

# Pharmacodynamic evaluation of the intracellular activity of neglected and disused antibiotics (NDAB) towards *Pseudomonas aeruginosa* after phagocytosis by human THP-1 monocytes

Emilien Drouot, Paul M. Tulkens, Françoise Van Bambeke

Pharmacologie cellulaire et moléculaire  
Louvain Drug Research Institute  
Université catholique de Louvain,  
Brussels, Belgium

<[www.facm.ucl.ac.be](http://www.facm.ucl.ac.be)>

# The battle against superbugs: who is going to win ?



<https://loonylabs.org/2015/01/04/antibiotic-resistance-2/>

# Worrying Superbugs

ESKAPE pathogens
<i>Enterococcus faecium</i>
<i>Staphylococcus aureus</i>
<i>Klebsiella pneumoniae</i>
<i>Acinetobacter baumanii</i>
<i>Pseudomonas aeruginosa</i>
<i>Enterobacter species</i>



## WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

### Priority 1: CRITICAL<sup>#</sup>

*Acinetobacter baumannii*, carbapenem-resistant  
*Pseudomonas aeruginosa*, carbapenem-resistant  
*Enterobacteriaceae\**, carbapenem-resistant, 3<sup>rd</sup> generation cephalosporin-resistant

### Priority 2: HIGH

*Enterococcus faecium*, vancomycin-resistant  
*Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant  
*Helicobacter pylori*, clarithromycin-resistant  
*Campylobacter*, fluoroquinolone-resistant  
*Salmonella spp.*, fluoroquinolone-resistant  
*Neisseria gonorrhoeae*, 3<sup>rd</sup> generation cephalosporin-resistant, fluoroquinolone-resistant

### Priority 3: MEDIUM

*Streptococcus pneumoniae*, penicillin-non-susceptible  
*Haemophilus influenzae*, ampicillin-resistant  
*Shigella spp.*, fluoroquinolone-resistant

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# Reviving old antibiotics: why and how ?

Intensive Care Med (2015) 41:1950–1953  
DOI 10.1007/s00134-015-3705-5

WHAT'S NEW IN INTENSIVE CARE



Matteo Bassetti  
Matthew E. Falagas  
Marin Kollef



Ten old antibiotics that will never disappear

*J Antimicrob Chemother* 2015; **70**: 2177–2181  
doi:10.1093/jac/dkv157 Advance Access publication 10 June 2015

Journal of  
Antimicrobial  
Chemotherapy

Reviving old antibiotics

Ursula Theuretzbacher<sup>1\*</sup>, Françoise Van Bambeke<sup>2</sup>, Rafael Cantón<sup>3</sup>, Christian G. Giske<sup>4,5</sup>, Johan W. Mouton<sup>6,7</sup>,  
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journal homepage: [www.elsevier.com/locate/ijantimicag](http://www.elsevier.com/locate/ijantimicag)

Themed Issue: Resurrection of old antibiotics

Revival of old antibiotics needs the state of evidence and expectations

Hiba Zayyad <sup>a</sup>, Noa Eliakim-Raz <sup>b,c</sup>, Leonard Leibovici <sup>b,c</sup>, Mical Paul <sup>a,d,\*</sup>

frontiers in  
**MICROBIOLOGY**

REVIEW ARTICLE  
published: 20 October 2014  
doi: 10.3389/fmicb.2014.00551



A new strategy to fight antimicrobial resistance, the revival of old antibiotics

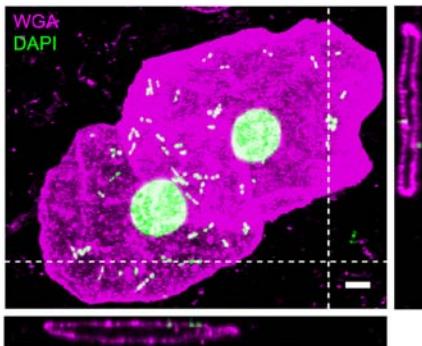
Nadim Cassir<sup>1,2\*</sup>, Jean-Marc Rolain<sup>1</sup> and Philippe Brouqui<sup>1,2\*</sup>

# The battle against superbugs: who is going to win ?

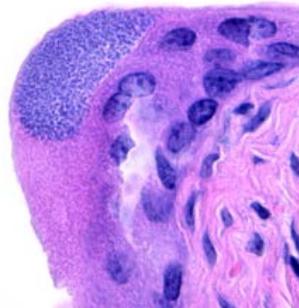


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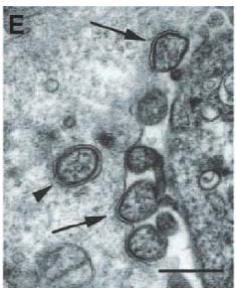
# Intracellular Superbugs



Korsley et al, PLoS One. 2013;8:e83637

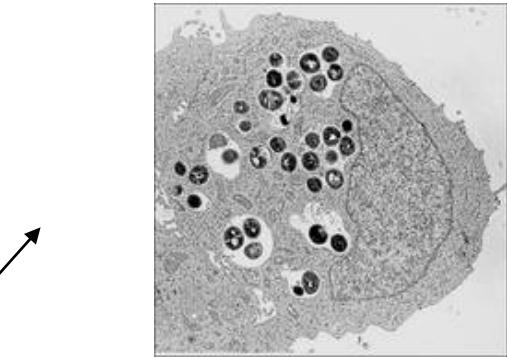


Rosen et al, Infect. Immun. 2008; 76:3337-45

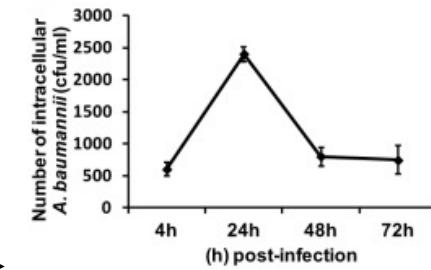


Darling et al, Cell Microbiol. 2004;6:521-33

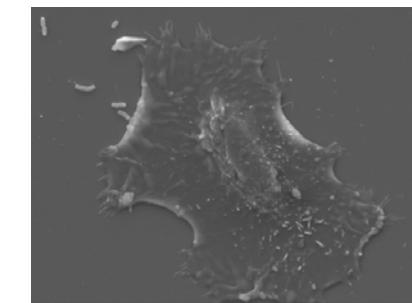
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Sinha et al, Cell. Microbiol. 1999; 1:101-17



