Optimisation de la prise en charge des infections dues à *Mycobacterium abscessus* basée sur les associations de bêta-lactamines et d'inhibiteurs de bêta-lactamases de seconde génération

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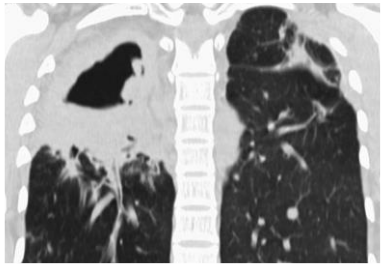
Conflits d’intérêts

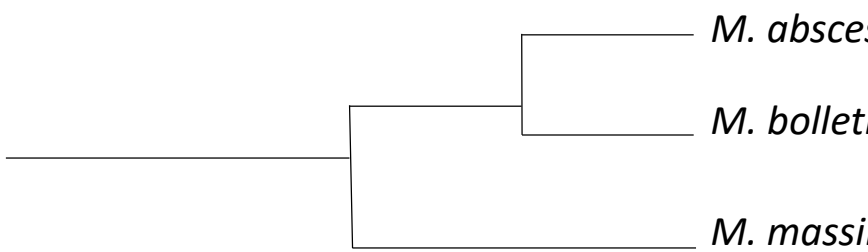
- Member of the scientific committee of the BioAster company (2018-2024)
- Member of the advisory boards of MSD Merck Sharp & Dohme (2021)
- Member of ECFS Conference Scientific Committee (2023-2025)

Mycobacterium abscessus

- Non-tuberculous mycobacteria
- Most frequent rapidly growing mycobacteria isolated in lung infections

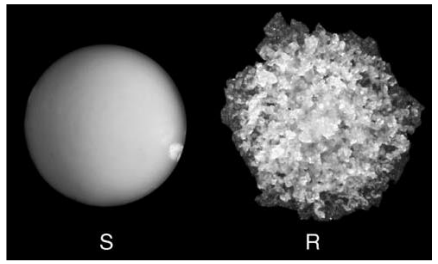


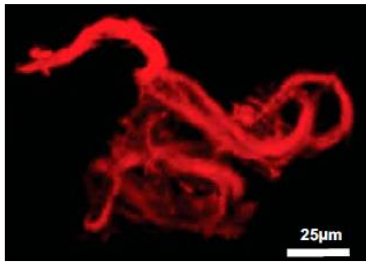
- 3 sub-species:



Adekambi *et al.*, 2017

- Two morphotypes : « S » and « R »





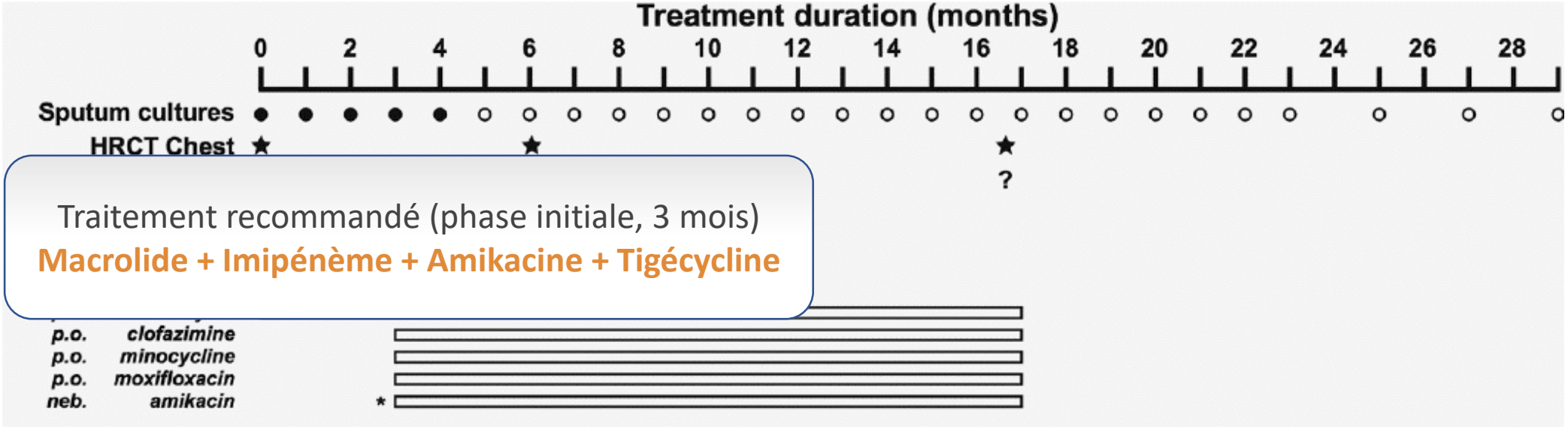
Bernut *et al.*, PNAS, 2014

Medjahed *et al.*, 2010

- Prevalence of pulmonary infections due to *M. abscessus* in CF patients:
  - 1% in France (Registre français de la mucoviscidose, 2023)
  - Up to 11% in European adults (ECFS Patient Registry Annual Report, 2021)
  - 4.2 % in the US (CFF Patient Registry Annual Data Report 2021)

Treatment of *M. abscessus* infections in CF patients

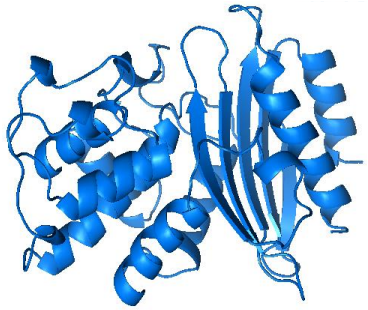
- Intrinsically resistant to a large array of antibiotics including anti-TB drugs
- Optimal drugs, regimen and duration of therapy are not known
- Typical treatment schedule:



Adapted from Floto *et al.*, Thorax, 2016

- The cure rate is 50% (culture conversion > 12 months) (Kwak *et al*, Eur Respir J 2019)
- But only 34% in case of macrolide resistance (50%)
- **Need for new therapeutic options**

β-lactam resistance: class A β-lactamase Bla_{Mab}



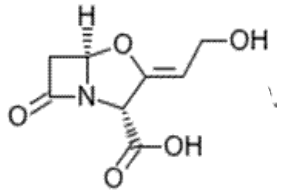
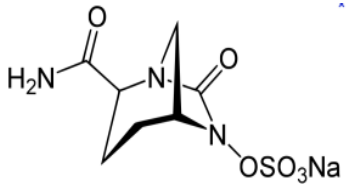
Hydrolysis efficacy of *M. abscessus* Bla_{Mab}

	Bla_{Mab}		
β-Lactam	K_m (μM)	k_{cat} (s^{-1})	k_{cat}/K_m ($M^{-1}\ s^{-1}$)
Penam			
ampicillin	1200±600	580±180	4.7×10^{5}
amoxicillin	890±200	780±50	8.8×10^{5}
benzylpenicillin	450±130	1700±170	3.8×10^{6}
piperacillin	190±30	16000±170	8.5×10^{6}
ticarcillin	580±150	62±8.0	1.1×10^{5}
temocillin	ND	$<1.7\times10^{-6}$	ND
Cephem			
nitrocefin	24±7.0	1000±70	4.3×10^{7}
cefalotin	17±1.0	6.7±0.1	4.1×10^{5}
cefamandole	800±180	220±30	2.7×10^{5}
cefuroxime	>350	>7.0	5.2×10^{3}
cefoxitin	500±270	0.003±0.001	6.7×10^{0}
ceftriaxone	>350	>0.30	5.0×10^{2}
cefotaxime	240±100	0.62±0.12	2.6×10^{3}
ceftazidime	>200	>0.03	8.3×10^{1}
Carbapenem			
meropenem	120±20	1.8±0.2	1.5×10^{4}
imipenem	90±40	2.7±0.3	3.0×10^{4}
doripenem	200±20	1.3±0.1	6.5×10^{4}
ertapenem	150±50	2.3±0.3	1.5×10^{4}
Monobactam			
aztreonam	2900±300	1.8±0.2	6.2×10^{2}

