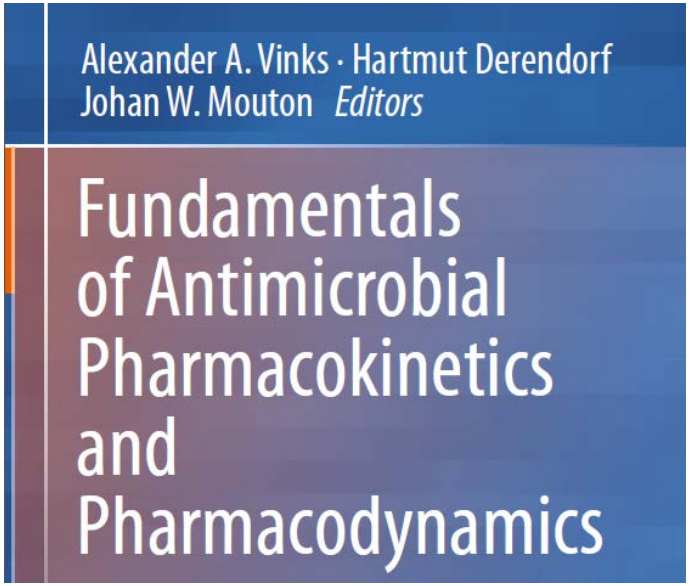
Association d'antibiotiques:
1. modèles planctoniques
2. biofilms

Modèles planctoniques

Un article de synthèse…



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Chapter 8
Drug–Drug Combinations

John Turnidge

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Pourquoi associer ?

Table 8.1 Rationale for drug combinations

Rationale	Target	Example
"Synergy"	Gram-negative bacteria	β-lactam + aminoglycoside β-lactam + fluoroquinolone Trimethoprim–sulfamethoxazole
Inhibition of degrading bacterial enzymes	Gram-negative bacteria *Staphylococcus* species	β-lactam + β-lactamase inhibitor
Inhibition of degrading human enzymes	Gram-negative and Gram-positive bacteria	Imipenem + cilastatin
Reduced toxicity from reduced dosage	*Cryptococcus neoformans*	Amphotericin B + flucytosine
Broadening of spectrum	Polymicrobial infections	β-lactam + aminoglycoside
Prevention of resistance selection during treatment	*Pseudomonas aeruginosa* *Mycobacterium* species Human immunodeficiency virus	β-lactam + aminoglycoside Combination antituberculous therapy Combination antiretroviral therapy (HAART)
Antibacterial plus antitoxin action	Panton-valentine leukocidin producing *S. aureus*	Cell-wall active agent + clindamycin or linezolid

La résistance se développe facilement en monothérapie

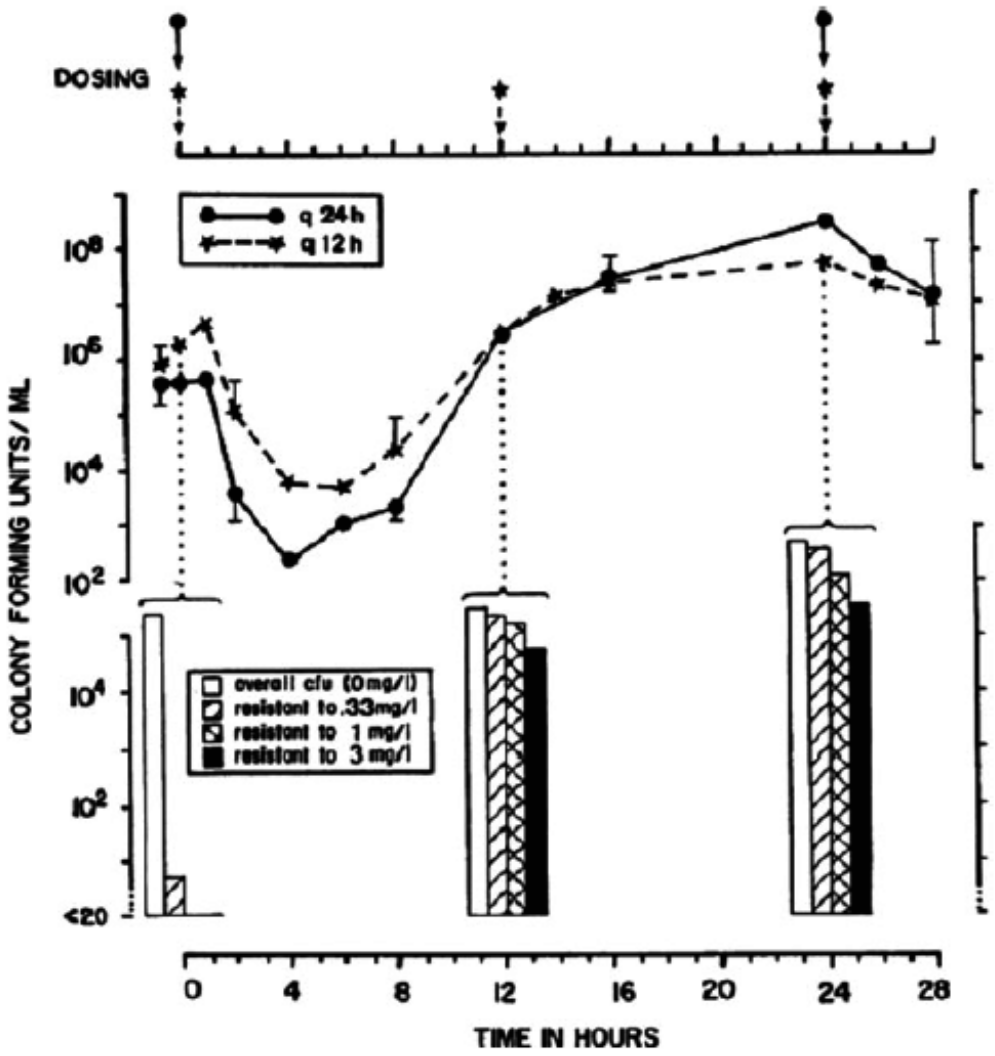

Fig. 8.1 Emergence of resistance to enoxacin in *P. aeruginosa* in an in vitro pharmacodynamic model (from Blaser et al. 1987)

Il y a de nombreuses preuves que l'association d'antibiotiques diminue le risque de résistance *in vitro*

1. Combinations of β-lactams with aminoglycosides prevent the selection of aminoglycoside- resistant mutants (Blaser et al. 1985 ; McGrath et al. 1993 ; Zelenitsky et al. 1998) and β-lactam-resistant mutants (Drusano et al. 2012), or both (Zinner et al. 1986).
2. Combinations of β-lactams with fluoroquinolones prevent the emergence offluoroquinolone- resistant mutants (Lister et al. 2006; Louie et al. 2010), combinations of β-lactams with colistin prevent the emergence of fluoroquinolone resistant mutants (Gunderson et al. 2003; Bergen et al. 2011).
3. the combination of a carbapenem with an aminoglycoside or fluoroquinolonecan be effective in killing and preventing resistance emergence even for strains that are not susceptible to one or both agents (Lister et al. 2006); similar observations have been made with colistin and a carbapenem for a colistin-resistant strain (Bergen et al. 2011).
4. Killing can occur even when the combination of a β-lactam and aminoglycosideare below the MICs throughout (den Hollander et al. 1997).
5. etc…

L'association d'antibiotiques diminue le risque de résistance *in vivo* (souris neutropénique)

36 similar studies with a large number of antibiotics

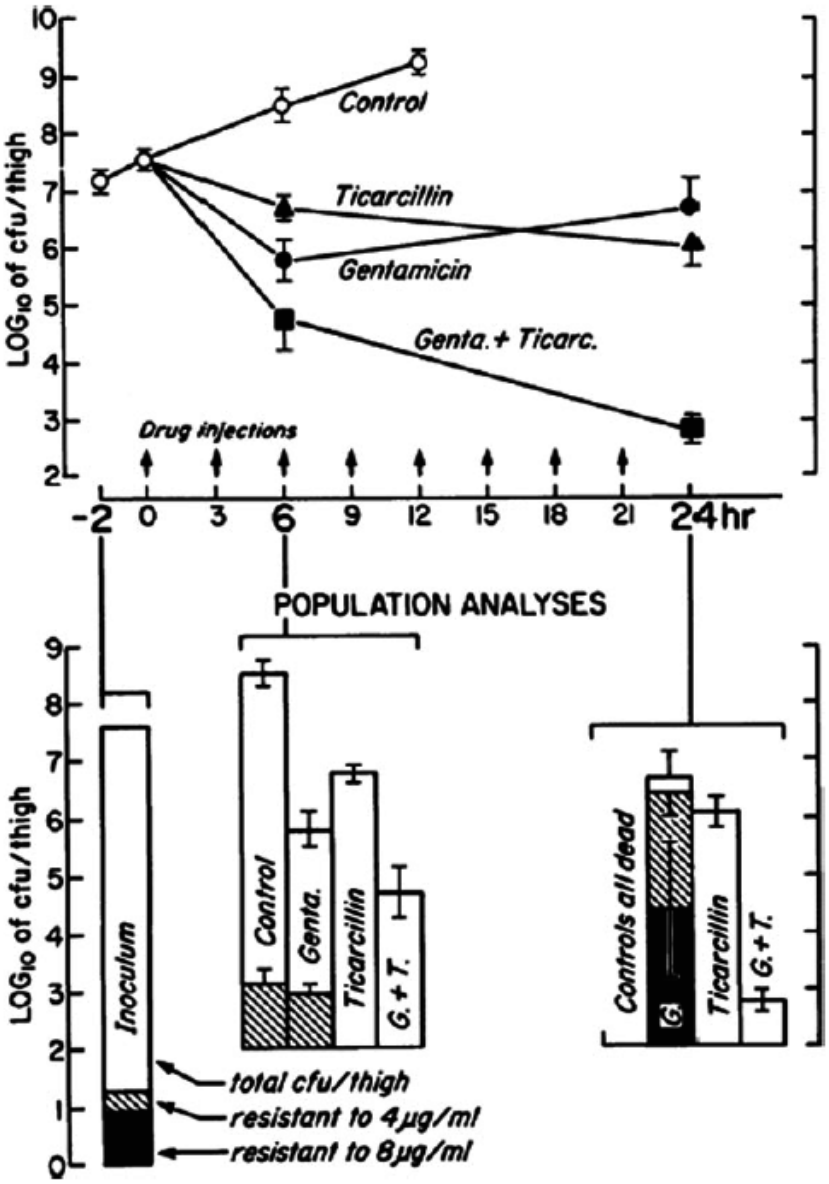

Fig. 8.2 Selection of resistance during treatment and suppression by combination therapy (from Gerber et al. 1982)

Data with a pharmacodynamic model of infected fibrin clot

Houlihan HH, Stokes DP, Rybak MJ (2000) Pharmacodynamics of vancomycin and ampicillin alone and in combination with gentamicin once daily or thrice daily against *Enterococcus faecalis* in an in vitro infection model. J Antimicrob Chemother 46:79–86

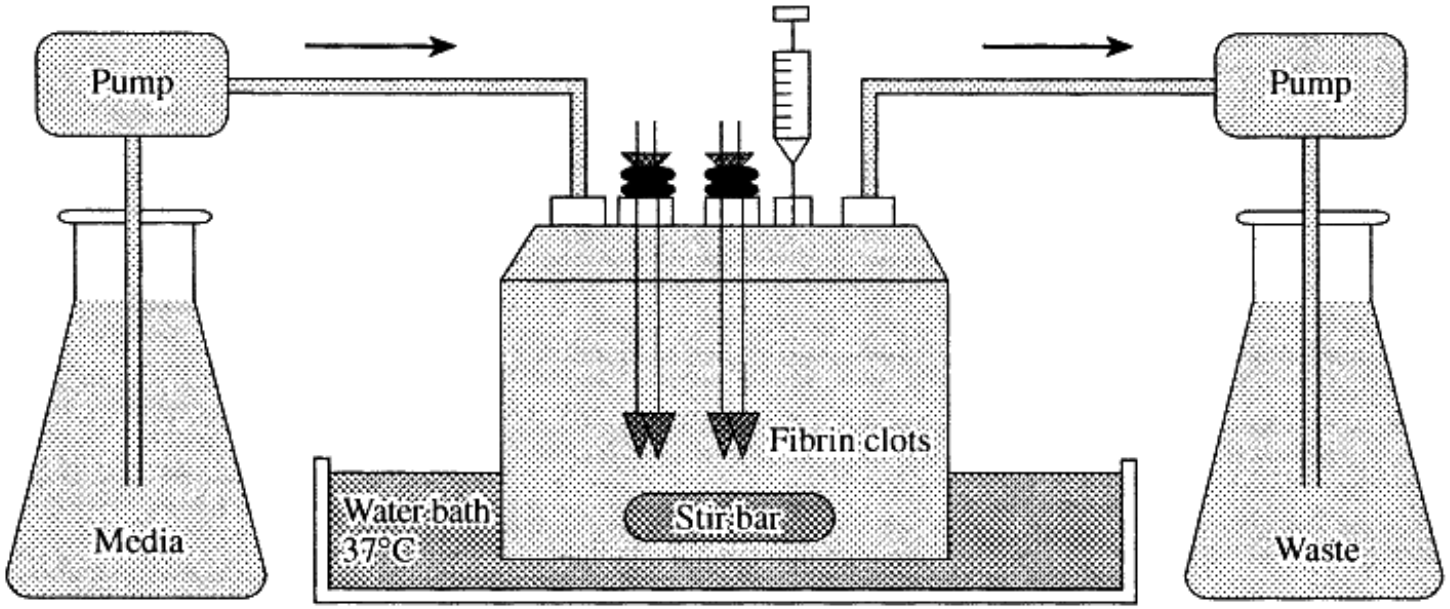

Figure 1. *In vitro* infection model with FPCs.