Bist et al, Infect Immun. 2014; 82: 1112–22



Mittal et al, J. Immunol, 2009, 183:6588-99

# The battle against superbugs: who is going to win ?

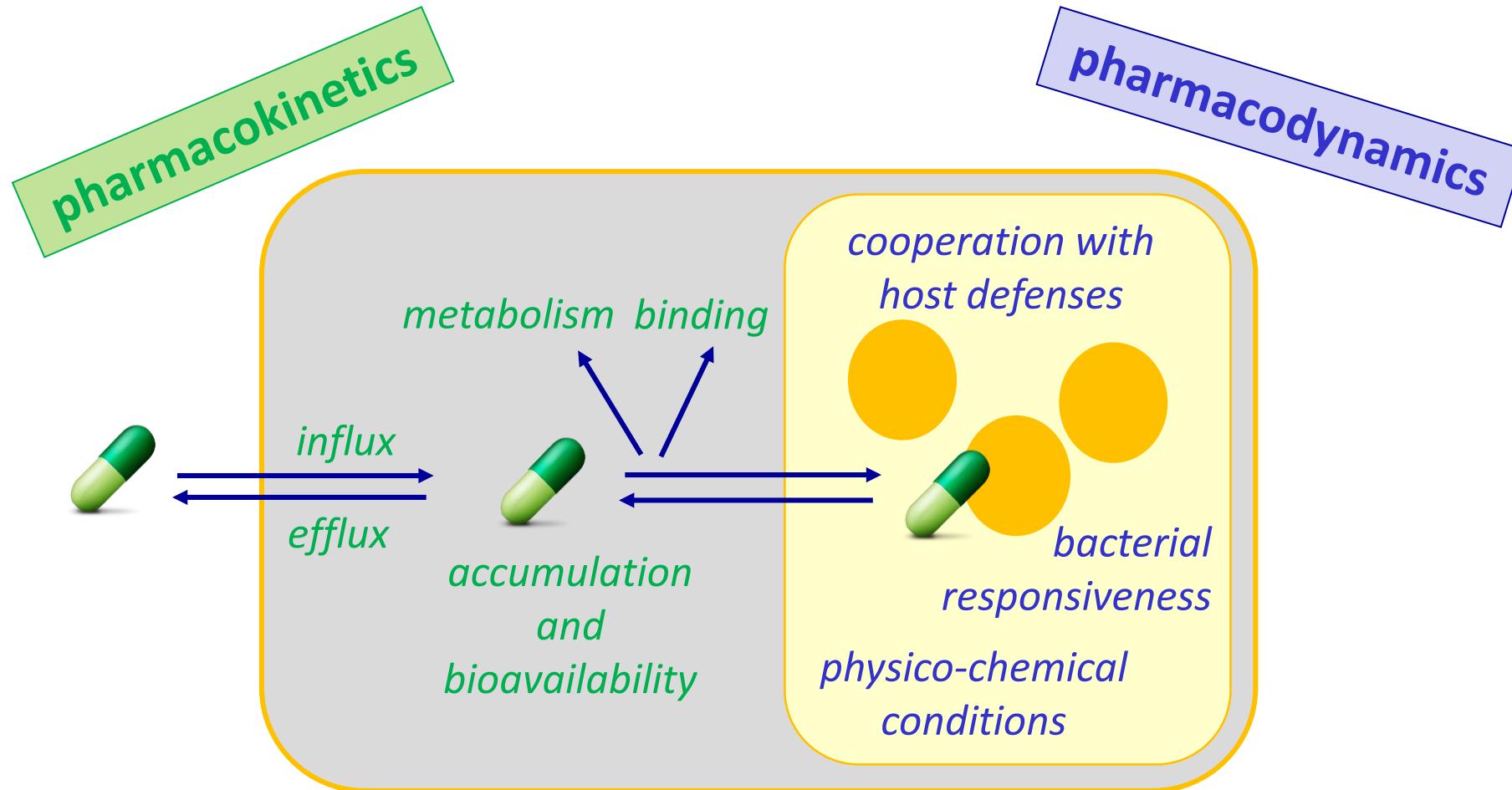
Optimize  
PK/PD ?



Adopt antibiotic  
“tolerant”  
lifestyles

<https://loonylabs.org/2015/01/04/antibiotic-resistance-2/>

# PK/PD parameters and intracellular infections



Carryn et al, Infect Dis Clin North Am 2003; 17:615-34

# Reviving old antibiotics: why and how ?

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International Society of Chemotherapy  
for Infection and Cancer

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### A new strategy to fight antimicrobial resistance, the revival of old antibiotics

Nadim Cassir<sup>1,2\*</sup>, Jean-Marc Rolain<sup>1</sup> and Philippe Brouqui<sup>1,2\*</sup>

## REVIEW

### Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective

A. E. Muller<sup>1</sup>, U. Theuretzbacher<sup>2</sup> and J. W. Mouton<sup>3,4</sup>

*Clin Microbiol Infect* 2015; **21**: 881–885

International Journal of Antimicrobial Agents 49 (2017) 98–101

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International Journal of Antimicrobial Agents

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Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia \*

Céline Pulcini <sup>a,\*</sup>, Simone Mohrs <sup>b</sup>, Bojana Beovic <sup>c</sup>, Inge Gyssens <sup>d,e</sup>, Ursula Theuretzbacher <sup>f</sup>, Otto Cars <sup>b</sup> on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), ReAct Working Group on Old Antibiotics <sup>1</sup>