Soroka *et al.*, 2013

- Amoxicillin is a great substrate for Bla_{Mab}
- In contrast to cefoxitin, imipenem is hydrolysed by Bla_{Mab}
- Combining imipenem with a β-lactamase inhibitor could improve its efficacy on *M. abscessus*
- No current recommendation for the use of a β-lactamase inhibitor in combination with imipenem

Activity of β-lactamase inhibitors on *M. abscessus* Bla_{Mab}

Inhibitor		Inhibition of Bla_{Mab}
Clavulanate (first-generation inhibitor)		**No** ! Hydrolysis
Avibactam Diazobicyclooctane (DBO) (second-generation inhibitor)		**Yes**! Rapid inhibition

Soroka *et al*. JAC 2014

Reaction scheme

$$E + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EI \underset{k_2}{\overset{k_2}{\rightleftharpoons}} EI^*$$

$$K_i = \frac{k_{-1}}{k_1}$$

Inhibition parameters of Bla_{Mab} by avibactam

Parameter	Avibactam
$K_2/K_i(M^{-1}S^{-1})$	(1.1 ± 0.1) X 10^5
K_{-2} (S^{-1})	(2.1 ± 0.7) X 10^{-5}

In vitro activity of β-lactam / Avibactam combinations

	MIC (µg/ml) in 7H9sB		
	CIP104536		Δbla_{Mab}
	Alone	+ Avibactam*	Alone
Amoxicillin	> 256	8	4
Cephalothin	> 256	8	4
Cefuroxime	32	8	4
Cefamandole	128	8	4
Ceftriaxone	64	8	8
Ceftazidime	> 256	> 256	> 256
Cefoxitin	16	8	8
Imipenem	4	2	2
Meropenem	4	4	4
Aztreonam	> 256	> 256	> 256

*Avibactam : 4 µg/ml

Dubée *et al*. JAC 2014

CLSI Clinical breakpoints (in mg/L)

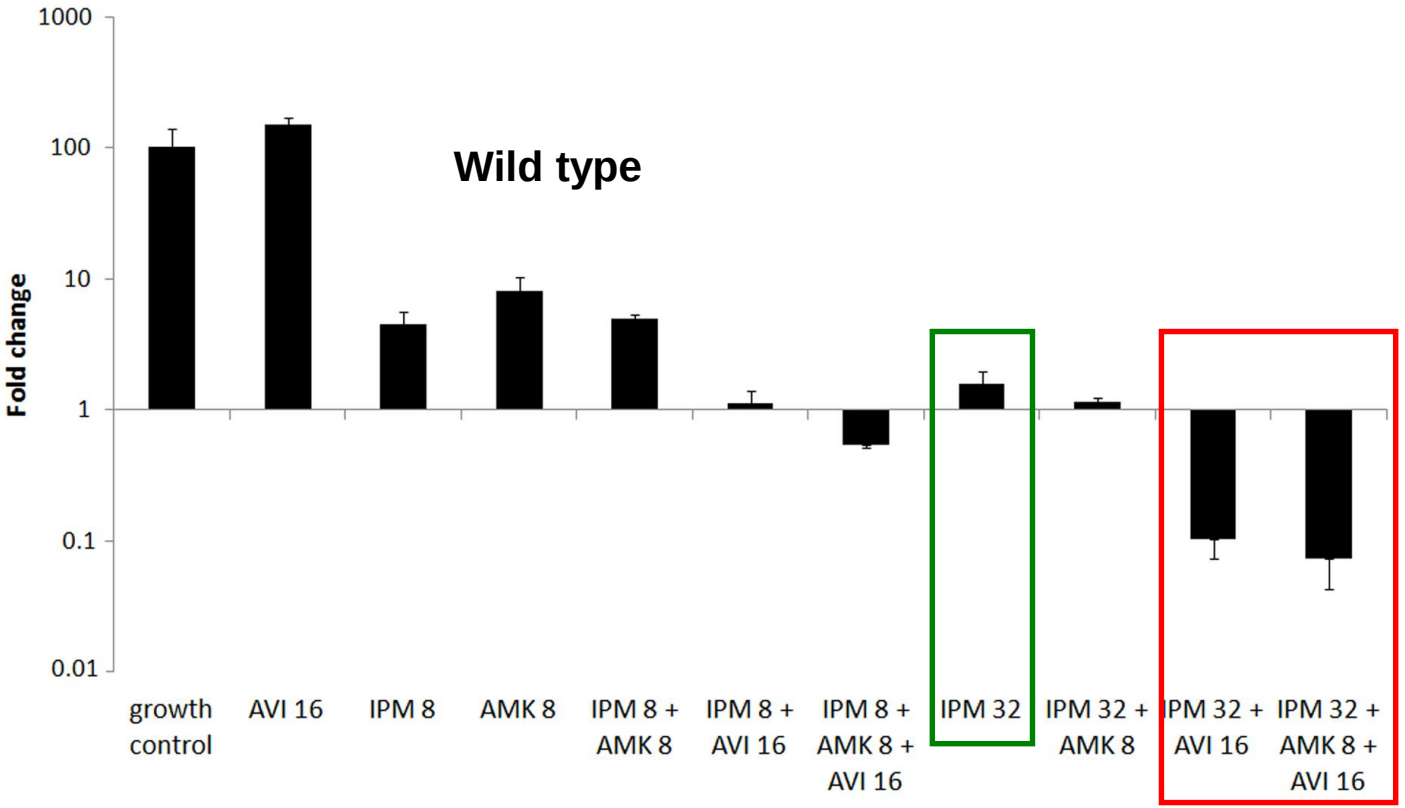
β-lactams	Breakpoints		
	Susceptible	Intermediate	Resistant
Cefoxitin	≤16	32 - 64	≥128
Imipenem	≤ 4	8-16	≥32

Avibactam:

- Is not available alone
- developed in combination with ceftazidime, which is not active against *M. abscessus*

