Nantes Université

CR2TI Centre de Recherche Translationnelle en Transplantation et Immunologie UMR 1064

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Immune therapy and non antibiotic treatments of hospital-acquired pneumonia

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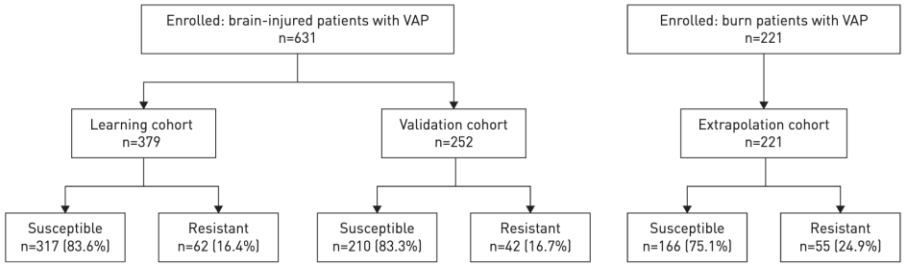
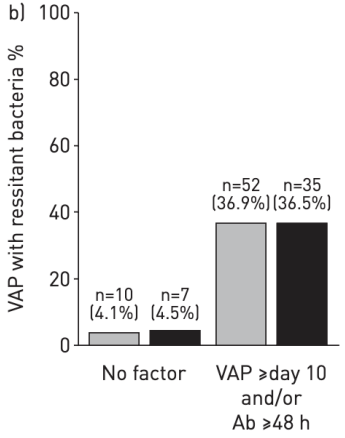
What for ?

Optimized antimicrobial therapy to solve the problem ?

Empiric antimicrobial therapy for ventilator-associated pneumonia after brain injury

Roquilly et al Eur Resj J 2016





	ATS/IDSA criteria #	Simplified score ¶
Learning cohort		
Sensitivity %	100	84
Specificity %	18	74
Positive predictive value %	19	38
Negative predictive value %	100	96
Positive likelihood ratio	1.2	3.2
Negative likelihood ratio	0.0	0.2
AUC	0.735	0.822
Validation cohort		
Sensitivity %	100	83
Specificity %	19	71
Positive predictive value %	20	37
Negative predictive value %	100	96
Positive likelihood ratio	1.2	2.9
Negative likelihood ratio	0.0	0.2
AUC	0.762	0.805

Clinical evaluation of the BioFire Respiratory Pathogen Panel for the guidance of empirical antimicrobial therapy in critically ill patients with hospital-acquired pneumonia: A multicenter, quality improvement project

Poulain et al. ACCPM 2024

	Baseline period	Intervention period	p-values
No. of patients (n=)	223	220	
Spectrum of empirical antimicrobial therapy, *yes, N, (%)*			
Efficient**	163 (84.9%)	152 (85.9%)	0.72
Unnecessary broad spectrum ***,	55 (27.8%)	58 (32.6%)	0.31
Optimal ****	111 (57.8%)	95 (54.0%)	0.46
Antimicrobial treatment modification after rapid multiplex PCR bacterial identification *, *yes, N, (%)*	3 (1.3%)#	22 (10.1%)	0.0001
HAP Recurrence on day 28, *yes, N (%)*	14 (6.3%)	22 (10.3%)	0.1354

Optimized antimicrobial therapy to solve the problem ?

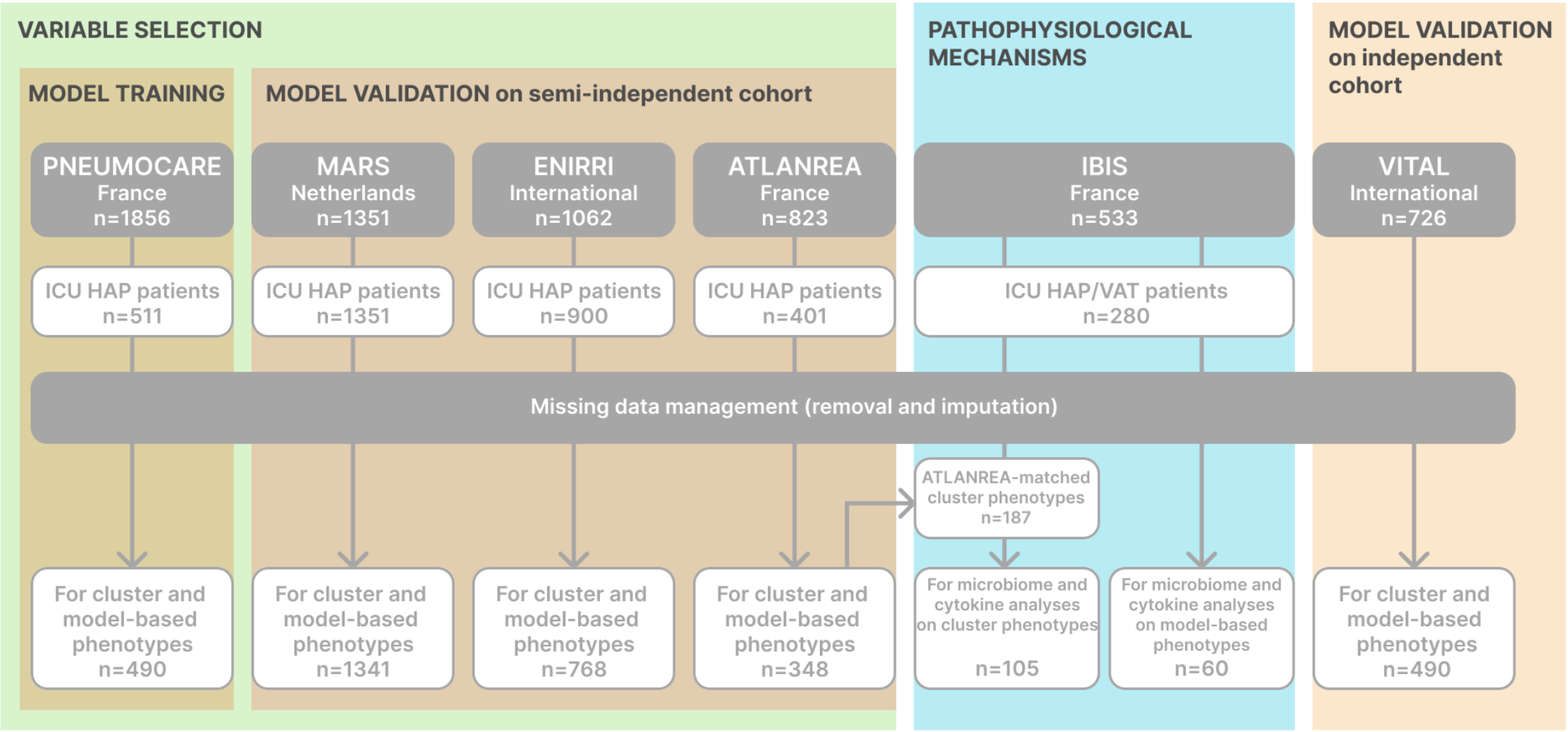
A multifaceted strategy to optimize pharmacokinetics of antimicrobial therapy in patients with hospital-acquired infections—a monocentre quality improvement project

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

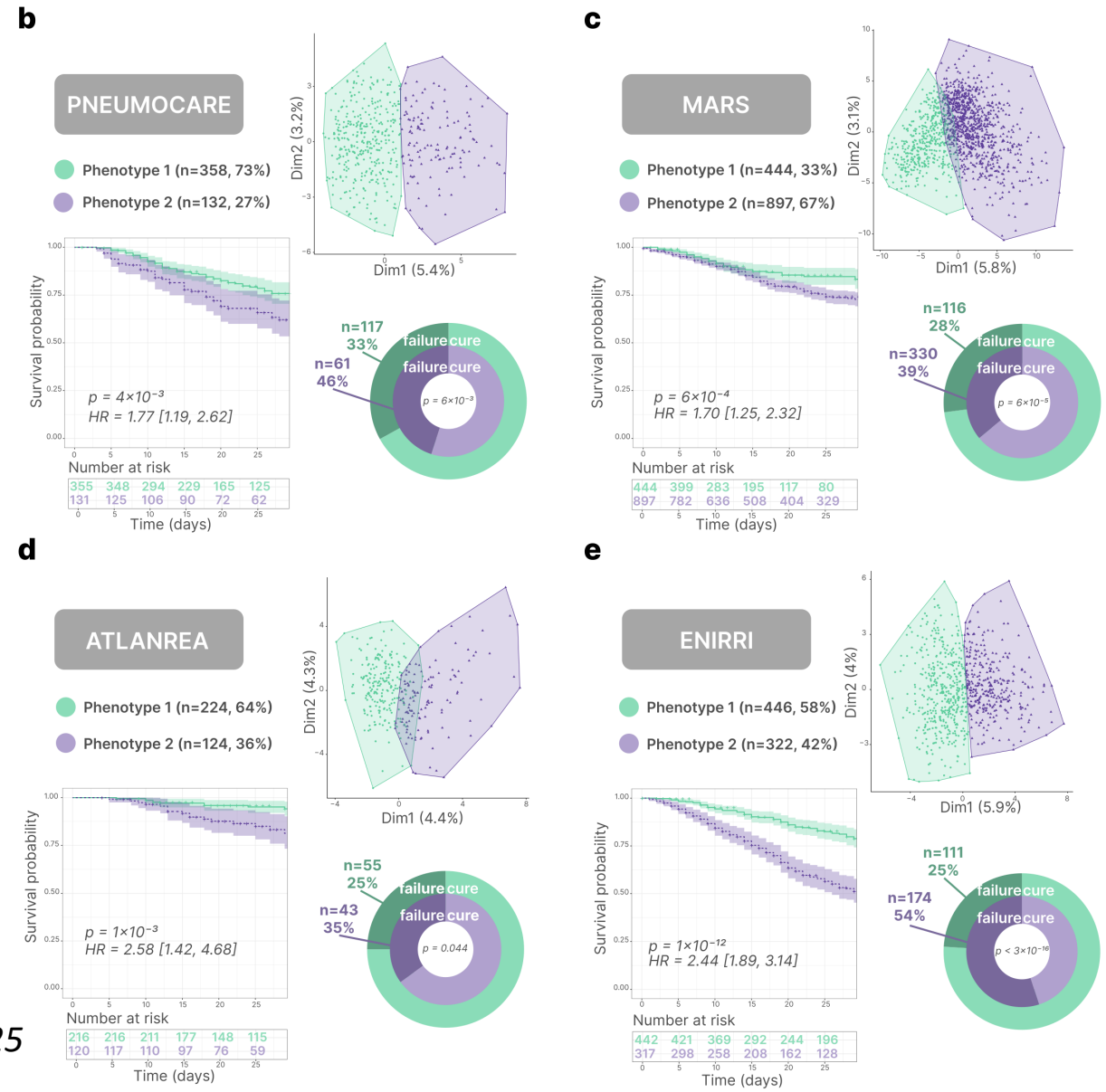
	Pre-intervention group *N*=58	Intervention group *N*=140	Adjusted hazard ratio (95%CI)
Secondary outcomes			*P* values
Treatment failure, *N* (%)	22 (37.9)	36 (25.7)	0.07
Relapse	11 (18.9)	18 (12.8)	0.28
Recurrence	11 (18.9)	18 (12.8)	0.21
Duration of invasive mechanical ventilation, days, mean (SD)	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



Martin FP et al Intensive Care Med 2025

Treatment failure : a worldwide matter



Martin FP et al Intensive Care Med 2025

An incomplete understanding of the pathophysiology ?

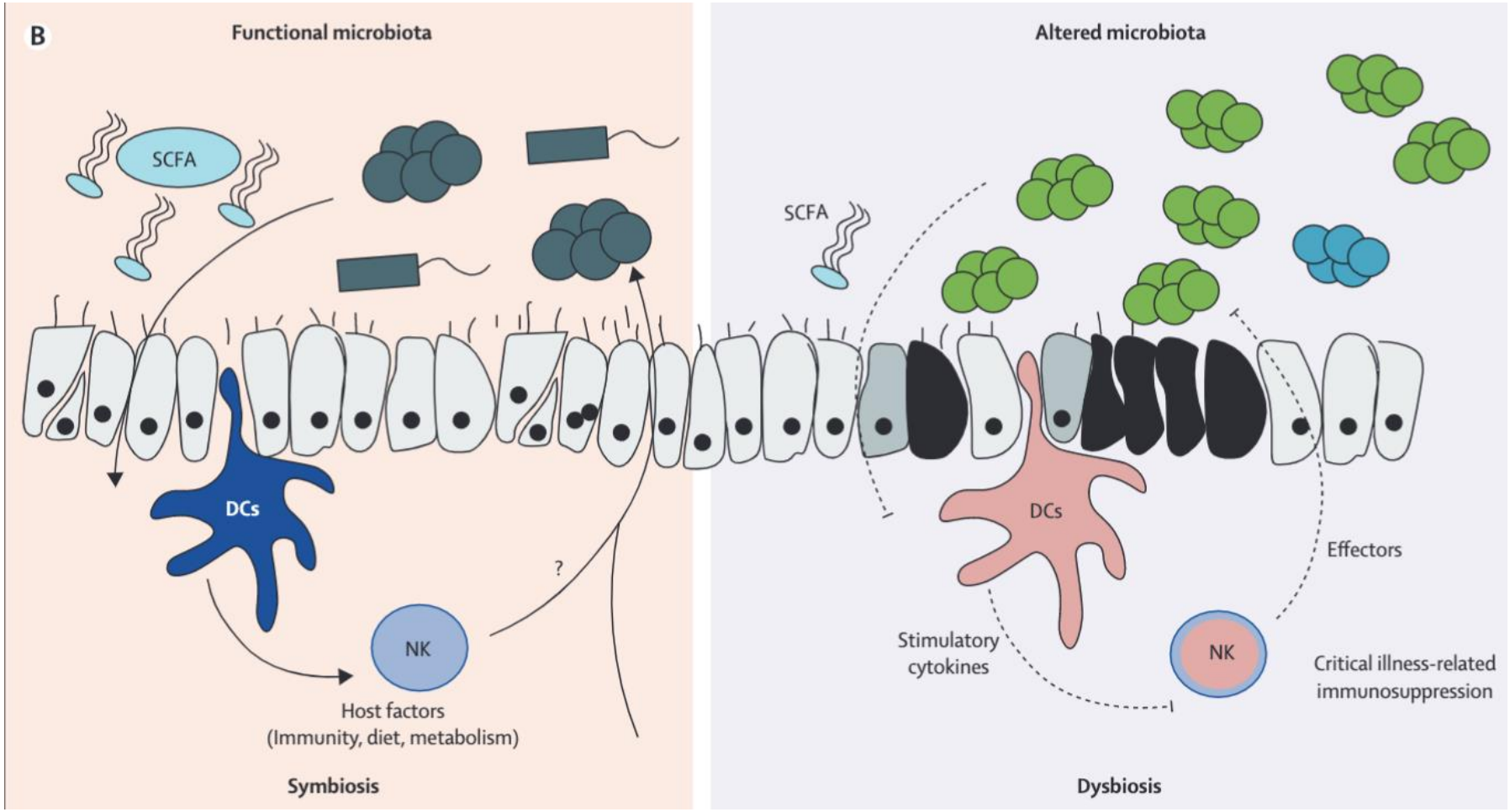
Weak association between clinical and microbiological cures

