In vitro pharmacodynamic models for the study of antibiotic activity against bacterial biofilms

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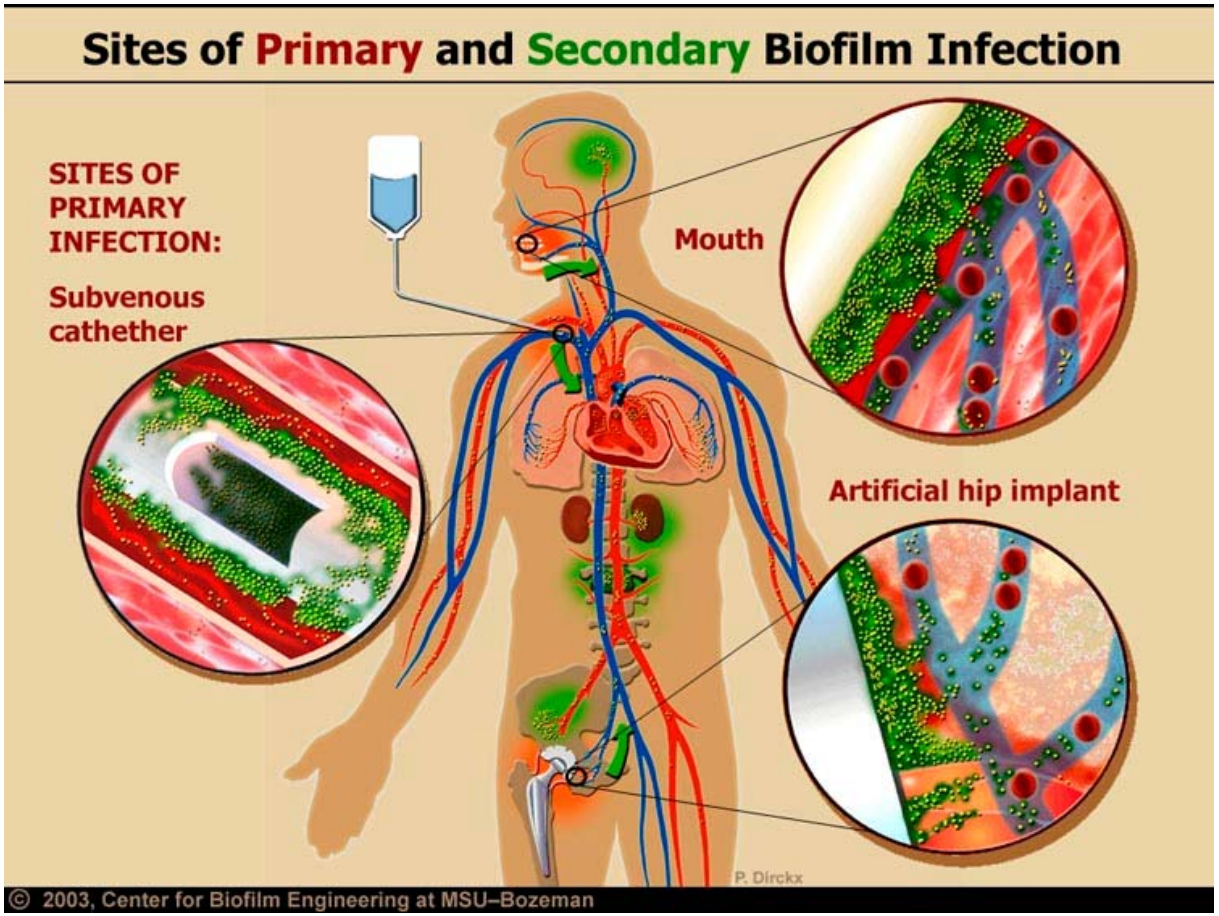
Université catholique de Louvain, Brussels, Belgium

Biofilms in human infections

Biofilms are associated to 65[a]-80[b] % of human infections and can colonize virtually all organs …



ear
nose
throat
mouth & teeth
eye
lung
heart
kidney
gall bladder
pancreas
nervous system
skin
bone
***
implanted medical devices

[a]CDC 1999; [b]Lewis et al, Nat Rev Microbiol. 2007; 5:48-56

Antibiotics and biofilms in clinical practice

Curr Opin Otolaryngol Head Neck Surg. 2013 Nov 22. [Epub ahead of print]

When and how should we treat biofilms in chronic sinusitis?

Jain R, Douglas R.

Journal of Endodontics

Volume 39, Issue 5, May 2013, Pages 712–718

Case Report/Clinical Techniques

Exuberant Biofilm Infection in a Lateral Canal as the Cause of Short-term Endodontic Treatment Failure: Report of a Case

Domenico Ricucci, MD, DDS*, Simona Loghin, DDS*, José F. Siqueira Jr., DDS, MSc, PhD†

AAC Journals.ASM.org

March 2013 Volume 57 Number 3 Antimicrobial Agents and Chemotherapy p. 1447–1454

Reduced Vancomycin Susceptibility in an *In Vitro* Catheter-Related Biofilm Model Correlates with Poor Therapeutic Outcomes in Experimental Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus*

Wessam Abdelhady,[a] Arnold S. Bayer,[a,b] Kati Seidl,[c] Cynthia C. Nast,[b,d] Megan R. Kiedrowski,[e] Alexander R. Horswill,[e] Michael R. Yeaman,[a,b] Yan Q. Xiong[a,b]

Int J Artif Organs 2011; 34(9): 737-751

REVIEW

Antibiotic-induced biofilm formation

Jeffrey B. Kaplan

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Contents lists available at ScienceDirect

Microbial Pathogenesis

Microbial Pathogenesis 51 (2011) 58–68

journal homepage: www.elsevier.com/locate/micpath

Biofilm formation or internalization into epithelial cells enable *Streptococcus pyogenes* to evade antibiotic eradication in patients with pharyngitis

Taiji Ogawa[a,e], Yutaka Terao[a], Hisashi Okuni[b], Keiko Ninomiya[c], Hiroshi Sakata[d], Yoshinobu Maeda[e], Shigetada Kawabata[a,*]

Vol. 41, No. 9

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2003, p. 4043–4048

0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.9.4043–4048.2003

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Biofilm Formation by Group A Streptococci: Is There a Relationship with Treatment Failure?

Joslyn Conley,[1] Merle E. Olson,[2] Linda S. Cook,[1] Howard Ceri,[3] Van Phan,[3] and H. Dele Davies[1,2,4]*

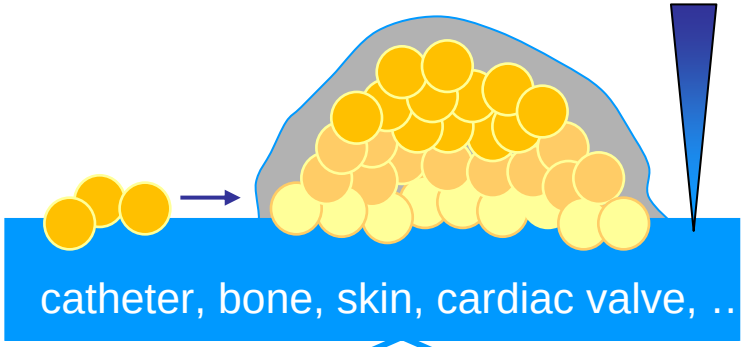
Pathog Dis. 2013 Nov;69(2):142-8. doi: 10.1111/2049-632X.12100. Epub 2013 Oct 7.

The presence of antibiotic-resistant nosocomial pathogens in endotracheal tube biofilms and corresponding surveillance cultures.

Vandecandelaere I, Matthijs N, Nelis HJ, Depuydt P, Coenye T.

→ Treatment failure is not rare…

PK/PD parameters in biofilms

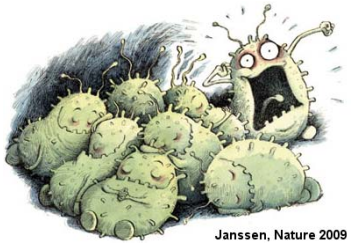


pharmacokinetics

- diffusibility through the matrix
- access to bacteria
- efflux out of bacteria

pharmacodynamics

- bacterial responsiveness (metabolic activity of bacteria)
- antibiotic expression of activity (local environment [O_2, pH, ..])



Main pathogens in biofilm-related diseases

Major pathogens involved in biofilm-associated disease

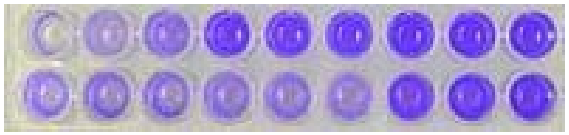
Bacterial species	Biofilm infection
Escherichia coli	Acute and recurrent urinary tract infection, catheter-associated urinary tract infection, biliary tract infection
Pseudomonas aeruginosa	Cystic fibrosis lung infection, chronic wound infection, catheter-associated urinary tract infection, chronic rhinosinusitis, chronic otitis media, contact lens-related keratitis
Staphylococcus aureus	Chronic osteomyelitis, chronic rhinosinusitis, endocarditis, chronic otitis media, orthopaedic implants
Staphylococcus epidermidis	Central venous catheter, orthopaedic implants, chronic osteomyelitis
Streptococcus pneumoniae	Colonization of nasopharynx, chronic rhinosinositis, chronic otitis media, chronic obstructive pulmonary disease
Streptococcus pyogenes	Colonization of oral cavity and nasopharynx, recurrent tonsilitis

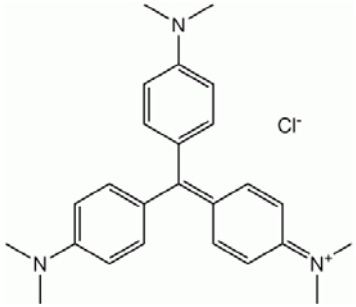
Römling & Balsalobre; J Intern Med. 2012; 272:541-61

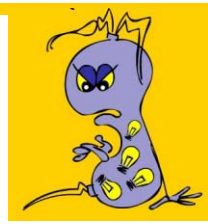
Quantifying biomass and metabolic activity in biofilms