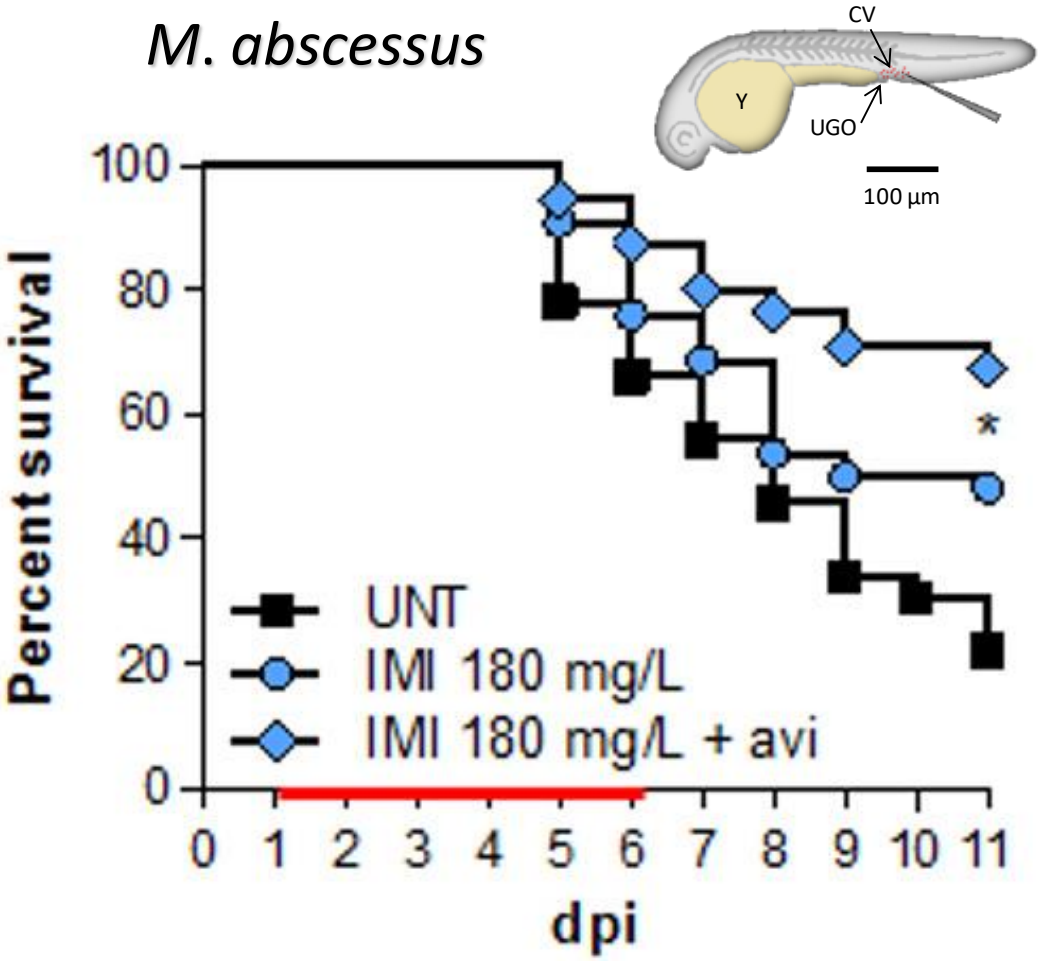
Activity of Imipenem-Avibactam

infected human macrophages



Killing: 90-93%

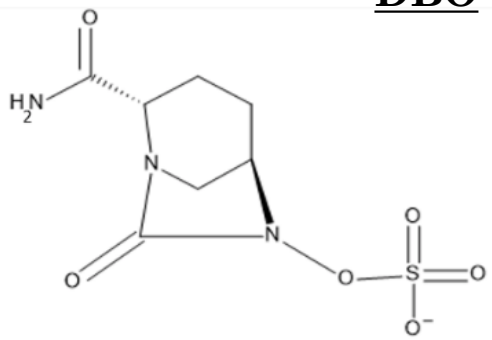
zebrafish infected with *M. abscessus*



Lefebvre *et al*; AAC 2017

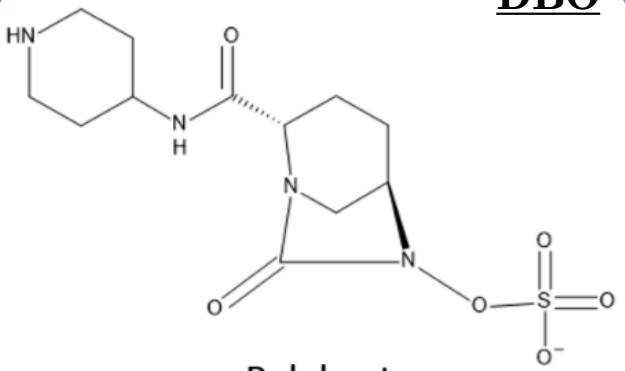
Other second-generation β-lactamase inhibitors

DBO



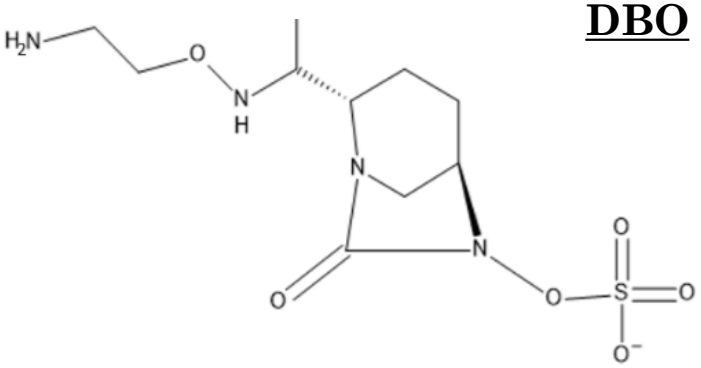
Avibactam

DBO



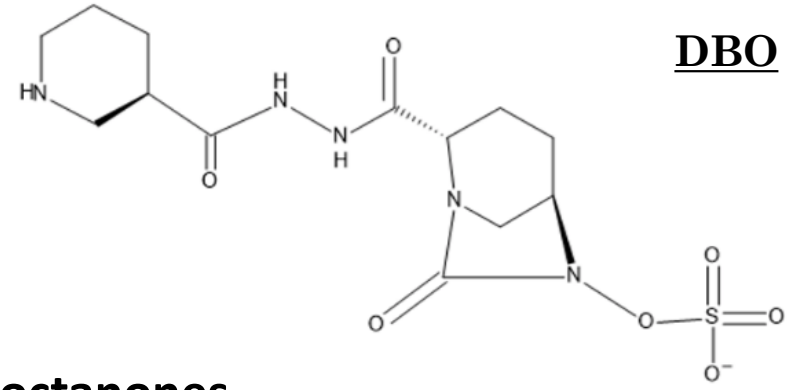
Relebactam

DBO



Nacubactam

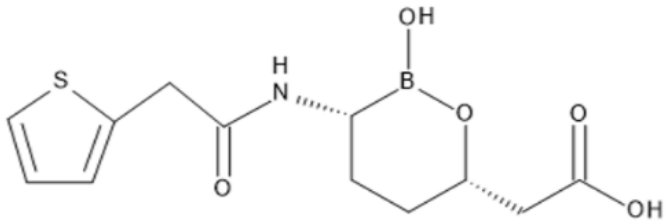
DBO



Zidebactam

Diazabicyclooctanones

Boronate



Vaborbactam

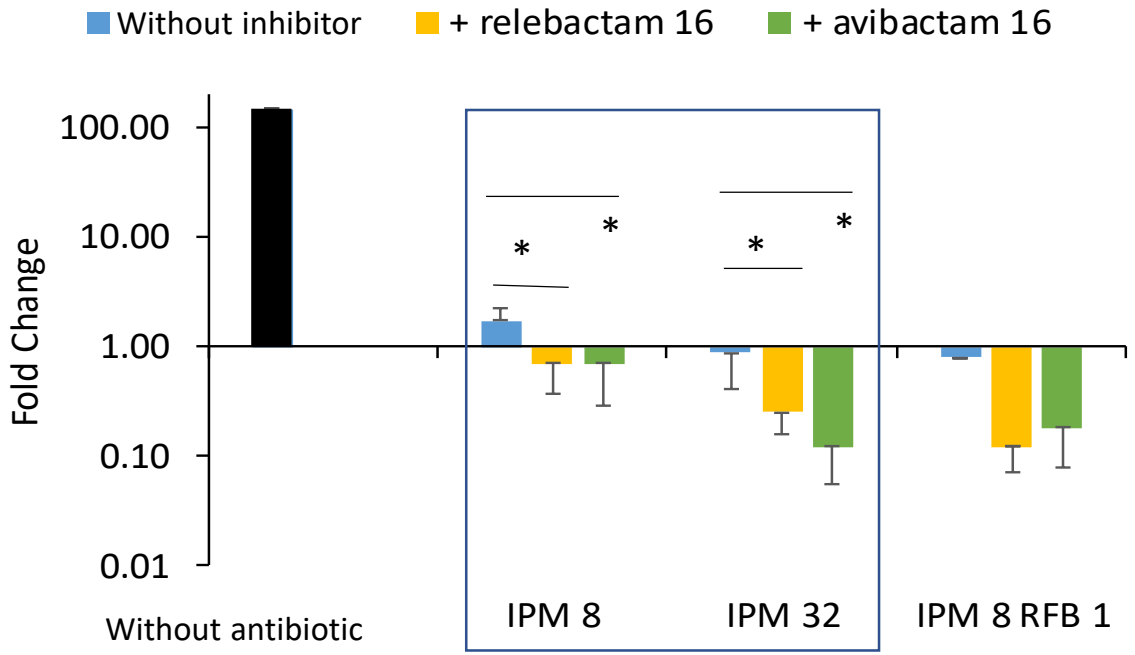
Activity of Imipenem combined with Relebactam