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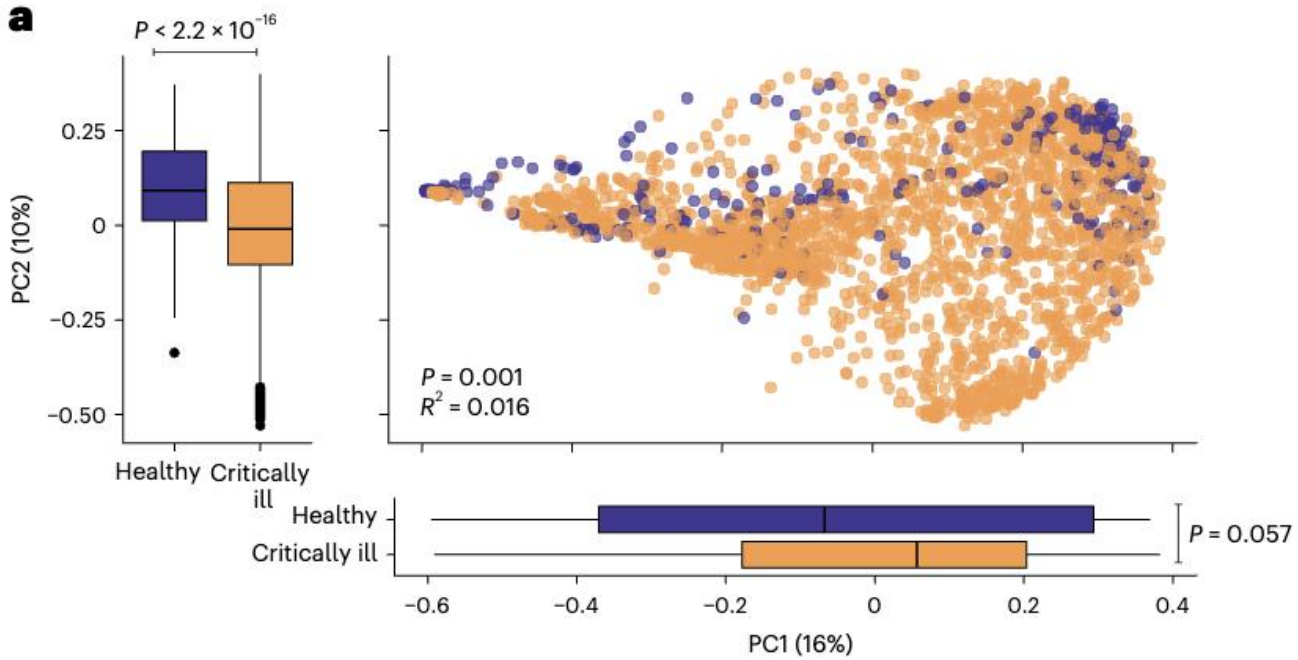
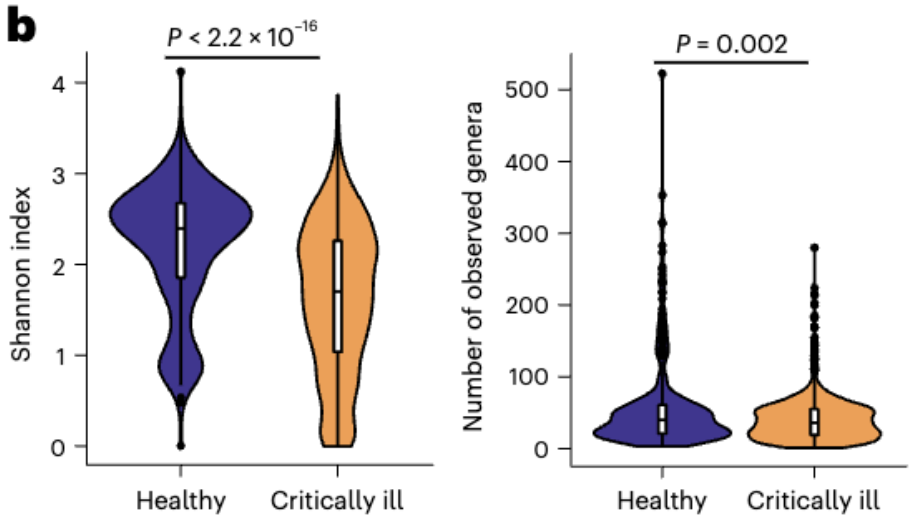
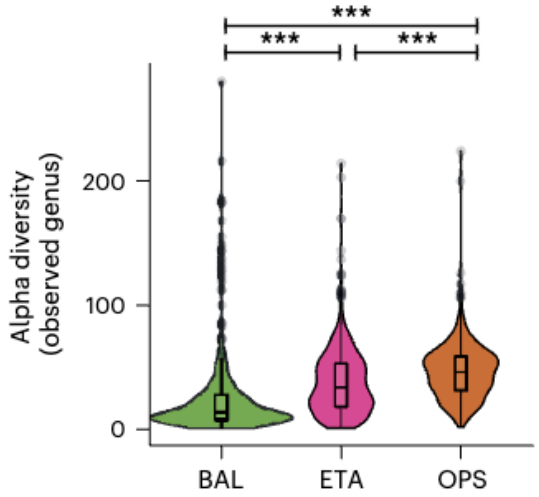
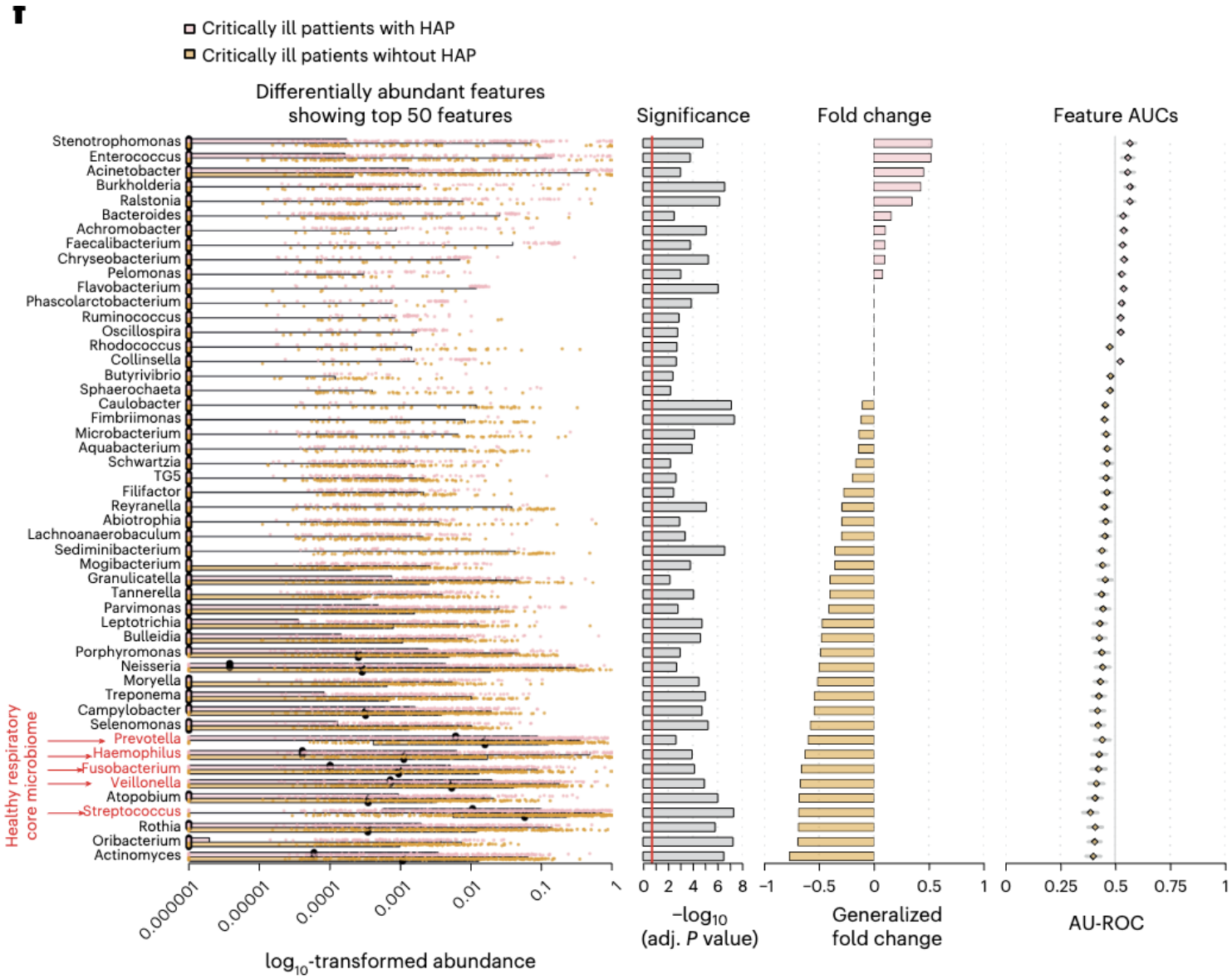
Emmanuel Montassier[1,2], Georgios D. Kitsios[3,4], Josiah E. Radder[3,4], Quentin Le Bastard[2], Brendan J. Kelly[5], Ariane Panzer[6], Susan V. Lynch[6], Carolyn S. Calfee[7], Robert P. Dickson[8,9,10] & Antoine Roquilly[1,11,12]



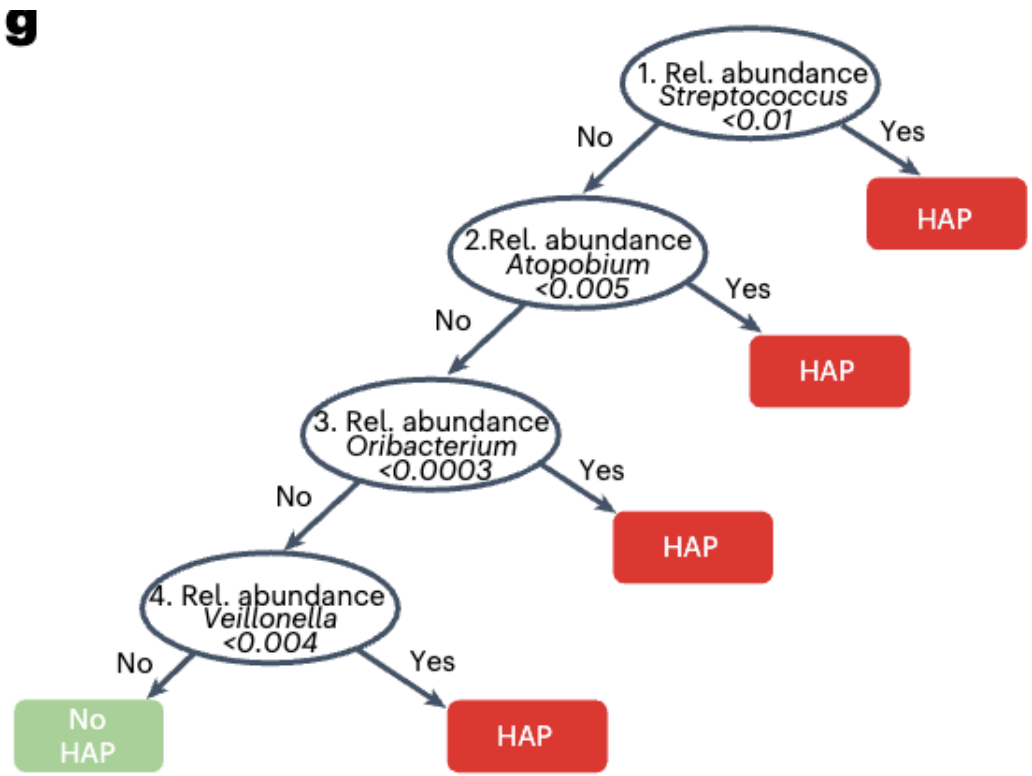


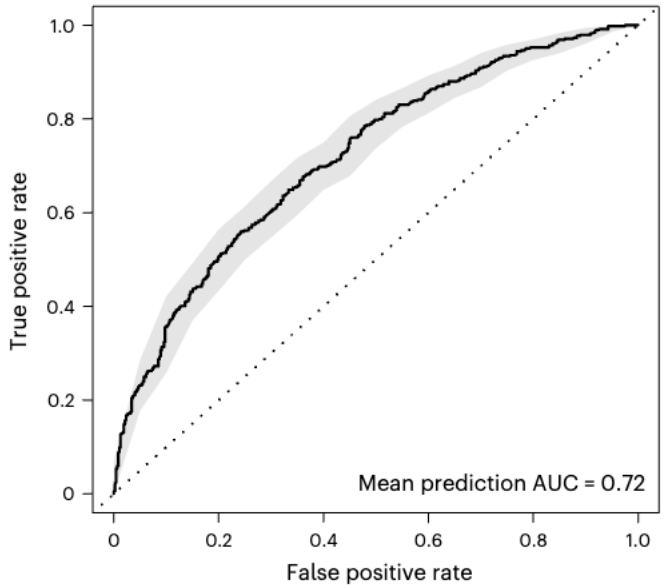


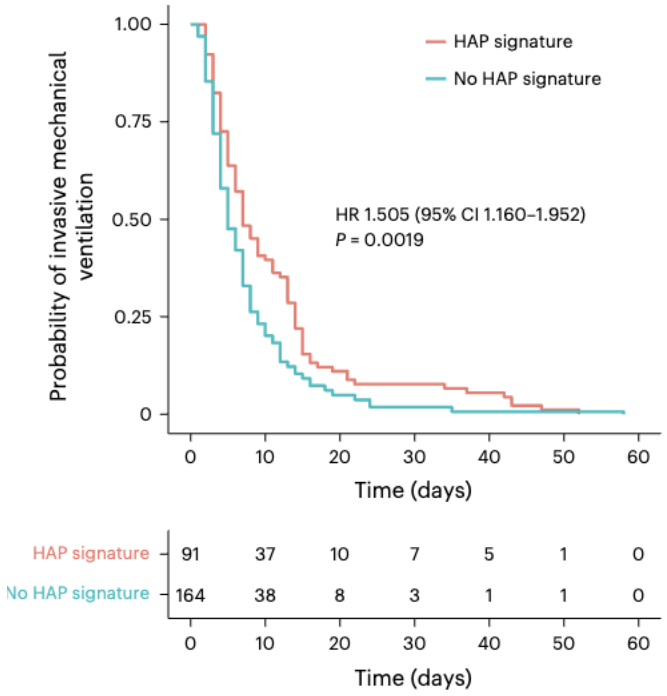
Respiratory microbiome alterations associated with HAP



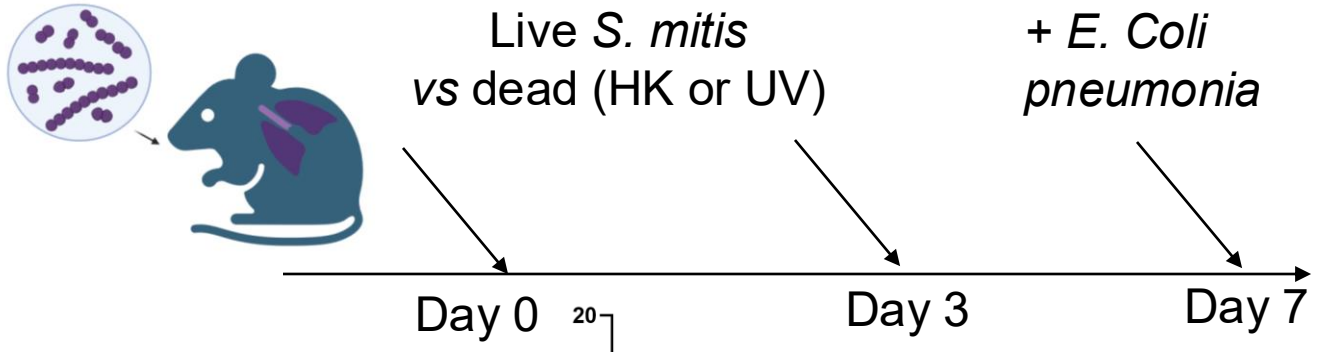
Human readable signature

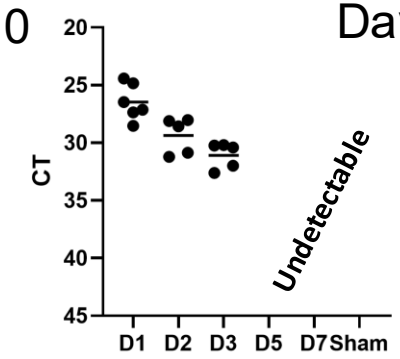


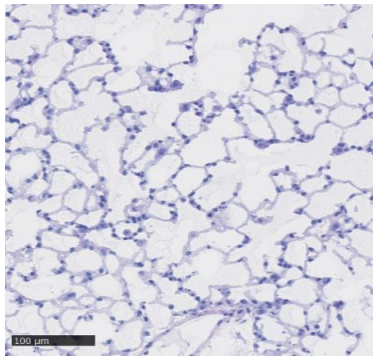


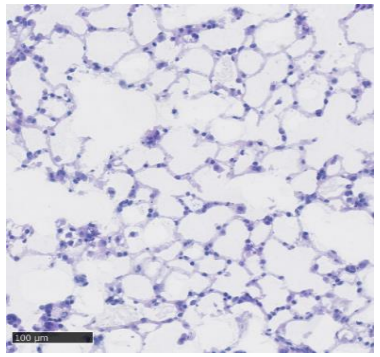


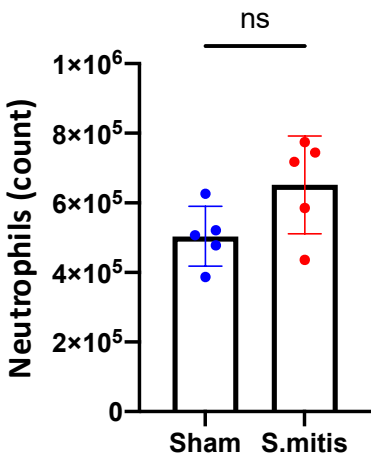
Effects of a single commensal bacterial taxa as a proof of concept