biofilm mass

crystal violet





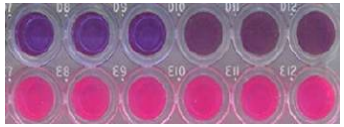


Gram(+) bacteria

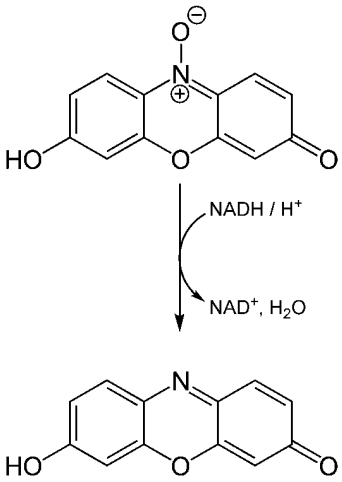
metabolic activity

Gram(-) bacteria

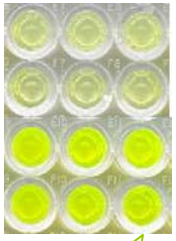
resazurin



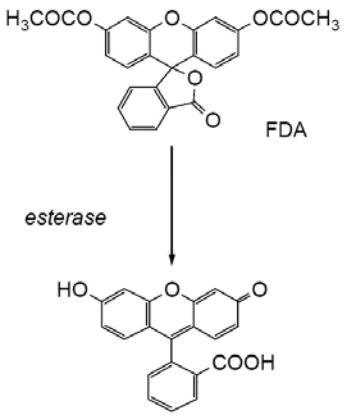
resorufin

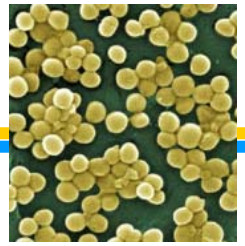


fluorescein diacetate



fluorescein

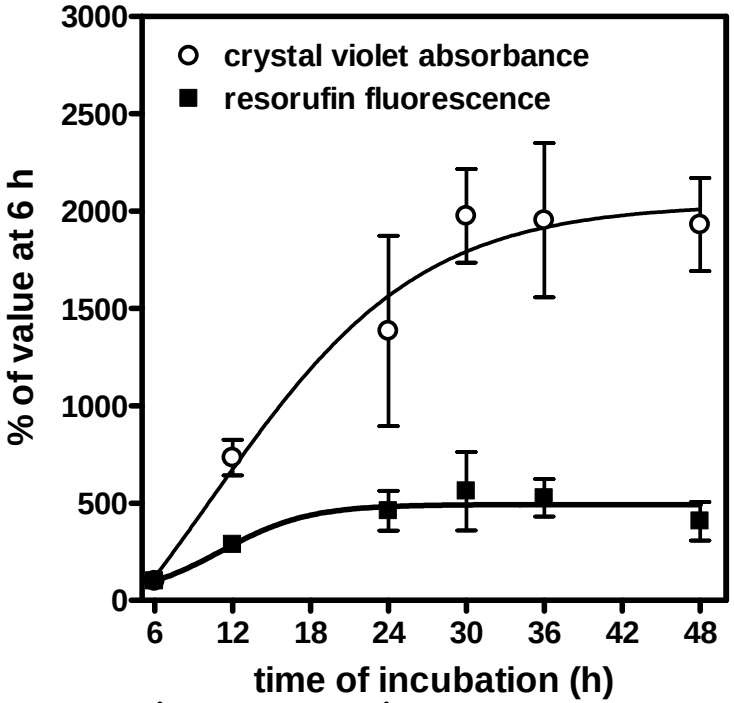




S. aureus & S. pneumoniae models

Kinetics of biofilm formation

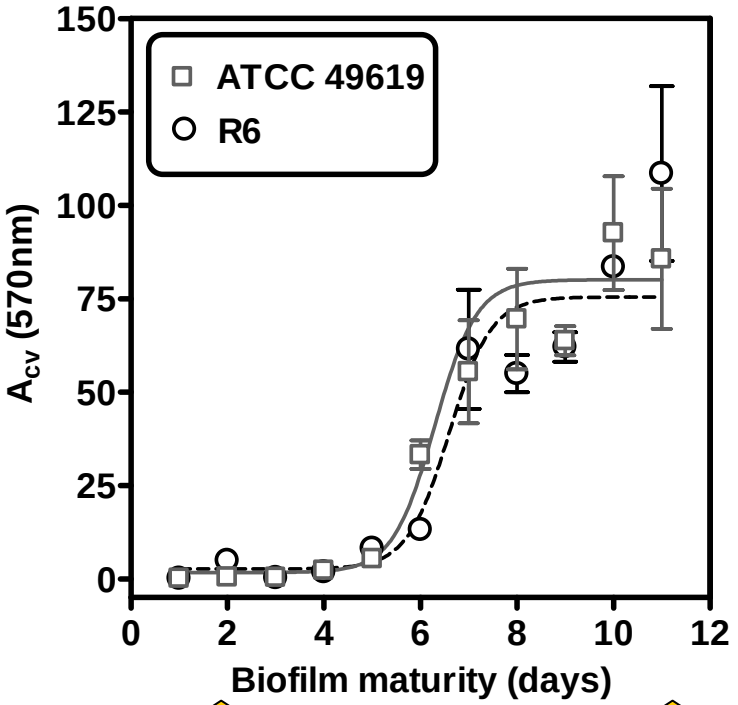
S. aureus



young biofilm

mature biofilm

S. pneumoniae

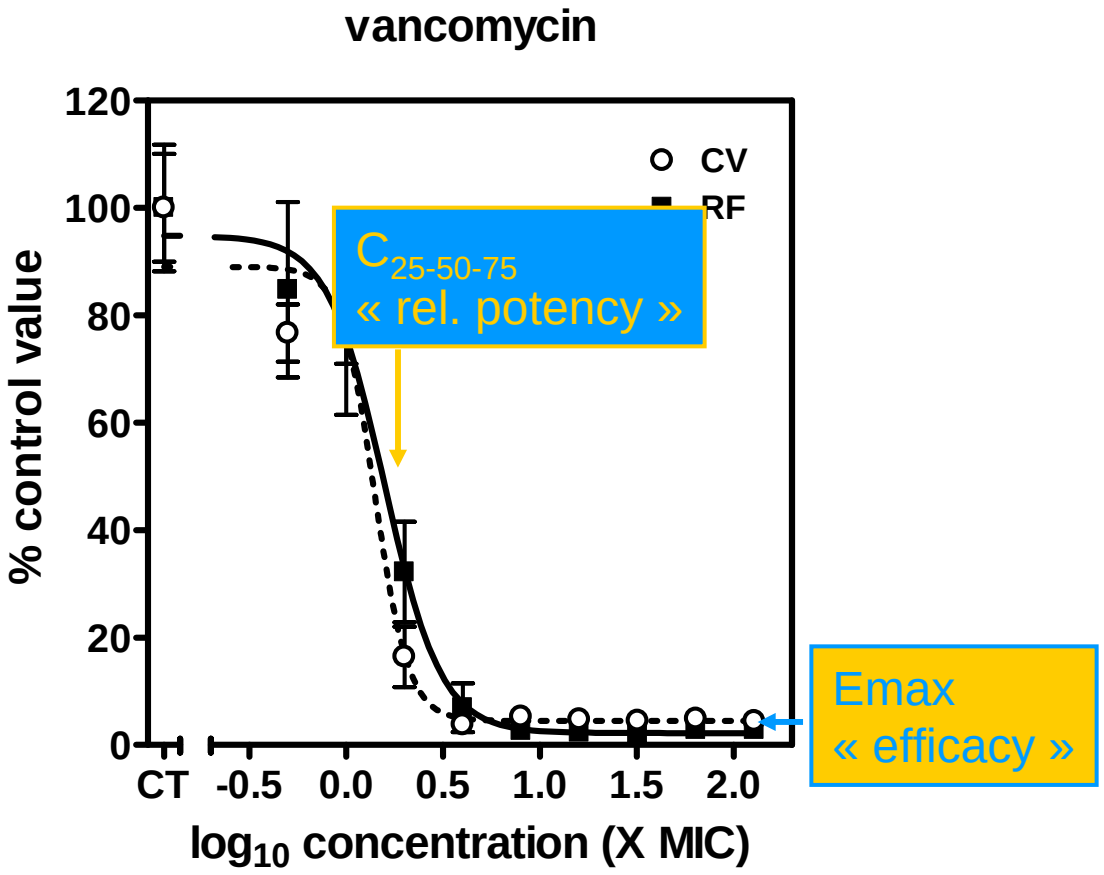


young biofilm

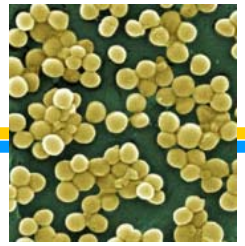
mature biofilm

Pharmacodynamic model for antibiotic activity

An example with young biofilm of *S. aureus*

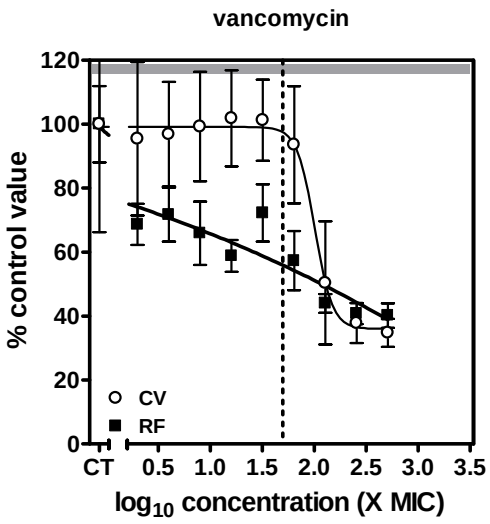


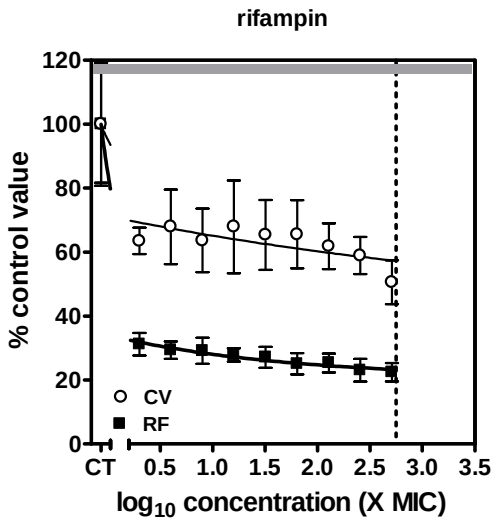
Bauer, Siala et al, Antimicrob Ag Chemother. 2013;57:2726-37

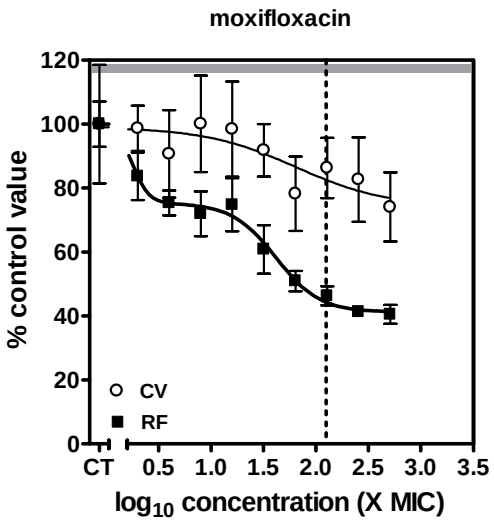


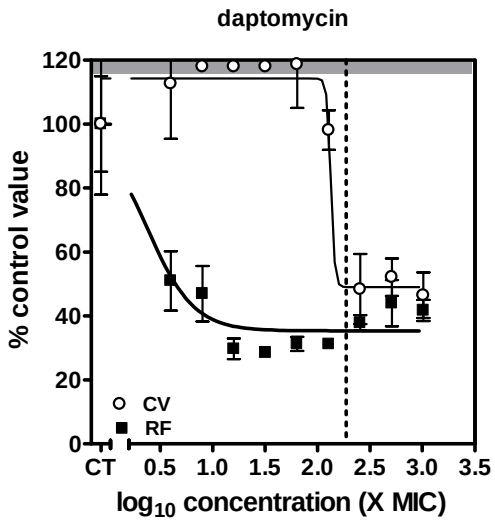
S. aureus (MRSA) mature biofilms

more effective and more potent on viability than on matrix







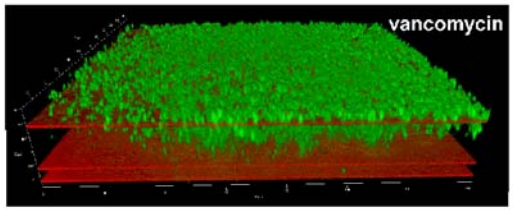


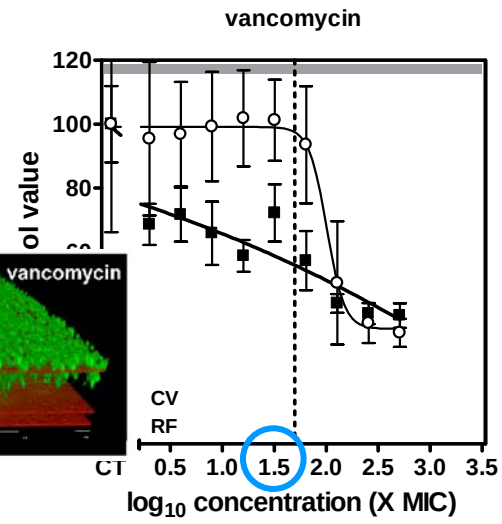
RIF and DAP more efficient at clinically achievable concentrations

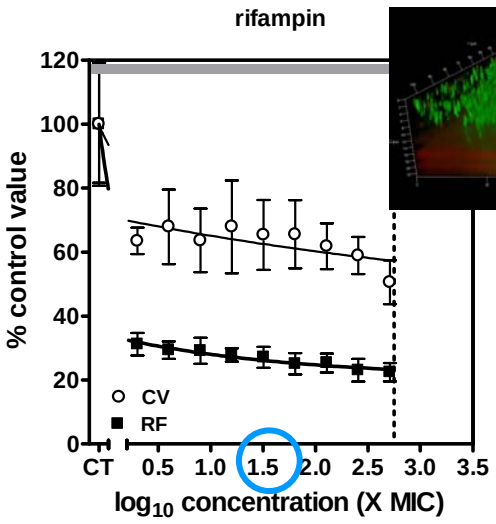
Bauer, Siala et al, Antimicrob Ag Chemother. 2013;57:2726-37