Developed in combination with imipenem

in vitro activity

		MIC (µg/ml)
		M. abscessus CIP104536S
Imipenem	Alone	8
	+ Relebactam 4 µg/ml	4
	+ Avibactam 4 µg/ml	2

Intracellular activity



Killing: 75-88%

Inhibition parameters of Bla_{Mab}

Parameter	Avibactam	Relebactam
K_2/K_i ($M^{-1}S^{-1}$)	(1.1 ± 0.1) X 10^5	(7.4 ± 0.4) X 10^2

150 times less active

Le Run, Arthur, Mainardi. JAC 2020

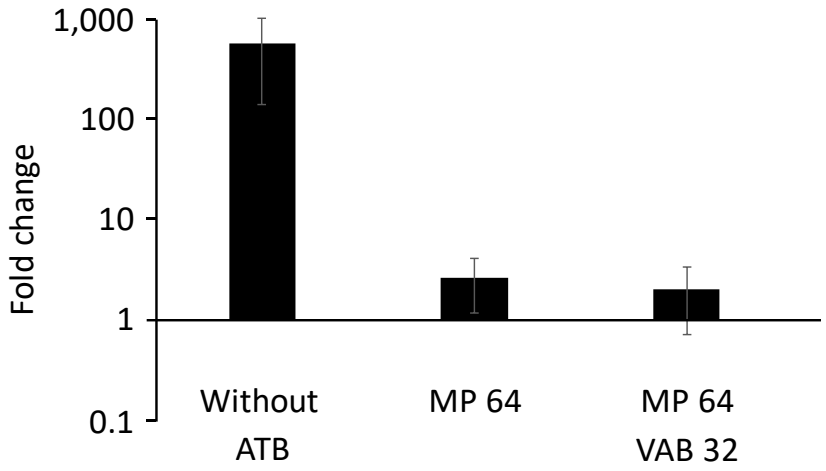
Evaluation of a boronate: Vaborbactam

- Developed in combination with meropenem

in vitro activity

β-lactam	Inhibitor	MIC (mg/L) CIP104536	MIC (mg/L) Δ*bla*$_{Mab}$
AMX	None	>1,024	8
	VAB 8 mg/L	128	8
	AVI 4 mg/L	16	4
MPM	None	16	4
	VAB 8 mg/L	8	4
	AVI 4 mg/L	4	4
IMI	None	4	2
	VAB 8 mg/L	2	2
	AVI 4 mg/L	2	2

Intracellular activity

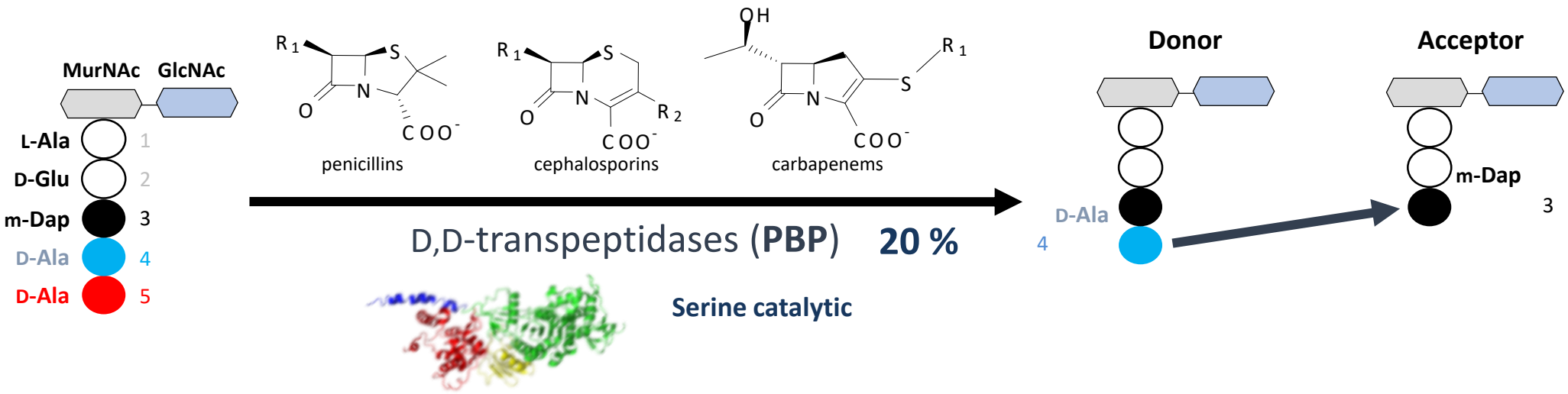


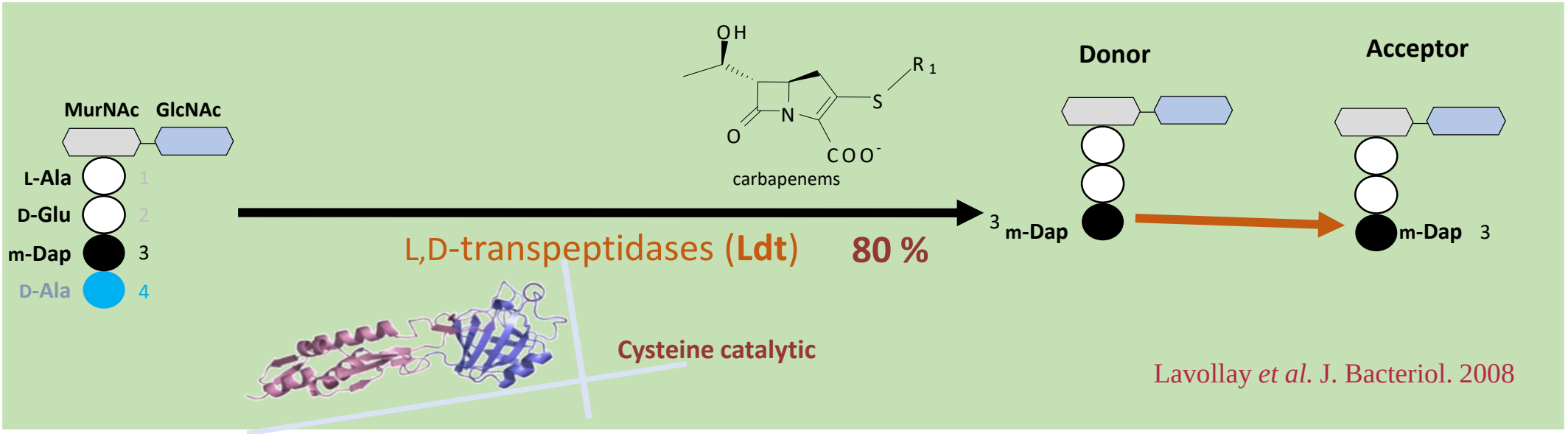
Inhibition parameters of Bla$_{Mab}$

Parameter	Vaborbactam	Avibactam	Relebactam
k_2/K_i ($M^{-1} s^{-1}$)	$(1.1 \pm 0.1) \times 10^4$	$(1.1 \pm 0.1) \times 10^5$	$(7.4 \pm 0.4) \times 10^2$

Sanchez et *al*,. JAC 2024

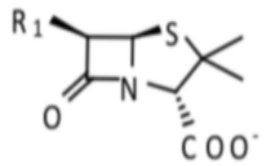
Inhibition of the two peptidoglycan synthesis pathways by combination of two β-lactams and DBOs in mycobacteria ?