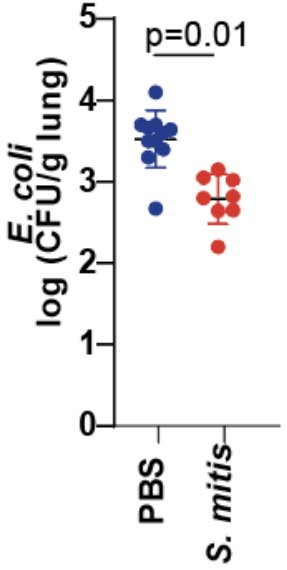


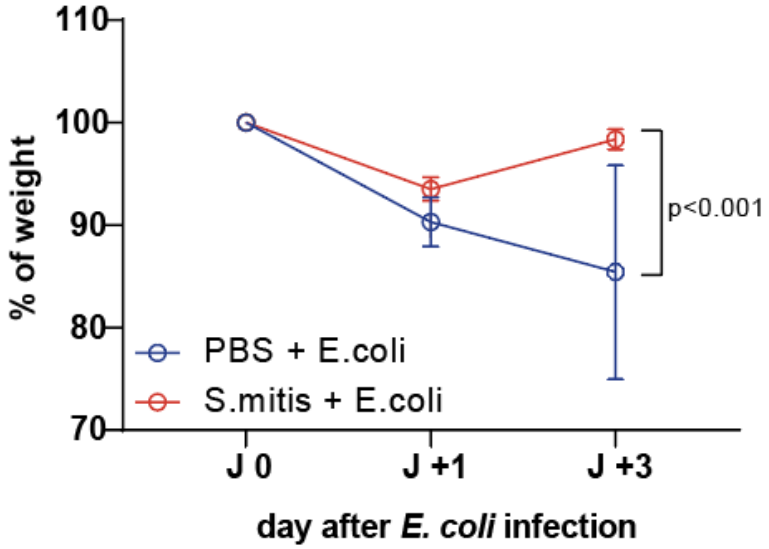










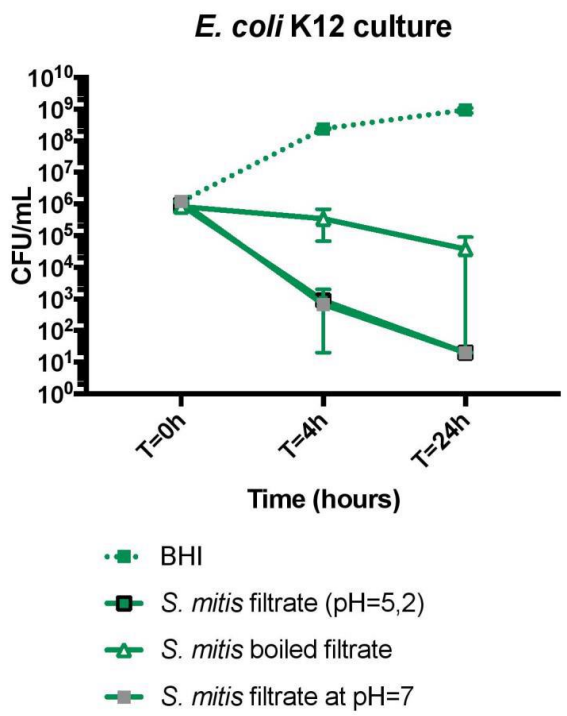


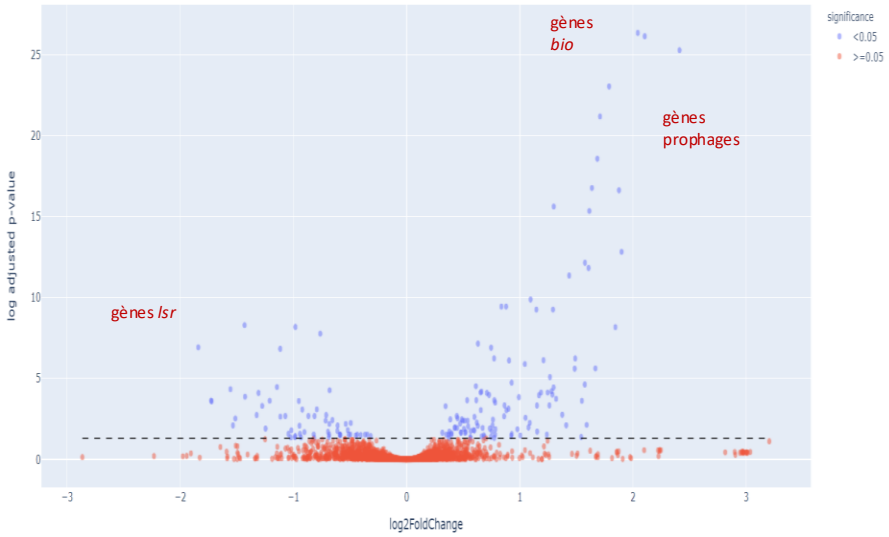
Personal unpublished data

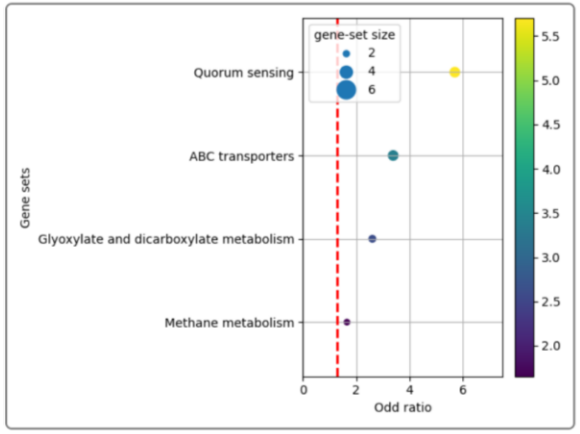
How does it work ?

Bacteria-bacteria interactions

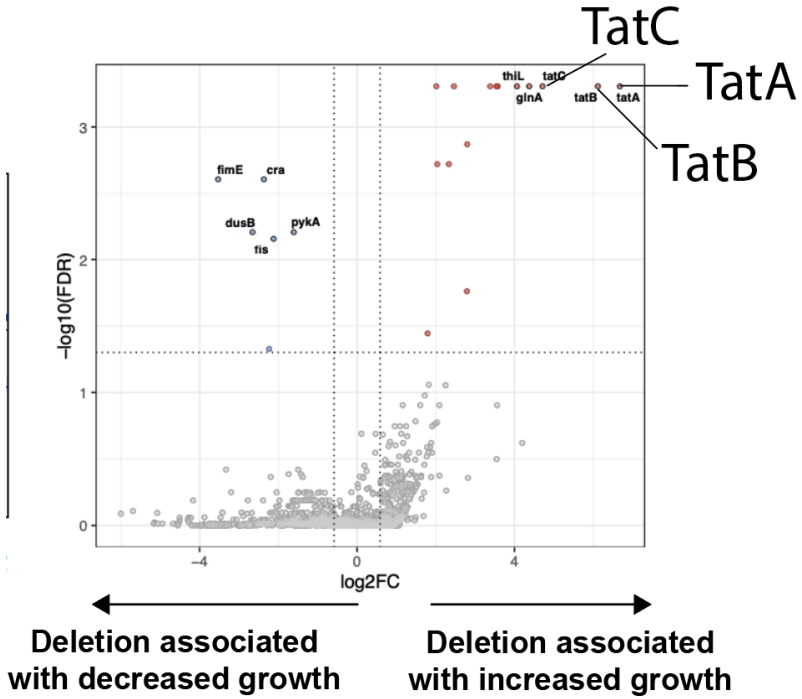
***Streptococcus mitis* (ATCC 49456) supernatant affects *E. coli* K-12**







Transcriptome

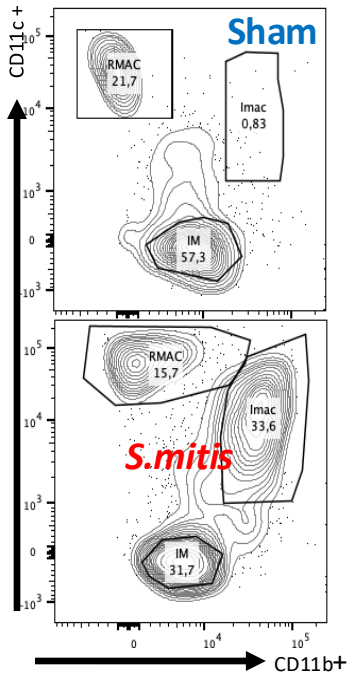


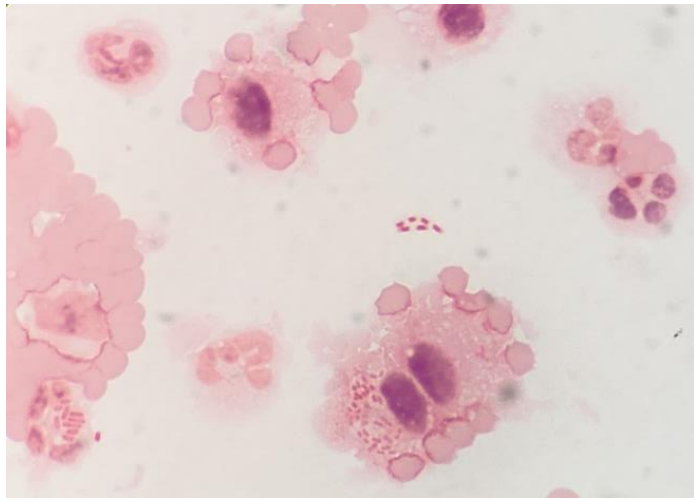
CRISP-R Screen

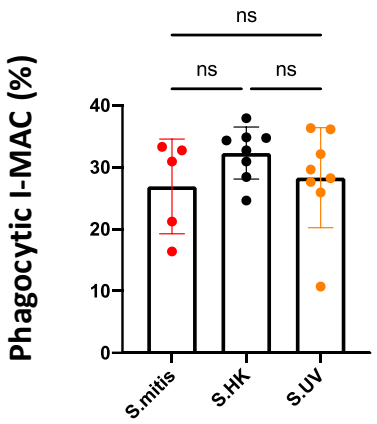
Personal unpublished data

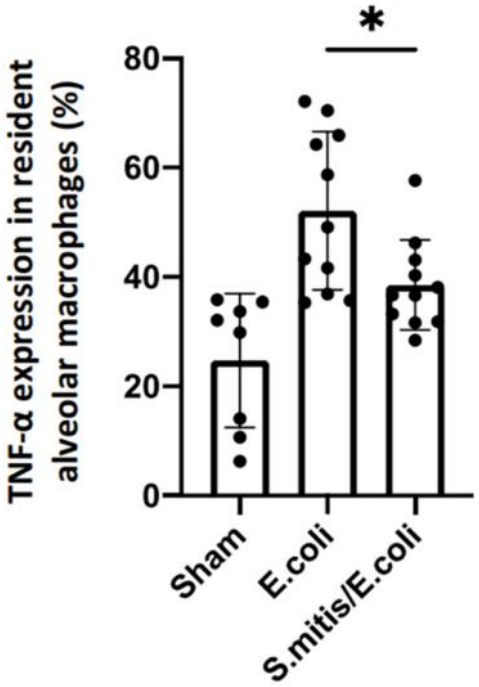
How does it work ?