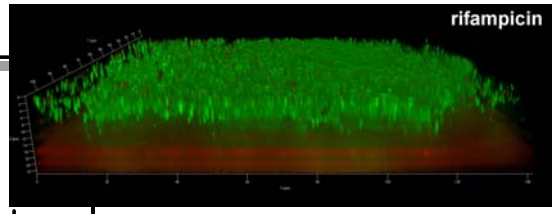
S. aureus (MRSA) mature biofilms

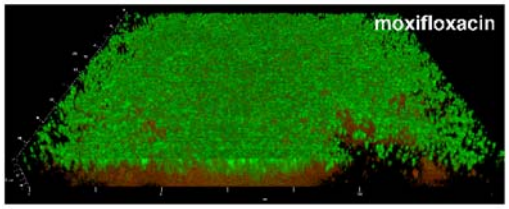
live
dead

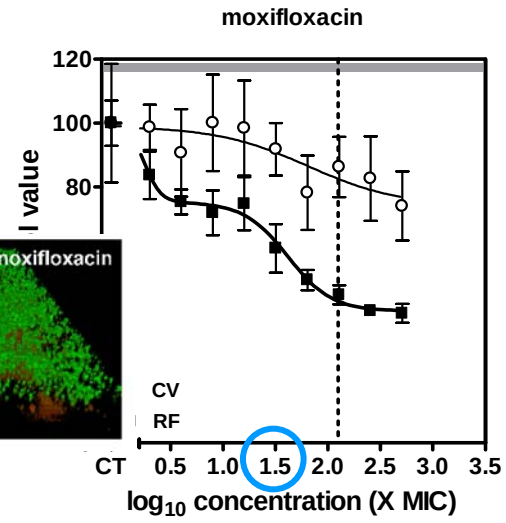


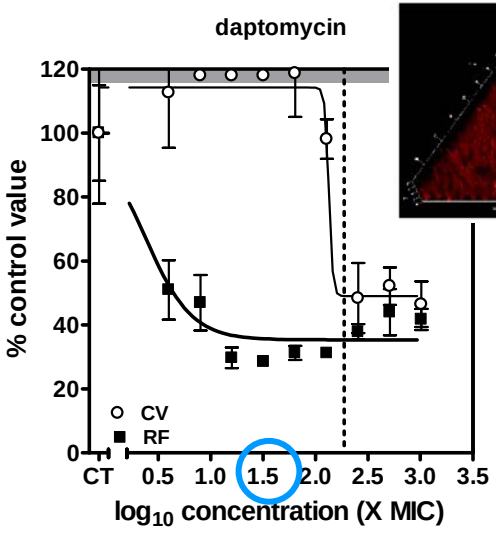


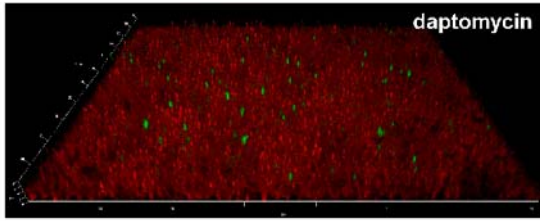






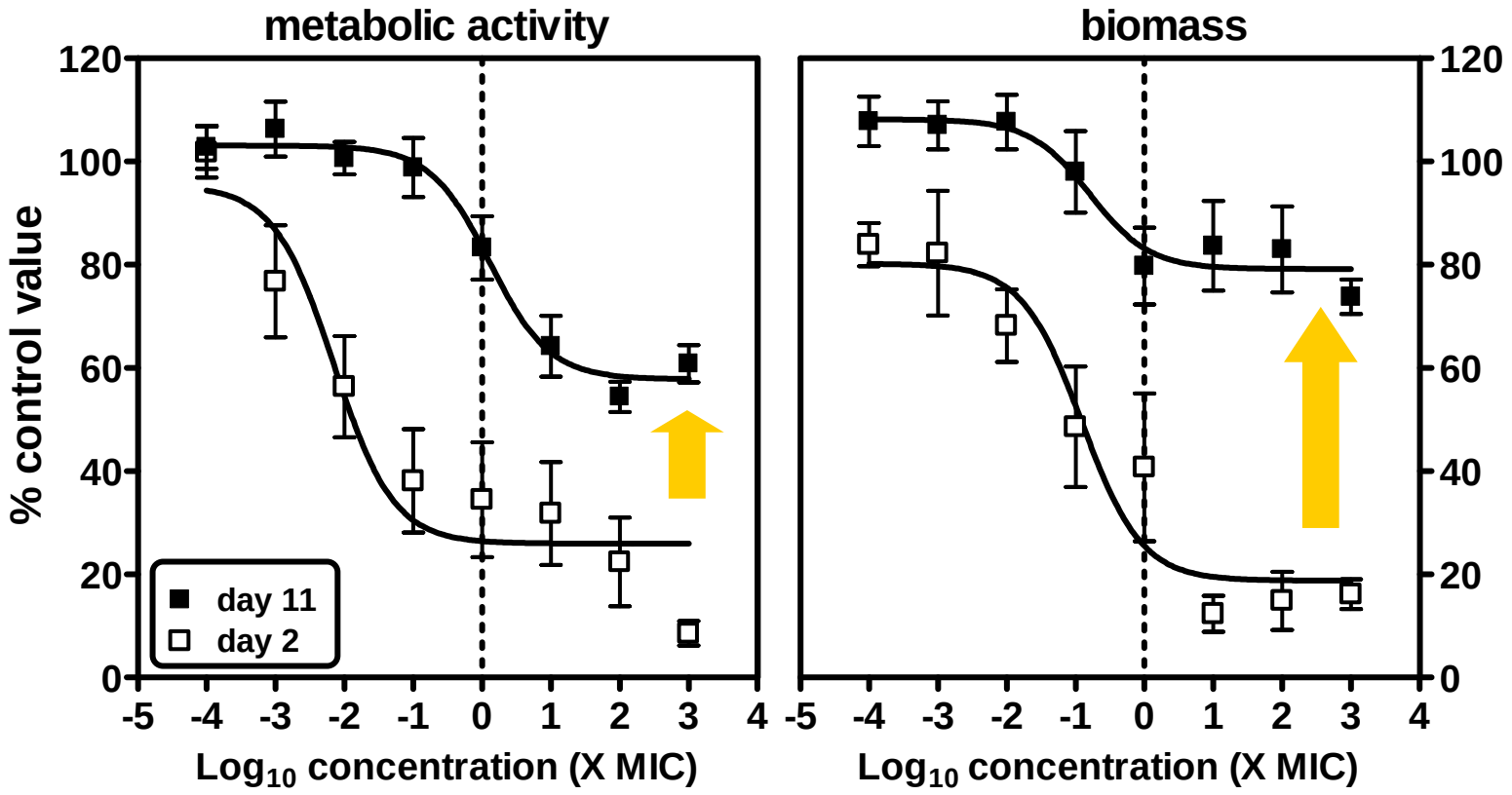






Bauer, Siala et al, Antimicrob Ag Chemother. 2013;57:2726-37

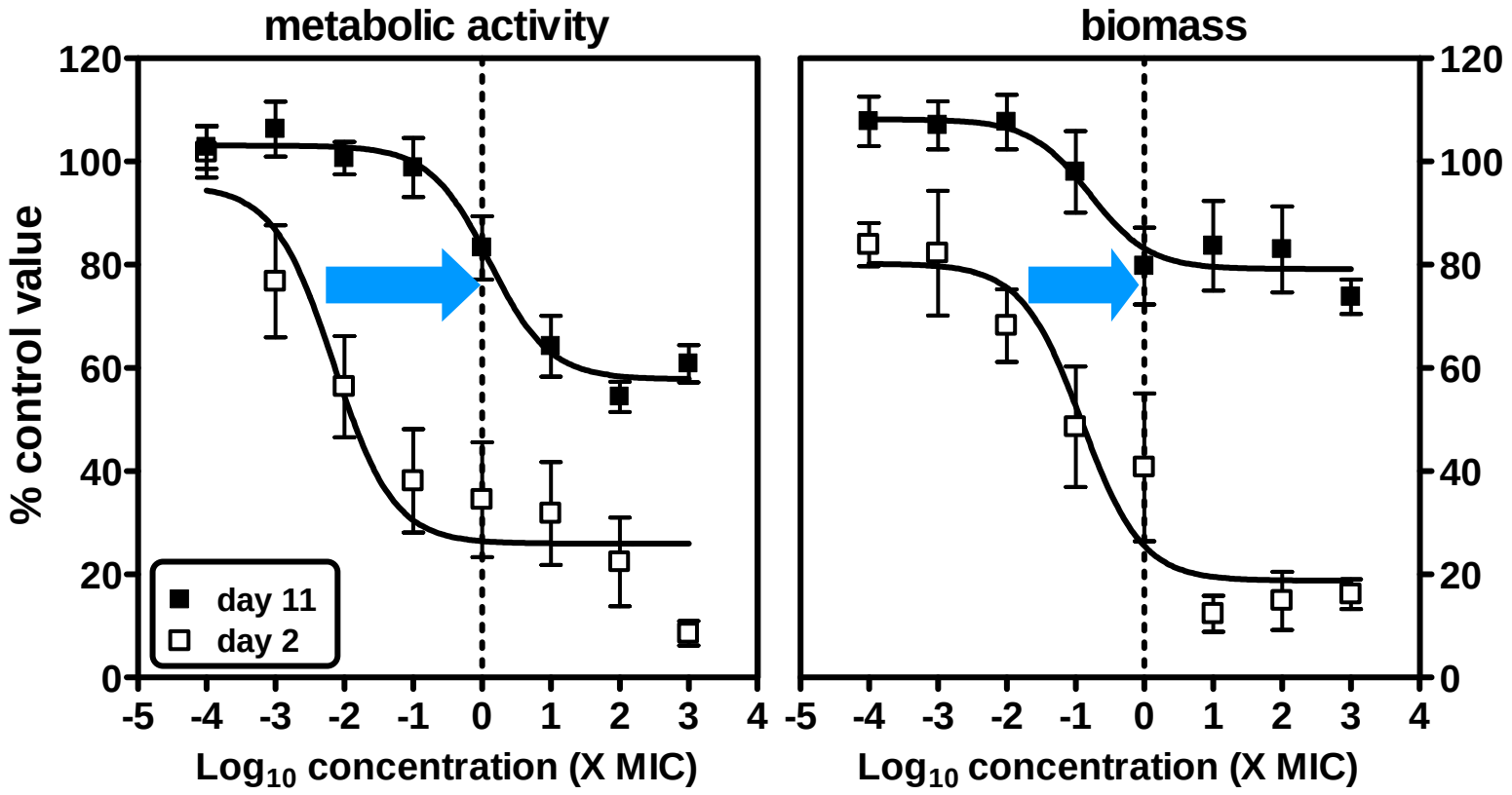
Moxifloxacin and *S. pneumoniae* biofilms



maximal efficacy ⇘ with maturity

Vandevelde et al, Antimicrob Ag Chemother. 2014; in the press

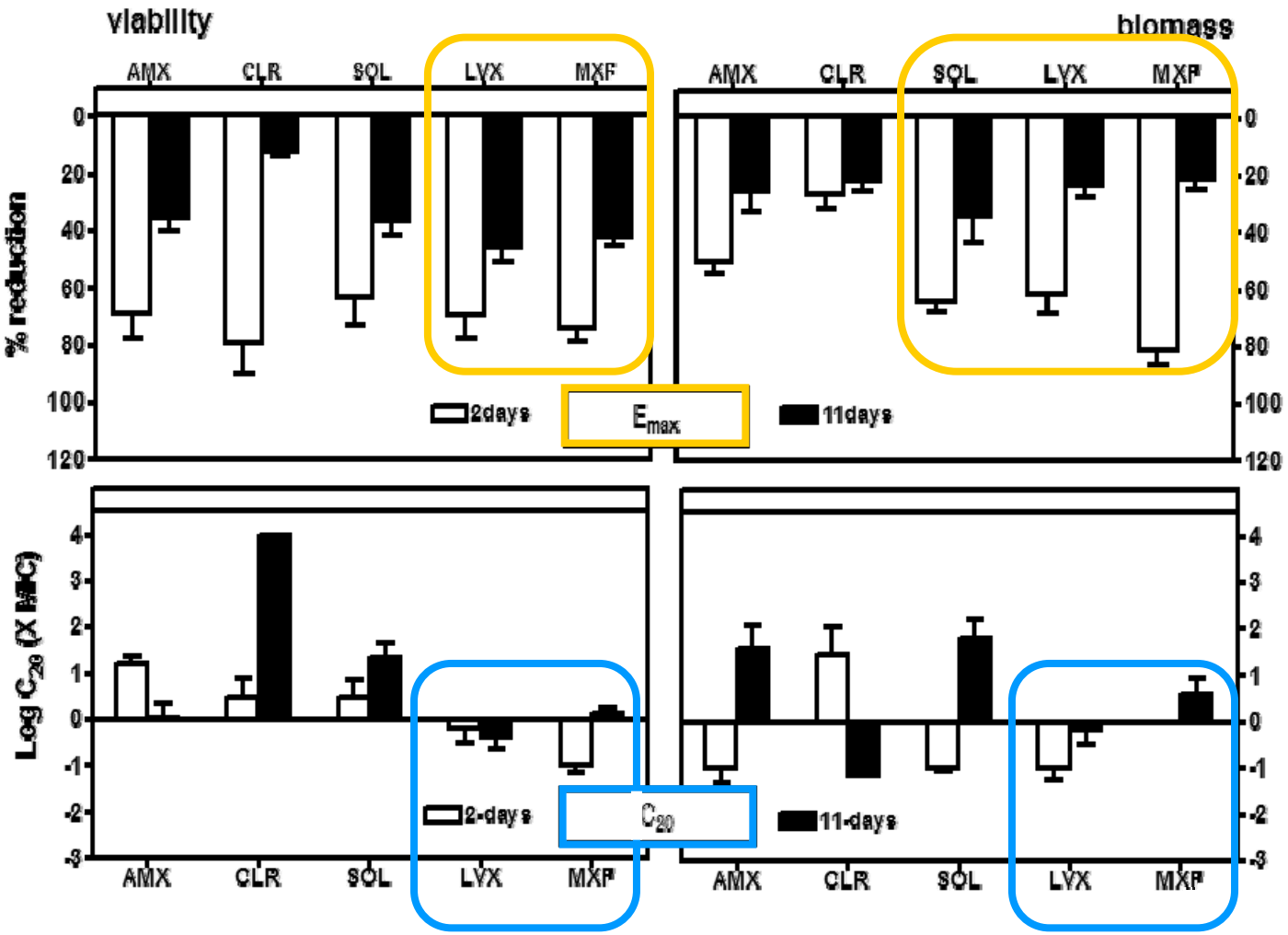
Moxifloxacin and *S. pneumoniae* biofilms



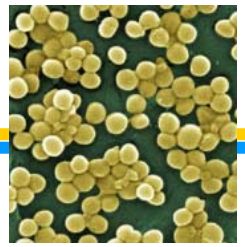
relative potency ⇘ with maturity

Vandevelde et al, Antimicrob Ag Chemother. 2014; in the press

Comparison of PD parameters



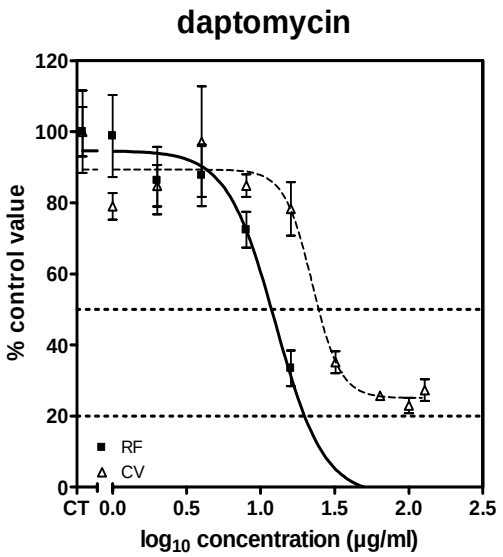
Bauer, Siala et al, Antimicrob Ag Chemother. 2013;57:2726-37

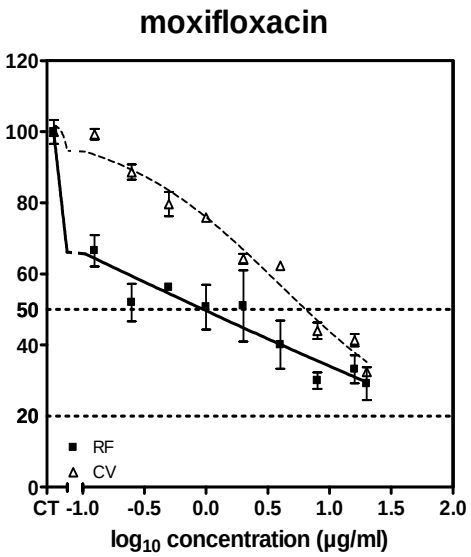


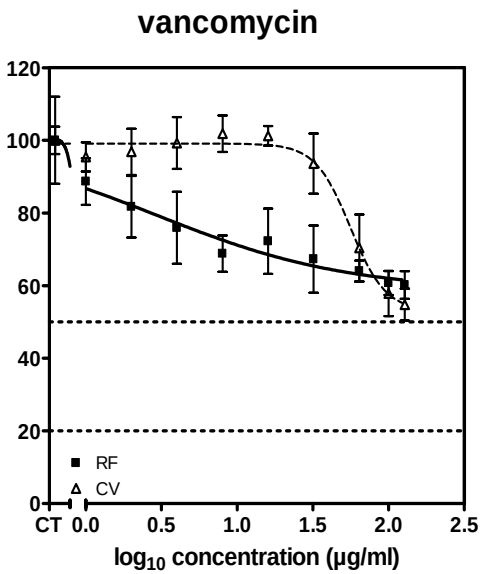
S. aureus isolates from persistent infections

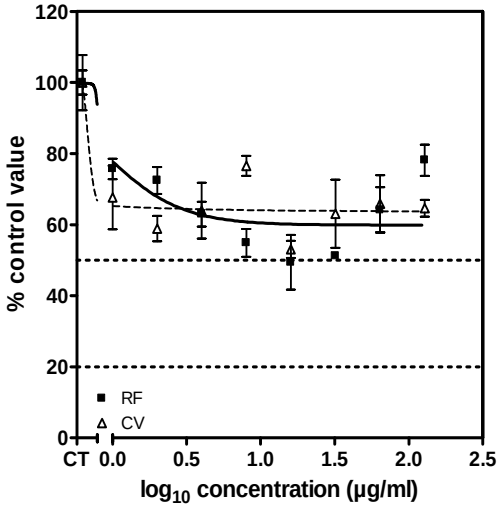
reference strain (ATCC33591)