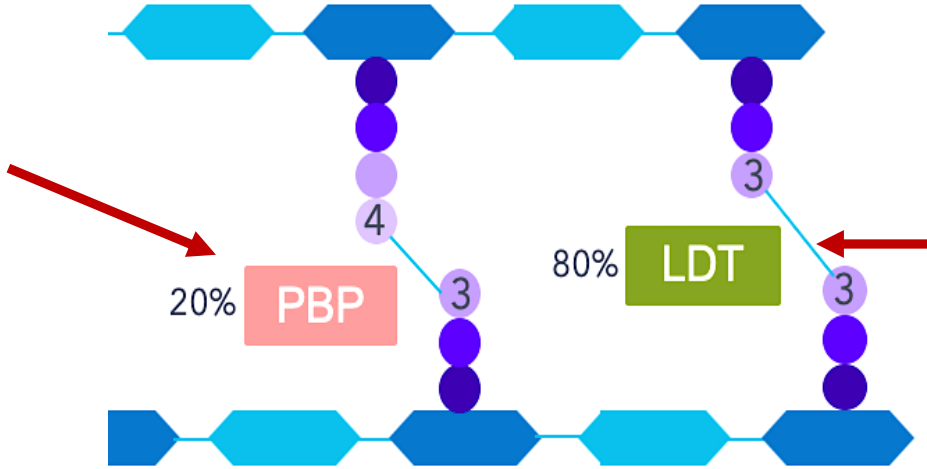


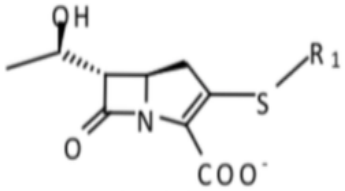
Lavollay *et al.* J. Bacteriol. 2008

DBOs ⊣ Bla_{Mab} —



Penicillin (Amoxicillin)





Carbapenems (Imipenem)

Hypothesis: combination of imipenem with other ß-lactams → Inhibition of two distinct PG synthesis pathways in the presence of DBOs.

In vitro activity of amoxicillin/imipenem/relebactam

β-lactam	Combination	MIC (mg/L)[a]
AMX	None	>2048
	+ REL 4 mg/L	64
	+ IPM 1 mg/L + REL 4 mg/L	1
IPM	None	8
	+ REL 4 mg/L	4
	+ AMX 4 mg/L + REL 4 mg/L	1

/64

/4

REL, relebactam

FIC Index		Effect
imipenem+ amoxicilline + relebactam	0.31	**SYNERGY**

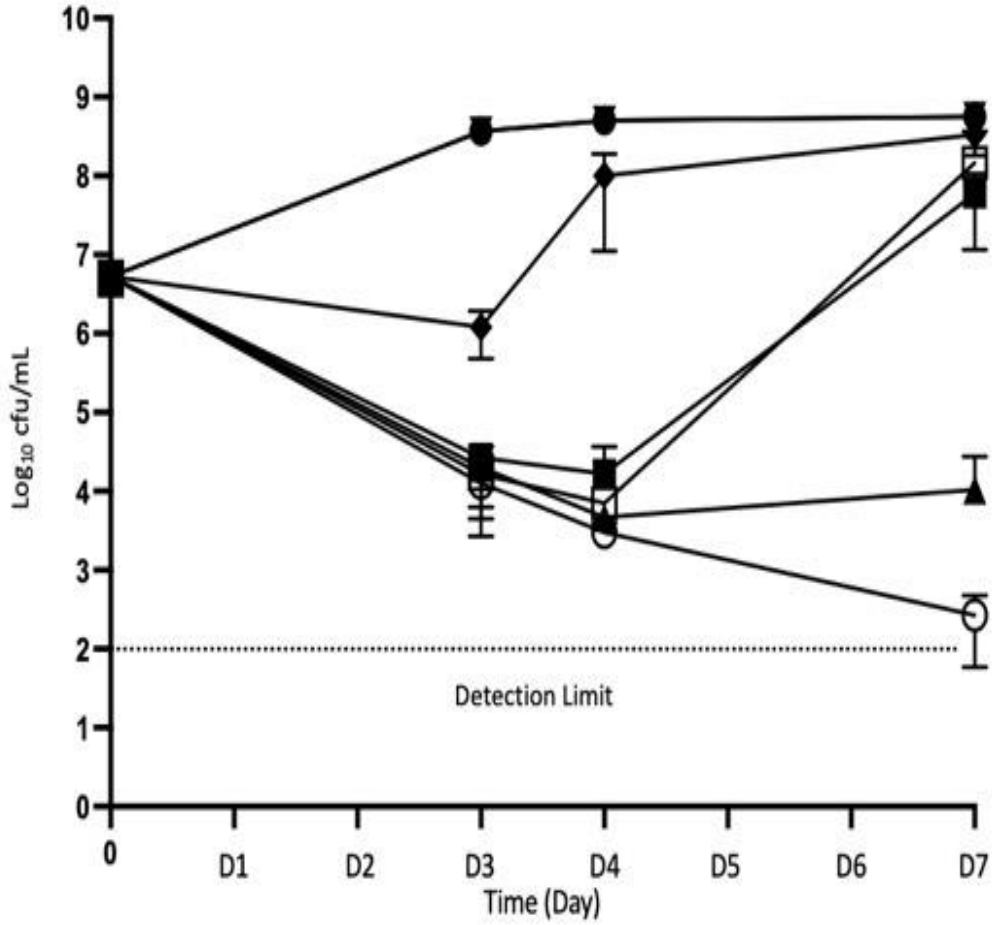
Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

Activity against clinical strains of *M. abscessus*

	MIC AMOX (IMI1 mg/L+RELE4 mg/L)	MIC IMI (AMOX4 mg/L+RELE4 mg/L)
M . abscessus CIP104536	1	1
M . abscessus subsp. *abscessus* (n=12)	0.5	1
M . abscessus subsp. *bollettii* (n=10)	32	2
M . abscessus subsp. *massiliense* (n=13)	8	2

Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

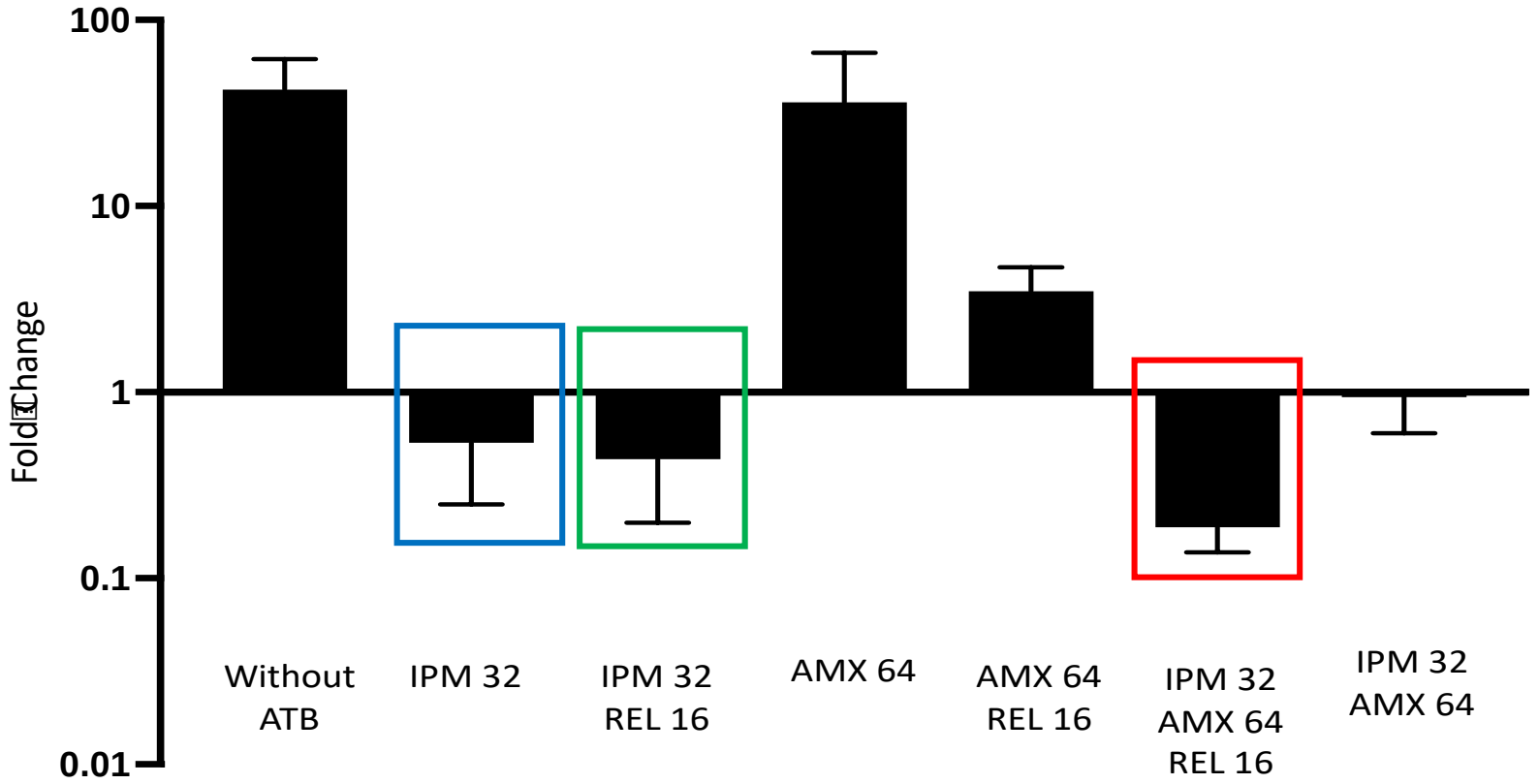
In vitro bactericidal effect of amoxicillin/imipenem/relebactam