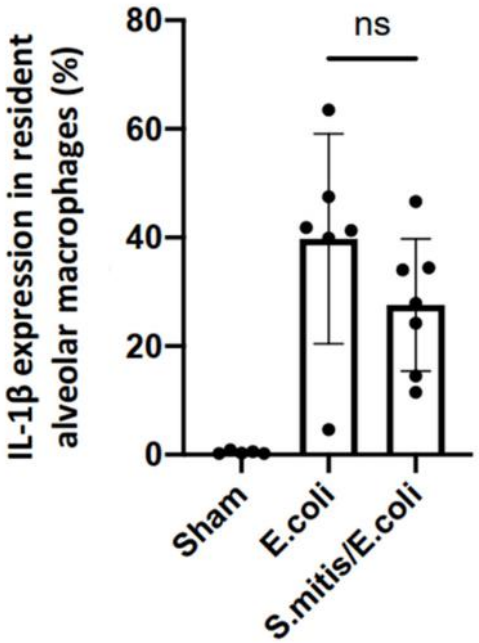
Bacteria-immune cell interactions



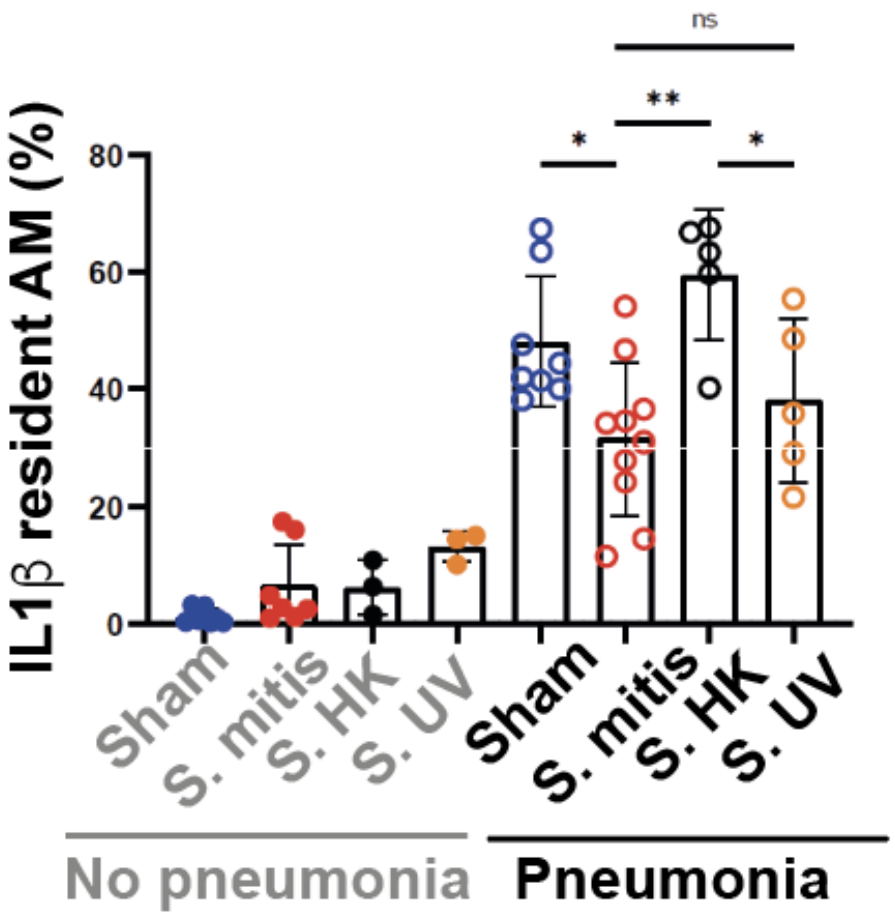


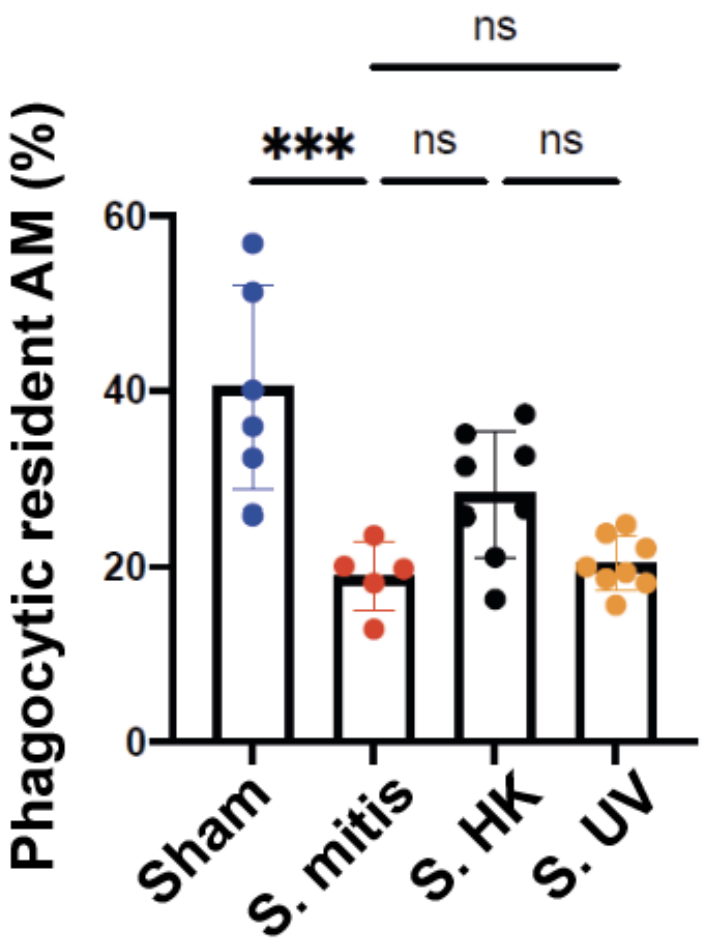






Metabolic activity of S. mitis is key

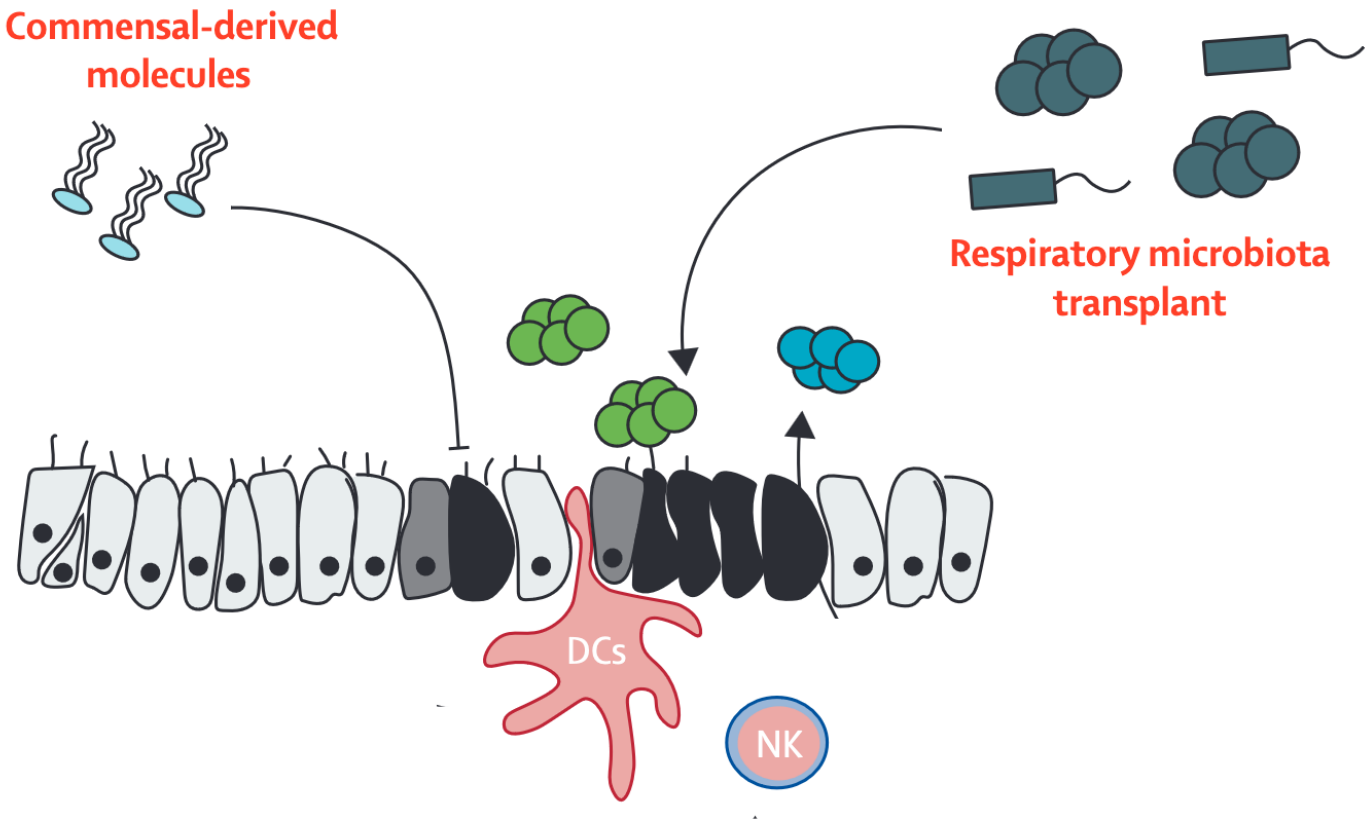




Proposed innovative therapeutical solution

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

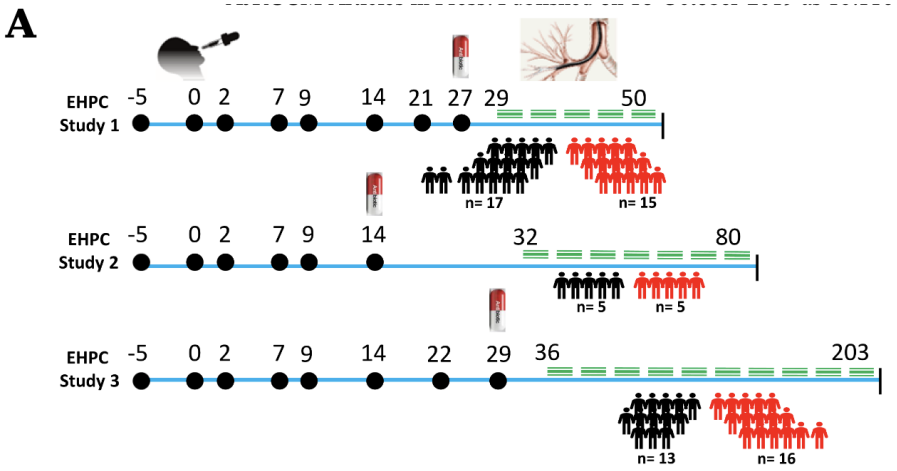
Associated with metabolites
Lactate acid
+ other (??)