Data with a pharmacodynamic model of infected fibrin clot

Houlihan HH, Stokes DP, Rybak MJ (2000) Pharmacodynamics of vancomycin and ampicillin alone and in combination with gentamicin once daily or thrice daily against *Enterococcus faecalis* in an in vitro infection model. J Antimicrob Chemother 46:79–86

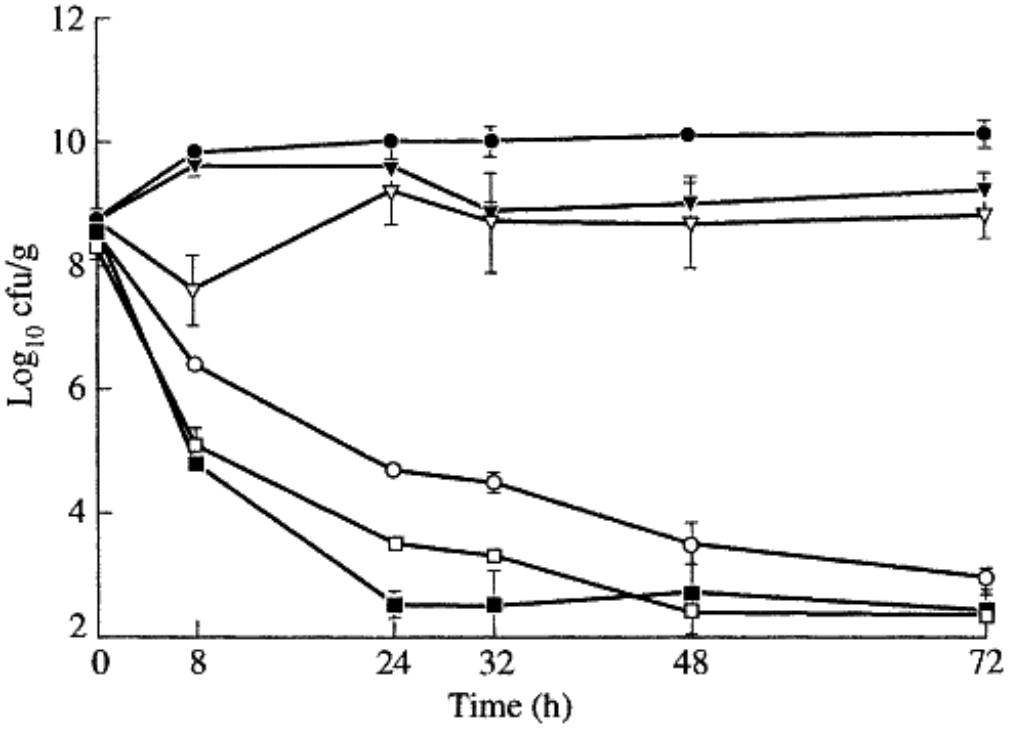

Figure 2. Bactericidal activity of ampicillin, gentamicin and the combination of ampicillin and gentamicin either q8h or q24h against *E. faecalis* OG1X. ●, Growth control; ▼, gentamicin q8h; ▽, gentamicin q24h; ○, ampicillin q6h; ■, ampicillin q6h + gentamicin q8h; □, ampicillin q6h + gentamicin q24h.

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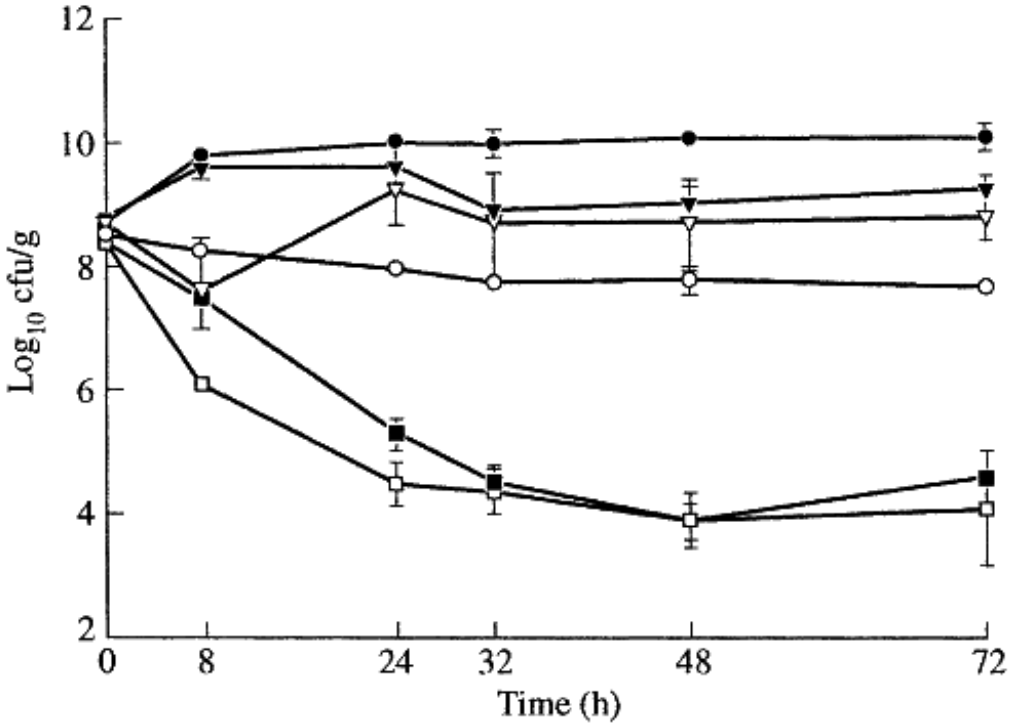

Figure 3. Bactericidal activity of vancomycin, gentamicin and the combination of vancomycin and gentamicin either q8h or q24h against *E. faecalis* OG1X. ●, Growth control; ▼, gentamicin q8h; ▽; gentamicin q24h; ○, vancomycin q12h; ■, vancomycin q12h + gentamicin q8h; □, vancomycin q12h + gentamicin q24h.

Data with a pharmacodynamic model of infected fibrin clot

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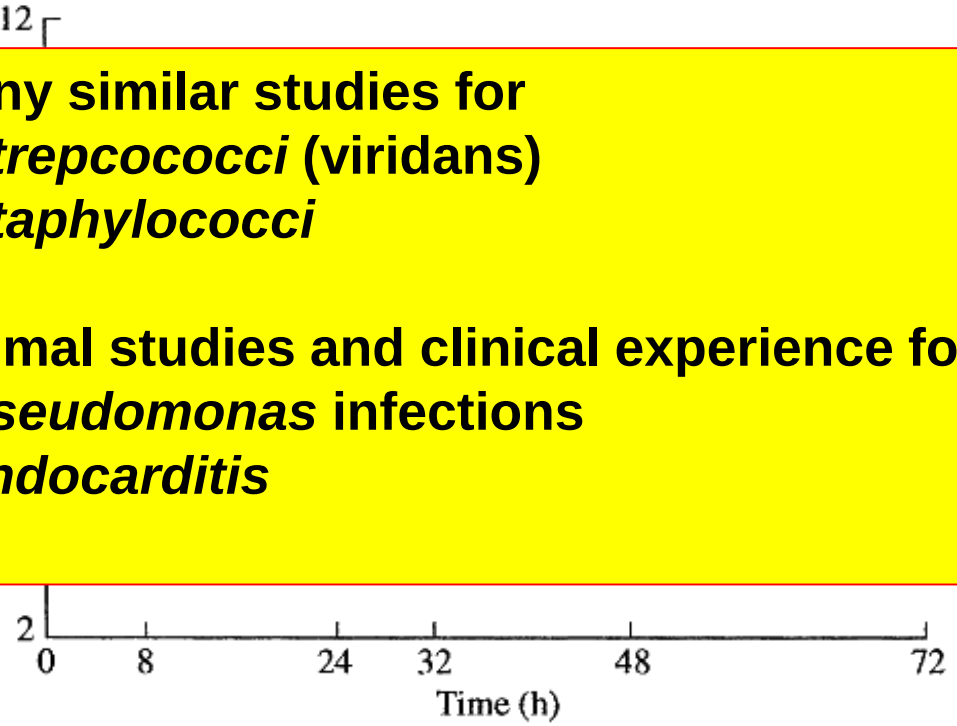
Many similar studies for
- ***Strepcococci* (viridans)**
- ***Staphylococci***

Animal studies and clinical experience for
- ***Pseudomonas* infections**
- ***endocarditis***



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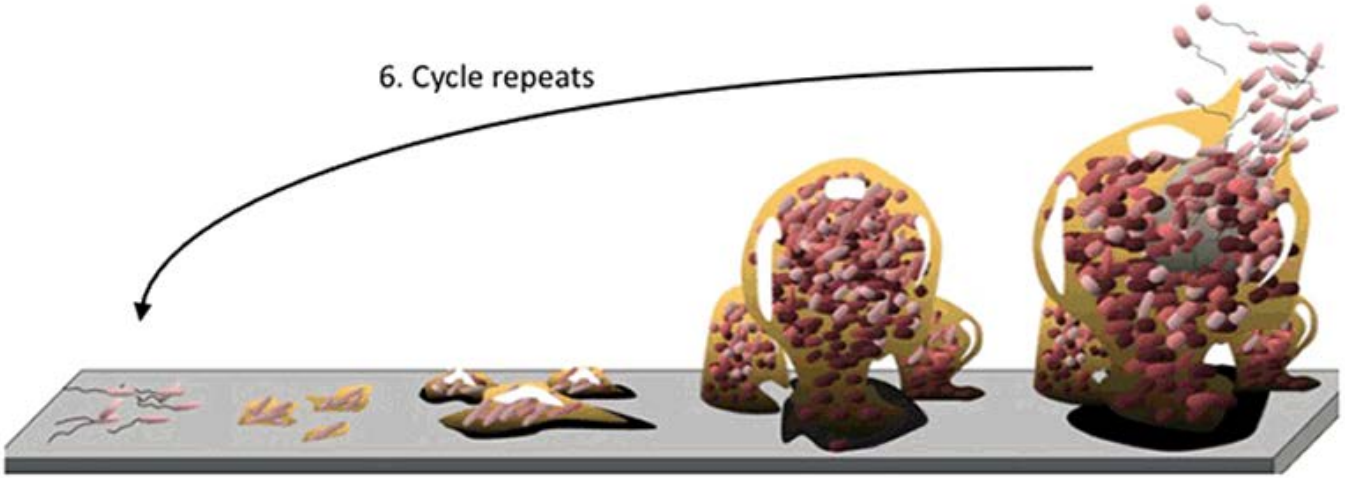
A conclusion that calls for the future

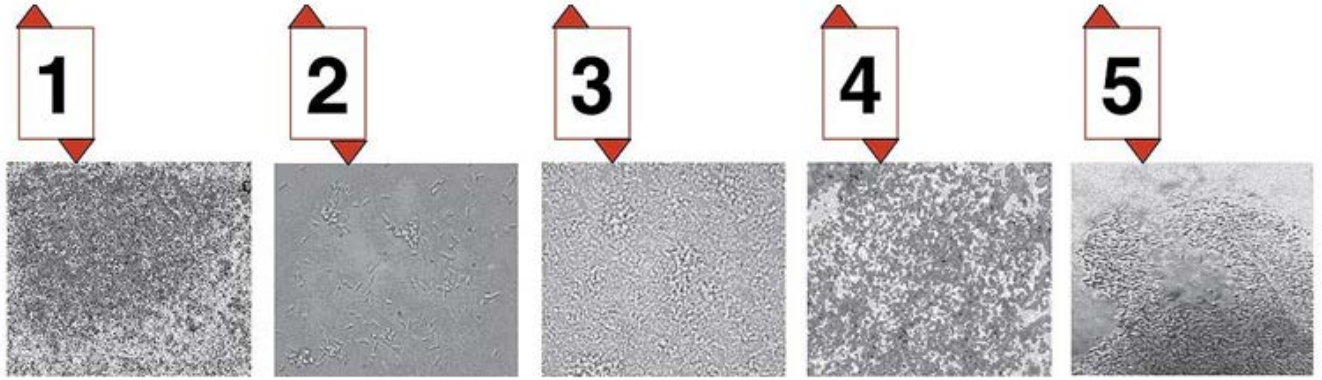
Conclusions

Combination therapy is widely used in the management of serious *P. aeruginosa* infection and Gram-positive endocarditis. Despite extensive in vitro static, pharmacodynamic and animal model studies, uncertainties persist about the utility of combinations, especially given the potential for toxicity associated with concomitant aminoglycoside use. Ultimately, an in vitro or animal model of the pharmacodynamic interaction of drug classes that can be shown to predict clinical outcomes is still required. Such a model does not currently exist.