LDR  
Louvain Drug Research Institute

## Evaluation of antibiotic activity in a model of intracellular infection by *P. aeruginosa*

- To determine the activity of different neglected and disused antibiotics (NDAB) towards intracellular infection using a previously developed *in vitro* model
- To compare pertinent pharmacological descriptors of antibiotic activity (maximal efficacy, relative potency) between NDAB and old, conventional antipseudomonal drugs

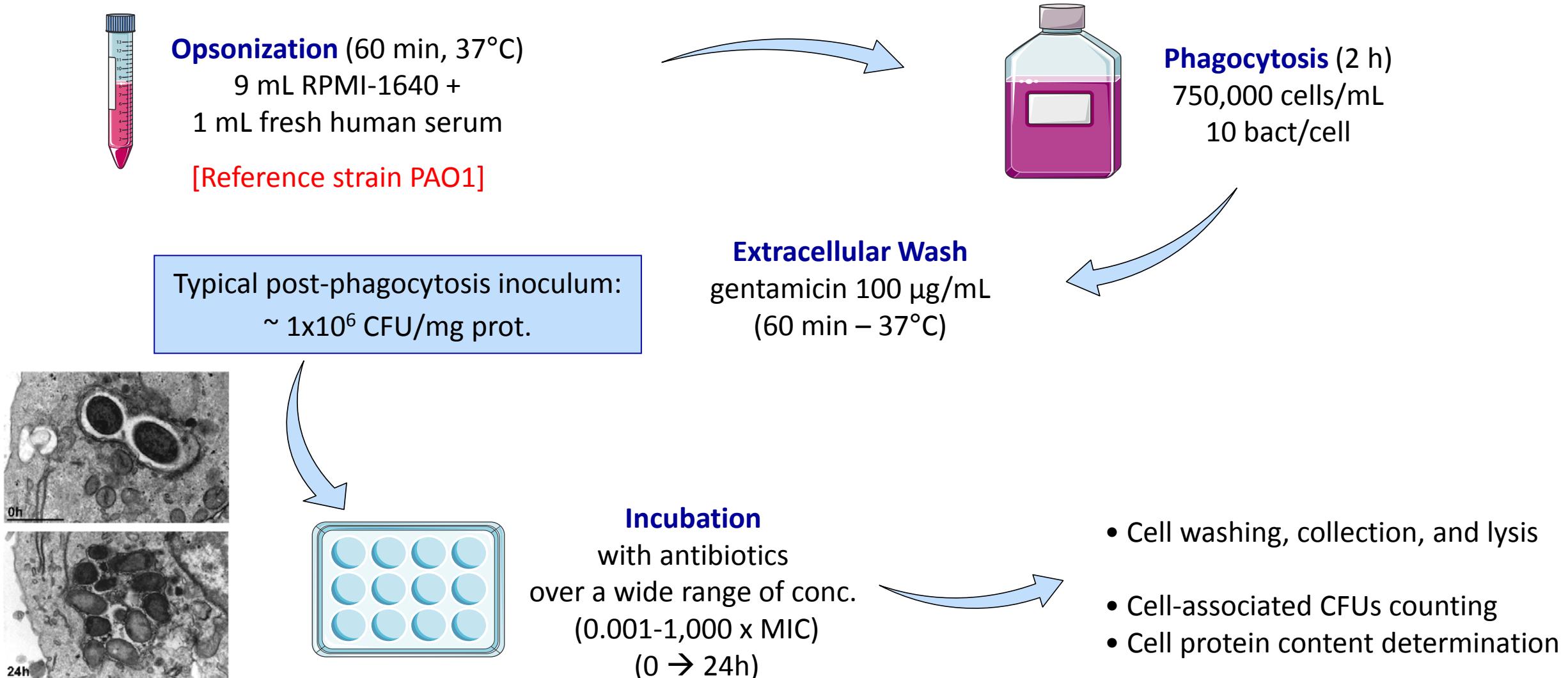
# Reviving old antibiotics: Bug and Drugs used in this work

ESKAPE pathogens
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<i>Staphylococcus aureus</i>
<i>Klebsiella pneumoniae</i>
<i>Acinetobacter baumanii</i>
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<i>Enterobacter species</i>

Old, conventional drugs			Old, neglected and disused drugs		
drugs	MIC* (mg/L)	Cellular accumul.	drugs	MIC* (mg/L)	Cellular accumul.
Colistin	2	ND	Polymyxin B	4	ND
Meropenem	1	1 x	Chloramphenicol	16	2-5 x
Amikacin	1	2-4 x (slow)	Rifampicin	16	2-10 x
Ciprofloxacin	0.06	5 x	Minocycline	16	2-4 x