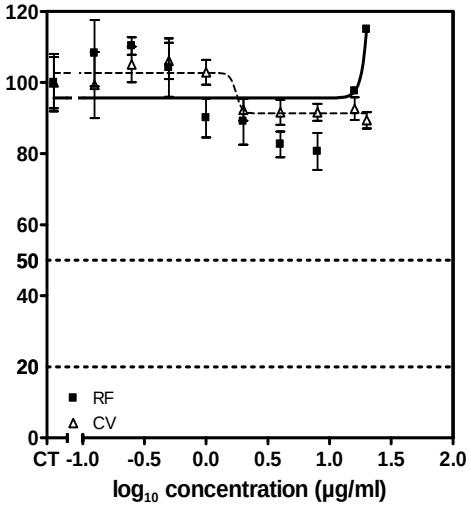
clinical isolate (2005/104)

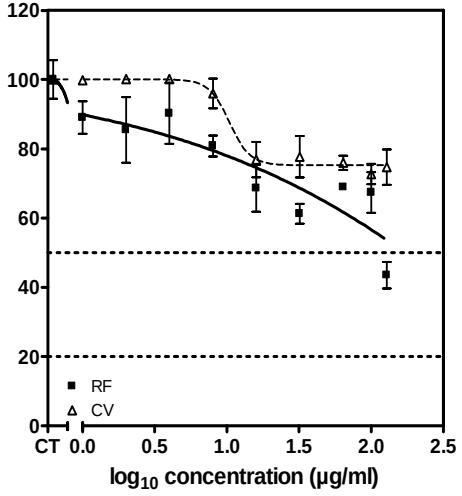




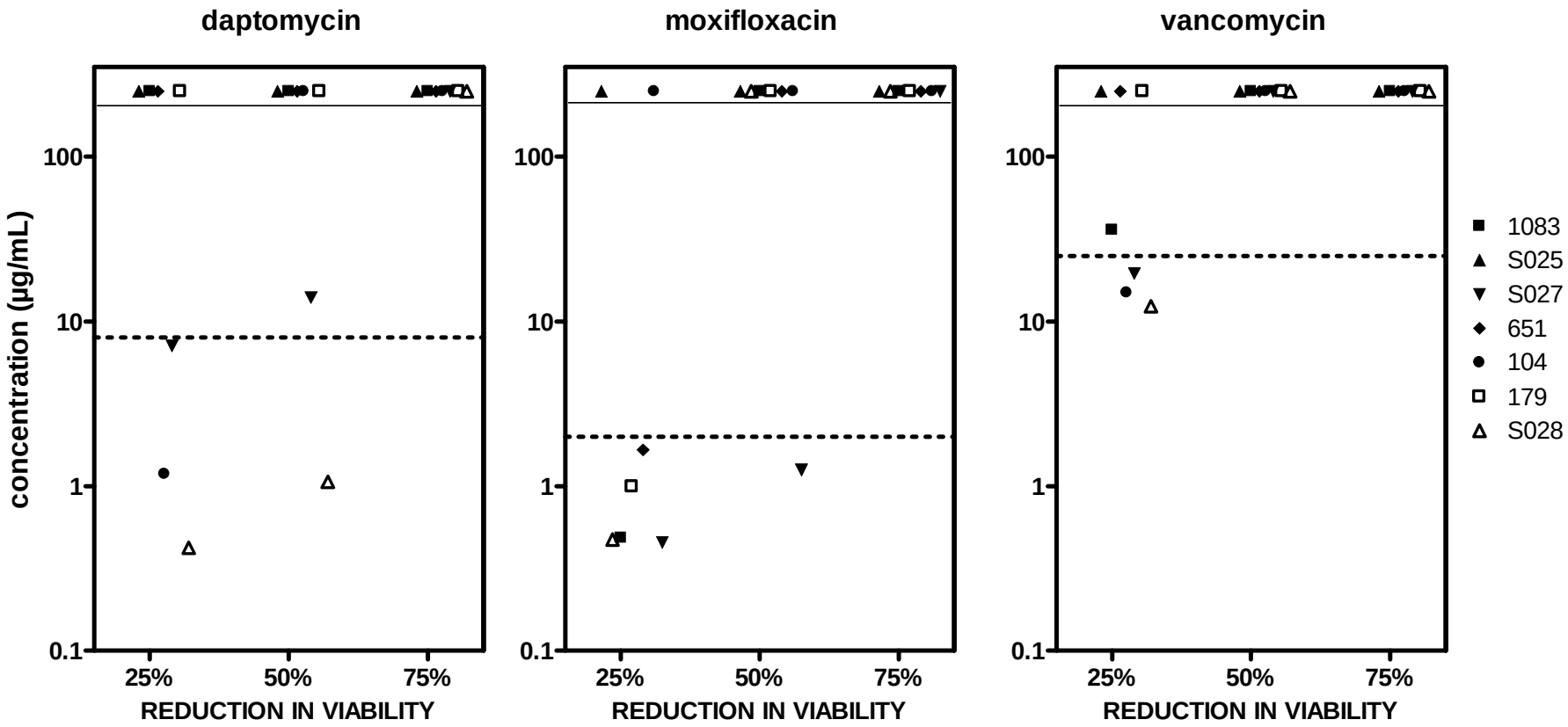






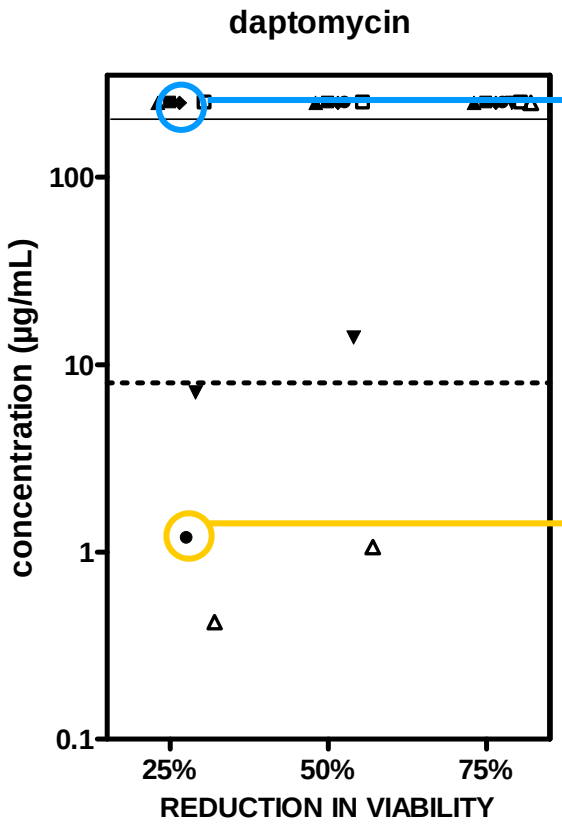


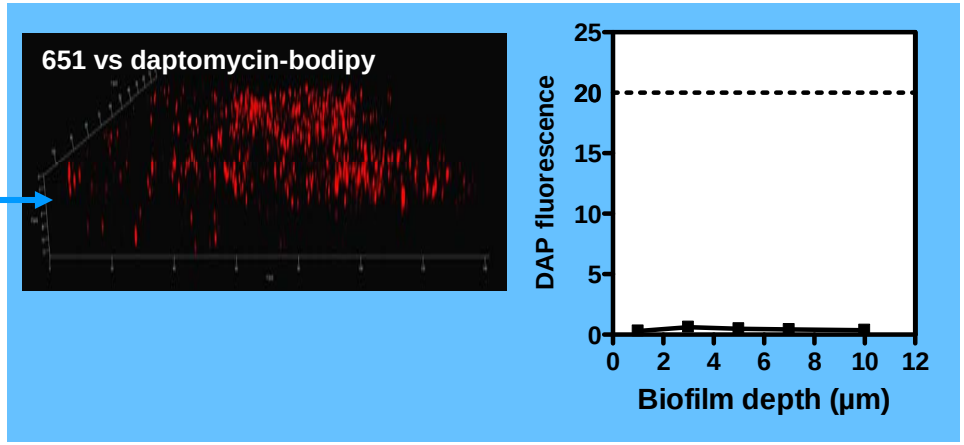
Antibiotic potency against clinical isolates of *S. aureus*

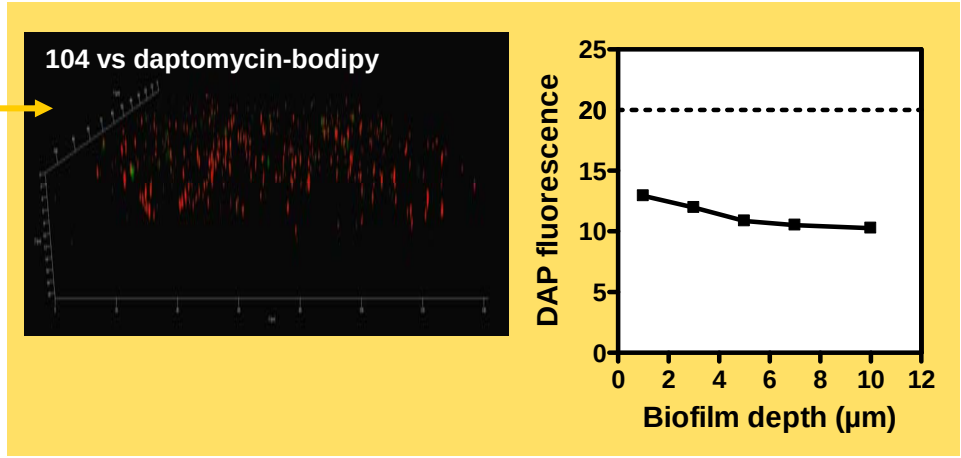


Antibiotic potency against clinical isolates of *S. aureus*

Bodipy-DAP
CTC

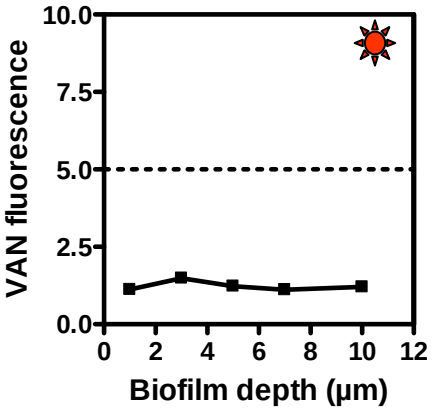


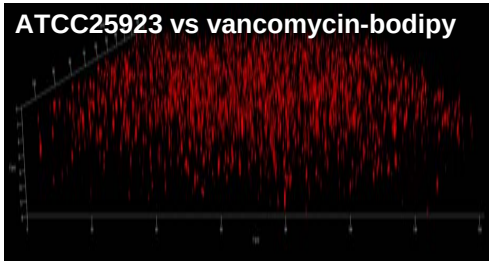


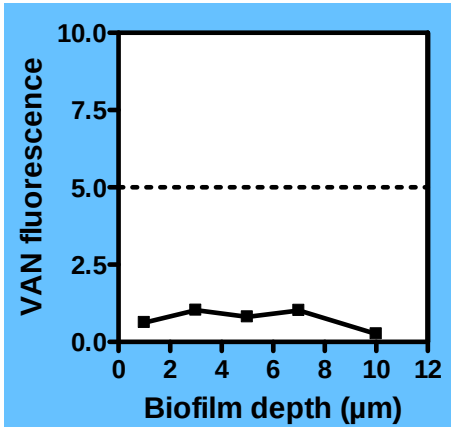


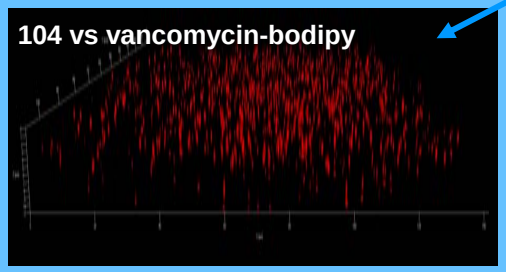
Antibiotic potency against clinical isolates of *S. aureus*