Modèles de biofilms…

Biofilms: what are we speaking about ?

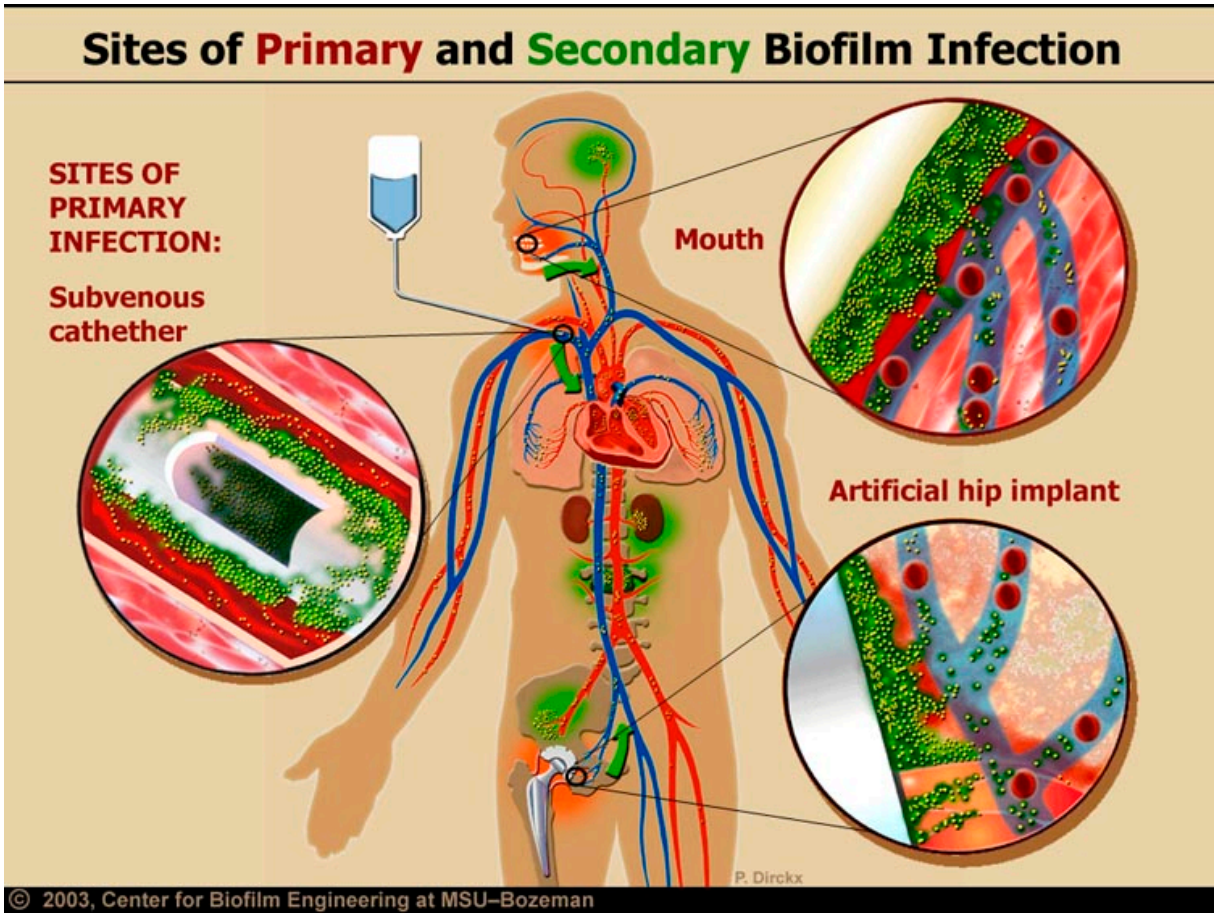




http://www.bayarealyme.org/blog/straight-talk-biofilms-new-answer-treating-lyme-disease/
Last visited: 28 Sep 2017

Biofilms in human infections

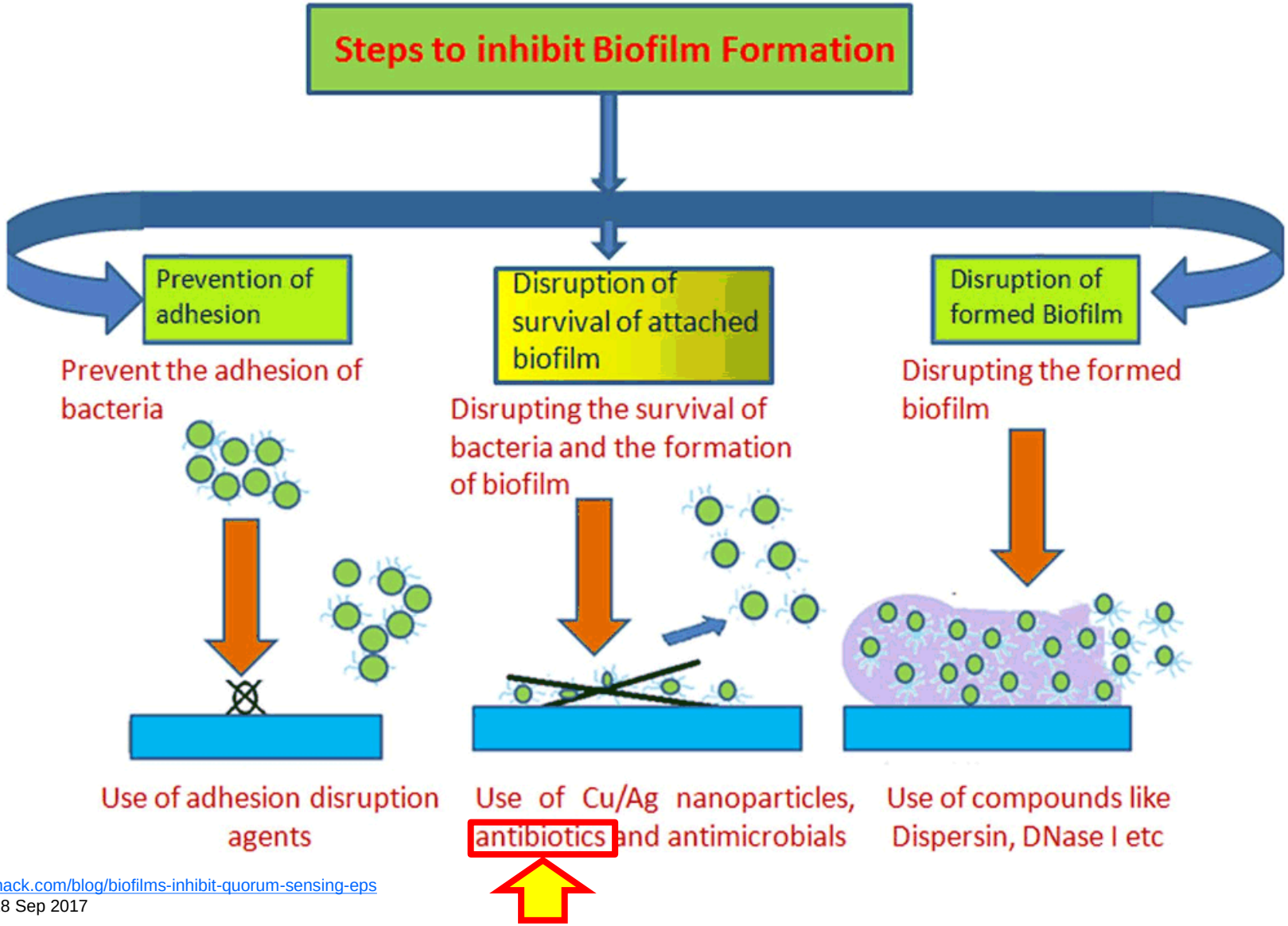
Biofilms are associated to 65[a]-80[b] % of human infections and can colonize virtually all organs …



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

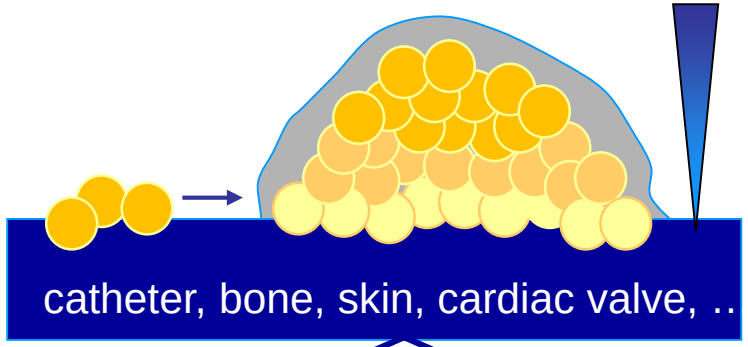
[a]CDC 1999; [b]Lewis et al, Nat Rev Microbiol. 2007; 5:48-56

Biofilms: what can you do ?



https://mybiohack.com/blog/biofilms-inhibit-quorum-sensing-eps
Last visited: 28 Sep 2017

PK/PD parameters in biofilms

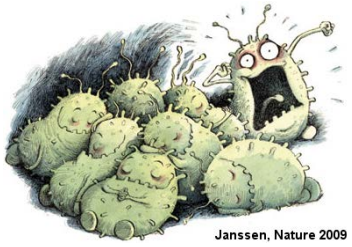


pharmacokinetics

- diffusibility through the matrix
- bioavailability within the biofilm
- access to bacteria
- efflux out of bacteria