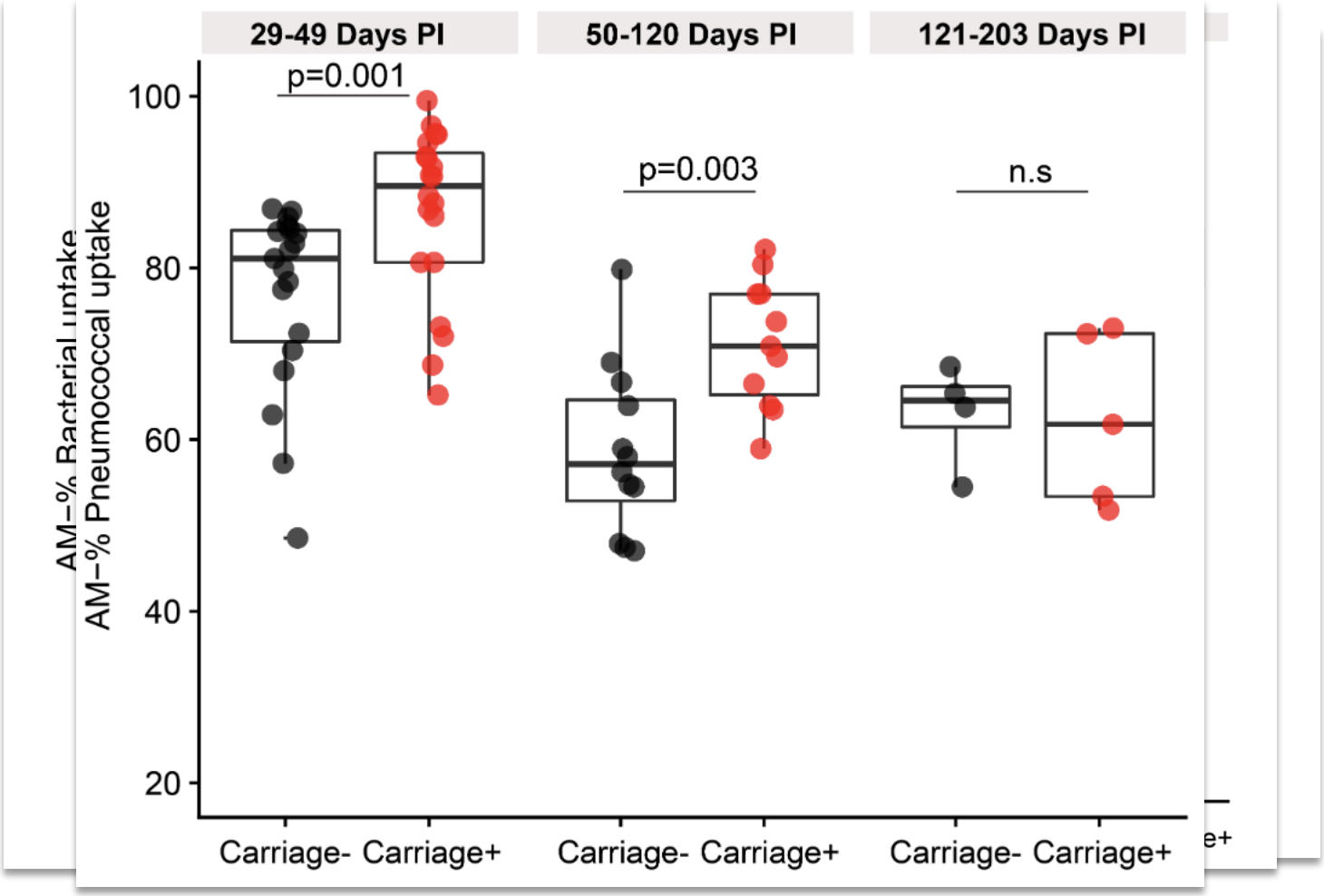


Roquilly et al. Lancet respir Med 2019

Microbiome enrichment to boost immunity

Proof of concept in humans





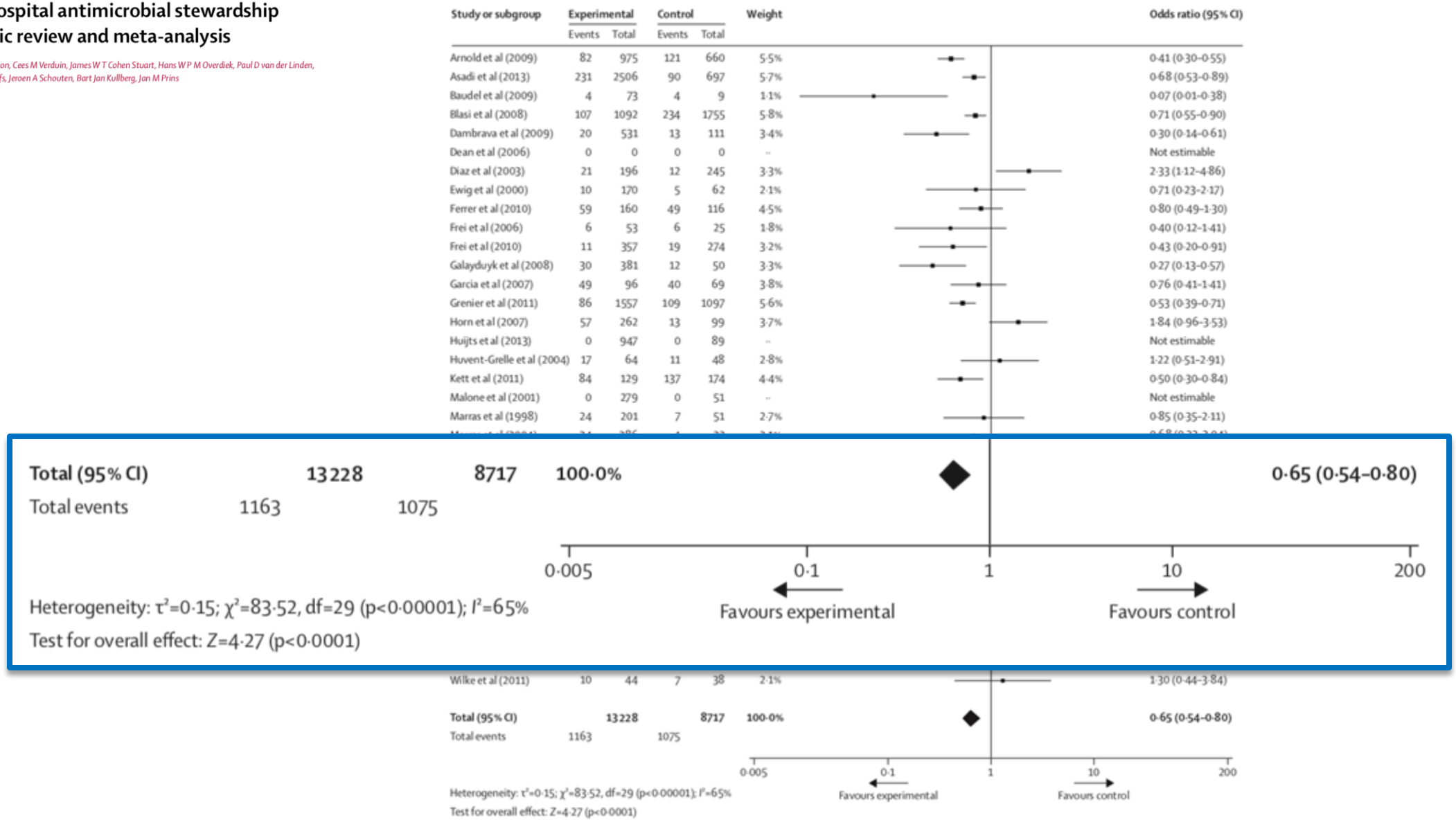
Mitsi *et al. AJRCCM 2019*

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



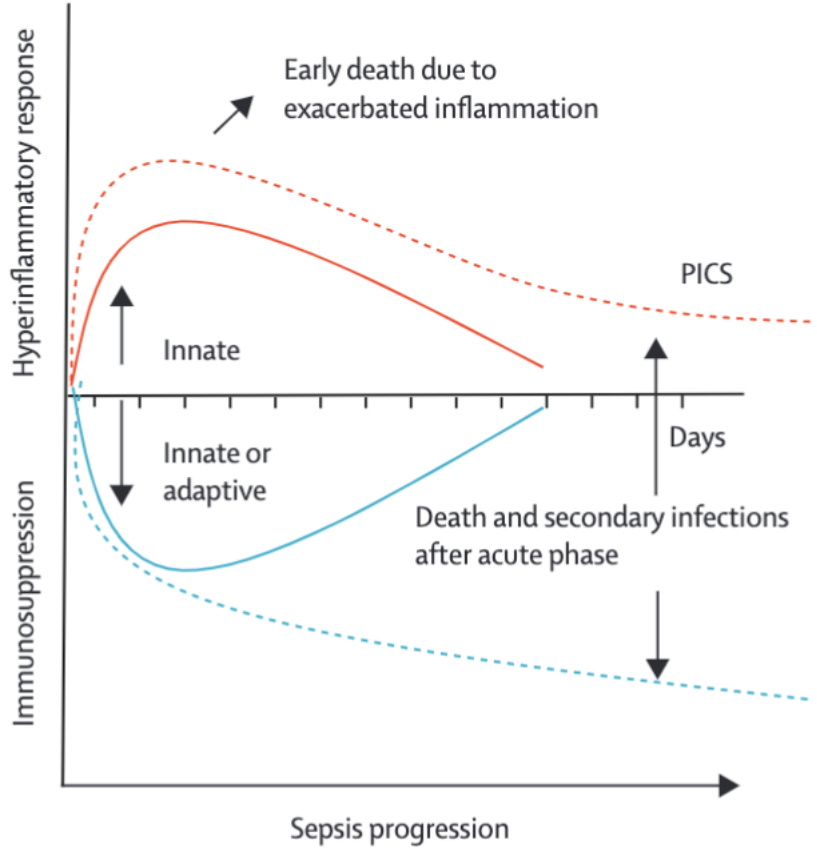
Immune therapy and pneumonia

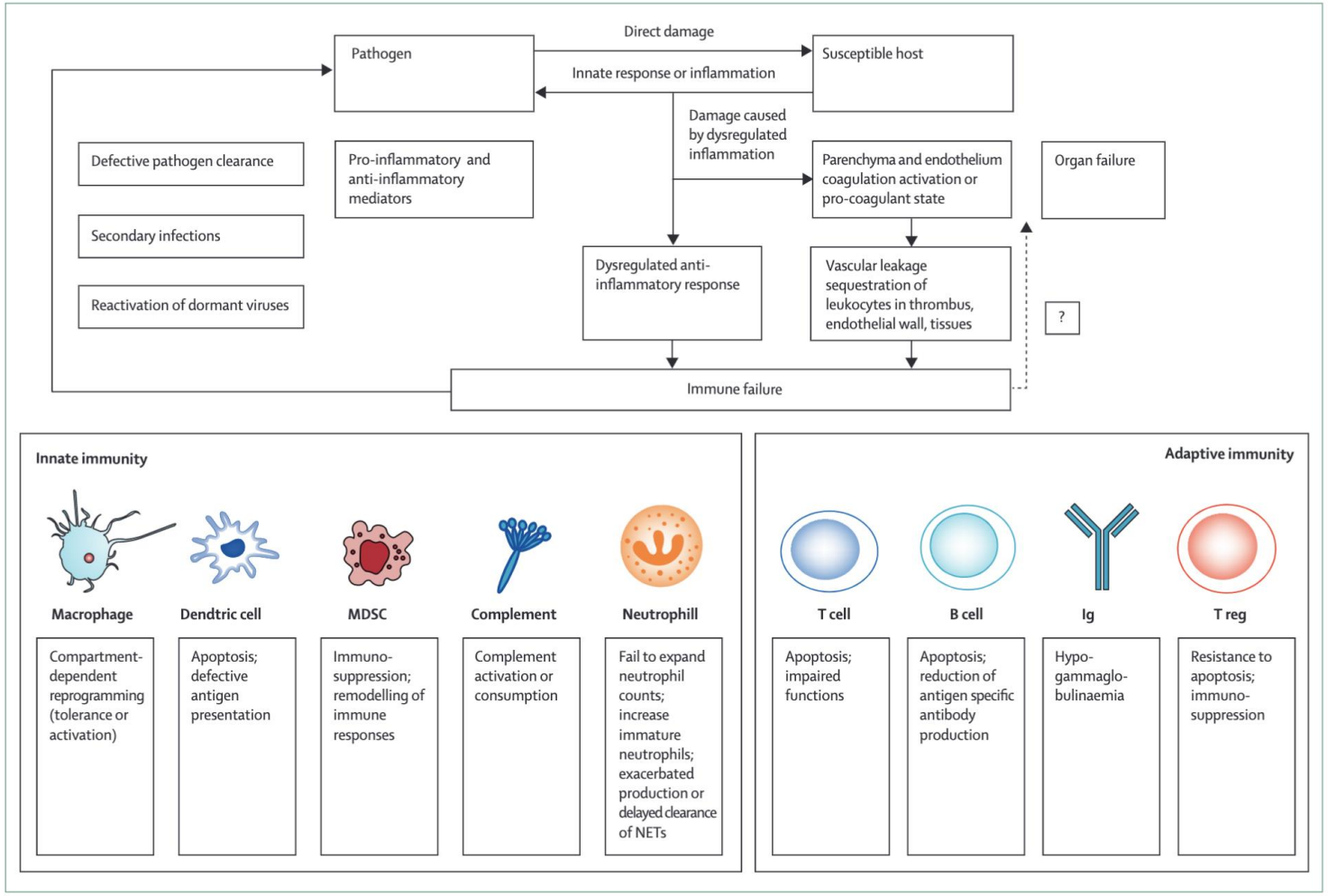
Immune pathophysiology and sepsis

Current gaps in sepsis immunology: new opportunities for translational research

Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki, Martin Sebastian Winkler, Gunnar Lachmann, Paul La Rosée, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Matthijs Kox, Jean-Marc Cavaillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Marta Martin-Fernandez, Raquel Almansa, Ignacio Martin-Loeches, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, André Scherag, Christian Meisel, Joerg C Schefold, Jesús F Bermejo-Martín

Lancet Infect Dis 2020





Interferons – off the shelf drugs for sepsis

Box 3 | **Clinical uses of interferons**

Interferons (IFNs) have been used in various clinical settings[6,136–138]. The diseases or syndromes in which different IFNs have shown clinical activity are summarized here.

IFN-α

Haematological malignancies. Chronic myeloid leukaemia | cutaneous T-cell lymphoma | hairy-cell leukaemia | multiple myeloma

Solid tumours. Malignant melanoma | renal-cell carcinoma | AIDS-related Kaposi's sarcoma

Viral syndromes. Hepatitis C | hepatitis B | severe acute respiratory syndrome

IFN-β

Multiple sclerosis

IFN-γ

Chronic granulomatous disease | severe malignant osteopetrosis

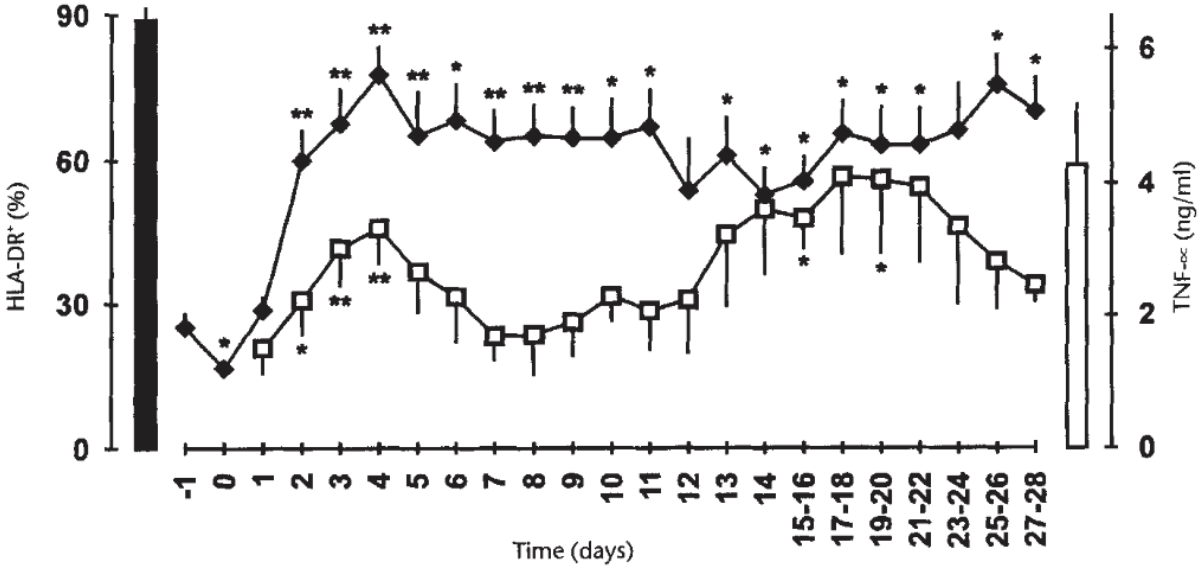
Platanias, Nature Rev Immunol 2005

© 1997 Nature Publishing Group http://www.nature.com/naturemedicine

ARTICLES

Monocyte deactivation in septic patients: Restoration by IFN-γ treatment

Wolf-Dietrich Döcke[1], Felix Randow[1], Uta Syrbe[1], Dietmar Krausch[2], Khusru Asadullah[1], Petra Reinke[3], Hans-Dieter Volk[1], Wolfgang Kox[2]



Nature Med 1997

Anti-interferon signalling drugs – off the shelf drugs for sepsis

Table 1 | **Progress with Janus kinase inhibitors for autoimmine, allergic and inflammatory diseases**

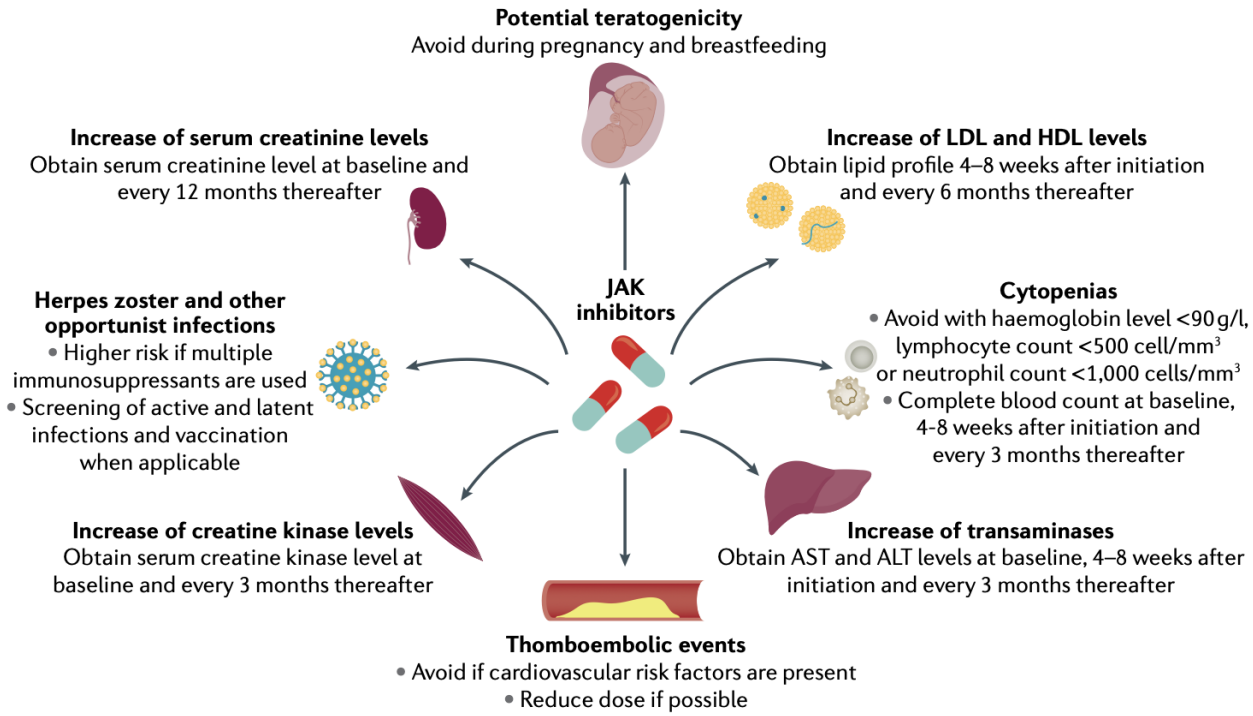
Indication	Approved	In phase III or IV trials[a]	In phase II trials[a]
Rheumatoid arthritis	Tofacitinib; baricitinib; peficitinib; upadacitinib; filgotinib	NA	Ritlecitinib (NCT02969044)
Polyarticular juvenile idiopathic arthritis	Tofacitinib	Baricitinib (NCT03773978)	NA
Systemic juvenile idiopathic arthritis	NA	Tofacitinib (NCT03000439); baricitinib (NCT04088396)	NA
Atopic dermatitis	Baricitinib; abrocitinib; topical delgocitinib	Upadacitinib (NCT03569293); topical ruxolitinib (NCT03745638)	Tofacitinib (NCT02001181); gusacitinib (NCT03531957); brepocitinib (NCT03903822)

Tanaka, Nature Rev Rheumatology 2022

Compound	Selectivity	Status	
		Crohn's disease	Ulcerative colitis
Tofacitinib	JAK1, JAK3	Development halted	Approved
Filgotinib	JAK1	Phase III recruiting	Phase IIb recruiting
Upadacitinib (ABT-494)	JAK1	Phase III recruiting	Phase III recruiting
Peficitinib (JNJ-54781532, ASP015K)	JAK1, JAK2(?), JAK3, TYK2	NA	Phase II completed
TD-1473	JAK1, JAK2, JAK3, intestinally restricted	Phase II recruiting	Phase IIb/III recruiting
PF-06651600	JAK3	Phase IIa recruiting	Phase II recruiting
PF-06700841	JAK1, TYK2	Phase IIa recruiting	Phase II recruiting

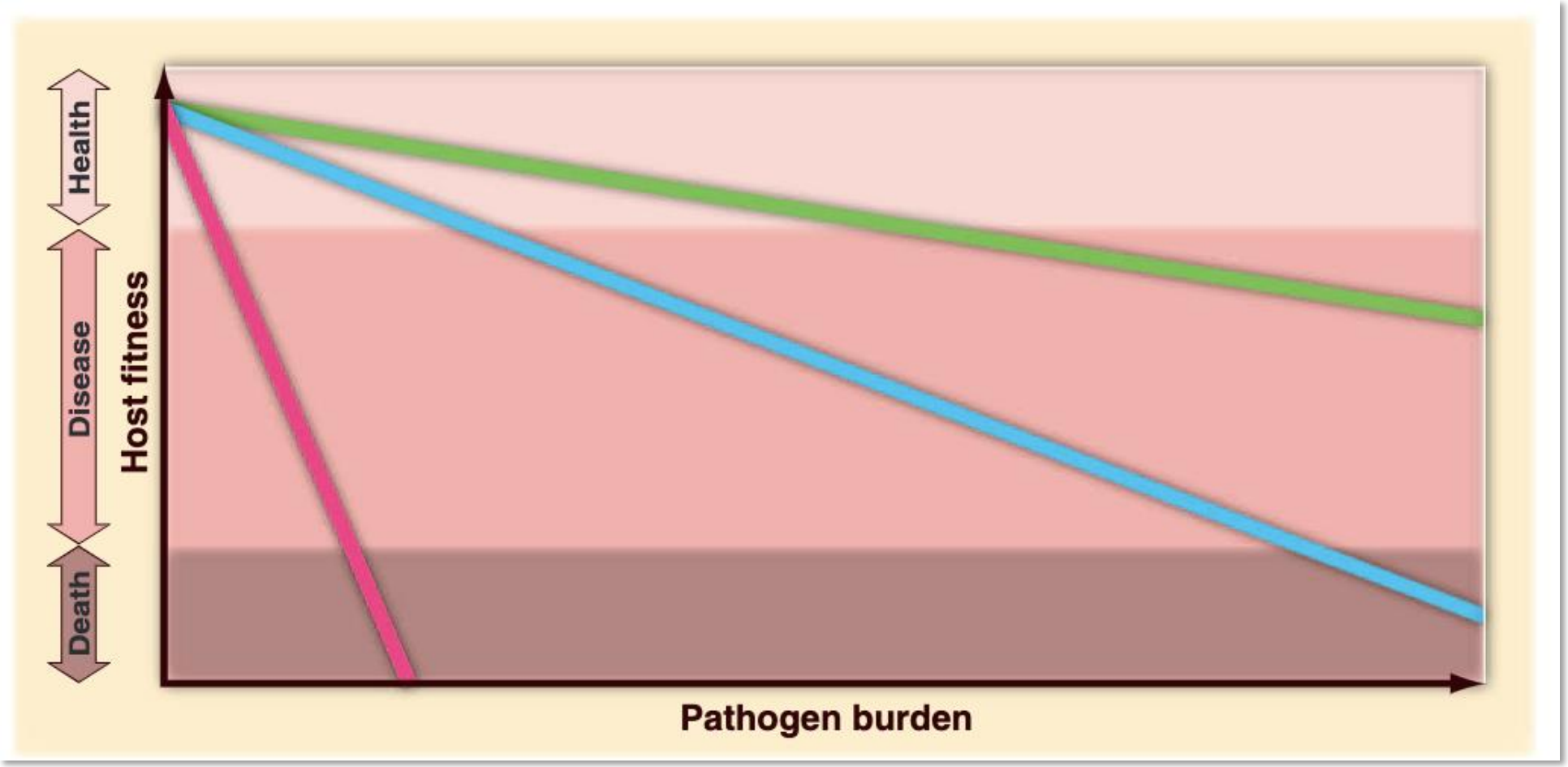
IBD, inflammatory bowel disease; JAK, Janus kinase; NA, not applicable; TYK, tyrosine kinase.