	Log_{10} cfu/mL at D7 (+/-SD)[b]	Variation[c]
Without antibiotic[a]	8.73 (0.02)	2.00
AMX 64	8.73 (0.63)	2.00
AMX 64 + REL 4	8.48 (0.91)	1.75
IPM 32 + AMX 64	8.13 (0.02)	1.40
IPM 32	7.80 (0.18)	1.08
IMP 32 + REL 4	4.00 (0.35)	-2.73
IPM 32 + AMX 64 + REL 4	2.43 (0.84)	-4.30

Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

Intramacrophage activity of amoxicillin/imipenem/relebactam



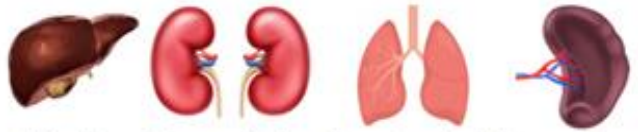
Killing: 82%

Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

In vivo activity of amoxicillin/imipenem/relebactam

Murine model C3HeB/FeJ

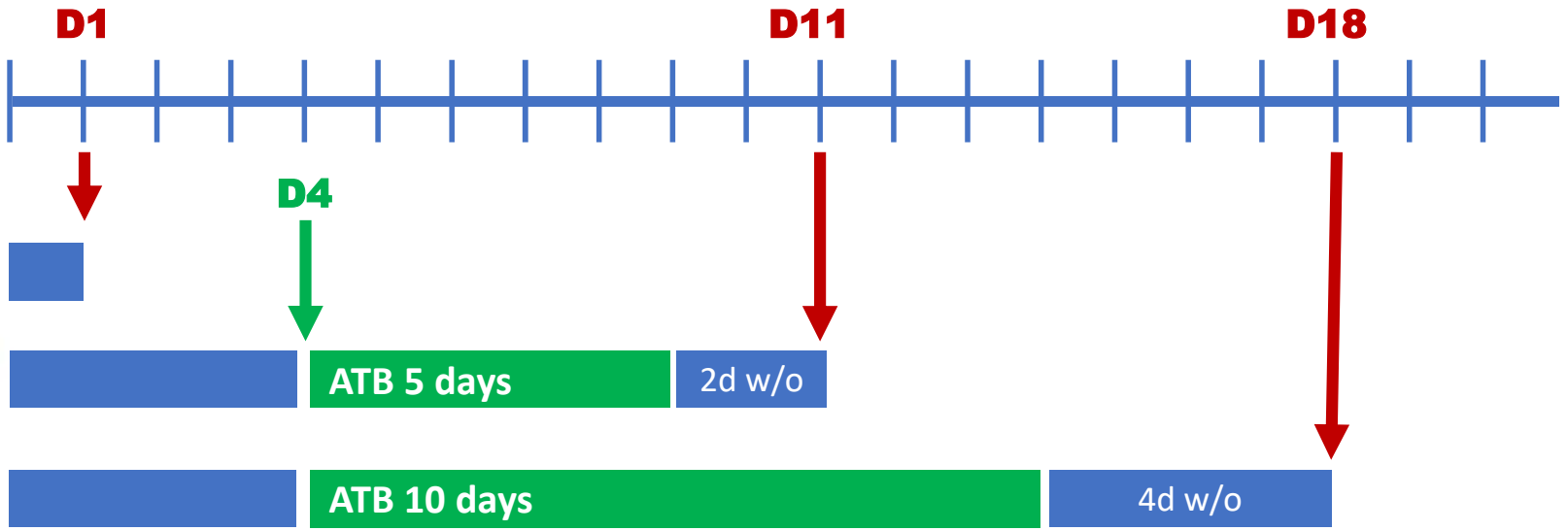
Sacrifice at D1, D11, D18



Evaluation of the bacterial load in 4 organs: liver, lungs, spleen and kidneys.