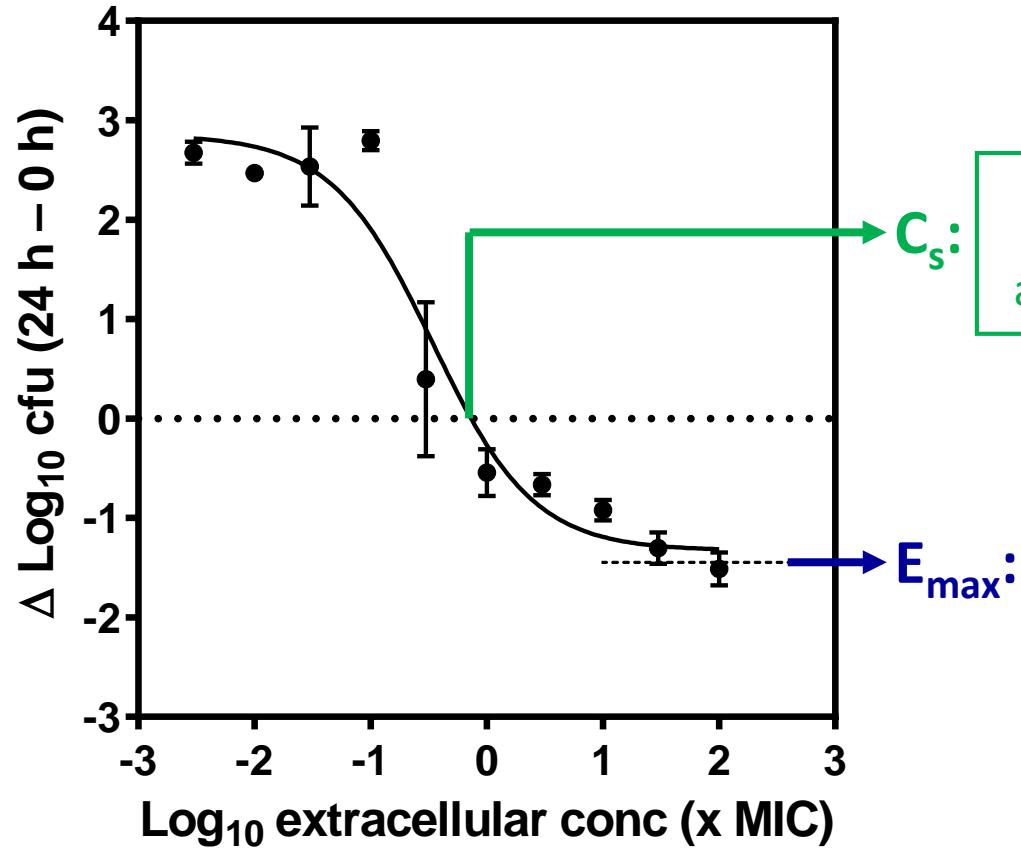
\* *P. aeruginosa* PAO1

# In vitro model of intracellular infection in THP-1 human monocytes



Buyck et al, AAC 2013; 57:2310-8

# Definition of pharmacodynamic parameters for intracellular infection

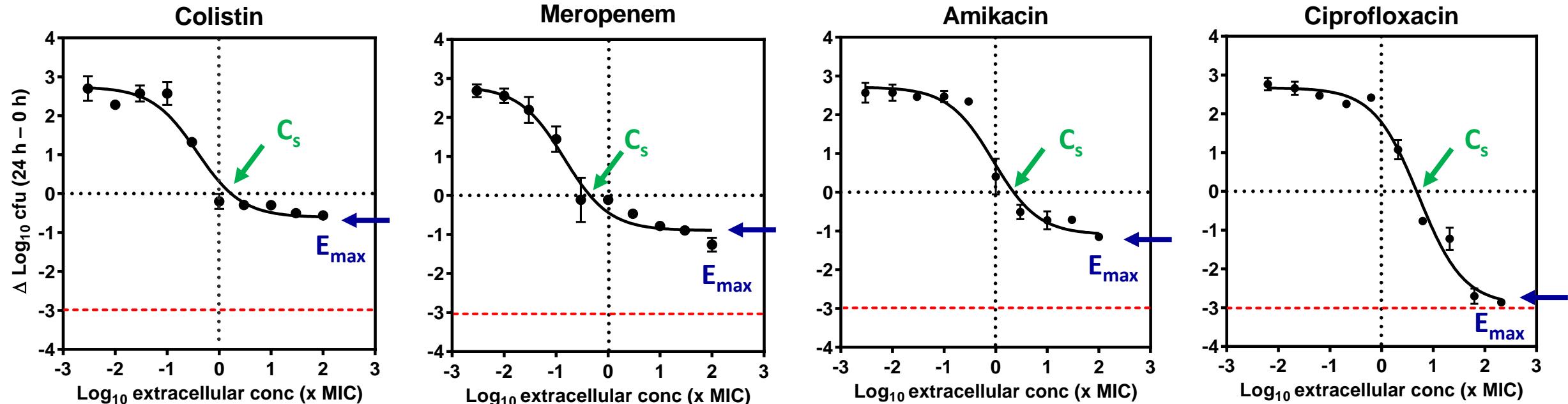


$C_s$ : extracellular concentration (total drug)  
resulting in no apparent bacterial growth (vs. initial inoculum),  
as calculated from the Hill equation of the concentration-response curve.

$E_{max}$ : log CFU decrease (at 24 h) from the corresponding original inoculum,  
as extrapolated for an infinitely large antibiotic concentration.