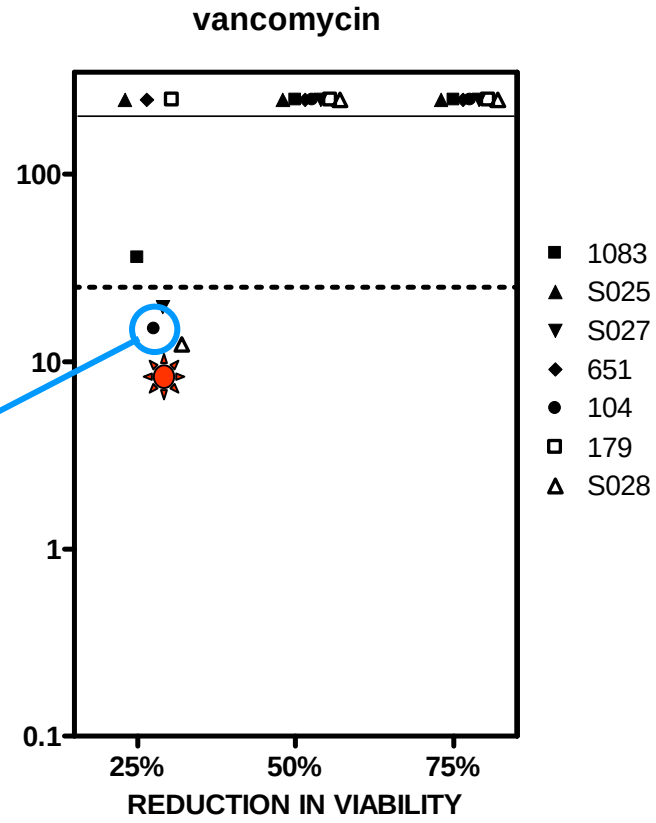
Bodipy-VAN
CTC



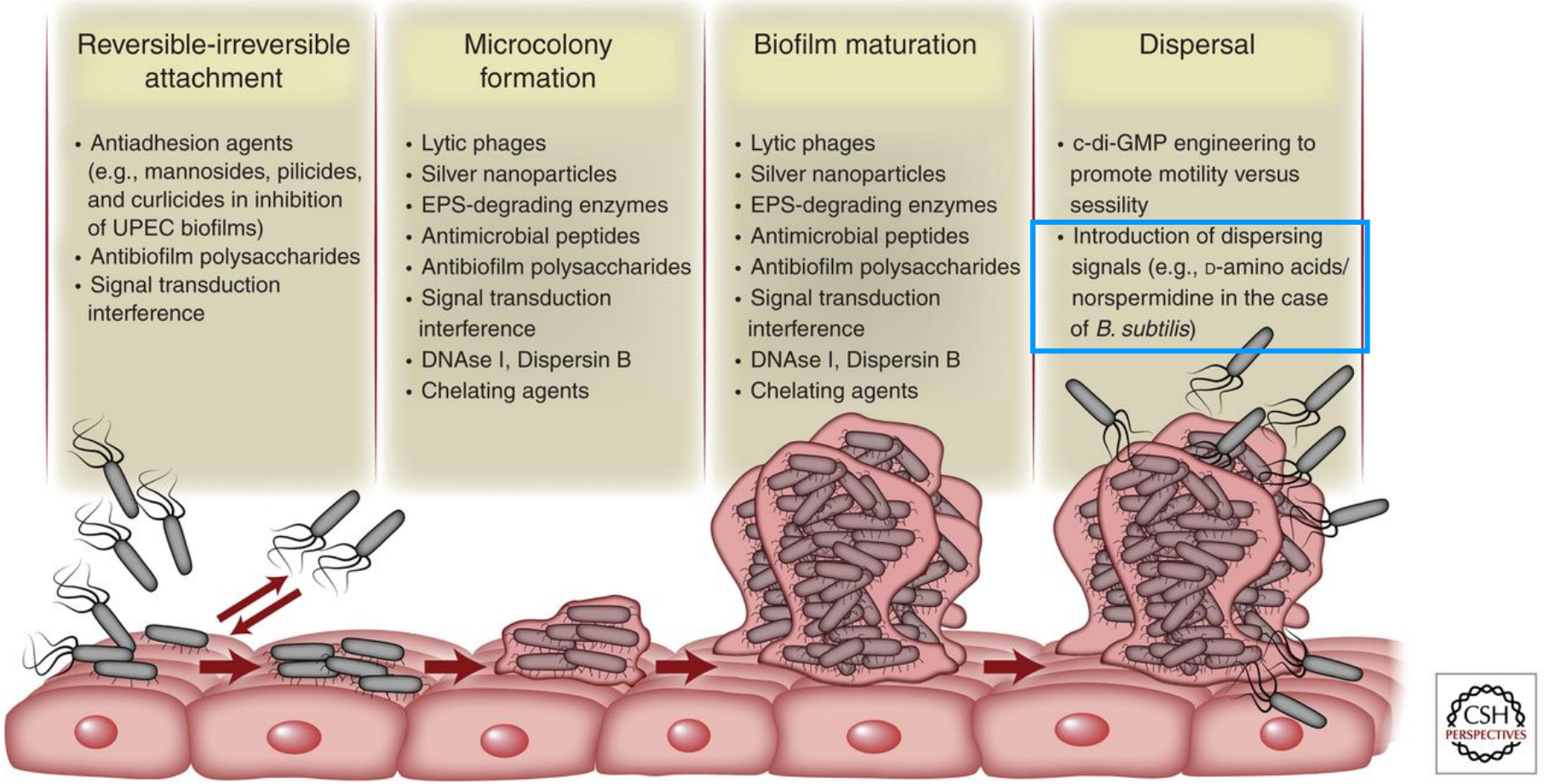






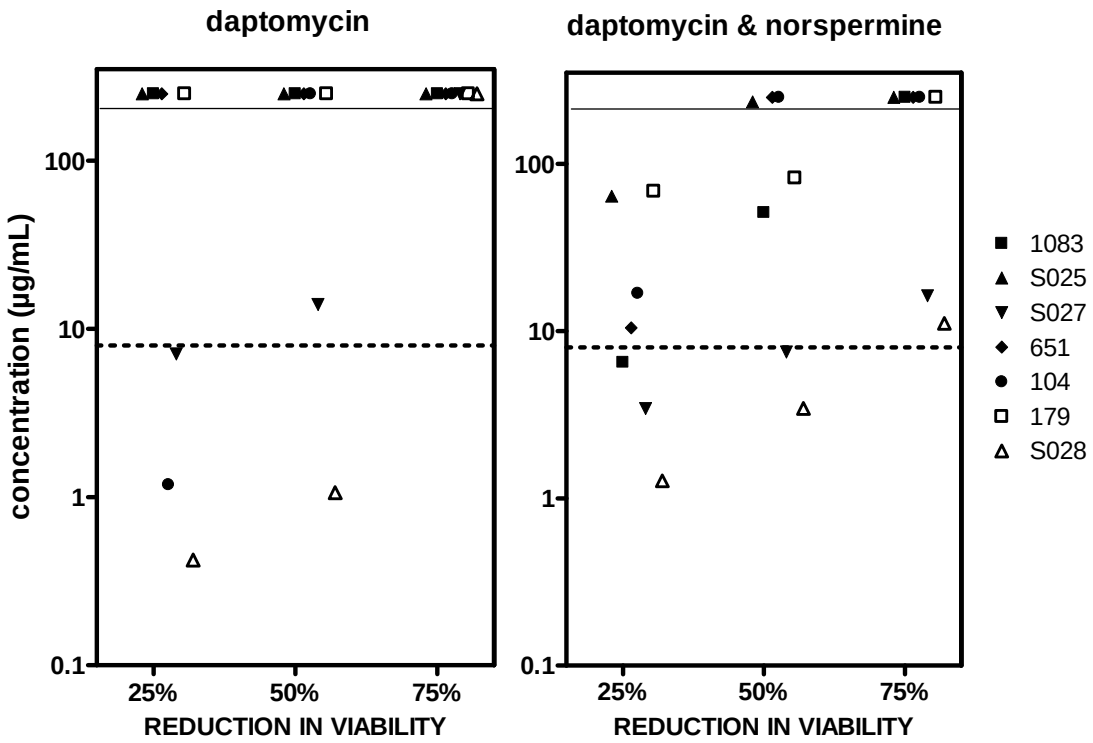


Anti-biofilm strategies ….

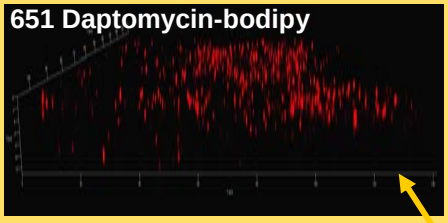


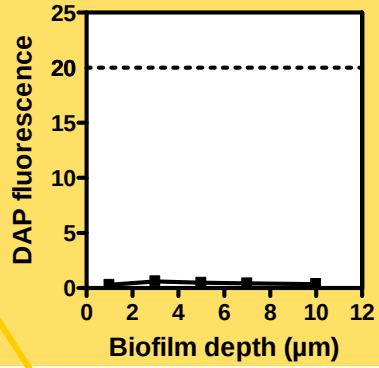
Kostakioti et al. Cold Spring Harb Perspect Med 2013;3:a010306

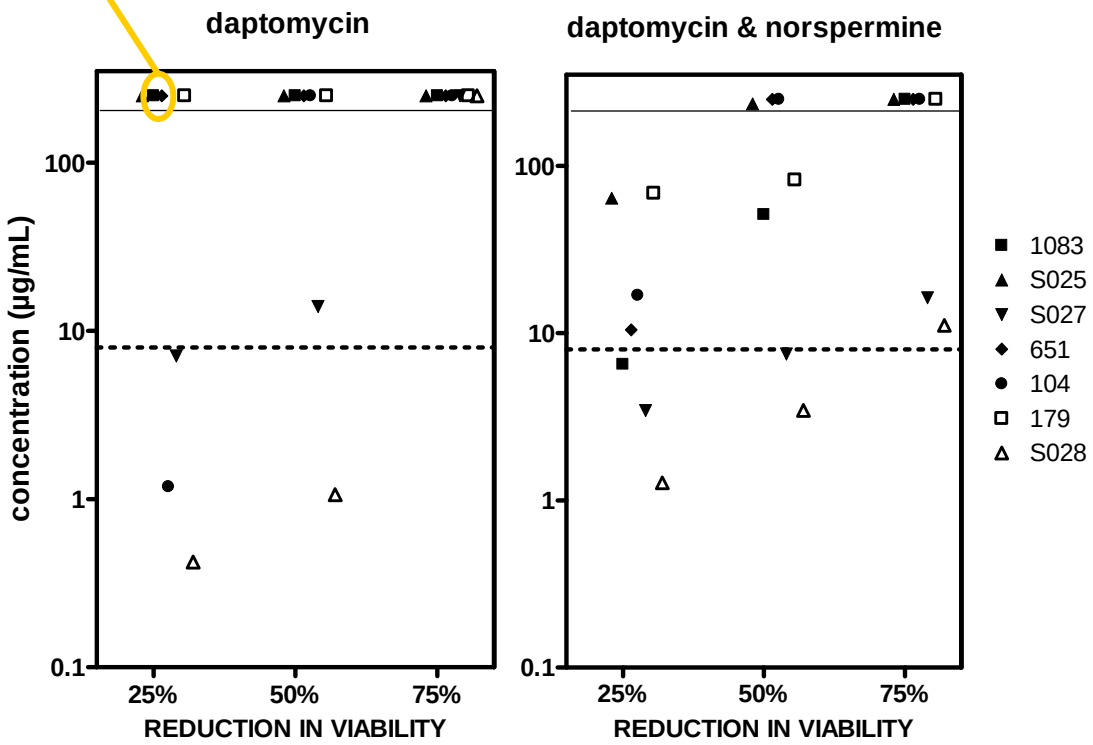
PK-related parameters: improving diffusion



PK-related parameters: improving diffusion

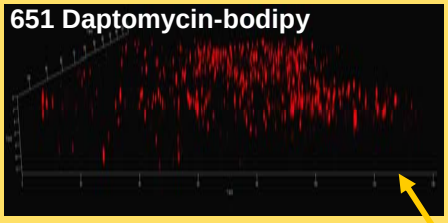


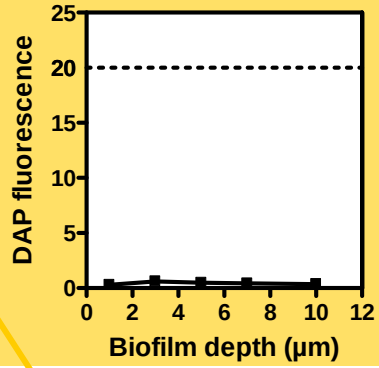


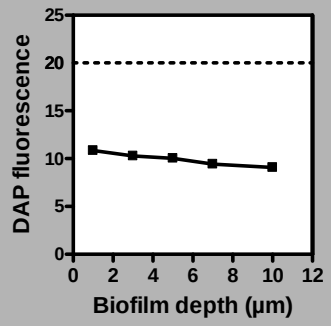


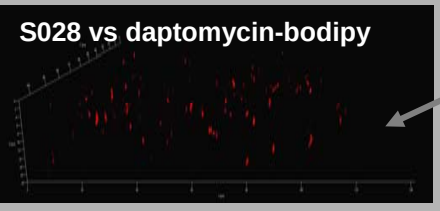
Bodipy-DAP
CTC

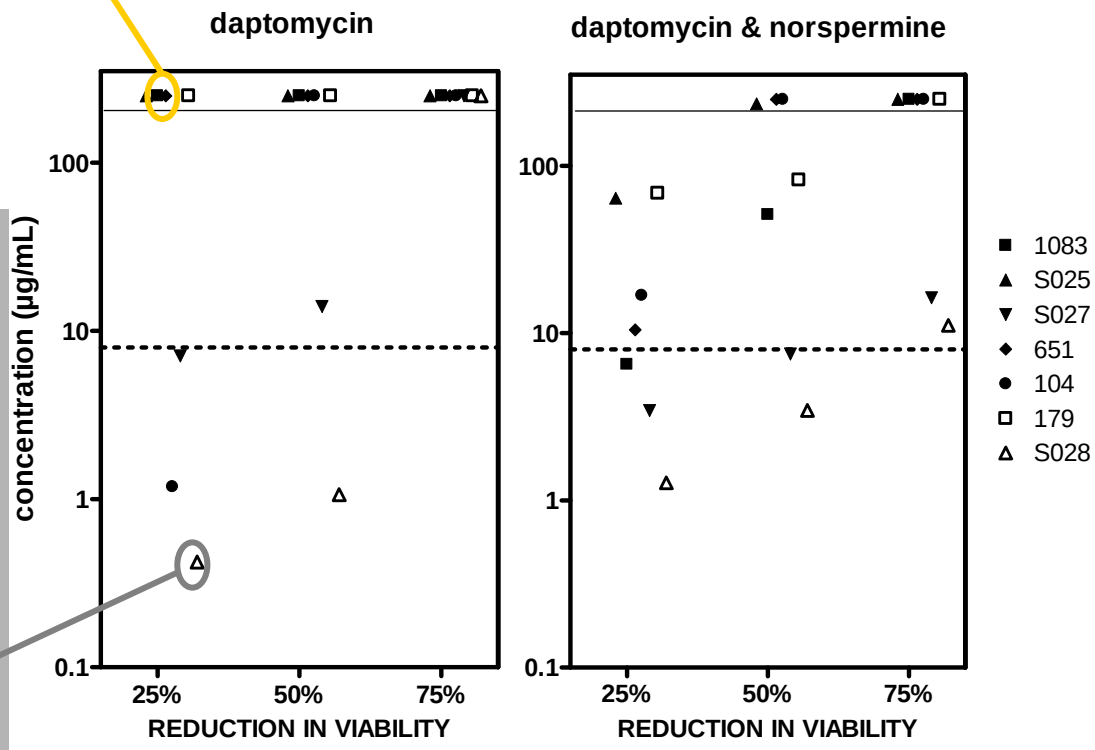
PK-related parameters: improving diffusion





