Fusidic acid (FUS) combined with daptomycin (DAP) is effective against *Staphylococcus aureus* biofilms in an *in vitro* dynamic model mimicking human exposure

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Introduction

Staphylococcus aureus causes chronic infections in humans, which are associated with its capacity to form biofilms that protect bacteria from the immune system and antimicrobial agents [1].

Over the years, *S. aureus* has become over the years resistant to most antibiotics, renewing the interest for old antibiotics like fusidic acid (FUS) in countries where they have not been used in the past and where resistance is therefore low [2]. Yet, FUS has to be used in combination to avoid resistance selection. Its activity against biofilms is unknown.

Aim

This study aims to evaluate the activity of FUS in combination with other antistaphylococcal antibiotics (daptomycin [DAP], vancomycin [VAN], and linezolid [LZD]) against *S. aureus* biofilms, using an *in vitro* pharmacodynamic model (CDC bioreactor).
This model allows exposing bacteria to shear forces and to mimic antibiotic human pharmacokinetics.

Materials and Methods

The reference strain ATCC25923 and a clinical isolate (80224422456) obtained from a patient suffering from osteomyelitis were used. Biofilms were grown on polycarbonate coupons in the CDC bioreactor (**Fig. 1**). After 20h preconditioning (medium: TSB supplemented with 1% glucose and 2% NaCl), antibiotics at their human fC_{max} were injected into the bioreactor and the flow was set up to simulate antibiotic human elimination half-lives. Coupons were aseptically removed over time. Bacteria were recovered by vortexing and sonication and CFUs counted after plating and overnight incubation. Aliquots of culture media were collected at the same time and used for determination of antibiotic concentrations by appropriate techniques (FUS, microbiological assay; DAP, fluorimetry; LZD, HPLC; VAN, immunoassay).

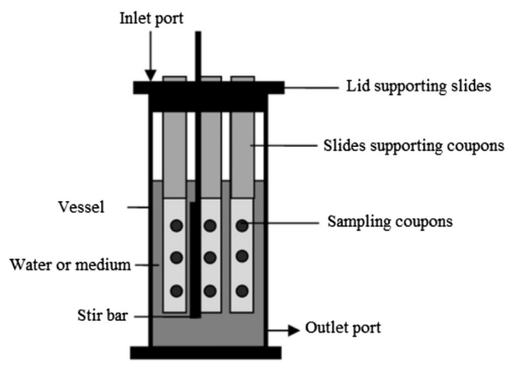
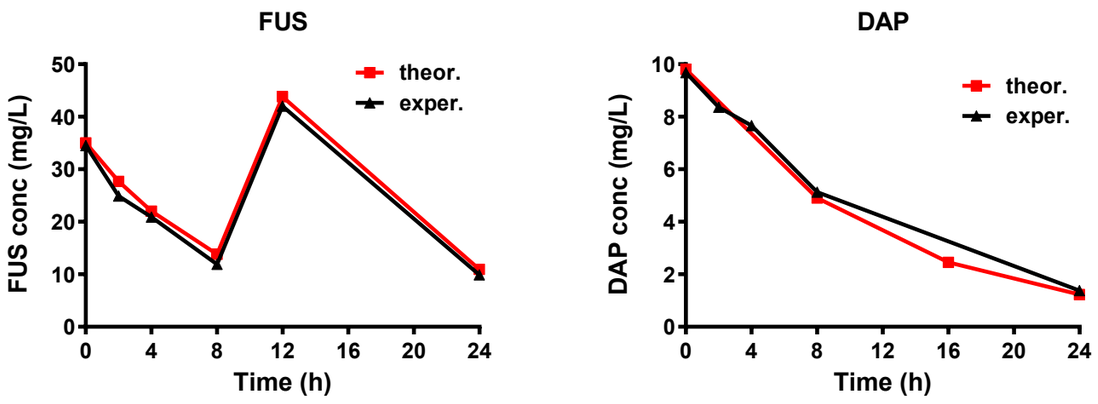


Fig 1: The CDC reactor [3]
Biofilms are grown on 12.7 mm diameter coupons, suspended in the bulk fluid by eight coupon holders