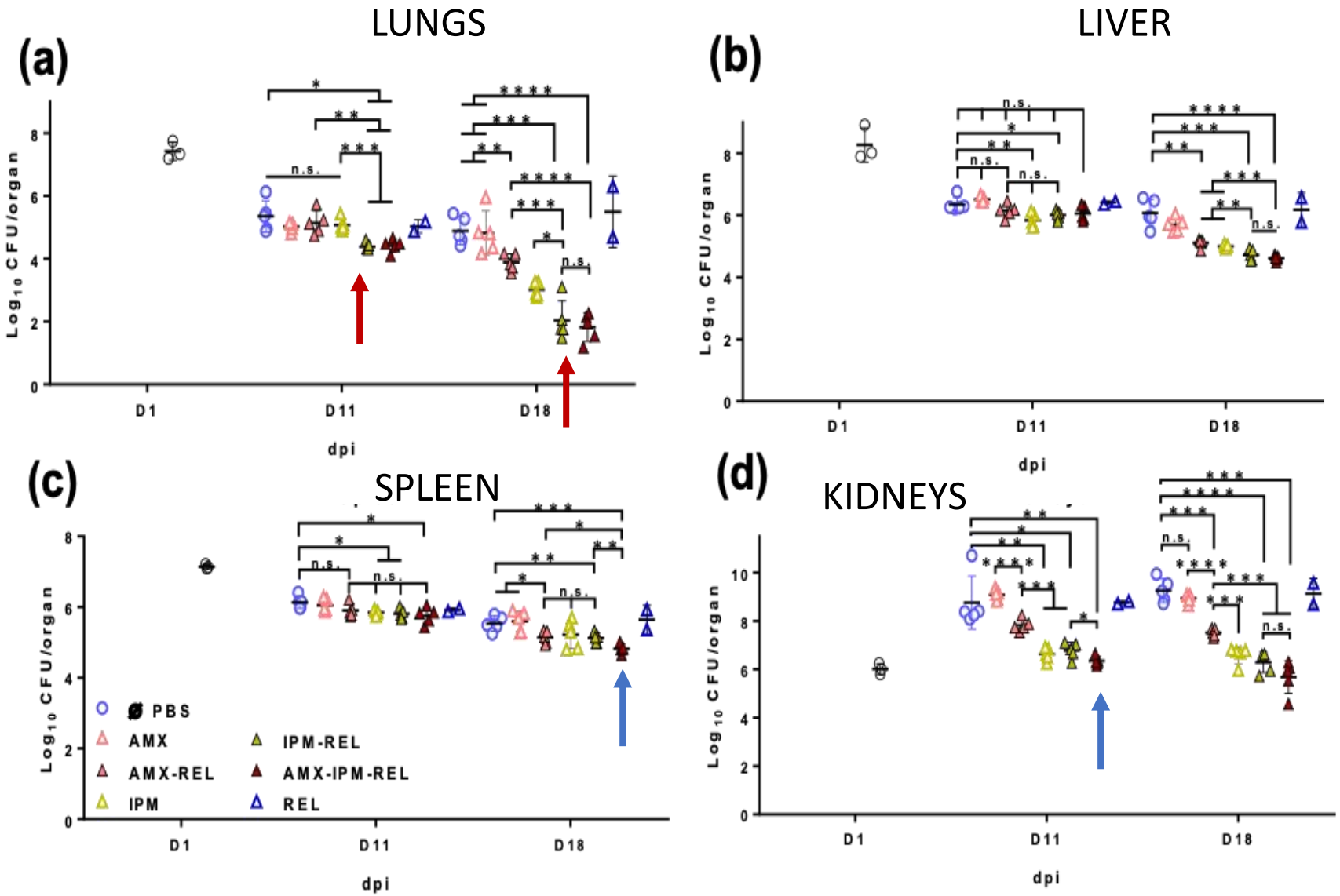
D0

Infection *M. abscessus* WT
S : 10^8 CFU/mL



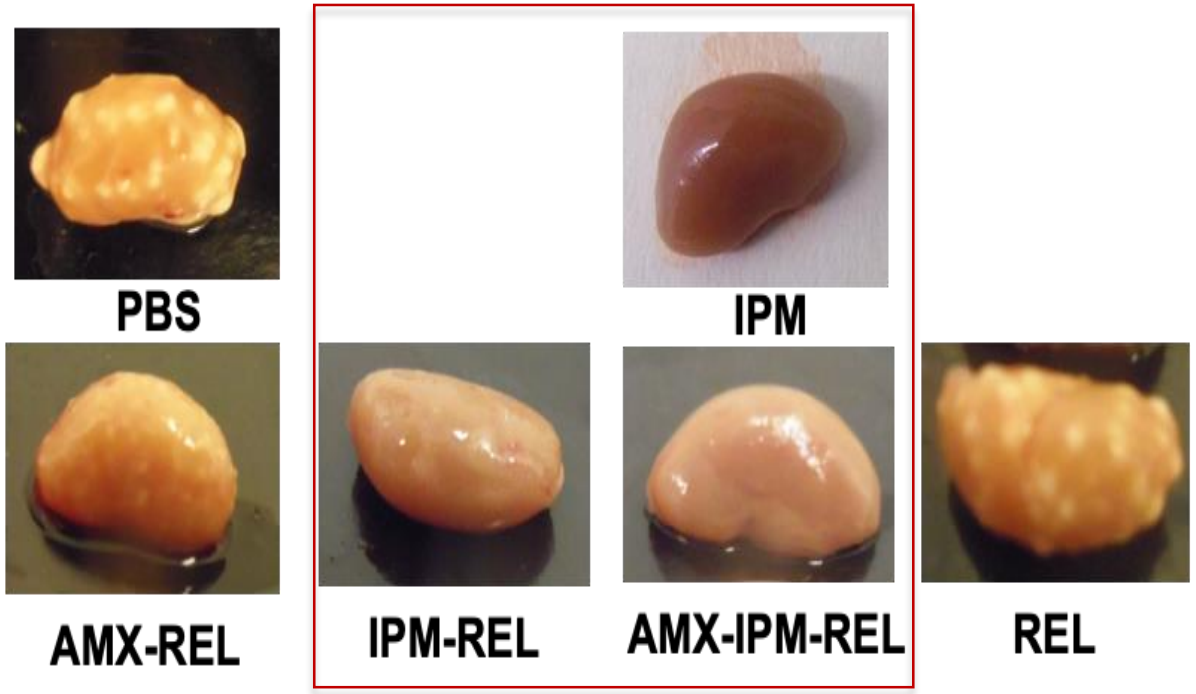
Imipenem or Amoxicillin +/- Relebactam: 100 Mg/Kg X 2/d

Mouse model



Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

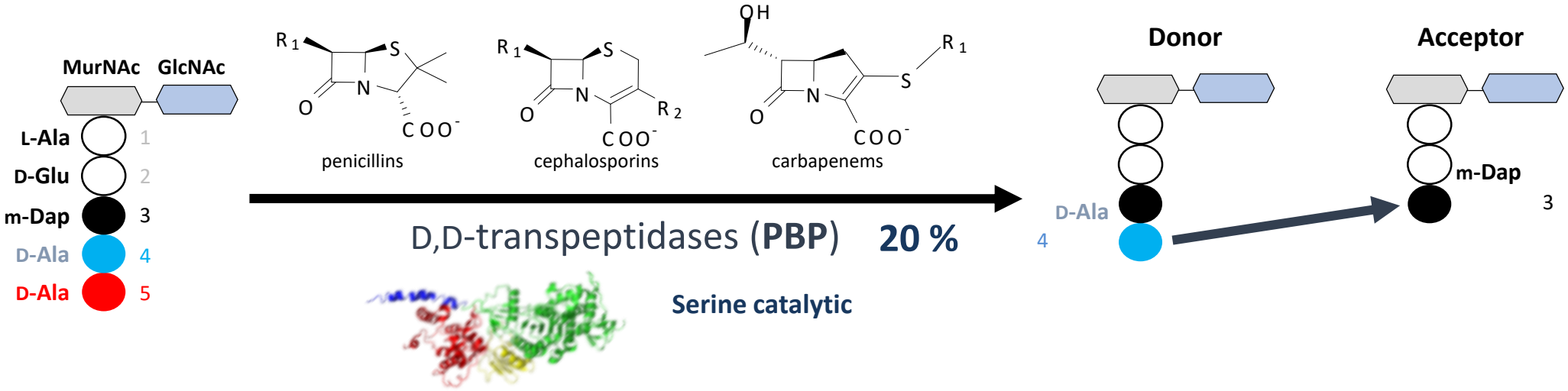
Macroscopic aspects of kidneys

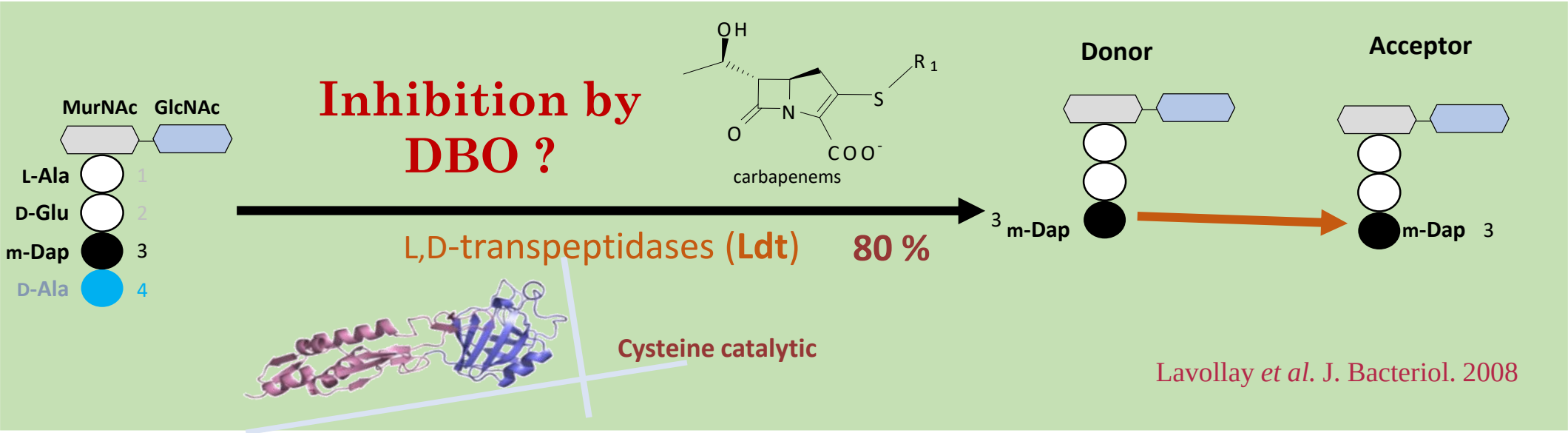


Imipenem, imipenem/relebactam and amoxicillin/imipenem/relebactam prevent the formation of abscesses