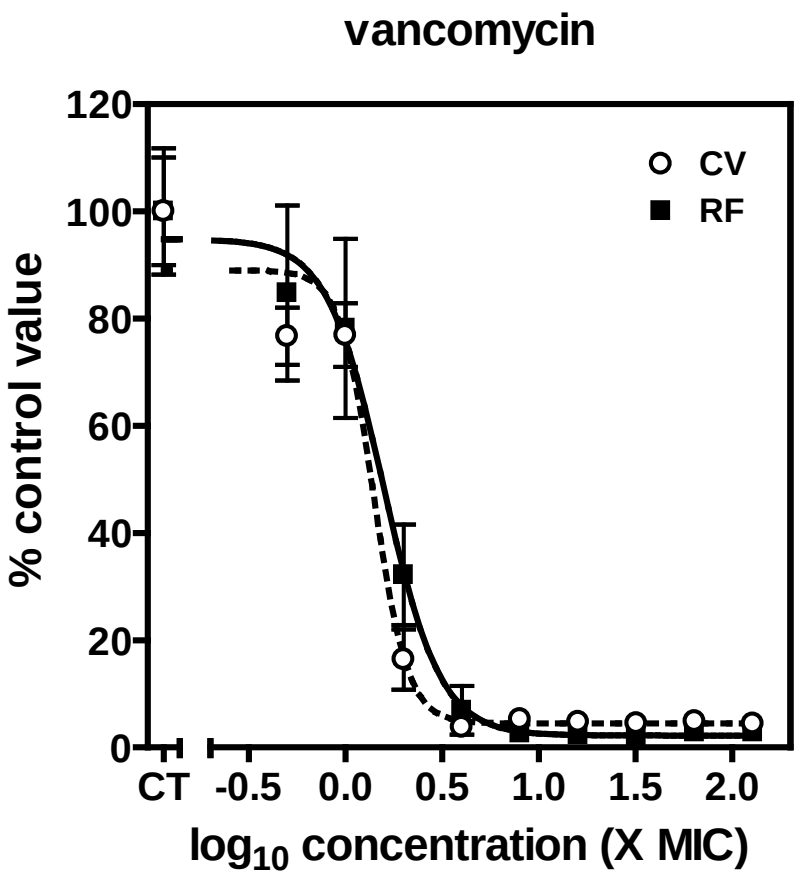
pharmacodynamics

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



Pharmacodynamic model for antibiotic activity

An example with a **young** biofilm of *S. aureus* - ATCC MSSA



Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

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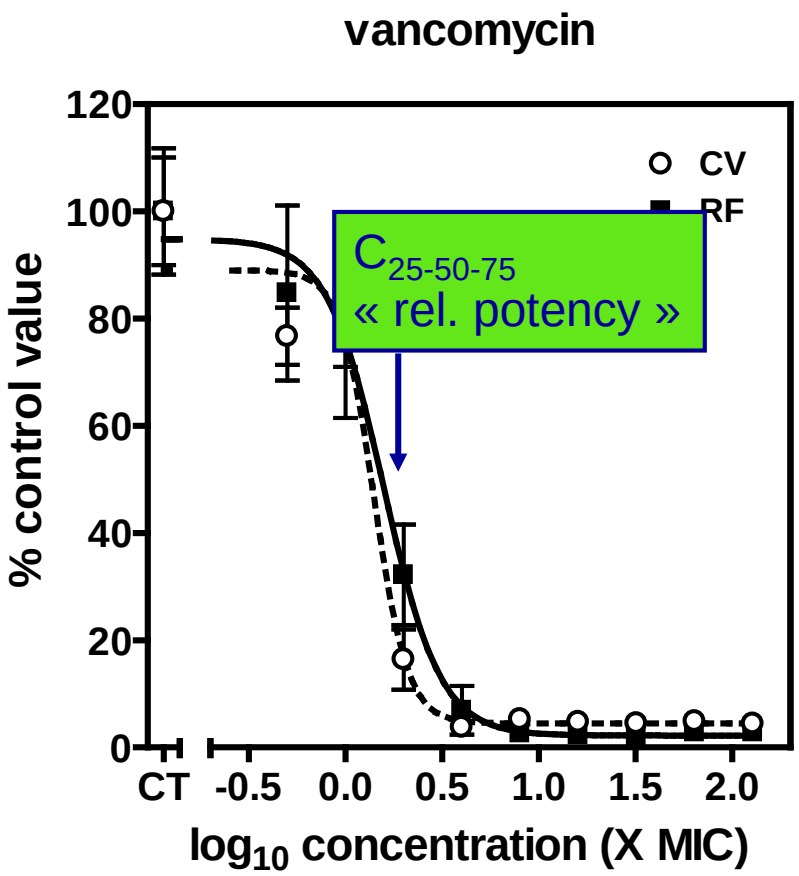

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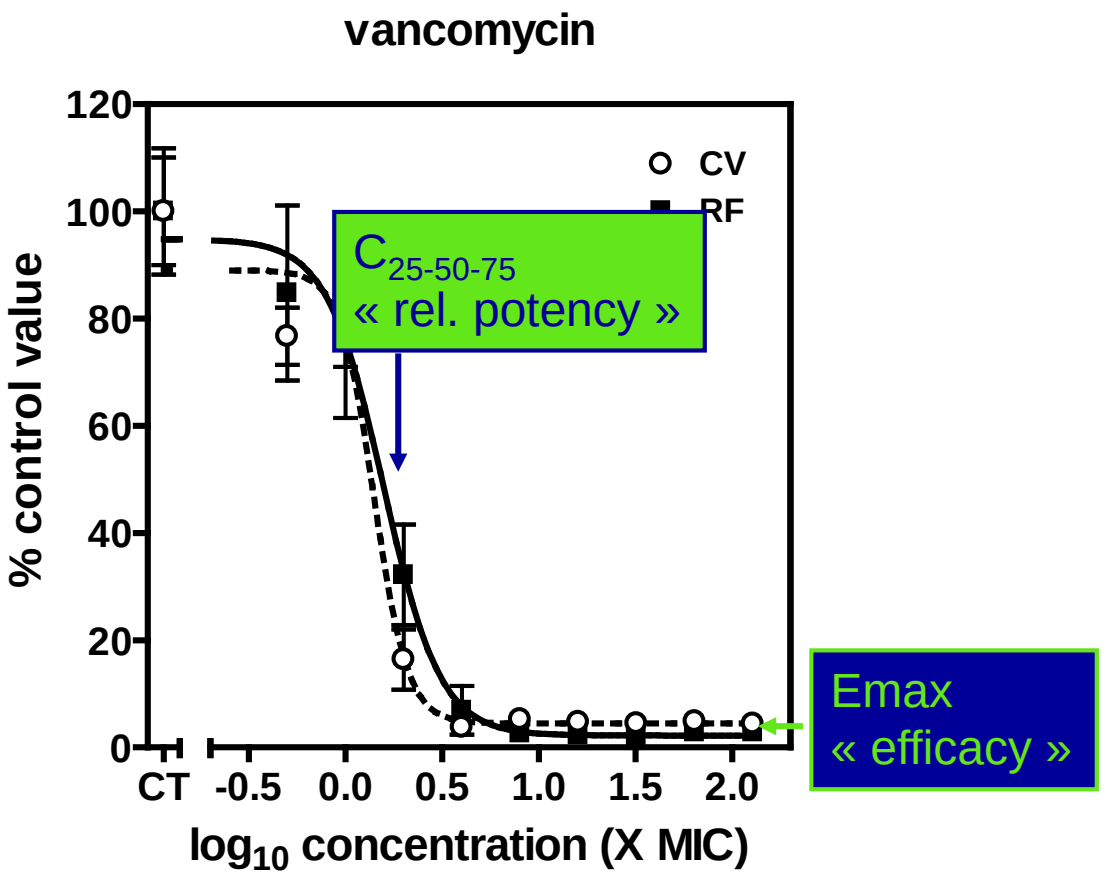
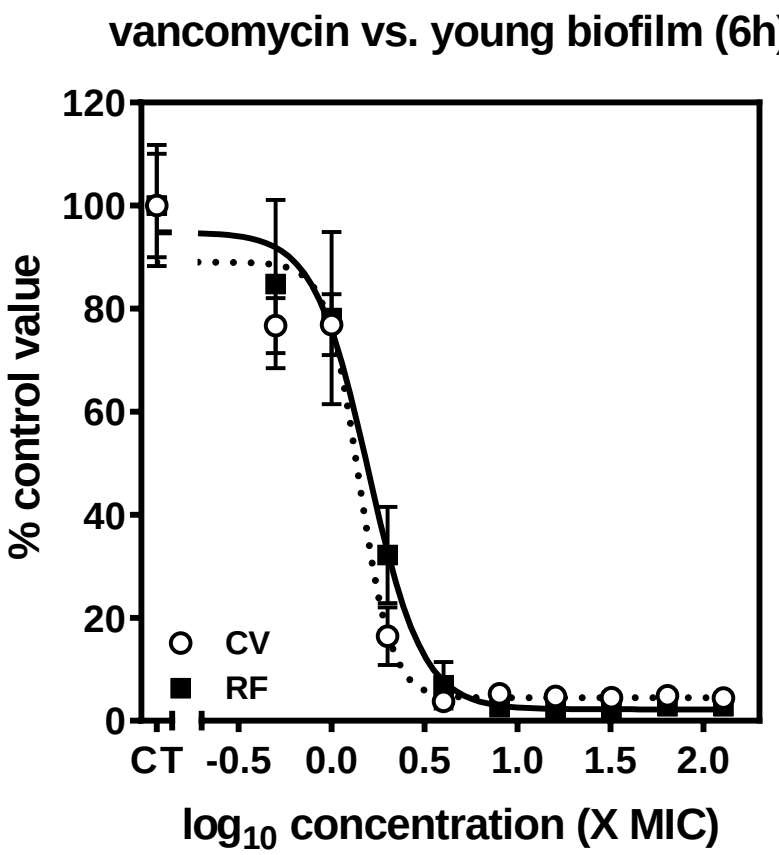
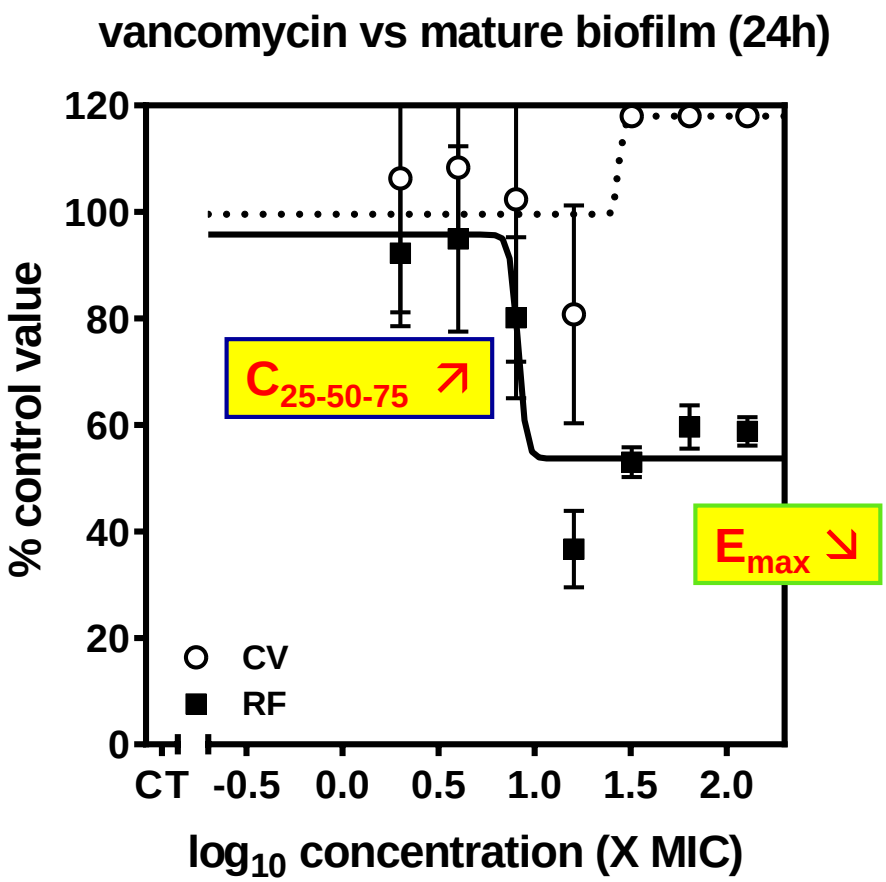


Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

Pharmacodynamic model for antibiotic activity

Young vs. **mature** biofilm of *S. aureus* - ATCC MSSA



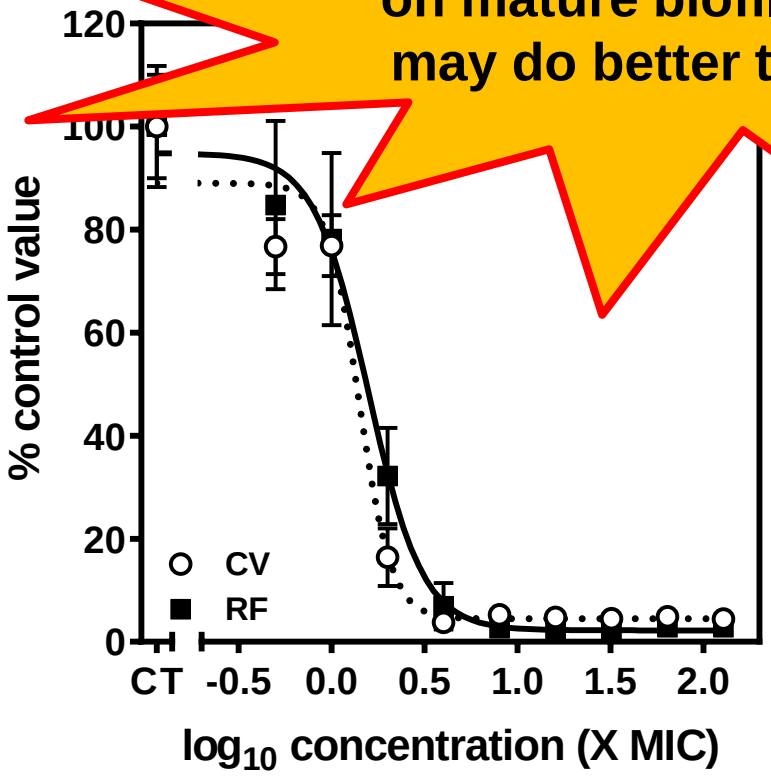


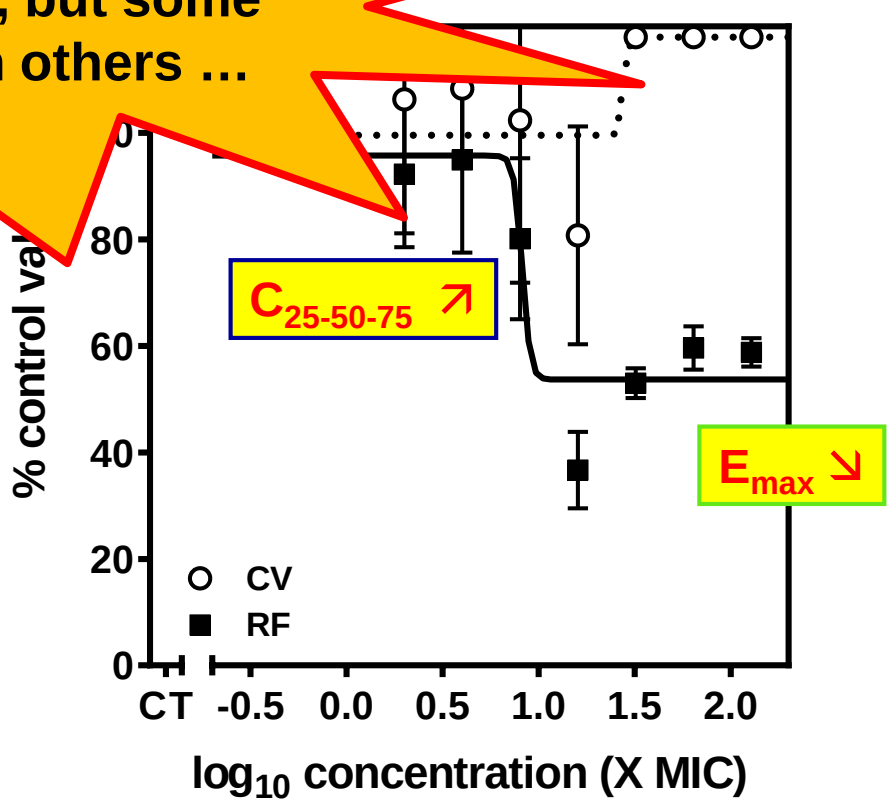
Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

Pharmacodynamic model for antibiotic activity

Young vs **ture** biofil… *aureus* - ATCC MSSA

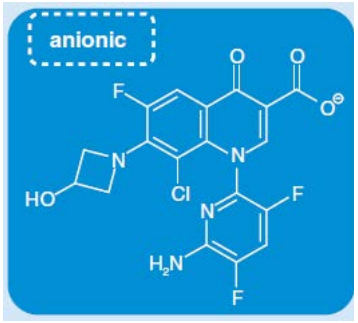
most antibiotics act poorly on mature biofilms, but some may do better than others …

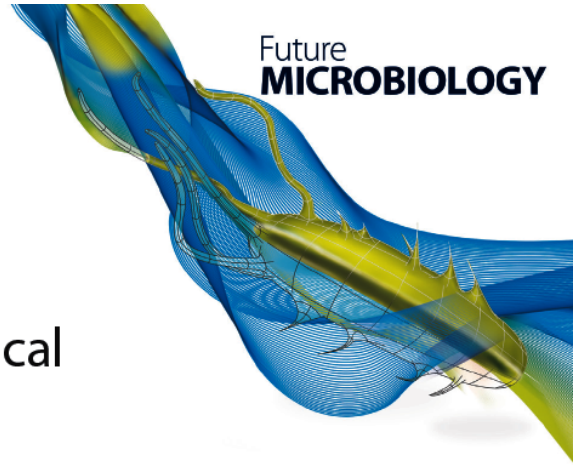




Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

Delafloxacin, a new fluoroquinolone





DRUG EVALUATION

Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy

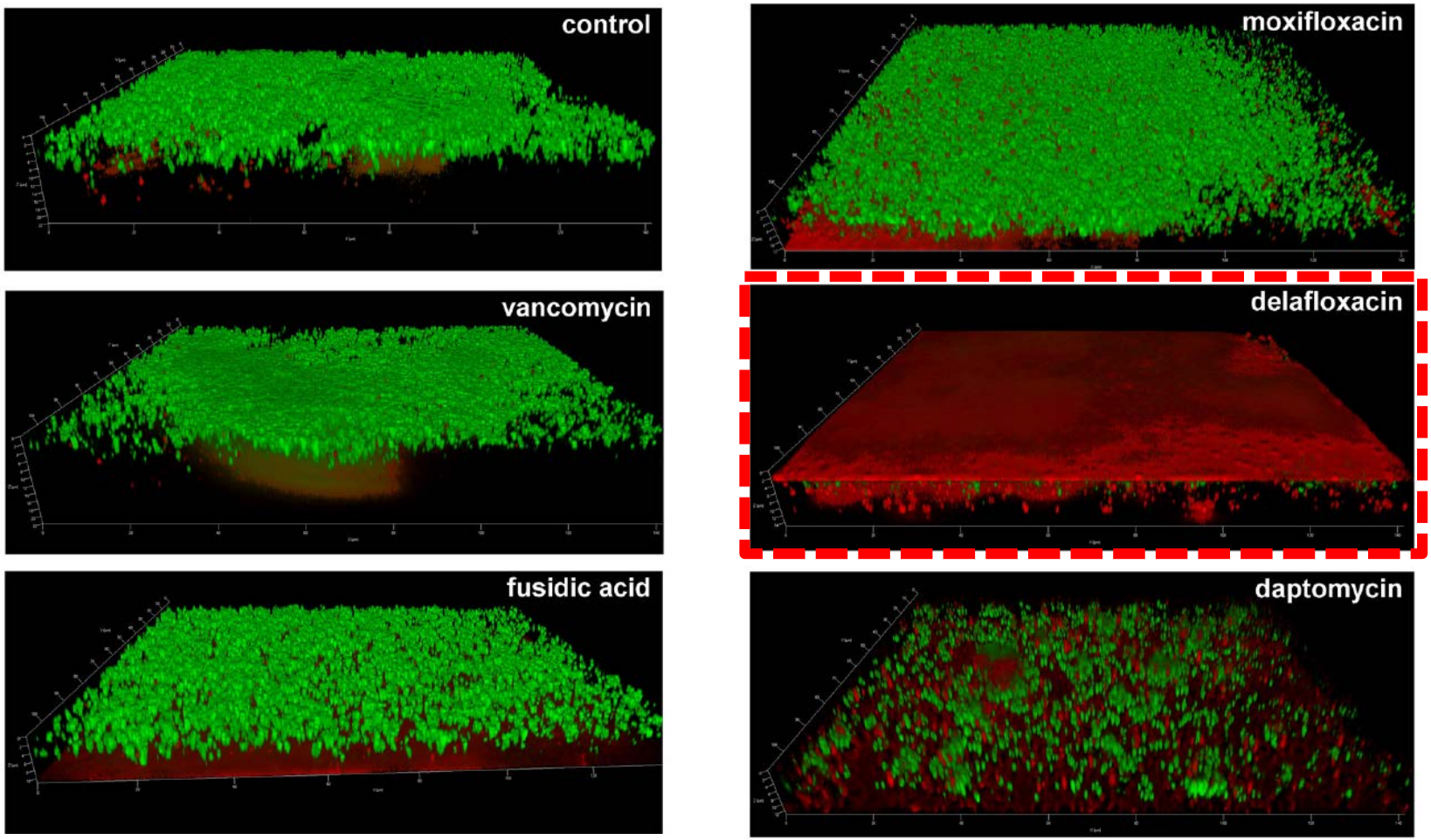
Françoise Van Bambeke*

ABSTRACT Delafloxacin is a fluoroquinolone lacking a basic substituent in position 7. It shows MICs remarkably low against Gram-positive organisms and anaerobes and similar to those of ciprofloxacin against Gram-negative bacteria. It remains active against most fluoroquinolone-resistant strains, except enterococci. Its potency is further increased in acidic environments (found in many infection sites). Delafloxacin is active on staphylococci growing intracellularly or in biofilms. It is currently evaluated as an intravenous and intravenous/oral stepdown therapy in Phase III trials for the treatment of complicated skin/skin structure infections. It was also granted as Qualified Infectious Disease Product for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, due to its high activity on pneumococci and atypical pathogens.

Van Bambeke F. Future Microbiology: Drug Evaluation review (2015) 10:1111–1123 – PMID: 26119479

Comparison of antibiotic activity in confocal microscopy

Live/dead staining (antibiotics at 32 X MIC) – ATCC MRSA



Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

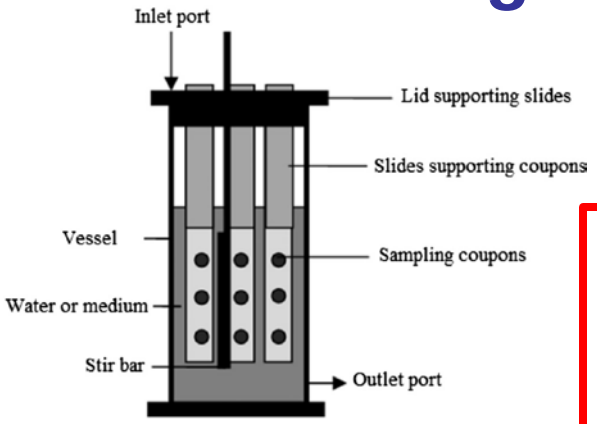
When one antibiotic (even at a large dose) is not enough…

https://www.pinterest.com/pin/433682639086749225/
Last visited: 28 Sep 2017

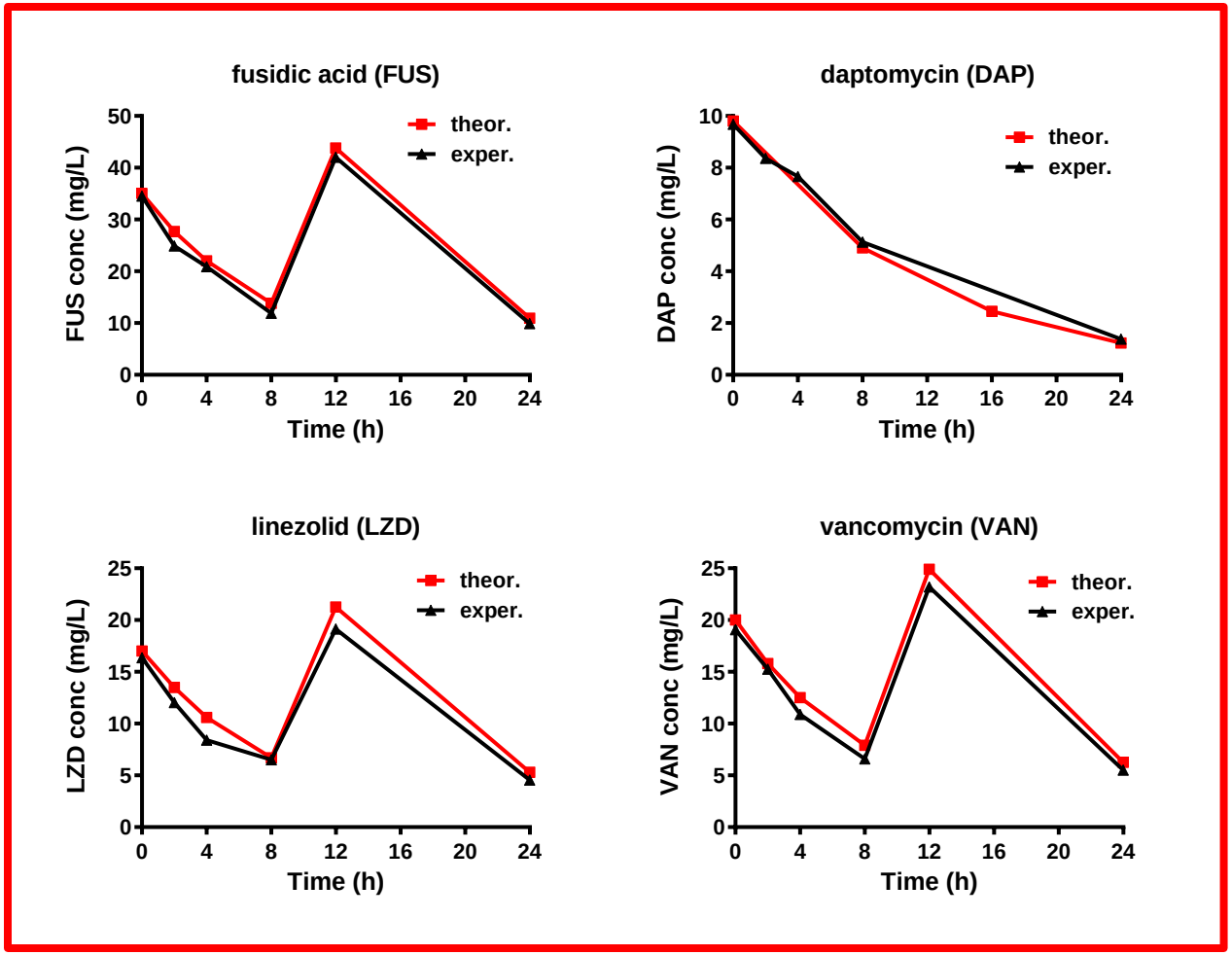
why not combing them at their normal (and safe) human doses ?