Salas, Nature Rev Gastroenterol 2020

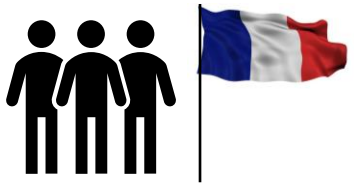


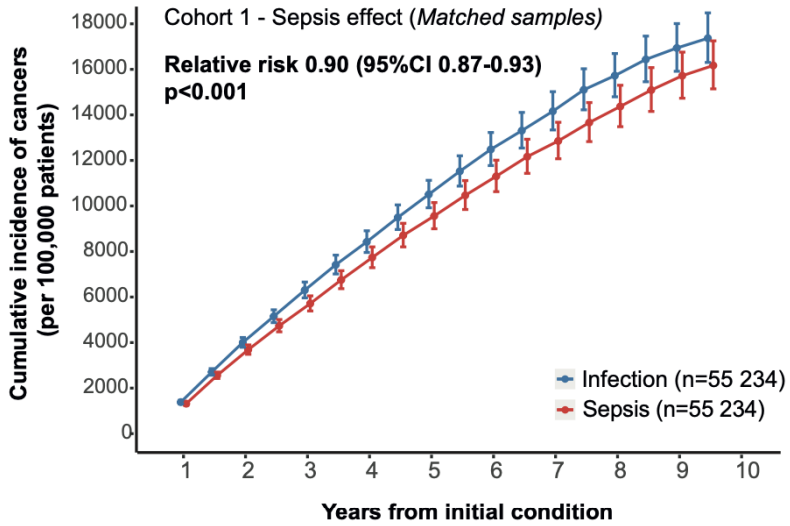
Boosting tolerance or immunity ?

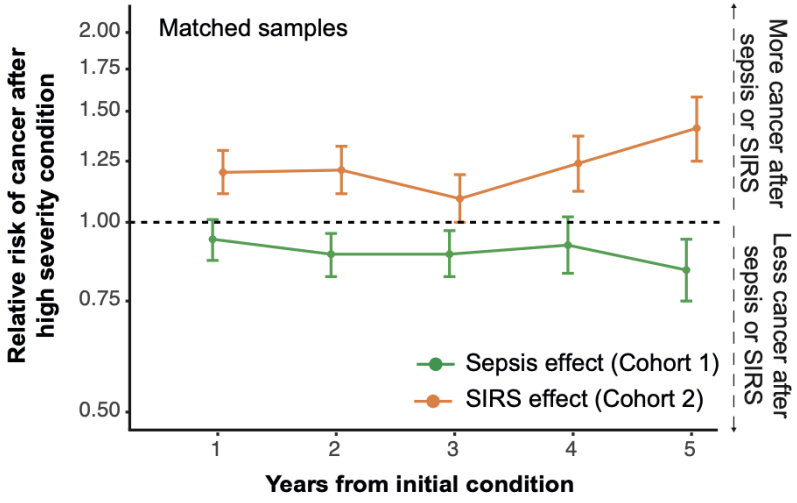
Disease Tolerance as a Defense Strategy
Ruslan Medzhitov, *et al.*
Science **335**, 936 (2012);
DOI: 10.1126/science.1214935

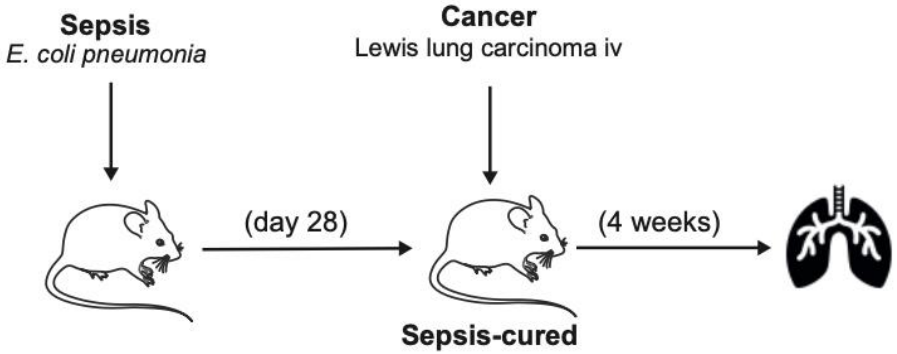


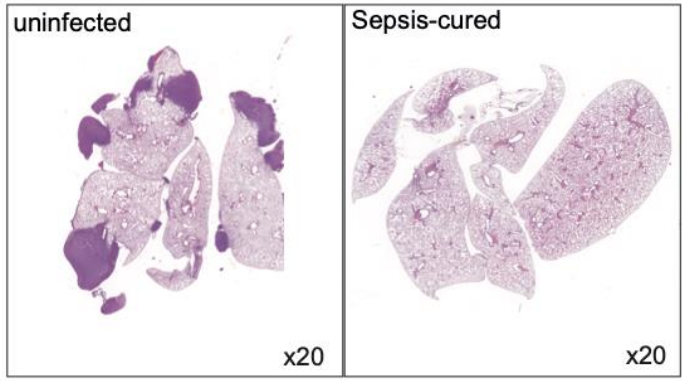
Epigenetic reprogramming of myeloid cells in ICU, immunosuppression or hyper-reactive trained immunity ?

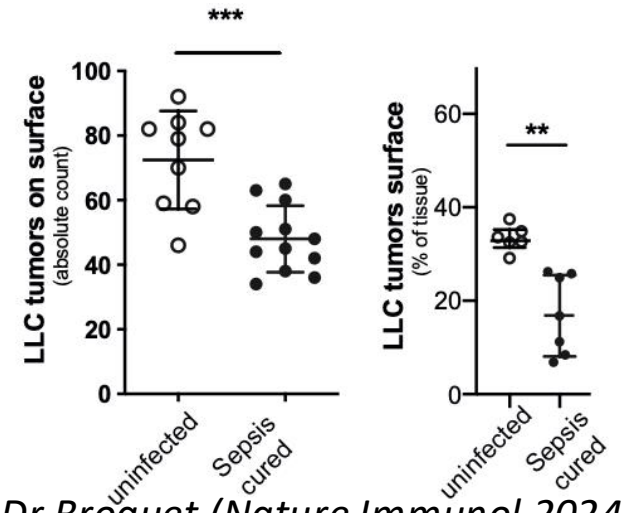










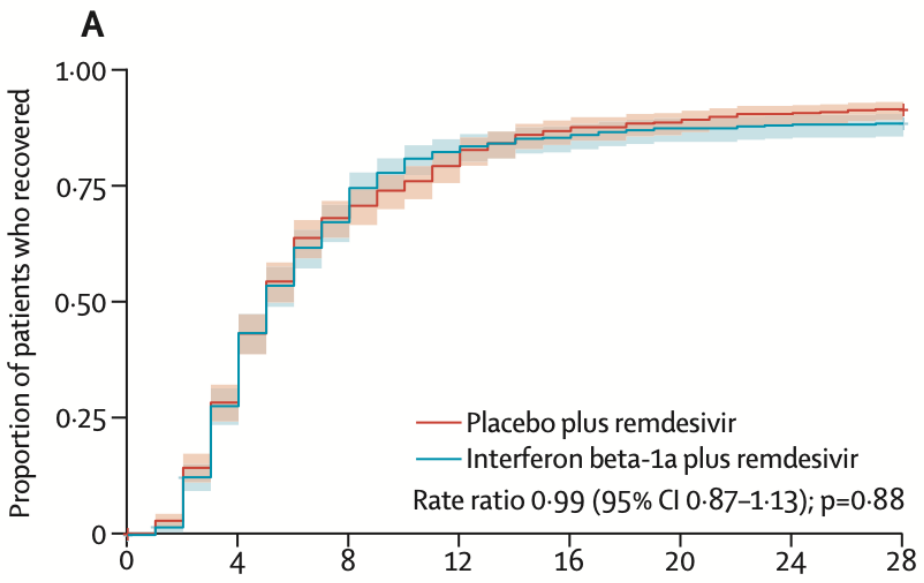


Dr Broquet (Nature Immunol 2024)

Type I Interferon for severe infections

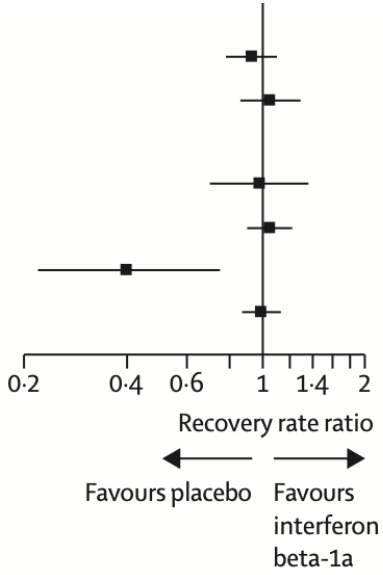
Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial

Andre C Kalil, Aneesh K Mehta, Thomas F Patterson, Nathaniel Erdmann, Carlos A Gomez, Mamta K Jain, Cameron R Wolfe,



Number at risk (number censored)								
Interferon beta-1a plus remdesivir	487 (12)	337 (14)	143 (14)	69 (14)	54 (14)	44 (14)	41 (14)	39 (53)
Placebo plus remdesivir	482 (8)	334 (8)	139 (8)	84 (8)	47 (8)	38 (8)	29 (8)	24 (32)

Sex				
Male	266	297	0·93 (0·78–1·10)	0·71
Female	216	190	1·05 (0·86–1·29)	0·73
Baseline clinical status ordinal score				
4	68	84	0·98 (0·70–1·36)	0·89
5	380	368	1·05 (0·90–1·22)	0·54
6	34	35	0·40 (0·22–0·75)	0·0031
Overall	**482**	**487**	**0·99 (0·87–1·13)**	**0·88**

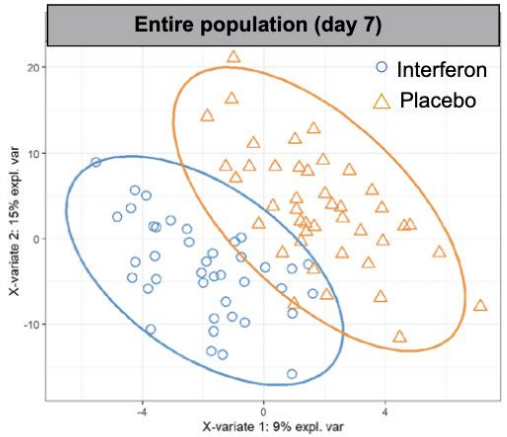


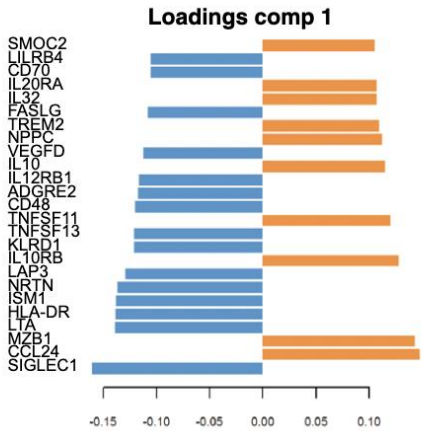
Type II Interferon for the prevention of hospital-acquired infections

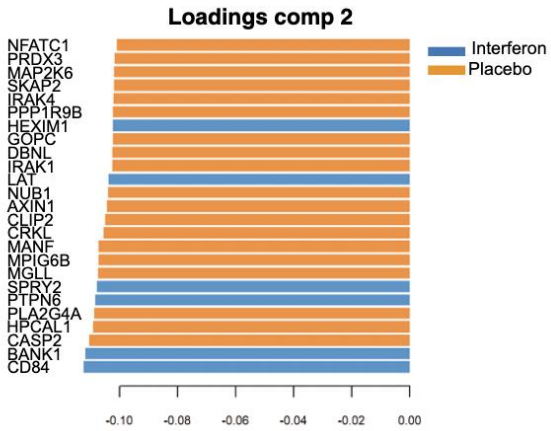
ORIGINAL

Interferon gamma-1b for the prevention of hospital-acquired pneumonia in critically ill patients: a phase 2, placebo-controlled randomized clinical trial

Roquilly, et al Intensive Care Med 2023







	Interferon-gamma group	Placebo group	Adj. OR (95% CI)[a] Adj. HR (95% CI)[a] or Adj. Difference (95% CI)
Primary outcome: HAP or all-cause mortality on day 28, *n/N* (%)	26/55 (47.3)	16/53 (30.2)	1.76 (0.94–3.29)
Components of the primary outcome, *n/N* (%)			
All-cause mortality at day 28, yes	7/55 (12.7)	9/53 (17)	0.68 (0.25–1.85)
HAP, yes	19/55 (34.5)	8/53 (15.1)	2.06 (0.92–4.57)

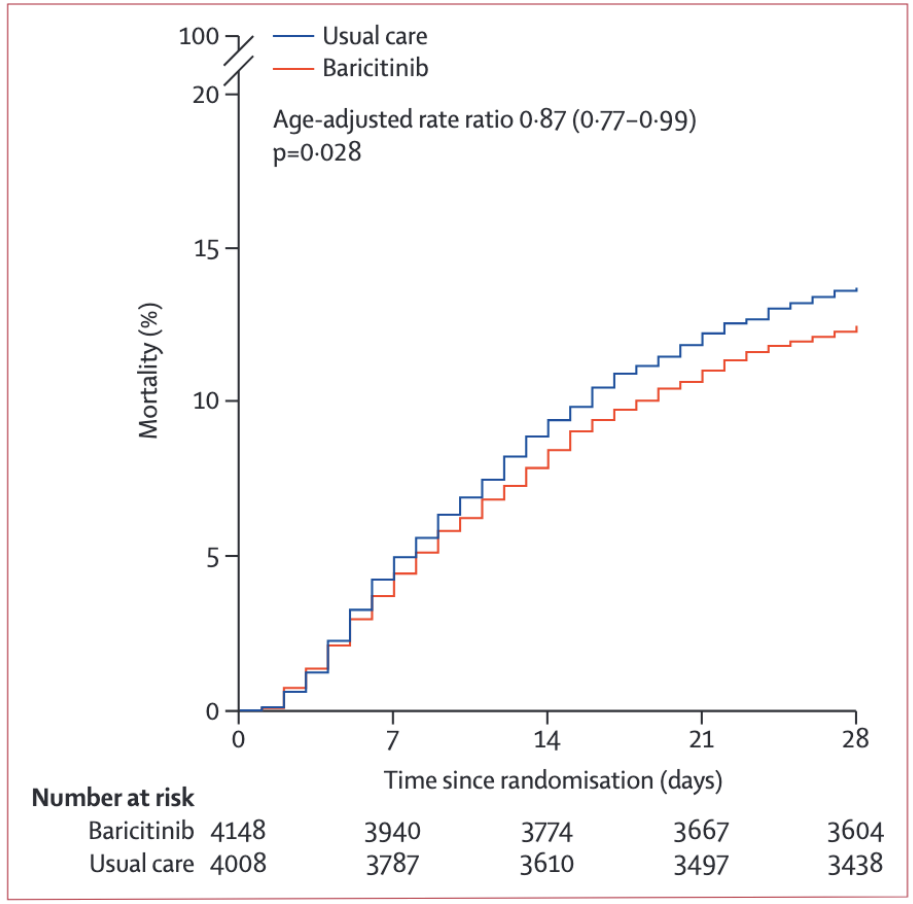
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847782.