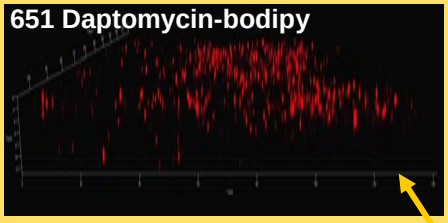


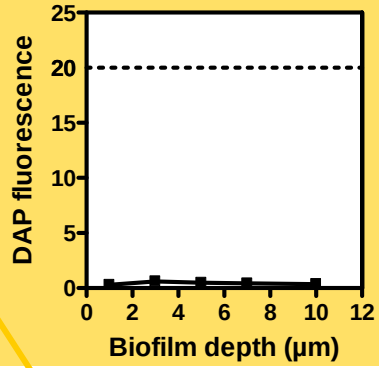


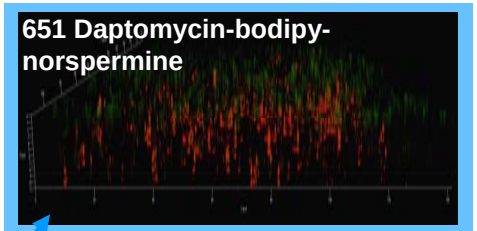


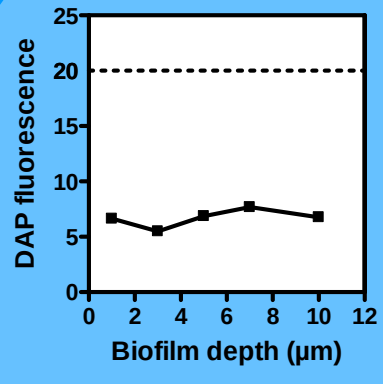
Bodipy-DAP
CTC

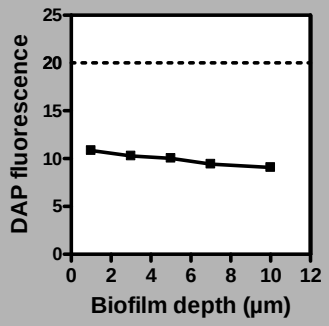
PK-related parameters: improving diffusion

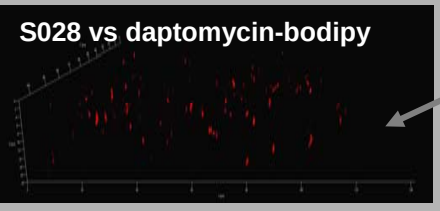


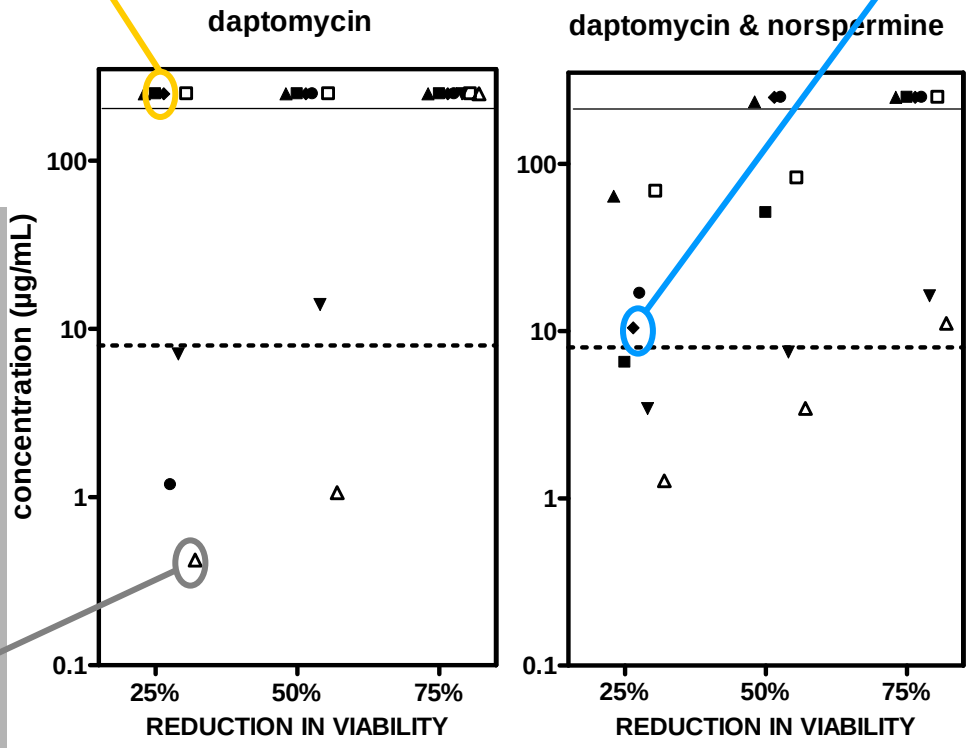






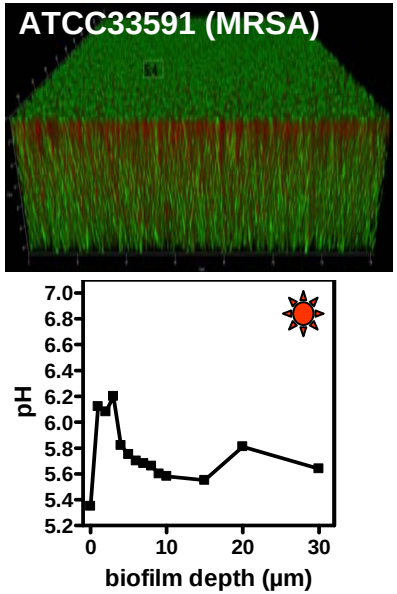


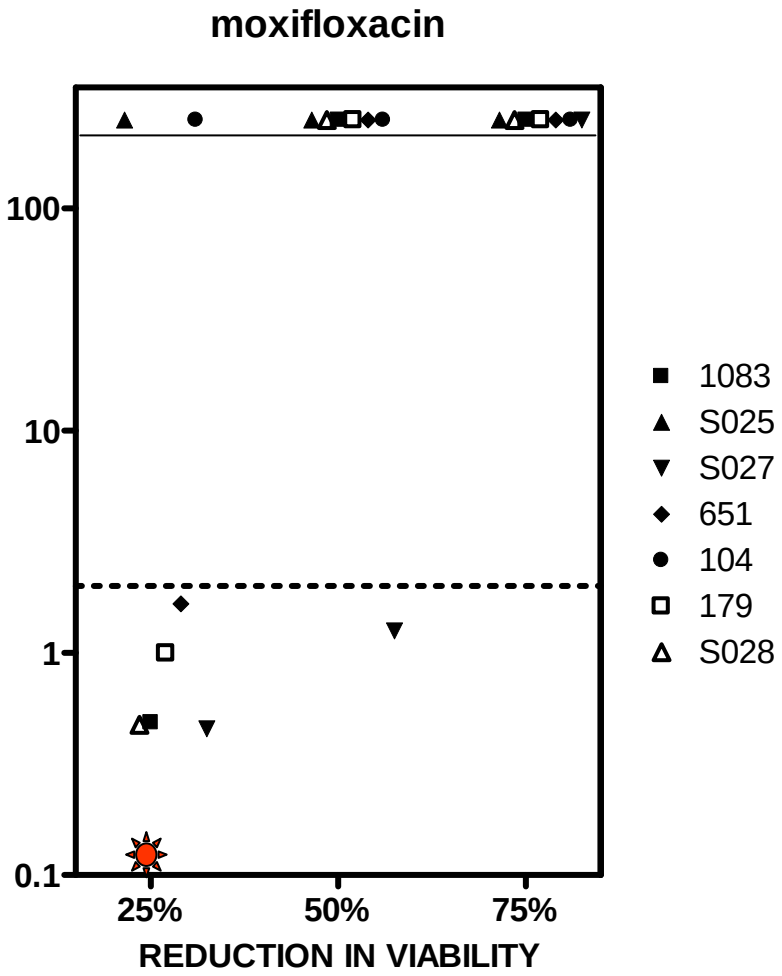




Bodipy-DAP
CTC

PD-related parameters: pH effect ?

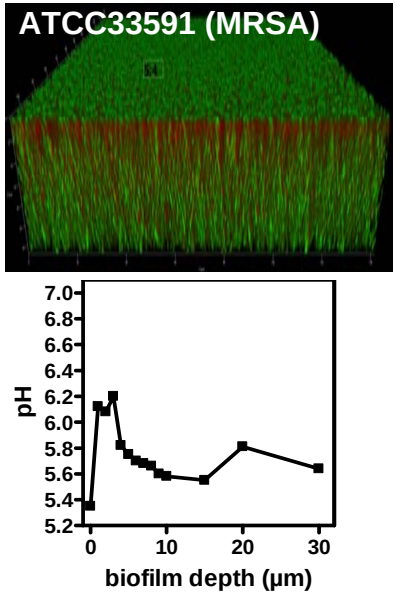


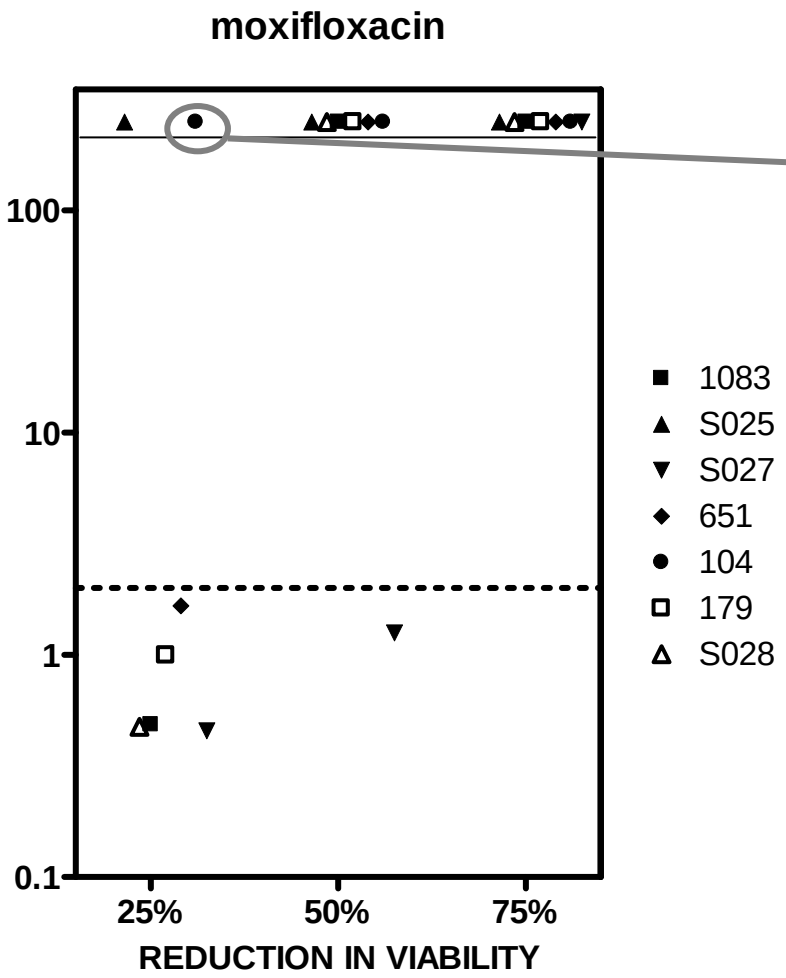


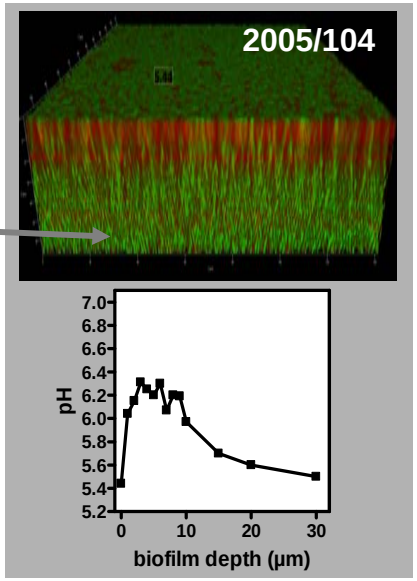
basic
acidic

Siala et al, Eurobiofilms 2013

PD-related parameters: pH effect ?