https://de.wikipedia.org/wiki/Heinrich_von_Opel
Last visited: 22 Oct 2016

Combining antibiotics in a dynamic model

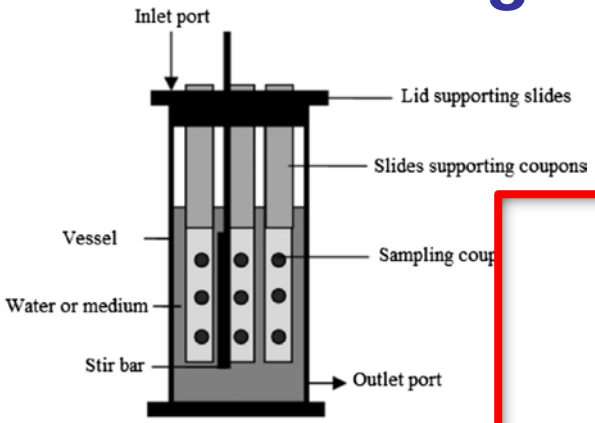


The CDC reactor:
Biofilms are grown on 12.7 mm diameter coupons, suspended in the bulk fluid by eight coupon holders and then exposed to antibiotic concentrations **mimicking their human pharmacokinetics**



Siala *et al*. 2016 ESCMID Conference on Antimicrobial resistance in microbial biofilms and options for treatment, Ghent, Belgium, 5-7 October 2016 - poster

Combining antibiotics in a dynamic model



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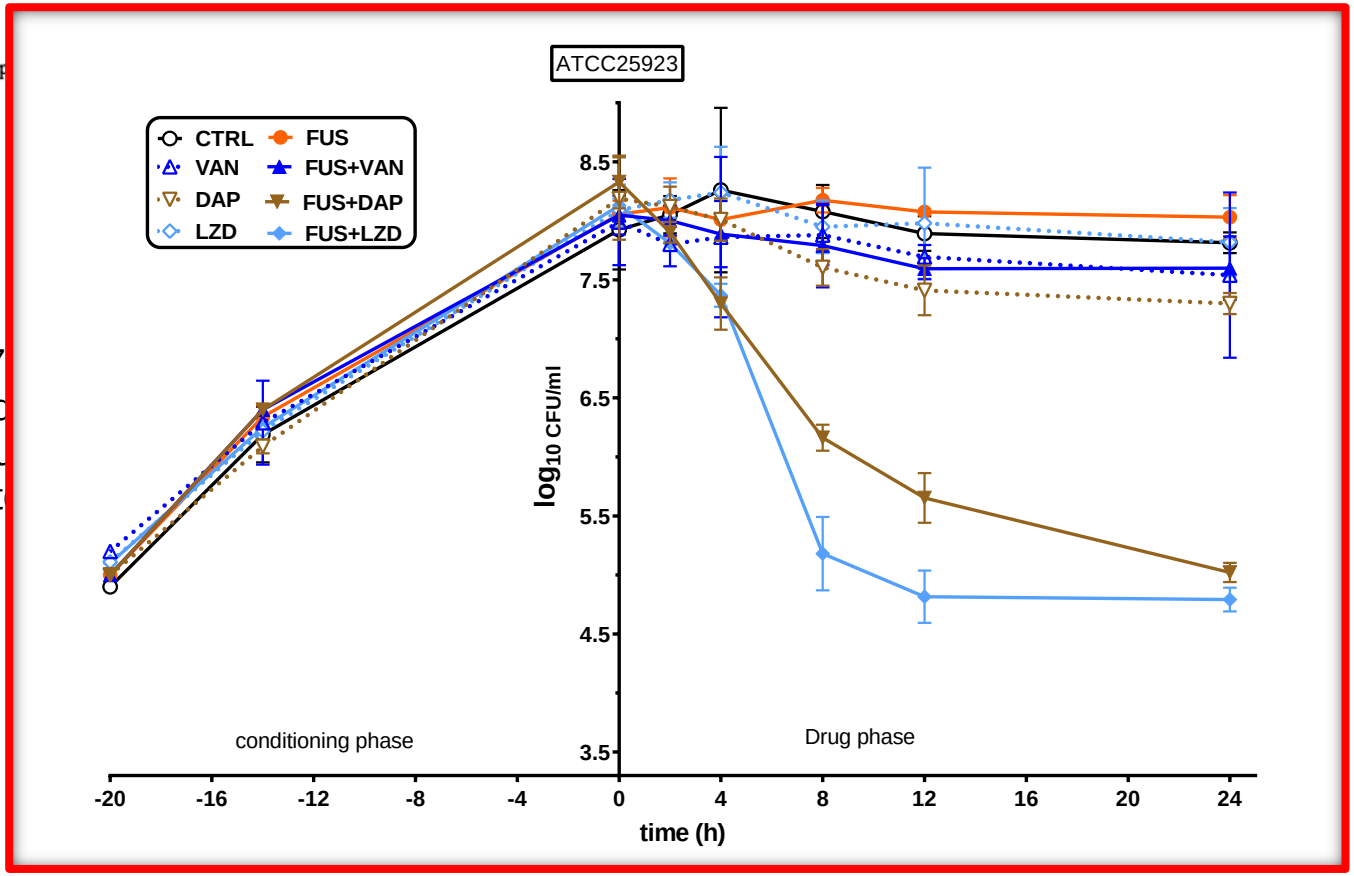

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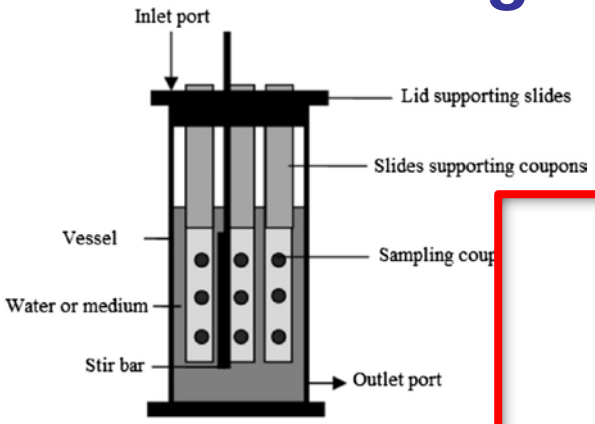

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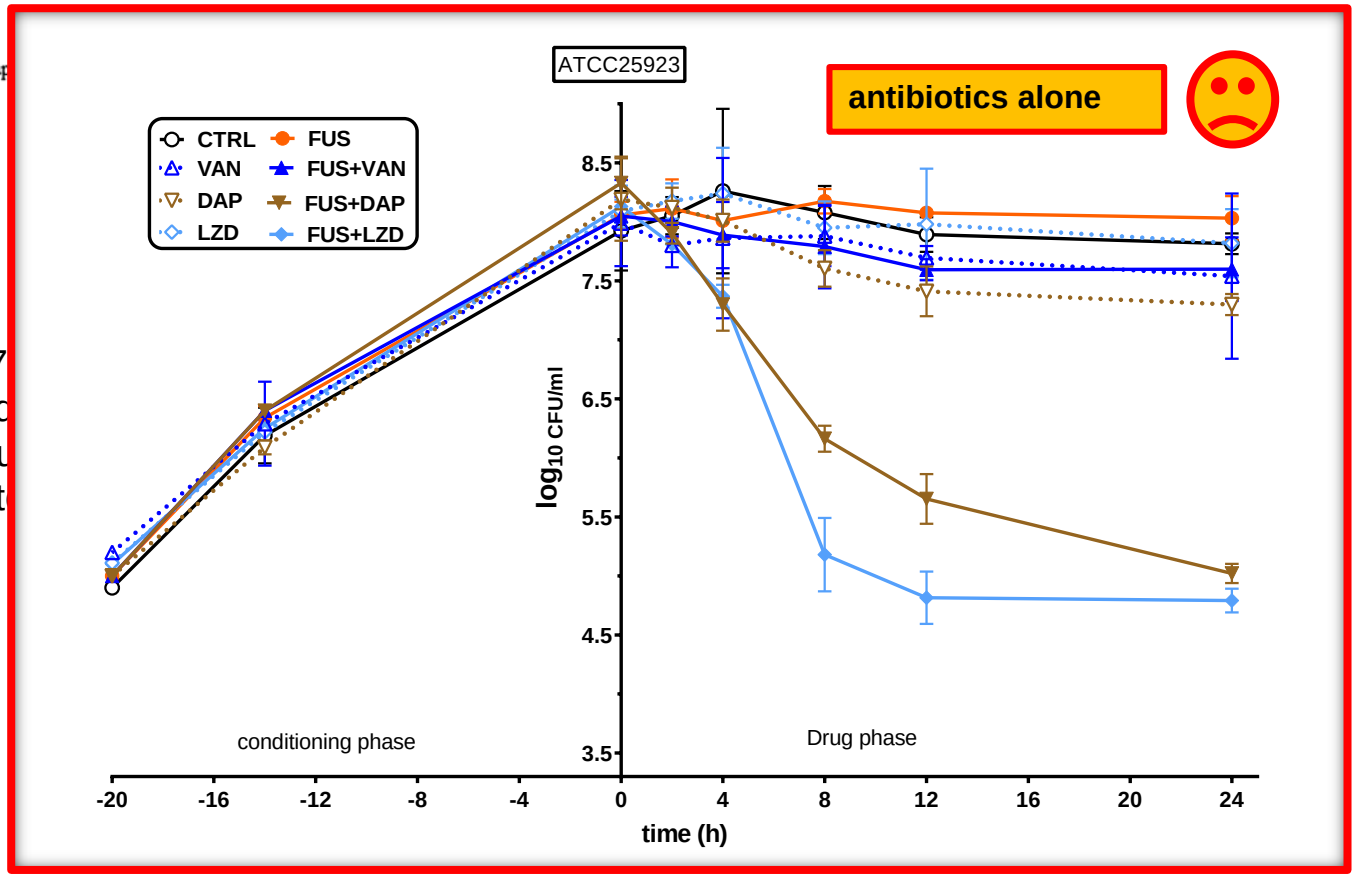

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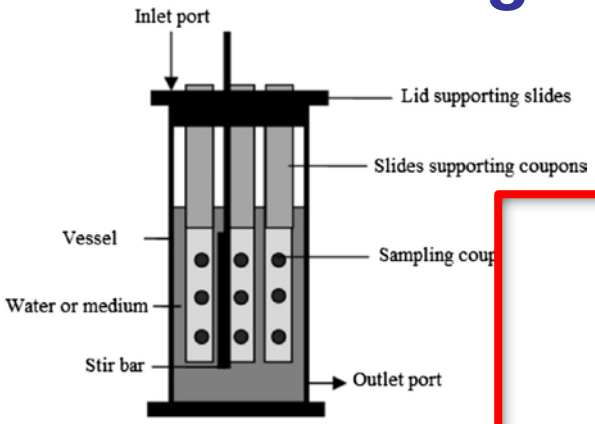