HAP²

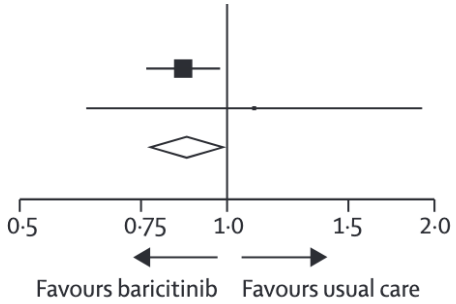
Anti JAK kinase inhibitor and COVID-19 pneumonia

Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

*RECOVERY Collaborative Group**



Use of corticosteroids (χ^2_1=0·7; p=0·42)			
Yes	488/3962 (12%)	523/3809 (14%)	0·86 (0·76–0·98)
No	25/183 (14%)	22/197 (11%)	1·09 (0·62–1·92)
All participants	**514/4148 (12%)**	**546/4008 (14%)**	**0·87 (0·77–0·99)**
			p=0·028

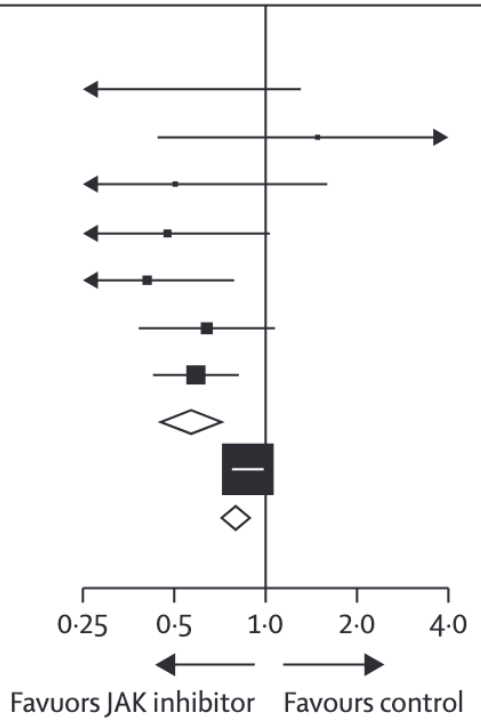


Anti JAK kinase inhibitor and COVID-19 pneumonia

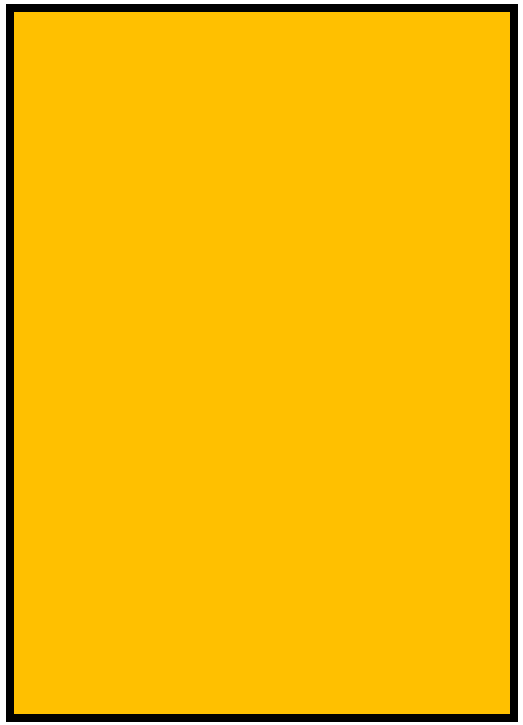
Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

*RECOVERY Collaborative Group**

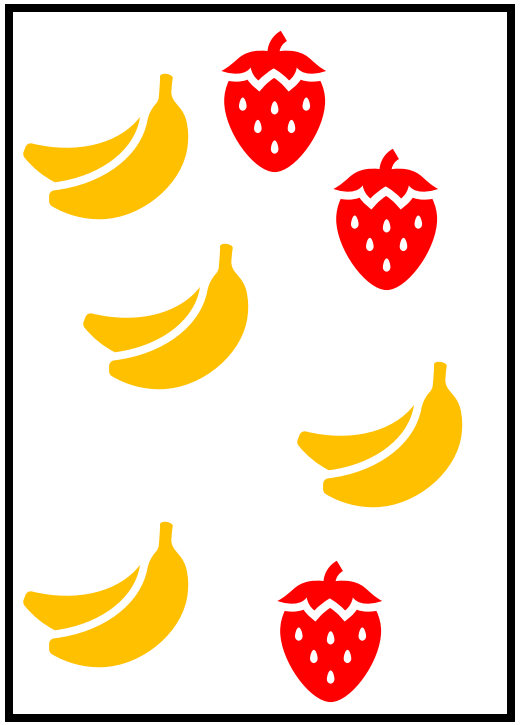
	Deaths/patients randomly assigned (%)		Observed minus expected deaths		Rate ratio of death rates (95% CI)
	JAK inhibitor group	Control group	(O–E)*	Var (O–E)	
Murugesan†	0/50 (0%)	0/50 (0%)	0·0	0·0	
Cao and colleagues†	0/20 (0%)	3/21 (14%)	–1·5	0·7	0·13 (0·01–1·31)
RUXCOVID†	9/287 (3%)	(3/145) ×2‡ (2%)	1·0	2·6	1·48 (0·44–4·99)
Guimarães and colleagues†	4/144 (3%)	8/145 (6%)	–2·0	2·9	0·50 (0·16–1·60)
COV–BARRIER (critically ill)	20/51 (39%)	29/50 (58%)	–4·7	6·4	0·47 (0·22–1·03)
RUXCOVID–DEVENT†	90/164 (55%)	(36/47) ×4‡ (77%)	–7·9	8·8	0·41 (0·21–0·79)
ACTT2	24/515 (5%)	37/518 (7%)	–6·4	14·4	0·64 (0·38–1·07)
COV–BARRIER	62/764 (8%)	100/761 (13%)	–19·2	36·2	0·59 (0·43–0·82)
Subtotal: 8 trials	**209/1995 (10%)**	**327/2023 (16%)**	**–40·7**	**72·0**	**0·57 (0·45–0·72)**
RECOVERY	514/4148 (12%)	546/4008 (14%)	–35·7	264·3	0·87 (0·77–0·99)
All trials	**723/6143 (12%)**	**873/6031 (14%)**	**–76·3**	**336·3**	**0·80 (0·72–0·89)**
Heterogeneity between RECOVERY and previous trials: χ^2_1=10·5 (p=0·0012)					p<0·0001



One fits all ?



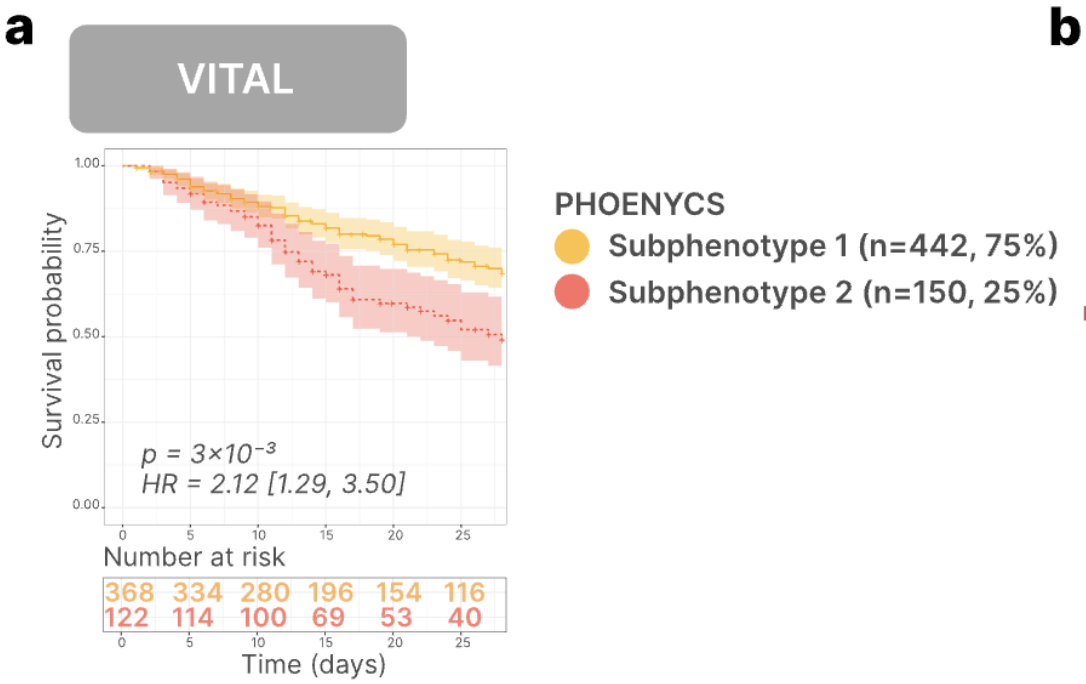
In vivo investigation of host-microbiome interactions

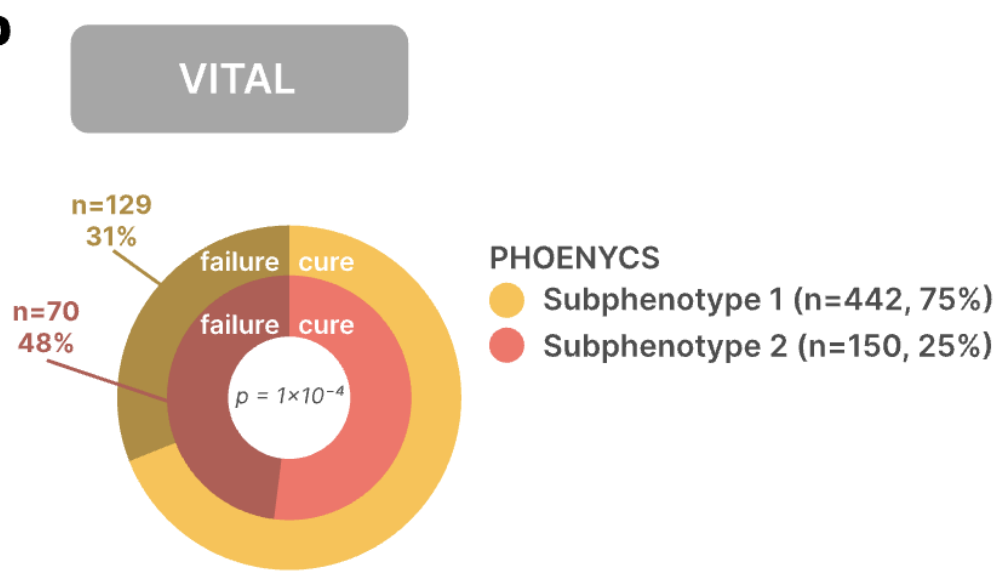


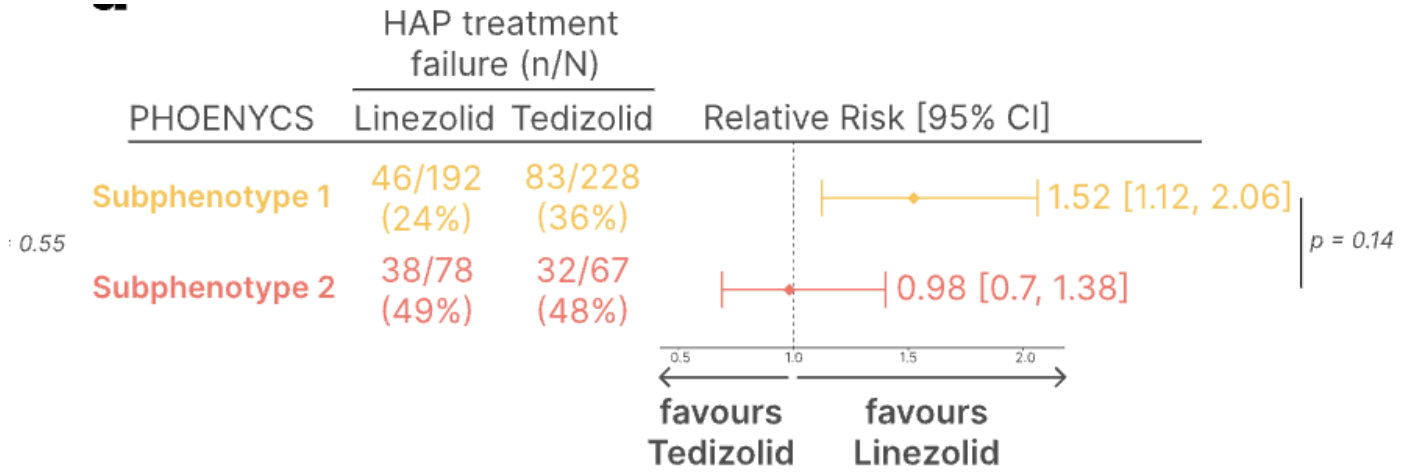
Pneumonia ----------▸ **Phenotypes**
Endotypes

Hospital-acquired pneumonia heterogeneity

And response to antimicrobial therapy

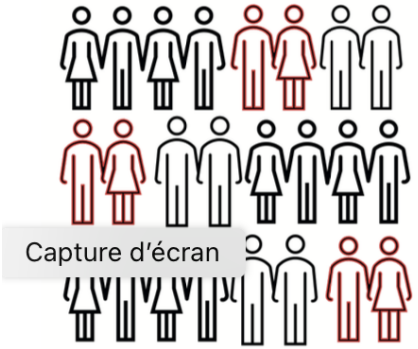




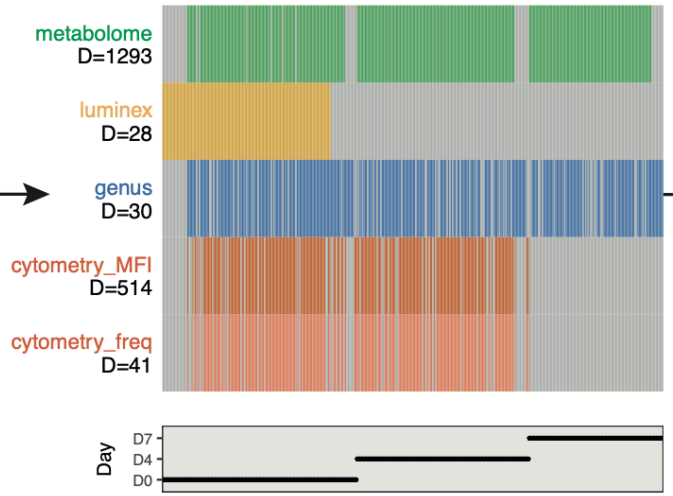


Hospital-acquired pneumonia heterogeneity

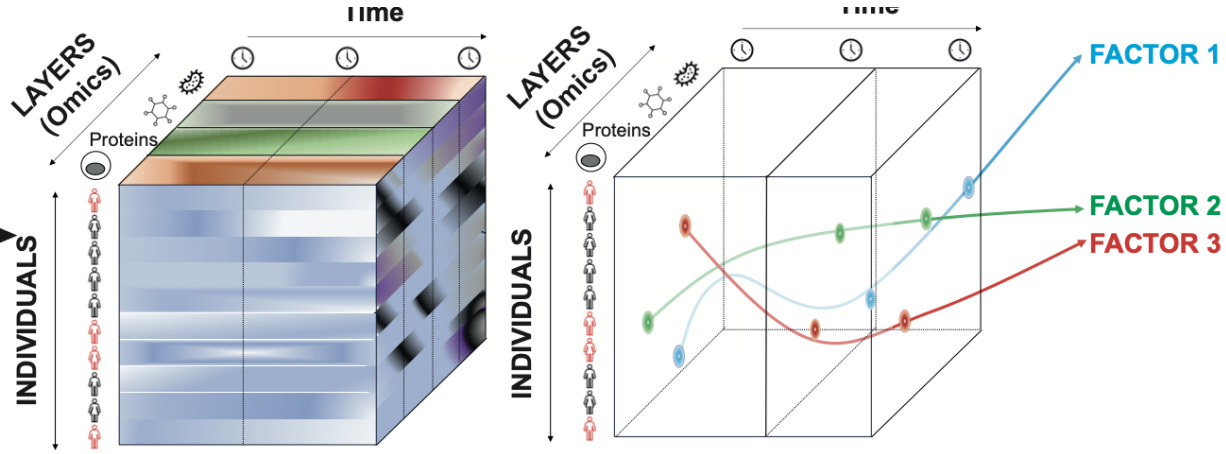
Temporo-spatial modelisation of host-microbiome interactions