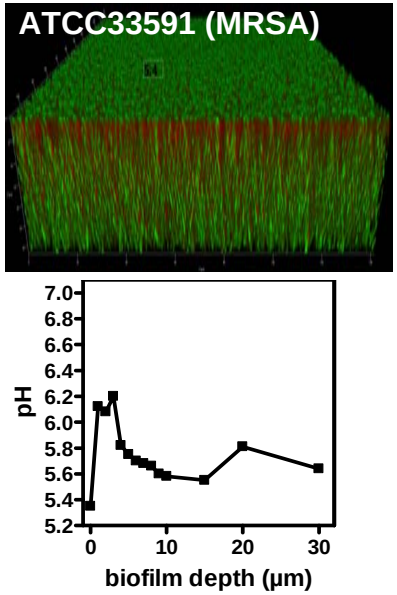


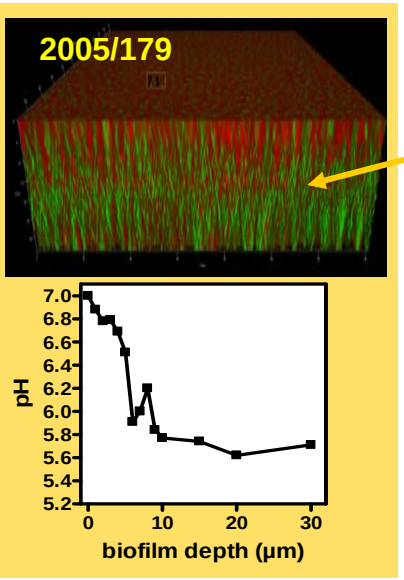


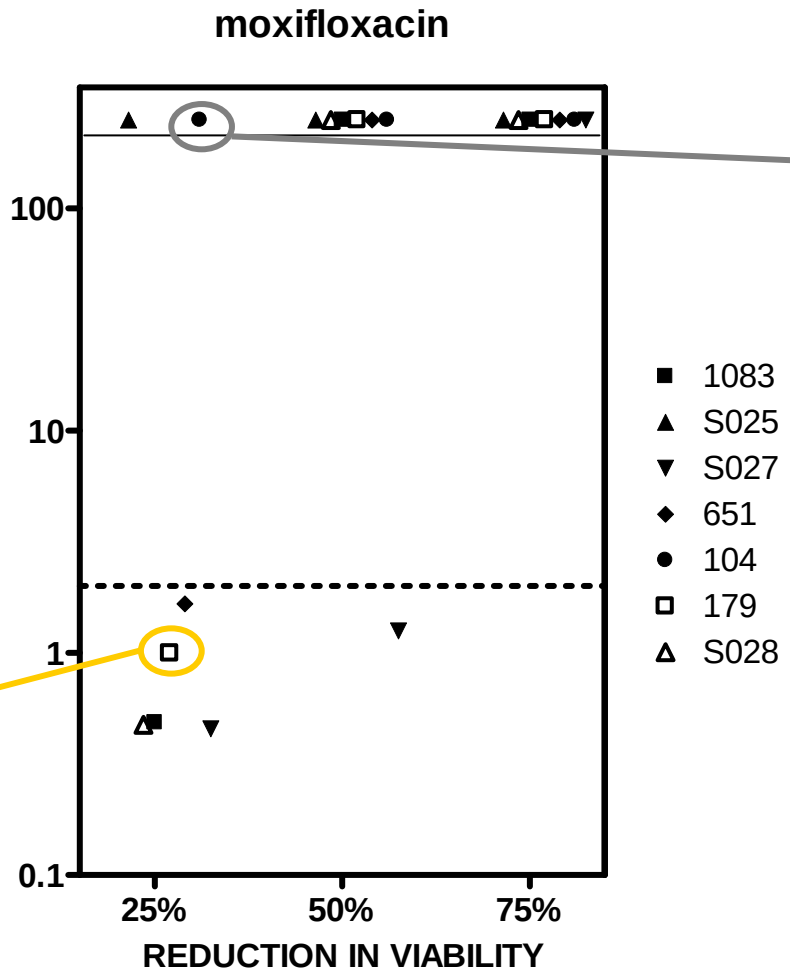
basic
acidic

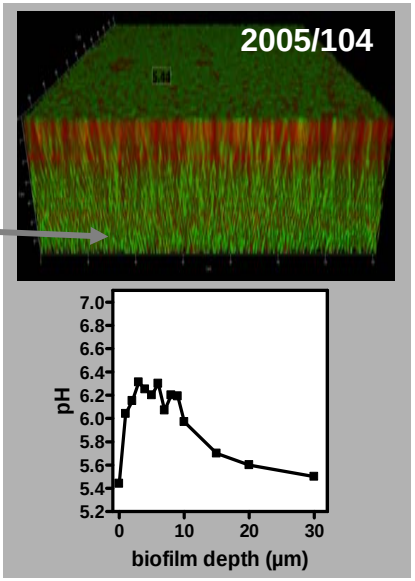
Siala et al, Eurobiofilms 2013

PD-related parameters: pH effect ?



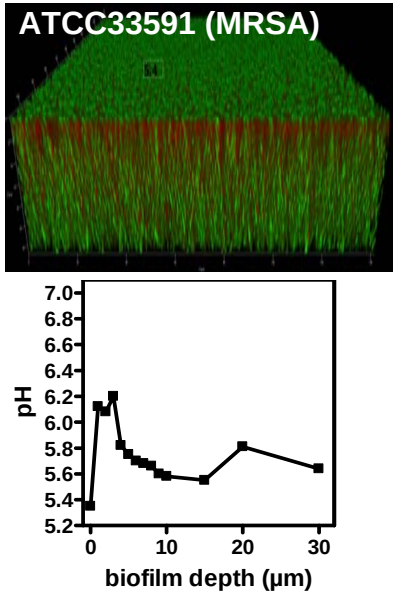


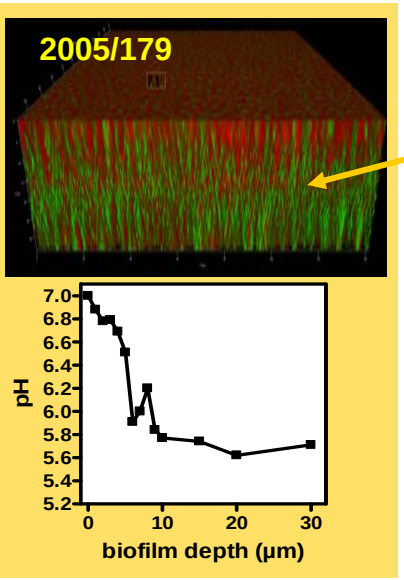


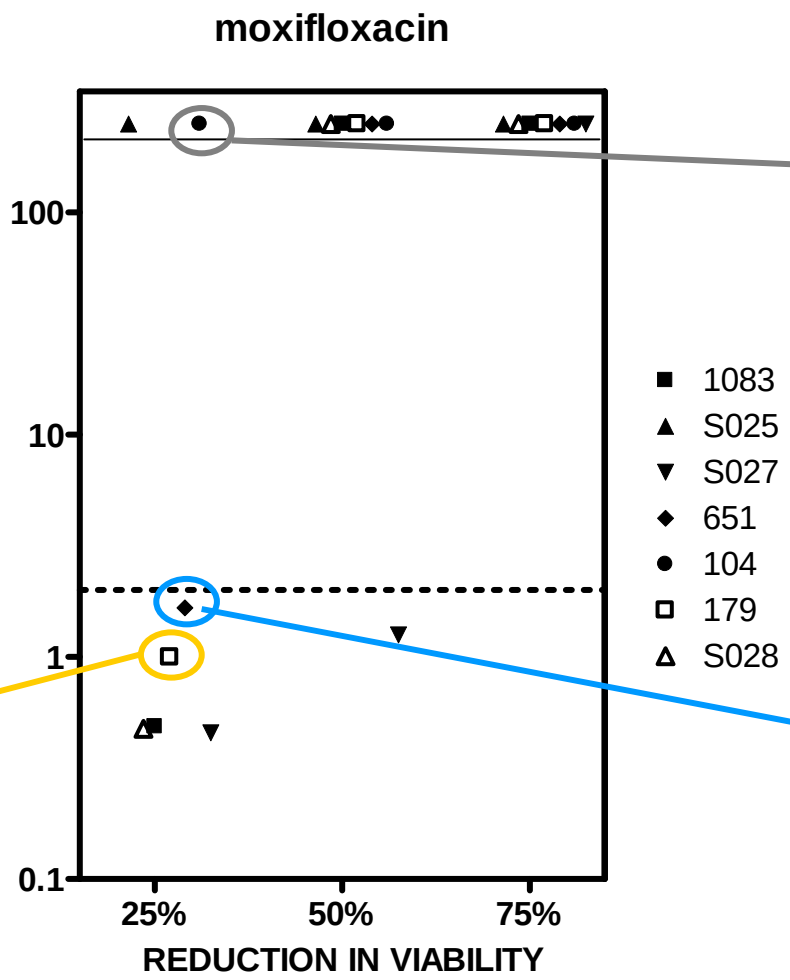


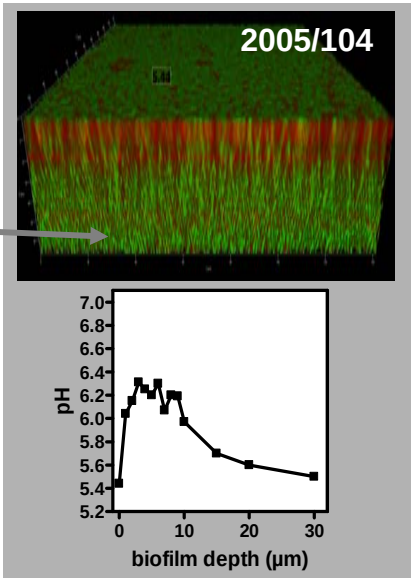
Siala et al, Eurobiofilms 2013

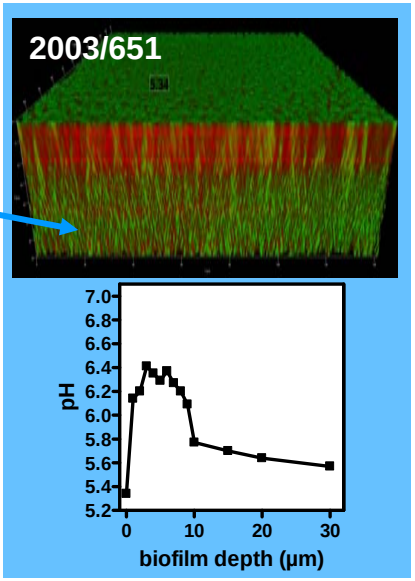
PD-related parameters: pH effect ?



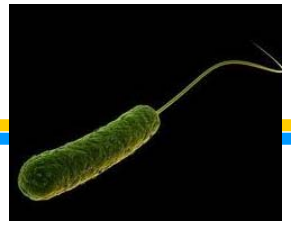








Siala et al, Eurobiofilms 2013

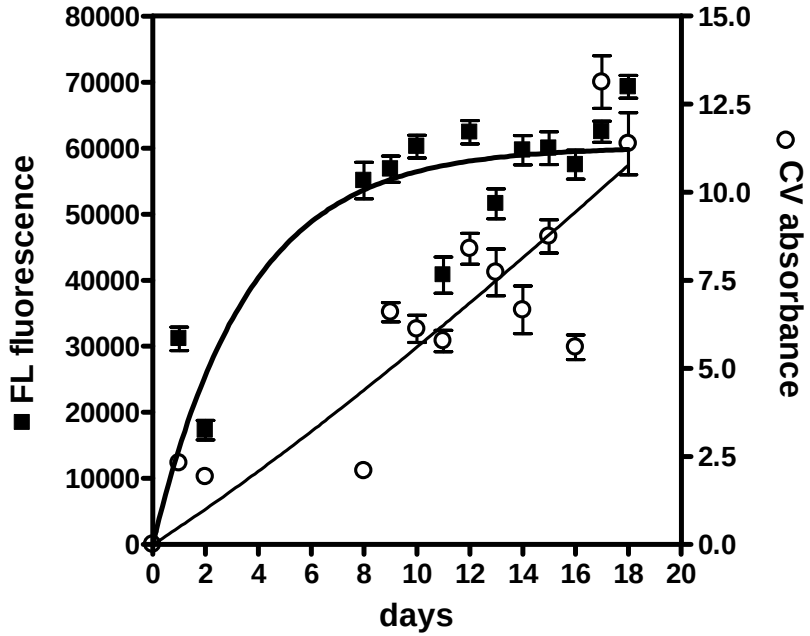


P. aeruginosa biofilms

Kinetics of biofilm formation

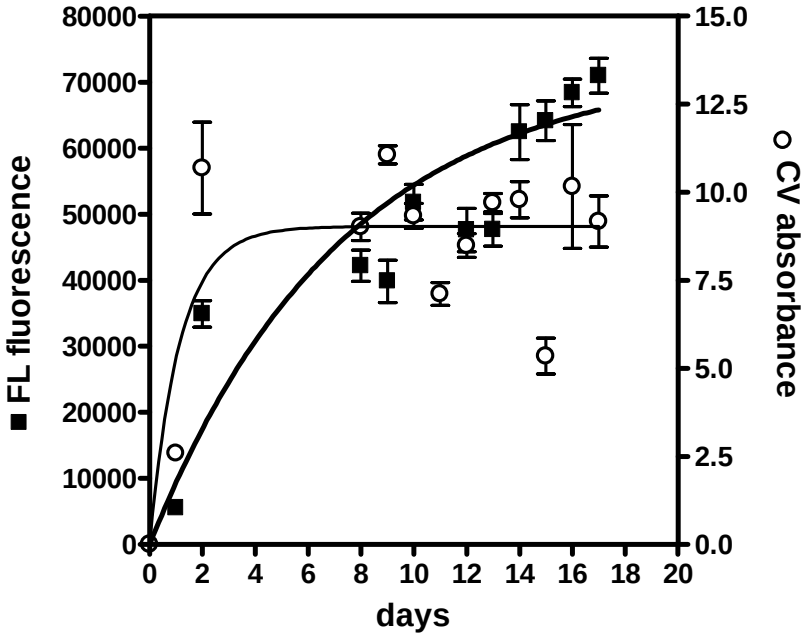
beef infusion solids, casein hydrolysate, starch

MHB



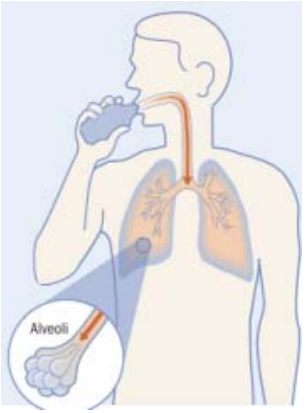
mucin, DNA, DTPA, casaminoacids, NaCl, KCl, tris base, egg yolk emulsion.

