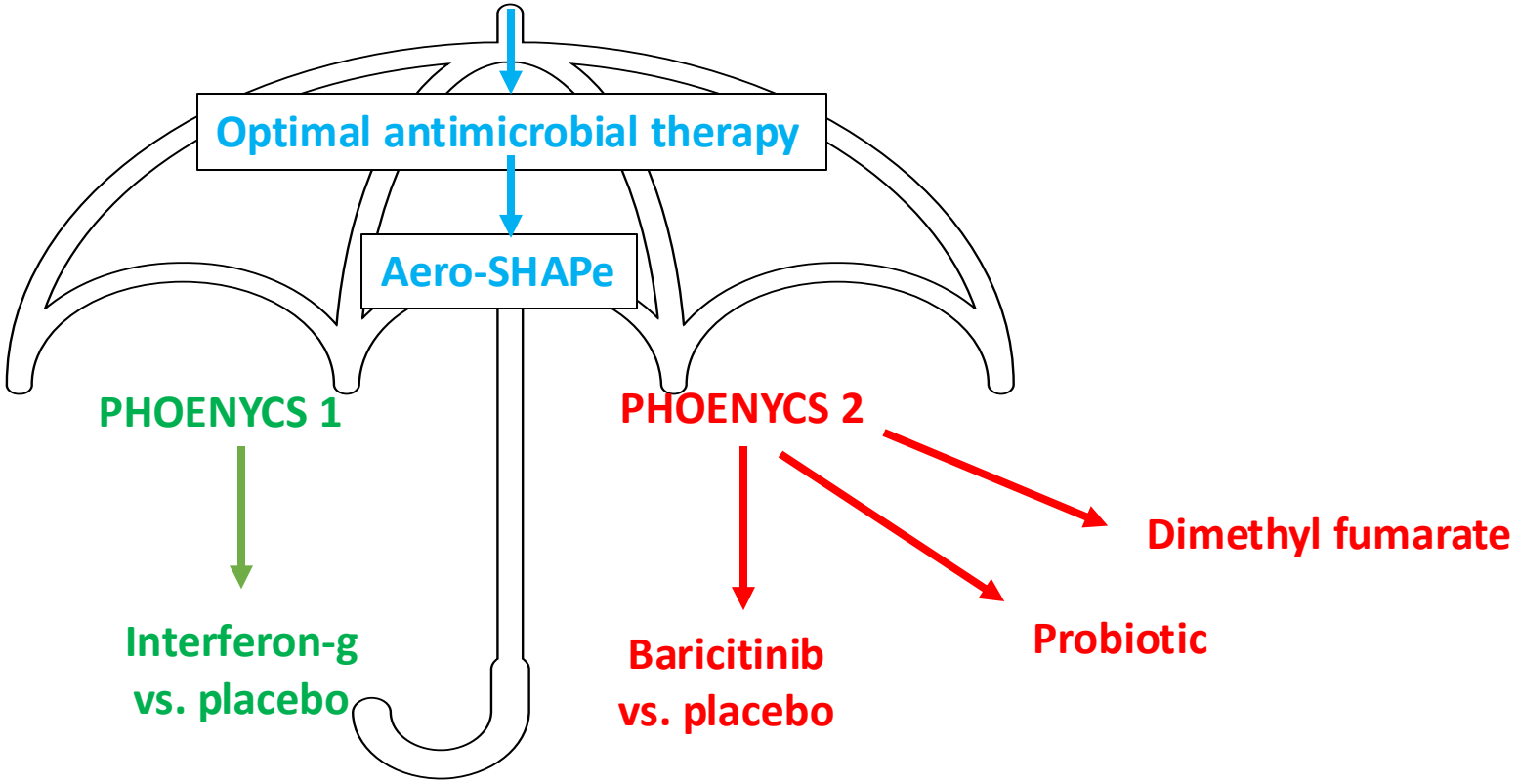
Roquilly et al. Lancet Respir Med 2019



Severe Hospital acquired pneumonia and precision medicine
Toward SHAPe platform trial

Inclusion criteria : Severe Hospital-acquired Pneumonia

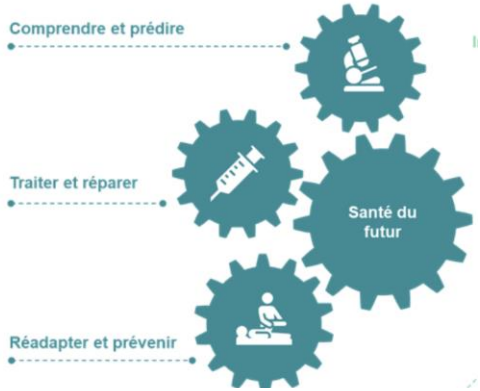
Metabolite-risk classification /
immuno-risk classification for study arm eligibility



Primary outcome : clinical cure and ACM day 28

Partners – towards immuno-infectiology institute

Nantes Université



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HAP²

HOMI-LUNG
PNEUMONIA IS A HEART MATTER TOO

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