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



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

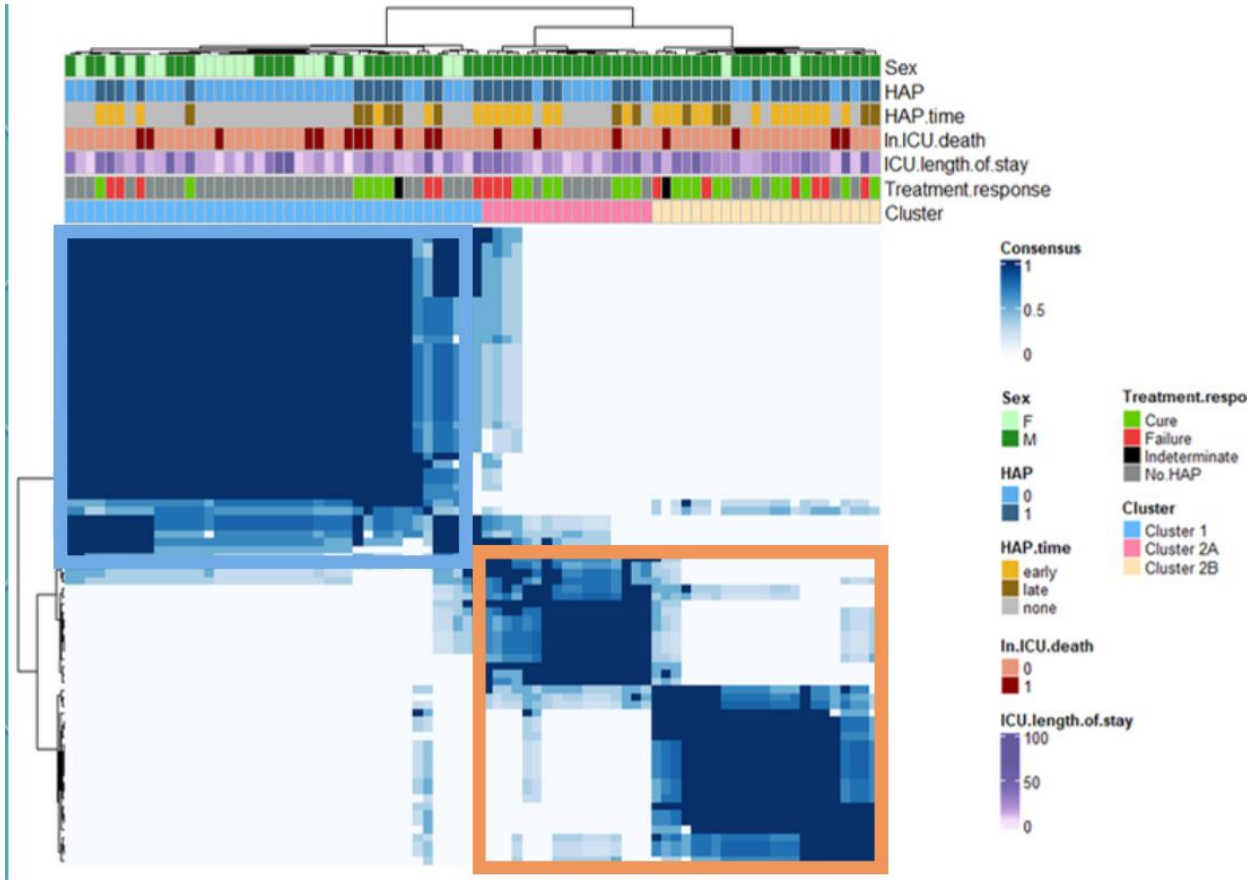


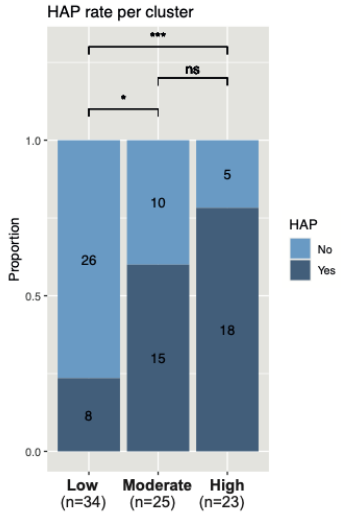
Identification of temporal and spatial patterns
of variation (MEFISTO)

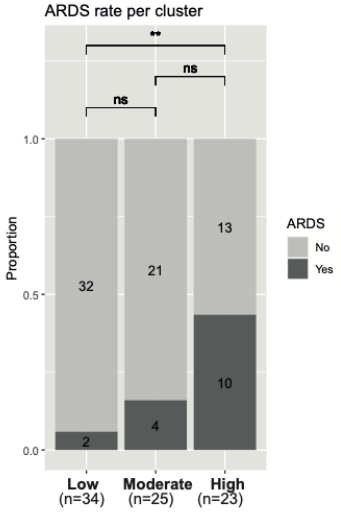
Personal unpublished data

Hospital-acquired pneumonia heterogeneity

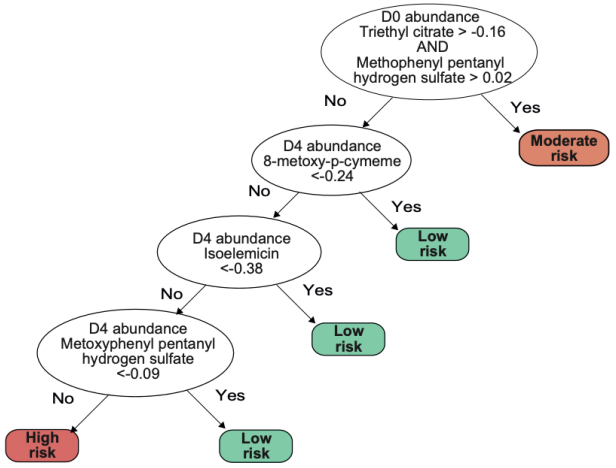
Metabolomic for HAP prediction

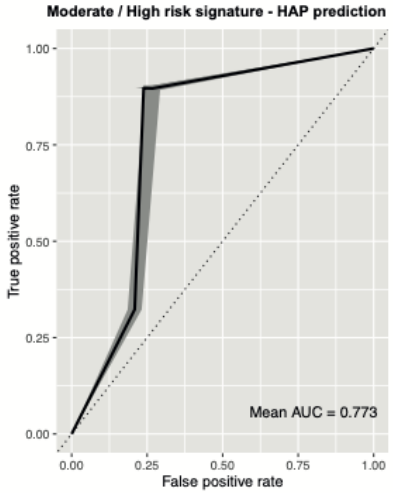






Strata — Low risk (n=34) — Moderate (n=25) — High risk (n=23)



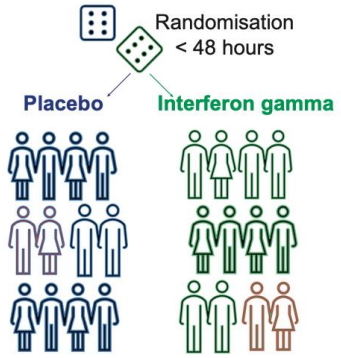


Personal unpublished data

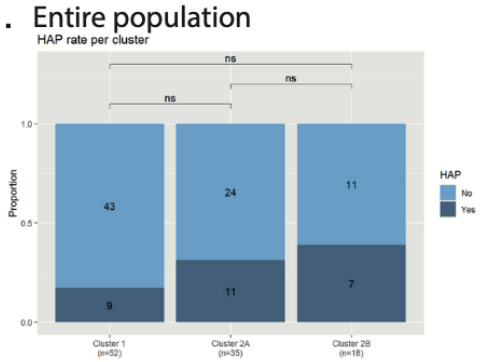
Hospital-acquired pneumonia heterogeneity

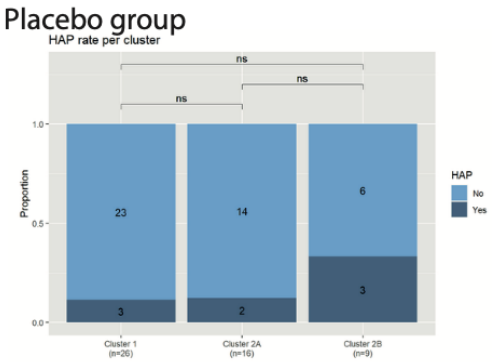
External validation

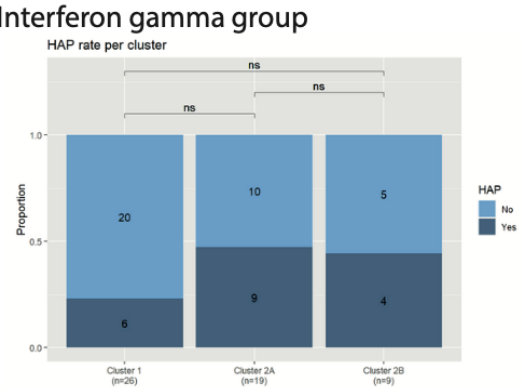
Randomized clinical trial (validation)

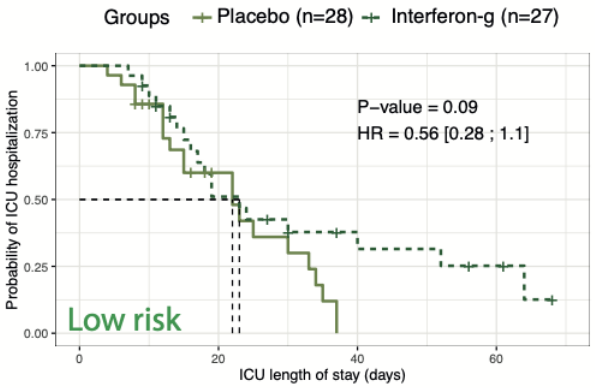


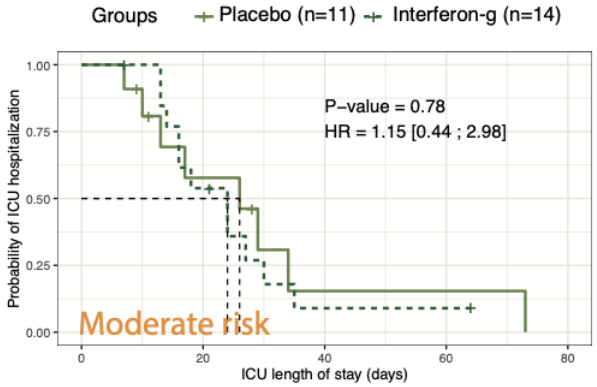
108 critically ill patients patients
(80% BI, 27 with HAP, 81 without HAP)

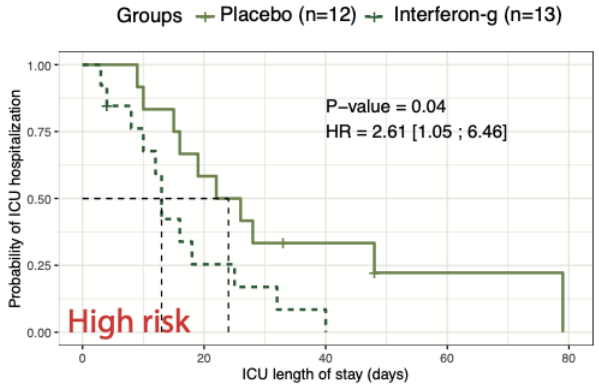


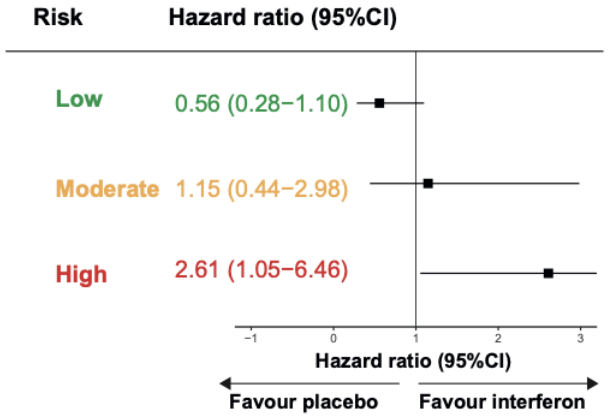












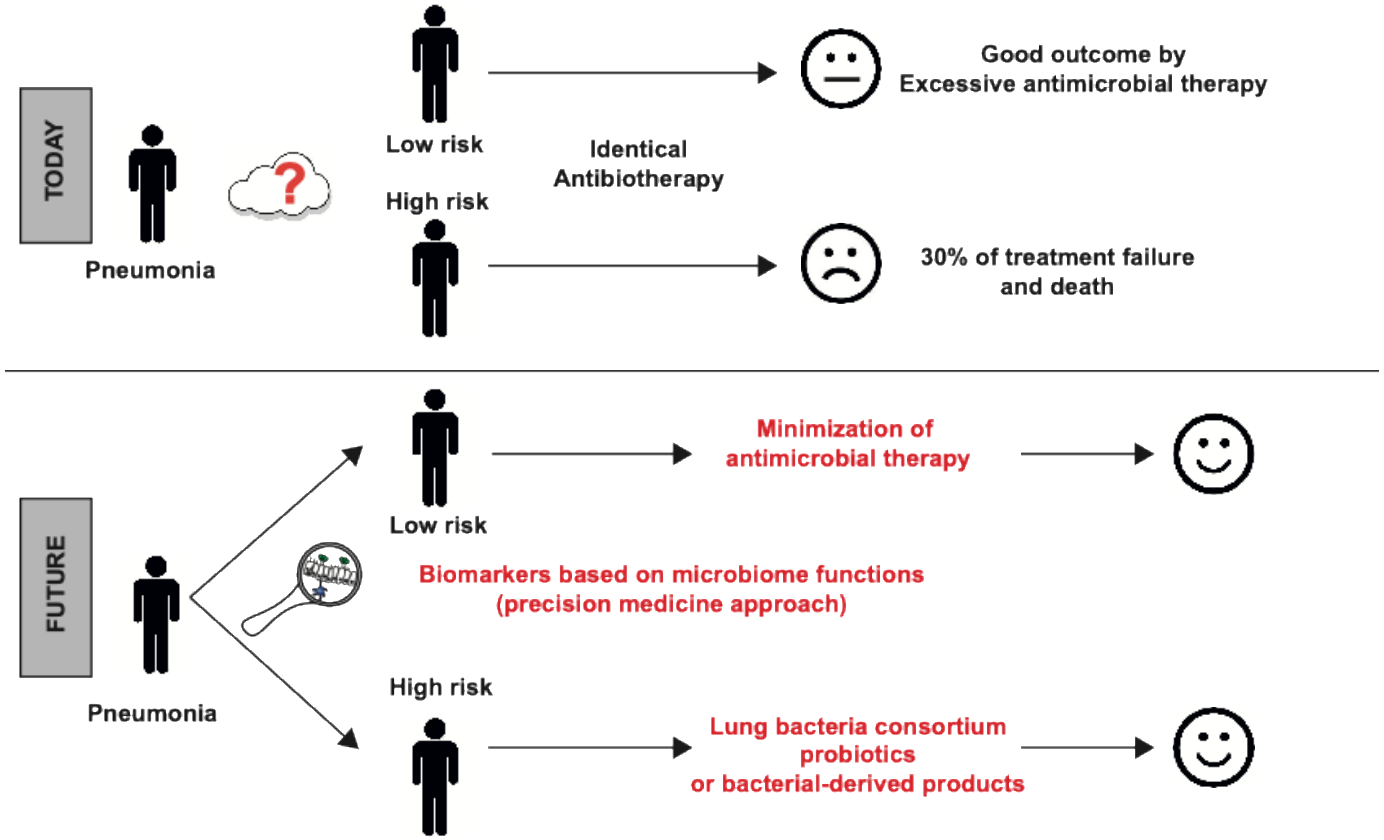
Personal unpublished data

Conclusion

- **Hospital-acquired pneumonia : dysbiosis (microbiome failure + hyperinflammatory)**
- **Antibimicrobial therapy failure ➔ is not an indication to pursue/broaden antimicrobial therapy**

Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia

Roquilly et al. Lancet Respir Med 2019



A collaborative vision

Team 6 - Pr Roquilly
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Benjamin Gaborit (MD,PhD)
Alexis Broquet (PhD)
Cédric Jacqueline (PhD)
Victor Gourain (PhD)
Debajyoti Sinha (PhD)
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