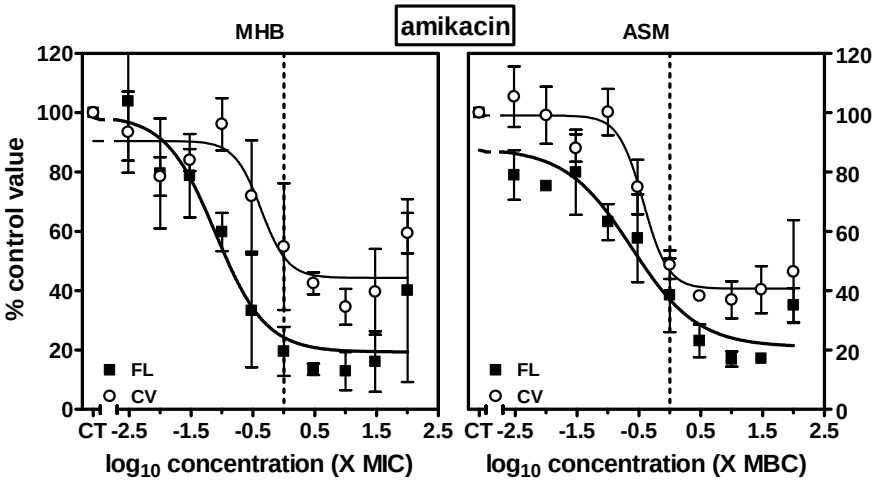
ASM

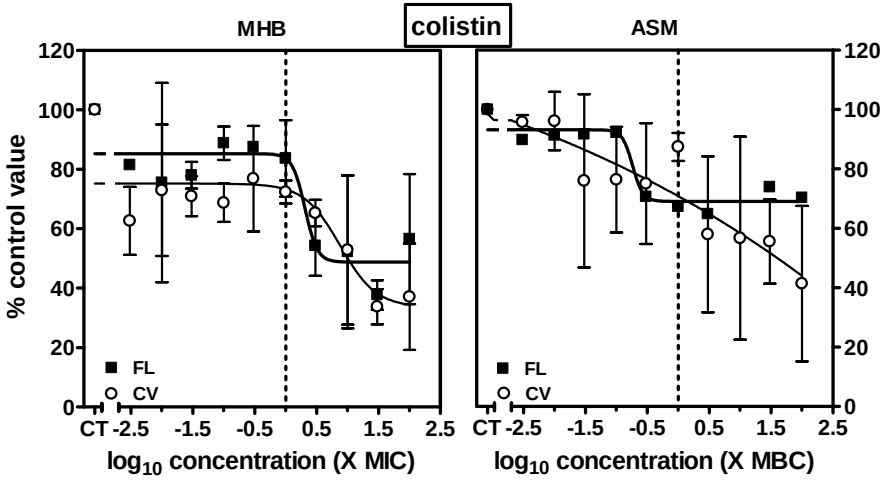


Antibiotics and *P. aeruginosa* mature biofilms

classes currently used by inhalation in cystic fibrosis patients

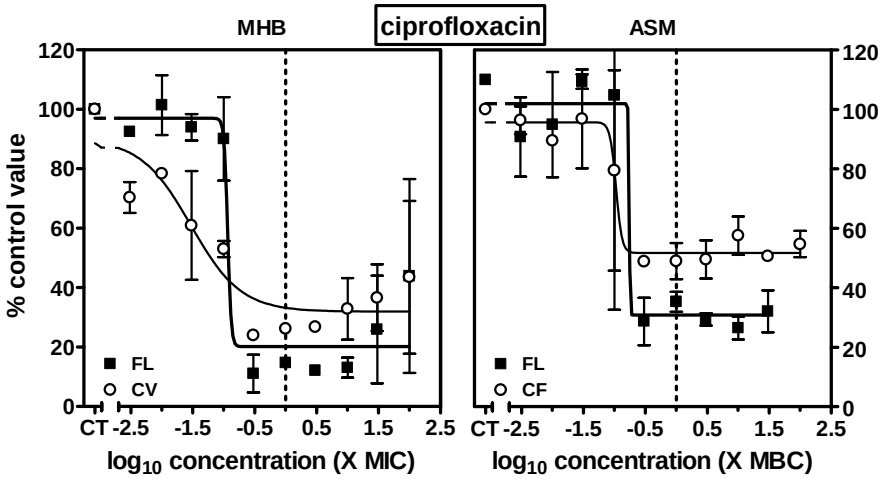




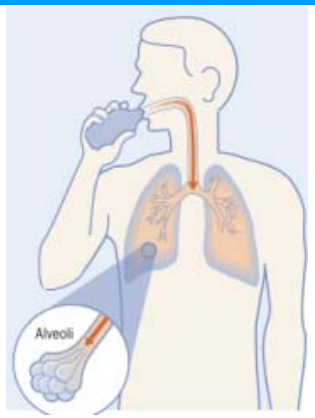


aminoglycosides >> polymyxins

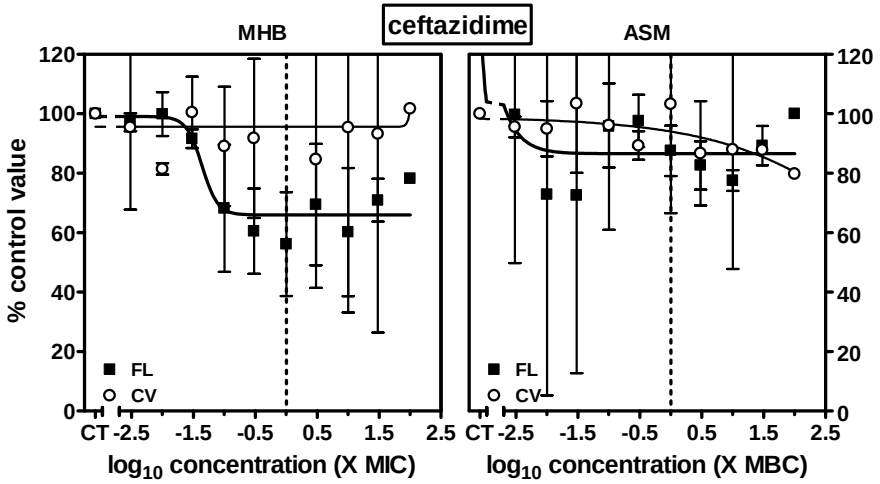
Antibiotics and *P. aeruginosa* mature biofilms



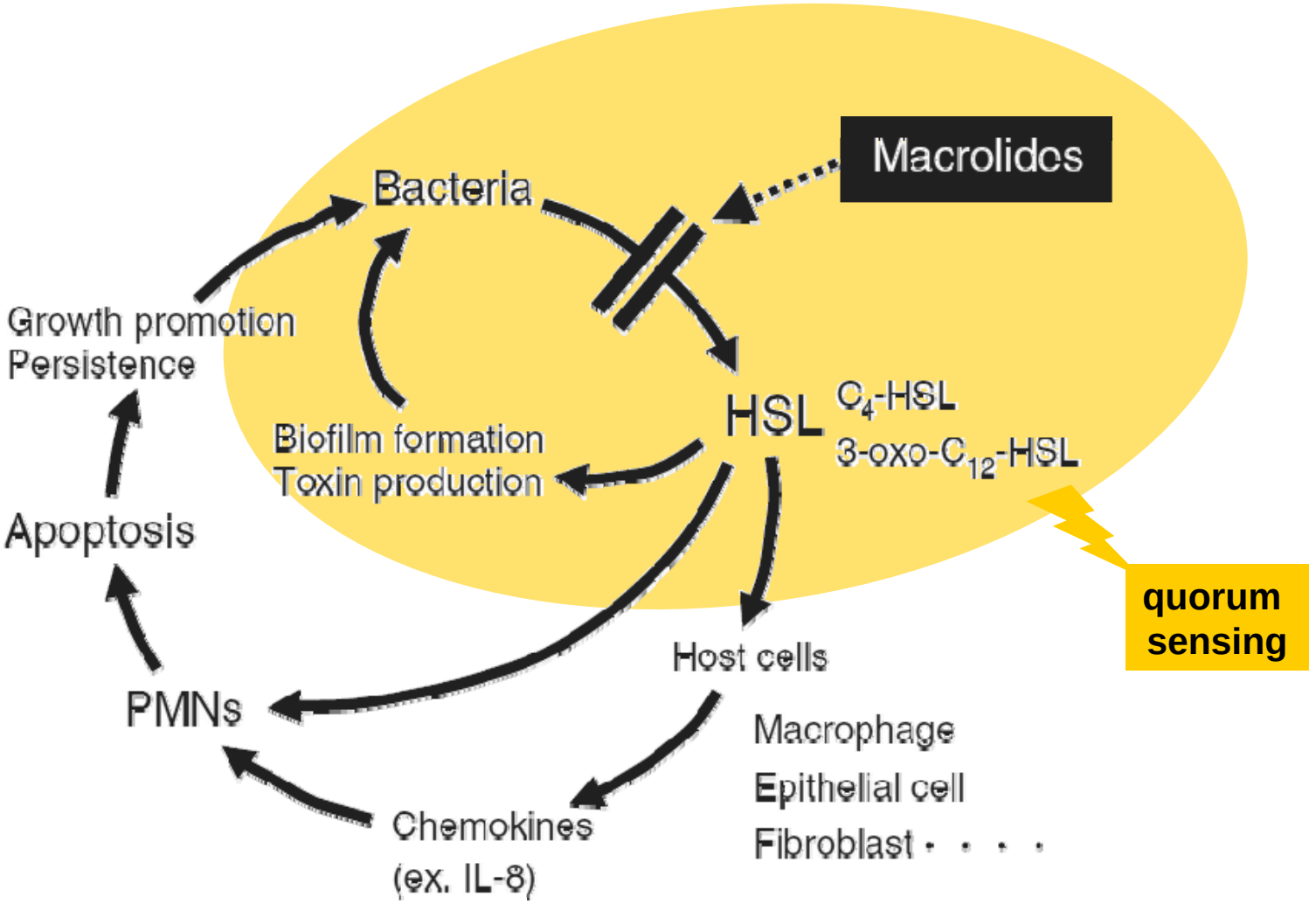
classes in development for inhalation in cystic fibrosis patients



fluoroquinolones >> β-lactams



Macrolides and biofilms



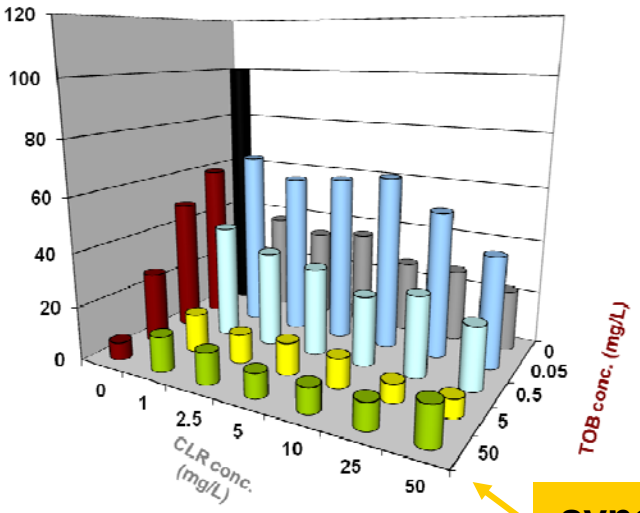
Tateda et al, J Infect Chemother. 2007;13:357-67

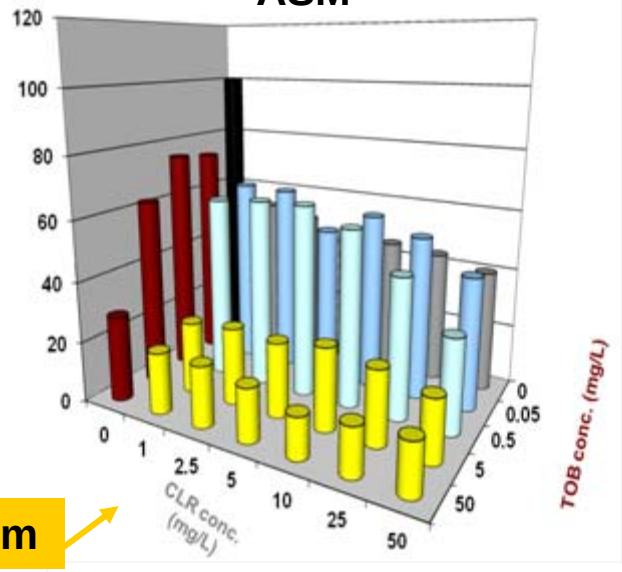
Aminoglycosides in combination with macrolides

MHB

ASM

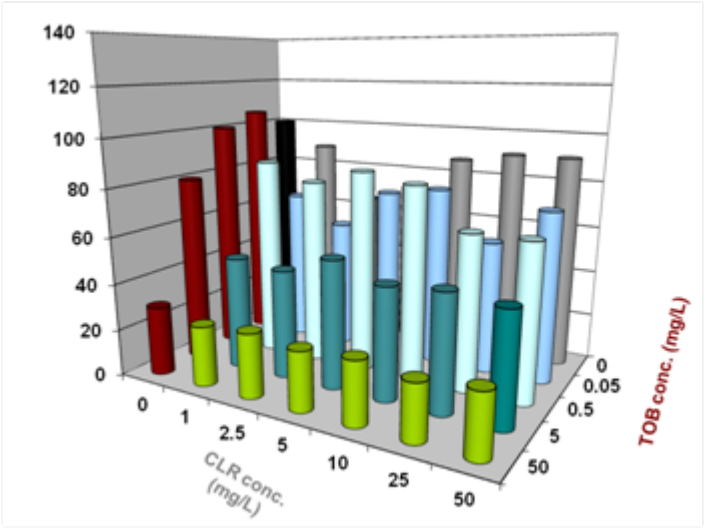
metabolic activity

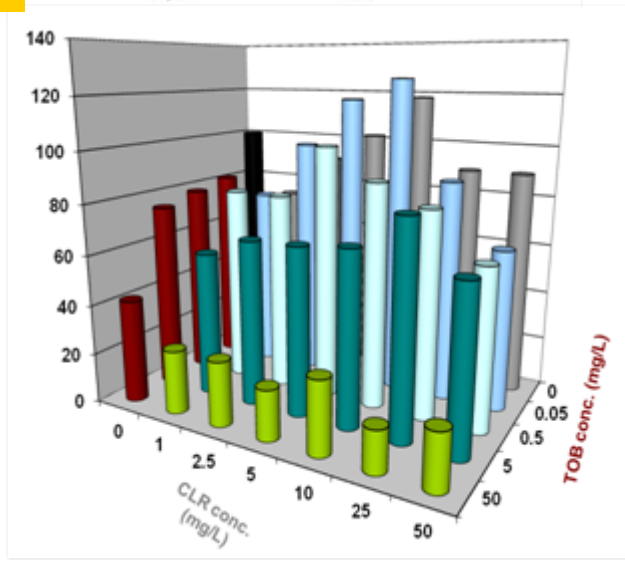




synergism

biomass





Basseres et al, Pseudomonas meeting 2013

Conclusions and perspectives

antibiotic efficacy and relative potency globally reduced against biofilms

effect on viability >> effect against biomass in G(+)

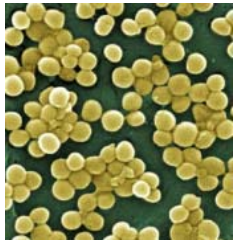
MICs do not predict activity → appropriate models required for screening

Combination of antibiotics with agents acting on QS or matrix may be useful

Strain-specific factors affecting PK (drug access) and PD (bacterial responsiveness)

mature biofilms much more resistant to antibiotics

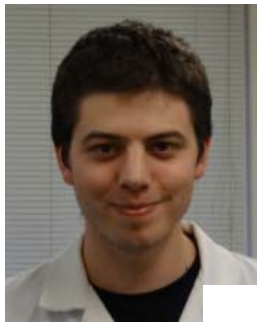
Acknowledgments



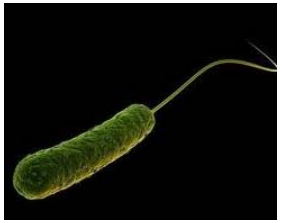
Julia Bauer

Wafi Siala

Nathalie Vandevelde



Yvan Diaz Iglesias



Eugénie Basseres

Thank you for your attention and ….

Merry Christmas!