# Intracellular activities of old, conventional antipseudomonal drugs

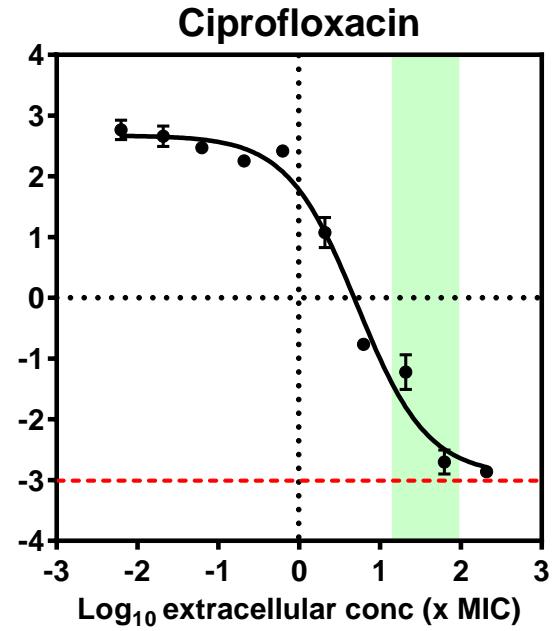
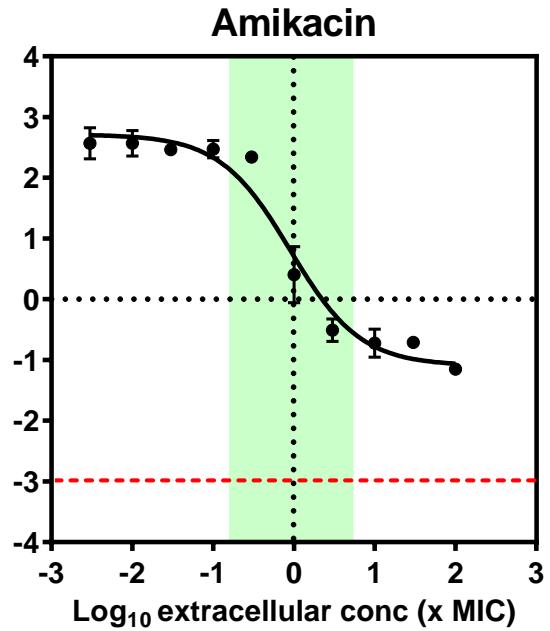
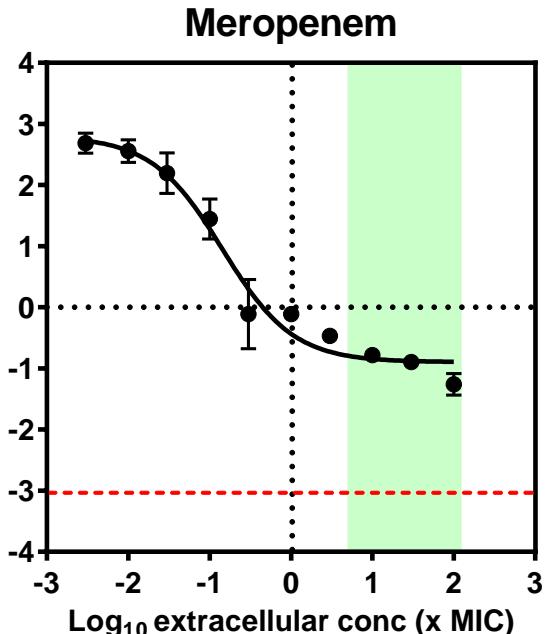
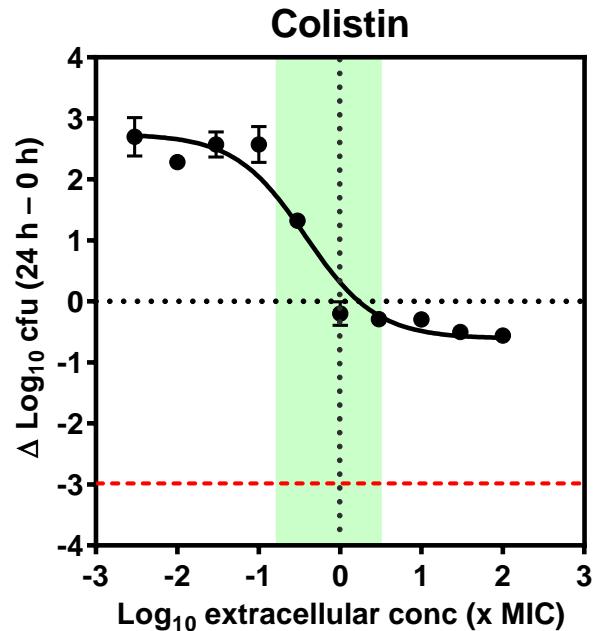
## Pharmacological comparison at equipotent concentrations



- $C_s$ : close to the MIC
- $E_{\max}$ : low (ciprofloxacin ~ bactericidal effect)

# Intracellular activities of old, conventional antipseudomonal drugs

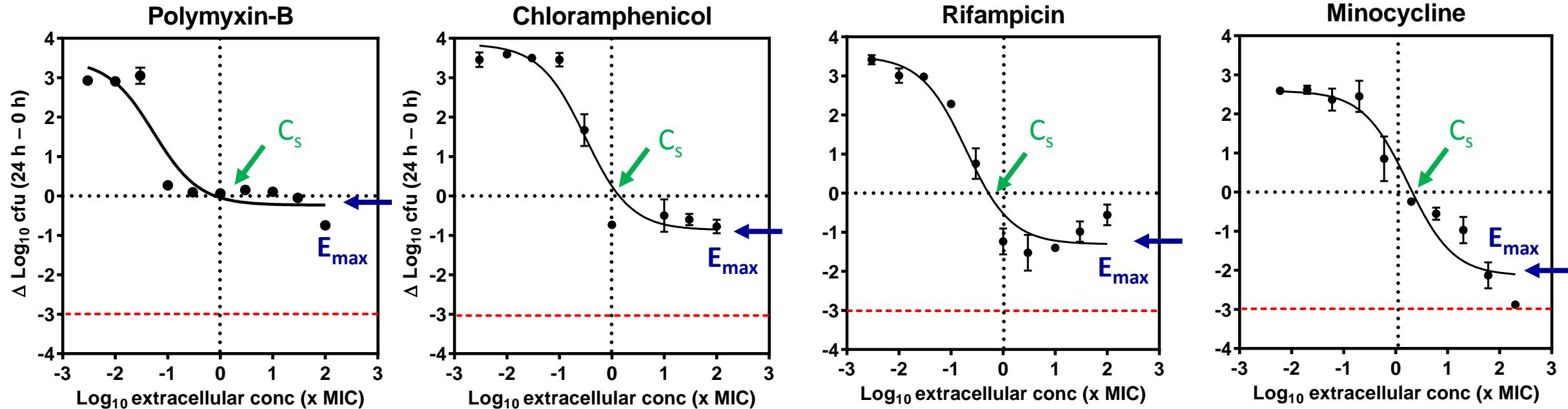
Clinically-oriented comparison at serum concentrations



- Meropenem → 1 log decrease in CFU
- Ciprofloxacin → ~ 3 log decrease in CFU at clinically-achievable concentrations