Bitar *et al*, Journal of Antimicrobial Chemotherapy 2025 Accepted

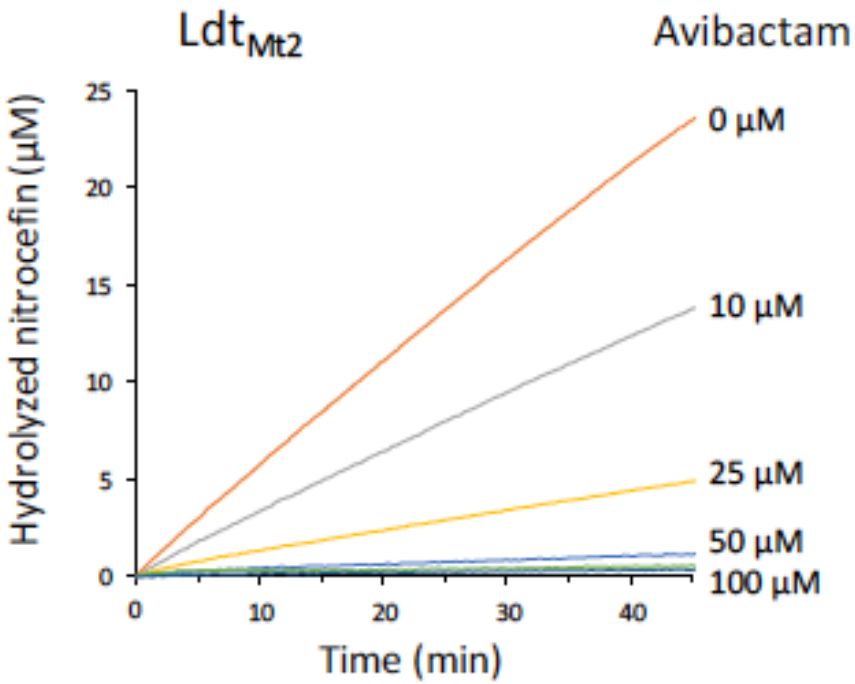
Dual activity of DBOs ?

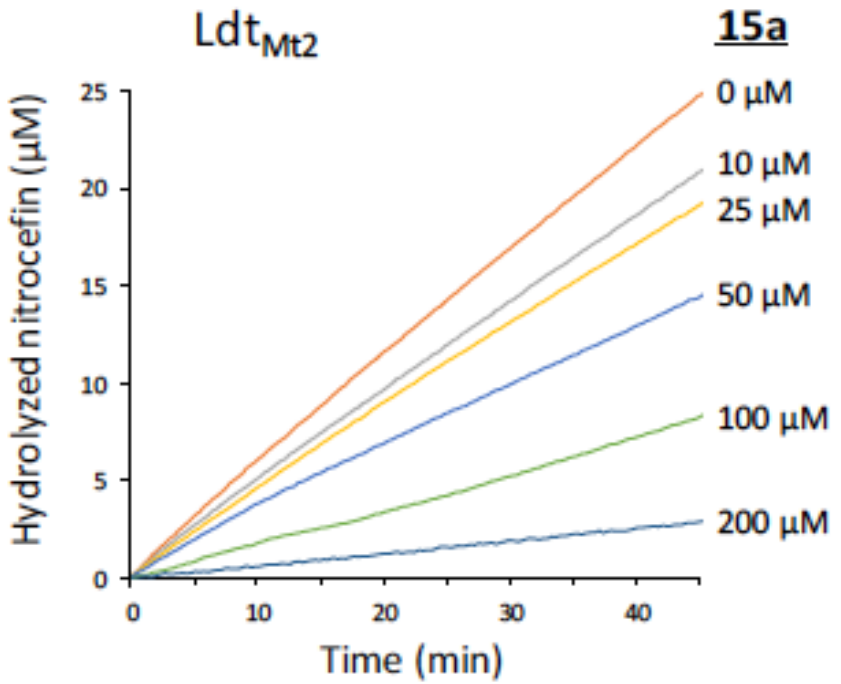




Lavollay *et al.* J. Bacteriol. 2008

Inhibition of *M. tuberculosis* L,D-transpeptidase by DBOs





Synthetized DBO

Edoo *et al*; Chemistry 2018

Patents: EP17306902.2 and EP17020591.8 (22/12/2017)

Conclusions/perspectives

- Avibactam, relebactam (and others DBOs) improve imipenem activity by Bla_{Mab} inhibition *in vitro*, in macrophage and animal models
  - Imipenem + relebactam as the first line therapy vs Imipenem alone ?
- The amoxicillin/imipenem/relebactam combination was synergistic *in vitro* and effective *in vivo* against *M. abscessus*.
- Since these drugs are clinically available, the triple combination should be considered by clinicians and further evaluated based on the reporting of the patient outcomes.
- Optimization of DBOs for inhibition of mycobacteria L,D-transpeptidases: attractive strategy to obtain selectively active antibiotics against mycobacteria

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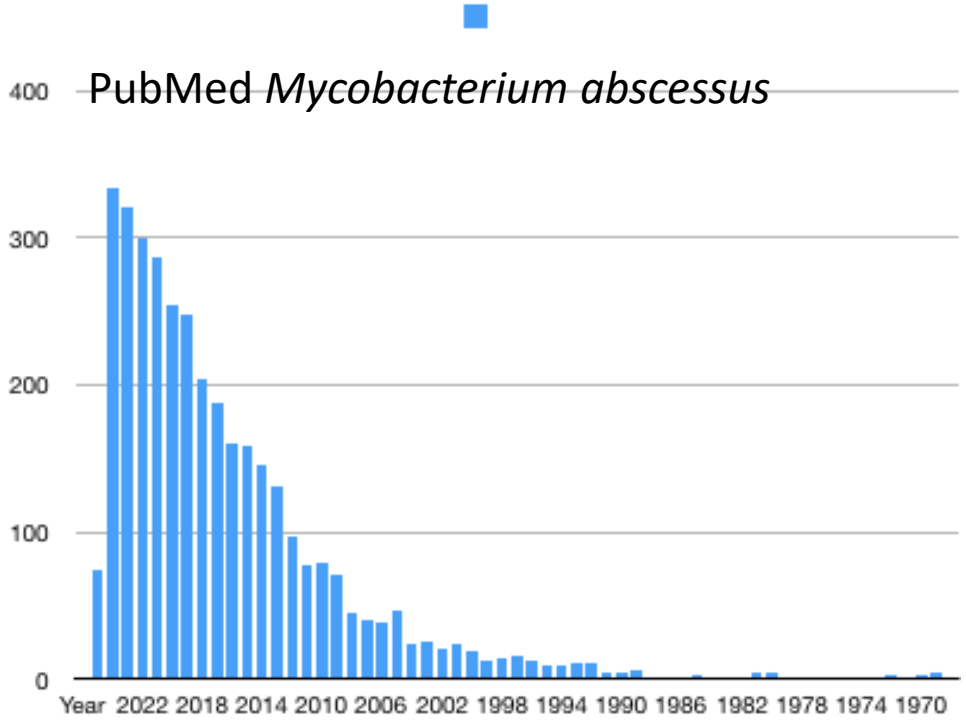
Questionnaire sur la prise en charge des infections pulmonaires à *Mycobacterium abscessus*



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