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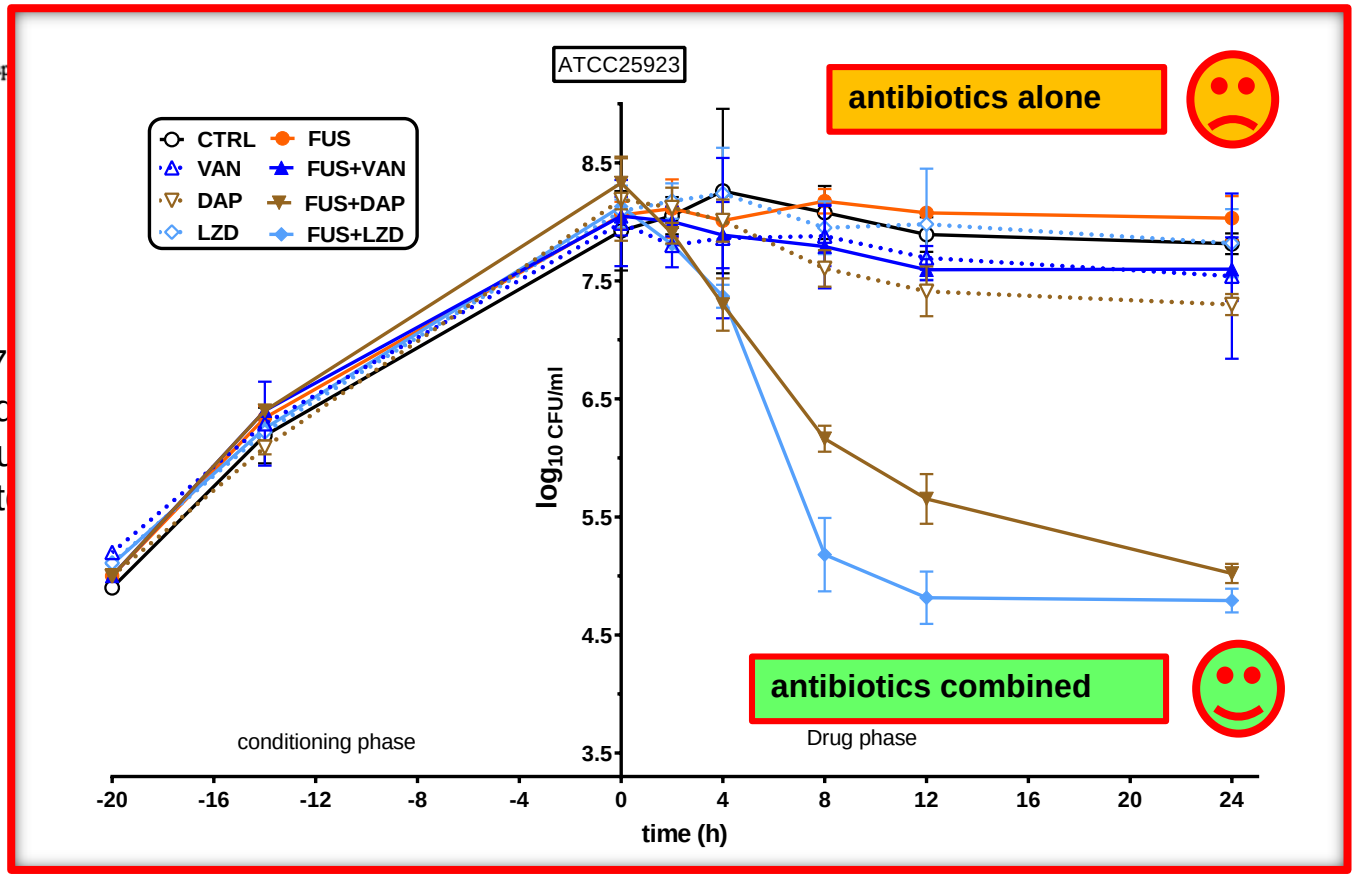
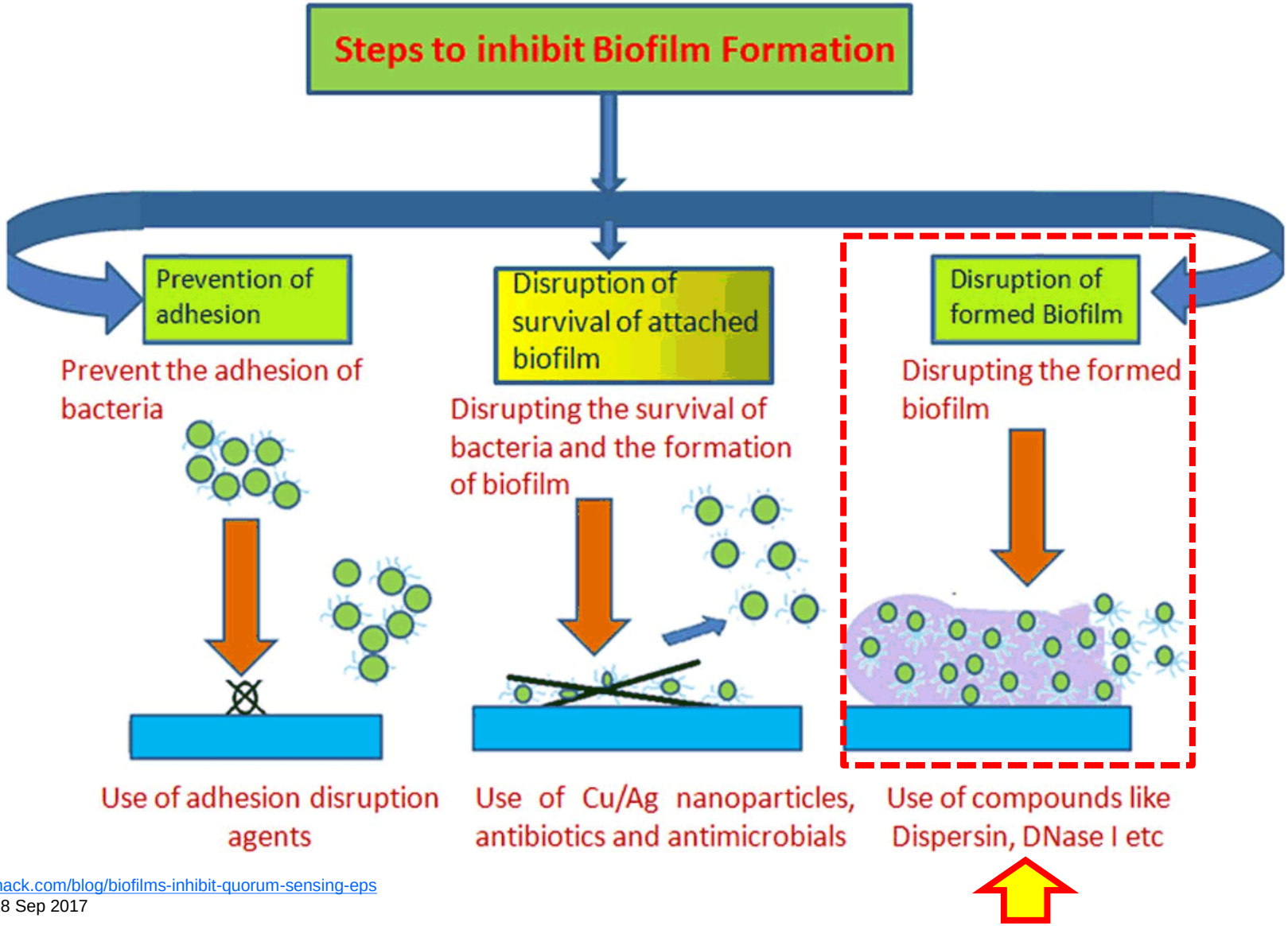


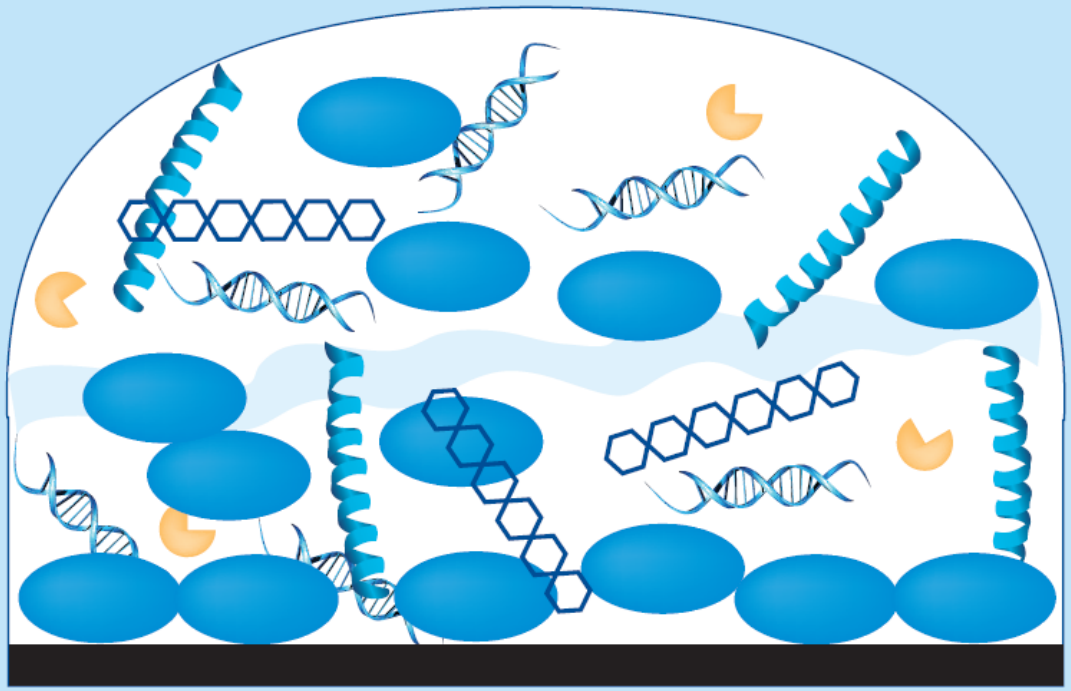
Siala *et al*. 2016 ESCMID Conference on Antimicrobial resistance in microbial biofilms and options for treatment, Ghent, Belgium, 5-7 October 2016 - poster

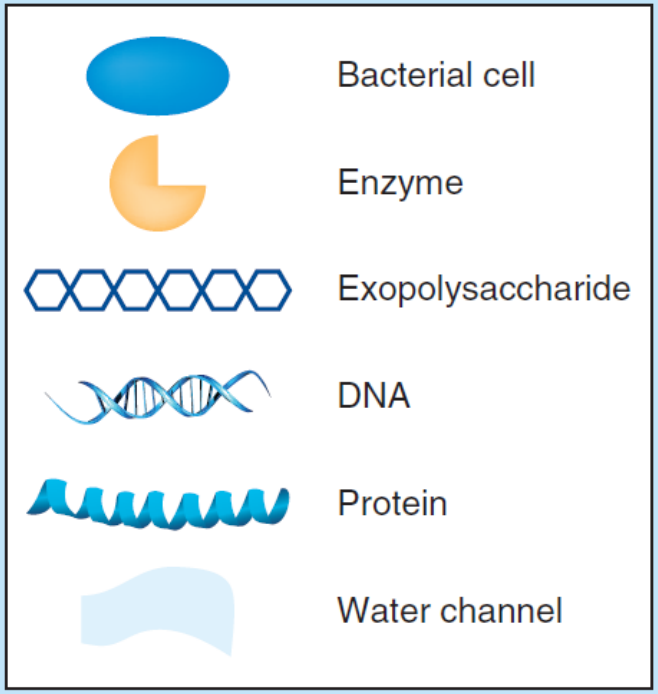
Biofilms: what can you do next ?



https://mybiohack.com/blog/biofilms-inhibit-quorum-sensing-eps
Last visited: 28 Sep 2017

Biofilm matrix: what is it made of ?