# Intracellular activities of neglected and disused antibiotics

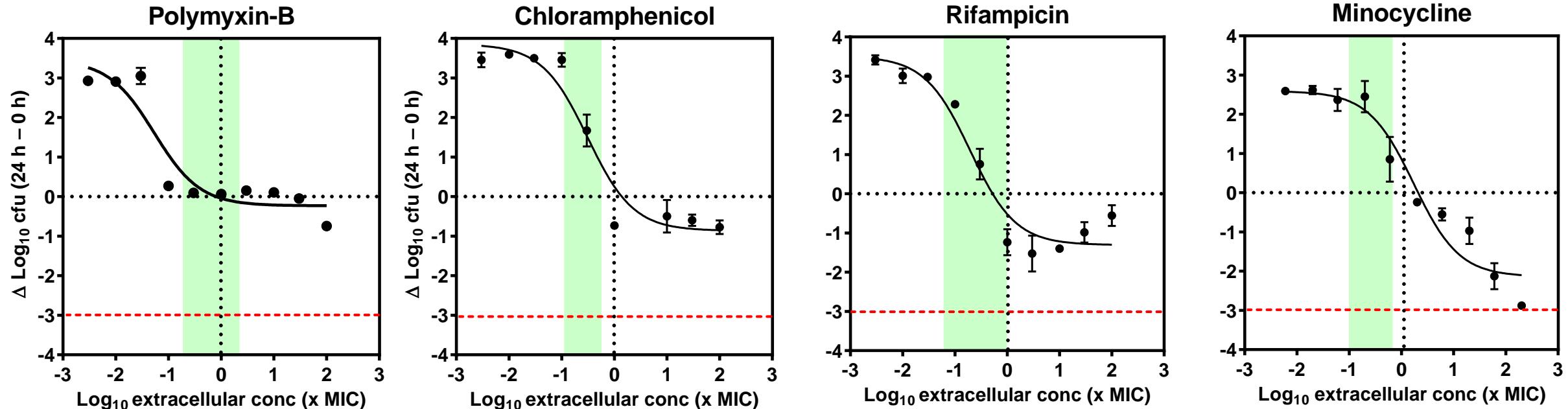
## Pharmacological comparison at equipotent concentrations



- $C_s$ : close to the MIC
- $E_{\max}$ : low (no bactericidal effect)

# Intracellular activities of neglected and disused antibiotics

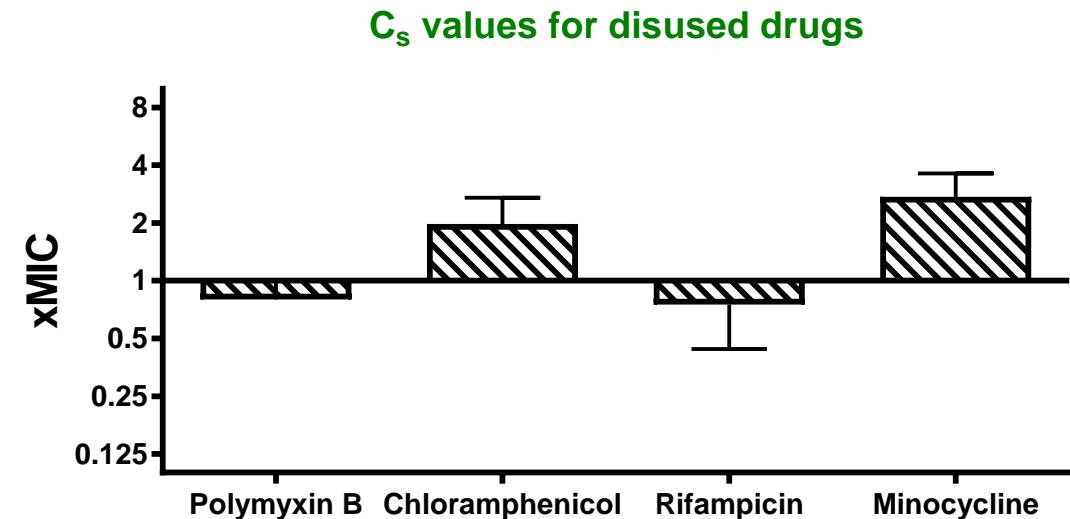
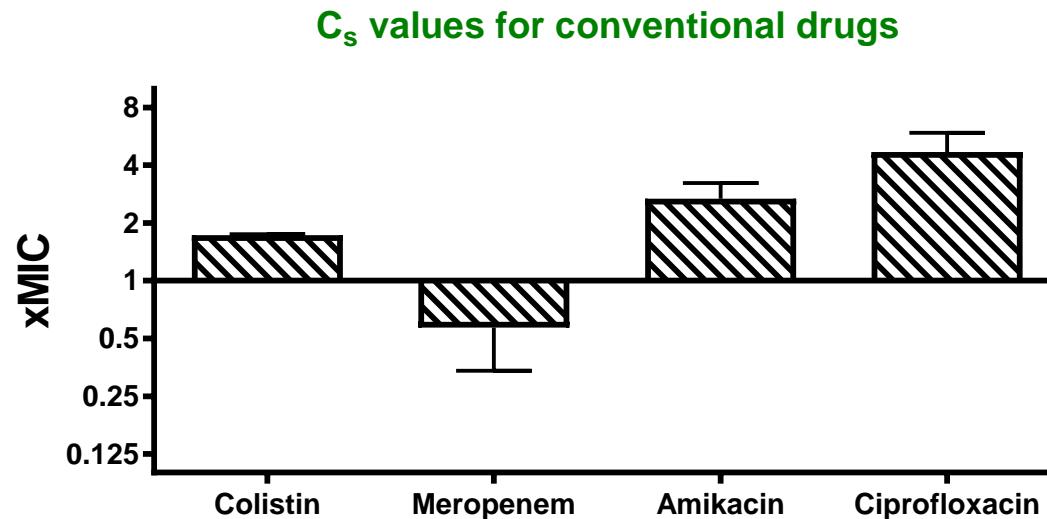
Clinically-oriented comparison at serum concentrations