Results



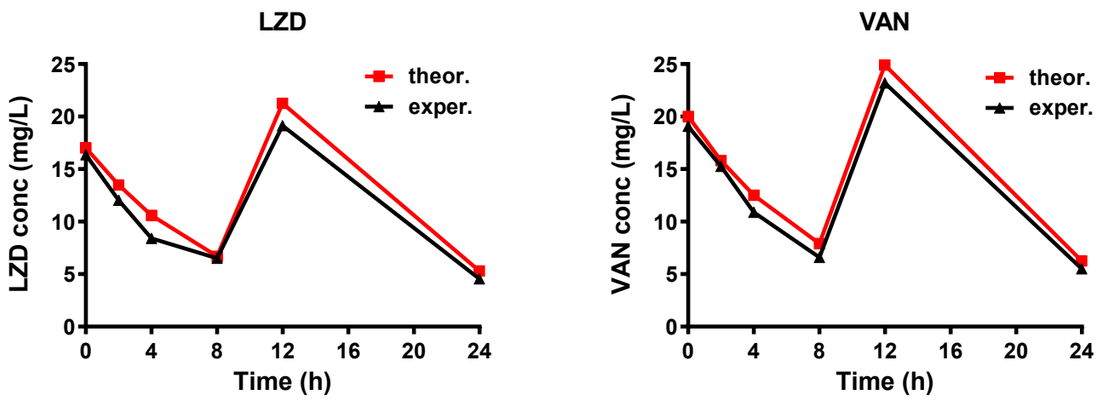


Fig 2:
Comparison of theoretical (theor.) and measured (exper.) antibiotic concentrations (mg/L) in the CDC bioreactor

antibiotic	fC_{max} (mg/L)	fC_{min} (mg/L)	k_{theor} /$t_{1/2}$ (h^{-1} /h)	k_{exper} (h^{-1})
FUS	35	11	0.12 (6 h)	0.15 ± 0.08
DAP	9.8	0.7	0.09 (8 h)	0.07 ± 0.02
LZD	17	9	0.12 (6 h)	0.28 ± 0.08
VAN	20	2.5	0.12 (6 h)	0.12 ± 0.06

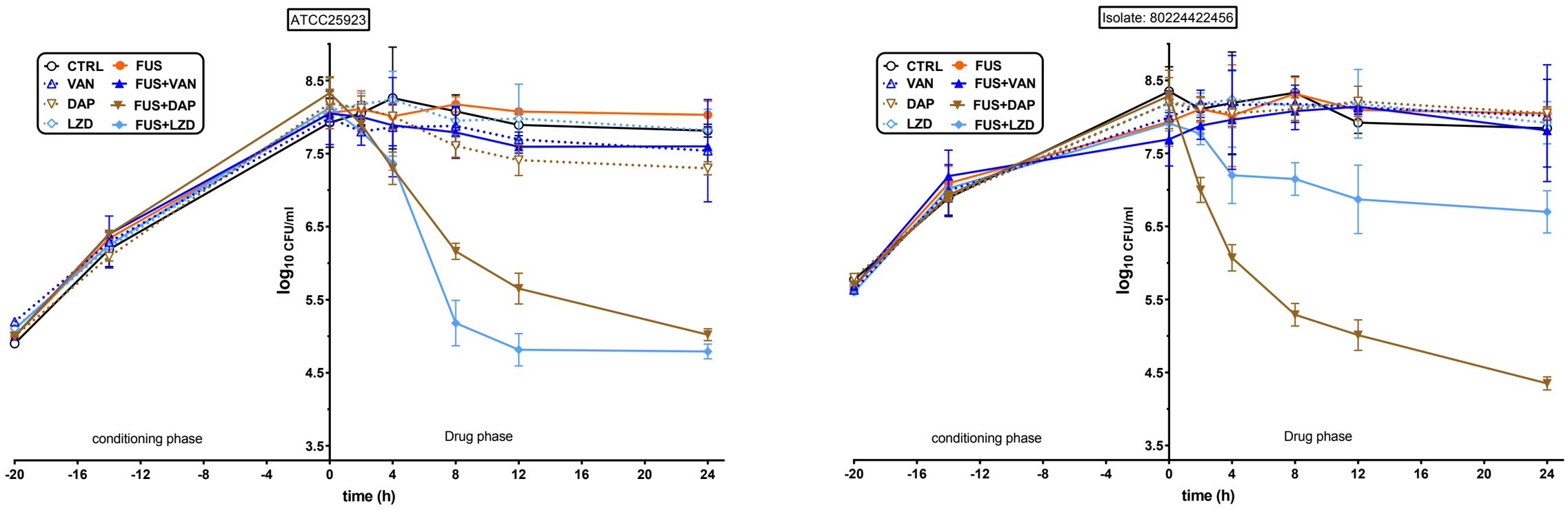


Fig 3: Activity of FUS alone or combined with DAP, VAN, LZD against *S. aureus* biofilms in a dynamic model.
FUS, VAN and LZD injected twice (T0 and T12); DAP injected once (T0).

Conclusions

Combining FUS with DAP proved most effective against biofilms from both a reference strain and a clinical isolate in this model, pointing to the potential interest of this combination for the treatment of biofilm-related infections.
Further investigations are warranted to unravel the mechanism of the observed synergy between these two drugs as well as of the difference in activity of the FUS-LZD combination between the two strains.

This poster will be available after the meeting at http://www.facm.ucl.ac.be/posters

References

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[3] Gomes et al, Water Research 2014; 62: 63-87.

Acknowledgements

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