Rabin et al., Future Med. Chem. 2015; 7:493–512

An unanticipated observation !

nature COMMUNICATIONS

ARTICLE

Received 23 Feb 2016 | Accepted 20 Sep 2016 | Published 3 Nov 2016

DOI: 10.1038/ncomms13286 OPEN

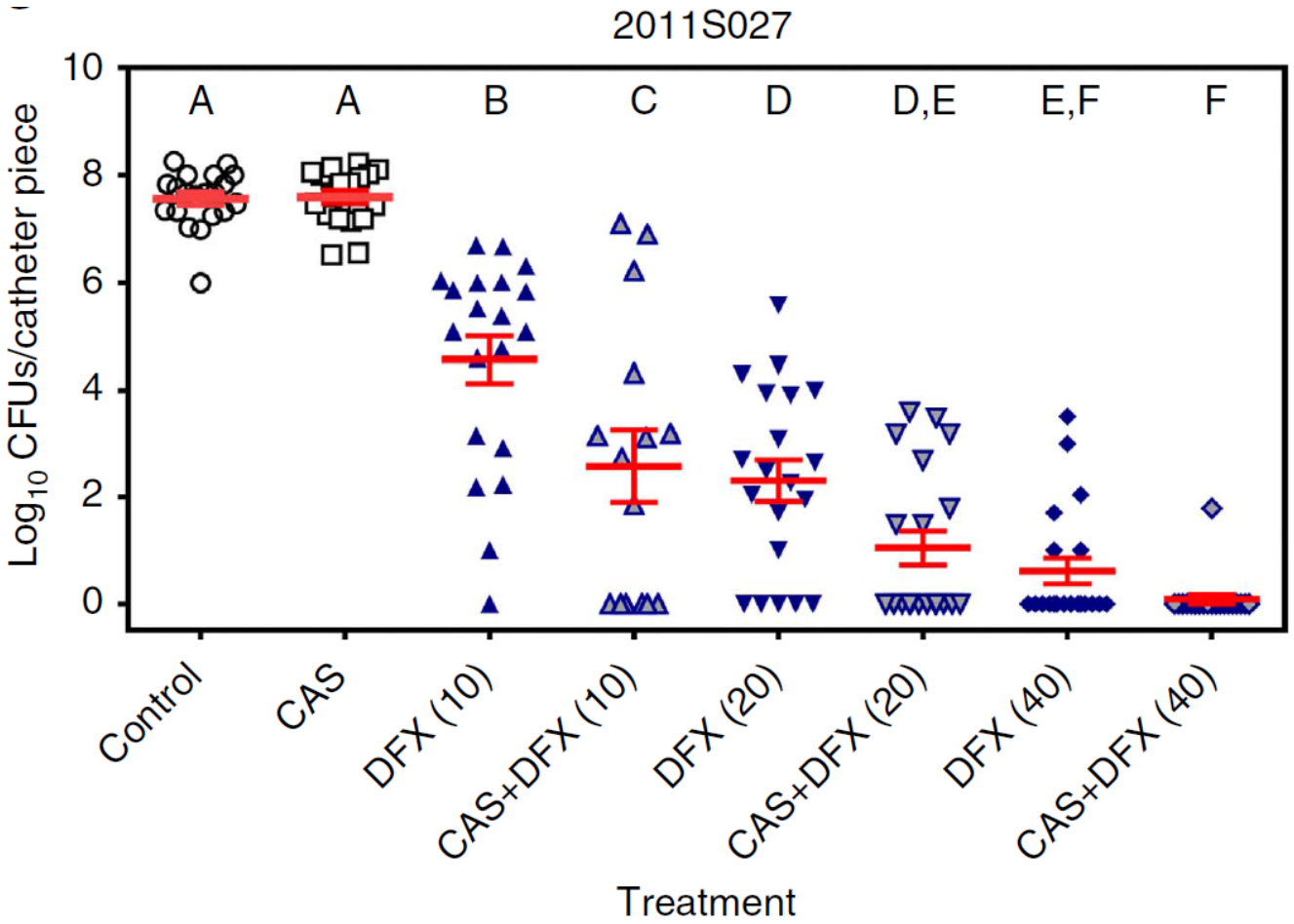
The antifungal caspofungin increases fluoroquinolone activity against *Staphylococcus aureus* biofilms by inhibiting *N*-acetylglucosamine transferase

Wafi Siala[1], Soňa Kucharíková[2,3], Annabel Braem[4], Jef Vleugels[4], Paul M. Tulkens[1], Marie-Paule Mingeot-Leclercq[1], Patrick Van Dijck [2,3] & Françoise Van Bambeke[1]

http://www.nature.com/articles/ncomms13286

Siala *et al*, Nature Communications 2016; 7:13286 – PMID: 27808087

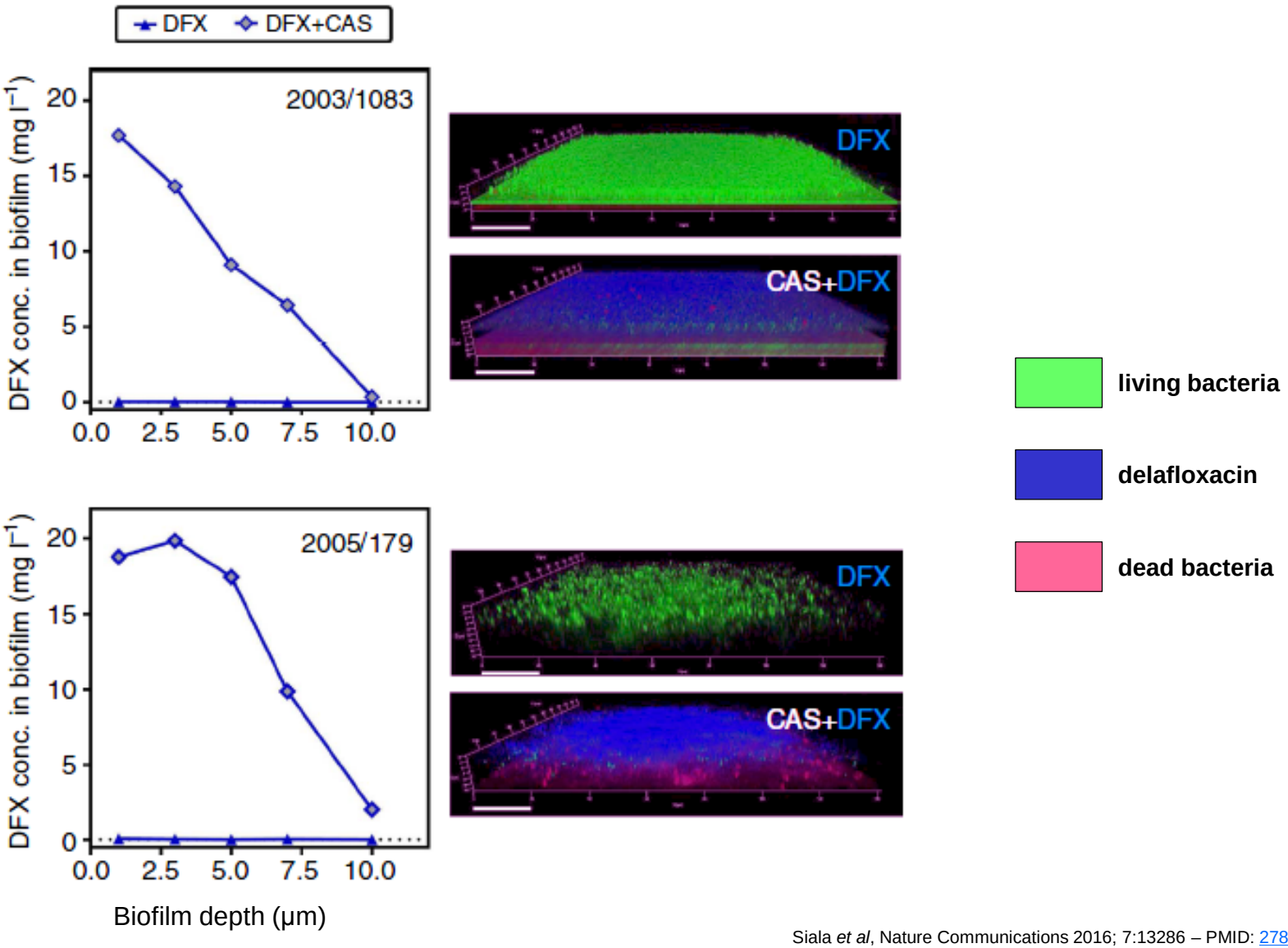
Caspofungin increases fluoroquinolone activity *in vitro* and *in vivo*



Caspofungin makes fluoroquinolones active at lower concentrations

Siala *et al*, Nature Communications 2016; 7:13286 – PMID: 27808087

Caspofungin increases fluoroquinolone penetration

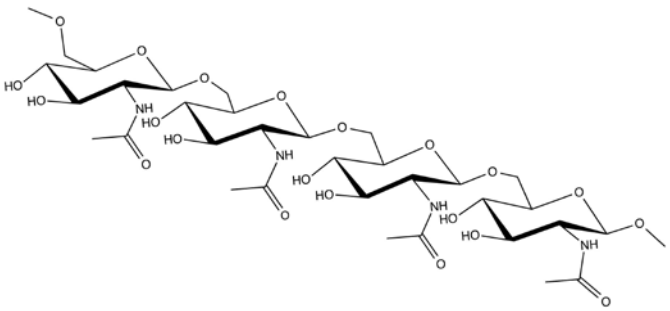


Siala *et al*, Nature Communications 2016; 7:13286 – PMID: 27808087

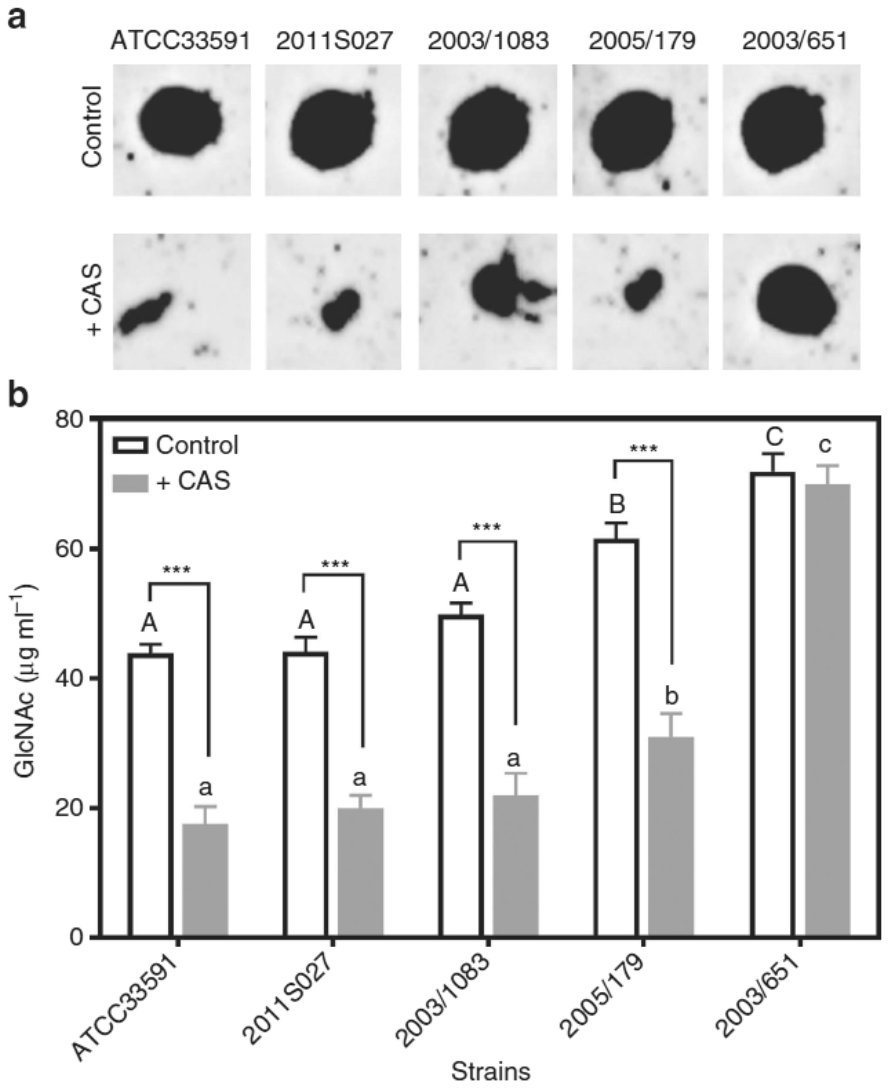
Effect of caspofungin on PNAG in biofilm matrix

a) Immunoblot analysis of PNAG purified from biofilms.

b) Determination of N-acetyl-glucosamine (GlcNAc) concentration



Poly-N-acetylglucosamine (PNAG)



CAS ↘ poly-N-acetylglucosamine content in biofilms

Siala *et al*, Nature Communications 2016; 7:13286 – PMID: 27808087