- Polymyxin B → bacteriostatic
- Others → barely active  
at clinically-achievable concentrations

# Summary of antibiotic PD parameters against intracellular *P. aeruginosa*

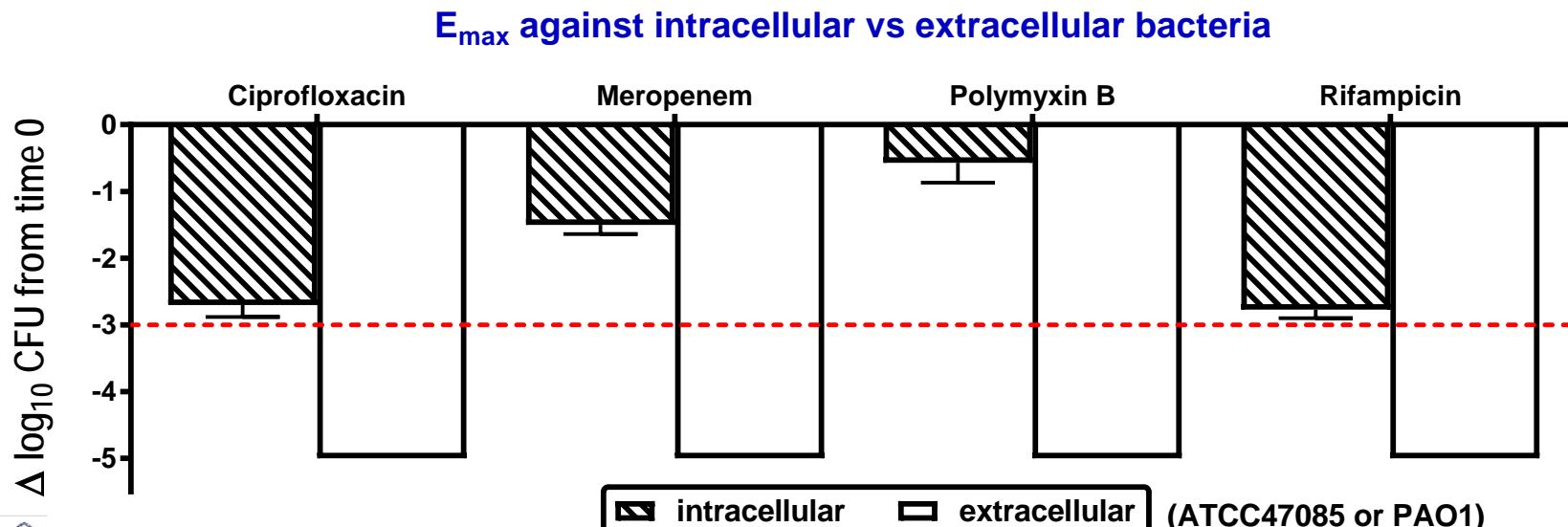
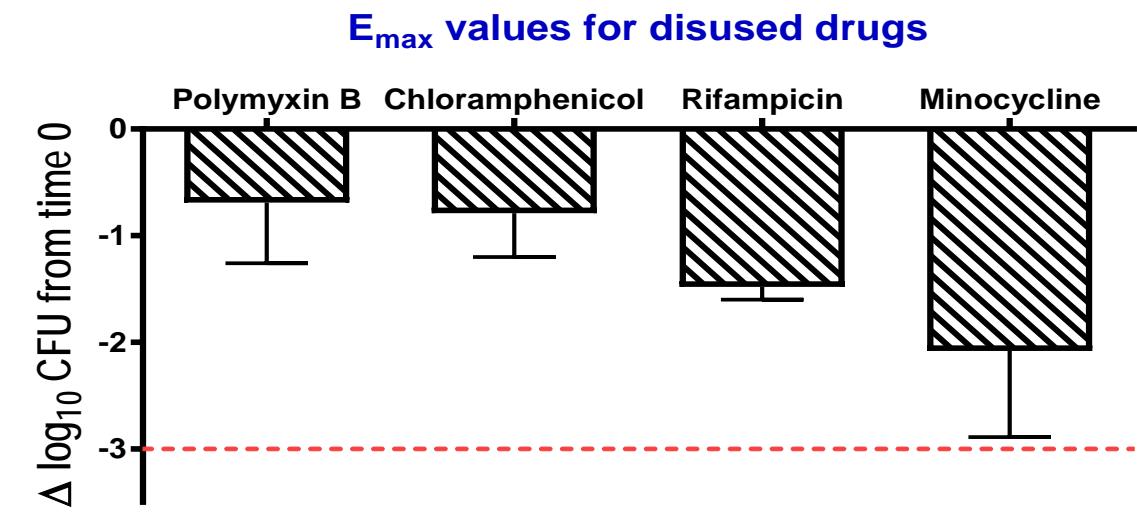
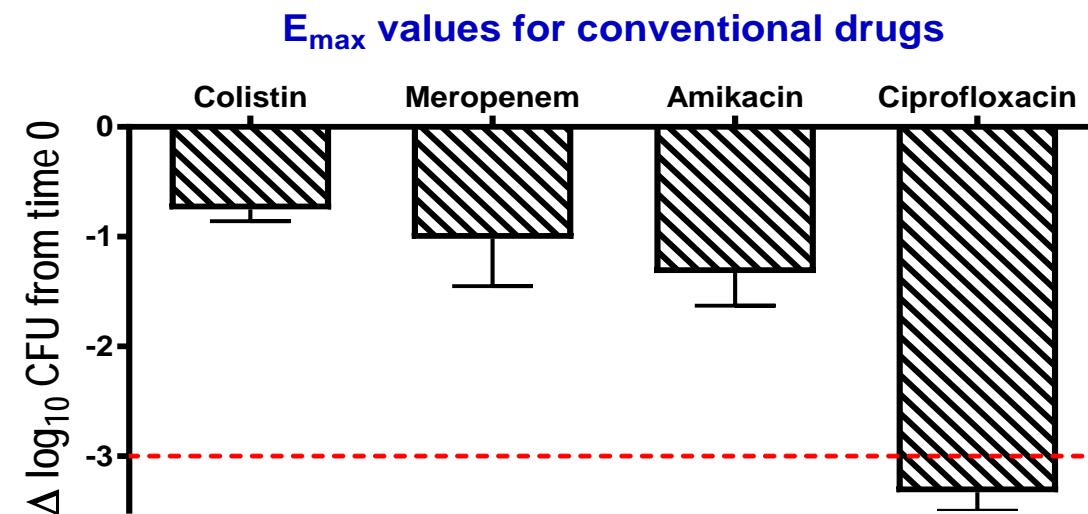
## Pharmacological comparison - Relative potency:



Intracellular MIC  $\sim$  extracellular MIC (2 dilution difference max)  
whatever the cellular accumulation level of the drug

# Summary of antibiotic PD parameters against intracellular *P. aeruginosa*

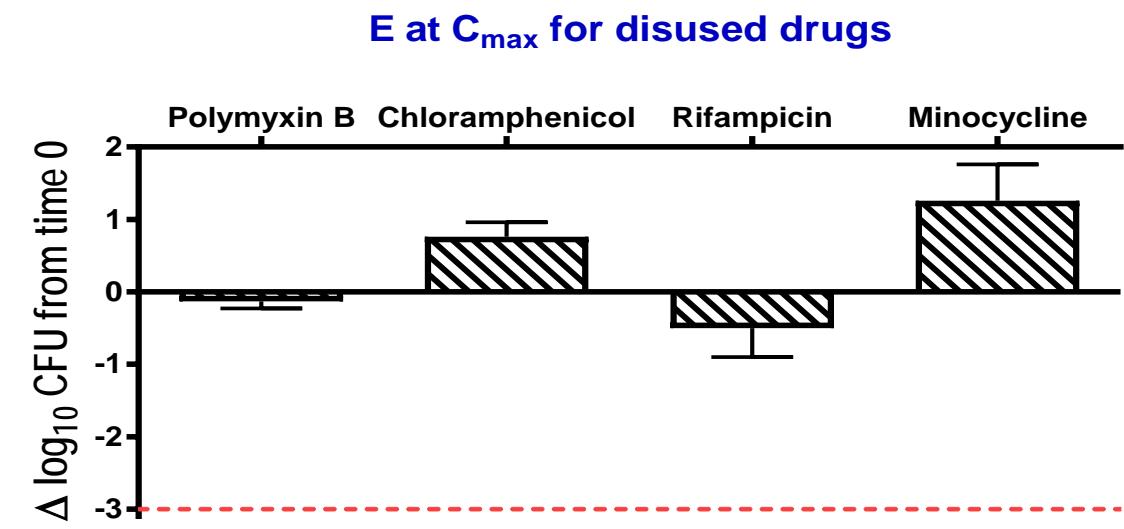
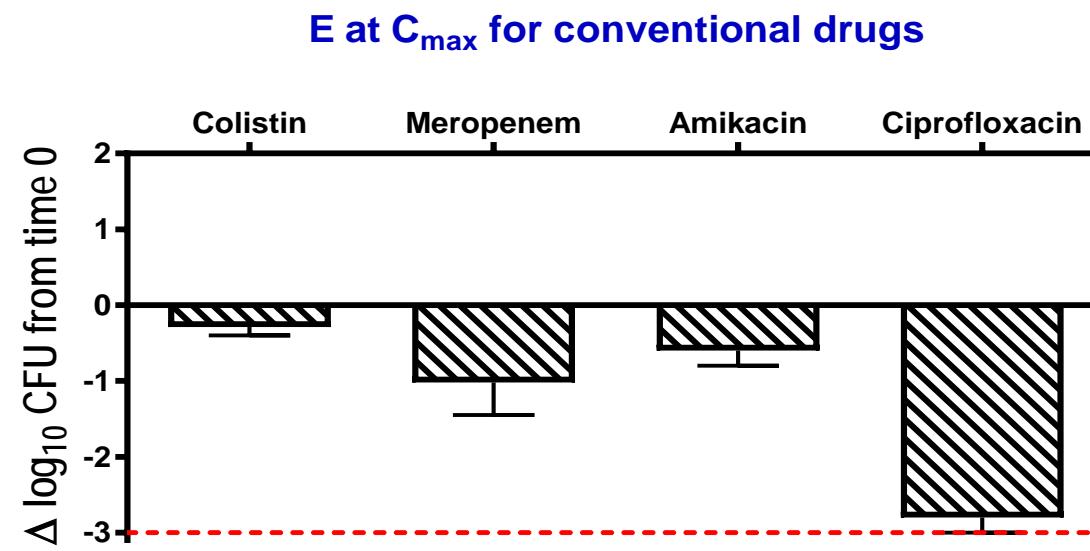
## Pharmacological comparison – Maximal efficacy:



Intracellular efficacy low  
(<< extracellular efficacy)

# Summary of antibiotic PD parameters against intracellular *P. aeruginosa*

## Clinically-oriented comparison – Efficacy at $C_{max}$ :



Neglected, disused antibiotics show no useful activity against intracellular *P. aeruginosa* at clinically-achievable concentrations

# Conclusions

- Relative potency is close to the MIC (whatever the antibiotic cell accumulation)
- Activity as determined in broth can to some extent predict intracellular potency (~ MIC) but not intracellular efficacy.
- Both old conventional and neglected and disused antibiotics are poorly effective against intracellular *P. aeruginosa*, regardless their mode of action.
- Among the antibiotics tested, only ciprofloxacin reached a bactericidal effect against intracellular *P. aeruginosa* at clinically-achievable concentrations.
- Neglected and disused antibiotics cannot be used alone to act against intracellular forms of [MDR] pathogens.

Still room for  
better ideas...



# Acknowledgments

## The other teams of our consortium



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